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Antioxidant And Antihypertensive Effects Of Methanol Leaf Extract Of Ficus Exasperata On N^{ω}-Nitro-L-Arginine Methyl Ester (L-NAME)-Induced Hypertension And Oxidative Stress In Rats

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Abstract
Introduction: *Ficus exasperata is a medicinal plant with antioxidant and cardio-protective effects. The study investigated the protective potential of extract of Ficus exasperata against N^{ω}-nitro-l-arginine methyl ester (L-NAME)-induced hypertension in rats.*
Methods: *Forty-eight (48) Wistar albino rats were divided into six (6) groups. Group A was the control group, given water ad libitum and feed while Group B was exposed to L-NAME only at 40 mg/kg body weight, Group C-E were treated with L-NAME at 40 mg/kg body weight orally and Ficus exasperata extracts at respective doses of 100 mg/kg, 200 mg/kg and 400 mg/kg body weight orally, Group F was treated with L-NAME at 40 mg/kg body weight and lisinopril at 10 mg/kg. All the groups were treated as specified for 21 days. Blood pressure measurement and electrocardiogram were performed. Markers of oxidative stress and antioxidant were evaluated in the cardiac and renal tissues.*
Results: *In the group treated solely with L-NAME, there was a significant increase in the systolic, diastolic and mean arterial blood pressure and levels of markers of oxidative stress including lipid peroxidation (Malondialdehyde), hydrogen peroxide (H_2O_2) and decrease in nitric oxide (NO). On the other hand, there was significant reduction in the blood pressure and an increase in the activities of reduced glutathione, glutathione peroxidase and supoxide dismutase and decreases in the levels of the markers of oxidative stress toward normal in rats co-treated with Ficus exasperata.*
Conclusion: *The extract exhibited antihypertensive, cardio-protective and antioxidant properties in a L-NAME induced hypertension and could be explored in the management of hypertension.*
Keywords: *Oxidative stress, Ficus exasperata, antioxidant, hypertension*

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I. Introduction

Hypertension, a chronic condition marked by persistently elevated blood pressure, remains a significant global health concern and a leading contributor to cardiovascular diseases, including stroke and heart failure (Luo *et al*., 2020; Sorato *et al*., 2021; Giao *et al*., 2025). Affecting approximately 1 billion individuals worldwide (Del Pinto *et al*., 2022), hypertension is responsible for an estimated 12.8% of annual global deaths (Wang *et al*., 2023). It is widely recognized as one of the most prevalent disorders and a major risk factor for various conditions, including coronary heart disease, atherosclerosis, and stroke (Georges & Bouatia-Naji, 2022; Hetherington & Totary-Jain, 2022; Poznyak *et al*., 2022). Additionally, hypertension has been linked to severe complications affecting kidney function and cerebrovascular health (Miglinas *et al*., 2020). Despite the availability of conventional antihypertensive medications, concerns regarding side effects and drug resistance have prompted research into alternative therapeutic approaches, including the use of medicinal plants. One such plant with potential pharmacological benefits is *Ficus exasperata*, commonly referred to as "sandpaper tree," which has been traditionally used in African and Asian medicine for the treatment of various ailments (Ahmed *et al*., 2012. Akinloye & Ugbaja, 2022a).

Oxidative stress, a condition resulting from an imbalance between free radicals and antioxidants, plays a crucial role in the pathophysiology of hypertension (Rodrigo *et al*., 2011). Growing evidence suggests that

excessive oxidative stress contributes to endothelial dysfunction, inflammation, and vascular remodeling; thereby exacerbating hypertensive conditions (Gallo *et al*., 2022, Shaito *et al*., 2022, Drożdż *et al*., 2023). Given the potential antioxidant and antihypertensive properties of *Ficus exasperata*, investigating its efficacy in managing oxidative stress-induced hypertension is both timely and significant.

The inhibition of nitric oxide (NO) synthesis by Nω-nitro-L-arginine methyl ester (L-NAME) plays a significant role in the development of hypertension, contributing to endothelial dysfunction and vascular complications (Pechanova, *et al*., 2022). Nitric oxide (NO) is a critical vasodilator involved in vascular homeostasis and blood pressure regulation. It is synthesized via nitric oxide synthase (NOS), which exists in three isoforms: neuronal NOS (nNOS), endothelial NOS (eNOS), and inducible NOS (iNOS) (Jankovic *et al*., 2021). NO is released in a Ca^{2+}-dependent manner from vascular endothelial cells, leading to relaxation of blood vessels through the stimulation of soluble guanylyl cyclase and the accumulation of cyclic guanosine monophosphate (cGMP) in smooth muscle cells (Cyr *et al*., 2020; Fernandes *et al*., 2023). Inhibition of NO synthesis by L-NAME, has been widely used to induce experimental hypertension in animal models, resulting in increased oxidative stress, endothelial dysfunction, and systemic inflammation (Cinelli *et al*., 2020). Given its vital role in vascular health, NO regulation remains a key focus in cardiovascular research and therapeutic interventions.

Ficus exasperata Vahl, commonly known as the sandpaper tree, is a deciduous, dioecious species in the Moraceae family, native to tropical Africa and parts of southern Asia (Ajala *et al*., 2020). Traditionally, it has been widely used in African and Asian medicine for its diverse therapeutic applications, including its role in managing conditions such as arthritis, rheumatism, gastrointestinal disorders, and infectious diseases (Ajala *et al*., 2020; Akinloye & Ugbaja, 2022a; Oso & Olaoye, 2023). Various parts of the plant—including its leaves, bark, and roots—are considered medicinally important and have been employed in folklore medicine without apparent toxic effects (Ozioma & Chinwe, 2019; Balick & Cox, 2020).

Phytochemical analysis of *Ficus exasperata* has revealed the presence of bioactive compounds such as flavonoids, tannins, steroids, phlobatannins, and saponins, which are known for their potent antioxidants and anti-inflammatory properties (Oso & Olaoye, 2023). These secondary metabolites help scavenge reactive oxygen species (ROS), regulate oxidative stress pathways, and improve endothelial function, potentially contributing to cardiovascular health. Previous studies have demonstrated the antihypertensive effects of plant extracts through mechanisms such as oxidative stress reduction and vascular relaxation. However, the specific role of *Ficus exasperata* in hypertension, particularly in models induced by Nω-nitro-L-arginine methyl ester (L-NAME), remains underexplored.

Given the increasing interest in plant-derived therapeutics for cardiovascular diseases, further research into the antihypertensive and antioxidant effects of methanol leaf extract of *Ficus exasperata* is crucial for validating its traditional use and understanding its role in oxidative stress-related hypertension. Findings may support the development of plant-based interventions for hypertension and contribute to improved cardiovascular health.

This study was designed to investigate the antihypertensive effects of methanol leaf extract of *Ficus exasperata* in L-NAME-induced hypertensive rats, assess its potential antioxidant activity by measuring oxidative stress biomarkers and provide scientific validation for its traditional use as an antihypertensive agent.

II. Methodology

Experimental Animals

Forty-eight male albino rats were obtained from the animal house of the Faculty of Veterinary Medicine, University of Ibadan with its weight ranging between 120 - 220g. The rats were kept in a well-ventilated cage at optimum temperature and 12 hours light / dark cycle and fed with standard commercial grower's mash and water.

They were given access to clean, well-ventilated cages under hygienic conditions to acclimatize for one week before the commencement of the experiment.

Preparation of Plant Extract

Fresh *Ficus exasperata* leaves were cut, air-dried, blended and soaked in N-hexane for 48 hours. This was done to remove the fat in the leaves. The leaves were sieved and re-dried. The re-dried leaves were then soaked in methanol for 72 hours, then squeezed using a cloth sieve to obtain the extract (fluid) from the leaves. Rotary evaporator was used to concentrate the extracted solution and to remove the methanol through evaporation. The plant extract was then reconstituted with distilled water.

Experimental Design and Dose Regimen

The animals were divided into six (6) groups with eight rats in each group, and the treatment was as follows: Group A, the Control group was given water, Group B was exposed to L-NAME only at 40mg/kg body weight, Groups C-E were treated with L-NAME at 40mg/kg body weight orally as used by Mali *et al*. (2012) and *Ficus exasperata* extract at respective doses of 100 mg/kg, 200 mg/kg and 400 mg/kg body weight orally, Group

F was medicated with L-NAME at 40 mg/kg body weight and lisinopril at 10 mg/kg, respectively for 21 days. The doses of *Ficus exasperate* Vahl used were less than 10 percent of LD_{50} determined and reported by (Akinloye & Ugbaja, 2022b) which was said to be more than 6000 mg/kg

Preparation of Serum and Tissues for Biochemical Assays

The blood was collected with a capillary tube via retro-orbital venous plexus into plain sample bottle. The blood was allowed to clot and centrifuged at 4000 rpm for 10 min to obtain the serum. The serum obtained was stored in a refrigerator at 4 ºC for biochemical analysis.

The rats were sacrificed by cervical dislocation, the animals were quickly dissected and the tissues (kidney and heart) were immediately excised, rinsed with distilled water, blotted with tissue paper, and weighed. They were then chopped into bits and homogenized in a universal bottle placed in a plastic beaker filled with ice cubes. The tissue homogenate in buffer solution (50 mM Tris-HCl pH 7.4) using a Teflon homogenizer. The resulting homogenate was centrifuged at 10,000 g for 5 min in a cold centrifuge (4 °C) to obtain the post mitochondrial fraction. The supernatant was collected and used for biochemical analysis.

Blood Pressure Measurement and Electrocardiography

The systolic, diastolic, and mean arterial blood pressures were determined non-invasively in conscious animals by tail plethysmography using an automated blood pressure monitor, (CODA SI, Kent Scientific Corporation, Connecticut, USA). A standard lead II electrocardiogram was used to record in a conscious rat. From the electrocardiogram, parameter such as heart rate, P-wave duration, PR-interval, QRS duration, R-amplitude, QT segment and QT interval were determined. The rats were anaesthetized with xylazine/ketamine 0.1 ml/100g of rats and was administered intramuscularly.

Biochemical Assay

The serum nitric oxide (NO) was evaluated by calculating the level of nitrite using the Griess reagent and myeloperoxidase activity were determined as described by Akinrinde *et al.* (2021) The level of Malondialdehyde was determined by Varshney & Kale, (1990) while the generation of hydrogen peroxide was estimated by Wolff (1994). The activity of the SOD was determined by Paoletti *et al.* (1986), while the level of the reduced glutathione was evaluated by Beutler *et al*. (1986). The Glutathione-S-tranferase activity was determined according to Coruh *et al.* (2007) while the protein and non-protein thiol were determined as described by Giustarini *et al.* (2012).

Statistical Analysis

The data were expressed as mean ± standard error of mean. The test of significance between two groups was estimated by student's t-test. One-way ANOVA with Tukey's post –hoc test of Graph pad prism 7.0 was carried out. The level of statistical significance was considered as $p< 0.05$.

III. Results

Oral administration of L-NAME alone led to a significant increase in the systolic, diastolic and mean arterial blood pressure when compared to the control group of rats. A significant decrease was however observed in the SBP, DBP and MAP of the hypertensive groups treated with extract at the dosages of 100, 200 and 400 mg/kg body weight and lisinopril (Figure 1). *Ficus exasperata* extract antihypertensive effect was dose-dependent and the effect was comparable to that of lisinopril. A significant increase ($p<0.05$) was observed in the ECG parameters of the hypertensive rats including heart rate, P waves, PR intervals, QRS intervals, QT and QTC intervals. The increases in the ECG parameters were reversed in variable degrees by different doses of the *Ficus exasperata* extract and by the lisinopril to a level that was comparable to those of the control group (Figures 2 and 3). The total protein level in the hypertensive group shows a significant decrease compared to the control, however, *Ficus exasperata* extract increased the levels of total protein in the renal and cardiac tissues and the serum (Figure 4). Co-treatment with extract also had effect on the serum biochemical indices of L-NAME induced hypertensive rats as there was an increase in Nitric Oxide and a significant decrease in MPO ($P<0.05$) levels when compared to the untreated groups. The MPO level was also significantly higher ($P<0.05$) in the hypertensive untreated group compared to the control and the extract treated groups (Figure 5).

In figures 6-11, treatment with the extract at dosages of 100, 200 and 400 mg/kg and lisinopril significantly potentiated the non-enzymatic (GSH, protein thiol and non-protein thiol) and enzymatic (GST, SOD and GPx) antioxidants as there were marked increases in their levels when compared to those of their respective untreated hypertensive group. A significant reduction was found in the antioxidant defense system in both the cardiac and renal tissues of hypertensive rats compared to the control group. There was significant increase in markers of oxidative stress such as H2O2 and MDA in the heart and kidney tissues of hypertensive rats when

compared to the control. Treatment of the extract and lisinopril caused a significant reduction in the levels of the marker of oxidative stress (Figures 12-13).

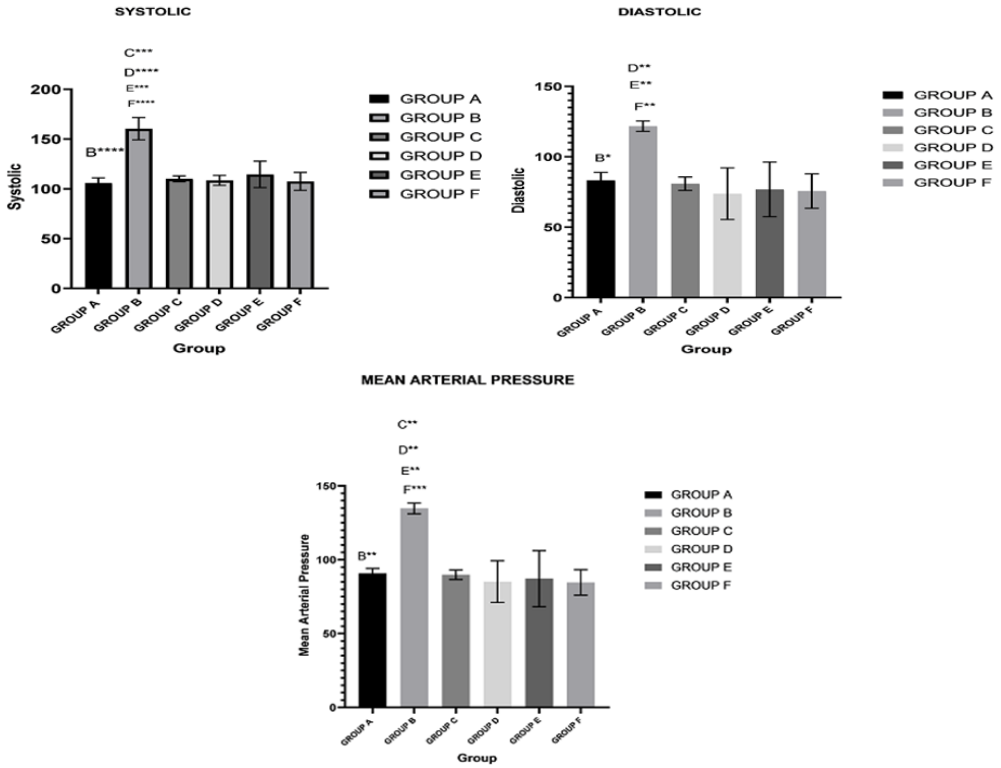

FIGURE 1: Effect of *Ficus exasperata* on the Systolic, Diastolic and Mean Arterial Pressure in L-NAME-induced hypertensive rats.

Group A: the Control group was given water only. Group B was given L-NAME only at 40mg/kg body weight. Groups C-E were treated with L-NAME at 40 mg/kg body weight orally and *Ficus exasperata* extract at respective doses of 100 mg/kg, 200 mg/kg and 400 mg/kg body weight orally. Group F was given L-NAME at 40 mg/kg body weight and lisinopril at 10 mg/kg body weight. Values are expressed as Mean ± SEM. For SBP, DBP and MAP Group A and B showed significant difference with groups represented as superscripts on them ($P< 0.05$).

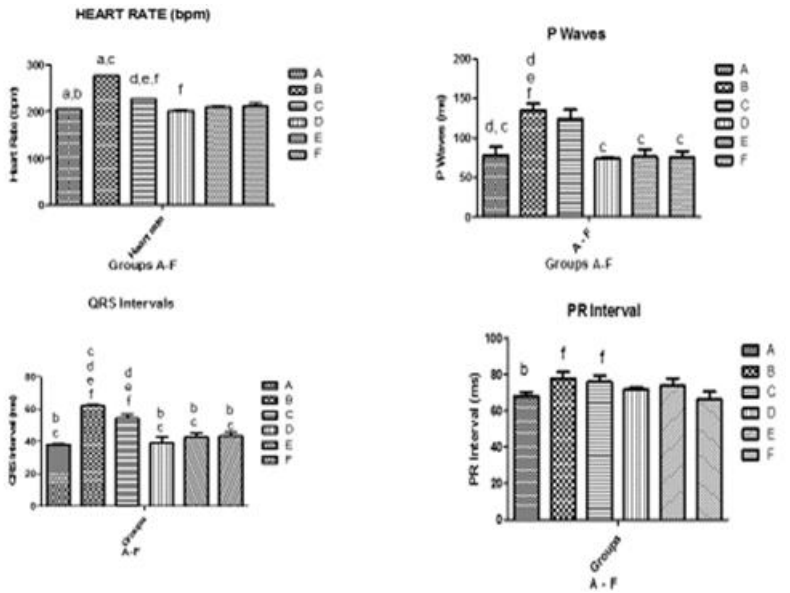

FIGURE 2: Effect of *Ficus exasperata on* the ECG parameters including the heart rate, P waves, QRS complex, and PR interval in L-NAME-induced hypertensive rats.

Group A: the Control group was given water only. Group B was given L-NAME only at 40 mg/kg body weight. Groups C-E were treated with L-NAME at 40 mg/kg body weight orally and *Ficus exasperata* extract at respective doses of 100 mg/kg, 200 mg/kg and 400 mg/kg body weight orally. Group F was given L-NAME at 40 mg/kg body weight and lisinopril at 10 mg/kg body weight. Values are expressed as Mean ± SEM. For the ECG parameters including HR, P waves, QRS Intervals and PR intervals, Group A - F showed significant difference with groups represented as superscripts on them (P< 0.05).

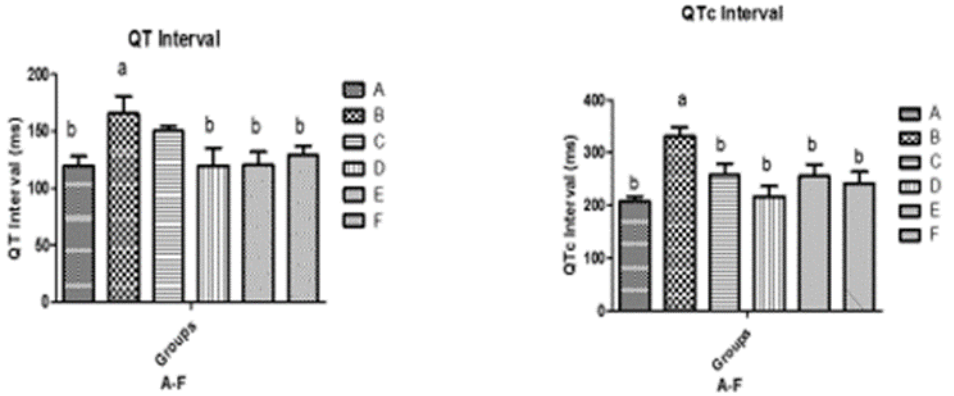

FIGURE 3: Effect of *Ficus exasperata* on the ECG parameters including the QT and QTc, in L-NAME-induced hypertensive rats.

Group A: the Control group was given water only. Group B was given L-NAME only at 40 mg/kg body weight. Groups C-E were treated with L-NAME at 40 mg/kg body weight orally and *Ficus exasperata* extract at respective doses of 100 mg/kg, 200 mg/kg and 400 mg/kg body weight orally. Group F was given L-NAME at 40 mg/kg body weight and lisinopril at 10 mg/kg body weight. Values are expressed as Mean ± SEM. For the ECG parameters including QT intervals and QTc intervals, Group A - F showed significant difference with groups represented as superscripts on them (P< 0.05).

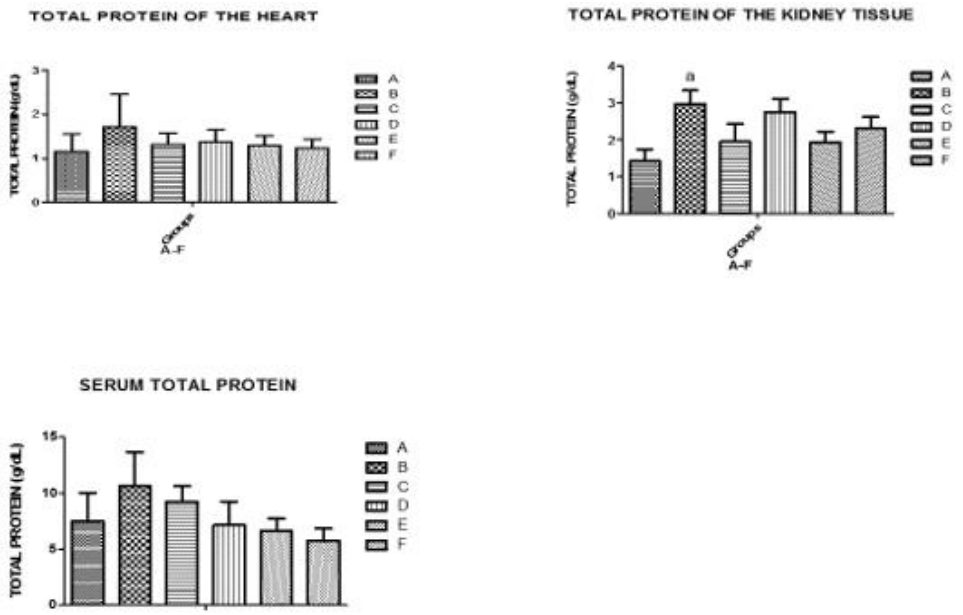

FIGURE 4: Effect of *Ficus exasperata* on the tissue (heart and kidney) and serum Total Protein level in L-NAME-induced hypertensive rats.

Group A: the Control group was given water only. Group B was given L-NAME only at 40 mg/kg body weight. Groups C-E were treated with L-NAME at 40 mg/kg body weight orally and *Ficus exasperata* extract at respective doses of 100 mg/kg, 200 mg/kg and 400 mg/kg body weight orally. Group F was given L-NAME at 40 mg/kg body weight and lisinopril at 10 mg/kg body weight. Values are expressed as Mean ± SEM. For the heart and kidney total protein, Group A - F showed significant difference with groups represented as superscripts on them (P< 0.05). While for the serum TP, there is no significant difference across the groups (P> 0.05).

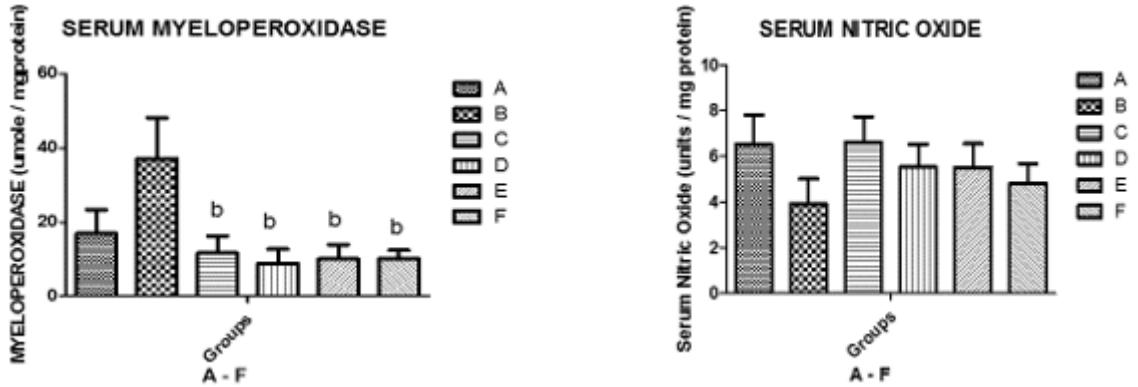

Figure 5: Effect of *Ficus exasperata* on Myeloperoxidase and Nitric Oxide level in the serum of L-NAME-induced hypertensive rats.

Group A: the Control group was given water only. Group B was given L-NAME only at 40 mg/kg body weight. Groups C-E were treated with L-NAME at 40 mg/kg body weight orally and *Ficus exasperata* extract at respective doses of 100 mg/kg, 200 mg/kg and 400 mg/kg body weight orally. Group F was given L-NAME at 40 mg/kg body weight and lisinopril at 10 mg/kg body weight. Values are expressed as Mean ± SEM. Values are expressed as Mean ± SEM. For the serum myeloperoxidase and nitric oxide, Group A - F showed significant difference with groups represented as superscripts on them (P< 0.05).

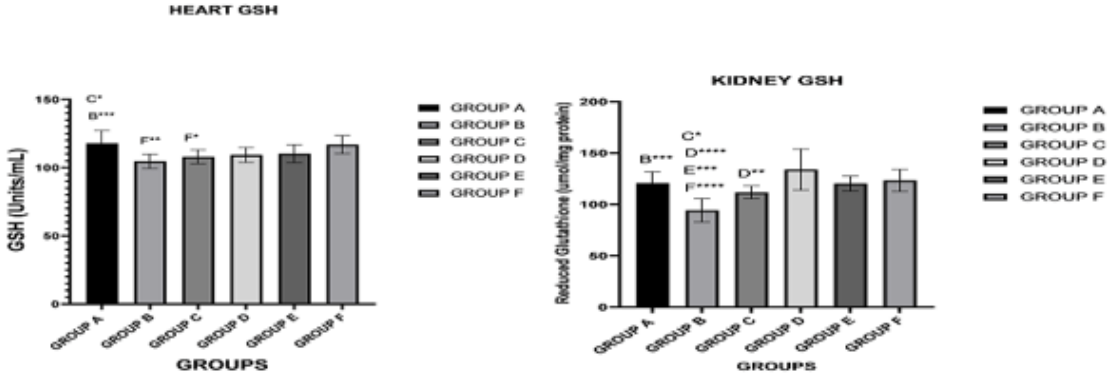

Figure 6: Effect of *Ficus exasperata* on Reduced Glutathione level in the Heart and Kidney of L-NAME-induced hypertensive rats

Group A: the Control group was given water only. Group B was given L-NAME only at 40 mg/kg body weight. Groups C-E were treated with L-NAME at 40 mg/kg body weight orally and *Ficus exasperata* extract at respective doses of 100 mg/kg, 200 mg/kg and 400 mg/kg body weight orally. Group F was given L-NAME at 40 mg/kg body weight and lisinopril at 10 mg/kg body weight. Values are expressed as Mean ± SEM. Values are expressed as Mean ± SEM. For the heart and kidney GSH, Group A - F showed significant difference with groups represented as superscripts on them (P< 0.05).

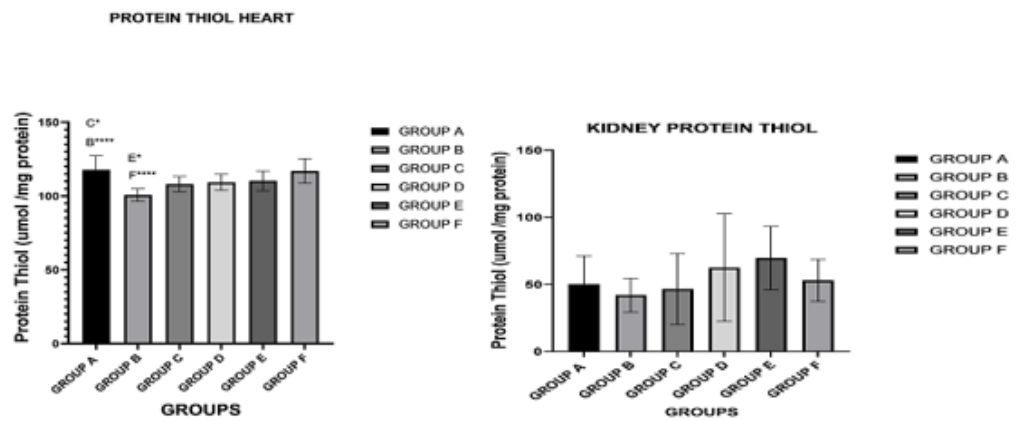

Figure 7: Effect of *Ficus exasperata* on Protein Thiol level in the Heart and Kidney of L-

A: the Group **NAME-induced hypertensive rats** Control group was given water only. Group B was given L-NAME only at 40 mg/kg body weight. Groups C-E were treated with L-NAME at 40 mg/kg body weight orally and *Ficus exasperata* extract at respective doses of 100 mg/kg, 200 mg/kg and 400 mg/kg body weight orally. Group F was given L-NAME at 40 mg/kg body weight and lisinopril at 10 mg/kg body weight

Values are expressed as Mean ± SEM. Values are expressed as Mean ± SEM. For the heart and kidney protein thiol, Group A - F showed significant difference with groups represented as superscripts on them (P< 0.05).

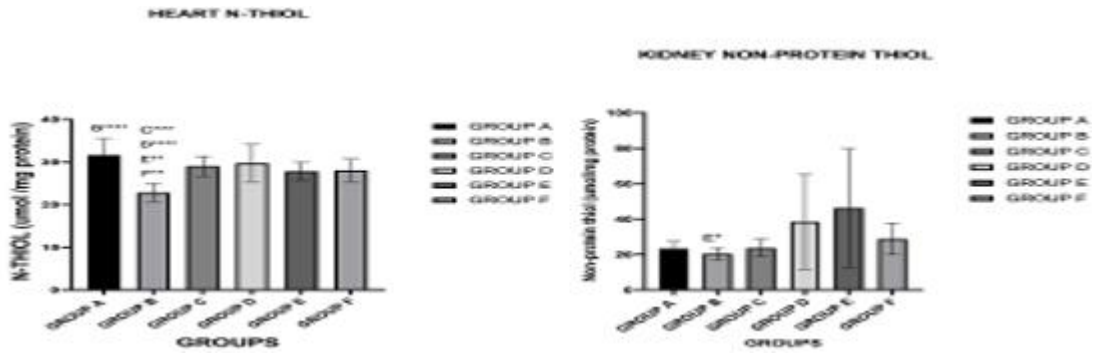

Figure 8: Effect of *Ficus exasperata* on Non-Protein Thiol level in the Heart and Kidney of L-NAME-induced hypertensive rats

Group A: the Control group was given water only. Group B was given L-NAME only at 40 mg/kg body weight. Groups C-E were treated with L-NAME at 40 mg/kg body weight orally and *Ficus exasperata* extract at respective doses of 100 mg/kg, 200 mg/kg and 400 mg/kg body weight orally. Group F was given L-NAME at 40 mg/kg body weight and lisinopril at 10 mg/kg body weight

Values are expressed as Mean ± SEM. Values are expressed as Mean ± SEM. For the heart and kidney non-protein thiol, Group A - F showed significant difference with groups represented as superscripts on them (P< 0.05).

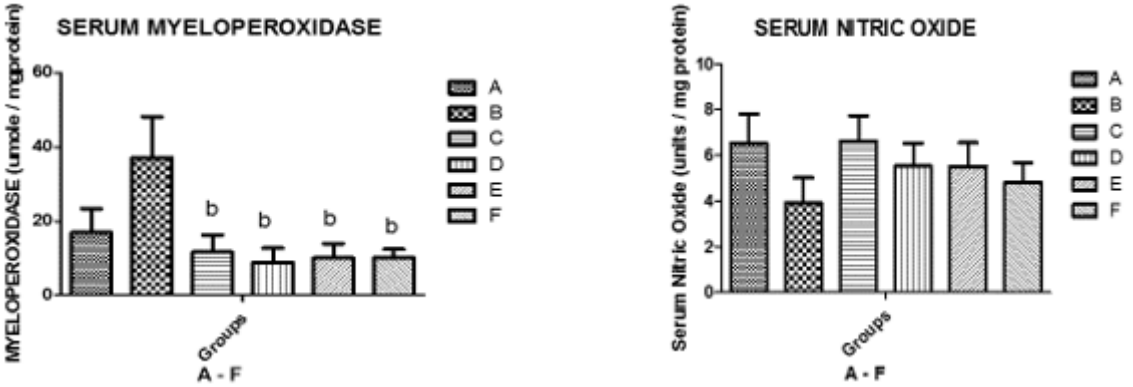

Figure 9: Effect of *Ficus exasperata* on Glutathione-S-Transferase level in the Heart and Kidney of L-NAME-induced hypertensive rats

Group A: the Control group was given water only. Group B was given L-NAME only at 40 mg/kg body weight. Groups C-E were treated with L-NAME at 40 mg/kg body weight orally and *Ficus exasperata* extract at respective doses of 100 mg/kg, 200 mg/kg and 400 mg/kg body weight orally. Group F was given L-NAME at 40 mg/kg body weight and lisinopril at 10 mg/kg body weight

Values are expressed as Mean ± SEM. For the heart and kidney GST, Group A - F showed significant difference with groups represented as superscripts on them (P< 0.05).

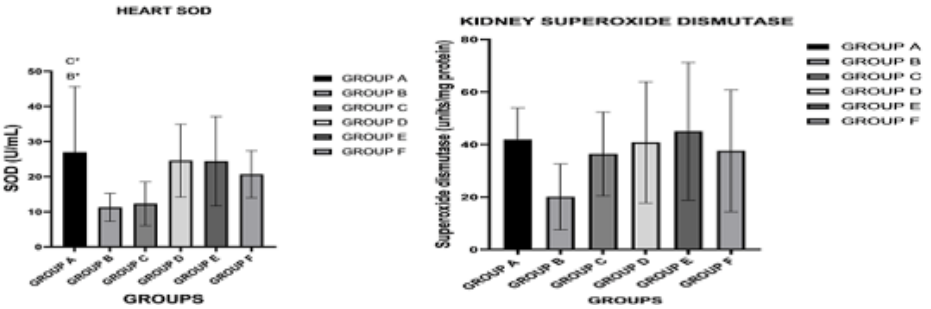

Figure 10: Effect of *Ficus exasperata* on Superoxide Dismutase activities in the Heart and Kidney of L-NAME-induced hypertensive rats

Group A: the Control group was given water only. Group B was given L-NAME only at 40 mg/kg body weight. Groups C-E were treated with L-NAME at 40 mg/kg body weight orally and *Ficus exasperata* extract at respective doses of 100 mg/kg, 200 mg/kg and 400 mg/kg body weight orally. Group F was given L-NAME at 40 mg/kg body weight and lisinopril at 10 mg/kg body weight. Values are expressed as Mean ± SEM. For the heart and kidney SOD, Group A - F showed significant difference with groups represented as superscripts on them ($P < 0.05$).

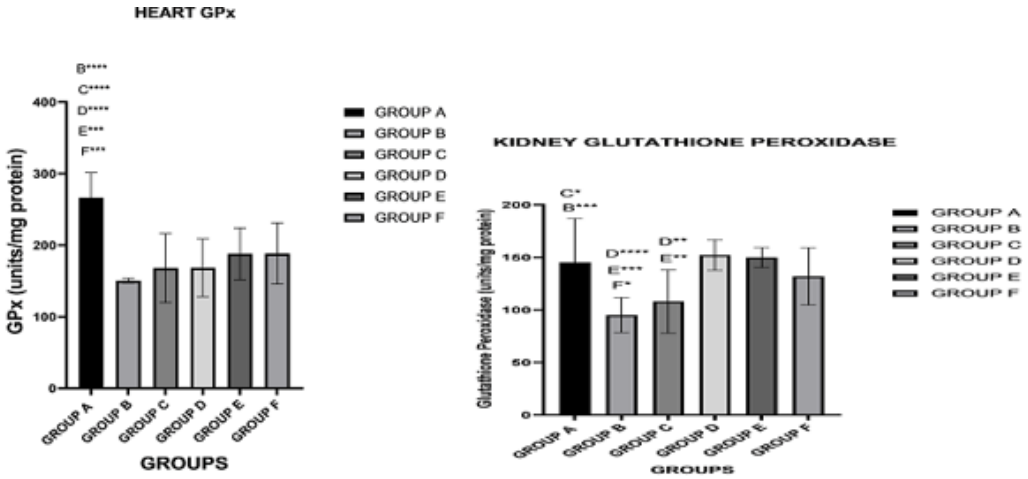

FIGURE 11: Effect of *Ficus exasperata* on Glutathione Peroxidase level in the Heart and Kidney of L-NAME-induced hypertensive rats.

Group A: the Control group was given water only. Group B was given L-NAME only at 40 mg/kg body weight. Groups C-E were treated with L-NAME at 40 mg/kg body weight orally and *Ficus exasperata* extract at respective doses of 100 mg/kg, 200 mg/kg and 400 mg/kg body weight orally. Group F was given L-NAME at 40 mg/kg body weight and lisinopril at 10 mg/kg body weight. Values are expressed as Mean ± SEM. For the heart and kidney GPx, Group A - F showed significant difference with groups represented as superscripts on them ($P < 0.05$).

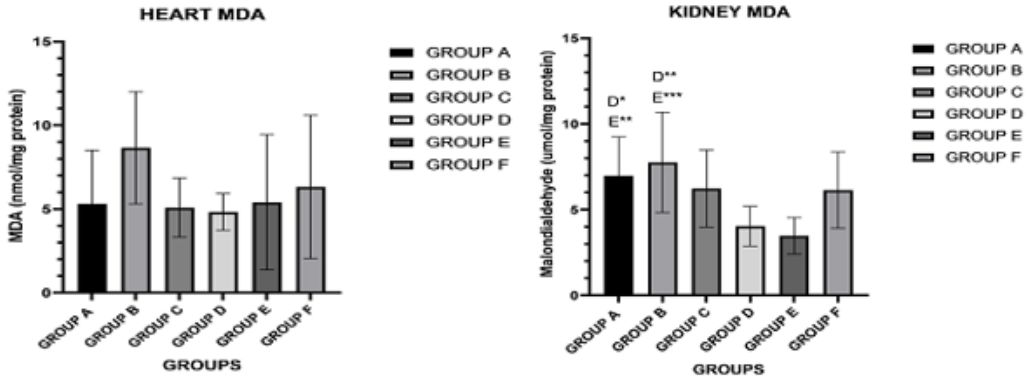

FIGURE 12: Effect of *Ficus exasperata* on Malondialdehyde level in the Heart and Kidney of L-NAME-induced hypertensive rats.

Group A: the Control group was given water only. Group B was given L-NAME only at 40 mg/kg body weight. Groups C-E were treated with L-NAME at 40 mg/kg body weight orally and *Ficus exasperata* extract at respective doses of 100 mg/kg, 200 mg/kg and 400 mg/kg body weight orally. Group F was given L-NAME at 40 mg/kg body weight and lisinopril at 10 mg/kg body weight.

Values are expressed as Mean ± SEM. For the heart and kidney MDA levels, Group A - F showed significant difference with groups represented as superscripts on them (P< 0.05). Groups without superscripts showed that the differences are not significant.

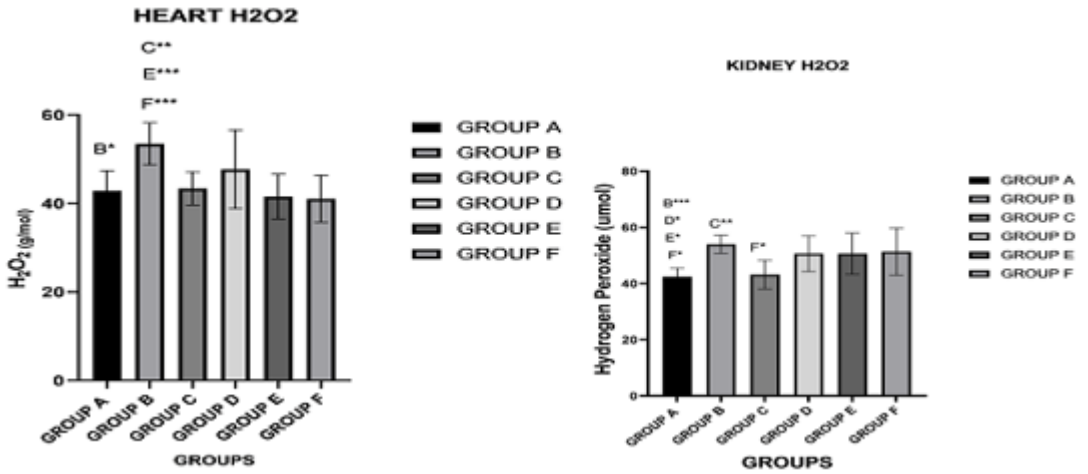

FIGURE 13: Effect of *Ficus exasperata* on Hydrogen peroxide level in the Heart and Kidney of L-NAME-induced hypertensive rats.

Group A: the Control group was given water only. Group B was given L-NAME only at 40 mg/kg body weight. Groups C-E were treated with L-NAME at 40 mg/kg body weight orally and *Ficus exasperata* extract at respective doses of 100 mg/kg, 200 mg/kg and 400 mg/kg body weight orally. Group F was given L-NAME at 40 mg/kg body weight and lisinopril at 10 mg/kg body weight.

Values are expressed as Mean ± SEM. For the heart and kidney hydrogen peroxide, Group A - F showed significant difference with groups represented as superscripts on them (P< 0.05).

IV. Discussion

Increasing awareness of the effectiveness of herbal medicines, besides the apparent side effects of synthetic drugs, has led to an increased interest in herbal medicines. This study reported various clinical, biochemical and markers of oxidative changes in the heart, kidney and serum that accompanied L-NAME-induced hypertension in rats and the ameliorative effect of *Ficus exasperata* extract in comparison to Lisinopril, a standard drug for the management of hypertension. From the electrocardiograph, L-NAME-induced hypertensive rats were observed to have increased in the P wave, QRS complex QT, QTC and PR interval. This impairment of ECG parameters is in line with the previous findings of (Conceição-Vertamatti *et al*., 2020) and also could be attributed to the effect of the decreased Nitric oxide production on vascular smooth muscle tone (Tran *et al*., 2022a). Comparable to findings in the group of rats treated with Lisinopril, rats treated with *Ficus exasperata* at the three doses had complete amelioration of the L-NAME-induced changes in ECG parameters after 21 days of treatment.

Based on the measurements of the Systolic BP (SBP), Diastolic BP (DBP), and the Mean Arterial Blood Pressure (MAP), it was observed that the oral administration of L-NAME was associated with a significant rise in SBP, DBP and MAP compared with the control rats, validating the induction of hypertension. These findings agree with previously described findings where L-NAME induced a prolonged increase in blood pressure (Jaarin *et al*., 2015). Similar to lisinopril, the administration of *Ficus exasperata* caused a significant decline of SBP, DBP and MAP in the hypertensive rats. *Ficus exasperata* decreased the SBP and DBP and MAP in all the doses used with the best anti-hypertensive result seen at the dosage of 200 mg/kg. This observed reduction in blood pressure in treated rats could be attributed to the hypotensive properties of *Ficus exasperata* (Adewole *et al*., 2011; Agunloye & Oboh, 2018). There was no significant difference in the SBP, DBP and MAP of the groups treated with the extracts compared to those treated with lisinopril. This might indicate a similar therapeutic efficacy of the antihypertensive component of *Ficus exasperata* compared to lisinopril.

Considering the changes in some biochemical indices in the tissues and serum of L-NAME hypertensive rats compared to control, it was observed that L-NAME caused depletion of nitric oxide which is associated with various end-organ damages mainly cardiac, renal and vasculature due to structural alterations in the microcirculation of these target organs (Abdel-Rahman *et al*., 2017; Kpemissi *et al*., 2022). In addition to

oxidative stress which appears to play a prominent role in L-NAME-induced hypertension (Jaarin *et al*., 2015; Abd Allah *et al*., 2020), nitric oxide, an endothelium-derived relaxing factor (EDRF), which is biosynthesized endogenously from L-arginine, oxygen, and NADPH by different nitric oxide synthase (NOS) enzymes (Perez & Laughon, 2015) is used by the endothelium (inner lining) of blood arteries to cause surrounding smooth muscle relaxation, thereby resulting in vasodilation and increased blood flow (Tran *et al*., 2022a). Hypertension is usually induced by deletion of the eNOS gene but is surprisingly almost absent after inactivation of other forms of NOS (Tran *et al*., 2022b), probably due to compensatory mechanisms. Studies have shown that flavonoids (Mikail *et al*., 2019) and antioxidant properties (Ajeigbe *et al*., 2021) in *Ficus exasperata are* able to enhance vascular endothelium by the increment of the bioavailability of nitric oxide. In the present study, there was significant decrease in nitric oxide in the hypertensive group whereas the groups treated with *Ficus exasperata* showed non-significant increase in nitric oxide availability by the extracts. The NO bioavailability were better with the extracts than the lisinopril even at the dose of 100 mg/kg, suggesting that the extract has ability to improve and potentiate the nitric oxide availability better than lisinopril.

Myeloperoxidase is a haeme-containing enzyme in mammalian neutrophil that catalyzes the oxidation of chloride ions and other halide ions in phagocytic process. In hypertension, the elevation of circulating levels of myeloperoxidase, possibly due to increased release from damaged cells have been described (Ndrepepa, 2019). Myeloperoxidase is known to catalyze the reaction between H_2O_2 and chloride ions producing hypochlorite (HOCl), an important oxidant in innate immunity and vascular inflammation associated with atherosclerosis, hypertension and ischemia-reperfusion injury. In this study, myeloperoxidase, a marker of inflammation, was significantly increased only in the hypertensive untreated group which confirms the anti-inflammatory properties of *Ficus exasperata* extracts. The level of MPO was lowered by all the doses of extracts comparable to that of lisinopril with the dosage of 200mg/kg of extract giving the best result and a better effect than lisinopril. The level of myeloperoxidase in the control was comparable to the level in the lisinopril treated groups.

Ficus exasperata was observed to have a modulating effect on oxidative stress biomarkers and antioxidant profile in L-NAME-induced hypertensive rats in a similar way to lisinopril. Oxidative stress is known to be a primary cause in the pathogenesis of hypertension due to endothelial cell dysfunction (Amponsah-Offeh *et al*., 2023). Growing evidence suggest a crosslink between nitric oxide deficiency and development of oxidative stress in the onset and progression of vascular impairments (Incalza *et al*., 2018). During the normal physiology, NO reduces superoxide anion (O^{2-}) production through a sustained suppression of NADPH oxidase, the major source of vascular oxygen radicals. In line with (Öktem *et al*., 2011), it shows that administration of L-NAME is associated with increased production of reactive oxygen and nitrogen species (ROS/RNS) and subsequently oxidative stress in both heart and kidney. Malondialdehyde (MDA) is a pro-oxidant produced as secondary metabolite of lipid peroxidation (LPO) and indirectly reflects the oxidative degeneration of polyunsaturated fatty acids (Demirci-Çekiç *et al*., 2022). In the present study, H_2O_2 and MDA were increased in the cardiac and renal tissues of L-NAME group. Additionally, a marked depletion of endogenous antioxidants such as reduced glutathione (GSH), superoxide dismutase (SOD), and glutathione peroxidase (GPx) was observed. These findings suggest that the L-NAME blood pressure-raising mechanism might not solely depend on nitric oxide (NOS) inhibition but may involve oxidative stress (Jaarin *et al*., 2015). Daily administration of *Ficus exasperata* was able to counteract the decrease in the antioxidant reserve in hypertensive rats. *Ficus exasperata* at the three dose levels restored GSH contents in cardiac and hepatic tissues and normalized MDA content in the cardiac, when compared to normal and lisinopril groups.

The thiols are organic compounds that contain sulphydryl group which constitute the major portion of the total body antioxidants which play an important role in defense against reactive oxygen species. Both intracellular and extracellular thiols are components of total thiol. In the present study, the levels of both protein and non-protein thiol decreased in the L-NAME group compared with the control group. These findings are in agreement with a study that found that the level of thiol reduced in some disease conditions (Altiparmak *et al.*, 2016). Treatment of *Ficus exasperata* and lisinopril caused a significant increase in the total thiol level and this gives further credence to the antioxidant property of *Ficus exasperata*.

Based on this study, all our findings indicate that supplementation with methanol extract of *Ficus exasperata* might be a safe and useful alternative in managing hypertension. Co-treatment with *Ficus exasperata* produced ameliorative effects through antihypertensive, antioxidant and anti-inflammatory activities.in hypertensive rats. There is needed for the isolation of the active ingredients in *Ficus exasperata* and further studies on the compounds therein in the pathway to drug development.

V. Conclusion

Taken together, all the results from the study indicate that methanol leaf extract of *Ficus exasperata* therapy might prove to be useful in combating hypertension. L-NAME-induced rats treated with *Ficus exasperata* extract had their systolic, diastolic and mean arterial pressure effectively lowered to a level comparable to that of the normotensive animals. *Ficus exasperata* extract also reduced the levels of markers of oxidative stress and

potentiated the antioxidant defense mechanism. These findings support the claim that *Ficus exasperata* leaves possess antioxidant and antihypertensive properties hence can be used for the management of hypertension with less side effects.

Conflict of Interest

Authors declare that there is no conflict of interest.

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