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Research Article
Senna occidentalis Leaf Extracts Ameliorate Biochemical Parameters of Diabetic Nephropathy in Diabetic Wistar Rats

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Abstract

Background and Objective: *Senna occidentalis* is widely used in the folkloric treatment and management of various diseases. Its therapeutic benefit for diabetic kidney disease however remains unexplored. This study evaluated the effects of leaf phenolic and alkaloid extracts of *Senna occidentalis* on biomarkers of diabetic nephropathy in diabetic Wistar rats. **Materials and Methods:** Forty-two male Wistar rats were grouped into seven groups of six animals each. Experimental diabetes was induced in all rats except group 1, control. Groups 2-7 were orally administered 1mL of distilled water, 14.3 mg kg^{-1} b.wt., metformin, 100 and 200 mg kg^{-1} b.wt., phenolics (SOLPE) and alkaloid (SOLAE) extracts of *Senna occidentalis* leaf respectively for 14 days. Data were analyzed by one-way analysis of variance followed by Tukey-post hoc test for multiple comparisons among means of five replicates at $p<0.05$ using GraphPad Prism version 6. **Results:** The results showed that the serum concentrations of uric acid, urea, cystatin C, creatinine, the renal concentration of tumour necrosis factor-α and malondialdehyde and parameters of oxidative stress which were compromised in the diabetic untreated rats were significantly reversed on treatment with SOLPE and SOLAE at 100 and 200 mg kg^{-1} b.wt. **Conclusion:** Thus, phenolic and alkaloid extracts of *Senna occidentalis* leaf possess ameliorative effects on the parameters of diabetic nephropathy in high-fat-diet/streptozotocin-induced diabetic rats and can be explored for the management of diabetic kidney disease.

Key words: Diabetic nephropathy, oxidative stress, tumor necrosis factor-α, cystatin C, *Senna occidentalis*, phenolics, alkaloids

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Diabetes mellitus is a chronic and complex metabolic disease characterized by a high level of plasma glucose that results in disturbances in the metabolism of fat, carbohydrate and protein[1]. The metabolic disturbances of diabetes mellitus culminate into acute and chronic consequential complications among which is diabetic nephropathy[2].

The global prevalence of diabetic nephropathy continues to increase with the rising prevalence of diabetes mellitus. In 2019 alone, 405.99 thousand people died from diabetic nephropathy among 2.62 million incident cases and 134.58 million patients worldwide. This is despite 13.09 million disability adjusted-life-years of Chronic Kidney Disease of Diabetes Mellitus (CKD-DM) worldwide with diverse socio-economic impacts[3]. About 40% of type 2 diabetics and 30% of type 1 diabetics develop diabetic nephropathy. Risk factors include increased albuminuria, hyperglycemia, hypertension, dyslipidemia, obesity and smoking[4].

Diabetic nephropathy is defined as the microvascular complication of the kidneys induced by diabetes mellitus and is characterized by albuminuria and progressive loss of kidney function[5]. Oxidative stress and inflammation induced by chronic elevations in blood glucose in diabetic patients are risk factors associated with the development of diabetic complications, especially in diabetic nephropathy[6]. Hyperglycemia and oxidative stress and inflammation are the driving forces for renal damage associated with diabetes[7]. Thus, diabetic nephropathy can be metabolically characterized by biomarkers of kidney injuries, oxidative stress and inflammation.

Senna occidentalis is one of the herbal plants that are extensively used among people of tropical and subtropical regions of the world. It is considered therapeutically versatile in the Nigerian traditional medical practice and thus, its roots, leaves, flowers, seeds and pods are used for various therapeutic purposes. In Nigeria, this plant is locally called "*Akidi Agbara*" in Igbo and "*Akorere*" in Yoruba. The plant has been used in different parts of the world by traditional healers in treating different forms of diseases[8]. The plant is widely consumed by local people as a coffee substitute. The seeds are brewed into a coffee-like beverage for asthma and a flower infusion (mixing the flowers with essential oils) is used to treat bronchitis. The roots are used as tonic, febrifuge and diuretic and they are also used for menstrual problems, tuberculosis, anaemia and liver complaints[9]. Decoction of the leaves, pods and seeds are used to treat diabetes. Dried roots and leaves of *Senna occidentalis* are milled and mixed with black soap and used to bathe for treatment of measles[10]. The leaves of the plant are used for the treatment of yaws, scabies, itches and ringworm among Yoruba people of Southwestern Nigeria. In addition to this, the leaves are also known to be effective against headaches, jaundice and toothache[11]. The role of the plant in the management of diabetic kidney disease has however remained untapped.

Thus, the study was designed to investigate the effect of *Senna occidentalis* leaf phenolic and alkaloid extracts on the parameters of renal injury, oxidative stress and inflammatory status for the assessment of diabetic nephropathy in a high-fat diet/streptozotocin-induced diabetic Wistar rats.

MATERIALS AND METHODS

Study area: The study was carried out at the animal holding unit of the Department of Biochemistry, Faculty of Pure and Applied Sciences, Kwara State University, Malete, Nigeria. The study was carried out between January-August, 2021.

Plant material and authentication: *Senna occidentalis* leaf was obtained from farmland at Ilorin, Kwara State. The plant was identified and authenticated at the Herbarium Unit, Department of Plant Biology, University of Ilorin, Kwara State, Nigeria and a voucher number (UILH001/1302/2021) was given.

Experimental animals: For this experiment, a total of forty-two male Wistar rats with an average weight of (142.33±3.75 g) were obtained for the research. The Wistar rats were kept in well-ventilated plastic cages and housed in the animal house of the Faculty of Pure and Applied Sciences, Kwara State University. All the animals were acclimatized to experimental conditions for one week and allowed access to water and feed *ad libitum*.

Chemicals and reagents: Chloroform, Diethyl ether and Acetone were products of Schar Lab S.L., Barcelona, Spain. Acetic acid, ethanol and ethyl acetate were products of LobaChemie Pvt Ltd., Mumbai, India. Streptozotocin used was a product of Elabscience, Texas, USA and the assay kits used were products of Randox Laboratories Ltd., Antrim, UK. All other reagents used were of analytical grade.

Methods

Preparation of phenolics extract of *Senna occidentalis* leaf: Fresh *Senna occidentalis* leaves were gently rinsed and air-dried. The air-dried leaves were pulverized into fine particles using an electric blender and stored in an air-tight container. The pulverized leaf powder was used for the extraction of phenolic using the two-phase solvent extraction method for the extraction of phenolics as previously described[12]. The Two-Phase Solvent System (TPSS) was prepared by mixing with 450 mL of ethyl acetate, 150 mL of acetic acid and 900 mL of water (3:1:6 v/v/v) together. The obtained system was agitated vigorously and left in contact till mutual saturation and separation into two phases on a separating funnel, by which the two phases were separated. One hundred and fifty grams of *Senna occidentalis* leaf was agitated in the 900 mL of the aqueous phase of the TPSS for 30 min and then in 600 mL of the organic phase for another 30 min. The resulting mixture was filtered using a Whatman No 1 filter paper. The filtrate was concentrated to dryness using a rotary evaporator and water bath at 45°C. The 1.3 g crude phenolic extract obtained (equivalent to 0.92% yield) was transferred to a 20 mL sterile plain bottle and stored in the refrigerator at 4°C before usage.

Determination of total phenolic content of *Senna occidentalis* leaf: The total phenolic content was determined using Folin-Ciocalteu method[13]. Exactly, 0.5 mL aliquots of 12.5, 25, 50 and 100 μg mL^{-1} methanol-gallic acid solutions were mixed with 2 mL of 10% Folin-Ciocalteu's reagent and 4 mL of 7% sodium carbonate solution to make a volume of 10 mL in a test tube. The obtained blue colour was shaken vigorously and allowed to stand for 60 min at room temperature. The absorbance was read at 765 nm using a UV-visible spectrophotometer.

Preparation of alkaloid extract of *Senna occidentalis* leaf: For the extraction of alkaloids, 150 g of the pulverized leaf powder was suspended in 1 L of the ethanol-acetic acid mixture (9:1 v/v) for 24 hrs with intermittent shaking. The mixture was filtered with Whatman No 1 filter paper (Whatman International Ltd, Maidstone, England). The filtrate was concentrated to about a quarter using a rotary evaporator (Bibby Scientific Limited, Stone, Staffordshire, UK). The pH of the concentrate was adjusted to 8 by the addition of ammonium hydroxide solution and was further extracted with 50 mL chloroform three times. The chloroform layer was separated using a separating funnel to obtain the extract. The crude extract was dried with an oven at 45°C and weighed. The crude extract was transferred to a 20 mL sterile plain bottle and stored in the refrigerator at 4°C before being used. The alkaloid extract yield was recorded to be 1.81 g which was equivalent to 1.21%.

Determination of total alkaloid content of *Senna occidentalis* leaf: For the determination of alkaloid content, 1 mg mL^{-1} of the extract residue was dissolved in 2N HCl and then filtered, 1 mL of the solution was transferred to a separating funnel and washed with 10 mL of chloroform thrice. The pH of the solution was adjusted to be neutral with 0.1 N NaOH. The phosphate buffer solution was prepared by adjusting the pH to 4.7 with 0.1 M citric acid. Atropine standard solution was made by dissolving 1 mg of pure Atropine in 10 mL distilled water. Accurately measured aliquots of atropine standard solution were transferred to different test tubes. Then, 5 mL of bromocresol green solution and 5 mL of phosphate buffer was taken and the mixture was shaken with extract residue and 1, 2, 3 and 4 mL of chloroform. The extracts were then collected in a 10 ml volumetric flask and then diluted to adjust the solution with chloroform. The absorbance of the complex in chloroform was measured at 470 nm using a UV-spectrophotometer[14].

Induction of experimental diabetes: The high-fat-diet/streptozotocin experimental diabetes model was used. The rats were fed with a high-fat diet, which consisted of 40% tallow (fat) thoroughly mixed with 60% standard rat chow, for three weeks (21 days) *ad libitum*. This was followed (on day 22) by a single intraperitoneal injection of 35 mg kg^{-1} b.wt., streptozotocin (freshly dissolved in ice-cold citrate buffer 0.1 M, pH of 4.5) after an overnight fast in which only the feeds were withdrawn. The animals in the control group were fed 100% standard rat chow and also intraperitoneally administered citrate buffer. Fasting blood glucose (FBG) was checked 48 hrs after streptozotocin injection using Accu-chek glucometer and compatible strips. Rats with FBG higher than 250 mg dL^{-1} were used in the study.

Experimental animal grouping: The animals were randomly divided into seven (7) groups with each group consisting of six rats. After the induction and confirmation of experimental diabetes mellitus in all animals except those in the control group, the animals were subjected to the following oral treatments once a day for 2 weeks: The control group were the non-diabetic rats administered 1 mL of distilled water, the diabetic untreated group were administered 1 mL of distilled water, the third group were diabetic rats administered

14.3 mg kg^{-1} of metformin, the fourth group were diabetic rats administered 100 mg kg^{-1} b.wt., of phenolic extract of *Senna occidentalis* leaf, the fifth group were diabetic rats administered 200 mg kg^{-1} b.wt., of phenolic extract of *Senna occidentalis* leaf, the sixth group were diabetic rats administered 100 mg kg^{-1} b.wt., alkaloid extract of *Senna occidentalis* leaf and the seventh group were diabetic rats administered 200 mg kg^{-1} b.wt., alkaloid extract of *Senna occidentalis* leaf.

Animal sacrifice: Twenty-four hours after the last treatment, after a twelve-hour fast, all the rats were sacrificed under diethyl ether anaesthetization. The neck region was cleared of fur for jugular vein exposure which was sharply cut with a sterile surgical blade for blood collection in sterile plain and EDTA bottles. The blood in the plain bottles was allowed to clot and was subjected to centrifugation at 1500 rpm for 5 min and the serum was carefully aspirated with a micro-pipette into another set of sterile plain sample bottles. The kidney was extracted and placed in sucrose buffer, it was homogenized and centrifuged at 3500 rpm for15 min.

Determination of biochemical parameters: The concentrations of cystatin C, urea, albumin, creatinine and uric acid were determined in the serum according to the methods described by Galteau *et al.*[15], Langenfeld *et al.*[16], Cray *et al.*[17], Moore and Sharer[18] and Milena *et al.*[19], respectively. The activities of Superoxide Dismutase (SOD) and catalase were determined in the kidneys as described by Weydert and Cullen[20] glutathione transferase was determined as described by Morou *et al.*[21] The concentrations of reduced glutathione and malondialdehyde were determined according to the method described by Zheng *et al.*[22] and Zeb and Ullah[23], respectively.

Statistical analysis: Data were expressed as Mean±S.E.M. of five replicates. Experimental data were analyzed using GraphPad Prism version 6 using one-way analysis of variance (ANOVA) followed by Tukey-posthoc test for multiple comparisons to determine significant differences among means of five replicates at $p<0.05$.

RESULTS

The serum concentrations of uric acid, urea ($p<0.01$), cystatin C ($p<0.001$) and creatinine were significantly increased when compared with the control group while serum albumin ($p<0.01$) concentration decreased ($p<0.05$) in the diabetic untreated group when compared to the control group (Fig. 1-4). However, the serum concentrations of uric acid, urea, cystatin C, creatinine and albumin were restored ($p<0.05$) in the groups treated with 100 and 200 mg kg^{-1} b.wt., of phenolic and alkaloid extracts of *Senna occidentalis* leaf.

There was a reduction in the concentration of reduced glutathione (GSH) in the kidneys and the activities of catalase, superoxide dismutase, glutathione peroxidase and glutathione S-transferase in the diabetic untreated group when compared with the control while there was an elevation in the concentrations of malondialdehyde and Tumour Necrosis Factor-α (TNF-α) in the diabetic untreated group when compared with the control (Fig. 5-8). Upon treatment with phenolic and alkaloid extracts of *Senna occidentalis* leaf at 100 and 200 mg kg^{-1} b.wt., the concentrations were restored.

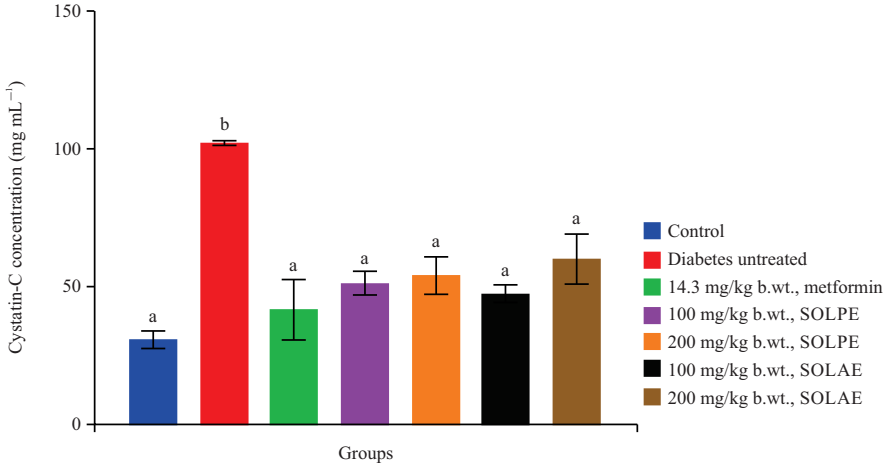

Fig. 1: Serum cystatin C concentration in different groups

Values are expressed as the mean of five replicates±SEM, error bars with different alphabets are significantly different ($p<0.05$), SOLPE: *Senna occidentalis* leaf phenolic extract and SOLAE: *Senna occidentalis* leaf alkaloid extract

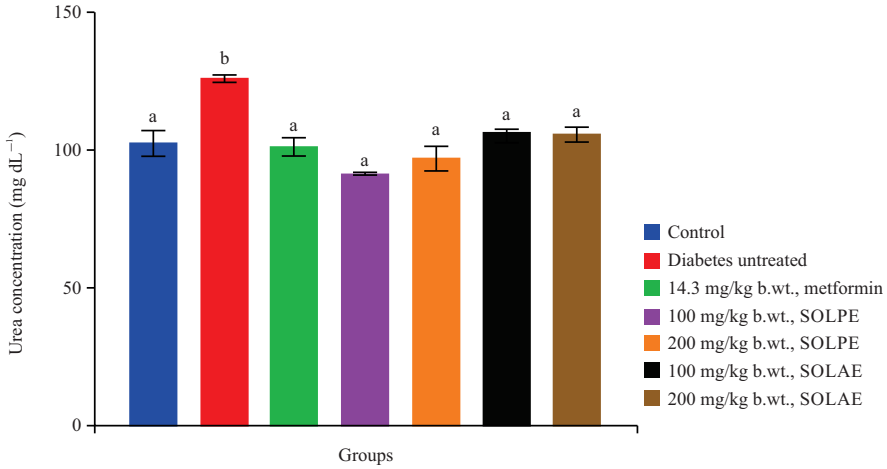

Fig. 2: Serum urea concentration in different groups

Values are expressed as the mean of five replicates±SEM, error bars with different alphabets are significantly different (p<0.05), SOLPE: *Senna occidentalis* leaf phenolic extract and SOLAE: *Senna occidentalis* leaf alkaloid extract

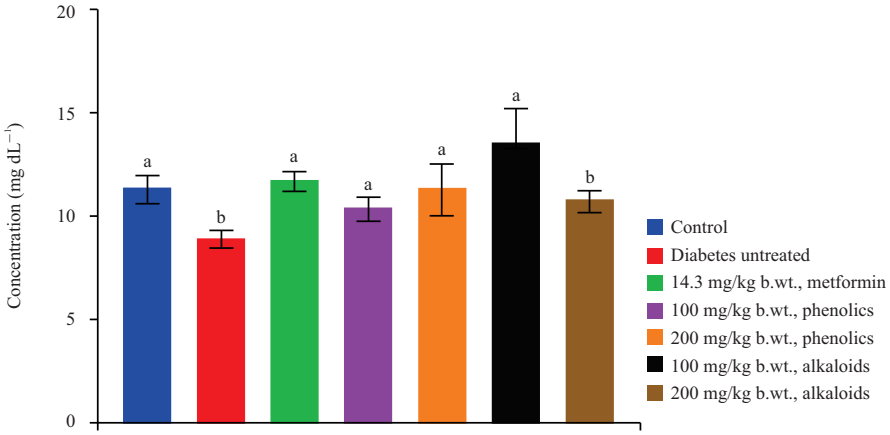

Fig. 3: Serum albumin concentration in different groups

Values are expressed as a mean of five replicates±SEM, error bars with different alphabets are significantly different (p<0.05), SOLPE: *Senna occidentalis* leaf phenolic extract and SOLAE: *Senna occidentalis* leaf alkaloid extract

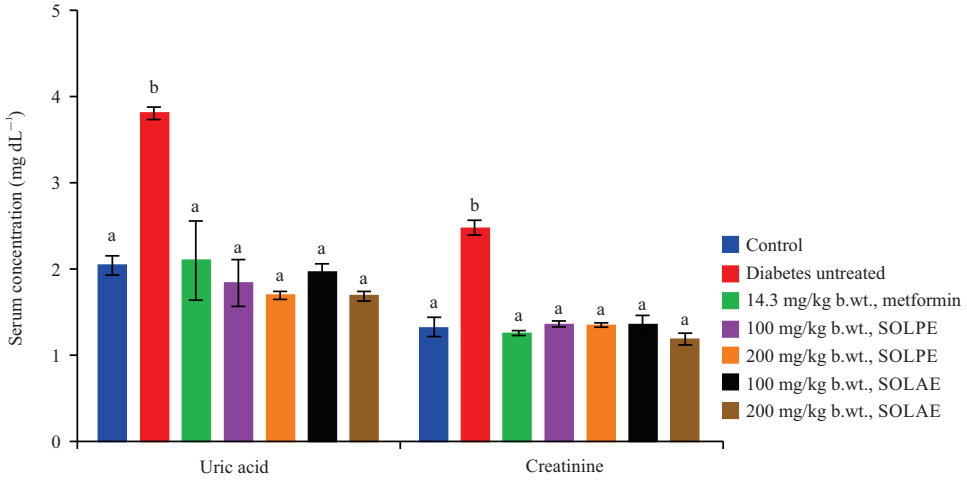

Fig. 4: Serum uric acid and creatinine concentrations in different groups

Values are expressed as a mean of five replicates±SEM, error bars with different alphabets are significantly different (p<0.05), SOLPE: *Senna occidentalis* leaf phenolic extract and SOLAE: *Senna occidentalis* leaf alkaloid extract

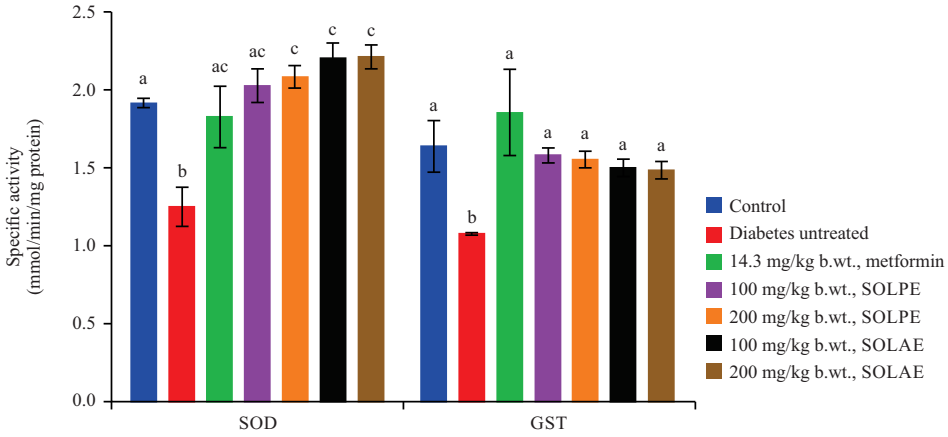

Fig. 5: Specific activities of kidneys antioxidant enzymes in different groups

Values are expressed as the mean of five replicates±SEM, error bars with different alphabets are significantly different (p<0.05), SOLPE: *Senna occidentalis* leaf phenolic extract and SOLAE: *Senna occidentalis* leaf alkaloid extract

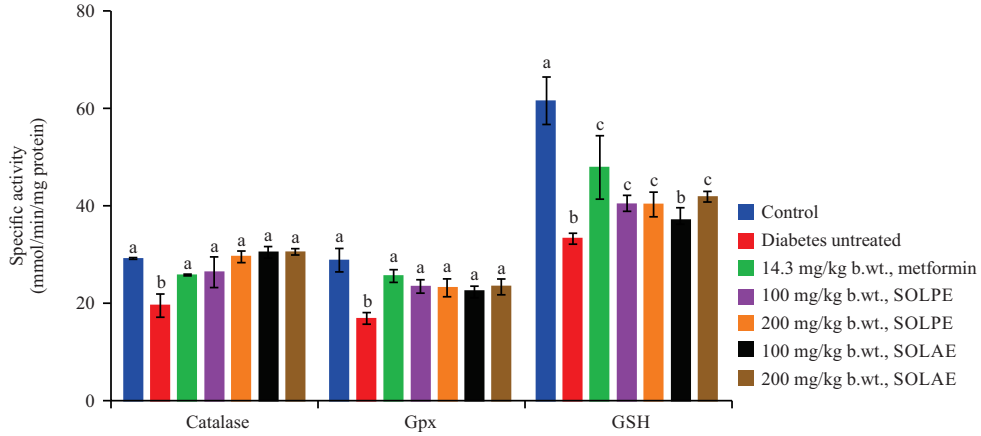

Fig. 6: Specific activities of kidneys antioxidant enzymes in different groups

Values are expressed as the mean of five replicates±SEM. Error bars with different alphabets are significantly different (p<0.05). SOLPE: *Senna occidentalis* leaf phenolic extract and SOLAE: *Senna occidentalis* leaf alkaloid extract

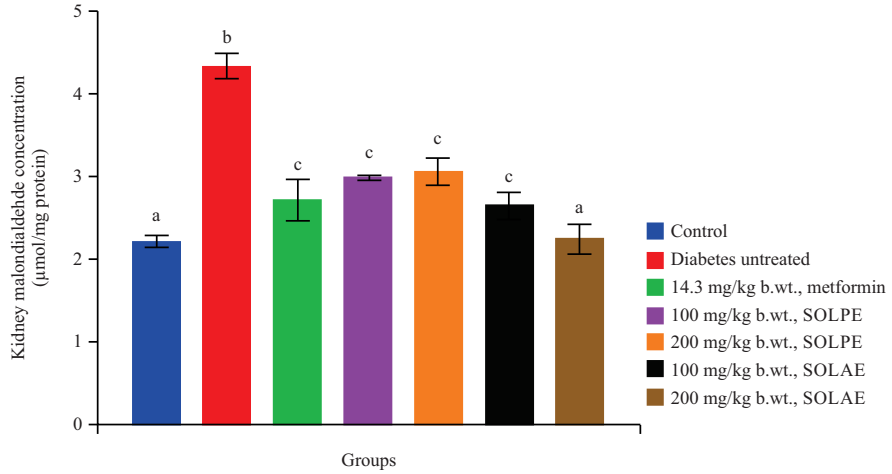

Fig. 7: Concentration of kidneys malondialdehyde in different groups

Values are expressed as the mean of five replicates±SEM. Error bars with different alphabets are significantly different (p<0.05). SOLPE: *Senna occidentalis* leaf phenolic extract and SOLAE: *Senna occidentalis* leaf alkaloid extract

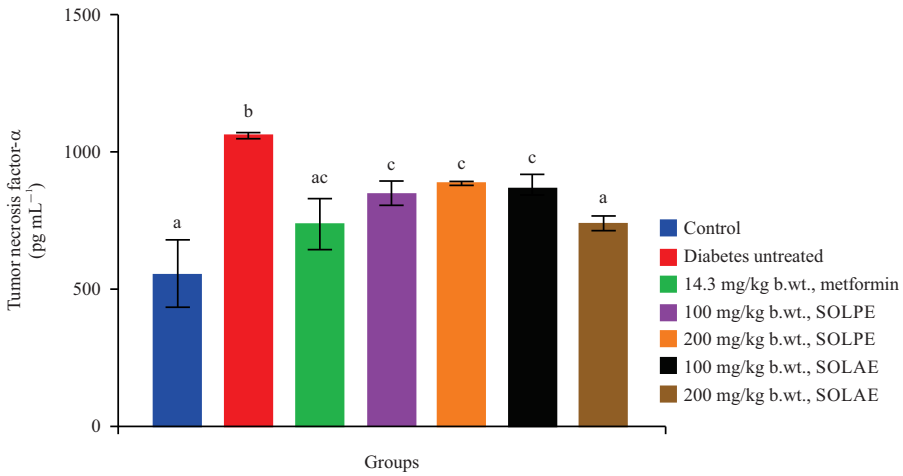

Fig. 8: Concentration of kidneys tumour necrosis factor-α in different groups

Values are expressed as the mean of five replicates±SEM, error bars with different alphabets are significantly different (p<0.05), SOLPE: *Senna occidentalis* leaf phenolic extract and SOLAE: *Senna occidentalis* leaf alkaloid extract

DISCUSSION

The chemotherapeutic interventions available for the management of diabetes mellitus are not only marred by their unavailability, inaccessibility and disturbing side effects, they are also not designed for the management of diabetic complications[24]. The necessity of searching for options from plants, for the management of diabetic complications, particularly diabetic nephropathy, is long overdue. *Senna occidentalis* is one of the plants that have been reported to possess antidiabetic potentials and is also beneficial in the management of kidney diseases through its anti-inflammatory and anti-oxidative activities[25].

Cystatin C is a cysteine protease inhibitor that is freely filtered by the glomeruli, metabolized by the proximal tubule and has been identified as a potential biomarker of renal failure. An increase in serum cystatin C levels of the diabetic untreated group ($p<0.05$) compared to the control group has been associated with an increased risk of developing end-stage kidney disease[26]. The reduction in serum cystatin C concentration when treated with 100 and 200 mg kg^{-1} b.wt., phenolic and alkaloid extracts of *Senna occidentalis* leaf can be adduced to the potentials of SOLPE and SOLAE to prevent the progression of kidney disease and hence, nephropathy in diabetes mellitus[27,28].

Serum albumin is a well-known predictor of mortality in patients with chronic kidney disease. The high serum albumin concentration is associated with a lower risk of mortality while low serum albumin concentration is associated with a higher risk of kidney function decline. Reduction of serum albumin concentration in the diabetic untreated group indicates drift towards kidney dysfunction which characterize diabetic nephropathy in diabetes mellitus[29]. The restoration of the serum albumin concentration when the diabetic animals were orally administered 100 and 200 mg kg^{-1} b.wt., of phenolic and alkaloid extracts of *Senna occidentalis* leaf is suggestive of the renal protective effect of the SOLPE and SOLAE in diabetes mellitus. This inference is consistent with that of Sundaram *et al.*[30] in which a higher concentration of albumin in the serum was linked to the protection of the kidneys against oxidative damage in diabetes mellitus. This is in addition to the fact that reduction in serum albumin concentration is widely considered an indication of the progression of renal damage[31]. At 200 mg kg^{-1} b.wt., alkaloid extract of *Senna occidentalis* leaf normalized serum albumin concentration which indicates that *Senna occidentalis* leaf at the given higher dosage restored normal kidney function[32].

Uric acid is a by-product of purine metabolism that is eliminated by the kidney. An increase in serum uric acid concentration of the diabetic untreated group is suggestive of hyperuricemia which has been reported to have a significant role in kidney dysfunction[33]. Treatment with 100 and mg kg^{-1} b.wt., phenolic and alkaloid extracts of *Senna occidentalis* leaf reduced the serum uric acid concentration of diabetic rats which indicated that *Senna occidentalis* leaf extracts dose-dependently lowered the serum uric acid concentration[34]. Urea is a major nitrogenous end product of the metabolic breakdown of protein in humans. It is dissolved in the blood and excreted by the kidney as a component of urine. Elevation of serum urea concentration in the diabetic untreated group is consistent with hyperuricemia associated with impaired kidney function and chronic kidney disease in diabetes

mellitus[35]. Treatment with 100 and 200 mg kg^{-1} b.wt., phenolic and alkaloid extracts of *Senna occidentalis* leaf restored the serum urea concentration which showed that *Senna occidentalis* leaf is dose-dependent in normalizing serum urea concentration and restored normal kidney function[36,37].

The significantly increased serum creatinine concentration of the diabetic untreated rats ($p<0.05$) compared with the control group indicates hypercreatininemia associated with progression of kidney dysfunction in diabetes mellitus[38]. More so, the concentration of creatinine in the serum has been associated with declining glomerular filtration rate and progressive chronic kidney disease[39]. Treatment with 100 and 200 mg kg^{-1} b.wt., phenolic and alkaloid extracts of *Senna occidentalis* leaf reduced the serum creatinine concentration showing that *Senna occidentalis* leaf normalized serum creatinine concentration and restored proper kidney function in diabetic conditions[40] and this also indicates hypocreatininemia usually associated with declining glomerular filtration rate and progressive chronic kidney disease[39].

Continuous free radical production, a consequence of persistent hyperglycemia, overwhelms the cellular enzymic and non-enzymic antioxidant machinery, leading to oxidative stress. Free radicals and the consequent oxidative stress are not only the unifying link between persistent hyperglycemia and diabetic complications in general, but they are also key players in the occurrence and progression of particularly diabetic nephropathy in diabetes mellitus. Oxidative stress is a significant component of the cascade of events that culminate, through hyperglycemia, into the kidney dysfunctions that characterize diabetic nephropathy in diabetes mellitus[41]. Thus, the significant reduction in the activities of superoxide dismutase, catalase, glutathione-s-transferase and glutathione peroxidase together with the significant reduction in the concentration of reduced glutathione in the kidneys of the diabetic untreated animals relates the overwhelmed antioxidative capacity of the kidneys of the diabetic rats which characterizes diabetic nephropathy[42-44]. The elevation of the activities of superoxide dismutase, catalase, glutathione-s-transferase and glutathione peroxidase with a concomitant increase in the concentration of reduced glutathione in the kidneys of animals treated with 100 and 200 mg kg^{-1} b.wt., phenolic and alkaloid extracts of *Senna occidentalis* leaf lend credence to the possibility of the benefits of the extracts in the management of diabetic nephropathy[45-49].

Malondialdehyde is a final decomposition product of lipid peroxidation, the determination of the kidney malondialdehyde content can reflect the degree of renal cell damage by oxidants that are consistently produced in poorly managed diabetes mellitus. In this study, the concentration of malondialdehyde significantly ($p<0.05$) increased in the diabetic rats which suggest the impairment of renal redox homeostasis, formation of lipid peroxides, indicating compromise to the membrane lipids in the kidneys[50]. Treatment with the phenolic and alkaloid extracts of *Senna occidentalis* leaf at 100 and 200 mg kg^{-1} b.wt., significant ($p<0.05$) decreased the concentration of malondialdehyde in the kidneys of the treated animals. This suggests a preventive effect of further damage in the renal cells caused by an accumulation of free radicals and lipid peroxidation[51,52].

Inflammation in diabetic nephropathy is activated by metabolic, biochemical and hemodynamic disorders which progressively and persistently lead to kidney injury. Inflammation may promote kidney damage through a variety of mechanisms including monocyte migration, complement activation, platelet function regulation and clearance of cellular debris from inflamed areas[53].

TNF-α is a non-glycosylated polypeptide and is produced by monocytes macrophages and by native renal cells such as the glomerular endothelial, mesangial and epithelial cells and tubular epithelial cells. They are stimulated to produce other cytokines and chemokines. In this study, there was an increase in the concentration of TNF-α in diabetic untreated rats, this may be due to free radicals and corroborates the depletion of antioxidants in the renal cells[54]. Treatment with phenolic and alkaloid extracts *Senna occidentalis* leaf at 100 and 200 mg kg^{-1} b.wt., restored the concentration of TNF-α suggesting ameliorative anti-inflammatory potentials of the extracts and reaffirming the possible beneficial roles of the phenolic and alkaloid extracts of *Senna occidentalis* leaf in the management of diabetic nephropathy[55]. Apart from the significant and promising ameliorative effect of the phenolic extract at 200 mg kg^{-1} b.wt., on diabetic nephropathy injury, the management of diabetic nephropathy will also benefit from the antioxidant and anti-inflammatory potentials of the *Senna occidentalis* leaf. Thus, the *Senna occidentalis* leaf could be explored in the development of leads for the management of diabetic kidney disease.

CONCLUSION

The results of this research confirm that phenolic and alkaloid extracts *Senna occidentalis* leaf possesses significant anti-hyperalbuminemic, anti-hypercreatininemic, anti-hyperuremic, anti-hyperuricemic, anti-inflammatory and antioxidant potential which qualify the extracts to be explored in the management of diabetic nephropathy. Bioactive

components of *Senna occidentalis* leaf alkaloid and phenolic extracts should be identified, isolated and explored for the development of drug leads that can be used in the management of diabetic nephropathy.

SIGNIFICANCE STATEMENT

This study discovers that apart from the known benefits of Senna occidentalis in the management of diabetes mellitus, its phenolic and alkaloid extracts are promising for the management of diabetic nephropathy. This research thus gives a pointer to a new repository of natural entities that could be explored by researchers for the development of therapies for the management of diabetic kidney disease.

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