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## Preventive effects of aqueous extract of the whole plant of *Eleusine indica* (Linn) Gaertn. (Poaceae) against L-NAME induced nephrotoxicity in rat

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### ABSTRACT

**Background:** The entire plant of *Eleusine indica* is used in Cameroonian folk medicine to treat several diseases including renal problems. We investigated the preventive effects of *Eleusine indica* aqueous extract (EIAE) against L-NAME induced renal damages in rats. **Methods:** Animals were divided into a control group (0.9 % saline, 10 mL/kg, ip) and 4 experimental groups. The rats in the negative control group received L-NAME (30 mg/kg, ip). The positive group was treated with losartan (12.5 mg/kg, *per os*) and L-NAME while the two last groups received EIAE (100 mg/kg or 200 mg/kg, *per os*) and L-NAME injection. After 60 days of treatment, blood pressure was measured; lipid profile, kidney and some oxidative stress parameters were evaluated. **Results:** Intraperitoneal injection of L-NAME induced a significant elevation in blood pressure, of total cholesterol, triglycerides and LDL-c, with a significant reduction of HDL-c levels as compared to the control groups. Nephrotoxicity was evidenced by significant elevation in serum levels of creatinine, urea and  $K^+$ , accompanied by a significant reduction of  $Na^+$  and GFR as compared to controls. Catalase, GSH and nitrites were significantly decreased in L-NAME injected group. L-NAME solution gave simultaneously with *Eleusine indica* prevented the rise of blood pressure, improve lipid profile, kidney function and antioxidant defenses. **Conclusion:** These results confirm the nephroprotective effects of *Eleusine indica* aqueous extract and highlight its protective properties in L-NAME-induced renal failure and its antioxidant capacities against kidney damages.

**Keywords:** *Eleusine indica*, L-NAME, nephroprotective effect, oxidative stress, rat.

### INTRODUCTION

Nitric oxide (NO) is mainly produced by the endothelium and plays an important role in local circulatory control [1]. The bioavailability depletion of this molecule contributes to the impairment of cardiovascular function which leads to the activation of the renin-angiotensin system (RAS) and consequently angiotensin II production [2]. Angiotensin II causes inflammation, production of reactive oxygen species, blood pressure elevation and may also be involved in hypertension-induced tissue damage [3]. Uncontrolled hypertension with associated endothelial damage leads to progressive renal function impairment in essential hypertension and increases cardiovascular morbidity and mortality [4]. Experimental models have been used to evaluate biological effect of drug on renal failure (nephrectomy, tissue extirpation and nephrotoxicity of chemical or drug) [5]. Short-term administration of a NO synthase (NOS) inhibitor results in an increase in the arterial pressure of rat [6]. Experimental chronic administration of N-G-nitro-L-arginine methyl ester (L-NAME) causes sustained hypertension in rats, which continued NO synthesis inhibition induces chronic hypertension remains to be identified [7]. L-NAME is known to increase the production of reactive oxygen species (ROS) [8]. Considering that oxidative stress is involved in L-NAME-induced toxicity, so, antioxidants could counteract with reactive oxygen species in L-NAME-induced hypertension in rats. *Eleusine indica* has been found to possess antioxidant activity in CCl<sub>4</sub>-mediated oxidative hepatic damage in rats [9]. *Eleusine indica* commonly called Wiregrass (Poaceae family) is used in traditional medicine to stimulate sweat, as a diuretic, to treat cough [10]. The decoction possesses anti-helminthic and febrifuge activities. The seed is sometimes used in the treatment of liver disorders. Studies have shown that C-glycosylflavones from *Eleusine indica* have anti-inflammatory effects on lipopolysaccharide-induced lung airway inflammation in mice [9]. The infusion of aerial parts of *Eleusine indica* is used in Brazil against pneumonia [11]. Information provided by traditional healers in Center Region of Cameroon indicates that the whole plant of *Eleusine indica* is used in the management of renal problems. Thus, we investigated the effects of the aqueous extract of *Eleusine indica* in L-NAME induced-nephrotoxicity in rats.

## MATERIAL AND METHODS

### Preparation of plant extract

*Eleusine indica* whole plant was harvested at Ngoa-Ekelle, Yaoundé (Center Region of Cameroon) in January 2015. The plant was authenticated at the National Herbarium of Yaoundé by Mister Ngansop Tchatchouang Eric, where a specimen (voucher N° 8356 SRF/CAM (YA)) was deposited. The fresh plant was washed thoroughly tap water, air dried at room temperature and reduced in powder. The powder (300 g) was boiled in 5 L of tap water during 20 minutes following the traditional healer's instructions. The decoction was filtered through Whatman No. 3 filter paper then, dried in the oven (45°C), giving 15.8 g of the aqueous extract (yield 5.27 %).

### Phytochemical profile

Phytochemical analyses of the aqueous extract were done following the procedures described by Sofowora [12] and Ayoola *et al.* [13]. The groups of compounds tested were alkaloids, saponins, flavonoids, cardiac glycosides, phenols, lipids, sugars and tannins.

### Animals

Twenty five male *Wistar* rats of 12 weeks old, weighting between 160-200 g were obtained from the animal house of the Department of Animal Biology and Physiology, Faculty of Science, University of Yaoundé 1, Cameroon. Animals were maintained under standard laboratory conditions (natural luminosity cycle) with free access to standard food and tap water. All procedures in this study followed the principles of laboratory animal use and care of the "European community" guidelines (EEC Directive 2010/63/EEC) and were approved by the "Animal Ethical Committee" of the Faculty of Science, University of Yaounde 1.

### Experimental procedure

Animals were randomly divided into five groups of five rats each: group I served as control and was treated intraperitoneally (ip) with 0.9 % NaCl simultaneously with distilled water (10 mL/kg, *p o*); Group II (negative control) received an injection of L-NAME (30 mg/kg) + distilled water (10 mL/kg, *p o*); Group III (positive control) received L-NAME (30 mg/kg, ip) + losartan (12.5 mg/kg, *p o*); Group IV and V received L-NAME(30 mg/kg, ip) + *Eleusine indica* aqueous extract (100 or 200 mg/kg). All groups received the treatment once a day for 60 days.

### Hemodynamic parameters recording

At the end of the experimental period, arterial blood pressure and heart rate of all rats were measured. The rats were anesthetized using urethane (1.5 g/kg, *ip*). The trachea was exposed and cannulated to facilitate spontaneous breathing. The arterial blood pressure was recorded by using the method of Van Vliet *et al.* [14].

### Assessment of kidney function and lipid parameters

Immediately after hemodynamic parameters measurement, blood was collected from carotid artery into clean dry test tubes. Serum was separated by centrifugation (3000 rpm at 4°C for 15 min) and collected for the determination of serum total cholesterol and HDL-cholesterol (HDL-c), triglycerides, uric acid, creatinine, urea, sodium (Na<sup>+</sup>) and potassium (K<sup>+</sup>) using commercial kit according to the instructions provided by the manufacturer. The LDL-cholesterol (LDL-c) levels were determined using the Friedewald *et al.* [15] formula: LDL-cholesterol (mg/dL) = total cholesterol - (triglycerides/5) - HDL-c. Glomerular filtration rate (GFR) was determined using the following formula [16]:

$$\text{GFR (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight}) \times k}{\text{Creatininemia } (\mu\text{mol/L})}$$

Weight in kg, age in year and k (coefficient) = 70

### Assessment of renal oxidative stress

Homogenate (20%) of kidney were prepared in Tris-HCl buffer solution (pH 7.4) and centrifuged at 3000 rpm at 4°C for 25 minutes. The supernatant was collected and stored at -20°C for further analyses. Reduced glutathione (GSH) was determined using respectively the procedures of Wilbur *et al.* [17] and Ellman [18]. Superoxide dismutase (SOD) and catalase were assessed as respectively described by Misra and Fridovich [19] and Sinha [20]. The nitrites concentration in tissue was measured by Griess method [21].

### Statistical Analysis

Values were expressed as mean ± standard error of mean (S.E.M). Analysis was performed using one-way analysis of variance (ANOVA) followed by the Turkey post hoc test. P<0.05 was considered significant. All analyses were performed using GraphPad Prism software 5.03 version.

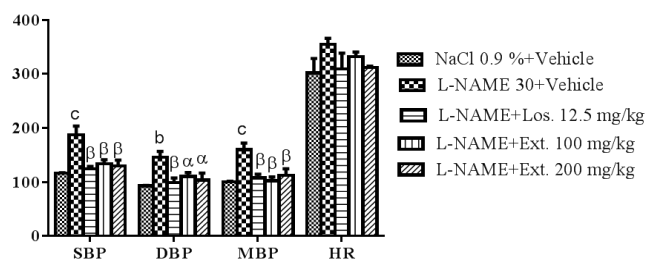
## RESULTS

### Phytochemistry profile

The aqueous extract of *Eleusine indica* contains primary as well as secondary metabolites: Alkaloids, saponins, flavonoids, cardiac glycosides, phenols and tannins were present, whereas lipids and sugars were absent.

### Preventive effects of the aqueous extract of *Eleusine indica* on L-NAME-induced hypertension in rats

As shown in Fig. 1, daily administration of L-NAME for 60 days caused a significant increase in systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean blood pressure (MBP) respectively by 61.21 % (p<0.001), 57.63 % (p<0.01) and 59.04 % (p<0.001) in comparison with normotensive rats. *Eleusine indica* aqueous extract (100 and 200 mg/kg) or losartan (12.5 mg/kg) significantly prevented the increase in these parameters as compared to L-NAME-induced hypertensive rats. The plant extract significantly prevented (p<0.01) the increase of SBP by 28.77 % (100 mg/kg) and 30.63 % (200 mg/kg) in comparison to L-NAME control rats. The increase of DBP was significantly prevented (p<0.05) by 24.67 % and by 28.87 % respectively at the doses of 100 and 200 mg/kg as compared to hypertensive rats. Likewise, the extract induced a decrease (p<0.01) of MBP respectively by 35.98 % (100 mg/kg) and by 29.56 % (200 mg/kg) as compared to hypertensive animals. There was no significant difference in heart rate in of all groups.



Each bar represents means ± S.E.M. of 5 rats. bp<0.01, cp<0.001 significantly different compared to normal rats. ap<0.05, bp<0.01, significantly different compared to L-NAME treated rats. L-NAME 30: L-NAME 30 mg/kg; Los. 12.5 mg/kg: losartan 12.5 mg/kg; Ext. 100 mg/kg: Extract 100 mg/kg; Ext. 200 mg/kg: Extract 200 mg/kg. SBP (systolic blood pressure), DBP (diastolic blood pressure) and MBP (mean blood pressure) in mmHg; HR (heart rate) in beat/min.

**Figure 1:** Effects of the aqueous extract of *Eleusine indica* on cardiovascular hemodynamic parameters

**Eleusine indica improves lipid profile on L-NAME induced-nephrotoxicity in rats**

Daily administration of L-NAME for 60 days caused a significant increase in total cholesterol, TG, LDL-cholesterol levels, and a significantly decrease in HDL-cholesterol as compared to the control group respectively by 34.82 % (p<0.05), by 48.72 % (p<0.05), by 250.65 % (p<0.001) and by 42.13 % (p<0.05) in comparison to L-NAME group (Table 1). Concomitant administration of the plant

extract (200 mg/kg) significantly prevented (p<0.01) the increase of total cholesterol by 36.51 % as compared to L-NAME treated rats. The plant extract (100 mg/kg) inhibited the increase of LDL-cholesterol and the decrease of HDL-cholesterol respectively by 94.98 % (p<0.001) and by 85.36 % (p<0.01); whereas the dose of 200 mg/kg inhibited the increase of LDL-cholesterol and the decrease of HDL-cholesterol respectively by 81.34 % (p<0.01) and by 60.65 % (p<0.05) as compared to L-NAME treated animals. Losartan used in the same condition significantly prevented the change in lipid parameters.

**Table 1:** Preventive effects of the aqueous extract of *Eleusine indica* on lipid profile on L-NAME-treated rats

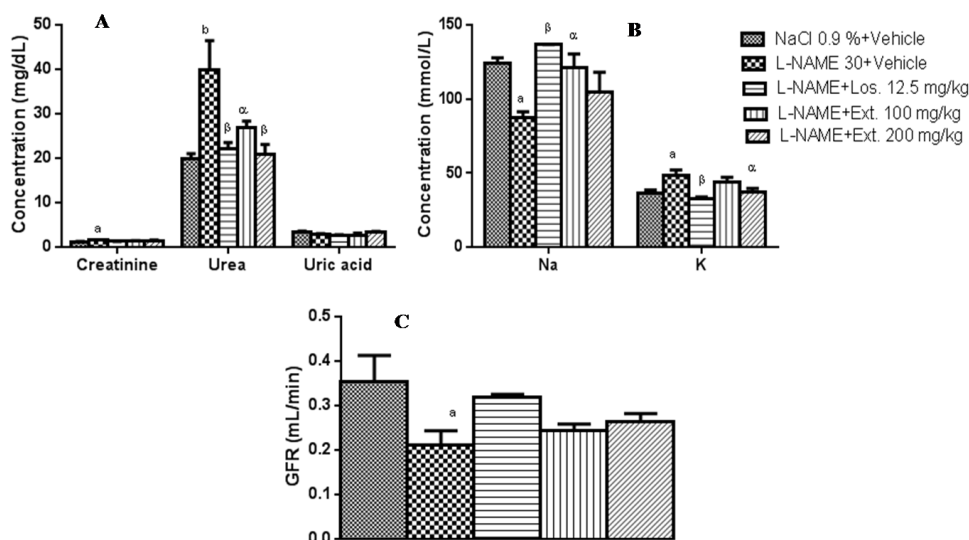
| Parameters                | Groups              |                           |                          |                         |                         |
|---------------------------|---------------------|---------------------------|--------------------------|-------------------------|-------------------------|
|                           | NaCl 0.9 %+ Vehicle | L-NAME 30+ vehicle        | L-NAME + Los. 12.5 mg/kg | L-NAME + Ext. 100 mg/kg | L-NAME + Ext. 200 mg/kg |
| Total cholesterol (mg/dL) | 62.18±4.48          | 83.83±2.77 <sup>a</sup>   | 63.83±2.12 <sup>a</sup>  | 65.36±2.94              | 53.22±7.69 <sup>β</sup> |
| Triglycerides (mg/dL)     | 90.23±7.22          | 134.18±11.81 <sup>a</sup> | 75.93±13.50 <sup>β</sup> | 141.54±4.21             | 139.79±7.56             |
| HDL-c (mg/dL)             | 33.40±1.70          | 19.33±4.86 <sup>a</sup>   | 33.80±4.49 <sup>a</sup>  | 37.69±1.15 <sup>β</sup> | 35.83±1.91 <sup>a</sup> |
| LDL-c (mg/dL)             | 10.74±4.01          | 37.66±4.15 <sup>c</sup>   | 14.85±3.57 <sup>β</sup>  | 6.82±3.15 <sup>γ</sup>  | 14.82±3.80 <sup>γ</sup> |

Values represent means ± S.E.M. of 5 rats. <sup>a</sup>p<0.05, <sup>c</sup>p<0.001 significantly different compared to normal rats. <sup>β</sup>p<0.01, <sup>γ</sup>p<0.001, significantly different compared to L-NAME treated rats. L-NAME 30: L-NAME 30 mg/kg; Los 12.5 mg/kg; losartan 12.5 mg/kg; Ext. 100 mg/kg; Extract 100 mg/kg; Ext. 200 mg/kg; Extract 200 mg/kg. HDL-c: HDL-cholesterol; LDL-c: LDL-cholesterol.

**Eleusine indica prevents L-NAME-induced changes in kidney function**

Fig. 2 (A, B and C) illustrates the effects of the aqueous extract of *Eleusine indica* on some parameters of kidney function. Concomitant administration of distilled water and L-NAME caused a significant increase in serum levels of creatinine, urea and K<sup>+</sup> and significant reduction (p<0.05) of the level of Na<sup>+</sup> and GFR in comparison to L-

NAME group. The extract (100 mg/kg) prevented (32.43 %, p<0.05) the increase in serum concentration of urea and the decrease in serum Na<sup>+</sup> (38.81 %) as compared to L-NAME treated group. The increase of urea and K<sup>+</sup> ions was inhibited respectively by 47.77 % (p<0.01) and 23.20 % (p<0.05) when the extract was administered at 200 mg/kg. Lorsatan treatment significantly improved urea, Na<sup>+</sup> and K<sup>+</sup> concentration.



Each bar represents means ± S.E.M. of 5 rats. <sup>a</sup>p<0.05, <sup>b</sup>p<0.01 significantly different compared to normal rats. <sup>c</sup>p<0.05, <sup>β</sup>p<0.01, significantly different compared to L-NAME treated rats. L-NAME 30: L-NAME 30 mg/kg; Los. 12.5 mg/kg; losartan 12.5 mg/kg; Ext. 100 mg/kg; Extract 100 mg/kg; Ext. 200 mg/kg; Extract 200 mg/kg, GFR: glomerular filtration rate.

**Figure 2:** Preventive effects of the aqueous extract of *Eleusine indica* on kidney function

**Eleusine indica aqueous extract prevents renal oxidative stress in L-NAME-induced nephrotoxicity**

Table 2 shows the effects of *Eleusine indica* extract on some parameters of oxidative stress in kidney. L-NAME injection induced a significant decrease of catalase (66.67%, P<0.01), GSH (38.88 %, p<0.01) and nitrites (23.33 % %, p<0.01) as compared to control group. Concomitant administration of L-NAME with plant extract

significantly (p<0.01) prevented the decrease in catalase activity by 225.00 % at the dose of 200 mg/kg. The plant extract exhibited an inhibition of GSH concentration by 63.64 % (p<0.01, 100 mg/kg) and 100.00 % (p<0.001, 200 mg/kg). Furthermore, the extract significantly (p<0.001) prevented the decrease in nitrites level by 67.39 % at the dose of 200 mg/kg. Losartan administered in the same condition significantly prevented the change in catalase activity, as well as GSH concentration.



**Table 2:** Preventive effects of *Eleusine indica* aqueous extract on some markers of oxidative stress

| Parameters  | Groups                 |                        |                             |                            |                            |
|---|------------------------|------------------------|-----------------------------|----------------------------|----------------------------|
|   | NaCl 0.9 %+<br>Vehicle | L-NAME 30+<br>Vehicle  | L-NAME +<br>Los. 12.5 mg/kg | L-NAME +<br>Ext. 100 mg/kg | L-NAME +<br>Ext. 200 mg/kg |
| SOD (U/g of tissue)   | 27.08±2.85             | 19.02±4.42             | 28.02±10.59                 | 28.65±6.58                 | 27.08±2.86                 |
| GSH (mmol/g of tissue)  | 0.18±0.02              | 0.11±0.01 <sup>a</sup> | 0.17±0.01 <sup>a</sup>      | 0.18±0.01 <sup>β</sup>     | 0.22±0.01 <sup>γ</sup>     |
| Catalase (μmol of H <sub>2</sub> O <sub>2</sub> /min/g of tissue) | 0.24±0.04              | 0.08±0.01 <sup>a</sup> | 0.24±0.03 <sup>a</sup>      | 0.21±0.04                  | 0.26±0.03 <sup>β</sup>     |
| Nitrites (μM)   | 0.6±0.32               | 0.46±0.20 <sup>b</sup> | 0.50±0.22                   | 0.56±0.24                  | 0.77±0.35 <sup>γ</sup>     |

Each value represents means ± S.E.M. of 5 rats. <sup>a</sup>p<0.05, <sup>b</sup>p<0.01 significantly different compared to normal rats. <sup>a</sup>p<0.05, <sup>β</sup>p<0.01, <sup>γ</sup>p<0.001 significantly different compared to L-NAME treated rats. L-NAME 30: L-NAME 30 mg/kg; Los. 12.5 mg/kg: losartan 12.5 mg/kg; Ext. 100 mg/kg: Extract 100 mg/kg; Ext. 200 mg/kg: Extract 200 mg/kg, SOD: superoxide dismutase; GSH: reduced glutathione.

## DISCUSSION

Hypertension is the major risk factor for many diseases such as stroke, heart diseases and renal failure [22]. Several plants are used in traditional medicine as effective antinephrotic drug. *Eleusine indica* plant is traditionally used to treat renal failure. The preventive effects of the whole plant aqueous extract of *Eleusine indica* against L-NAME induced nephrotoxicity in rat were investigated.

In this study, SBP, DBP and MBP were increased in rats receiving L-NAME as compared to control rats. It is well documented that, a deficiency in NO production provokes a vasoconstriction due to the increase in vascular resistance and consequently high blood pressure [23]. L-NAME is a NO synthase (NOS) inhibitor. When administered, it causes a prompt increase in the arterial pressure due to NO deficiency and the raise in oxidative stress increases [6]. The concomitant administration of L-NAME and aqueous extracts of *Eleusine indica* prevented the rise in blood pressure of L-NAME treated rats. These results suggest the biological activity of *Eleusine indica* on some parameters involved in the initiation process of high blood pressure. These structures imply vascular resistance, peripheral muscle tone, myocardial contractility and volume overload. Phytochemical studies have revealed that the aqueous extract of *Eleusine indica* contains flavonoids, whose antihypertensive activities have been documented including the preservation of endothelium integrity and relaxation of vascular smooth muscle fibers [24].

Chronic L-NAME administration caused a significant increase in serum levels of total cholesterol, triglycerides and LDL-C, with a concomitant decrease of HDL-C as compared to control rats. Saravanakumar and Raja [25] obtained similar results after oral administration of L-NAME to rats for 4 weeks at the dose of 40 mg/kg. In fact, L-NAME administration lowers the activity of hepatic carnitine palmitoyltransferase the rate-limiting enzyme of fatty acid oxidation, leading to hyperlipidemia. The hypolipidemic potential of *Eleusine indica* may therefore be due, at least in part to the stimulation of fatty acid oxidation, related to the presence of alkaloids and phenols involved in lipid metabolism. Phytochemical studies revealed the presence of phenols and alkaloids compounds whose hypolipidemic activities were shown. Phenols bind to cholesterol in the digestive tract in order to prevent their intestinal reabsorption and to increase their elimination [26]. Alkaloids stimulate hepatic catabolism of LDL to HDL and reduction in the level of LDL in favor of HDL leading to the reduction in cholesterol [27].

These results showed that L-NAME injection in rats increased the concentration of creatinine and urea, and the reduction of GFR. These results indicate nephrotoxicity. It is well known that angiotensin II (Ang II) induces peripheral vasoconstriction and results to thickening and arterial stiffness. In the kidney, Ang II inhibits renal function, resulting in the increase in renal vascular resistance and capillary glomerular pressure (P<sub>GC</sub>), and also the decrease in glomerular filtration rate (GFR) [8]. Creatine breakdown and its clearance are indicators allowing suspecting alteration of the glomerular filtration rate [28]. It is well known that renal failure is characterized by the impairment of

glomerular filtration which induced the increase of urea concentration [29]. In addition, the enhancement of serum creatinine and urea are used as indicator of renal dysfunction [30, 31]. *Eleusine indica* aqueous extract counteracted these effects contributing to improve glomerular filtration in rats receiving both L-NAME injection and plant extract. The protective role of *Eleusine indica* aqueous extract may be explained by its capacity to prevent the increase in renal vascular resistance, P<sub>GC</sub>, and GFR due to the inhibition of NO synthesis and Ang II sensibility.

We observed a significant increase in serum level of potassium, with a significant depletion in sodium level in L-NAME treated rats as compared to controls. These results are different to those obtained by Yang and Chen [3]. The decrease of Na<sup>+</sup> and the increase of K<sup>+</sup> observed in this study are probably due to the generation of free radicals and the inhibition of Na<sup>+</sup>-K<sup>+</sup> ATPase pump. The concomitant administration of L-NAME and the aqueous extract of *Eleusine indica* has decreased the level of K<sup>+</sup> and an increased of Na<sup>+</sup>, suggesting that the extract might interfere with the generation of free radicals and the inhibition of Na<sup>+</sup>-K<sup>+</sup> ATPase pump. Indeed, cardiac glycosides and phenols present in the extract act by stimulating the synthesis of the genes responsible of cellular regeneration of renal tissue [32].

The administration of L-NAME induced a significant decrease in the GSH, nitrites concentrations and catalase activity suggesting that L-NAME causes severe oxidative stress [8, 33]. Therrien *et al.* [34] reported that NO has a role in the occurrence of renal failure caused by L-NAME because the absence of NO could contribute to tubular damage. L-NAME inhibits the activity of eNOS at two levels: either by directly inhibiting its activity or by down-regulating the expression of its mRNA. The administration of the aqueous extract of *Eleusine indica* has almost normalized the level of antioxidant defence, suggesting that the extract may prevent the generation of free reactive oxygen species and the destruction of cell membranes. This could be explained by the antioxidant activity and modulatory effects of the bioactive compounds contained in this extract. These biological activities of the extract may be linked to the presence of secondary metabolites including flavonoids, tannins, alkaloids which scavenge ROS from cells [35].

## CONCLUSION

The administration of L-NAME for 60 days results in the increase of systemic blood pressure. Hypercholesterolemia and hypertriglyceridemia were also observed. Furthermore, renal parameters creatinine, urea and K<sup>+</sup> increased while, Na<sup>+</sup> and GFR decreased. Antioxidant status has shown a decrease of catalase activity, nitrites and GSH concentration. However, concomitant administration of L-NAME with the plant extract prevented blood pressure elevation, improved lipid profile, renal parameters and antioxidant status. These results suggest that *Eleusine indica* aqueous extract exhibited nephroprotective effects. These effects could be due to its antioxidant activity and attests the traditional use of the whole plant of *Eleusine indica* in the management of renal problems.

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