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Gongronema latifolium Benth methanol leaf extract reduces blood pressure in L-NAME-induced hypertension in rats via modulation of aortic endothelial nitric oxide synthase

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Abstract

Gongronema latifolium is a climbing shrub traditionally used in Nigerian ethnomedicine for hypertension, diabetes, malaria, digestive disorders, and as a nutrient-rich vegetable high in proteins, vitamins, and minerals. This study aimed to evaluate the effects of methanol leaf extract of *G. latifolium* (GLE) on blood pressure, electrocardiographic (ECG) parameters, oxidative stress, organ function, lipid profiles, histoarchitecture, and endothelial nitric oxide synthase (eNOS) expression in L-NAME-induced hypertensive rats. *G. latifolium* leaf was washed, dried and extracted with 70% methanol. Thirty-five male Wistar rats (150-200 g) were divided into seven groups (n=5): control (distilled water), L-NAME (40 mg/kg), GLE alone (100 mg/kg), L-NAME + GLE (50, 100, 200 mg/kg), and L-NAME + captopril (40 mg/kg). Oral treatments lasted 28 days. Non-invasive tail-cuff blood pressure, ECG, serum biomarkers (lipids, liver/kidney enzymes, electrolytes, oxidative stress markers), immunohistochemistry for eNOS, was assessed. Data were analyzed via one-way ANOVA with Tukey's post-hoc ($P < 0.05$). L-NAME significantly elevated systolic/diastolic/mean arterial blood pressures, heart rate, prolonged ECG intervals (P, PR, QRS, QTc), increased MDA, liver/kidney markers, lipids (T-CHOL, TG, LDL, VLDL, CRI), and chloride, It reduced HDL, antioxidants (GSH, SOD, CAT, GST, nitrite), and eNOS expression in the aorta and heart, GLE dose-dependently reduced blood pressures, normalized most ECG parameters (except QTc prolongation at 200 mg/kg), boosted antioxidants/nitrite, normalized organ/lipid/electrolyte markers (LDL reductions 9.6-18.1%, CRI 10.6-17.6%), and upregulated aortic eNOS.

Keywords: *Gongronema latifolium*, L-NAME, endothelial nitric oxide synthase (eNOS), atheroprotective, ECG

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Introduction

Endothelial nitric oxide synthase (eNOS) derived nitric oxide (NO) plays a central role in modulating cardiac autonomic control and electrophysiological activity, as reflected in electrocardiographic (ECG) parameters (Tran *et al*., 2022). Nitric oxide enhances parasympathetic (vagal) activity while suppressing sympathetic tone, resulting in bradycardia in conscious rats, overexpression of eNOS in the nucleus tractus solitarius (NTS) has been shown to reduce heart rate and blood pressure, underscoring nitric oxide's importance in autonomic cardiovascular regulation (Hirooka *et al*., 2003). Although direct studies on the relationship between eNOS and P wave duration are limited, NO's influence on autonomic tone suggests it may modulate atrial conduction (Hari *et al*., 2018). In pathological conditions such as diabetes, alterations in ECG parameters, including prolonged P-wave duration, have been observed, likely due to reduced nitric oxide (NO) bioavailability. Additionally, NO plays a significant role in atrioventricular (AV) nodal conduction (Sharma and Khanna, 2013). Inhibition of NO synthesis using L-NAME in rats resulted in prolonged PR intervals, indicating that NO is essential for maintaining normal AV conduction (Wang, 2001).

Beyond atrial and AV conduction, NO also influences ventricular electrical activity. The QRS complex, which represents ventricular depolarization, is affected by NO levels; in rat models with left ventricular hypertrophy; administration of NO donors shortened QRS duration, suggesting enhanced ventricular conduction (Švehlíková *et al*., 2016). Nitric oxide's role extends further into repolarization, where it impacts both QT and corrected QT (QTc) intervals. Elevated NO levels have been linked to QTc prolongation, while NO inhibition has been shown to attenuate such prolongation, indicating its regulatory effect on repolarization dynamics (Tamargo *et al*., 2010) These effects are particularly evident in disease models such as diabetes, where significant QTc changes occur due to altered NO signaling (Wang, 2001). NO exerts its effects by stimulating guanylyl cyclase, increasing cyclic GMP (cGMP) levels, which then activate cGMP-dependent protein kinases (Derbyshire *et al*., 2012). These kinases can inhibit slow inward calcium currents, thereby affecting action potential duration and overall cardiac excitability (Lamore *et al*., 2017). However, the precise contribution of these molecular mechanisms to specific ECG alterations remains an area of ongoing investigation.

The N^G-Nitro-L-arginine-methyl ester (L-NAME) is a compound mainly used to induce experimental hypertension in animal models, providing an insight into the physiological mechanism that regulates blood pressure and the impact of nitric oxide (NO) on the cardiovascular system (Li, *et al*., 2020). Nitric oxide is a vital molecule that acts as both a neurotransmitter and a neuromodulator, which is produced by the endothelial cell lining of the blood vessels. It plays a crucial role in regulating vascular tone by dilating blood vessels, thereby decreasing blood pressure. In hypertension, there is inhibition of nitric oxide, leading to vasoconstriction and increased blood pressure (Tousoulis *et al.*, 2012; Gheibi *et al*., 2018). The function of NO, both injurious and protective, is involved in the development of liver injury, and L-Arginine, a precursor of NO, can attenuate liver injury (Angele *et al*., 2000; Abu-Amara *et al*., 2012). N^G-nitro-L-arginine methyl ester (L-NAME) is an inhibitor of NO biosynthesis, blocking the activity of nitric oxide synthase (NOS) and inducing hypertension (Rajeshwari *et al*., 2014; Seth *et al*., 2016; Chen *et al*., 2019). The vasoconstrictive effect leads to systemic hypertension in animal models induced with L-NAME. Moreover, L-NAME serves as a valuable tool in experimental studies to evaluate the relationship between nitric oxide, vascular function, and hypertension (Kakabadze *et al*., 2021) The ability to induce hypertension by inhibiting nitric oxide production underscores the significance of nitric oxide in maintaining cardiovascular homeostasis and serves as a potential target for therapeutic intervention in hypertensive conditions (Bryan, 2022).

Fresh fruits and medicinal plants rich in antioxidants and phytochemicals offer safer alternatives for managing heart disease, hyperlipidemia, and hypertension (Nakajima *et al*., 2014). Despite limited understanding of their mechanisms, natural remedies are favored in low-income regions due to affordability and accessibility (Aware *et al*.,2020). *Gongronema latifolium*, traditionally used in African medicine, is gaining attention for its antihypertensive potential. The plant is known by various names, such as Utazi (Igbo) and Arokeke (Yoruba) (Edim *et al*., 2012). It has a sharp, bitter-sweet taste and is used both as food and medicine (Eleyinmi, 2007). Nutritionally, its leaves are rich in proteins, vitamins, and minerals (Offor *et al*., 2015). Its leaves contain bioactive flavonoids (e.g., luteolin, quercetin), alkaloids, tannins, and saponins, supporting its antihypertensive potential amid limited access to synthetic drugs in low-income African regions. (Okonkwo, *et al* 2025). Various parts of *G. latifolium* have been mentioned for use as antihypertensive in Nigeria (Obode *et al*., 2020). Traditional preparations help treat parasites, colic, and digestive issues. It's a climbing shrub with soft stems, yellow flowers, and dehiscent seed pods (Osuagwu *et al*., 2013). *G. latifolium* contains bioactive compounds like flavonoids and tannins, used to treat conditions like malaria and nausea (Owu *et al*., 2012; Mosango *et al*., 2022). Extract of *G. latifolium* has been shown to lower blood pressure in rats (Beshel et al., 2019). This study aimed at evaluating the effect of methanol leaf extract of *G. latifolium* on electrocardiogram changes and endothelial nitric oxide synthase (eNOS) in L-NAME-induced hypertension in rats.

Materials and Methods

Drugs and Reagents

N^G-Nitro-L-arginine-methyl ester (L-NAME) was product of Santa Cruz Chemicals (USA), and Captopril was obtained from Kunle-Ara Pharmaceuticals (Ibadan, Nigeria). All chemicals used in this study were of analytical grade.

Preparation of plant extract

Fresh *Gongronema latifolium* leaves were collected at the University of Ibadan Botanical Garden. The plant was authenticated at the Department of Botany, University of Ibadan comparison with voucher specimen number UIH-23453. Fresh leaves were dried at room temperature and ground into powder, soaked in 6 liters of 70% methanol, shaken periodically at room temperature for seventy-two hours, and sieved. The extract was concentrated using a vacuum rotary evaporator under reduced pressure (RE 100B, Bibby Sterilin, United Kingdom) to reduce the volume at 40ºC and then oven-dried to a constant weight, and 32 g of crude methanol extract was obtained with 93.5% yield, labeled as GLE and stored at 4ºC.

Animals

Thirty-five male Wistar rats (8–12 weeks old, 150–200 g) were obtained from the Central Animal House, University of Ibadan. The animals were housed in transparent plastic cages under standard conditions (12h light-dark cycle, 25–28°C) with food and water *ad libitum*. The rats were acclimatized for 14 days before the experiment. The study received ethical approval (UI-ACUREC/175-1124/18) from the University of Ibadan Animal Care and Use Research Ethics Committee, and the approved procedure also adhered to the National Institutes of Health's Guide for the Care and Use of Laboratory Animals.

Induction of high blood pressure in rats

In order to elucidate the effect of *Gongronema latifolium* on electrocardiographic parameters and blood pressure, L-NAME was administered orally at 40 mg/kg daily for 4 weeks (Moncada *et al*., 2018). Thirty-five rats were divided into seven groups of five rats each as follows: rats of group 1 received distilled water, group 2 received L-NAME only (40 mg/kg), groups 3 received GLE (100 mg/kg), groups 4, 5 and 6 received in addition to L-NAME, GLE (50, 100 and 200 mg/kg), respectively, while group 7 received captopril (40 mg/kg). Animals were treated orally daily for four consecutive weeks.

Non-Invasive Blood Pressure (NIBP) assessment

At the end of the 28 days treatment, blood pressure was assessed using the BP-2010N AUL system which was connected to PowerLab® and configured with LabChart for pulse and pressure channels. A tail cuff with Volume Pressure Recording (VPR) measured systolic, diastolic, and mean arterial pressure, as well as heart rate. Rats were placed in a stress-minimizing holder with a nose cone to allow free breathing and reduce motion. The tail extended out for proper cuff placement. Animal body temperature was maintained at 20ºC to enhance tail blood flow and ensure accurate readings. The pressure cuff and pulse transducer were aligned with the tail's ventral side over the caudal artery. Recording began with cuff inflation until the pulse disappeared, and data were captured via LabChart. (Bilanda *et al*., 2017)

Electrocardiographic measurement

After blood pressure measurement at the end of the treatment, the rats were anesthetized using ketamine and xylazine intraperitoneal (75 mg/kg and 5 mg/kg, respectively), and an electrocardiogram was measured using an ECG machine (Rms Salus Portable EMG NCV EP) (Foser *et al*., 2018).

Assessment of oxidative stress parameters

Serum reduced glutathione (GSH) level was determined using Ellman's reagent in deproteinzed sample by incubating with 5, 5'-dithiobis-(2-nitrobenzoic acid) (DTNB), and absorbance at 405 nm using a microplate reader (Jollow *et al*., 1974). Lipid peroxidation was assessed as malondialdehyde (MDA) at 532 nm according to the thiobarbituric acid-reactive substances (TBARS) assay described by (Nagababu *et al*., 2010). Serum nitrite levels, a marker of nitrergic stress, was determined by mixing equal volumes of supernatant with Griess reagent [1% sulfanilamide in 5% phosphoric acid and 0.1% N-(1-naphthyl) ethylenediamine dihydrochloride (NED)], with absorbance measured at 540 nm (Green *et al*., 1982). Catalase activity in the serum was measured using a colorimetric assay based on the formation of a yellow complex with molybdate and H_2O_2 (Goth *et al*., 1991). Superoxide dismutase (SOD) activity was evaluated using the adrenaline auto-oxidation method (Misra and Fridovich, 1972) while glutathione-S-transferase (GST) activity was monitored kinetically as described by (Habig *et al.,* 1974).

Lipid profile, liver enzymes and kidney function parameters

Retroorbital blood was collected from anesthetized rats into plain tubes. Blood was centrifuged at 3000 rpm for 15 min at room temperature to obtain serum. Total cholesterol (Chol), triglycerides (TG), HDL-Cholesterol (HDL-Chol), Bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) creatinine, urea, Na^+, K^+ and Cl^- ions levels were determined using commercial diagnostic kits (Fortress, UK indication). LDL-Cholesterol

(LDL-Chol) level was determined following the formula described by Friedewald *et al*., (1972).

Immunohistochemical staining for expression of aortic and cardiac eNOS

Immunohistochemical staining of aortic and cardiac tissues for expression of eNOS was performed following procedure previously described by Hofman, and Taylor (2013). Paraffin-embedded aortic and cardiac tissues were sectioned at 4 µm thickness. The sections underwent deparaffinization, rehydration, and antigen retrieval before being incubated overnight with primary antibodies against eNOS (Elabscience, Wuhan, China). The slides were incubated with a goat anti-rabbit secondary antibody, followed by streptavidin peroxidase and diaminobenzidine (DAB) staining. Counterstaining with hematoxylin was performed. The expression of eNOS was visualized using photomicroscope Leica ICC50 E Digital Camera (Germany), a computer interface (Magna fire), and an Olympus binocular research microscope (Olympus, New Jersey, USA).

Statistical analysis

Data were expressed as mean ± S.E.M. Statistical significance was performed using one-way analysis of variance (ANOVA) followed by the Tukey's post hoc test (multiple comparisons) using GraphPad Prism® software version 8.03 (GraphPad Software, Inc. La Jolla, CA 92037 USA). A value of $P < 0.05$ was considered statistically significant.

Results

Effect of G. latifolium on blood pressure

The results demonstrate that L-NAME induced a significant increase in systolic blood pressure [$F_{(6, 21)} = 10.69$, $P < 0.0001$] compared to the control group. Treatment with GLE significantly reduced systolic blood pressure by 30%, 35.6%, and 29.6%, respectively, when compared to the L-NAME-induced group. There was no significant difference in systolic blood pressure reduction between the groups treated with low, medium, or high doses of GLE and the group treated with captopril as the standard drug (Figure 1A). Similarly, administration of L-NAME caused a significant increase in diastolic blood pressure [$F_{(6, 21)} = 9.830$; $P < 0.0001$] when compared to the control group. Treatment with GLE resulted in a significant reduction in diastolic blood pressure (40%, 53%, and 39.8%), respectively, when compared to the group induced with L-NAME alone. There was no significant reduction in diastolic blood pressure for groups treated with GLE when compared to the group treated with captopril (Figure 1B). L-NAME caused a significant increase in mean arterial pressure [$F_{(6, 21)} = 13.85$; $P < 0.0001$]. GLE evoked significant reduction in MAP (37%, 46%, 36%), respectively, similar to that of captopril (Figure 1C).

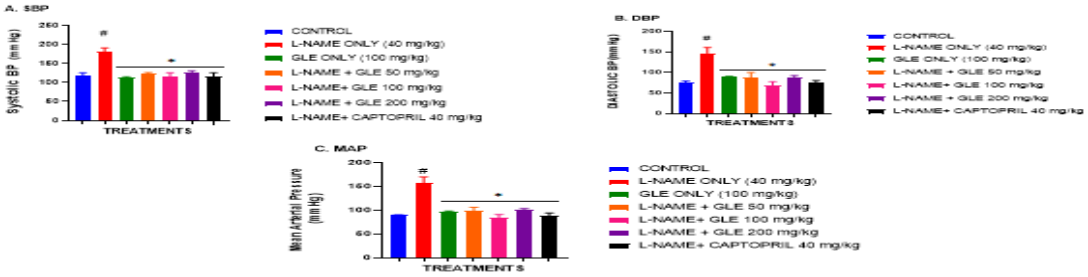

Fig 1: Effect of GLE on systolic blood pressure in L-NAME induced hypertensive rat. (A) Systolic Blood pressure, (B) Diastolic blood pressure, (C) Mean arterial pressure effect. Values represented as Mean ± SEM (n=5). (a) #$P < 0.05$ vs control. (b) *$P < 0.05$ vs L-NAME only. (c) a$P < 0.05$ vs L-NAME + Captopril (40 mg/kg). One-way ANOVA followed by Turkey's

Effect of GLE on ECG parameters in L-NAME-treated male Wistar rats.

Administration of L-NAME caused a significant increase in heart rate when compared to the control [$F_{(6, 28)} = 6.926$; $P < 0.0004$]. (Table 1). A significant reduction in heart rate was evident with GLE (low, 15.3% and high dose; 13.4%) and Captopril (7.3%) administration. Administration of L-NAME significantly increased the P wave and PR wave durations compared to the control group [$F_{(6, 28)} = 8.008$, $P < 0.0001$]. (Table 1) Significant reductions were observed in the PR wave duration following administration with: GLE captopril (Table 1). Administration of L-NAME significantly increased the R wave amplitude compared to the control group [$F_{(6, 21)} = 9.652$, $P < 0.0001$]. Significant increases in R wave amplitude were evident treatment with. The administration of L-NAME significantly increased the QRS complex duration [$F_{(6, 28)} = 19.46$, $P < 0.0001$] and QTc interval [$F_{(6, 21)} = 24.88$, $P < 0.0001$]. when compared to the control group. There was no significant difference in QRS complex duration between the groups treated with GLE: (100 and 200 mg/kg) and the group treated with captopril. Increase in the QTc interval was observed in the groups treated with GLE alone, GLE (50 and 100 mg/kg and

captopril when compared to the L-NAME-induced group (Table 1). There was no significant difference in the QTc interval between the GLE-treated groups and the captopril group, except for the group treated with GLE 200 MG/KG (Table 1 and Figure 2f).

Table 1: Effect of GLE on ECG parameters in L-NAME-induced hypertensive rats.

Treatment groups	Heart rate (bpm)	P (ms)	PR (ms)	R (mV)	QRS (ms)	QTC (ms)
Control	209.2 ± 19.2	29.33 ± 1.7	51.4 ± 1.702	0.25 ± 0.03	16.0 ± 0.7	131.7 ± 3.8
L-NAME Only (40 mg/kg)	261.0±4.0#	40.92 ± 2.2#	65.00 ± 0.8#	0.37 ± 0.05 #	25.0 ± 1.4 #	194.9 ± 6.8 #
GLE Only (100 mg/kg)	176.3 ± 16.7*	27.33 ± 2.3*	56.67 ± 0.5*	0.25 ± 0.02*	17.3 ± 0.4 *	164.3 ±16.7*
L-NAME +GLE (50 mg/kg)	221.0 ± 2.1*α	34.67 ± 1.9	59.67 ± 1.0	0.31 ± 0.01	20.7 ± 1.5*	159.7 ± 5.2 *
L-NAME +GLE (100 mg/kg)	249.8 ± 1.3	29.0 ± 2.5*	54.66 ± 1.0*	0.23 ± 0.03*	21.7 ± 0.3	163.3 ± 11.1 *
L-NAME +GLE (200 mg/kg)	226.3 ± 6.1*	25.67 ± 1.2*	53.67 ± 3.5*	0.39 ± 0.04 α	24.0 ± 1.1	218.0 ± 7.4 *α
L-NAME +Captopril (40 mg/kg)	241.7 ± 1.9 *	29.0 ± 1.9*	53.33 ± 0.9*	0.19 ± 0.03*	22.2 ± 0.8	153.3 ± 8.0 *

Values represented as Mean± SEM (n=5). #*P* < 0.05 vs control; *P < 0.05 vs L-NAME only; a P < 0.05 vs L-NAME + Captopril (40 mg/kg). (One-way ANOVA followed by Turkey's post-hoc test).

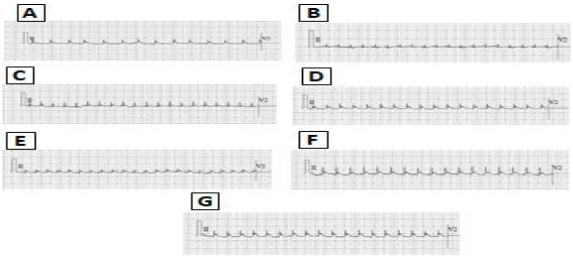

Fig 2 (A-G). Showing the ECG changes associated with L-NAME-treated male Wistar rats. A. CONTROL, B. L-NAME ONLY, C. GLE ONLY (100 mg/kg), D. L-NAME+GLE 50 mg/kg, E. L-NAME+GLE 100 mg/kg, F. L-NAME+GLE 200 mg/kg, and G. L-NAME+Captopril (40 mg/kg).

Effect of G. latifolium on the body weight of animals

Results revealed a significant difference in body weight ($P < 0.05$) with treatment [$F_{(4, 165)} = 66.09$; $P < 0.0001$] and time [$F_{(6, 165)} = 5.939$; $P < 0.0001$] and no significant difference in

the interaction effect [$F_{(24, 165)} = 0.2574$; P=0.9999] between treatment and time of the body weights of the animals at week 1,2,3,4 in group treated with GLE (50 and 100 mg/kg (Figure 3A and 3B).

GLE prevented increase in organ (heart) weight in L-NAME-induced hypertensive rats in a dose-dependent manner. Fig. 3C demonstrates that the relative organ weight of the heart significantly reduced following L-NAME administration [$F_{(6, 35)} = 8.039$, $P < 0.0001$]. Treatment with the extract alone significantly increased relative organ weight when compared to the L-NAME-induced group (Figure 3C).

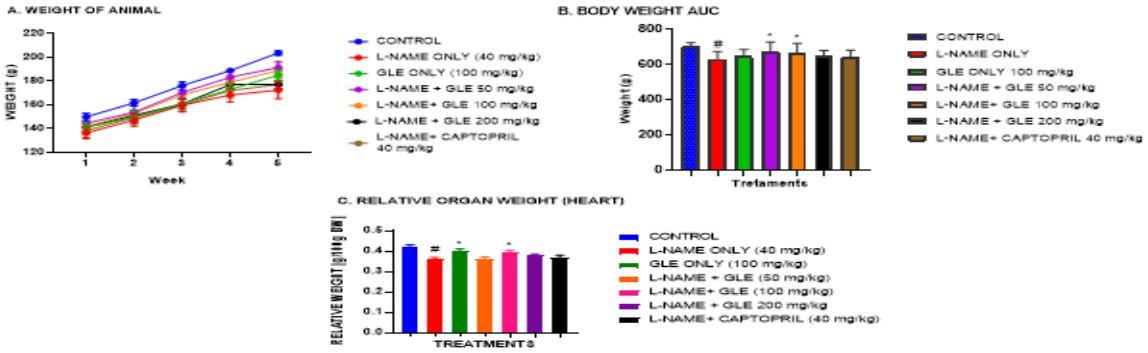

Fig 3: (A) Body weight of rats. (B) AUC of body weight. (C) Relative Organ Weight (heart). Values represented as Mean ± SEM (n=5). (a) #$P < 0.05$ vs control. (b) *$P < 0.05$ vs L-NAME only. (c) a$P < 0.05$ vs L-NAME + Captopril (40 mg/kg). Two-way ANOVA followed by Tukey's multiple comparison tests. GLE: *Gongronema latifolium* extract.

Effect of G. latifolium extract on oxidative stress and antioxidant parameters of L-NAME-induced hypertensive rats

L-NAME induced lipid peroxidation in rats, as evidenced by increased levels of malondialdehyde (MDA), a biomarker of tissue injury (Figure 4A). Treatment with GLE (200 mg/kg) and captopril significantly reduced MDA levels by 22% and 22.5%, respectively. The GLE treated groups showed a significant increase in GSH levels [$F_{(6, 21)} = 136.4$, $P < 0.0001$] compared to the L-NAME-induced untreated group (Figure 4B). L-NAME reduced serum nitrite levels, an indicator of nitric oxide. Administration of GLE resulted in a significant increase in nitrite levels [$F_{(6, 21)} = 29.82$, $P = 0.0430$]. (Figure 4C). GLE significantly [$F_{(6, 21)} = 28.24$, $P < 0.0001$] improved tissue catalase enzyme level (Figure 4D), increased serum SOD activity [$F_{(6, 21)} = 17.34$, $P < 0.0001$, Figure 4E] and increased tissue GST activity [$F_{(6, 21)} = 102.5$, $P < 0.0001$, Figure 4F], in L-NAME-induced hypertensive rats.

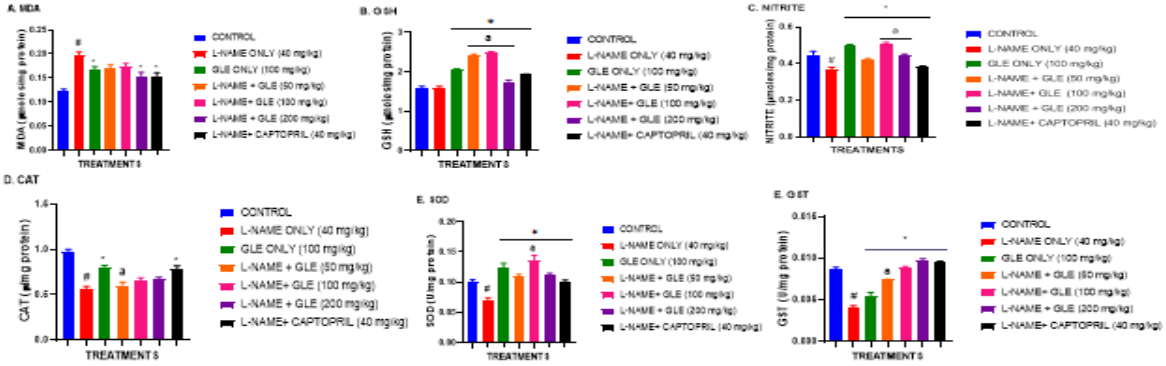

FIG 4: Effect of GLE on oxidative stress in L-NAME-induced hypertensive rats. Heart (A) Malondialdehyde (B) Reduced glutathione (C) Nitrite (D) Catalase (E) Superoxide dismutase (F) Glutathione-S-transferase. Values represented as Mean ± SEM (n=5). (a) #$P < 0.05$ vs control. (b) *$P < 0.05$ vs L-NAME only. (c) a$P < 0.05$ vs L-NAME + Captopril (40 mg/kg). One-way ANOVA followed by Tukey's multiple comparison tests

Effect of G. latifolium extract on liver enzymes and liver function of L-NAME-induced Hypertensive rats

A significant increase in liver enzymes was observed in the L-NAME-induced untreated group [$F_{(6, 21)} = 145.3$, $P < 0.0001$]. AST, ALT and ALP were reduced in GLE-treated groups and captopril compared to the L-NAME-induced untreated group (Figure 5A, B and C). L-NAME caused a significant increase in the level of bilirubin [$F_{(6, 21)} = 15.79$; $P < 0.0001$), which was attenuated by GLE treatment (Figure 5D]

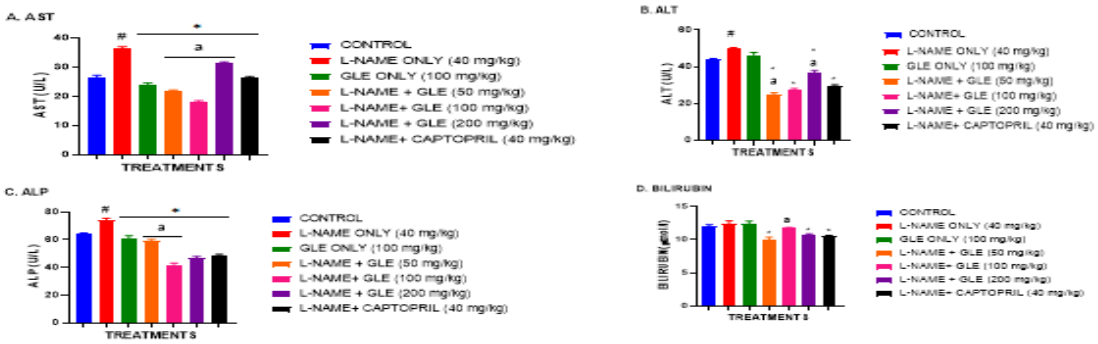

Fig 5: Effect of GLE on markers of liver function markers in L-NAME induced hypertensive rat. (A) aspartate aminotransferase (B) alanine aminotransferase (C) alkaline phosphatase (D) bilirubin. Values represented as Mean ± SEM (n=5). (a) #$P < 0.05$ vs control. (b) *$P < 0.05$ vs L-NAME only. (c) a$P < 0.05$ vs L-NAME + Captopril (40 mg/kg). One-way ANOVA followed by Turkey's multiple comparison tests.

Effect of G. latifolium extract on the kidney function of L-NAME-induced hypertensive rats

The administration of L-NAME significantly [$F_{(6, 21)} = 26.13$; $P < 0.0001$] increased the concentration of blood urea nitrogen (BUN) (Figure 6A). However, BUN was significantly reduced by 36.8%, 55.3%, 26.8% by GLE (50, 100 and 200 mg/kg) and captopril (39.5%) respectively. L-NAME-induced caused significant increase in creatinine level [$F_{(6, 21)} = 9.398$; $P < 0.0001$]. was reduced by GLE (50, 100 and 200 mg/kg) by 17.3%, 20.9%, and 14% respectively (Figure 6B). Administration of L-NAME caused an increase in sodium level and a decrease in potassium levels which were not significantly affected by GLE (Figure 6Cand D). L-NAME-induced a significant increase in chloride ion level which was significantly reduced by GLE treatment [$F_{(6, 21)} = 6.552$; $P = 0.0005$, Figure 6E].

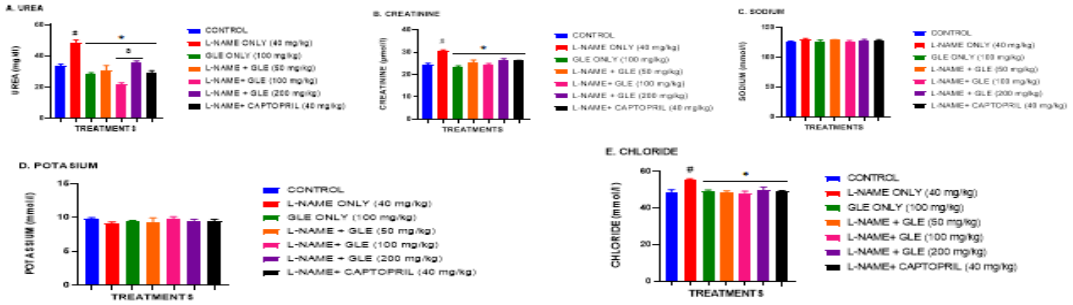

Fig 6: Effect of GLE on kidney function markers in L-NAME induced hypertensive rat. (A) Urea (B)creatinine (C) sodium (D) potassium (E) chloride activity. Values represented as Mean ± SEM (n=5). (a) #$P < 0.05$ vs control. (b) *$P < 0.05$ vs L-NAME only. (c) a$P < 0.05$ vs L-NAME + Captopril (40 mg/kg). One-way ANOVA followed by Turkey's multiple comparison tests.

Effect of G. latifolium extract on serum lipid profile of L-NAME-induced hypertensive rats.

L-NAME administration significantly ($P < 0001$) elevated total cholesterol, triglycerides, LDL and VLDL levels, while reducing HDL, P=0.0028]. It also non-significantly lowered the HDL/LDL ratio and raised the Coronary Risk Index (CRI) $P < 0.0001$]. GLE treatment (50, 100, 200 mg/kg) markedly reversed these effects.

Total cholesterol decreased significantly across all GLE doses (Table 2). Triglycerides were reduced significantly by GLE (50 and 200 mg/kg). HDL was increased non-significantly, LDL was reduced, VLDL was reduced. HDL: LDL ratio was significantly increased while CRI declined by GLE (Table 2)

Table 2: Effect of *Gongronema latifolium* extract on lipid profile of L-NAME-induced hypertensive rats

Lipid profile	Control	L-NAME Only (40 mg/kg)	GLE Only (100 mg/kg)	L-NAME +GLE (50 mg/kg)	L-NAME +GLE (100 mg/kg)	L-NAME+GLE mg/kg)	L-NAME +Captopril (40 mg/kg)
Total cholesterol (mg/dL)	3.07±0.02	3.22±0.04#	3.33±0.04*	2.85±0.04*a	3.04±0.01	2.87 ± 0.012*a	3.08 ± 0.011
Triglyceride (mg/dL)	0.76±0.01	0.85±0.01#	0.86±0.019	0.75±0.02*	0.79±0.01	0.72 ± 0.027*	0.74 ± 0.018*
High-density lipoprotein HDL-C (mg/dL)	0.90±0.02	0.80±0.01#	0.89±0.004*	0.86±0.003	0.85±0.03	0.83 ± 0.013	0.87 ± 0.010
Low-density lipoprotein LDL-C	2.01±0.03	2.25±0.04#	2.26±0.05	1.84±0.05*a	2.04±0.02*	1.89 ± 0.007* a	2.06 ± 0.014*
Very low-density lipoprotein VLDL-C	0.41±0.01	0.36±0.01#	0.39±0.01	0.47±0.01*	0.42±0.02	0.45 ± 0.018*	0.42 ± 0.007*
High-density/low-density lipoprotein ratio (HDL/LDL)	0.15±0.002	0.17±0.004	0.17±0.001	0.15±0.01	0.16±0.002*	0.14 ± 0.005*	0.15 ± 0.005*
Coronary-risk index (CRI)	3.41±0.06	4.02±0.082#	3.74±0.06	3.31±0.05*	3.60±0.04*	3.44 ± 0.145*	3.55 ± 0.037*

Values represented as Mean ± SEM (n=5). (a) #P < 0.05 vs control. (b) *P < 0.05 vs L-NAME only. (c) a P < 0.05 vs L-NAME + Captopril (40 mg/kg). One-way ANOVA followed by Tukey's multiple comparison tests.

Effect of GLE on aortic Endothelial Nitric Oxide Synthase (eNOS) in L-NAME induced hypertensive rats.

L-NAME caused a significant decrease in the expression of eNOS in the aorta compared to the control group [$F_{(6, 28)}$ = 19.46; P < 0.0001, Figure 9]. There was a significant increase in eNOS expression in all the groups treated with GLE. Similar effects were observed in the heart

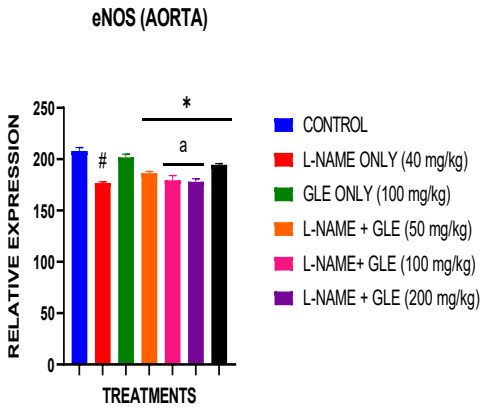

Figure 9: Effect of GLE on aortic tissues eNOS expression in L-NAME induced hypertensive rat. Relative expression of eNOS. Values represented as Mean ± SEM (n=5). (a) #P < 0.05 vs control. (b) *P < 0.05 vs L-NAME only. (c) a *P* < 0.05 vs L-NAME + Captopril (40 mg/kg). One-way ANOVA followed by Turkey's multiple comparison tests.

Discussion

Due to the absence of early symptoms, persistent high blood pressure is frequently referred to as the "silent killer," and it involves a persistent increase in arterial blood pressure (Ahmad, 2020). Although the exact cause of most hypertension cases remains unclear, genetic predisposition, diets high in salt, and psychological stress are considered contributing factors (Marwaha, 2022). The study demonstrated that L-NAME-induced hypertension was accompanied by increased systolic, diastolic, and mean arterial blood pressure; this finding is consistent with L-NAME's non-specific inhibition of nitric oxide synthase, leading to hypertension (Chaswal *et al*., 2011, and Kakabadze *et al*., 2021). GLE's blood pressure-lowering effects are attributed to vasodilation (nitric oxide modulation), antioxidant/anti-inflammatory activity, and RAAS regulation (Ugwu *et al*., 2014; Beshel *et al*., 2019).

L-NAME (N^G-nitro-L-arginine methyl ester) significantly increased heart rate, confirming the successful induction of hypertension and its effect on heart rate. *Grongrenema latifolium* significantly reduced heart rate in L-NAME-induced hypertensive rats reinforcing its potential antihypertensive effect. However, the lack of strong dose-dependency suggests a plateau in its effect. *Gongronema latifolium* (GLE) did not significantly alter heart rate indicating no direct effect in normotensive conditions. L-NAME significantly increased P wave duration and PR interval indicating impaired atrial conduction. GLE significantly reduced the prolonged P wave duration in L-NAME-treated groups, suggesting a protective effect on atrial conduction. GLE did not significantly alter the P wave duration, further supporting its specificity in hypertensive conditions. Clinically, this suggests that hypertension may increase atrial conduction risks, and GLE may offer protective benefits. GLE l significantly reduced R amplitude implying a protective effect, suggesting no direct effect on ventricular depolarization in normotensive conditions. If GLE reduces ventricular hypertrophy, it could aid in managing hypertensive heart disease and lowering heart failure risk, indicating an impact on ventricular conduction. suggesting a protective effect on ventricular conduction. This reduction highlights GLE's potential in mitigating hypertension-related conduction abnormalities, supporting its role in maintaining proper ventricular function, indicating prolonged ventricular repolarization and a potential risk for arrhythmias. However, GLE unexpectedly increased the QTc interval, raising concerns about potential proarrhythmic effects. The observation that GLE at 200 mg/kg prolonged the QTc interval compared to L-NAME-induced controls warrants cautious interpretation, as QTc extension (>450-500 ms in rodents, adjusted for heart rate) signals potential risk for torsades de pointes and sudden cardiac death (Li and Ramos, 2017; Skullbacka *et al*., 2022). This finding contrasts with lower GLE doses, which showed neutral or beneficial cardiac profiles, suggesting dose-dependent cardiotoxicity. L-NAME, via nitric oxide synthase inhibition, induces endothelial dysfunction and hypertension, potentially confounding baseline QTc; thus, GLE's effect may reflect

incomplete reversal or off-target ion channel modulation. This necessitates careful monitoring and further investigation before considering GLE for clinical use, as prolonged QTc intervals pose significant arrhythmia risks. Phytochemicals in plants natural products could inhibit hERG potassium channels (Kratz, *et al*., 2017), delaying repolarization akin to known QT-prolongators like quinidine (Yan et al., 2016). High-dose accumulation might enhance calcium influx via L-type channels or sympathetic overstimulation, exacerbating QTc. Alternatively, GLE's antioxidant effects at lower doses may protect against L-NAME oxidative stress on cardiomyocytes, while higher dose could trigger pro-oxidant shifts.

Oxidative stress is known to be caused by the decreased activity of antioxidants and antioxidant enzymes, as well as increased levels of reactive oxygen species (ROS) or reactive nitrogen species (RNS), such as peroxynitrite. Increased activities of free radicals have been proposed to be a major pathway of hypertension (Ahmed *et al*., 2020). Although L-NAME can inhibit endothelial nitric oxide synthase to cause hypertension through increased peripheral resistance (Campbell, 2006). In this study, L-NAME administration resulted in oxidative stress and vascular damage, as evidenced by increased MDA (a lipid peroxidation/oxidative stress biomarker) and decreased antioxidant defenses, including GSH, GST, CAT, and SOD activities. The elevated MDA levels indicate oxidative damage, while the reduction in essential antioxidants highlights impaired detoxification mechanisms, increased lipid peroxidation, and vascular dysfunction (Tang *et al*., 2019; Johnkennedy *et al*., 2021). Additionally, L-NAME inhibited NO synthase, reducing NO availability, which led to vasoconstriction, elevated blood pressure, and cardiovascular complications (Okon *et al*., 2022). GLE treatment effectively countered these effects, showing antioxidant and cardioprotective properties comparable to captopril. GLE reduced MDA levels, restored GSH and GST activities, and enhanced CAT and SOD functions, thereby improving cellular defense mechanisms and mitigating oxidative stress-related damage (Johnkennedy *et al*., 2021). These findings are consistent with others where GLE was shown to significantly boost antioxidant enzyme activity (like SOD, GPx, CAT) and reduce oxidative stress markers (MDA) in various models, particularly in diabetic or toxin-induced conditions, protecting tissues from damage by scavenging radicals, inhibiting lipid peroxidation, and increasing glutathione levels (Effiong et al., 2013; Iweala *et al*., 2013; Agwaramgbo et al., 2014; Okon *et al*., 2022).

The AST, ALT, ALP, and bilirubin are key markers of liver function, oxidative stress, and metabolic dysfunction. L-NAME-treated rats showed increased AST and ALT, indicating oxidative stress-induced hepatocellular damage, while elevated ALP suggested hepatic injury and possible bile duct obstruction (Li *et al*., 2020). L-NAME also slightly elevated bilirubin, likely due to oxidative stress, hemolysis, or impaired bile excretion (Wang and Bautista, 2015). GLE supplementation significantly reduced AST, ALT, ALP, and bilirubin, providing hepatoprotective effects (Chigaemezu *et al*., 2021). While captopril also lowered these markers, GLE was more effective, highlighting its superior liver-protective potential (Omadiro *et al*., 2021; Ujong *et al*., 2022). The ability of GLE to restore these markers suggests its therapeutic potential for oxidative stress-related liver disorders, including hypertension-induced liver damage, non- alcoholic fatty liver disease (NAFLD), cholestatic liver diseases, and metabolic syndrome (Ojo *et al*., 2020).

Elevated urea and creatinine indicate renal impairment (Cachofeiro *et al*., 2002). L-NAME increased creatinine and led to urea accumulation via reduced NO. GLE lowered urea (Ujong *et al*., 2022) and creatinine (Sulaiman *et al*., 2021), suggesting nephroprotection GLE may benefit from hypertension-induced renal dysfunction (Ogbonnaya *et al*., 2014). L-NAME-induced hypertension was not sodium-dependent (Hu *et al*., 1994), as GLE didn't alter sodium levels, indicating safety for kidney and cardiovascular health (Ujong *et al*., 2022). Potassium levels were also stable, suggesting no potassium dysregulation in L-NAME hypertension (Zhu *et al*., 2018). L-NAME increased chloride, possibly via NO deficiency-induced electrolyte imbalance (Wangensteen *et al*., 2006), while GLE and captopril reduced chloride, indicating restored kidney function and electrolyte balance (Usoh *et al*., 2016). Clinically, elevated chloride levels may indicate a shift toward metabolic acidosis, a condition that can arise due to kidney dysfunction or impaired acid-base regulation. Since GLE reverses the chloride increase, it could be explored as a natural intervention for managing electrolyte imbalances in hypertensive or kidney disease patients.

L-NAME, a nitric oxide synthase inhibitor, induces endothelial dysfunction, oxidative stress, and hypertension, mirroring metabolic syndrome features. It significantly elevates total cholesterol (T-CHOL), triglycerides, LDL, VLDL, and CRI, -key cardiovascular disease (CVD) predictors, while depleting HDL, promoting atherogenesis via lipid peroxidation and plaque formation. In this study, GLE has been found to potently reverses this dyslipidemia. It lowers T-CHOL, triglycerides, LDL, VLDL, and CRI while boosting HDL, indicating robust hypolipidemic efficacy. The phytochemical mechanisms underpinning GLE's effects may include its antioxidant action such as flavonoids that may scavenge L-NAME-induced ROS, inhibit HMG-CoA reductase and reduce hepatic cholesterol synthesis (Li et al., 2020; Katchy *et al*., 2020). In addition, GLE might be inhibiting pancreatic lipase and intestinal cholesterol absorption; upregulates LDL receptors via PPAR-α/γ activation (Mota *et al*., 2018; Lee *et al*., 2022).

Endothelial nitric oxide synthase (eNOS) plays a crucial role in maintaining vascular health, as it produces nitric oxide (NO), which helps regulate blood vessel dilation, blood pressure, and overall endothelial function**.** L-NAME-

induced reduction in eNOS mimics endothelial dysfunction**,** which is a hallmark of hypertension, atherosclerosis, and cardiovascular diseases (Campbell 2006, Silva *et al*. 2022). Treatment with *Gongronema latifolium* increased eNOS expression. This suggests its potential cardioprotective and antihypertensive properties through the restoration of nitric oxide (NO) levels. More so, Captopril, an ACE inhibitor, also increased eNOS expression **aligning** with its known role in improving endothelial function and reducing hypertension (Quaschning *et al*., 2001; Talukder *et al***.**, 2004**;** Lu, 2023).

Conclusion

This study demonstrates the therapeutic potential of *Gongronema latifolium* leaf extract (GLE) in mitigating L-NAME-induced hypertension in rats. GLE exhibited cardioprotective, antioxidant, hepatoprotective, renoprotective, and hypolipidemic effects, evidenced by reduced blood pressure, stabilized ECG parameters, attenuated oxidative stress, normalized liver enzymes, preserved serum electrolytes and lipid profiles, and upregulated eNOS expression. Furthermore, GLE conferred atheroprotection by lowering coronary risk indices, thereby impeding hypertension-associated atherosclerosis progression.

Ethics statement

The animal study was approved by the University of Ibadan Animal Care and Use Research Ethics Committee (UI-ACUREC).

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The research was conducted following the local legislation and institutional requirements.

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