

Full Length Research Paper

Evaluation of the blood pressure lowering activity of leaf extract of *Acalypha torta* Muell

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The leaf of *Acalypha torta* Muell. (Euphorbiaceae) is used as folk remedy in Nigeria for the treatment of hypertension. Effects of extracts of *A. torta* leaf on the blood pressure of anaesthetized cats were studied to examine this claim. The ethanol extract produced a significant ($p < 0.0001$) and dose - dependent fall in arterial blood pressure. The extract inhibited adrenaline - induced contraction of isolated rabbit aortic strips and produced a significant ($p < 0.0001$) and dose - dependent increase in the rate of flow of physiologic fluid through the rat hind-quarters preparation. Both evidences indicate relaxant effect of the ethanol extract on vascular smooth muscle. Calcium chloride - induced tachycardia was abolished following administration of the extract. It had no effect on the rate of contraction of the isolated rabbit heart, but reduced the force of contraction. Column chromatography was performed and Fraction L, eluted with distilled water, was found to be responsible for the reduction in blood pressure.

Key words: *Acalypha torta*, hypertension, antihypertensive, cat.

INTRODUCTION

The risk of elevated blood pressure, commonly known as hypertension, has been determined from several large scale epidemiological surveys and it has been reported to be a leading risk factor for stroke, coronary heart disease, heart failure and renal failure (Afolabi, 2000; Oladipo, 2000). Anti-hypertensive therapy is therefore aimed at reducing morbidity and mortality due to fatal and non-fatal cardiovascular events and thereby prolonging life.

Although many drugs with proven pharmacological activity are available clinically to ameliorate cases of individuals with hypertension and other associated clinical symptoms, herbal medicines are growing in popularity in both developing and the developed world (Aschwanden, 2001).

Many plant species including *Nauclea latifolia* Sm (Rubiaceae), *Tridax procumbens* Linn. (Compositae), *Bridelia Atroviridis* Muell. Arg. (Euphorbiaceae) and

Hibiscus sabdariffa have been used in ethnomedicine for the management of hypertension (Nworgu et al., 2008; Salghdeen et al., 2004; Carallo et al., 1997; Obiefuna and Owolabi, 1993). Extracts of these plants have been tested in various animal models and are shown to possess hypotensive properties supporting their use in the treatment of hypertension.

Plants of the family Euphorbiaceae are frequently used in tradomedical practices. Their pharmacological properties include anti-tumor, anti-bacterial, anti-fungal and anti-malarial activities (Eno et al., 2007; Irobi and Bansa, 1994).

Traditionally, the leaves of *A. torta* Muell are also used in the Western and Southern States of Nigeria as treatment to reduce blood pressure. There is, however, no published report on the hypotensive property of this plant. In view of this, the present study was carried out to investigate the effects of various extracts of *A. torta* leaf on the blood pressure of anaesthetized cats and also establish the plausible pharmacological basis for the action.

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MATERIALS AND METHODS

Mature *A. torta* Muell leaves were collected from Abagana, Anambra state, Nigeria. The plant was identified and authenticated by Mr E. C Ekekwe in the Department of Botany, University of Nigeria, Nsukka. Voucher specimen was prepared and deposited in the International Centre for Ethnomedicine and Drug Development (INTERCEDD) herbarium with no.8256.

Experimental animal models

Twelve mature healthy normotensive cats (1.5 to 2.3 kg), 3 adult healthy male albino rabbits (1.7 to 2.5 kg) and 9 wistar albino rats (160 to 200 g) were obtained from the animal house of the Department of Pharmacology and Therapeutics, College of Medicine, University of Nigeria, Enugu. All the animals were kept in the animal house of the Department of Biochemistry, Nnamdi Azikiwe University, Awka, for two weeks to allow for acclimatization with free access to standard diet (Bendel Feeds and Flour Mills Plc) and water.

Chemicals

Drugs used were thiopentone, heparin, adrenaline, atropine, acetylcholine, histamine and promethazine. All the drugs were purchased from Sigma. The chemicals used, chloroform, ethanol, methanol, sodiumcarboxymethylcellulose, calcium chloride and potassium chloride were purchased from BDH Ltd, Poole, England. All other reagents used were of analytical grade.

Preparation of extracts for preliminary activity testing

Fresh leaf samples were dried at room temperature and pulverised. Four hundred grams of the powder were extracted thrice by macerating in 2.0 L of chloroform:methanol (2:1) for 24 h. Combined extract was filtered with cheese cloth and Whatman no.1 filter paper. The filtrate gave two layers (aqueous methanol and chloroform layers) on addition of 0.2 vol. of distilled water. The two layers were separated with the aid of a separating funnel and each fraction evaporated to dryness using a rotary evaporator to yield methanol extract (3.8 g) and chloroform extract (5.3 g).

The residue from chloroform:methanol extraction was dried and re-extracted thrice in 2.0 L of ethanol, at room temperature, for 24 h. Combined extract was filtered and evaporated to dryness with a rotary evaporator to yield ethanol extract (2.3 g).

The residue from ethanol extraction was dried and re-extracted thrice in 2.0 L of distilled water by following the same procedure outlined under ethanol extraction to obtain the aqueous extract (3.8 g).

The four kinds of extracts (chloroform, methanol, ethanol, and water) prepared were used for the preliminary activity screening of the *A. torta* leaf.

Biological activity tests

Blood pressure measurements

Ten male normotensive cats (1.5 to 2.0 kg) out of the 12 cats originally obtained from the animal house were used for this study. Each animal was anaesthetized with thiopentone (50.0 mg/kg body wt.) intraperitoneally. The animal was laid on its back on the thermostatic Brown-Schuster myographic stand (C.F. Palmer, London).

The femoral vein was cannulated for administration of drugs, while the carotid artery was cannulated and connected to a mercury

manometer through a three-way stop cock with a syringe filled with heparinized saline. The trachea was exposed and cannulated to facilitate spontaneous respiration. The mercury manometer was then connected via a writing lever to a smoked paper on a Brodie-Startling kymographic drum rotating at a speed of 16 mm/min. The animal's body temperature was maintained at $37.0 \pm 1.0^\circ\text{C}$ by means of the thermostatically controlled dissecting table.

After a 30 min period of equilibration, the initial (basal) arterial blood pressure was noted before administration of normal saline as control or any drug. The crude chloroform extract was solubilized in tween-80, methanol and ethanol extracts were dissolved in 1.0% carboxymethyl cellulose (CMC), whereas water extract and the reference drugs, adrenaline (100.0 $\mu\text{g}/\text{kg}$ body wt.) and histamine (0.2 $\mu\text{g}/\text{kg}$ body wt.) were solubilised in normal saline. Their effects on the blood pressure of the cat were evaluated as the delta of fall on the mercury manometer. The same dose of the various extracts of *A. torta* was tested on five animals. The arterial blood pressure was allowed to return to the resting level between injections.

The internationally accepted principles for laboratory animal use and care as found in the US guidelines (NIH publication #85 to 23, revised in 1985) were strictly observed in the design and execution of this study.

Effects of varying doses (6.0 to 20.0 mg/kg body wt.) of the active ethanol extract on the blood pressure of the anaesthetized cats were studied in another five cats.

Studies on isolated rabbit aortic strips

Adult male rabbit weighing 1.98 kg was used and the method employed was according to Furchgott and Bhadrakom (1953). The aorta was cut through, as near the heart as possible, dissected free for as long a distance as possible, and mounted in a dish containing Krebs's solution at 37°C to maintain physiological condition of muscle as if they are intact. This solution acts like internal body condition. The composition of the solution in mM was as follows: NaCl, 120.0; KCl, 5.9; NaHCO_3 , 25.0; NaH_2PO_4 , 1.2; CaCl_2 , 2.5; MgCl_2 , 1.2; and glucose, 5.5 It was equilibrated with a mixture of oxygen (95%) and carbon dioxide (5%) to give the physiological solution the pH of 7.4 resembling the internal environment. Continuous aortic strips were then prepared and mounted in the organ bath connected to a lever writing on a smoked drum. Drugs were added directly to the 50 ml tissue baths in bath fluid. They were usually left in contact with the tissue until an equilibrium steady state response was achieved. A 45 to 60 min. equilibration period was allowed between additions. The effect of *A. torta* extract was first noted and then viability of the tissue confirmed by the introduction of different doses, 10.0, 30.0, and 60.0 μg of adrenaline standard. The effects of adrenaline (60.0 μg) in the presence of two doses, 10.0 and 20.0 mg of *A. torta* extract were then recorded. In both cases, the extract was allowed 8 min of incubation with the tissue before the injection of adrenaline.

Effect on perfused rat-hindquarters preparation

The effect of ethanol extract on blood vessels was studied using rat-hindquarters preparation according to the method of Hutchings et al. (1980). The hind-quarters preparation was placed on wire mesh on a plastic funnel to facilitate collection of the fluid with a measuring cylinder. The physiological fluid (Ringer- Locke) solution was constantly aerated with 5% CO_2 in O_2 and the pressure at which the physiological fluid and extract perfuse the vessels was kept constant. The flow rate was calibrated by recording the volume of fluid dropped at 5.0 min. intervals until a constant volume was obtained. After 30 min. equilibration, alterations of flow rate caused by three bolus doses (10, 12.5 and 20 mg) of ethanol extract were then recorded.

Studies on rabbit heart preparation

A modified method of Amos et al. (2003) was adopted. Heart preparations isolated from male rabbits weighing between 1.5 and 2.0 kg were used. The physiological fluid used for isolation was ice-cold Ringer-Locke solution maintained at 0°C. After isolation, the heart was transferred to a perfusion apparatus. Ringer-locke's solution in a reservoir maintained at a constant pressured served as the perfusion fluid. Equilibration time of 30 min. was allowed before appropriate bolus dose of the extract (2.0 to 5.0 mg) was introduced through the rubber tubing connecting the reservoir to the perfusing cannula. Temperature of 37°C was maintained by water circulated from a thermostat. The effects of CaCl₂ (3.0 and 6.0 mg) were then recorded, and the effect of the ethanol extract on response of tissue to calcium chloride investigated.

Chromatographic separation

Three grams of the ethanol extract was subjected to chromatographic separation in silica gel G column (Kieselgel 60 to 200 mesh, Merck Art.No 7731) using chloroform / butanol / xylene(2:2:3) and distilled water as solvent systems. Eluents were controlled with TLC using chloroform/butanol/xylene (2:2:3) mobile system. Fractions with similar R_f values were combined as follows: fr.A(1-2), fr.B(3-12), fr.C(13-19), fr.D(20-38), fr.E(39-43), fr.F(44-52), fr.G(53-59),fr.H(60-62), fr.I(63-67), fr.J(68-72), fr.K(73-76), fr.L(77-80), and fr.M(81-89). Fractions J- M were obtained with distilled water.

Identification of the hypotensive fraction

The effects of fractions A to M on the arterial blood pressure were then tested in anaesthetized normotensive male cats weighing 1.9 to 2.3 kg by following the procedures outlined under blood pressure measurements section.

Acute toxicity testing

Forty-eight adult albino mice weighing 39.0 to 50.0 g were divided into eight groups of six mice each based on their body weights. After overnight fasting, test groups were intraperitoneally treated with fraction L in 100, 200, 500, 1000, 2000, 4000, and 8000 mg/kg body wt. doses, while the control group of animals received 1.0 ml/kg of the vehicle (normal saline). The animals were then allowed free access to water and standard animal feed and were observed for 24 h for changes in behaviour and mortality.

Phytochemical analysis

Tests for the presence of alkaloids, flavonoids, cardiac glycosides, saponins, and tannins in the bioactive fraction L were carried out, using standard phytochemical screening methods (Sofowora, 1982; Evans, 1989).

Statistical analysis

Averages were expressed as arithmetic means \pm standard deviation of the mean (SD). Student's t-tests were performed comparing the results obtained from each drug concentration with measurements from control experiments and a P value of <0.05 taken as indicating a statistically significant difference. Analysis of variance was then performed to evaluate differences between the doses using a

one-way analysis of variance (ANOVA). Subsequently, Bonferroni's Multiple Comparison Test was done to identify the source of any statistically significant difference. For each reading, the average % change \pm SD was calculated for each dose of drugs or ethanol extract of *A. torta* administered.

RESULTS

Four types of extracts were obtained and tested for their blood pressure lowering potentials. The four different extracts in addition to adrenaline and histamine were tested on five anaesthetized cats and the results calculated as arithmetic mean \pm Standard deviation. The chloroform and methanol extracts at 12.5 mg/kg body wt. each did not have any effect on the arterial blood pressure of the anaesthetized cats. Water extract (12.5 mg/kg. body wt.) consistently elevated blood pressure of the cat by (27.0 \pm 6.39 mmHg). The observed increase in blood pressure due to water extract was comparable to that (28.4 \pm 6.95 mmHg) caused by adrenaline standard (100.0 μ g/kg body wt.). In contrast, the ethanol extract of *A. torta* (12.5 mg/kg body wt.) produced an average reduction of 39.8 \pm 4.92 mmHg in the arterial blood pressure which was analogous to 41.0 \pm 3.61 mmHg average fall in blood pressure elicited by 100 μ g/kg body weight of histamine. The *A. torta* extract always had rapid on-set of action, but the decrease in blood pressure produced was always transient, returning to basal level within 2 minutes. Figure 1 shows one of the tracings obtained following administration of these drugs to the cats. In another series of experiments involving five cats, the ethanol extract was found to possess dose-dependent blood pressure lowering effect (Figure 2). Maximum activity was recorded at a dose of 20.0 mg/kg body wt. which lowered the arterial blood pressure by 86.33 mmHg. The animal died shortly afterward and the lethal dose was not repeated subsequently. Analysis of variance of the three test doses of 6, 10 and 12.5 mg/kg showed that the hypotensive effects produced were statistically significant ($p = 0.0006$). When the values were compared using Bonferroni multiple comparison test, it was found that the difference in the blood pressure lowering effect of 10 mg/kg dose versus that of 12.5 mg/kg was not statistically significant ($p > 0.05$) whereas it was significant when 6 mg/kg dose is compared with 10 mg/kg dose ($p < 0.05$) or 12.5 mg/kg dose ($p < 0.001$). The blood pressure lowering effect of the extract was affected by both atropine and promethazine, and at 20 μ g/kg the effect was completely abolished.

In the rabbit arterial preparation, 60 μ g injection of adrenaline induced a remarkable contraction of the rabbit arterial preparation. Incubation of the strips with *A. torta* ethanol extract (10 mg) for 2 min before repeating the injection of adrenaline (60 μ g) caused a reduction of 16.7 \pm 3.52% in the height of adrenaline induced contraction. A higher dose (20 mg) of the extract diminished the height of contraction of the arterial strips by 33.3 \pm 4.54% within 10 min of administration, and the effect of

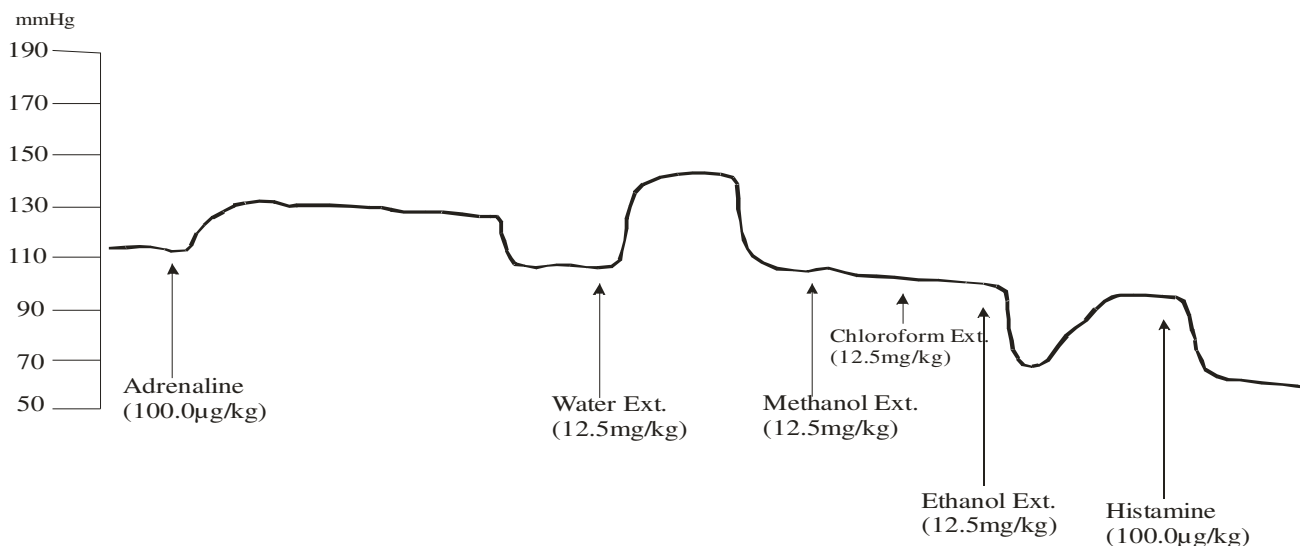


Figure 1. Manometer tracing showing effects of adrenaline, histamine, and various extracts of *Acalypha torta* leaf on the blood pressure of anaesthetized cat. Only the ethanol extract out of the four extracts had blood pressure lowering activity.

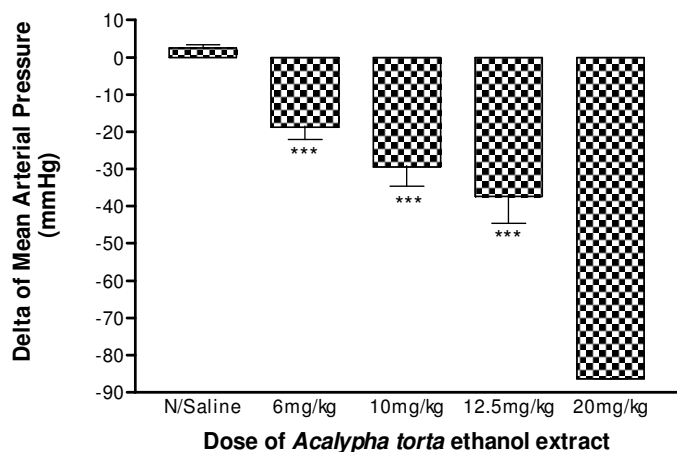


Figure 2. Bar chart representing the blood pressure lowering action of increasing doses of ethanol extract of *Acalypha torta* leaf. The effects produced were dose dependent and statistically significant compared to the normal saline control which elevated the blood pressure. ANOVA: $p = 0.0006$ Bonferroni: 6 mg/kg vs 10 mg/kg $p < 0.05$; 6 mg/kg vs 12.5 mg/kg $p < 0.001$; 10 mg/kg vs 12.5 mg/kg $p > 0.05$. *** $p < 0.0001$.

adrenaline completely disappeared after 20 min. It was also observed that the ethanol extract increased the flow rate of physiological fluid in the rat hind-quarters preparation. The increase in flow rate was found to be dose dependent with the extracts given as bolus injections of 10, 12.5 and 20 mg (Table 1). One-way analysis of variance (ANOVA) comparing the three different doses of *A. torta* ethanol extract (10, 12.5 and 20 mg) shows statistically significant difference in flow rate ($p < 0.0001$). Bonferroni comparison test revealed, however, that whereas the difference between effects

due to 10 and 20 mg on one hand and 12.5 and 20 mg on the other hand were statistically significant ($p < 0.001$), the effect caused by 10 mg compared to that of 12.5 mg was not ($p < 0.05$).

In the Langendorff heart preparation, the ethanol extract had no effect on the rate of contraction of the isolated rabbit heart but the height of contraction, indicating contractility of the heart, showed dose-dependent decrease with a peak reduction of 81.6% (From 15.5 ± 1.32 to 2.85 ± 0.98 mm) by 5 mg of the extract. Calcium-chloride induced tachycardia was also abolished by the same dose of the extract. Figure 3 is a bar chart comparing the effects of different doses of ethanol extract of *A. torta* leaf on the force of contraction of isolated Langendorff heart. The extracts showed dose-dependent reductions that are statistically significant compared to the values produced by the normal saline.

When the active ethanol extract was subjected to column chromatographic separation (using silica gel 60 to 200 (stationary phase), and chloroform:butane:xylene, and distilled water (mobile phases), thirteen fractions, A to M, were obtained and their blood pressure lowering effects tested. Fractions E, J, K and M caused slight increases in the arterial blood pressure of normotensive cats, whereas fraction L only reduced the blood pressure of the cat. All other fractions had no observed effect on cat blood pressure.

In acute toxicity test, no visible signs of toxicity were observed. Treatment of rat with 500, 1000, 2000, 4000, and 8000 mg/kg body wt. of the fraction, caused deaths of 2, 3, 5, 6 and 6 animals respectively and the LD_{50} was extrapolated as 1000 mg/kg body wt. There were no deaths in the groups of animals that received normal saline or 100 and 200 mg/kg of fraction L.

Phytochemical screening indicated the presence of

Table 1. Effect of three different doses of ethanol extract of *A. torta* on rat hindquarter preparation flow rate (ml/5 min.). Drug was given as a bolus dose contained in 0.1ml. N = 5 ANOVA: p < 0.0001 Bonferroni: 10 mg vs 12.5 mg p > 0.05; 10 mg vs 20 mg p < 0.001; 12.5 mg vs 20 mg p < 0.001.

Dose (mg)	Flow rate at equilibration	Flow rate at peak activity	Volume change (ml)	% volume change	Average % volume change \pm SD
10	7.3	8.1	0.8	11.0	17.3 \pm 4.21
	6.4	7.8	1.4	21.8	
	6.9	8.2	1.3	18.8	
	8.2	9.5	1.3	15.5	
	10.2	12.2	2.0	19.6	
12.5	7.8	9.4	1.6	20.5	23.5 \pm 5.28
	9.4	11.2	1.8	19.1	
	8.3	11.0	2.7	32.5	
	8.5	10.5	2.0	23.5	
	10.0	12.2	2.2	22.0	
20	5.4	7.2	1.8	33.3	36.4 \pm 2.89
	7.2	9.8	2.6	36.1	
	6.4	8.8	2.4	37.5	
	9.6	12.9	3.3	34.4	
	9.1	12.8	3.7	40.7	

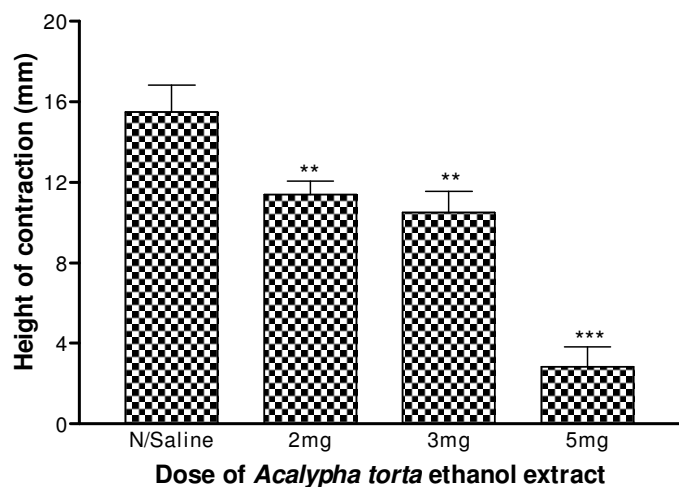


Figure 3. Bar chart comparing the effects of different doses of ethanol extract of *Acalypha torta* leaf on the force of contraction of isolated Langendorff heart. The extracts showed dose-dependent reductions that are statistically significant compared to the values produced by the normal saline. **p < 0.0005; *** p < 0.0001.

flavonoids, cardiac glycosides and steroids. Traces of alkaloids and tannins were also observed.

DISCUSSION

The differential extraction of *A. torta* leaves in the three solvent systems - chloroform: methanol (2:1), ethanol and

water, yielded four extracts (methanol, chloroform, ethanol and water extracts). When the effects of the four extracts (12.5 mg/kg body wt. each) on the blood pressure of anaesthetized cats were investigated, results showed that the ethanol extract lowered the arterial blood pressure of the cats. The evidence that this ethanol extract of *A. torta* consistently produced dose-dependent fall in blood pressure of anaesthetized cats validates the claim that *A. torta* leaves possess a strong blood pressure lowering property. The active blood pressure lowering principle is soluble in ethanol. The blood pressure lowering action of *A. torta* was also found to be rapid but unsustainable, always returning to the baseline within two minutes. Rapid onset of action may suggest that the bioactive compound may be a low-molecular weight substance that is rapidly absorbed and distributed to its sites of action (Eno et al., 2007), and that vasodilatation is partly responsible for the reduction in blood pressure. The transient blood pressure lowering effect may indicate direct relaxation of vascular smooth muscle, or direct depressant action on the myocardium (Smith, 1961).

Hypertension is a haemodynamic disorder in which elevated arterial pressure may result from increased cardiac output or increased total peripheral resistance or a combination of both factors (Alper, et al 2002). Therefore the target of many antihypertensive agents is to reduce cardiac output and, or total peripheral resistance. The cardiac output is a function of the force and rate of contraction of the heart, and the elasticity and distensibility of the conducting arteries, whereas the total

peripheral resistance depends on the area available for blood flow (Oates and Brown, 2001). Mechanistic studies of the blood pressure lowering potential of *A. torta* were therefore, focused more on its effects on the blood vessels, and heart.

During this study, it was shown that the extract has no effect on the rate of contraction of perfused rabbit heart but the force of contraction (depicted by height) was dose- dependently reduced. The *A. torta* extract caused up to 71% reduction of the height of contraction.

These effects could result from the relaxation of the cardiac muscles due to the inhibitory action of the extract on the β -adrenoceptors of the myocardium. (Nworgu et al., 2008). The fact that ethanol extract of leaf of the *A. torta* inhibited adrenaline-induced contraction of isolated rabbit aortas gives credence to this suggested mechanism of action.

The observed significant increases in the rate of flow of physiological fluid through the vessels of the rat hind-quarters preparation also indicated vasodilatation of the peripheral blood vessels. Since calcium ion is involved in several physiological and biochemical processes in the body including the excitation-contraction coupling, calcium channel blockers lower arterial blood pressure by relaxing smooth muscles of the vessels (dilatation) and cardiac muscles (Taddel et al., 2001). The ethanol extract of *A. torta* was found to interfere with calcium utilising processes since the calcium chloride- induced dysrhythmia of the perfused rabbit heart which caused abnormally rapid increase in the force and rate of contraction was remarkably antagonized by the extract. Thus, this mechanism could also be contributing to the blood pressure lowering effect of the extract. Interestingly, Smith (1961), in his analysis of effects of drugs on the cardiovascular system, suggested that any hypotensive drug which produced a fall in blood pressure that lasted for less than two minutes was likely to be producing the fall either through direct vascular smooth muscle relaxation, or direct depressant action on the myocardium, but certainly not through the autonomic nervous system.

In view of the fact that increase in extracellular K^+ is responsible for opening of Ca^{2+} channels leading to increase in intracellular free Ca^{2+} available to bind with calmodulin, K^+ channel blockers would be expected to close the Ca^{2+} channels thereby inhibiting binding of calcium to the contractile elements (Gutkind, 1998; Dorn and Brown, 1999; Dempsey et al., 2000). Therefore, blocking of K^+ channels could contribute to the vascular relaxation elicited by ethanol extract of *A. torta* leaf.

From the foregoing it is reasonable to conclude that ethanol extract of *A. torta* lowers the blood pressure of the anaesthetized cat by both reducing the cardiac output and the peripheral resistance. Since the percent decrease in the contractility of the myocardium was greater than the percent increase in flow rate, it is reasonable to conclude that reduction in cardiac output

contributes more to the blood pressure lowering effect of the extract.

When the effect of fractions from the active ethanol extract were tested on the blood pressure of anaesthetized cat, fraction L was the only fraction that lowered the blood pressure, indicating that the bioactive principle of *A. torta* extract is present in this fraction and is hydrophilic in nature since this fraction was eluted with distilled water. Phytochemical screening of the fraction showed that it is rich in flavonoids, and cardiac glycosides. Flavonoids have been reported to have hypotensive activities in laboratory animals (Xue et al., 2002; Zhu et al., 2005). Furthermore, flavonoids have been widely described in literature as vasodilator compounds (Duarte et al., 1993; Fitzpatrick et al., 1993; Herrera et al., 1996; Nworgu et al., 2008). The hypotensive activity of the cardiac glycosides have also been reported (Ayachi and Brown, 1980; Wilhem and Georgios, 2007). These compounds may therefore be contributing to the blood pressure lowering activity of the ethanol extract of *A. torta* leaves. The fact that the LD_{50} of this fraction L was estimated to be 1000 mg/kg body wt. indicated very low toxicity of the fraction.

Conclusion

The leaf of *A. torta* Muell was found to possess blood pressure lowering activity. The bioactive ingredient was extractable in ethanol. The antihypertensive activity may be a combination of vasodilatation which would reduce peripheral vascular resistance and negative inotropic property which would reduce cardiac output. The leaf ethanol extract of *A. torta*, considering its pharmacological actions as demonstrated in this study, can, not only be a safe and cheap folkloric remedy for hypertensive conditions, but can also be used to alleviate the pains associated with various ischaemic heart diseases.

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