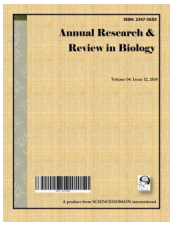

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Haematological and Biochemical Changes Associated with Treatment of Experimentally-Induced Hypertensive Wistar Rats with *Lagenaria breviflora* Roberty Fruit or *Xanthosoma sagittifolium* Exell Corm

Olayinka A. Oridupa[1*], Feyisola L. Ojojugbo[1] and Naomi O. Ovwighose[1]

[1]Department of Veterinary Pharmacology and Toxicology, University of Ibadan, Ibadan, Nigeria.

Authors' contributions

This work was carried out in collaboration between all authors. Author OAO designed the study, carried out the experiment and wrote the protocol and final draft of the manuscript. Author FLO carried out the experiment and performed the statistical analysis. Author NOO wrote the first draft of the manuscript, managed the analyses of the study and literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aim: The toxicity profile of management of hypertension in Wistar rats with the methanol extracts of the whole fruit of *Lagenaria breviflora* Roberty or corms of *Xanthosoma sagittifolium* was assessed in this study.
Place and Duration of Study: The study was carried out at the Animal House of the Department of Veterinary Pharmacology and Toxicology, University of Ibadan, Ibadan, Nigeria, between November, 2016 and January, 2017.
Methodology: Forty male Wistar rats were divided into 8 groups (n=5). Group 1 served as the control and was administered with distilled water. Hypertension was induced in groups 2-8 by intraperitoneal administration of DOCA-salt twice weekly and daily inclusion of 1% sodium chloride

**Corresponding author: E-mail: olayinkaolumide2000@yahoo.com, oa.oridupa@mail.ui.edu.ng;*

in drinking water. Group 2 (hypertensive but untreated), groups 3 and 4 (lisinopril or hydrochlorothiazide), groups 5 and 6 (*L. breviflora* at doses of 100 or 200 mg/kg), and groups 7 and 8 (*X. sagittifolium* at doses of 100 or 200 mg/kg). Urine samples (over 24 hours) and blood samples were collected for urinalysis, hematology and serum biochemistry respectively.

Results: Management of hypertension with the extracts of *L. breviflora* or *X. sagittifolium* showed that the extracts did not further progress the haematological and metabolic derangement associated with hypertension. *L. breviflora* showed non-significant haematopoietic and immunomodulatory effects, while the extract of *X. sagittifolium* reversed renal damage caused by hypertension. Both extracts showed potent hypocholesterolemic effects and the atherogenic index of plasma of rats treated with the extracts also improved, indicating reduction of risks of development of coronary arterial disease or heart disease (CAD or CHD).

Conclusion: Management of hypertension with fruit of *Lagenaria breviflora* or corm of *Xanthosoma sagittifolium* is safe and the haematological and metabolic derangement associated with hypertension will not further deteriorate but will rather improve.

Keywords: Hypertension; Lagenaria breviflora; Xanthosoma sagittifolium; haematology; biochemistry.

1. INTRODUCTION

Traditional system of medicine is gradually gaining more recognition in the world over, thus the use of medicinal plants has increased for treatment of human and animal diseases. Traditional (or herbal) medicine is in an evolutionary process as communities and individuals continue to discover new techniques that can transform practice in the field of medicinal sciences [1]. In Nigeria and many other Africa countries, institutionalization of traditional medicine in parallel with orthodox medicine is the focus of the new health agenda. Effective health cannot be achieved in Africa by orthodox medicine, thus the natural health care scheme, in order to move national health agenda to the next level [2].

The recent finding of hypertension in some companion and exotic animals such as dogs and horses, has necessitated research into antihypertensive agent which will be suitable for treatment of hypertension in these animals [3,4,5]. Currently the cost of available orthodox drugs is not economical for animal production and its efficacy may not be optimal in animals. Also, the high cost of orthodox antihypertensive drugs to the common rural dweller has led to uncontrolled hypertension and the sequel organ/system effects in many human patients [6]. The use of medicinal plants as herbal remedy for diseases such as hypertension is common practice in several regions of the world including Africa [7].

There is therefore an immediate need to determine the safety of these plants in other to prevent further damage to already deranged body systems. This study is focused on assessing toxicity or adverse effects that may result from treatment of hypertension with the extracts of *Lagenaria breviflora* and *Xanthosoma sagittifolium*, locally recommended for management of hypertension. *L. breviflora* (Family Cucurbitaceae) is a medicinal plant known to possess potent antioxidant, anti-inflammatory and analgesic activities [8,9,10]. It was reported to have haematopoietic and immunostimulatory effects [11,12]. *X. sagittifolium* (Family Araceae), commonly known as Cocoyam, on the other hand is a medicinal food plant known to possess potent antioxidant properties [13] and now recommended to diabetic patients as a replacement source for dietary carbohydrate. Folasire et al. [14] demonstrated its antihyperglycemic effect in alloxan-induced diabetic rats.

Plants are well known for their toxicity in addition to the pharmacological effect. Safety of these plants is not necessarily considered compared to the attention paid to their efficacy. Determination of toxic potential of medicinal plants is therefore very imperative to further drug development to ensure that pharmacological effects/benefits outweigh the toxic effect. Changes in the haematology, serum biochemistry and urinalysis are clinically relevant indicators of toxicity. Hypertension in itself is associated with derangement in haematology and biochemistry. Thus, this study aims to determine if treatment of hypertension with *Lagenaria breviflora* or *Xanthosoma sagittifolium* can alleviate haematological and biochemical anomalies associated with the disease or further progress these derangements.

2. MATERIALS AND METHODS

2.1 Preparation of the Methanol Fruit Extract

Fresh fruit of *Lagenaria breviflora* Roberty and corms of *Xanthosoma sagittifolium* Schott were obtained from Agbowo and Oje Markets, Ibadan, Nigeria. Herbarium specimens of the plants were deposited with Voucher Numbers UIH-21778 and UIH-22013 respectively. A total of 5 kg of fresh fruit of *L. breviflora* were washed and cut into small pieces and dried with a hot air oven at a temperature of 25°C. The bark of the *X. sagittifolium* corms were peeled and cut into small pieces and were air dried. A total of 525g dry weight was obtained from the corms.

2.2 Extraction of the Fruit Samples

The dried whole fruit and corms were separately extracted by cold maceration in methanol (96%) for 72 hours in well labeled glass flasks. The filtrate obtained was clarified by filtration through celite on water pump and was then concentrated *in vacuo* using rotary evaporator at low temperatures. The methanol remaining in the extract was finally removed by placing small volumes in porcelain dishes in the oven set at low temperature of 30°C. The extracts were stored at 4°C and reconstituted fresh daily.

2.3 Anti-hypertensive Study

Forty male Wistar rats used for the study were purchased from and housed at the Experimental Animal House, Department of Veterinary Physiology, Biochemistry & Pharmacology, University of Ibadan. The rats were fed with commercial rat pellet and water *ad libitum*, and randomly divided into eight groups (n=5). Group 1 served as control and was normotensive through the course of the study. Hypertension was induced in groups 2 – 8 by intraperitoneal administration of deoxycorticosterone acetate (DOCA-salt) twice weekly and daily inclusion of sodium chloride (NaCl; 2%) in drinking water. The rats were concurrently administered with the extract or antihypertensive drug for the 5 weeks period of the study. Group 2 rats were hypertensive but untreated through the course of the study. Groups 3 and 4 rats were administered with known antihypertensive drugs; lisinopril (0.07 mg/kg) or hydrochlorothiazide (0.18 mg/kg). Groups 5 and 6 were administered with whole fruit extract of *L. breviflora* Roberty at the dose of 100 or 200 mg/kg, while groups 7 and 8 were administered with corm extract of *X. sagittifolium* (L) Schott. Blood pressure was measured by non-invasive method. All experimental protocols were in accordance with the recommendation of the Animal Care Use and Research Ethics Committee of the University of Ibadan, Ibadan, Nigeria (UI-ACUREC/App/10/2016/015) and internationally acceptable best practices in experimental animal care and use.

2.4 Sample Collection

On the last day of week 5, the rats were placed in metabolic cages for 24 hours and urine was collected for urinalysis. Blood samples (about 5ml) were thereafter collected from the retro-orbital sinus of each rat for haematological and biochemical analysis. Haematological parameters determined according to Cole's method (15) were packed cell volume (PCV), red blood cell count (RBC), haemoglobin concentration and red cell indices such as mean corpuscular volume(MCV), mean corpuscular haemoglobin(MCH) and mean corpuscular haemoglobin concentration (MCHC). White blood cell count (WBC) and its differentials; lymphocytes, neutrophils, eosinophils and monocytes, and platelet count were also determined.

Serum was obtained for biochemical analysis by centrifugation of blood for 10 minutes and at 3000 rpm. The serum was stored at -20°C until used. Biochemical parameters determined includes total cholesterol, triglycerides, High density lipoprotein cholesterol, atherogenic index of plasma, blood urea nitrogen and creatinine. Presences of leucocytes, blood cells and bilirubin were determined in urine samples collected, as well as the pH and specific gravity of the urine samples.

2.5 Statistical Analysis

The data obtained were expressed as mean±Standard Error of Mean (SEM). The differences between the mean values were determined at $p<0.05$ using one way ANOVA and Duncan post-hoc test.

3. RESULTS

3.1 Haematology

There was an increase in the PCV of rats in all the treatment groups (45.2±2.68%, 43.8±1.07%,

48.2±1.28%, 44.6±2.07%, 46.2±0.93% and 45.0±0.95%) when compared to the control group (41.8±2.1%). The mean total red blood cell count and haemoglobin concentration (Hb) also increased, while MCV, MCH and MCHC were significantly unchanged (Table 1).

WBC of hypertensive rats administered with Lb at the dose of 100 mg/kg ($4.58\pm0.43X10^3$ µL), lisinopril ($4.83\pm0.39X10^3$ µL) and hydrochlorothiazide ($4.30\pm0.48X10^3$ µL) were within range of that observed in control rats ($4.52\pm0.29X10^3$ µL). However, hypertensive untreated rats and other rats treated with Lb ($6.19\pm 0.56X10^3$ µL) or Xs ($7.66\pm0.17X10^3$ µL and $7.50\pm 0.10X10^3$ µL) showed increased WBC. The differential counts were within range of the control values except for lymphocytes and neutrophil counts for rats administered with Xs at dose of 200 mg/kg (62.6± 3.38% and 34.4±3.99%) which were significantly lower and higher respectively compared to the control group (70.2±1.46% and 28.6±1.86%) (Table 2).

There is a marginal increase in the mean values of the control groups A (2.00± 0.45%), than the test group C (1.40± 0.25%), G (2.00± 0.23%), H (1.80±0.35%) but the test group B (2.60± 0.25%), D (2.40± 0.60%), E (2.40±0.51%) have a significant ($p<0.05$) increase than the control group. There is a significant ($p<0.05$) increase in the mean value of platelets of rats administered with hydrochlorothiazide ($5.68\pm0.46X10^5$/µL) and Lb at the dose of 200 mg/kg (2.97 ± 0.15 $X10^5$/µL) compared to the control group A (1.48±0.20%) (Table 2).

3.2 Serum Biochemistry

Mean total cholesterol (TC) values were higher in all the test rats compared to the control rats (42.05±2.33 mg/dl), but TC of rats administered with Lb at the dose of 200 mg/kg (42.05±2.35 mg/dl) was statistically unchanged, while hypertensive untreated rats had TC of 64.22±4.60 mg/dl. Mean triglyceride values were statistically unchanged in rats administered with the extract except Xs at 100mg/kg (84.73±1.68 mg/kg) compared to the control rats (71.66± 8.58 mg/dl). Mean high-density lipoproteins significantly ($p<.05$) increased in all the test rats with the highest levels observed in Lb at 100mg/kg (93.90±2.82 mg/dl) compared to the control rats (56.47± 4.27 mg/dl). Atherogenic index of plasma was significantly reduced in all the test rats with the least observed in rats administered Lb at 100 or 200mg/kg (-0.110 and -0.109) compared to the control rats (0.103) and hypertensive untreated rats (0.240). BUN values of all the test groups were significantly ($p<.05$) lower when compared to the control group (65.18± 5.85 mg/dl), while creatinine levels significantly increased ($p<.05$) compared to the rats in the control (0.36± 0.03 mg/dl) (Table 3).

3.3 Urinalysis

The color of urine samples from rats in all groups were normal (yellow to amber). Urinalysis showed the presence of leucocytes and bilirubin in urine of all test rats, which were absent in the control group. Increases in presence of proteins and urine pH of all test rats, with presence of blood cells in all test rats except rats administered with Xs extract was observed. The urine specific gravity was statistically unchanged except for rats administered with Lb at 100 mg/kg (1.022) and Xs at 100 mg/kg (1.042) which had lower and higher values respectively compared to control rats (1.030) (Table 4).

4. DISCUSSION

In this study, experimentally-induced hypertensive rats were treated with the extracts of the fruit of *Lageneria breviflora* Roberty or corms of *Xanthosoma sagittifolium* Schott. Hypertension is a medical condition associated with persistently elevated blood pressure, and may lead to damage primarily in the heart and other organs such as the kidneys, brain and eyes. Drugs for treatment are required to be safe for use, thus the need to assess safety of these extracts to blood cells and plasma.

Findings from this study showed that packed cell volume and red cell indices of all hypertensive rats increased, but rats treated with the extract of *L. breviflora* had significant ($p<0.05$) increases which agrees with a previous study on the fruit extract, where it was demonstrated to possess haematopoietic effect [11]. The basis increment in the hypertensive rats may be a compensation for the underlying medical condition. The mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH) and mean corpuscular haemoglobin concentration (MCHC) were unchanged, which indicates that the red cells were matured cells. This homogeneity in size may be due to the period of the study which is long enough for haematopoiesis to occur and maturation of the cells. Mean MCV values increases and MCH decreases when reticulocytes are present in the blood. Increase in

Table 1. Packed cell volume and red cell indices of hypertensive Wistar rats treated with extracts of *Lagenaria breviflora* or *Xanthosoma sagittifolium*

Group	PCV (%)	Hb (g/dl)	RBC(X10^6/µL)	MCV (*f*l)	MCH (pg)	MCHC (g/dl)
Ctrl	41.8±2.31	13.44±0.81	6.64±0.046	59.14±2.77	20.29±0.42	32.32±1.82
Hypert	46.8±3.42	15.18±2.68	7.64±0.48	61.4±0.69	19.87±0.19	32.52±0.38
Lisinop	45.2±2.68	15.82±2.68	7.86±0.32	57.41±2.01	20.22±0.64	35.45±.93
Hydrochl	45.2±2.68	14.44±0.27	7.33±0.17	60.13±0.87	17.71±1.98	33.31±0.27
Lb100	48.2±1.28	15.78±0.44	8.19±0.28	58.38±0.87	19.27±0.20	32.73±0.12
Lb200	44.6±2.07	14.58±0.73	8.19±0.28	59.51±0.54	19.44±0.15	32.73±0.12
Xs100	46.2±0.93	14.58±0.73	7.66±0.17	60.17±0.99	20.03±0.29	33.3±0.35
Xs200	45.0±0.95	15.02±0.09	7.66±0.17	59.43±0.52	20.02±0.22	33.39±0.18

Table 2. White cell parameters of hypertensive Wistar rats administered with extracts of *Lagenaria breviflora* or *Xanthosoma sagittifolium*

Group	WBC (X10^3/µL)	Lymphocyte (%)	Neutrophils (%)	Monocyte (%)	Eosinophils (%)	Platelet (X10^5/µL)
Ctrl	4.52±0.29	70.2±1.46	28.6±1.86	2.40±0.24	2.00±0.45	1.48±0.20
Hypert	6.09±0.11	69.4±1.97	25.8±1.75	2.20±0.38	2.00±0.45	1.53±0.45
Lisinop	4.30±0.48	67.4±1.92	30.0±1.71	1.40±0.25	1.40±0.25	1.95±0.86
Hydrochl	4.83±0.39	73.0±1.59	22.4±1.64	2.00±0.31	2.40±0.40	5.68±0.46
Lb100	4.58±0.43	74.2±2.33	22.6±2.21	2.00±0.40	2.40±0.60	1.38±0.86
Lb200	6.19±0.56	67.4±2.34	27.0±2.17	2.80±0.38	2.40±0.51	2.97±0.15
Xs100	7.66±0.17	61.6±1.05	27.0±2.17	2.00±0.23	2.00±0.23	1.43±0.07
Xs200	7.50±0.10	62.6±3.38	34.4±3.99	1.80±0.40	1.80±0.35	1.24±0.18

Table 3. Lipid profile, Creatinine and BUN of hypertensive Wistar rats administered with extracts of *Lagenaria breviflora* or *Xanthosoma sagittifolium*

Group	TC (mg/dl)	TG (mg/dl)	HDL-C (mg/dl)	AIP	BUN (mg/dl)	Creatinine (mg/dl)
Ctrl	42.05±2.33	71.66± 8.58	56.47±4.47	0.103	65.18± 5.85	0.36±0.03
Hypert	64.22± 4.60	89.01±1.79	51.20± 7.88	0.241	31.67± 3.92	0.55± 0.07
Lisinop	60.27±7.20	71.46± 1.21	66.47± 3.33	0.031	22.51± 3.47	0.42± 0.04
Hydrochl	59.38±7.82	71.85± 3.38	83.51± 8.22	-0.065	25.64± 2.63	0.72±0.07
Lb100	63.68± 3.80	72.86± 1.94	93.90± 2.82	-0.110	30.18± 2.82	0.57± 0.08
Lb200	42.05±2.35	70.35± 2.02	90.39±3.95	-0.109	28.68±3.57	0.46± 0.06
Xs100	50.17± 5.47	84.73± 1.68	91.22± 4.74	-0.032	38.16± 5.68	0.44± 0.03
Xs200	63.19±6.01	77.38±2.54	72.26± 3.96	0.030	44.88± 4.83	0.46± 0.02

Table 4. Urinalysis of hypertensive rats administered with extracts of *Lagenaria breviflora* or *Xanthosoma sagittifolium*

Group	Leucocyte	Protein	Bilirubin	Blood	pH	Specific gravity
Ctrl	-	+	_	_	7.5	1.030
Hypert	+	2+	+	+	8.5	1.034
Lisinop	+	3+	+	+	8.5	1.038
Hydrochl	+	4+	+	+	8.5	1.034
Lb100	+	3+	+	+	8.0	1.022
Lb200	+	+	+	+	8.0	1.033
Xs100	+	3+	+	_	8.5	1.042
Xs200	+	+	+	_	8.5	1.030.

circulating RBC occurs in response to stimulation of the erythropoietic system. Reticulocytosis occur as the initial response to stimulation of the erythropoietic system [16] and is often characterized by macrocytic and hypochromic red blood cells with increased MCV and decreased MCH and MCHC values [16], which compares with the findings in the test rats in this study. Plants in the Cucurbitaceae Family, to which *L. breviflora* belong, especially *Telfaria occidentalis* have also been reported to have haematinic effect and have proven to be of therapeutic value in conditions of anaemia [17,18].

The differential cell analysis for the white blood cells indices showed an increased WBC in hypertensive rats and rats treated with extract of *X. sagittifolium* and high dose of *L. breviflora*. Hypertension has an inflammatory basis which may explain the presence of inflammation, but the lower dose of *L. breviflora* reversed this inflammatory process and stimulated lymphocytosis. Increase in circulating lymphocyte values is associated with enhanced immunological status of the body [19] especially the cell-mediated immune response [20]. Cucurbitacin E, a phytochemical from this plant family was previously reported to induce and maintain high proliferation rates of lymphocytes [21], but when co-cultured with cancer cells, an interesting lymphocyte-mediated cytotoxicity was observed [22]. These corroborate the immunomodulatory action of *L. breviflora* earlier reported by Saba et al. [11].

Circulating neutrophils was reduced in the rats administered with the extracts in this study, except in rats administered with high dose of *X. sagittifolium*. Circulating neutrophil increase is usually associated with inflammatory response and bacterial infection in the body [23]. *L. breviflora* has been reported to have both anti-inflammatory and antibacterial effect [24,25], which have also reflected in this study. This effect is comparable to that observed in rats administered with hydrochlorothiazide. The higher dose of *X. sagittifolium*, however showed an inflammatory response.

Results of serum biochemistry revealed that the lipid profile showed a significant ($p<0.05$) increase in total cholesterol levels of all hypertensive rats except rats administered with the lower dose of *Lagenaria breviflora*. Triglycerides levels were significantly reduced in the rats treated with the plant extracts. The plant extract showed potent hypocholesterolemic effects with significant ($p<0.05$) increases in the High density lipoprotein- cholesterol. The atherogenic index of plasma (AIP) calculated for rats in this study showed that the plant extract lowered the risk of development of coronary heart disease (CHD) and other cardiovascular disorders. The lowest value obtained for *X. sagittifolium* was comparable to that for lisinopril and *L. breviflora* had much better AIP values, shows the plants are safe and also reduce the risk. AIP, a mathematical relationship between the logarithm of triglycerides and high density lipoprotein- cholesterol (HDL-C), is used to assess cardiovascular (CV) risk factors [26,27].

Blood urea nitrogen values significantly ($p<0.05$) decrease in all hypertensive rats, but creatinine levels increased. Increase in both or either biochemical parameters is usually indicative of renal injury [28,29]. In this study, the highest creatinine level recorded was in rats administered the diuretic antihypertensive, hydrochlorothiazide. Rats administered with the extracts did not exhibit a further deterioration in the metabolic derangement.

The urinalysis showed glomerular compromise in the hypertensive rats observed as leucocyturia, haematuria, proteinuria and bilirubinuria. The pH and specific gravity were also increased. Rats administered with extracts of *L. breviflora*, however, showed a reversal of the renal damage. *X. sagittifolium* showed a more remarkable reversal of the renal damage.

5. CONCLUSION

In conclusion, management of hypertensive rats with the extracts of *Lagenaria breviflora* and *Xanthosoma sagittifolium* showed that the extracts did not further progress the metabolic derangement associated with hypertension. *L. breviflora* showed a non-significant haemotopoietic and immunomodulatory effects, while the extract of *X. sagittifolium* reversed renal damage caused by hypertension. Both plant extracts showed potent hypocholesterolemic effects and the atherogenic index of plasma of rats treated with the extracts also improved indicating reduction of risks of development of coronary arterial diseases or heart diseases (CAD and CHD). In the overall, treatment of hypertension with these medicinal plants is safe and the metabolic derangement will not deteriorate with treatment, but will rather improve.

ETHICAL APPROVAL

All authors hereby declare that "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed, as well as the code of conduct of Animal Experimentation set by Animal Care and Use Research Ethics Committee (ACUREC), University of Ibadan, Nigeria. All experiments have been examined and approved by the ethics committee

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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