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Antihypertensive and electrolyte modulatory effect of ethanol extract of *Terminalia catappa* leaf following L-NAME induced hypertension in male Wistar rats

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Abstract

Background; Hypertension is the major leading risk factor for atherosclerosis and other diseases, especially renal and cardiovascular disorders, including myocardial infarction, stroke, and heart failure. Blood pressure may be influenced by either genetic and/or lifestyle factors including nutrition, smoking, high blood glucose and high body-mass index. Global mortality due to hypertension is currently over 30 million and may increase to 40 million annually by 2030.

Objectives: This research work was designed to evaluate the antihypertensive and electrolyte modulatory effect of ethanol extract of *Terminalia catappa* leaf following L-NAME induced hypertension in male Wistar rats.

Methods: In this present work, thirty- five (35) Wistar male rats was allowed to acclimatize for a period of 7 days, in a well-ventilated room at room temperature and relative humidity of 29°C and 70% respectively with 12 hours natural light-dark cycle Hypertension was induced by intraperitoneal administration of L-N^G-nitro arginine methyl ester (L-NAME) (40 mg/kgb.wt/day in distilled water. Treatment was carried out as follows: group 1 (normal control) received only the vehicle (Normal saline) orally, group 2 (hypertensive control) received L-NAME (40 mg/kgb wt/day) intraperitoneally for 2 successive weeks; group 3 (standard control) L-NAME (40 mg/kgb .wt/day) +20mg/kg b.wt /day of amlodipine while group 4 and 5 (reference groups) received L-NAME + extract of *T. catappa* (200 and 400 mg/kg b .wt/day respectively for 2 successive weeks. Blood was collected by cardiac puncture under plane sterile tubes for serum electrolytes and lipid profile.

Results: The result displayed that *T. catappa* leaf produced a significant (p<0.05) decrease in serum Na^+, K^+, Ca^{2+}, Cl^- ion concentration when compared with normotensive and hypertensive. The extract significantly (p<0.05) increased serum HDL and triacyl glycerides, but lowered the serum LDL, total –cholesterol when compared with normotensive, hypertensive and standard control.

Conclusion: It can be inferred from this present work that extract of *Terminalia catappa* might inhibit predisposition to hypertension and/ or contain some bioactive compounds with antihypertensive effect and might be useful in the management of pathological conditions associated with cardiovascular dysfunction possibly by deactivation of either the brain renin–angiotensin–aldosterone system (RAAS) or sympathetic nervous system.

Keywords: Antihypertensive; Amlodipine; Intraperitoneal; L-NAME; Electrolyte profile; Predisposition; Cardiovascular diseases

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1. Introduction

High blood pressure is classified primarily either as essential hypertension or secondary hypertension (1). About 90-95% of cases are primary i.e high pressure due to non-specific lifestyle and genetic factors (2). Lifestyle factors that increase the risk include excessive salt in the diet, excess body weight, smoking and alcohol use. The remaining 5-10% of cases are categorized as secondary high blood pressure, since they have an identifiable cause such as chronic kidney disease, narrowing of the kidney arteries, an endocrine disruptor or the use of birth control pills (3). Blood pressure may also be classified by two measurements, the systolic and diastolic pressures, which are the minimum and maximum pressures respectively. For most adults, normal blood pressures at rest are within the range of 100–130-millimeter mercury (mmHg) systolic, and 60-80 mmHg diastolic (4). For most adults, high blood pressure is present if the resting blood pressure is persistently at or above 130/80 or 140/90mmHg (4).

Lifestyle changes and medications can lower blood pressure and decrease the risk of health complications (5). Lifestyle changes include weight loss, physical exercise, decrease in salt intake and a healthy diet. If lifestyle changes are not sufficient then blood pressure medications can be used.

Recent attention has been focused on the herbal preparations as alternative agents for the treatment and prevention of cardiovascular problems. Ethnobotanical surveys of various medicinal plants indicate their vast use in the management of cardiovascular disorders typical of this plant *Terminalia catappa*.

Terminalia catappa is a large tropical tree in the Leadwood family (*Combretaceae*), that grows mainly in the tropical regions of Asia, Africa and Australia (6). Common names of *Terminalia catappa* in English include country almond, India almond, beach almond (7). *Terminalia catappa* innumerable medicinal roles ranging from hepatoprotective, hypoglycemic, anti-oxidant, anti-inflammatory, ace-inhibitory, anti-diabetic activities among others (6). Aqueous and ethanol extracts of the of *T. catappa* shows different degrees of activities against *Pseudomona saeruginosa*, *Pseudomona stestosterone*, *Pseudomonas pseudoalcaligenes*, *Staphylococcus aureus*, *Staphylococcu ssubflava*, *Proteusmirabilis*, *Proteusvulgaris*, *Proteusmorgana*, *Bacilluscerus*, *Bacillussubtilis*, *Bacillusm egaterium*, *Escherichiacoli*, *Streptococcus agalactiae* candida (Sharma and Rana, 2017) (8).

Inhibition of nitric oxide (NO) synthase (NOS) by NG-nitro-L-arginine methyl ester (L-NAME) is a well-established model of experimental hypertension, cardiovascular and renal disease (8). The cardiovascular effect of L-NAME includes endothelial dysfunction, vascular remodeling, inflammation, and myocardial hypertrophy (9). The mechanism of L-NAME-induced hypertension and cardiovascular disease(s) involves more than removal of the tonic vasodilator action of NO by NOS inhibition, and there is evidence for contributions from the renin–angiotensin system (RAS), sympathetic nervous system (SNS), prostaglandins, and superoxide anions to this process. Chronic L-NAME administration increases plasma rennin levels (7, 10) and cardiac and vascular angiotensin-converting enzyme (ACE) activity (7) and causes a transient increase in both type 1 (AT_1) and type 2 (AT_2) angiotensin II receptors in the heart (8). Acute administration of ACE inhibitor (ACEI) or AT_1 receptor blocker (ARB) causes only modest reduction in blood pressure of L-NAME hypertensive rats (11,3) but chronic ACEI or ARB administration normalizes blood pressure (9,10) and prevents the vascular remodeling, inflammation, and myocardial hypertrophy due to L-NAME administration (8,12,9).

L-NAME induced hypertensive rats have increased plasma noradrenaline and adrenaline levels (11) and showed a marked fall in blood pressure with pentolinium administration (11) suggesting an important contribution by the SNS to L-NAME hypertension. Sympathectomy, and the α1 blocker, prazosin, also reverse L-NAME induced hypertension (13,14). Reversal of L-NAME hypertension by both RAS and SNS inhibition suggests that the hypertension may be due to an altered balance between NO and angiotensin II in the central nervous system, resulting in increased sympathetic tone that might be normalized by RAS inhibition (15).

L-NAME hypertension is also associated with increased vascular and renal expression of cyclooxygenase-2 (COX-2), and COX-2 inhibition considerably attenuates the hypertension and proteinuria that accompany L-NAME administration (16)

L-NAME hypertension may be associated with increased vascular production of superoxide anions (11). Simultaneous administration of the anti-oxidant N-acetylcysteine prevented development of hypertension and vascular inflammation, and augmented NOS activity, in L-NAME-treated rats (17). However, N-acetylcysteine had only a modest effect on blood pressure of rats with established L-NAME hypertension (18). Chronic ACEI and ARB therapy prevented the increased vascular superoxide production (18,19,1). Suggesting that angiotensin II-stimulated vascular NAD(P)H oxidases are responsible for the increased superoxide production that accompanies L-NAME administration. Angiotensin II-

stimulated superoxide production may cause down-regulation of endothelial dihydrofolate reductase, resulting in uncoupling of endothelial NOS (eNOS) and further reducing NO bioavailability (18,1,17).

An electrolyte is a substance that produces an electrically conducting solution when dissolved in polar solvent, such as water. The dissolved electrolytes separate into cation and anions which disperse uniformly through the solvent (20). Electrolytes are important because they are what cells (especially nerve, heart and muscle cells) use to maintain voltages across their cell membranes. Electrolytes have different functions, and an important one is to carry electrical impulses between cells (21). Kidneys work to keep the electrolyte concentrations constant despite changes in the body. For example, during heavy exercise; electrolytes are lost in sweat, particularly in the form of sodium and potassium (22). The kidneys can also generate dilute urine to balance sodium levels (22). These electrolytes must be replaced to keep the electrolyte concentrations of the body fluids constant. Hyponatremia, or low sodium, is the most common type of electrolyte imbalance (23).

Electrolyte imbalance is thought as one of the prominent underlying mechanisms of hypertension. It is therefore imperative to ascertain the safety and risk potential of ethanol leaf extract on serum electrolytes and lipid profile following L-NAME induced hypertension in male Wistar rats.

2. Materials and Methods

2.1. Materials

2.2. Plant Materials

Fresh leaves of *T.catappa* were collected from the UNICROSS environment, Okuku, Cross River State, Nigeria. The leaves were taken to the University of Calabar, Department of Botany for identification and authentication. The voucher number of 206 has been deposited for future reference at the department's herbarium.

2.3. Experimental animals

Thirty-five (35) male Wistar rats were obtained from the animal holding unit of the Department of Medical Biochemistry, University of Cross River State. The animals were allowed to acclimatize for a period of 7 days, in a well-ventilated room at room temperature and relative humidity of 29°C and 70% respectively with 12 hours natural light-dark cycle. They were allowed food and water *ad libitum*. Good hygiene was maintained by daily cleaning and removal of faeces and spills from their cages.

2.4. Preparation of extract of *T.catappa* leaf

The leaves of *T.catappa* was collected around UNICROSS and air dried at room temperature for a period of 21days until constant weight was obtained. The dried leaves were then pulverized to powdery form by a machine blender and sieved. Thereafter, 400g of the pulverized plant material (*T.catappa*) was dissolved in 1200ml of 70% petroleum ether for 72 hours. This was followed with vacuum filtration and extracts was concentrated using an evaporator water bath at 40°C to obtain a solvent free extract, and stored in a refrigerator at 4°C.

2.5. Experimental design

Hypertension was induced according to (24) by intraperitoneal administration of L-NAME (40 mg/kgb.wt/day in distilled water. Treatment was carried out as follows: group 1 (normal control) received only the vehicle (Normal saline) orally, group 2 (hypertensive control) received L-NAME (40 mg/kg b. wt/day) intraperitonially for 2 successive weeks; group 3 (standard control) L-NAME (40 mg/kgb .wt/day) +20mg/kg b .wt /day of amlodipine while group 4 and 5 (reference groups) received L-NAME + extract of *T. catappa* (200 and 400 mg/kg b .wt/day respectively for 2 successive weeks

2.6. Blood sample collection

Blood was collected from all the test rats and control by cardiac puncture under plane sterile tubes for serum electrolytes, preceded by centrifuging and separation of the blood plasma with standard pipette. The specimens were labelled with the identification alphabets/ number. The samples were kept at room temperature until processing, which occurred within 30 minutes of collection.

3. Results

The result below displayed the effect of extract of *T. catappa* leaves on serum electrolytes following L-NAME-induced hypertensive Wistar rats. The extract produced a significant ($p<0.05$) decrease in serum Na^+, K^+, Ca^{2+}, Cl^- ion concentration when compared with normal and positive control in the normotensive groups and groups co-administered with graded doses of extract of *Terminalia catappa* and L-NAME induced hypertensive groups but portrays a significant ($p<0.05$) decrease when compared with the negative control in all the test groups (table 1).

Table 1 Effect of extract of *T. catappa* leaves on serum electrolytes following L-NAME-induced hypertensive Wistar rats

Groups	Na^+ (mmol/l)	K^+ (mmol/l)	Ca^{2+} (mmol/l)	Cl^- (mmol/l)
Normal control	64.00 ± 0.71^a	4.50 ±0.07^a	52.40± 0.25^a	67.40± 0.75^a
Negative control	84.76 ± 0.75^b	9.58 ±0.07^b	67.60±1.44^b	92.00± 0.84^b
Positive control	45.80 ± 0.92^a	5.24 ±0.10^c	51.80± 2.58^c	44.14± 9.62^c
200mg/kg b.wt TC	73.80 ± 0.66^d	6.48 ±0.12^d	53.40± 0.40^a	46.00± 0.71^{dc}
400mg/kg b.wt TC	76.00 ±0.32^d	6.64 ± 0.14^d	52.40± 0.40^a	48.20± 1.07^{ec}
200TC +40L-name	45.40 ± 1.03^{eb}	3.84 ±0.15^e	50.60± 1.08^a	63.00± 1.79^a
400TC+40L-name	41.40 ± 1.72^f	4.30 ± 0.07^a	50.60± 0.93^a	63.60±0.75^a

Values are expressed as mean±SEM. (n = 5). Values with different superscript along the columns are statistically significant ($P<0.05$). Legend: Normal control = group which received normal saline; Negative control = group treated with 40mg/kg b.wt L-NAME; Positive control = group which received 40 and 5mg/kg b.wt L-NAME and Amlodipine, respectively; 200mg/kg b.wt TC = group treated with 200mg/kg b.wt*T. catappa*; 400mg/kg b.wt TC = group treated with 400mg/kg b.wt *T. catappa*; 200TC+40L-NAME = group treated with 200 and 40mg/kg b.wt*T. catappa* and L-NAME, respectively and 400TC+40L-NAME = group treated with 400 and 40mg/kg b.wt*T. catappa* and L-NAME, respectively.

Table 2 Effect of extract of *T. catappa* leaf on serum lipid profile following L-NAME-induced hypertensive Wistar rats

Groups	TAG (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	T. Chol (mg/dl)
Normal control	138.80 ± 0.37^a	43.60 ± 0.25^a	28.00 ± 0.32^a	101.80± 0.86^a
Negative control	127.80±1.28^b	41.40 ± 0.40^a	34.80 ± 1.02^b	122.20 ± 0.20^b
Positive control	161.20 ± 0.58^c	60.00±1.41^b	23.00± 0.78^c	117.60± 1.86^c
200mg/kg b.wt TC	145.80± 1.02^{de}	66.80±1.32^c	22.00± 0.71^c	75.20± 0.86^d
400mg/kg b.wt TC	148.00±0.55^e	73.60± 0.51^e	19.80± 0.80^e	74.40± 0.93^d
200TC +40L-name	143.40±0.51^{fg}	63.40±0.60^d	23.00± 0.45^c	83.40± 0.75^f
400TC+40L-name	144.20±1.02^{dg}	64.60± 0.51^{cd}	23.00± 0.45^c	83.60±0.75^{ef}

Values are expressed as mean±SEM. (n = 5). Values with different superscript along the columns are statistically significant ($P<0.05$). Legend: Normal control = group which received normal saline; Negative control = group treated with 40mg/kg b.wt L-NAME; Positive control = group which received 40 and 5mg/kg b.wt L-NAME and Amlodipine, respectively; 200mg/kg b.wt TC = group treated with 200mg/kg b.wt*T. catappa*; 400mg/kg b.wt TC = group treated with 400mg/kg b.wt*T. catappa*; 200TC+40L-NAME = group treated with 200 and 40mg/kg b.wt*T. catappa* and L-NAME, respectively and 400TC+40L-NAME = group treated with 400 and 40mg/kg b.wt*T. catappa* and L-NAME, respectively.

4. Discussion

Hypertension is the major leading risk factor for atherosclerosis and several diseases, especially renal and cardiovascular disorders, including myocardial infarction, stroke, and heart failure (24). Blood pressure is influenced by various genetic and lifestyle factors including nutrition smoking, high blood glucose, and high body-mass index, all responsible for approximately 29 million deaths globally (25). According to the World Heart Federation, hypertension is the most important risk factor for stroke which causes about 50% of ischaemic strokes (26). Nutrition has an

important impact on blood pressure with sodium (salt) playing a prominent role. However, potassium, in addition to calcium, and possibly also chloride, exert at least some effects on blood pressure.

Sodium is an important mineral which, besides its functions in fluid balance, action potential generation, digestive secretions and absorption of many nutrients, also plays an important role in blood pressure regulation with a reduced sodium intake being associated with a reduction in systolic and diastolic blood pressure (27). Therefore, independent of body weight, sex and age, too much dietary salt (sodium chloride) is regarded as an established risk factor for hypertension (28).There are several mechanistic explanations for the association between high sodium intake and blood pressure like enhanced reabsorption and retention of filtered sodium through the renal tubules (29) or activation of the brain renin–angiotensin–aldosterone system (RAAS), which is suggested to increase blood pressure through angiotensin II and aldosterone promoting locally oxidative stress and activating the sympathetic nervous system (30). Furthermore, based on the "vasodysfunction theory" of salt induced hypertension, salt loading results in subnormal decreases in systemic vascular resistance leading to an increase in blood pressure (31). The significant increase in serum sodium ion concentration following the administration of ethanol leaf extract of *Terminalia catappa* suggest that the extract of *Terminalia catappa* induced hypernatreamia, due to alteration in the physiologic and metabolic role of the kidney. This effect was found to be lowered following L-NAME induced hypertension which may suggest a synergistic interaction possibly by deactivation of either the brain renin–angiotensin–aldosterone system (RAAS) or sympathetic nervous system.

Potassium intake or supplementation has also been repeatedly shown to reduce the blood pressure of hypertensive individuals (28). In addition to the well-known advice to reduce the consumption of dietary sodium (<1500 mg/day or at least 1000 mg/day decrement) for adults with normal and elevated blood pressure (32). Also, several studies and meta-analysis showed that potassium supplements reduce blood pressure and also the risk of hypertension (33). Suggested mechanisms of the blood pressure lowering effects of potassium are; improvement of endothelial function and NO release, vasodilatation by lowering cytosolic smooth muscle cell calcium, increasing natriuresis, and lowering the activity of the sympathetic nervous system (28). In this study the extract produced a significant increase in potassium ion concentration; following L-NAME induced hypertension suggest that the extract might reduce the risk of hypertension or predisposition to hypertension by improving the release of NO and triggering vasodilatation.

It has also been documented that calcium supplementation has been shown to exert beneficial effects on the risk for gestational hypertension in women with low dietary calcium intake (34). Besides the interdependent effect of sodium and potassium, calcium has also been implicated in the regulation of blood pressure (35). The effects of calcium were primarily restricted to the prevention of gestational hypertension. On the other hand, low dietary calcium intake is shown to be a risk factor for the development of hypertension especially for women with a history of gestational hypertension (36). In this regard the World Health Organization recommends daily calcium supplementation of 1.5–2.0 g oral elemental calcium for pregnant women in populations with low dietary calcium intake to reduce the risk of pre-eclampsia and related complications (27). In this research the significant increase in calcium ion concentration suggests that *Terminalia catappa* extract might reduce the risk of gestational hypertension associated with low calcium level.

More so, Chloride has an independent effect on blood pressure (37). Several studies and meta-analysis have shown that replacing chloride with bicarbonate, citrate or phosphate as the anion for sodium would not lead to increases in blood pressure in humans compared to sodium chloride (38). Interestingly, lowered serum chloride levels were associated with higher cardiovascular and all-cause mortality risk in epidemiological studies (39). In this research the extract produced a significant increase in serum chloride ion concentration when compared with the normal and positive group. This significant increase in chloride ion concentration suggests that *Terminalia catappa* can reduced the risk of cardiovascular disease associated with low serum chloride levels.

The serum lipid levels are very good hypertensive biomarkers. High levels of cholesterol and low-density lipoproteins have been implicated as causative agents of hypertension, since they are directly involved in atherogenicity, while high density lipoprotein is noted for its ability to prevent hypertension as it functions as anti-atherogenic lipid (40). HDL-cholesterol (HDL-C) is known to have a protective effect against cardiovascular disease, since it removes excess cholesterol from circulation and carries it back to the liver where it is degraded or converted into bile acid Also, HDL-C is considered to have anti atherogenic properties. It has also been shown that an increase in HDL-cholesterol correlates inversely to atherosclerosis, hypertension, and coronary heart disease among others. It can therefore be inferred that the significant increase in serum level HDL-cholesterol suggests that the extract of *Terminalia catappa* may be used to reduce the risk factor of atherosclerosis and other cardiovascular related disorders or suggests that the extract might exert a protective effect against atherosclerosis or increases estradiol which might promote apolipoprotein A1 (Apo A1) production, and reduce hepatic lipase activity, resulting in increased production of high-density lipoproteins (HDL)

during pregnancy their by inhibiting pregnancy induced hypertension. It may also suggest that the extract contain some bioactive agents that may elicit antihypertensive property. (41) reported that phytochemical constituents such as saponins, flavonoids, and sesquiterpene lactones may ameliorate hypertensive and hyperlipidemic conditions. Hyperlipidemia is directly related to high cholesterol levels in the blood (40). This has a consequent occlusion of the vessel wall, with a resultant increase in the force required to pump and circulate blood through and round the body thus resulting in hypertensive condition. For the extracts to decrease the total cholesterol levels at both 200 and 400 mg/ kg body weight of the blood, it shows that it has anti-hyperlipidemic properties. Also, the high and low levels of triacylglycerol and low-density lipoprotein respectively showed that the extract has the tendency to ameliorate hypertensive condition.

5. Conclusion

It can be inferred from these present results that extract of *Terminalia catappa* might inhibit predisposition to hypertension and might be useful in the management of medical conditions associated with cardiovascular diseases possibly by deactivation of either the brain renin–angiotensin–aldosterone system (RAAS) or sympathetic nervous system.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that there is no conflict of interest related to this work.

Statement of ethical approval

Ethical approval for the study was obtained from the Faculty of Basic Medical Science Animal Research Ethical Committee of Cross River University of Technology, Calabar, Nigeria (approval number FBMS/UNICROSS/24/020).

Author's contribution:

All authors contributed substantially to the conception, design, and interpretation of data presented in this review. They were actively involved in the analysis of existing literature, drafting of the figures, writing of the manuscript, and critical revision of its intellectual content. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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