Journal of Biosciences and Medicines, 2025, 13(6), 196-215
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Ricinodendron heudelotii Stem Bark Extract Protects against L-NAME-Induced Hypertension, Dyslipidemia and Oxidative Stress Damages in Rat

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How to cite this paper: Kojom, J.J.W., Lappa, E.L., Bogning, C.Z., Njehawobe, M.S.T.L. and Dongmo, A.B. (2025) *Ricinodendron heudelotii* Stem Bark Extract Protects against L-NAME-Induced Hypertension, Dyslipidemia and Oxidative Stress Damages in Rat. *Journal of Biosciences and Medicines*, **13**, 196-215.
https://doi.org/10.4236/jbm.2025.136018

Received: May 19, 2025
Accepted: June 22, 2025
Published: June 25, 2025

Abstract

Aim of Study: *Ricinodendron heudelotii* (Baill.) (RH) commonly called "Djansang" in Cameroon, has already been reported to possess cardioprotective effect, vasorelaxant and antioxidant properties. This study was undertaken to explore the effect of RH on the development of essential hypertension through nitric oxide (NO) inhibition. **Material and Methods**: NO deficiency was induced in Wistar rats by oral administration of L-NAME (40 mg/kg/day) for 4 weeks, concomitantly with aqueous extract of RH stem bark (6, 20 and 40 mg/kg, p.o.) or captopril (20 mg/kg, p.o.). Body weight, heart rate, and arterial blood pressure were registered twice weekly throughout the experimental period, using the tail-cuff noninvasive method (CODA system, 4.1). At the end of the treatment, biochemical parameters and oxidative stress markers were assessed in the blood, liver, kidney, heart and aorta homogenates according to standard protocols. The histopathological analyses were also performed on the organs mentioned above. **Results**: *Ricinodendron heudelotii* significantly decreases the systolic blood pressure (SBP), the diastolic blood pressure (DBP) and the mean blood pressure (MBP) without modification of heart rate (HR) after 4 weeks of concurrent L-NAME administration. Also, RH improved liver (transaminases, alkaline phosphatase, total proteins) and kidney markers (urea and creatinine), lipid profile (total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides), oxidative status (superoxide dismutase, catalase, glutathione reductase, nitrites and malondialdehyde), and reduced aortic media thickness. **Conclusion**: These results suggest that RH,

due to its antihypertensive, antioxidant and antihyperlipidemic properties, is a promising preventive agent against hypertension and vascular disorder induced by NO deficiency.

Keywords

Ricinodendron heudelotii, Hypertension, Lipid Profile, Antioxidant

1. Introduction

Hypertension is a chronic medical condition characterized by a persistent increase of systolic and/or diastolic blood pressure (≥140/90 mmHg) [1]. It has been recognized as a cardiovascular risk factor which affects approximately 1.39 billion adults and contributes to about 10.4 million deaths annually [2] [3].

Complex and poorly understood mechanisms are implicated in the pathogenesis of hypertension [4] [5]. Some of these factors and signaling pathways incriminated in short and long-term regulation of blood pressure include cardiac output, peripheral vessel resistance, activation of the sympathetic nervous system and renin-angiotensin-aldosterone system [6]. Actually, a wide range of evidence supports oxidative stress, vascular remodeling and endothelial dysfunction in most cases of hypertension [4] [7].

It is well documented that, endothelial dysfunction is characterized by a reduction in nitric oxide availability or an imbalance between relaxing and contracting factors produced by endothelial cells, deeply implicated in the pathologic process of cardiovascular disorders, especially essential hypertension [8] [9]. Reactive oxygen species may directly alter vascular function or cause changes in vascular tone by several mechanisms including altered nitric oxide bioavailability or signaling [10]. This is due, in large part, to the superoxide anion (O_2^-) excess mainly produced enzymatically through NADPH oxidase (NOX) activity; consequently, it rapidly inactivates endothelium-derived nitric oxide. So, nitric oxide (NO) deficiency underlies the development of oxidative stress-related hypertension [11].

Experimentally, NO deficiency can be induced in animals using the nitric oxide synthesis inhibitor, Nω-Nitro-L-arginine methyl ester hydrochloride (L-NAME). This model is well used by many authors as it mimics essential hypertension in humans [12] [13]. Therefore, targeting endothelial dysfunction appeared as a valuable therapeutic resource to highlight the beneficial effects of natural products and/or plant extracts against hypertension [14].

The use of a medicinal plant that has antioxidant and vasorelaxant properties has been the focus of studies and are increasingly accepted for alternative antihypertensive therapies among which there is *Ricinodendron heudelotii* (Baill.) Pierre (Euphorbiaceae). Traditionally, the bark of this species is widely used to treat cough, malaria, anaemia, cancer, intestinal disease and stomach pain, and it equally has diuretic functions [15]-[17]. Additionally, RH has been previously reported to exhibit antihypertensive, antioxidant and vasorelaxant properties prob-

ably due to the presence of alkaloids compounds, which seemed to dominate the phytochemical profile [18] [19]. However, there remains a need to confirm and validate these effects further in other models of hypertension pathogenesis. Therefore, this study was undertaken to explore the effect of aqueous extract of RH stem bark on the development of hypertension in L-NAME-induced hypertensive rats.

2. Materials and Methods

2.1. Drugs and Chemicals

Analytical-grade chemicals and drugs were used. Nω-nitro-L-arginine methyl ester (L-NAME) was purchased from Sigma Aldrich (Germany). Captopril was purchased from Denk Pharma (Germany). Enzymatic and colorimetric commercial kits were purchased from SGMItalia (Rome, Italy).

2.2. Plant Material and Extraction Process

The stem bark of *Ricinodendron heudelotii* was recolted in the West Region-Cameroon (Malantouen) in December 2021 and identified at the National Herbarium in Yaoundé (Cameroon) under reference number 19695 SRF/Cam. The aqueous extract preparation was previously described by Kojom *et al.* 2022 [18]. Briefly, fresh samples were cut out, dried in the shade and then crushed. About 100 g of the powder was infused in 1 liter of distilled water (boiled, 100˚C) for 20 minutes, then the filtrate was evaporated at 40˚C using the oven. This process yielded 1.21 g (1.21%) of dry powder.

2.3. Animals

The experiment was carried out on adult male and female Wistar rats aged 10 - 12 weeks and weighing 150 - 200 g. The rats were housed in plastic cages and maintained in the animal house of the Faculty of Science, University of Douala, under standard laboratory conditions (12 h light/dark cycles at 25 - 27˚C). Food and water were made available to the animals *ad libitum*. The animals were used according to the national guidelines established by the Institutional Ethic Committee of the University of Douala and all procedures followed the protocol for laboratory animals handling and welfare approved (N˚2759 CEI-UDo/05/2021/T) by the committee.

2.4. Experimental Design and Treatment

Rats were priorly acclimatized for a period in the experimental environment then, 36 normotensive rats weighing 150 to 200 g were selected, divided into 6 groups (n = 6 per group) and treated as follows: group 1 (control group) received distilled water (10 mL/Kg), group 2 (hypertensive group) received L-NAME (25 mg/kg/day), group 3 (standard group) received simultaneously L-NAME + captopril (20 mg/kg), and groups 4, 5, and 6 (tests groups) received simultaneously L-NAME + RH at the doses of 6, 20 and 40 mg/kg respectively. All drugs were dissolved in distilled water and daily administrated *per os* to animals within 4

weeks between 08.00 am and 09.00 am. During the experiment period, daily rat weight, blood pressure, and heart rate measurements were performed after the baseline values had been recorded.

2.5. Blood Pressure and Heart Rate Recording

Systolic, diastolic, and mean blood pressure and heart rate were measured non-invasively by using the occlusion tail-cuff method in awake rats prior to the experiment onset and twice weekly. Each animal was placed in the retention holder and, after 30 min of warm-up period, the hemodynamic parameters were registered using a volume pressure recording transducer (CODA, Kent Scientific, USA). The measurement was done four times per session and the mean for every trial of animal was calculated [20].

2.6. Samples Collection

At the end of the experiment, the rats were anesthetized by intraperitoneal injection of diazepam (10 mg/kg) and ketamin (50 mg/kg). Blood samples were obtained by retro orbital punction in heparinized tubes and centrifuged at 3000 g for 15 min. The serum obtained was conserved at −20˚C for the determination of biochemical parameters. After blood collection, animals were killed and the entire liver, kidney, heart and aorta were surgically removed, washed in ice-cold saline solution and weighed. Parts of the heart and aorta were crushed in Mac Even solution while parts of the liver and kidney were crushed in Tris-HCl to prepare 20% homogenate. After centrifugation (3000 rpm for 30 min), the supernatant obtained was used to estimate oxidative stress parameters. The other parts of the kidney, liver, heart and aorta were fixed in 10% buffered formalin for histopathological examination.

2.6.1. Biochemical Analysis

Serum samples were used to determine alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatse (ALP), creatinine, urea, bilirubin, triglycerides (TG), total protein level, high density lipoprotein cholesterol (HDL-C), and total cholesterol (TC) using colorimetric kits. Low density lipoprotein cholesterol (LDL-C) was calculated using Friedewald equation [21]. All the measurements were done spectrophotometrically according to the manufacturer's instructions (SGM Italia, Italy).

2.6.2. Measurement of Oxidative Stress Parameters

Tissue concentration of malondialdehyde (MDA), nitrite level, glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT) activities were estimated spectrophotometrically according to the methods described by Wilbur *et al.* (1949) [22], Ikeda *et al.* (2003) [23], Ellman, (1959) [24], Misra and Fridovich, (1972) [25], Sinha, (1972) [26] respectively.

2.6.3. Histopathological Examination

A representative fragments of the kidney, liver, heart and aorta were fixed in 10%

formalin, dehydrated in gradual ethanol (50% - 100%), embedded in paraffin wax, cut into 5 µm sections with a microtome and stained with hematoxylin/eosin. The photomicrographs were taken and examined under a light microscope to visualize structural architecture [20]. Image J software was used to measure the media thickness of aorta images.

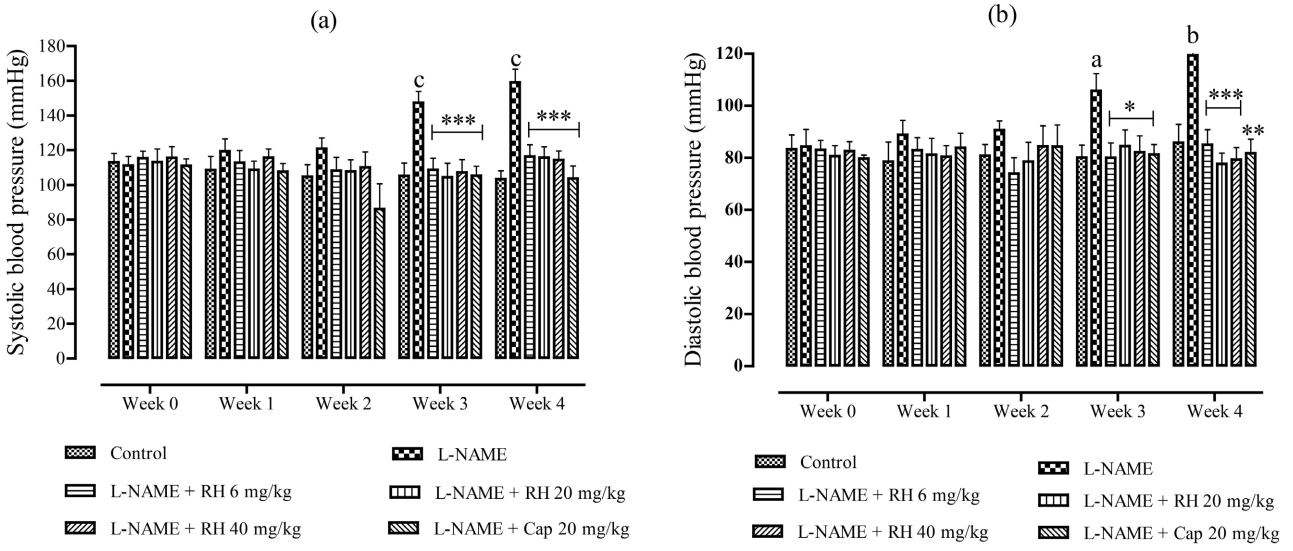
2.7. Statistical Analysis

Data are expressed as mean ± standard error of the mean (SEM). All statistical analysis was performed using non-parametric one-way analysis of variance (ANOVA), followed by the Kruskal-Wallis post-test for multiple comparisons to determine the difference of continuous variables between treatment groups. Two-way ANOVA repeated measures followed by the Bonferroni post-hoc test were used to analyze data with two variables. SigmaStat version 3.5 software was used for data analysis and means were considered significantly different at $p < 0.05$. The aorta tunica media thickness was measured using the software Image J version 1.4.3.67.

3. Results

3.1. Blood Pressure and Heart Rate

At baseline, there was no significant difference in SBP, DBP and MBP among the groups (**Figures 1(a)-(c)**). After 4 weeks of treatment, L-NAME-induced gradual increase ($p < 0.01$ - 0.001) of blood pressure in the hypertensive group as compared to the control group. The maximum values were 54.16% (SBP), 39.10% (DBP) and 53.29% (MBP) at the end of treatment. Administration of RH (6, 20 and 40 mg/kg) or captopril (20 mg/kg) significantly ($p < 0.01$) inhibited the increase of SBP (by 34.83%, 26.87%, 27.23% and 28.18%), DBP (by 28.70%, 31.96%, 33.51% and 31.55%), and MBP (by 25.83%, 25.76%, 26.62% and 31.90%) respectively when compared to hypertensive group after 4 weeks.



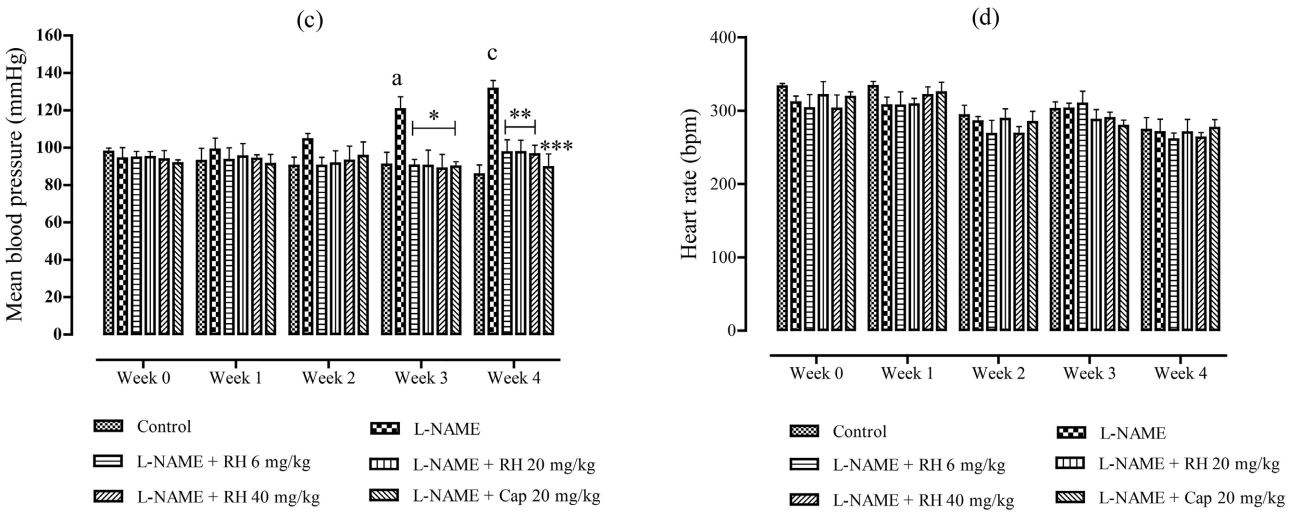


Figure 1. Effect of RH extract on systolic blood pressure (a), diastolic blood pressure (b), mean blood pressure (c) and heart rate (d) in L-NAME-induced hypertension in rats. Each bar represent mean ± SEM; n = 6; $^{a}p < 0.05$, $^{b}p < 0.01$ and $^{c}p < 0.001$ significant differences *versus* control group; $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$ significant differences *versus* hypertensive group. RH: *Ricinodendron heudelotii*; Cap: captopril.

None of the treatments significantly affected the heart rate after the four weeks of treatment, when compared to the control group (**Figure 1(d)**).

3.2. Effect of RH on Body and Relative Organ Weight

The effects of RH on the relative weight of organs are summarized in **Table 1**. The results showed that the relative weight of the liver and heart increased significantly in the hypertensive group *vs* the control group. Oral administration of RH at the different doses (6, 20 and 40 mg/kg) was reduced the relative weight by 16.15% ($p < 0.001$), 16.43% ($p < 0.001$) and 11.90% ($p < 0.01$) for the liver and by 14.63% ($p < 0.05$), 17.07% ($p < 0.01$) and 17.07% ($p < 0.01$) for the heart *vs* hypertensive group. Captopril used as a standard drug also produces similar effects.

3.3. Effect of RH on Biochemical Parameters

3.3.1. Renal and Liver Function

Chronic administration of L-NAME alone for 4 weeks, produced a significant rise of ALT ($p < 0.001$), AST ($p < 0.05$), APL ($p < 0.001$) and total bilirubin ($p < 0.05$) compared to the control group. The concomitant administration of L-NAME and RH at the doses of 6, 20 and 40 mg/kg produced a remarkable reduction of ALT (48.69%, 49.23% and 50.27%, $p < 0.001$), AST (75.81%, 63.53% and 64.67%, $p < 0.001$), ALP (60.44%, 57.43% and 42.44%, $p < 0.001$) and total bilirubin (35%, $p < 0.05$) as compared to hypertensive group. Captopril (20 mg/kg) used as standard also reduced the increase of ALT (48.66%, $p < 0.001$), AST (57.70%, $p < 0.001$), PAL (43.24%, $p < 0.001$) and total bilirubin (51.87%, $p < 0.001$) at the end of the treatment (**Figures 2(a)-(d)**).

Table 1. Effects of RH extract on relative organ weight in L-NAME-induced hypertension in rats.

	Relative organ weight (g/100g of body weight)				
	Doses (mg/kg)	**Liver**	**Kidney**	**Heart**	**Aorta**
Control	-	3.18 ± 0.05	0.60 ± 0.02	0.31 ± 0.01	0.09 ± 0.01
L-NAME	-	3.53 ± 0.06^{a}	0.63 ± 0.03	0.41 ± 0.03^{c}	0.12 ± 0.01
L-NAME + RH	**40**	3.11 ± 0.07**	0.57 ± 0.02	0.34 ± 0.02**	0.10 ± 0.01
L-NAME + RH	**20**	2.95 ± 0.10***	0.57 ± 0.03	0.34 ± 0.01**	0.10 ± 0.01
L-NAME + RH	**6**	2.96 ± 0.07***	0.59 ± 0.02	0.35 ± 0.01*	0.11 ± 0.01
L-NAME + Cap	**20**	3.15 ± 0.11*	0.59 ± 0.03	0.31 ± 0.01**	0.10 ± 0.01

Data represent the mean of relative organ weight ± SEM; n = 6; $^{a}p < 0.05$ and $^{c}p < 0.001$, significant differences *versus* control group; $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$, significant differences *versus* hypertensive group. RH: *Ricinodendron heudelotii*; Cap: captopril.

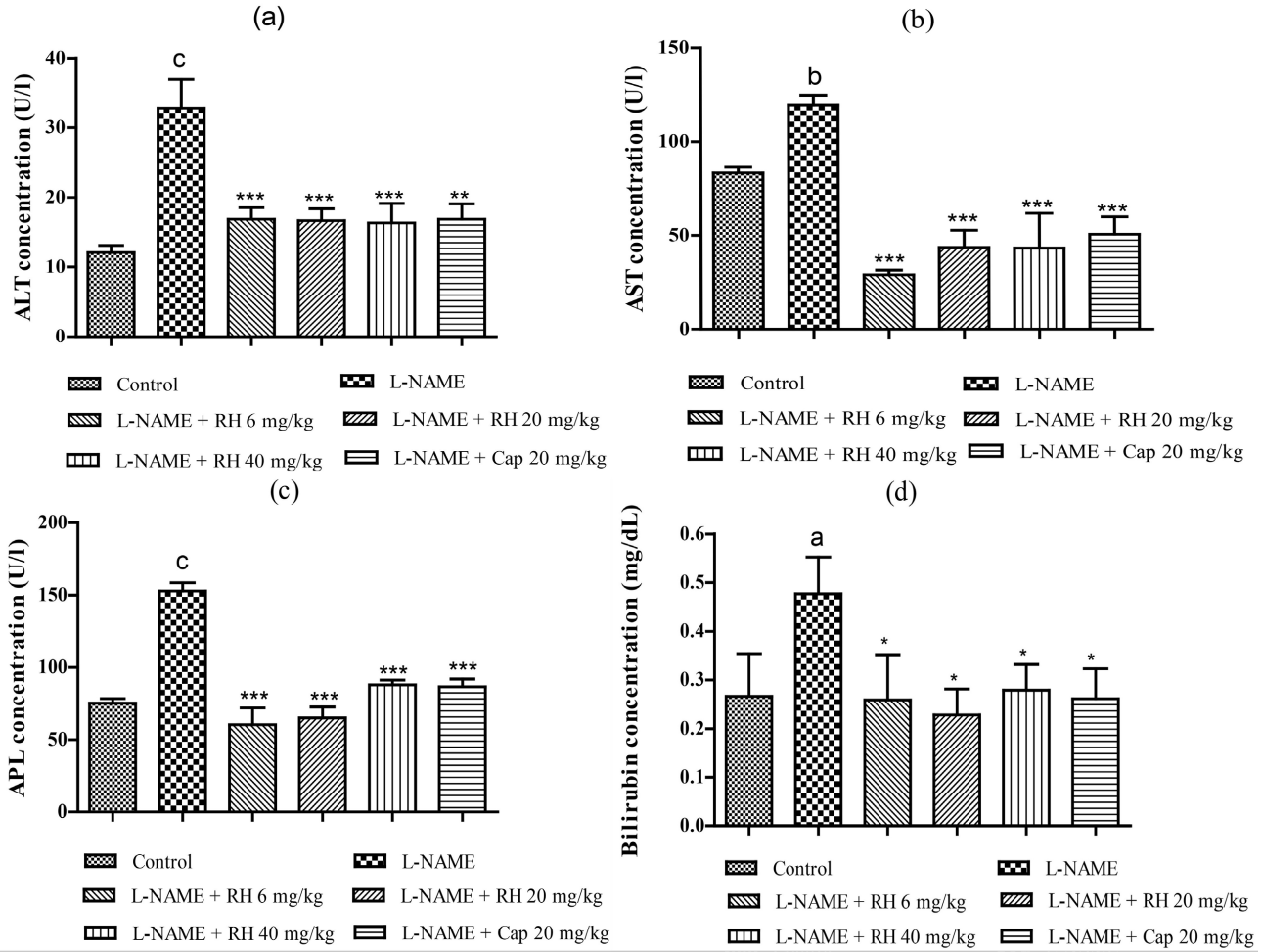


Figure 2. Effect of RH extract on ALT (a), AST (b), ALP (c) and Bilirubin (d) in L-NAME-induced hypertension in rats. Each bar represent mean ± SEM; n = 6; $^{a}p < 0.05$, $^{b}p < 0.01$ and $^{c}p < 0.001$ significant differences *versus* control group; $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$ significant differences *versus* hypertensive group. RH: *Ricinodendron heudelotii*; Cap: captopril.

As shown in Figure 3, repeated administration of L-NAME resulted in a significant ($p < 0.01$) increase in creatinine (70.59%) and urea (42.96%) levels compared to the control group. Treatment with RH (6, 20 and 40 mg/kg) or captopril (20 mg/kg) significantly ($p < 0.05$ - 0.01) reduced the increase of creatinine (25.79%, 25.21% and 27.30%), and urea (26.16 %, 25.71% and 28.99%) concentration respectively, when compared to hypertensive group (Figure 3(a) & Figure 3(b)).

3.3.2. Lipid Profile

Table 2 summarizes the results of the serum lipid profile of the treated groups after 4 weeks. A significant rise in serum total cholesterol (54.62%, $p < 0.01$) coupled with a depletion level of HDL-cholesterol (43.06%, $p < 0.05$) was observed in the hypertensive group *vs* control whereas non significant increase in LDL-cholesterol was noted. However, treatment with RH significantly reduced the increases in total cholesterol by 35.90% (6 mg/kg, $p < 0.01$), 36.32% (20 mg/kg, $p < 0.01$) and 35.55% (40 mg/kg, $p < 0.001$) and LDL-cholesterol ($p < 0.05$) by 47.97% (6 mg/kg) and 53.29% (40 mg/kg). Extract at the dose of 6 mg/kg increased HDL-cholesterol by 75.19% ($p < 0.05$). Similar significant results were obtained with captopril at 20 mg/kg as compared to hypertensive group. The values were 28.88% ($p < 0.01$) for total cholesterol and 86.47% ($p < 0.001$) for HDL-cholesterol.

All the treatments did not significantly alter the concentration of triglycerides compared with the control group.

3.3.3. Total Proteins

It was also depicted in Table 2, the significant increase ($p < 0.05$) in total serum proteins of rats treated with L-NAME alone for four consecutive weeks. Oral administration of RH (6, 20 and 40 mg/kg) as well as captopril used as a standard drug significantly dropped protein levels by 28.44% ($p < 0.01$), 22.95% ($p < 0.01$), 22.23% ($p < 0.01$) and 19.36% ($p < 0.05$) respectively *versus* hypertensive group.

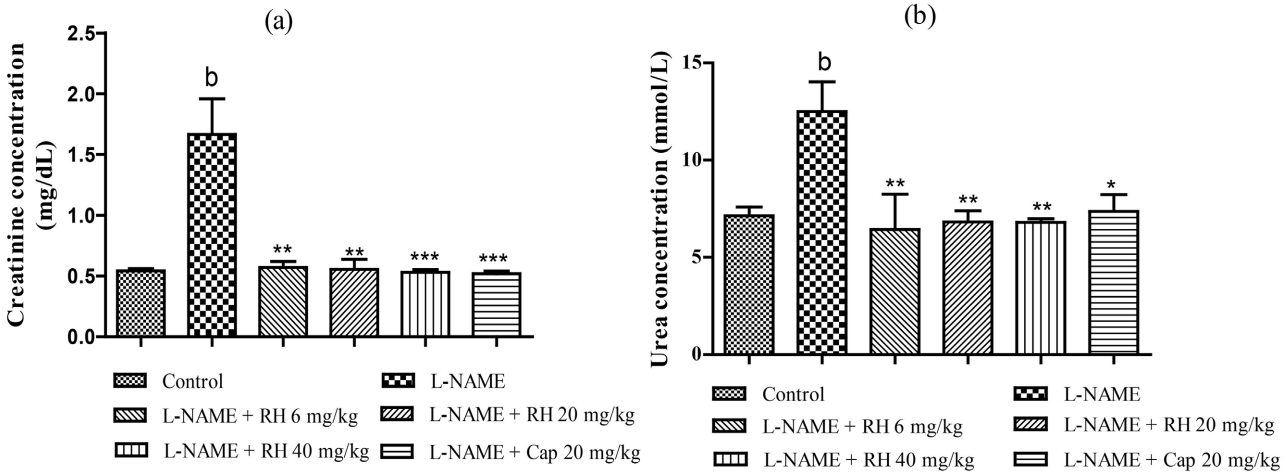


Figure 3. Effect of RH extract on creatinin (a) and urea (d) concentraton in L-NAME-induced hypertension in rats. Each bar represent mean ± SEM; n = 6; $^{b}p < 0.01$ significant differences *versus* control group; $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$ significant differences *versus* hypertensive group. RH: *Ricinodendron heudelotii*; Cap: captopril.

Table 2. Effect of the aqueous extract of RH on lipid profile and total proteins in L-NAME-induced hypertension in rats.

	Control	L-NAME	L-NAME + RH			L-NAME + Cap
Parameters	-	-	**6 mg/kg**	**20 mg/kg**	**40 mg/kg**	**20 mg/kg**
CHL (mg/dL)	57.3 ± 4.5	88.6 ± 8.1^{b}	56.7 ± 3.1**	56.4 ± 5.2**	55.3 ± 3.5***	63.0 ± 3.9*
HDL (mg/dL)	23.5 ± 2.5	13.3 ± 2.6^{a}	23.3 ± 1.3*	22.0 ± 1.4	21.0 ± 1.3	24.8 ± 3.1**
LDL (mg/dL)	22.1 ± 3.9	35.1 ± 3.0	18.3 ± 5.3*	25.2 ± 6.2	16.4 ± 2.5*	22.0 ± 5.1
Trig (mg/dL)	65.5 ± 11.6	76.2 ± 12.6	68.1 ± 2.5	70.4 ± 6.7	69.5 ± 5.6	67.7 ± 9.8
Prot (mg/dL)	75.2 ± 3.7	97.3 ± 5.9^{b}	69.6 ± 2.7**	75.0 ± 3.5**	75.6 ± 3.9**	78.5 ± 4.7*

Values are expressed as mean ± SEM; n = 6; $^{a}p < 0.05$ and $^{b}p < 0.01$, significantly different *vs* control; $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$, significantly different *vs* hypertensive group. RH: *Ricinodendron heudelotii*; Cap: captopril; CHL: total cholesterol; HDL: high density lipoprotein; LDL: low density lipoprotein; Pro: total protein; Trig: triglycerides.

3.4. Effect of RH on Oxidative Stress Parameters

3.4.1. CAT, SOD and GSH Activities

Figure 4(a) presents the activity of the antioxidant enzyme CAT in liver, kidney and heart in all groups treated. The activity of CAT was significantly decreased in the liver (34.84%, $p < 0.001$), kidneys (63.70%, $p < 0.01$) and heart (37.92%, $p < 0.05$) tissue homogenates of l-NAME-induced animals compared to a control group. However, oral administration of extract upregulated CAT concentration in the liver (at the dose of 6 mg/kg, $p < 0.01$), heart (at the dose of 40 mg/kg, $p < 0.05$) and kidneys (at the doses of 6, 20 and 40 mg/kg, $p < 0.05$ - 0.01 respectively) in comparison with hypertensive group. Treatment with a standard drug (captopril) increased significantly ($p < 0.05$) CAT concentration in kidneys.

Four weeks of administration of L-NAME alone caused a significant decrease in SOD activity in the liver ($p < 0.001$) and kidneys ($p < 0.05$) compared to a control group. Treatment with plant extract at different doses, significantly provoked a rise of SOD concentration in the liver at 6 mg/kg (91.18%, $p < 0.001$), at 20 mg/kg (74.11%, $p < 0.01$) and at 40 mg/kg (69.93%, $p < 0.05$), in the heart of and 69.66% ($p < 0.05$), 72.83% ($p < 0.05$) 85.05% ($p < 0.01$) respectively at the same doses and in kidneys at 40 mg/kg (70.75%, $p < 0.05$) when compared to the hypertensive group. A significant rise of SOD activity in the liver ($p < 0.001$) and kidneys ($p < 0.01$) was also observed in the rats treated with captopril (20 mg/kg) (Figure 4(b)).

In the liver and kidneys, there was no significant change in GSH concentration in a hypertensive group compared to a control group, however a significant decrease of GSH concentration (39.39%, $p < 0.05$) was observed in the heart while simultaneous treatment with RH or captopril reversed the effect of L-NAME by causing a significant increase of GSH concentration in these organs(Figure 4(c)). The maximum values were obtained at 40 mg/kg for the liver (97.52%, $p < 0.05$) and for the heart (73.53%, $p < 0.001$) and at 6 mg/kg for kidneys (93.08%, $p < 0.05$).

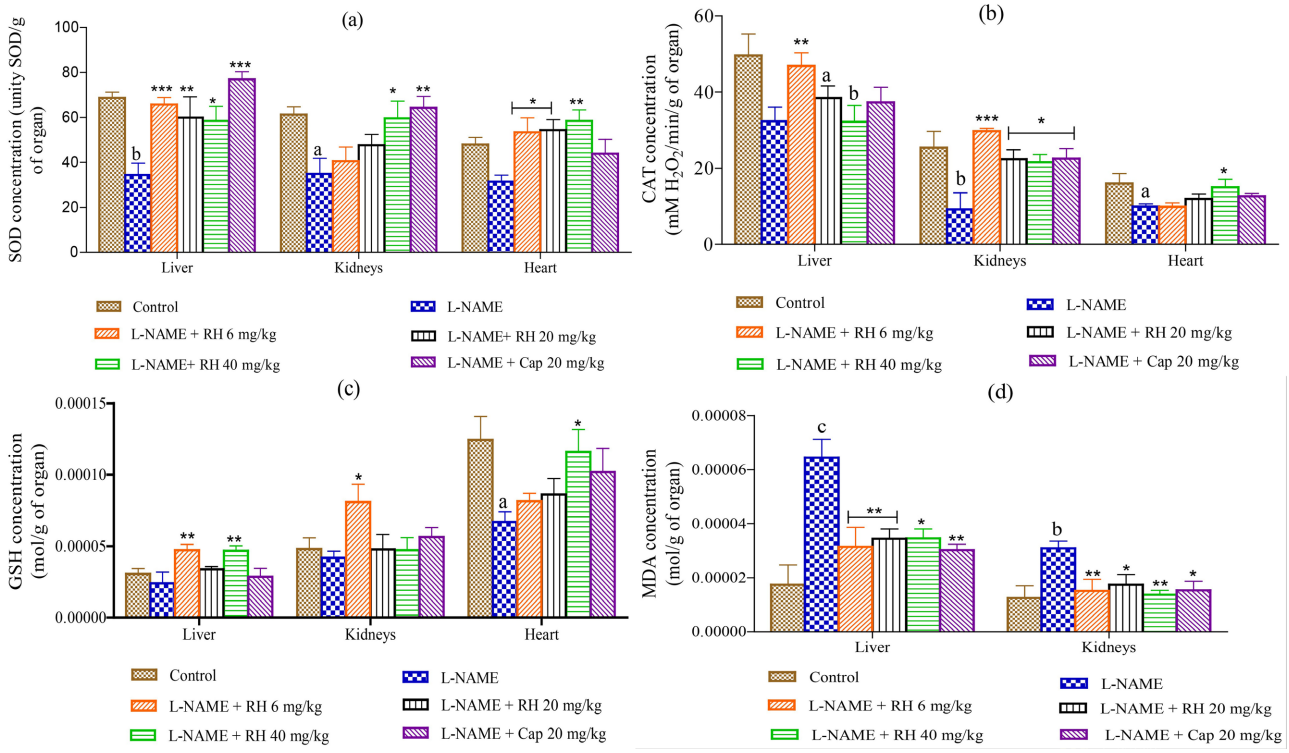


Figure 4. Effect of RH extract on CAT (a), SOD (b), GSH (c) and MDA (d) concentraton in L-NAME-induced hypertension in rats. Each bar represent mean ± SEM; n = 6; $^{a}p < 0.05$, $^{b}p < 0.01$ and $^{c}p < 0.001$ significant differences *versus* control group; $*p < 0.05$, $**p < 0.01$, and $***p < 0.001$ significant differences *versus* hypertensive group. RH: *Ricinodendron heudelotii*; Cap: captopril.

3.4.2. MDA Concentration

Repeated administration of L-NAME alone, also significantly raised MDA level in the liver ($p < 0.001$) and kidneys ($p < 0.01$) as compared to normotensive rats. Co-treatment with all doses of RH (6, 20 and 40 mg/kg) or captopril (20 mg/kg) significantly ($p < 0.05$ - 0.01) prevented the MDA level lowering compared to hypertensive group. The maximum inhibition percentage were 55.60%, 43.63%, 50.88% and 53.10% in the liver homogenate, and 46.30%, 46.52%, 51.14% and 50.37% in the kidneys homogenate at the end of the experiment (**Figure 4(d)**).

3.4.3. Nitrites Level

As shown in **Figure 5**, hypertensive rats presented a significant ($p < 0.05$, $p < 0.001$) depletion in nitrites levels in the liver (41.18%), kidneys (72.59%,), heart (80.43%) and aorta (79.79%) in comparison with normotensive rats. The increased MDA level in hypertensive group was significantly improved on co-administration of aqueous extract of RH in kidney (6 mg/kg, $p < 0.05$) and in aorta (6 mg/kg, 20 mg/kg and 40 mg/kg, $p < 0.05$, $p < 0.001$). Captopril used as standard drug significantly ($p < 0.05$ and $p < 0.001$ respectively) improved the nitrites level in the same organs.

3.5. Effect of RH on Histological Structure of the Liver, Kidney, Heart and Aorta

Histological examination of the liver, kidney and heart tissues did not show any

alterations between control group and treated groups. However, analysis of aorta section revealed a marked thickening of the tunica media in rats treated only with L-NAME as compared to rats received distilled water (Figure 6(b) and Figure 6(g)). Administration of plant extract (6 and 20 mg/kg) or captopril (20 mg/kg) significantly prevented the thickening of the tunica media when compared to hypertensive group (Figures 6(d)-(g)). At the dose of 40 mg/kg (Figure 6(c) and Figure 6(g)), the reduction of media thickness was maximum (17.01%, $p < 0.001$) and the aorta architecture was close to control group (Figure 6(a) and Figure 6(g)).

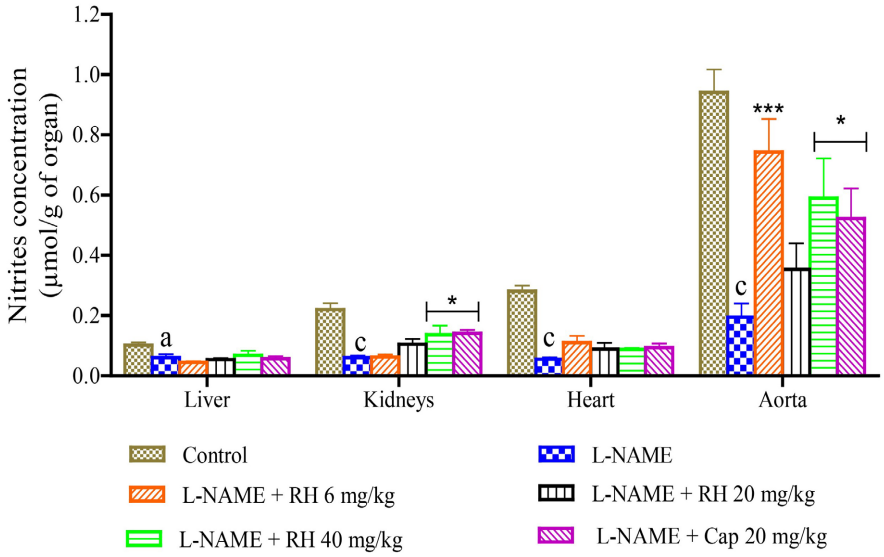
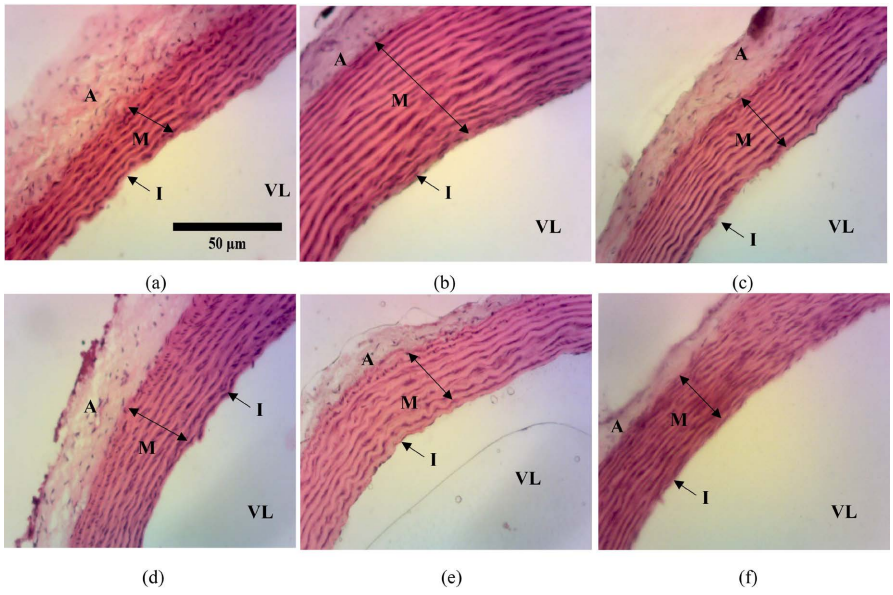
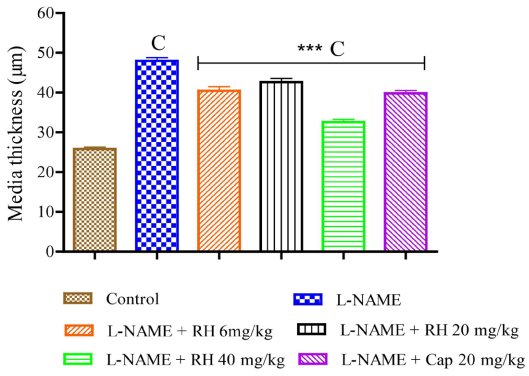


Figure 5. Effect of RH extract on nitrites concentraton in L-NAME-induced hypertension in rats. Each bar represent mean ± SEM; n = 6; $^{a}p < 0.05$ and $^{c}p < 0.001$ significant differences *versus* control group; $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$ significant differences *versus* hypertensive group. RH: *Ricinodendron heudelotii*; Cap: captopril.





(g)

Figure 6. Photomicrographs of aorta stained with H&E (200x) (a): control group showing normal histological structure, (b): hypertensive group showing thickening of the tunica media, (c): L-NAME + RH 40 mg/kg; (d): L-NAME + RH 20 mg/kg; (e): L-NAME + RH 6 mg/kg; (f): L-NAME + Captopril (20 mg/kg) showing reduction in the wall thickness of tunica media) and thickness of tunica media on treated groups (g). $^{c}p < 0.001$ significant differences *versus* control group; $^{***}p < 0.001$ significant differences *versus* hypertensive group. RH: *Ricinodendron heudelotii*; Cap: captopril; I: intima; M: media; A: adventice; VL: vascular lumen.

4. Discussion

Arterial hypertension (AHT) is one of the main risk factors for cardiovascular death, and can be caused by endothelial dysfunction characterized by an inability of endothelial cells to produce adequate amounts of bioactive NO [27]. Experimentally, L-NAME (a nitric derivative) perfectly mimics the medical manifestations of essential hypertension in humans [13], and it is frequently used as an inducing agent to evaluate the cardiovascular effects of new therapeutic agents [28].

L-NAME is known to inhibit the endothelial nitric oxide synthase (eNOS) activity, thus reducing NO production, which contributes to peripheral resistance vessels and leads to hypertension [29]. Besides this, it is well documented that, induction of hypertension through L-NAME long-term administration involves other mechanisms, such as activating the renin-angiotensin-aldosterone system, increasing the sympathetic nervous system as well as interference with calcium channels and arachidonic acid derivatives [30] [31]. Therefore, the significant increase in SBP, DBP and MBP after chronic L-NAME (25 mg/kg) administration to normotensive rats during 4 weeks was well justified in the present study and corroborates some results obtained by many researchers [20] [32].

The oral administration of aqueous extract of RH significantly prevented the rise of blood pressure as compared to hypertensive rats. These results suggested that the sympathoexcitation suppression and vasodilation could be a pathway used by extract to exert its cardioprotective effect against L-NAME induced hypertension. The presence of magnoflorine and tetrahydropalmatine, alkaloids compounds known to possess hypotensive and antihypertensive activities, could explain and confirm the cardioprotective effects obtained previously with this extract [18]. In addition aqueous extract of RH has been also demonstrated to pos-

sess vasorelaxant properties through NO pathways responsible for the activation of eNOS followed by the release of NO [19]. Similar results have been also obtained with captopril, an inhibitor of angiotensin-converting enzyme commonly used for the treatment of hypertension [14].

Several studies have explained that chronic NOS inhibition with L-NAME increases sympathetic activity release and heart rate [33] [34]. At the end of treatment, no significant change was observed for heart rate parameters in all groups treated with L-NAME, extract plant or captopril when compared to the normotensive and hypertensive rats. Similar results were obtained by Kojom *et al.* [20], who demonstrated that L-NAME did not affect heart rate. Since co-treatment with RH extract did not change this parameter, it seems that the lowering of blood pressure may be due to its ability to reduce peripheral resistance via its vasorelaxant property [19]. Captopril has been already related to increasing renal blood flow, reducing aldosterone secretion and minimally affecting heart rate [14] [35].

Organs weight constitutes one of the most sensitive drug toxicities indicators, and its changes often precede morphological alterations [36]. In this study, hypertension induced by oral administration of L-NAME during four weeks of treatment leads to cardiac hypertrophy. Generally, cardiac hypertrophy is defined as an adaptive response to chronic pressure or volume overload. This is closely related to fibrosis and cardiomyocytes remodeling associated with NO deficiency [37] [38]. So preventing and reversing the development of cardiac hypertrophy may be an effective therapeutic strategy for the treatment of hypertension and heart failure. This finding supports the argument that, RH extract would be able to reduce the synthesis of angiotensin II involved in cardiac hypertrophy and may consolidate its cardioprotective effect as mentioned above. Also, many studies reported that ACE inhibitor such as Captopril possesses the ability to prevent cardiac hypertrophy [38].

A relationship between NO levels/concentration and hepatic injury was reported [39]. Most of these studies show that, a reduction of NO synthetase (eNOS) in liver sinusoidal endothelial cells can lead to liver injury and vacuolation [39] [40]. Additionally, the reduction of NO bioavailability underlines the development of renal dysfunction associated with impaired renal markers, deteriorated glomerular filtration and increased urinary protein excretion [23] [41]. As observed in this study, animals concomitantly treated with plant extract captopril demonstrated marked protection against L-NAME-induced alteration in biochemical values of transaminases (ALT and AST), total bilirubin, alkaline phosphatase, total protein and, creatinine and urea as compared to hypertensive group. These results indicate the protective role of the extract on liver and kidney tissue according to Kojom *et al.* [18], they reported that antioxidant compounds (magnoflorine, citric acid, dihydrobenzaldehyde) from RH protect against liver and renal injury.

Another factor to be considered in this study is the dyslipidemia associated with high blood pressure [33] [42]. Reduced fatty acid oxidation may explain the in-

crease in serum triglycerides, cholesterol and LDL-cholesterol associated with a decrease of HDL-cholesterol observed in hypertensive rats [43]. The fact that NOS blockage by L-NAME could lead to an alteration of lipid profile by decreasing the activity of enzymes responsible for fatty acid oxidation has been reported [3]. Conversely, these modifications were reversed by treating rats with a plant extract or a standard drug (captopril). It is therefore possible that the effect of RH aqueous extract on reducing hyperlipidemia is due to its ability to increase NO, which in turn modulates lipid metabolism and enhances antioxidant enzymes [19] [44]. Furthermore, captopril appears to exert a beneficial effect on the lipid profile by acting as an antioxidant agent [45] [46].

L-NAME-induced hypertension and dyslipidemia may also be associated with the production of reactive oxygen species [47], which increases the expression of renin and angiotensin-converting enzyme (ACE) to lead to increased vascular superoxide (O_2^-) formation through the activation of NADPH oxidases (NOX), the major source of vascular oxygen radicals [10] [48]. The link between ROS generation and RAS activation has been established [37] [49]. Consistent with our results, many studies have found that NO-deficient hypertensive rats possess increased levels of the lipid peroxidation product MDA and low levels of antioxidant enzymes, including superoxide dismutase, glutathione peroxydase and catalase [50] [51]. The increase in the activities of these enzymatic antioxidants as well as the decrease in the level of MDA could be due to the previously revealed *in vitro* antiradical activity of the RH extract and, probably mediated by some phytoconstituents identified in this extract (alkaloids, organic acids and phenolic compounds and known for their antioxidant properties [52]-[54]. Similarly, many studies have demonstrated that angiotensin converting enzyme inhibitors, such as captopril have beneficial effects against ROS [47].

Histopathological analysis of the heart and aorta revealed no alterations in liver, kidney and heart tissues. However, an increase in aortic wall thickness induced by L-NAME was observed in hypertensive rats compared to normotensive rats. One of the proposed mechanisms for vascular damage is the activation of renin-angiotensin system, which increases ROS responsible for structural organ injury [55] [56]. Indeed, the renin-angiotensin system seems to play a major role in the vascular remodeling process through the activation of various intracellular proteins [49] [57]. Treatment with plant extract or captopril significantly attenuated these alterations. At the dose of 40 mg/kg, the reduction in vascular wall thickness was more pronounced, and its architecture was comparable to that of the control group. This suggests that the aqueous extract may have a cardioprotective effect, probably due to its vasorelaxant and antioxidant properties.

Altogether, these findings suggest that the aqueous extract of stem bark RH has the potential to improve L-Name-induced hypertension and reduce lipid peroxidation/oxidative stress in Wistar rats. This protective role can be mainly attributed to its phytochemical compounds [18]. Unfortunately, we could not isolate the marker compounds that are liable for these activities. Therefore, it is important to understand the influence that processing will have on the phytochemical and food

matrix to predict bioavailability [58]. Further studies need to be done to determine the possible involvement of the renin-angiotensin aldosterone system, and to evaluate the effect of the extract on vascular reactivity, in an attempt to gain more insight into its mechanism of action.

5. Conclusion

This study confirmed that RH exerts a notable antihypertensive effect in L-NAME-induced hypertension without significative structural damage or negative impact on biochemical parameters. The mechanisms involved in these effects could be due to its ability to increase NO production by upregulation of the eNOS protein associated with the strong antioxidant activity of some phytoconstituents. Therefore, RH may be considered an interesting therapeutic candidate in the management of arterial hypertension associated with NO deficiency. However, further research is needed to isolate, identify and characterize the active components and elucidate the precise mechanism(s) of action underlying its biological effects.

Author Contributions

J.J.W.K., E.L.L., A.B.D. conceived and designed the experiment. J.J.W.K, C.Z.B., M.S.T.L.N. performed the animal experiments. J.J.W.K., A.B.D. analyzed the data acquisition. J.J.W.K., E.L.L., A.B.D. drafted original paper. A.B.D. supervised this work. All the authors equally reviewed and approved the final draft version.

Data availability

All data presented in this manuscript are available from the corresponding author on reasonable request.

Acknowlegments

This work was partially supported by an equipment grant from the Alexander von Humboldt Foundation. The authors would like to acknowledge Pr. Dr. Alain Bertrand Dongmo (Faculty of Sciences, University of Douala-Cameroon) for providing the facilities in accomplishing this research work.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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