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Nephroprotective Property of *C. chayamansa* Aqueous Leaf Extract in Diabetic Rats

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Authors' contributions

This work was carried out in collaboration among all authors. Author JDD designed the study, wrote the protocol and wrote the first draft of the manuscript. Author RTK managed the analyses of the study and performed the statistical analysis. Authors TOJ and JLD managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aim: To evaluate the nephroprotective property of *Cnidoscolus chayamansa* aqueous leaf extract in diabetic rats.
Study Design: Rats were randomly divided into five groups with group 1 as the normal control. Diabetic was induced in groups 2-4. Group 2 was used as the test control while groups 3 and 4 were treated with different concentrations of the leaf extract; group 5 was treated with the standard drug, glipizide.
Place and Duration of Study: Departments of Biochemistry and Anatomy, University of Jos, Nigeria, between August to November, 2019.
Methodology: Fourty (40) male albino Wistar rats were grouped into five groups. The rats were treated for fourteen days and then sacrificed by decapitation after anaesthesia. Blood was collected for biochemical parameters; kidney was excised and stored in formaldehyde until required for

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histopathological study. Serum urea, creatinine, uric acid, sodium, potassium, chloride and bicarbonate were determined using appropriate methods.
Results: The test control had a significant ($P < .05$) decrease in the concentrations of Na^+, Cl^- and HCO_3^- ions; significant ($P < .05$) increases in serum K^+ ion, urea, uric acid and creatinine. Treatments of the test groups with the different doses of the leaf extract and the standard drug increased the concentration of Na^+ ion which was not significantly ($P < .05$) different from the test control. On the other hand, the concentration of Cl^- and HCO^- ions were significantly ($P < .05$) increased; the concentrations of K^+, urea, uric acid and creatinine were significantly ($P < .05$) decreased. The histochemistry of the kidneys revealed that the injury brought about under diabetic condition was ameliorated with the treatments with the low and high doses of the leaf extract, and the standard drug.
Conclusion: The results show that the aqueous leaf extract has nephroprotective property.

Keywords: Nephroprotective; potential; properties; aqueous; leaf extract; Cnidoscolus chayamansa; diabetics.

1. INTRODUCTION

Traditional medicine generally includes the knowledge, skills, and practices which are based on the theories, beliefs, and experiences indigenous to different cultures, employed in the curative, preventive and maintenance of good health using plant materials [1]. Plants have extraordinary abilities to synthesize a wide array of secondary metabolites (phytochemicals), which Man exploits and uses to treat and manage some disease conditions. Many drugs in modern medicine derived their origin from plant sources. Examples of such drugs include aspirin made from willow bark and other salicylate-rich plant extracts [2], digoxin, a cardiac glycosides extracted from foxglove plant digitalis lanata [3], quinine, an alkaloid is gotten from cinchona bark extract and opium derived from the milky juice in unripe seed pods of opium poppy [4].

In developing countries, millions of people depend on wild resources including wild medicinal and edible plants for their healthcare and to meet dietary needs [5,6]. The tendency of populations in developing countries to favour traditional medicinal plants is mainly due to inaccessibility of modern medical care as well as economic and cultural factors [7,8]. *Cnidoscolus chayamansa* (*C. chayamansa*) commonly known as chaya or tree spinach, is a large, fast-growing leafy perennial shrub that is believed to have originated in the Yucatán Peninsula of Mexico [9]. It has succulent stems which exude a milky sap when cut. It can grow to about 6 meters tall, but is usually pruned to about 2 meters for easier leaf harvest. It is a popular leaf vegetable in Mexican and Central American cuisines, similar to spinach. The leaves are always cooked before being eaten, as the raw leaves contain a high content of toxic hydrocyanic acid. To be safely eaten, the required cooking time is 5-15 minutes [10].

Plants in the *Chayamansa* group are the most widely cultivated, because they lack stinging hairs on the leaves. It is divided into four cultivars based on leaf morphology: '*Chayamansa'* (most common), '*Estrella*', '*Picuda*', and '*Redonda* [10]. Pic. 1 shows the picture of the plant.

Rural and urban populations in some parts of West Africa use certain plant species for therapeutic and dietary purposes, most plant extracts from leaves, barks, roots, seeds and fruits serve as major sources of active ingredients and products of secondary metabolites used for treating diseases, production of drugs as well as maintaining good health by both the traditional and conventional medical practitioners [11].

Among the plants traditionally used by people with scarce economic resources is a cultivated plant belonging to the *Euphorbiaceae* family [12], *C. chayamansa*, which is frequently consumed as spinach (English), *efo iyana ipaja, or efo* jerusalam (Yoruba in Nigeria). It is commonly found growing in the western part of Nigeria. It is an ornamental, evergreen, drought deciduous shrub of 3 to 6m tall [10]. The palmate lobed leaves are large, 32cm long and 30cm wide alternatively arranged on chartacious and succulent petioles.

It is cultivated in domestic gardens rather than in agricultural fields and as such can be used throughout the year. It is a widely distributed annual plant ranging from temperate to tropical zones and has a long history of use as both a medicinal and an edible plant [13]. It has been

Pic. 1. *C. chayamansa* plant gotten from Aco Estate, Zone D, Abuja Municipal Area Council, Federal Capital Territory, Abuja, Nigeria

observed in use as diuretic, circulation and lactation stimulants and has also been recommended for diabetes, obesity, kidney stones and eye problems [14].

According to the National Institute of Nutrition in Mexico, ingesting *chaya* will improve blood circulation, help digestion, improve vision, dis-inflame veins and haemorrhoids, help lower cholesterol, help reduce weight, prevent cough, augment calcium in bones, decongest and disinfect the lungs, prevent anemia by replacing iron in the blood, Improve memory and brain function and combat arthritis and diabetes [15].

Chaya leaf is commonly used as a source of nutrients and for medicinal benefits especially among rural communities such as kuchigoro community in Abuja Municipal Area Council, Federal Capital Territory, Abuja, where pregnant women and diabetic patients use the extract of this leaf to boost their Packed cell volume (PCV) and to lower blood glucose. The benefits they claim to have from this leaf extract may come along with injury or damage to vital organs such as the kidney. The kidney plays a vital role in filtration and removal of toxic metabolic waste products from the cell. If this fear is true, the usage of this shrub could shorten their life-span as the assault from this extract on the kidney over an extended period could overstretch the defense line of the kidney, leading to kidney diseases and eventually death.

The usage of the leaf extract of *C. Chayamansa* by pregnant women and diabetes patients to boost their haematological parameters and to lower their blood glucose in a rural community of Abuja Municipal Area Council in the Federal Capital Territory, Abuja, Nigeria, needs to be verified and test for possible toxicity to the kidney using a rat model. The kidney of the rats will be evaluated for possible toxic effect of the aqueous leaf extract on the liver. The result of this work will serve as a source of information for the rural community.

Therefore, this work intends to study the effect of treatment of alloxan induced diabetic rats with graded concentrations of *C. chayamansa* aqueous leaf extract and a standard drug to evaluate its toxicological effect on the kidney injury parameters. Alloxan is commonly used to produce diabetes mellitus in experimental rats due to its ability to destroy the β-cells of the pancreas possibly by generation of excess reactive oxygen species such as H_2O_2, O_2, and HO, thereby preventing the pancreas from producing insulin.

2. MATERIALS AND METHODS

2.1 Materials

2.1.1 Animals

Fourty (40) male albino Pending Wistar rats weighing between 150g–200g, gotten from animal farm of the University of Jos, were used in this study. The rats were randomly divided into five (5) groups with eight (8) rats in each

group. Sigma-Aldrich Alloxan monohydrate gotten from Pharmacy Department, University of Jos, was used for induction of diabetes mellitus in the rats.

2.2 Methods

The adult male albino Wistar rats were randomly divided into five groups with eight rats in each group. The rats were allowed to acclimatize for one week on normal rat feed.

2.2.1 Induction of diabetes mellitus

Diabetes mellitus was induced by a single intraperitoneal injection of freshly prepared solution of Alloxan monohydrate at 150 mg/kg body weight in physiological saline after overnight fasting for 12 hours [16] in four groups of the rats. The rats were left for three days after which their blood glucose levels were measured and weights taken.

2.2.2 Extract and administration

100g of *C. chayamansa* leaf with reference number UJH 16000250, identified by Mr. Rumji Pandang of the Herbarium unit of Plant Science Department, University of Jos, was boiled in 500ml of water and allowed to stay for 1day in order to obtain the leaf extract.

The aqueous leaf extract of *C. chayamansa* was administered through the oral route at a low and high dose of 100 mg/kg and 250 mg/kg [17] body weight in two groups of the rats, while the third group was administered a standard diabetic drug, glipizide at 10mg/Kg body weight [18].

2.2.3 Treatment protocol

Fourty (40) male albino wistar rats grouped into five with eight rats in each group was treated as follow;

GROUP 1 (Normal control) - consist of non - diabetic rats fed with normal diet for two weeks.

GROUP 2 (Test control) - consist of alloxan induced diabetic rats that were fed with normal diet but not treated for two weeks.

GROUP 3 - Consists of diabetic rats fed with normal diet and treated with 100 mg/kg of *C. chayamansa* aqueous leaf extract daily using intra-gastric tube for two weeks.

GROUP 4 - Consists of diabetic rats fed with normal diet and treated with 250 mg/kg of *C. chayamansa* aqueous leaf extract daily using intra-gastric tube for two weeks.

GROUP 5 - Consist of diabetic rats fed with normal diet and treated with standard anti-diabetic drug Glipizide 10mg/kg intra-peritoneal for two weeks [18]. The choice of glipizide was due to the fact that some of the patients attending clinic in the study area were being treated with the drug. The rats were then sacrificed by decapitation after anaesthesia. Blood was collected for biochemical parameters; kidney was excised and stored in formaldehyde until required for histopathological study. Serum urea, creatinine, uric acid, sodium, potassium, chloride and bicarbonate were determined using appropriate methods.

2.2.4 Experimental parameters and methods

Urea, uric acid, creatinine, Na^+, K^+, Cl^- and HCO^- and histopathological analysis of the kidney were carried out using appropriate methods as follows.

Qualitative phytochemical analysis was carried out by Trease and Evans method [19]. Serum urea assay was determined by the method of Tobacco et al [20], using Randox commercial kit, while Serum creatinine was determined by the method described by Hare [21], using Randox commercial kit. Serum uric acid determination was carried out using the method of Fossati et al [22]. Serum Sodium and Potassium were determined using flame photometry method [23] and Serum Chloride and Bicarbonate were determined by Mercuric Nitrate titrimetric method of Schales and Shales [24]. The rats were sacrificed by decapitation after anaesthesia. Kidney excised, washed with ice cold saline to remove blood and stored in saline until required for histopathological study.

3. RESULTS

3.1 Qualitative Phytochemical Analysis of Aqueous Leaf Extract of *C. chayamansa*

Phytochemical analysis of aqueous leaf extract of *C. chayamansa* showed the presence of alkaloids, tannins, saponins, terpenes and steroids, balsam, carbohydrates, resins and phenols but absence of flavonoids and cardiac glycosides as shown in Table 1.

Table 1. Qualitative phytochemical analysis of aqueous leaf extract of *C. chayamansa*

Phytochemical constituents	Results
Alkaloids	+
Flavonoids	-
Tannins	+
Saponins	+
Terpenes and steroids	+
Cardiac glycosides	-
Balsam	+
Carbohydrates	+
Resins	+
Phenols	+

Key: + denotes presence, - denotes absence

3.2 Effect of Treatment with the Low and High Doses of *C. chayamansa* Aqueous Leaf Extract and the Standard Drug on the Concentrations of Na^+, K^+, Cl^- and HCO^- in Diabetic Rats

Fig. 1 shows the effect of treatment with the low and high doses of *C. chayamansa* aqueous leaf extract and the standard drug on Na^+, K^+, Cl^- and HCO^- in diabetic rats. The concentration of Na^+ ions was significantly ($P < .05$) decreased in the test control as compared to the normal control; treatments with the low and high doses of the leaf extract and the standard drug showed no significant difference ($P > .05$) between the Na^+ ions of the test control and the test groups. On the other hand, the concentration of K^+ ion significantly ($P < .05$) increased in the test control when compared to the normal control; treatment of test groups with the two doses of the leaf extract and the standard drug decreased the concentration of K^+ ion significantly ($P < .05$), while treatments with the high dose of the leaf extract and the standard drug had no significant difference ($P > .05$) with the normal control. The concentrations of Cl^- and HCO^- ions were significantly ($P < .05$) decreased in the test control when compared to the normal control but treatments with the low and high doses of the leaf extract and the standard drug significantly ($P < .05$) increased their concentrations when compared with the test control.

3.3 Effect of Treatment with the Low and High Doses of *C. chayamansa* Aqueous Leaf Extract and the Standard Drug on the Concentrations of Urea, Uric Acid and Creatinine in Diabetic Rats

Fig. 2 shows the effect of different treatments with the low and high doses of *C. chayamansa* aqueous leaf extract and the standard drug on urea, uric acids and creatinine in diabetic rats. The concentrations of urea, uric acid and creatinine all significantly ($P < .05$) increased in the test control when compared to the normal control. Treatments of the test groups with the low and high doses of the leaf extract and the standard drug showed significant ($P < .05$) decreases in the concentrations of urea, uric acid and creatinine when compared to the test control.

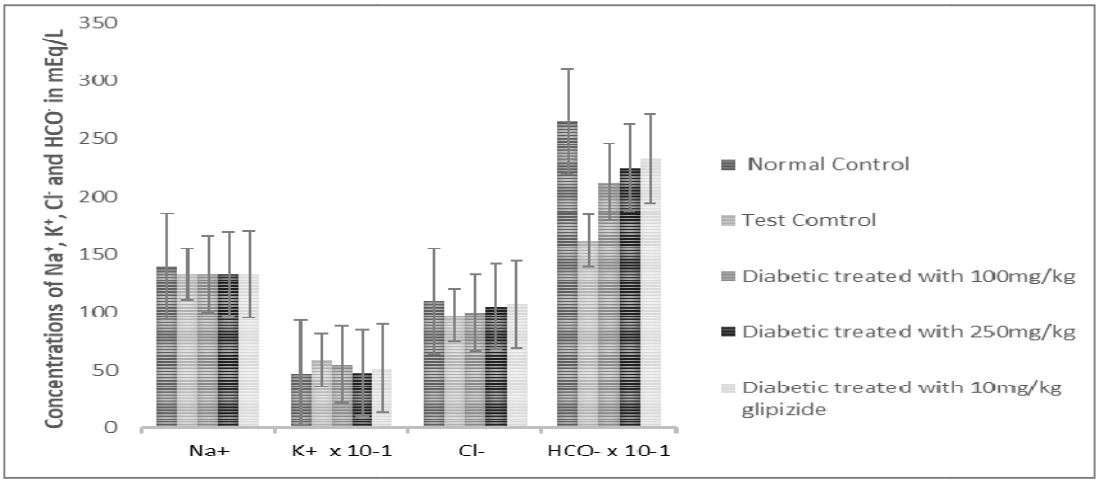

Fig. 1. Effect of treatment with the low and high doses of *C. chayamansa* aqueous leaf extract and standard drug on the concentrations of Na^+, K^+, Cl^- and HCO^- in diabetic rats

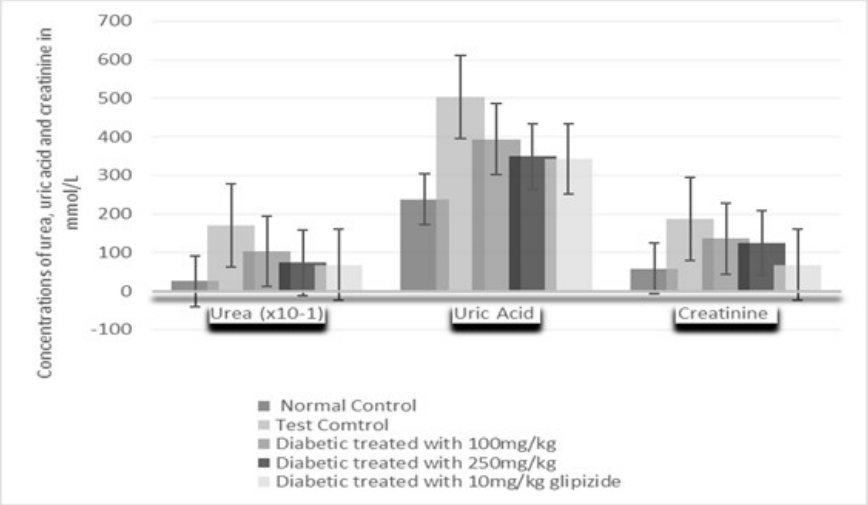

Fig. 2. Effect of treatment with *C. chayamansa* aqueous leaf extract on the concentrations of urea, uric acid and creatinine in diabetic rats

3.4 Effect of Treatments with the Low and High Doses of *C. chayamansa* Aqueous Leaf Extract and the Standard Drug on the Histochemistry of the Kidney of Diabetic Rats

Plates 1-5 show the effect of treatment with the low and high doses of the aqueous leaf extract and the standard drug on the histochemistry of the kidneys. The histochemistry of the kidney of the normal control rats appeared relatively normal but that of the test control had tubular necrosis, glomeruli atrophy, mononuclear cell infiltration, and inter-tubular haemorrhage. Treatments of the diabetic rats with the two doses of the leaf extract and the standard drug alleviated the damage that was observed in diabetic condition. The results show that the injury brought about under diabetic condition was ameliorate with the treatments with low and high doses of the leaf extract and the standard drug as shown below.

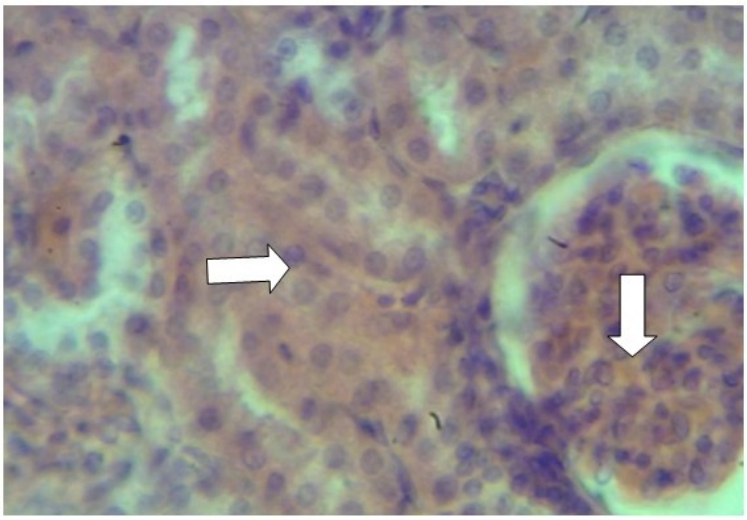

Plate 1. x400 Kidney section of the normal control rats showing normal glomerulus (down-pointing arrow) with normal arrangement of nuclei within the convoluted tubules (right-pointing arrow)

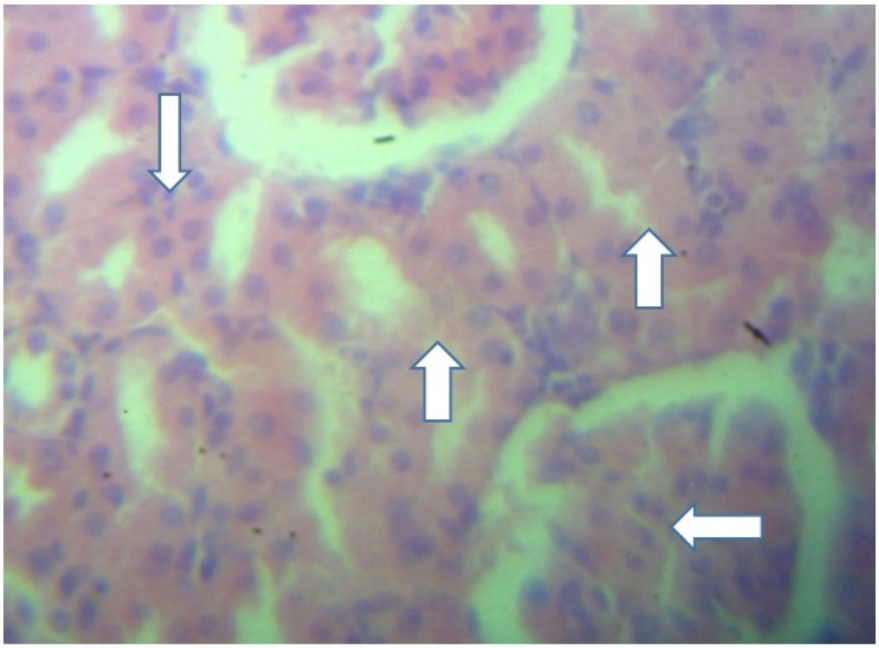

Plate 2. x400 Kidney section of the test control rats showing relatively normal glomerulus with sparse nuclei (left-pointing arrows) with relatively normal arrangement of nuclei within the collecting ducts (down-pointing arrows), but with some loss of nuclei within the convoluted tubules (up-pointing arrow)

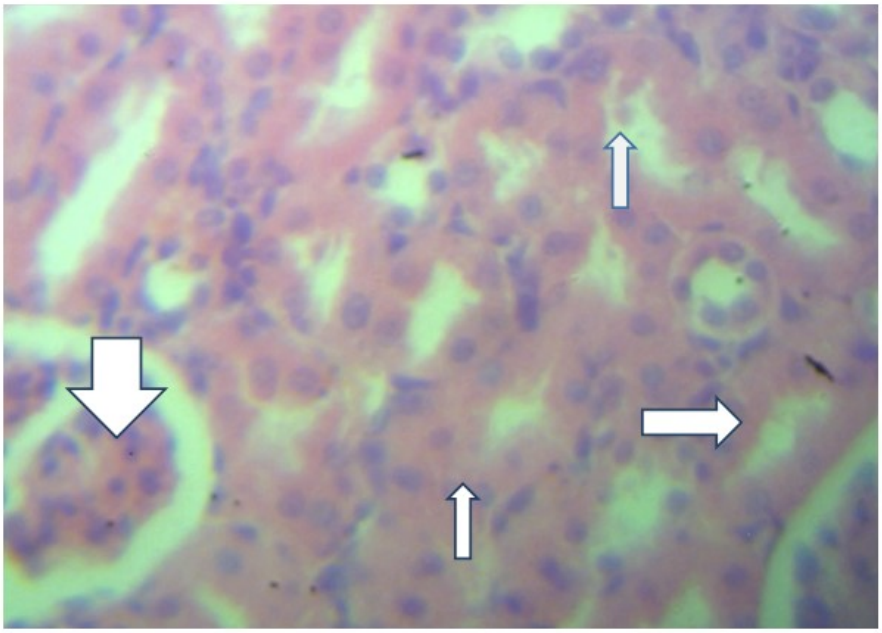

Plate 3. x400 Kidney section of the rats treated with 100mg/Kg body weight of the leaf extract showing relatively normal glomerulus (down-pointing arrow) with relatively normal arrangement of nuclei within the collecting ducts (right-pointing arrow), but with some loss of nuclei within the convoluted tubules (up-pointing arrows)

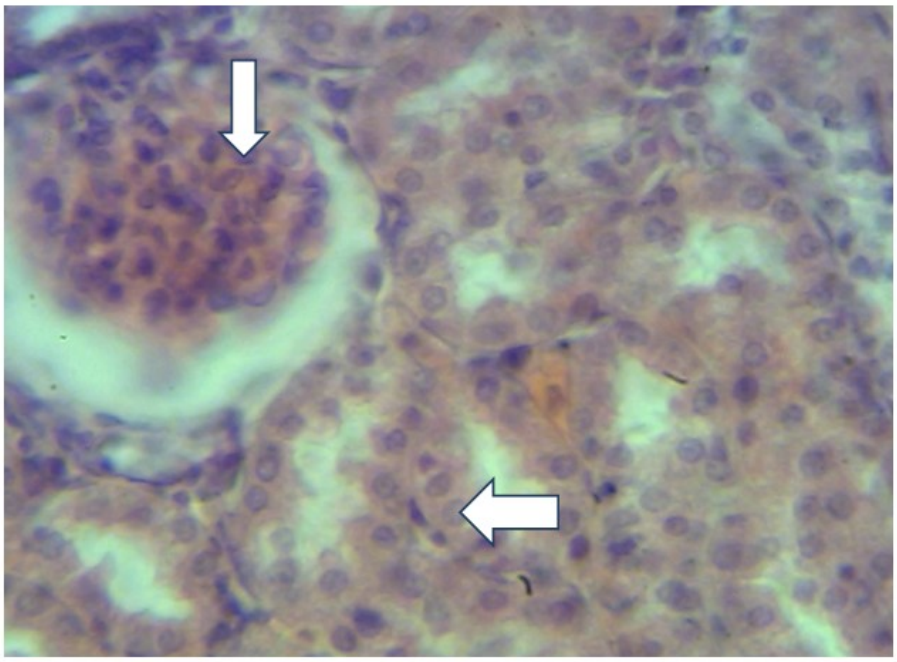

Plate 4. x400 Kidney section of the rats treated with 250mg/Kg body weight of the leaf extract showing relatively normal glomerulus (down-pointing arrow) with relatively normal arrangement of nuclei within the collecting ducts (left-pointing arrow)

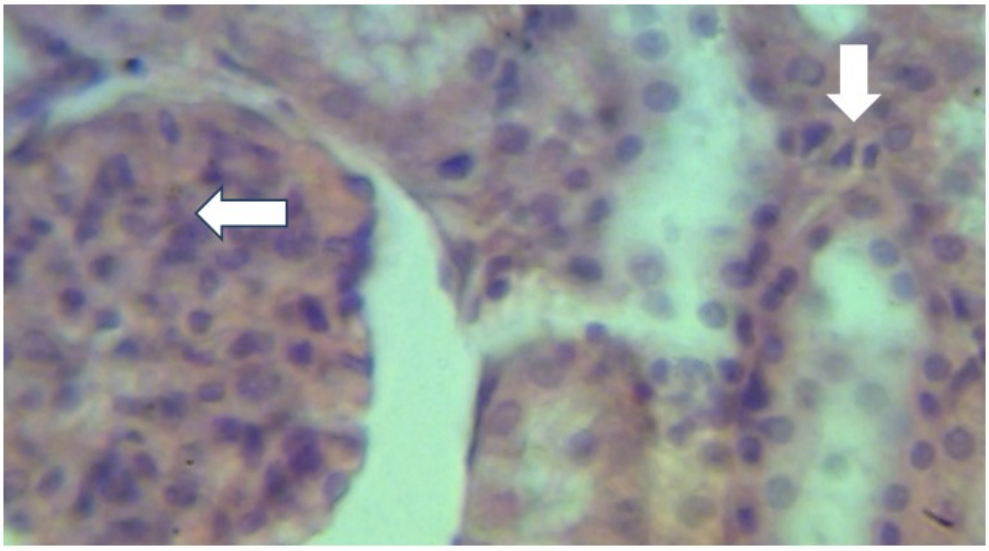

Plate 5. x400 Kidney section of the rats treated with glipizide showing relatively normal glomerulus (left-pointing arrow) with relatively normal arrangement of nuclei within the collecting ducts (down-pointing arrow)

4. DISCUSSION

Literatures abound to show that the therapeutic values of medicinal plants are attributable to their phytochemical constituents [25-28]. Alkaloids are known to have a lot of physiological activities, for example, morphine is used to treat acute and chronic severe pains, as well as pains resulting

from myocardial infarction and labour [29]. Capsaicin has the ability to heat up the tongue and skin if touched. Studies have shown that capsaicin encourages the release of endorphins. It has also been used in skin ointments because it aids receptor cells in sensing heat and relieving minor pains and those caused by damage to the cells of the peripheral nervous system [29]. Terpenes play an important role in cellular membrane fluidity, as a result of the triterpenes which serve as a precursor molecule for cholesterol. Polyphenols from medicinal plant extracts, include the isoflavones, flavones, quercetin, glucosides, anthocyannins, which have been identified to possess antioxidant activities. In addition, anticancer activities in cultured cells of the breast, colon, lungs and prostate has been detected in anthocyanins and quercetins. This is probably due to the protective functions of antioxidants [30]. Tannins have been reported to react with proteins by forming irreversible complexes which is useful in the treatment of inflamed or ulcerated tissues, and also have anticancer activities [30]. Saponins have antifungal and anti-inflammatory effects [31]. Their amphiphylic property makes them useful surfactants *in-vivo*. They enhance the penetration of proteins through cell membranes [32]. Saponins aid pharmacological and immunological agents by enhancing the recipients' immune response to a supplied antigen [32]. Saponins are useful cholesterol lowering agents, they work in the digestive system by binding with bile and dietary cholesterol; this prevents cholesterol re-absorption thereby increasing its excretion [33]. The expectorant property of saponin is used in the relief of cough; it increases bronchial secretion resulting in the dilution of sputum [33].

The result of this study shows that there was significant decrease in Na^+ ion concentration and a significant increase in K^+ ion concentration in the test control (diabetic control) when compared with the normal control. This could mean that there were altered Na^+ and K^+ ion concentrations which could be as a result of renal function impairment due to impaired Na+-K+-ATPase enzyme activity. The dysregulation of chief electrolytes especially Na^+, K^+ and Ca^{2+} have been reported to be the characteristic feature in the renal and cardiovascular diseases [34]. Most of the studies in literatures indicate that elevation of intracellular Na^+ and increase in K^+ ions was associated with a reduced activity of erythrocyte Na+-K+-ATPase pump [35]. Inhibition of Na+-K+-ATPase enzyme activity is said to be the main factor as in most of the kidney and cardiovascular diseases, inhibited or reduced ATPase activity has been observed. The decreased serum Na^+ and increase in serum K^+ ions concentrations in renal patients indicates that hyperkalemic state might have developed from a shift of potassium from intracellular to extracellular compartment or it could have been secondary to decreased renal potassium excretion [36]. This increased potassium could also result from decreased renin production, which affects the aldosterone synthesis due to adrenal defect, which then could produce renal tubular secretory defect leading to abnormal distribution of potassium between intra and extracellular compartments [37]. Treatments with the low and high doses of *C. chayamansa* aqueous leaf extract and the standard drug revealed that K^+ ion concentrations which was significantly increased in the test control decreased significantly, with the high dose of the leaf extract and the standard drug treatments having no significant difference with the normal control. From the foregoing, it could be said that *C. chayamansa* aqueous leaf extract improved the Na+-K+-ATPase enzyme activity in the diabetic rats.

The concentrations of Cl^- and HCO_3^- ions were significantly decreased in the test control when compared with the normal control but after the treatments with the leaf extract and the standard drug, there was significant increase in their concentrations. Cl^- ion is the major anion found in the fluid outside of cells and in the blood. Cl^- ion plays a role in helping the body maintain a normal balance of fluids. The balance of Cl^- ion is closely regulated by the cell. Significant decreases or increases in chloride can have deleterious or even fatal consequences. Elevations in Cl^- ion have been seen in certain kidney diseases, diarrhea and sometimes in over-activity of the parathyroid glands. Decreased Cl^- ions in the cell could be as a result of lost in the urine, sweat, and stomach secretions. Excessive loss could also occur from adrenal gland and kidney disease, heavy sweating and vomiting [38]. In this work, the decrease in the Cl^- ion concentration in the test control could be as a result of kidney impairment caused by diabetics, and the various treatments ameliorated the kidney damage and hence the increase in chloride ion as was observed.

Bicarbonate (HCO_3^-) ion acts as a buffer to maintain the normal levels of acidity (pH) in blood and other fluids in the cell. HCO_3^- levels are

measured to monitor the acidity of the blood and body fluids. The acidity is affected by the functions of the kidneys, lungs and the foods or medications that is ingested [39]. In this study, the decrease in the bicarbonate ion concentration in the test control could also be as a result of kidney damage from diabetics and the various treatments ameliorated the kidney damage and hence the increase in HCO_3^- ion as was observed.

The effects of diabetics on urea, uric acids and creatinine in diabetic rats revealed that their concentrations where all significantly elevated in the serum of the test control when compared with the normal control. Treatments with the low and high doses of the leaf extract and the standard drug showed significant decrease in the concentration of the urea, uric acid and creatinine between the test control and the test groups. It is common knowledge that in diabetic patients, there is hyperglycemia. Hyperglycemia is known to induce oxidative stress which is responsible for diabetic's complications [40]. Oxidative stress in diabetes is the result of a series of pathological events that lead to an imbalance between the pro-oxidant levels and counteracting antioxidant defense mechanisms, consequencetly, both kidney and nerves which are essential parts of an organism are susceptible to hyperglycemia-induced oxidative damage [41,42]. The antioxidant effects on the diabetic kidney [43] and nerves [44] disorders were positively correlated with medicinal herbs supplementation. This could be as a result of the phytochemicals in the *C. chayamansa* leaf extract which are known to have anti-oxidant and anti-inflammatory effects as discussed above. Previous studies have shown that hyperglycemia can induce similar early renal and neural complications in diabetic rats [45,43,46]. The serum uric acid, urea and creatinine levels were found to be increased in the diabetic control rats which could be linked to decrease in glomerular filtration rate, as shown in the histochemistry of the kidney. Treatments with the leaf extract and the standard drug ameliorated the kidney impairment, thereby lowering the serum levels of urea, uric acid and creatinine in the test groups, signifying nephroprotective effect. However, the nephroprotective property was found to be higher with the high dose treatment with the leaf extract when compared to the low dose treatment. These results point to fact that there was improved renal function by the more enhanced clearance of urea, creatinine and uric acid after the treatments.

The histochemistry of the kidney section of the normal control rats appeared relatively normal but that of the test control had tubular necrosis, glomeruli atrophy, mononuclear cell infiltration, and inter-tubular haemorrhage. Treatments of the diabetic rats with the two doses of the leaf extract and the standard drug alleviated the damage that was observed in diabetic condition. The result of the histochemistry therefore is in agreement with the biochemical parameters which showed that the injury brought about under diabetic condition was ameliorated.

5. CONCLUSION

This study suggests that *C. chayamansa* aqueous leaf extract has nephroprotective potential which improved kidney function in alloxan-induced diabetic rats. This demonstrates that the aqueous leaf extract of *C. chayamansa* is relatively safe at the doses used in this work. The use of the aqueous leaf extract of *C. chayamansa* by the locals especially among the rural kuchigoro community in Nigeria, have some credence. The toxicological concerns on the kidney that triggered this study is allayed as the histochemistry of the kidney revealed that the tubular necrosis, glomerular atrophy, mononuclear cell infiltration, and inter-tubular haemorrhage observed in the test control was drastically ameliorated with the high dose of the leaf extract.

CONSENT

It is not applicable.

ETHICAL APPROVAL

All authors hereby declare that "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed, as well as specific national laws where applicable. All experiments have been examined and approved by the appropriate ethics committee.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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