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Research Article

ANTI-INFLAMMATORY, ANTICONVULSANT AND ANTIPYRETIC PROPERTIES OF ETHANOLIC EXTRACT OF *VITEX DONIANA* SWEET STEM BARK

Tijjani M.A.[1], Abdurahaman F. I.*[1], Khan I. Z.[1] and Sandabe U. K.[2]
[1]Department of Chemistry, Faculty of Science, University of Maiduguri, P.M.B 1069, Maiduguri, Borno State, Nigeria
[2]Department of Veterinary Physiology, Pharmacology and Biochemistry, University of Maiduguri, P.M.B 1069, Maiduguri, Borno State, Nigeria

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*Email: fannas3@yahoo.com

ABSTRACT
Anti-inflammatory, anti-convulsion and anti-pyretic activities of ethanolic stem bark extract of V.doniana were evaluated on laboratory rats. The stem bark of V. *doniana* Sweet (2kg) was macerated for five (5) days, filtered and concentrated in vacuo and subsequently phytochemically screened for secondary metabolites. Inflammation was induced in paw of laboratory rats using egg albumen (0.1ml) and paw size was measured and analyzed. The anti-convulsant and antipyretic effects of the extracts were evaluated using standard procedures. The acute toxicity both intraperitoneal and orally were estimated using lorke method. The ethanolic extracts yield was estimated to be 14.8%$^{w}/_{w}$. Phytochemical analysis of the V. *doniana* stem bark extract revealed the presence tannins, phlobatannins, saponins, carbohydrate, cardioactive glycoside, flavonoids, steroids and terpenes. The ethanolic extract demonstrates dose-dependent reduction of egg albumen induced oedema conferring 86.5% inhibition of inflammation at a high extract dose of 400mg/kg body weight. The extract also conferred 80% protection in rats treated with convulsive dose of Penetylene tetrazole (PTZ) as compared with the control. The stem bark extract further exhibited some antipyretic properties which were seen in the dose dependant reduction of fever induced by brewer's yeast in treated rats. This finding collaborate the use of *Vitex doniana* stem bark in folkloric medicine and demonstrates its possible neurological effect as observed in the dose dependant reduction of Inflammation, anticonvulsant activity and reduction of induced pyrexia
Keywords: *Vitex doniana*, anti-inflammation, anticonvulsant, pyrexia

INTRODUCTION

There has been a rapid expansion of allopathic system of medical treatment in many countries during the past century. However, some of these drugs have adverse effect and people are going back to nature with hope of safety. On the other hand, herbs are safe, cheaper, easily available and with no fear of any side effects. A number of interesting outcomes have been found with the use of a mixture of natural products or plant extracts to treat diseases[1].It is evident that many valuable herbal drugs have been discovered by knowing that particular plant was used by the ancient folk healers for the treatment of some kind of ailment. Moreover, the medicinal plant wealth is our national heritage and it seems to be the first and foremost line of defense for the treatment of various diseases mostly in tribal and rural communities[2].The study of natural products has had a number of rewards. It has led to the discovery of a variety of useful drugs for the treatment of diverse diseases and contributed to the development of separation of science and technology, spectroscopic methods of structure elucidation and synthetic methodologies that is now the basis of analytical organic chemistry. In recent years, traditional medicine has received renewed interest from scientists because of the advent of multidrug resistant microorganisms, serious side-effects obtained with a number of synthetic drugs, and because of the incurable nature of a number of diseases, where modern medicine seems to have failed to make any positive impact.

The demand for herbal medicines is increasing rapidly due to their fewer of side effects. Further as health care costs continue to escalate, the attraction for low-cost remedies has stimulated consumers to re-evaluate the potential of alternatives[3] .

Literature has shown that some plants have found application in medicine. In Africa, particularly in Nigeria, herbal medicine has become a part of peoples culture though this form of medicine is not well organize as in China and India[4]. The Nigerian flora has made and would continue to make great contributions to health care of Nigerians. In fact the indigenous medicinal plants form an important component of the natural wealth and culture of Nigeria[5]. Natural plant products have been used in Nigeria especially in the tropical rain forest zone of Southern Nigeria in local medicinal practice but very little of such substance has been subjected to scientific verification[6].

Vitex doniana Sweet, a plant commonly known black plum, in English, Prunier noir in French, dinya in Hausa , ucha koro in Igbo, oori-nla in yoruba and ngarmi in Kanuri is a medium-sized deciduous tree, 8-18m high, with a heavy rounded crown and a clear bole up to 5m. V. *doniana* is from *Verbenaceae* family and abundantly occurring in savannah regions. Vitex specie has a lot of medicinal importance. It has been has been traditionally used to treat a number of ailments, but with particular emphasis on menstrual disorders and related hormonal problems[7,8]. Vitex possesses anti-inflammatory and antibacterial properties[9] it has been reported that one of the *Vitex* specie called vitex negundo antihistamine properties[10]. Also there is a reported anti-inflammatory and antipyretic properties of methanolic leaf extracts of *Vitex doniana*[11]. This study aim at evaluating anti-inflammatory, anticonvulsant and antipyretic activities of stem bark ethanolic extract of V. *doniana* Sweet

MATERIAS AND METHODS

Sample collection and identification

The stem bark of V*itex doniana* leaves were collected in Kawuri village of Konduga (11°39′6″N 13°25′10″E) Local Government Area of Borno state of Nigeria. The plant specimen was identified and authenticated by a Plant Taxonomist, Prof. S.S. Sanusi of the Department of

Biological Sciences, Faculty of Science, and University of Maiduguri. The herbarium specimen with a voucher number 555C was deposited at the Research Laboratory, Department of Chemistry. The stem bark of the *Vitex doniana* was cleaned and air-dried in the laboratory. Two kilogram (2kg) of the stem bark of *Vitex doniana* was pulverized into a coarse powder.

Extraction of stem bark and Phytochemical analysis

The weighed powdered air-dried sample (2kg) was macerated with 95% ethanol for five days filtered and evaporated in vacuo at 40°C using a rotary evaporator. The extract concentrate was labeled and the percentage yield was calculated in $^{w/}_{w.}$ The ethanolic extract was subjected to qualitative chemical screening for identification of secondary metabolites such as flavonoids, alkaloids, sterols, triterpenes, saponins, anthracenosides, tannins, polyuronides, emodol[12,13,] .

Pharmacological Evaluation

Animals

Eighty (80) Albino wister rats of both sexes weighing 100-150g and thirty (30) mice of both sexes weighing 20-30g. They were obtained from a colony of rats maintained at the animal house of the Institute of Trypanosomiasis Research Vom, Nigeria. They were housed in clean cages and had access to feeds (ECWA FEEDS) and water *ad libitum*. They were allowed to acclimatize for two (2) weeks in the Veterinary Physiology, Pharmacology and Biochemistry Laboratory before the commencement of the study. All the animals were handled according to the guiding principles of biomedical research involving animals as certified by the ethics committee of Faculty of Veterinary Medicine, University of Maiduguri, Nigeria[14].

Acute Toxicity studies (LD_{50})

The acute toxicity (LD_{50}) value of the crude stem bark ethanolic extract of *Vitex doniana* will be determined using standard conventional procedures as described by Lorke[15] . In this study two different routes of administration will be considered, that is the oral and intra-peritoneal. In phase I rats will be divided into 3 groups of three rats for each route (a total of nine rats) and then treated with crude ethanolic extract at doses of 10, 100 and 1000 mg/kg body weight intraperitoenally and orally and observed for 24 hours for mortality. In the phase II, the animals in group for each route will be divided into 4 groups(one animal in group 1, two in group 2, three in group 3 and five in group 4) and the ethanolic extract administered at doses to be determined after the phase one. The final LD_{50} value will be calculated as the geometric mean of the surviving group and the death group in the second phase.

Anti-inflammatory Evaluation

Twenty five male rats weighing between 150-200g was used. They were placed into 5 groups five rats each A, B, C, D, and E, group A served as the control while groups B, C, and D were treated with various dose levels 100mg/kg, 200mg/kg, 400mg/kg of the stem bark extract .Group E was given 60mg/kg dose of aspirin .The extract and the drug treatment were intrapriteoneally injected 30 minutes prior to the induction of edema. Edema was induced by injecting 0.1ml of egg album into right paw of the rats. Using vernier caliper, the diameter of the paws was measured after every hour for 5 hours, with the final reading taken 24 hours after edema induction[16]. Percentage inhibitions were calculated using the formula of Hernandex-Perez *et al*[17].

$$\text{Percentage inhibition} = \frac{(C_t - Co)\ \text{control} - (C_t - Co)\ \text{treated}}{(C_t - Co)\ \text{control}} \times 100$$

Where C_t = Linear paw circumference 3 hours after extract injection

C_o = Linear paw circumference before extract injection

Anticonvulsant Evaluation

Anticonvulsant Evaluation of Pentylene Tetrazole-Induced Convulsions (Seizures) in Mice

Adult mice weighing 20-30g of either sex was used for this experiment. food was withdrawn twelve (12) hours before the experiment, but water was remain available *ad libitum* until the start of the experiment. The animals were randomly divided into groups of 5 mice each and were treated as follows: Group A was given a convulsive dose of pentylene tetrazole (PTZ, 100 mg/kg), subcutaneously. Groups B-D received graded doses (mg/kg) of the ethanolic extract (i.p.), 30 minutes later, pentylene tetrazole (leptazole) (100 mg/kg) was injected subcutaneously (s.c.) on the back of the neck of the animals. Seizures were manifested as tonic convulsions (tonic hind limb extension). The ability to prevent this feature or prolong the latency or onset of the tonic hind-limb extension over a 24 hour period was taken as indication of anticonvulsant activity. The onset of tonic convulsions and the number of mice presenting convulsions per minute and the duration of convulsions were recorded. Animals that do not show tonic hind limb extension during the period of observation was considered not having convulsed. The mice was also be monitored for instances of death up to 24 hours after the experiment[18, 19, 20](Williamson *et al*., 1996; Nwafor, 1998; Abdulrahman, 2004).

Antipyretic Evaluation

The procedure described by Besra *et al*., (1996) was adopted. Thirty rats of both sexes were used for this experiment. The rats were given a solution of 20% Brewer's yeast (1ml) subcutaneously at the neck region and fasted to induce fever. About Eighteen hours thereafter, their body weight and temperature were recorded. Twenty rats with elevated temperature were selected and divided into four groups of five rats each. Group A served as the control and was given distilled water only; while groups B, C and D were given various doses 100mg/kg, 200mg/kg, 300mg/kg of the ethanolic extract .The body temperature of the rats in the various groups was determined at 1 hour interval following the administration of the ethanolic extract

Statistical Analysis

Data expressed as mean±SD and mean±SEM. Test of Significance between control and treatment means were carried out by Analysis of Variance (ANOVA) using Graph Pad Software[21] .

RESULTS AND DISCCUSION

The extracts concentrate yields of ethanol is 14.8%w/w. Preliminary phytochemical analysis of the ethanolic stem bark extract of V. *doniana* revealed the presence of tannins, phlobatannins, saponins, carbohydrates, cardioactive glycoside, flavonoids, steroids and terpenes .Alkaloids and anthracenosides is absent in the extract (table 1). The phytochemicals found are implicated to have many medicinal importances.The intraperitoneal LD_{50} in rats was found to be 2154.06mg/kg. On administration of 5000mg/kg dose of the extract via oral route, there was no dead which makes it impossible to estimate LD_{50} via oral route using the Lorke method[15] . According the classification of Clarke and Clarke[22] substances that have an intraperitoneal LD_{50} between

50 and 500mg/kg are considered toxic and Onyeyilli *et al*[23] categorized an intraperitoneal LD_{50} of 1400mg/kg under low toxicity.

The result of table 2. shows the effect of different dosages of the V. *doniana* stem bark extract and Aspirin (60mg/kg) on the egg albumen induced edema. The results demonstrate that the extract reduced the mean paw diameter when compared with the control which is distilled water. Also, the extract at doses of 400mg/kg and 300mg/kg conferred the high percentages inhibitions of 86.45% and 69.32% in laboratory rats after five (5) hours. The extract produced dose dependant reduction of increased paw diameter induced by the egg albumen. The paw mean size diameter (mm) decreases from 6.14± 0.33 on administration of 1000mg/kg to finally 3.45±.0.12 on treatment with 400mg/kg of the V. *doniana* ethanolic extract when compared to the control which reduced the paw size by 7.30± 1.33. Asprin(60mg/kg) has a percentage inhibitions of 25.40%, 43.20% and 63.45% respectively after 3, 4, and 5 hours of administration to the laboratory rats. Thus the V. *doniana* stem bark ethanolic extract at 300mg/kg and 400mg/kg has higher percentage of inhibition when compared to the aspirin (60mg/kg), a standard anti-inflammatory drugs that inhibit prostaglandin synthesis[24]. This result clearly demonstrated the anti-inflammatory properties of V. *doniana* stem bark ethanolic extract. The anti-inflammatory activities of the extract may be due to its content of tannins, and tannins apart from acting as astringent are known to inactivate enzymes[25] and these may be responsible for anti-inflammatory activities. This observation is an indication of possible usage of the plant for treatment of inflammatory conditions

In the anticonvulsant studies the rats that received the 600mg/kg of stem bark ethanol extract had 80% protection against PTZ induced convulsion while those that received 300mg/kg dose of the extract had 60% protection as shown in table 3. The mean onset of convulsion for 600mg/kg was 13.60±011 (min) and the mean onset of death is 27.40±0.23 (min), and only one rats convulsed in this group. Convulsion is a symptom of dysfunction in the gray matter of the brain rather than disease itself[26] . PTZ act by stimulation of the medulla[27] .The ability of the V. *doniana* extract to protect against rats stimulated with PTZ may be an indication of depressant effect on the spinal cord and brain stem. The ability of the extract to protect animals from induced seizures shows that it contains some chemical components that are capable of antagonizing chemically induced seizures. This depressant activities may be due to presence of phytochemical like saponins, flavones tannins glycosides which may have singly or in combination brought about the anticonvulsant activities This is accordance with the works of Abdurahaman *et al*,[28] who use this method to study this anticonvulsant properties of different plant extracts.

The stem bark extract of V.*doniana* also possess antipyretic properties as shown in table 4. High dose of 400mg/kg significantly reduced rectal temperature from 40.12±0.05 ^{0}C after 18 hours of induction of fever by Brewers yeast to 39.30 ±0.13^{0}C after one hour on administration of the extract. Four hours later the rectal temperature reduce to 37.81±0.67 ^{0}C. Also Aspirin (60mg/kg) reduced the rectal temperature from 39.90±0.25* on 18 hours of fever induction to 38.14±0.2^{0}C. after just one hour and subsequently to 37.50 ±0.01 after 5 hours. The effects of the aspirin (60mg/kg) are high as compared to the extract as seen in table 4. Thus the stem bark extract demonstrated an antipyretic properties. This observation supports the claim of local people in folkloric treatment of fever. Fever may a result of infection or one of the consequence of tissue damage inflammation or other diseases state[11] . Antipyretic drug reduces elevated body temperature and this activity may be due to presence of flavonoid compounds as some flavonoidal compound are predominant inhibitors of cyclooxygenase and lipooxygenase[13]. This antipyretic properties of the extract due to brewer yeast induced pyrexia is in accorandance with the similar work on *Terminalia avicennoides Morinda Lucinda* and *Khaya senegalensis*[29]

CONCLUSION

This research shows that the ethanolic extract of V. *doniana* possesses significant antipyretic, anti-inflammatory, anti-convulsant properties on laboratory rats. The phytochemicals found such as flavonoid, tannins, steroids, saponins, carbohydrates, terpenes and cardio-active glycosides are implicated in having the pharmacological actions that was observed This finding collaborate the use of *Vitex doniana* stem bark in folkloric medicine and demonstrates its possible neurological effect as observed in the dose depandant reduction of Inflammation, anticonvulsant activity and reduction of induced pyrexia.

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Table 1. Phytochemical analysis of Stem bark ethanolic extract of V.*doniana*

S/N	Class of Chemical Components	Results
1.	**Terpenoid test**	+
2.	**Test for soluble starch**	-
3.	**Test for phlobatannins**	+
4.	**Test of Alkaloids**	
	Dragendoff reagent	-
	Mayers reagent	-
5.	**Test for Flavonoid**	
	Shinoda Test	++
	Lea acetate test	++
	Sodiuhydroxide test	++
	Ferric Chlorides test	++
6.	**Test for carbohydrate**	
	General Test (Molish test)	+
	Test of monosaccharide	-
	Test for reducing sugar (Fehling test)	++
	Combine reducing sugar test	++
	Test for ketoses	+
	Test for pentose	-
7.	**4. Test for tannins**	
	Ferric chloride	++
	Lead acetate	++
	Hydrochloric acid test	-
8.	**Test for free Anthraquinones**	-
	(Bontrase)	-
	Test for combined anthraquinone	
9.	**Test for cardio active glycoside**	
	Salkowski test	++
	Liebermann Burchard test	++
10.	**Test for Saponins**	
	Frothing test	++
	Fehling's test	+

Key + = Present, ++ = Present in Moderate Concentration, - = Absent

Table 2. Effect of ethanolic extract of V. *doniana* stem bark on egg albumen induced oedema in laboratory rats

Extract dose (mg/kg)	Mean paw size diameter (mm±SEM)	Percentage Inhibitions (%)		
		3hrs	4hrs	5hrs
Control(DW)	7.30± 1.33	1.30	1.60	2.30
100	6.14± 0.33	19.10	24.54	32.33
200	5.58± 0.45	23.50	39.14	51.30
300	4.23± 0.23*	26.70	45.33	69.32
400	3.45±.0.12*	38.30	64.63	86.45
Asprin 60	5.04±0.35 *	25.40	43.20	63.45

P< 0.05 significantly different from the control

Table 3 . Effect of ethanolic stem bark extract of V. *doniana* on Pentylenetetrazole (PTZ) induced convulsion

Extract pre-treatment (mg/kg)	Mean ± SD onset of convulsion (min)	Mean±SD onset death (min)	Quantal death	Survival %
Control + 50mg/kg of PTZ	3.40±0.55	10.5±0.57	5/5	0
100mg/kg of extract + 50mg/kg of PTZ	6.23±0.67	16.21±093	3/5	40
300mg/kg of extract + 50mg/kg of PTZ	9.36±0.33	21.90±0.11	2/5	60
600mg/kg of extract + 50mg/kg of PTZ	13.60±011	27.40±0.23	1/5	80

Table 4: Effect of ethanolic stem bark extract of *Vitex doniana* on Brewer's yeast induced hyperpyrexia in rats

Treatment groups (mg/kg)	Rectal Temperature ^{0}C			Mean ±SD		
After yeast injection	After drugs Administration					
I.P	0(min	18(hrs)	120(min	60(min))	180(min)	240(min)
Control (DW)	37.0	39.7 ±0.22	39.6 ±0.32	38 .8±0.61	38.6 ±0.72	38.2 ±0.05
100	37.1	40.63 ±0.34*	39.17 ±0.22*	39.02 ±0.56*	38.10 ±0.11	37.3 ±0.34
200	37.4	40.47 ±0.22	38.82 ±0.39*	38.01 ±0.38*	37.53 ±0.27	37.30 ±0.45
300	37.3	39.01 ±0.49*	38.01±0.26*	37.96 ±0.69	37.30 ±0.11	37.30 ±0.10
400	37.8	40.12 ±0.05*	39.30 ±0.13	38.10 ±0.80	37.9 ±0.23	37.81±0.67
Aspirin (60mg/kg)	37.5	39.90±0.25*	38.14±0.23*	37.82±0.14*	37.52 ±0.67*	37.50 ±0.01*

*P<0.0001 significant compared to control

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