JCTEI
JOURNAL OF CLINICAL TRIALS AND EXPERIMENTAL INVESTIGATIONS
Year: 2025 Volume: 4 Issue: 3

ORIGINAL ARTICLE

10.5281/zenodo.17148460

Nephroprotective effect of propionic acid via mitigation of oxidative stress and inflammation in experimental type 2 diabetic rats

Oluwatosin Okunlola[1], Folasade Omobolanle Ajao*[1], Kehinde Samuel Olaniyi[1], Noheem Olaoluwa Kalejaiye[1], Marcus Olaoye Iyedupe[1]

1. *Physiology Department, Faculty of Basic Medical Science, College of Health Science, Ladoke Akintola University of Technology, P.M.B. 4000, Ogbomoso, Oyo State, Nigeria*

Correspondence
Ajao Folasade O. Department of Physiology, Ladoke Akintola University of Technology, P.M.B. 4000 Ogbomoso, 210214, Nigeria. Tel: +2348034659049.

e-mail
foajao@lautech.edu.ng

Received: 14 August 2025
Revised: 7 September 2025
Accepted: 14 September 2025
Published: 30 September 2025

Keywords
- Propionic acid
- kidney biomarkers
- lipid profile
- oxidative stress and inflammation

ORCID ID of the author(s):
OO: 0009-0003-5315-8530
FOA: 0000-0001-8839-4689
KSO: 0000-0002-8229-9688
NOK: 0009-0007-3949-8220
MOI: 0000-0003-0992-6857

Abstract

Objective: Discovering a novel compound from medicinal plants as alternative medicine to manage diabetes and related complications is a global issue. This study investigated the renoprotective effects of propionic acid in high-fat diet (HFD)/streptozotocin (STZ)-induced rat model.

Materials and methods: Fifty male mature rats (200 - 220 g) were used. Rats were fed with HFD for 8 weeks. A repeated dose of freshly prepared STZ (30 mg/kgb.wt) was injected intraperitoneally to induce diabetes. The rats were grouped into 5 groups (n=10). Group I: control; Group II: control + 60 mg/kgb.wt propionic acid; Group III: diabetic control; Group IV: diabetic + 60 mg/kgb.wt propionic acid; Group V: diabetic + 200 mg/kgb.wt metformin. The rats were anaesthetized and sacrificed after 21 days of treatment. Serum retrieved from the blood samples and supernatant plasma obtained from kidney homogenates after centrifugation were used for biochemical assay.

Results: Insulin, fasting blood glucose (FBG), glycated hemoglobin (HbA1c), kidney potassium, creatinine, urea, uric acid, triglycerides, total-cholesterol (TC), low-density-lipoprotein (LDL-C), malondialdehyde, tumor-necrosis-factor-α (TNF-α), transformation-growth-factor-beta (TGF-β), interleukin-6 (IL-6),and caspase-3 significantly ($p<0.001$) increased in diabetic rats. Body weight, high-density-lipoprotein (HDL-C), chloride bicarbonate, sodium, superoxide dismutase (SOD), catalase, reduced glutathione (GSH) and Bcl-2 decreased significantly. Propionic acid administration reduced insulin, FBG, HbA1c, kidney biomarkers, triglycerides, TC, LDL-C, malondialdehyde and inflammatory markers. Body weight, antioxidant activity, HDL-C and Bcl-2 levels were improved.

Conclusion: Propionic acid attenuated kidney oxidative stress and inflammation. Therefore, propionic acid could be used to prevent renal damage and improve renal function in diabetes.

Cite as: Okunlola O, Ajao FO, Olaniyi KS, et al. Nephroprotective effect of propionic acid via mitigation of oxidative stress and inflammation in experimental type 2 diabetic rats. J Clin Trials Exp Investig. 2025;4(3):77-88.

Introduction

The global prevalence of diabetes mellitus was 536.6 million in 2021 and is projected to increase to 642.7 million by 2030 and 783.2 million by 2045, which is almost 46% increase in the prevalence (1). Global estimates indicate that one in ten adults are currently living with diabetes, of which over 90% of cases are attributed to Type 2 diabetes mellitus T2DM (2).

T2DM is a common metabolic disorder that is caused as a result of inability of tissues to respond properly to insulin produced by beta-cell of pancreas (3). The organs involved in T2DM development include the pancreas (β-cells and α-cells), kidneys, liver, skeletal muscle, brain, small intestine, and adipose tissue (4). T2DM is the most common form of diabetes mellitus (DM) with several complications (5).

The pathological relationship between oxidative stress and inflammation has devastating outcomes that lead to the progression of T2DM complications (6). Oxidative stress normally arises due to the excessive production of free radicals, especially reactive oxygen species (ROS) that severely affect the neutralizing capacity of intracellular antioxidants (7). Generally, oxidative stress may induce its destructive effects through causing damage to DNA, proteins, and lipids. Uncontrolled oxidative stress aggravates the micro-vascular and macro-vascular complications related to diabetes such as nephropathy, retinopathy, neuropathy and cardiomyopathy (8).

During T2DM, elevated blood glucose levels lead to an undesired inflammatory response, which may be exacerbated by inflammatory intermediaries produced by adipocytes and macrophages in adipose tissue. This process may initiate the low-grade, chronic inflammatory state that cause deficit insulin secretion, there by leading to chronic hyperglycemia which facilitate the release of inflammatory cytokines and uncontrolled inflammation response has been positioned among the foremost factors in the pathogenesis of T2DM and associated complications (9).

The kidney is a vital organ that play significant roles in the body, including eliminating of toxic waste products out of the body, body fluid physiological levels maintenance, regulation of blood pressure via renin-angiotensin-aldosterone system, production of 1, 25-dihyrdocholecalciferol bone formation, and releasing of erythropoietin hormone for erythrocytes production (10). Unmanaged chronic hyperglycemia causes metabolic disturbances that consequence in enlargement of glomerular tissue, glomerulosclerosis, inflammation in tubular interstitial, and fibrosis are suggested to be patho-etiology of nephropathy in diabetes (11). Diabetic nephropathy is common complication developed in both type 1 and type 2 diabetes patients (12). This can be the foremost common complication for proteinuric and non-proteinuric end-stage renal disease and later advanced into kidney disease in diabetes patients, which cause morbidity in prolonged diabetic nephropathy (13, 14).

There are several glucose-lowering agents that are available globally to manage T2DM; one of which is metformin (a first-line oral antidiabetic drug). However, the available drugs are limited by their several undesirable and unwanted side effects, such as diarrhea and lactic acidosis demonstrated by metformin (15, 16). There is a growing need for an affordable alternative therapy with efficient blood glucose lowering potentials without adverse toxicity; and natural products like medicinal plants have been validated to offer a significant contribution due to their numerous bioactive compounds (17). *Anacardium occidentale* (Anacardiaceae), is a medicinal plant, commonly known as "Cashew" with remarkable therapeutic effects (18). A comparative study has been done on its leaf, nut and stem bark which revealed its anti-hyperglycemic properties (19). *Anacardium occidentale* nut has been reported to attenuate dyslipidemia in rats (20). *Anacardium occidentale* nuts are rich sources of various chemical compounds such as unsaturated fatty acids (UFAs) oleic acid (-9) and linoleic acid (-6), flavonoids, anthocyanins, tannins, tocopherols, fiber and folate which are potent antioxidants that protect cells from damage caused by free radicals and reduce chronic diseases risk (21). A previous study by Ajao *et al.* (2023) revealed the bioactive constituents of *A. occidentale* nut related for diabetes treatment using gas chromatography-mass spectrometry and molecular docking (22). The gas chromatography-mass spectrometry and molecular docking of *A. occidentale* nut methanolic extract revealed that oleic acid, 3-(p-methoxyphenyl)-propionic acid and tridecanoic acid from *Anacardium occidentale* nut methanolic extract is excellent molecules with drug-likeness owing to their inhibitory potentials on selected proteins related to diabetes mellitus pathogenesis progression (22). However, this compounds with the best drug-like candidate for diabetes therapy, have not been experimentally confirmed in mitigating organ damage in diabetes. Therefore, the present research first investigated the renoprotective effects of propionic acid in type 2 diabetic rats.

Materials and methods

Chemicals and drugs: Streptozotocin, iced-cold phosphate buffer, distilled water, normal saline, ketamine, propionic acid and metformin.

Experimental animals

Fifty adult male Wistar rats weighing 200-220g were used in this study. The animals were kept inside a clean polypropylene cage at the Animal House of Department of Physiology, Ladoke Akintola University of Technology, Ogbomoso, Oyo State, Nigeria. The animals were acclimatized for 2 weeks with access to feed and water *ad libitum* under pathogen-free standard laboratory conditions, relative humidity (45-50%); temperature (25-27°C) and 12:12 hrs light/dark cycle. All procedures were strictly followed the guidelines of National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals.

Induction of diabetes

Forty rats were fed with a high-fat diet (HFD) and 10 rats were fed with a normal diet for 8 weeks prior to diabetes induction. After the 8 weeks, the animals were fasted overnight (12 hours) and diabetes was induced in the HFD animals with repeated low doses of a freshly prepared streptozotocin (STZ) (30 mg/kgb.wt) solution injected at the peritoneal cavity for 5 consecutive days according to Tan *et al.* method (23). The rats were administered with 20% glucose solution following the STZ injection to prevent drug-induced hypoglycemic death. Diabetes induction was confirmed 72 hours after streptozotocin injection using Accu-check glucometer. Animals that had a blood glucose level higher than 200mg/dL were selected as diabetic for this study.

Animal grouping

Ten non-diabetic rats served as control and forty rats were rendered diabetic. The animals were randomly distributed into 5 groups, 10 rats/group as follows:

- Group I: Control (non-diabetic)
- Group II: Control + 60 mg/kgb.wt Propionic Acid (PA)
- Group III: T2DM control
- Group IV: T2DM + 60 mg/kgb.wt Propionic Acid (PA)
- Group V: T2DM + 200 mg/kgb.wt Metformin (MET)

The treatment lasted for 6 weeks. Food and water consumption were taken daily. Body weight was recorded weekly.

Oral glucose tolerance test (OGTT) and fasting blood glucose (FBG) determination

Oral Glucose Tolerance Test (OGTT) was performed on all the animals after 6 weeks of treatment. The rats were fasted overnight for 14 hours and were given glucose solution (2 g/kgb.wt) via oral route, using Salahuddin and Jalalpure method (24). Blood glucose levels of each animal were taken using the rats' pricked tail vein blood dropped on a glucometer at time intervals 0 min (before glucose administration) and at 30, 60, 90, and 120 minutes after being given the glucose solution.

Biochemical assays

After six weeks of treatment, the rats were fasted overnight (12 hours), anaesthetized with ketamine (40 mg/kgb.wt) injected intraperitoneally and sacrificed by dislocation of the cervical. The hearts were accessed through thoracotomy, and blood samples were collected from the apex beat of the animals via cardiac puncture. The blood samples were centrifuged at 3000 rpm for 15 minutes at -4°C and the serum collected was used for estimation of biochemical analysis.

The kidneys were isolated, washed in normal saline, homogenized in iced-cold phosphate buffer and centrifuged at 5000 rpm for 10 minutes using a cold centrifuge at (-4°C). The supernatant plasma obtained was used for the biochemical assays.

Insulin and glycated hemoglobin (HbA1c) levels were measured using the enzyme-linked immunosorbent assay (ELISA) method with rat insulin and HbA1c assay kits.

kidney electrolytes and biomarkers sodium (Na^+) potassium (K^+), Chloride (Cl^-), bicarbonate ($HCO3^-$) creatinine, blood urea nitrogen (BUN) and uric acid were determined with available commercial kits following the manufacturer's guidelines.

Kidney triglycerides (TG), total cholesterol (TC), and high-density lipoprotein-cholesterol were determined using an enzymatic colorimetric method with commercial kits according to the manufacturer's instructions, and kidney low-density lipoprotein-

cholesterol (LDL-C) was calculated by Friedewald *et al*. (25) method: LDL-C = TC – (HDL-C + TG/5).

Kidney malondialdehyde (MDA) level and antioxidant superoxide dismutase (SOD) and catalase (CAT) levels were measured by enzyme linked immunosorbent assay (ELISA) methods using Rat MDA, SOD and CAT commercial Elisa Kit (Elabscience, China) according to manufacturer's instruction. Glutathione reductase (GSH) was measured based on the Gupta and Gupta method.

Pro-inflammatory cytokines - tumor necrosis factor-alpha (TNF-α), anti-inflammatory interleukins-6 (IL-6), caspase-3 (apoptotic marker), and B cell lymphoma-2 (Bcl-2, anti-apoptotic marker) were determined by enzyme-linked immunosorbent assay (ELISA) method using each assay specific ultrasensitive rats sandwich-ELISA kits following manufacturer's protocols.

Statistical analysis

Data were expressed as standard error of the mean (mean ± SEM). Data were statistically analysed using GraphPad Prism (version 5.0 software, Inc, USA) with one-way analysis of variance (ANOVA) followed by a Bonferroni *posthoc* test for multiple groups comparison to determine significant differences. Statistical significances were considered at $p<0.05$.

Results

Effect of Propionic acid on feed intake, water intake, body weight and relative kidney weight in HFD/STZ-induced diabetic rats

Feed and water intake increased ($p<0.001$) significantly in the diabetic rats compared with control. The treatment of diabetic rats with propionic acid significantly reduced food and water intake compared with the diabetic group. The body weight of diabetic rats reduced ($p<0.001$) significantly compared with control while the relative kidney weight significantly ($p<0.001$) increased compared with control. In the treated group, administration of propionic acid significantly improved the body weight and relative kidney weight compared with diabetic rats. No significant difference in relative kidney weight in the metformin treated group (Table 1).

Effect of Propionic acid on OGTT and FBG level in HFD/STZ-induced diabetic rats

Diabetic group exhibited a significant ($p<0.001$) increase in oral glucose tolerance test at 0, 30, 60, 90 and 120 mins compared to the control group. The administration of propionic acid and metformin significantly ($p<0.001$) decreases oral glucose concentration at 0, 30, 60, 90 and 120 mins in the treated group as compared to the diabetic group (Figure 1A). Diabetic rats showed a significant ($p<0.001$) increase in the FBG levels compared with the control group. However, administration of propionic acid significantly decreased the FBG levels compared to the diabetic group (Figure 1B).

Effect of Propionic acid on insulin and HbA1c level in HFD/STZ-induced diabetic rats

There was a significant ($p<0.001$) increase in insulin and HbA1c levels in diabetic rats when compared with the control. Administration of propionic acid significantly ($p<0.001$) decreased the insulin and HbA1c levels compared to the diabetic group (Figure 1C and 1D).

Effect of Propionic acid on kidney electrolytes in HFD/STZ-induced diabetic rats

Bicarbonate, sodium, and chloride levels significantly ($p<0.001$) decrease in the diabetic rats compared with the control. Administration of propionic acid significantly ($p<0.001$) increased the bicarbonate, sodium and chloride levels compared with diabetic rats (Figure 2A, 2B and 2C). Potassium level significantly ($p<0.001$) increased in the diabetic rats compared with the control. Administration of propionic acid significantly ($p<0.001$) decreased the level of potassium compared with T2DM rats (Figure 2D).

Effect of Propionic acid on kidney function biomarkers in HFD/STZ-induced diabetic rats

Urea, creatinine and uric acid levels significantly ($p<0.001$) increase in the diabetic rats compared with the control. Administration of propionic acid significantly ($p<0.001$) decreases the urea, creatinine and uric acid levels compared with diabetic rats (Figure 2E, 2F and 2G).

Effect of Propionic acid on kidney lipid profile in HFD/STZ-induced diabetic rats

TG, TC, and LDL-C levels significantly ($p<0.001$) increased in the diabetic rats compared with the control. HDL level was significantly ($p<0.001$) reduced in the diabetic rats compared with the control. Administration of propionic acid significantly ($p<0.001$) increased the kidney HDL and reduced the TG, TC and LDL-C levels compared with diabetic rats (Table 2).

Effect of Propionic acid on kidney oxidative stress marker in HFD/STZ-induced diabetic rats

In the kidneys of diabetic rats, reduced glutathione, superoxide dismutase, and catalase levels were significantly ($p<0.001$) reduced while, malondialdehyde (MDA) concentration significantly ($p<0.001$) increased compared with control rats. However, administration of propionic acid significantly ($p<0.001$) increased reduced glutathione, superoxide dismutase, and catalase activity and significantly reduced ($p<0.001$) MDA level compared with diabetic rats (Table 2).

Effect of Propionic acid on kidney inflammatory markers in HFD/STZ-induced diabetic rats

The levels of tumor-necrosis factor alpha (TNF-α), transforming growth factor beta (TGF-β) and interleukin-6 (IL-6) significantly ($p<0.001$) increased in diabetic rats compared with control rats. However, in the type 2 diabetic rats treated with propionic acid, there was a significant ($p<0.001$) decrease when compared with T2DM rats (Figure 3A, 3B and 3C).

Effect of Propionic acid on kidney apoptotic and anti-apoptotic markers in HFD/STZ-induced diabetic rats

Diabetic rats showed a significant ($p<0.001$) increase in kidney apoptotic marker caspase-3 and a significant ($p<0.001$) decrease in kidney anti-apoptotic marker B-cell lymphoma-2 (Bcl-2) compared with control rats. The administration of propionic acid significantly lowered the kidney caspase-3 and raised the kidney Bcl-2 levels compared with diabetic rats (Figure 3D and 3E).

Table 1: Effect of Propionic acid on food intake, water intake, body weight and kidney weight in HFD/STZ-induced diabetic rats

Parameters	CON	CON + PA	T2DM control	T2DM + PA	T2DM + MET
Food Intake (g/day/rat)	34.86±1.38	29.76±0.65	37.36±0.67[a]	29.48±1.17[b]	38.24±0.50[b]
Water Intake (ml/day/rat)	35.02±1.10	36.12±1.26	53.07±0.84[a]	34.55±1.65[b]	35.60±1.53[b]
Body Weight (g)	262.75±7.36	254.75±5.78	179.00±7.46[a]	224.75±6.49[b]	227±6.70[b]
Relative Kidney Weight (g)	0.65±0.01	0.64±0.01	0.77±0.02[a]	0.79±0.03[b]	0.73±0.04[b]

Values are expressed as mean ± SEM (n=10). [a]represents significant at p<0.001 vs CON, [b]represents significant at p<0.001 vs diabetic rats. CON: Control, PA: Propionic acid

Table 2: Effect of Propionic acid on kidney lipid profile and oxidative stress marker in HFD/STZ-induced diabetic rats

Parameters	CON	CON + PA	T2DM (control)	T2DM + PA	T2DM + MET
TG (mmol/l)	0.52±0.07	0.52±0.00	0.97±0.01[a]	0.54±0.03[b]	0.53±0.03[b]
TC (mmol/l)	2.19±0.07	2.00±0.26	3.23±0.15[a]	2.11±0.06[b]	2.17±0.05[b]
LDL (mmol/l)	1.50±0.10	1.35±0.25	2.86±0.15[a]	1.45±0.09[b]	1.48±0.02[b]
HDL (mmol/l)	0.58±0.03	0.54±0.00	0.18±0.01[a]	0.56±0.04[b]	0.58±0.05[b]
GSH (mM)	0.74±0.03	0.78±0.07	0.20±0.01[a]	0.78±0.05[b]	0.76±0.03[b]
CAT (U/mg protein)	7.68±0.43	7.74±0.30	3.81±0.24[a]	8.30±1.13[b]	7.91±0.67[b]
SOD (U/ml)	1.39±0.04	1.36±0.07	1.25±0.03[a]	0.78±0.06[b]	1.11±0.05[b]
MDA (µM)	1.02±0.02	1.11±0.01	1.91±0.02[a]	1.22±0.12[b]	1.10±0.12[b]

Values are expressed as mean ± SEM (n=10). [a]represents significant at p<0.001 vs CON, [b]represents significant at p<0.001 vs diabetic rats. CON: Control, PA: Propionic acid

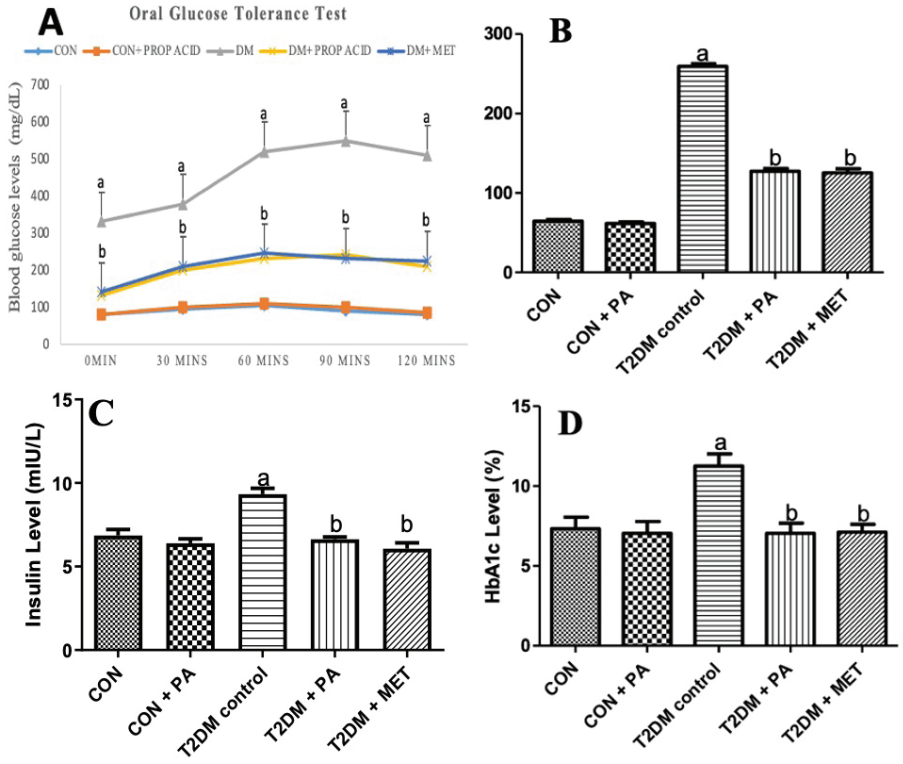

Figure 1: Effect of Propionic acid on (A) OGTT, (B) FBG, (C) Insulin, (D) HbA1c in HFD/STZ-induced diabetic rats. *Values are expressed as mean ± SEM (n=10). [a]represents significant at p<0.001 vs control, [b]represents significant at p<0.001 vs diabetic rats.*

Discussion

T2DM is one of the most serious health problems in the 21st century (26). Long-term hyperglycemia subsequently leads to the development of diabetic complications, including retinopathy, neuropathy, and diabetic nephropathy (27). Hyperglycemia, the clinical diagnosis of diabetes, present several common noticeable symptoms, including polyphagia, polydipsia, polyuria and body weight loss (21). Similar to diabetes symptoms observed in Iheagwam et al (28) study, hyperglycemia, hyperinsulinemia and reduction in body weight with other diabetes features, including frequent urination, increase in food and water intake were observed in the diabetic rats of this study. This reduction might be due to an alteration in the energy metabolism and excessive proteolysis following insulin deficiency (29). Insufficient insulin secretion prevents the body from obtaining glucose from the blood into the body's cells to be metabolized as energy, therefore causing overall body weight loss (30). Also, insulin deficit has a negative consequence on the leptin hormone that stimulates the satiety center in the hypothalamus, thereby giving rise to the release of ghrelin hormone for excessive food intake (31). Further, elevated blood glucose above the threshold that the kidney can uptake causes excessive loss of glucose in urine stimulates the thirst center in the hypothalamus, resulting in dehydration, and subsequently leads to an increase in water intake (31). An increase in insulin level is a compensatory mechanism for elevated blood glucose (31). Treatment with propionic acid decreased the blood glucose, modulated the insulin levels and body weight recovery, decreased the food intake, and water intake. These revealed that propionic acid possesses anti-hyperglycemic properties by facilitating peripheral tissues glucose uptake, inhibit hepatic glycogenolysis and gastrointestinal release of α-glucosidase and α-amylase enzymes, and increase glucose availability as an energy (ATP) for restoring muscle protein, thereby consequent in blood glucose reduction and body weight recovery via insulin action, which accords with the findings of Omoboyowa et al (30). These findings suggest that propionic acid inhibits the stimulation of the thirst center, prevents dehydration by improving kidney glucose reabsorption to decrease glucose loss via urine, which reduces water intake. Reduction in food intake implies that propionic acid represses ghrelin hormone release from the hypothalamus and modulates the leptin hormone circulation to reduce food intake, similar to Adoga et al (31) findings on the kolaviron effect on hyperglycemia in diabetic rats.

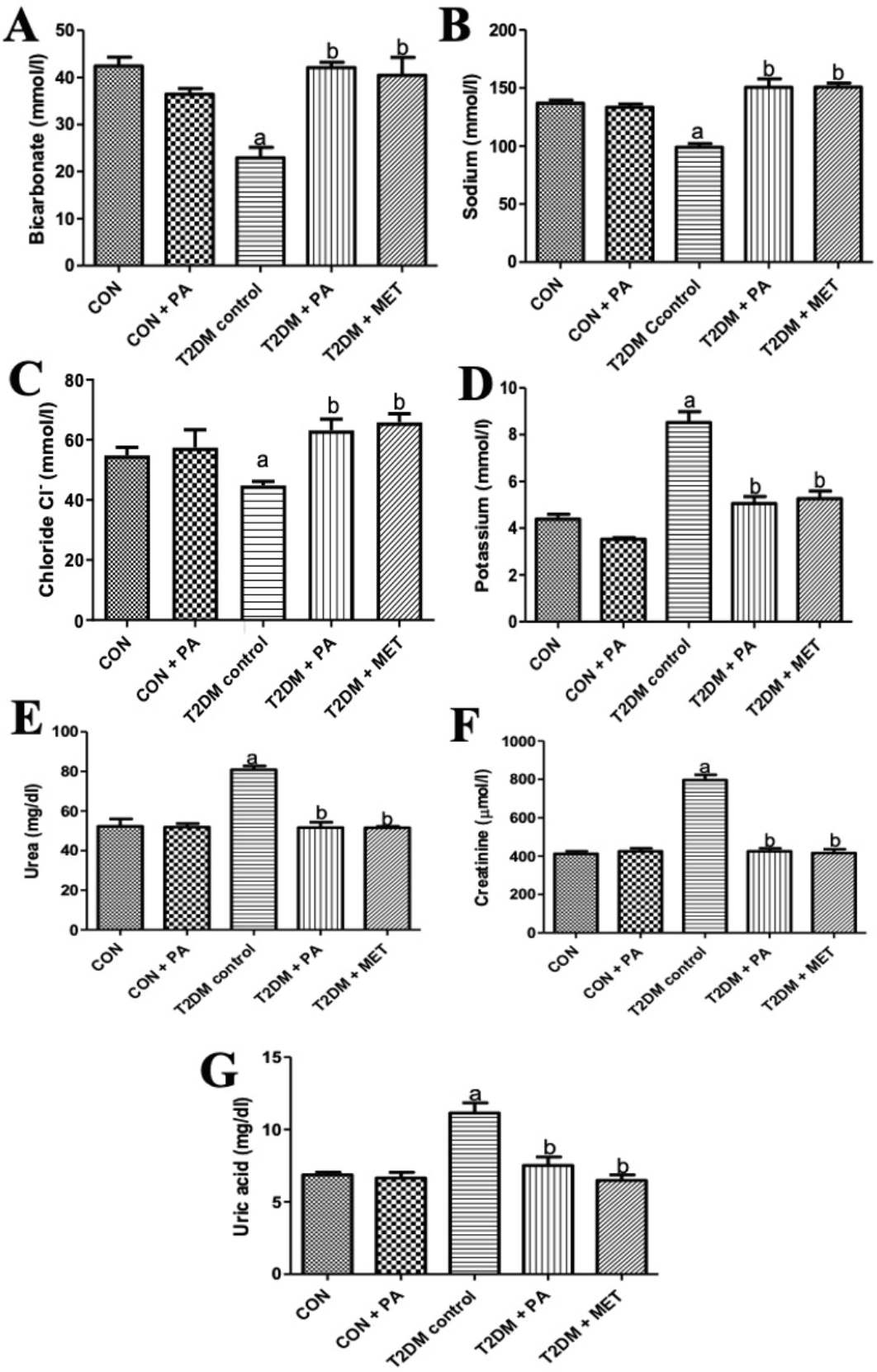

Figure 2: Effect of Propionic acid on (A) Bicarbonate, (B) Sodium, (C) Chloride, (D) Potassium, (E) Urea, (F) Creatinine, (G) Uric acid levels in HFD/STZ-induced diabetic rats. *Values are expressed as mean ± SEM (n=10).* [a]*represents significant at p<0.001 vs control,* [b]*represents significant at p<0.001 vs diabetic rats.*

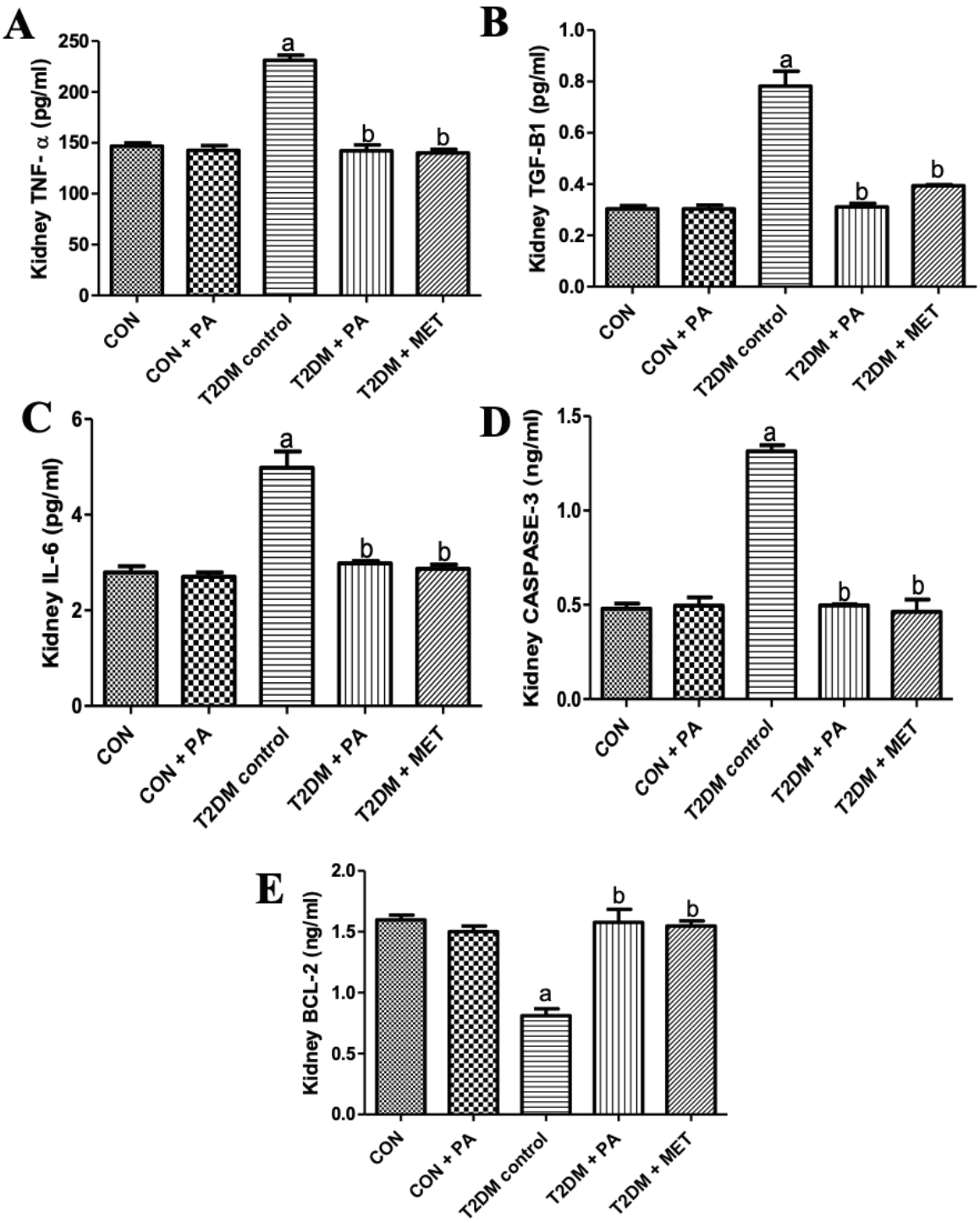

Figure 3: Effect of propionic acid on kidney (A) TNF-α, (B) TGF-β, (C) IL-6, (D) Caspase-3, (E) Bcl-2 levels in HFD/STZ-induced diabetic rats. *Values are expressed as mean ± SEM (n=10). [a]represents significant at p<0.001 vs control, [b]represents significant at p<0.001 vs diabetic rats.*

Renal dysfunction caused by hyperglycemia can lead to electrolyte imbalance by disrupting the kidney electrolyte absorption and reabsorption process (32). People with diabetes often develop diverse electrolyte derangements such as hyponatremia, hyperkalemia, hypochloremia, and bicarbonate (32). Electrolyte imbalance in diabetes is traced to impaired glucose and insulin levels as well as renin-angiotensin-aldosterone system inhibition (33). Electrolyte imbalance triggers kidney failure and has been considered as one of the factors contributing to diabetes complications and other metabolic disorders progression. In addition, hyperglycemia promotes osmotic diuresis in the internal environment, causing a dilutional effect on

electrolyte levels (34). Hyponatremia, hypochloremia, hyperkalemia, and low bicarbonate observed in this study also establish electrolyte imbalance in the diabetic rats. This may be linked with osmotic diuresis build up by hyperglycemia, thereby resulting in body fluids and electrolyte loss (35). However, the administration of propionic acid averts a simultaneous increase in potassium level and upsurges the level of bicarbonate, sodium, and chloride, which corresponds with the findings of Olorunnisola et al (36).

Serum biomarkers such as creatinine, urea and uric acid are usually used in clinical diagnostics to assess kidney function (37). Kidney function deficiency is also established through metabolic impairment. Serum urea and uric acid are byproducts of protein and purine nucleotide metabolism. Elevated levels of these biomarkers serve as indicators of deficiency in kidney function, reflecting a reduction in the kidney's ability to filtrate or reabsorb efficiently (38,39). In diabetes patients, high levels of urea, uric and creatinine are an indication of renal damage and have been linked with uncontrolled hyperglycemia (40). In line with the previous findings of Soji-Omoniwa et al (41), diabetic rats of the present study exhibited renal dysfunction, evidenced by an increase in serum biomarkers urea, creatinine and uric acid levels. The increases in these biomarkers suggest progression of renal necrosis and reduction in tubular reabsorption (41). However, the administration of propionic acid significantly reduces the urea, creatinine and uric acid levels. This corresponds to the findings of Almatroodi et al. on 6-Gingerol, a bioactive compound of ginger attenuates renal damage (42).

Dyslipidemia in hyperglycemia is a typical rise in blood triglyceride (TG), total cholesterol, low-density lipoprotein-cholesterol (LDL-C), and high-density lipoprotein-cholesterol (HDL-C) (43). In line with findings of Adelakun et al. (44), diabetic rats in this study exhibited high levels of TG, TC and LDL, accompanied by decreased HDL levels in the kidney. This could be a result of dysregulation of hormone-sensitive lipase activity by insulin deficiency (45). However, administration of propionic acid significantly reduced the TG, TC and LDL levels and increased the HDL levels. This proves that propionic acid possesses hypolipidemic properties by clearing the excess fat deposition from the kidney due to improved insulin sensitivity action (46).

Persistent hyperglycemia and hyperlipidemia alter the cellular homeostasis, leading to the induction of oxidative stress that exacerbates overproduction of free radicals which is known as a contributing factor in diabetic nephropathy development (27). The imbalance between oxidation and antioxidant systems, and excessive reactive oxygen species (ROS) generation are the key pathogenic factors in renal disease (42). Antioxidants glutathione and catalase levels were reduced and malondialdehyde concentration increased in diabetic rats of this study, which is in accord with findings of Omiyale et al (47). The imbalance in the physiological level of renal oxidative stress consequently damages the kidney and facilitates the loss of renal function (48). Administration of propionic acid to the diabetic rats improves the kidney antioxidant activities and decreases oxidative stress markers, suggesting that propionic acid is a strong bioactive compound with anti-oxidative properties in scavenging free radicals, thereby preventing oxidative damage in the kidney. As previously reported, activation of 5' adenosine monophosphate-activated protein kinase (AMPK) signalling and nuclear factor erythroid 2-related factor 2 (NRF2) regulate the oxidative stress imbalance. AMPK signalling diminish reactive oxygen species generation by modulating insulin secretion for glucose uptake and inhibit lipid synthesis, and activation of NRF2 enhance the up regulation of glutathione peroxidase and catalase via inhibition of gluconeogenesis by supress the glucose metabolism hormones (49). Propionic acid may exert this anti-oxidative effect via activation of AMPK signaling, and NRF2 pathways, consistent with the report of Naidoo et al (50), on the likely mechanism Gossypetin attenuates the oxidative stress in liver.

Persistent hyperglycemia generates excess free radicals that overwhelm the antioxidant defense system promote renal inflammation response and mitochondrial dysfunction (51). Increased levels of inflammatory mediators in blood have been attributed to the consequence of chronic hyperglycemia and these pro-inflammatory cytokines are found at higher concentrations in individuals with diabetes, thereby resulting to cellular apoptosis (52). In this study, an increase in TNF-α, TGF-β and IL-6 levels was observed in the diabetic rats, which agrees with Ahmad et al (53) findings. Studies involving natural products and compounds have demonstrated potential in the attenuation of diabetic nephropathy by the inhibition of the inflammatory process (42). The administration of propionic acid remarkably inhibits the overexpression of those inflammatory markers and could be due to the strong anti-oxidative neutralizing potential possessed by propionic acid, which supports the report of Dare et al (54) on L-ergothioneine and its combination with metformin attenuates renal dysfunction in type-2 diabetic rat model by activating Nrf2 antioxidant pathway.

Apoptosis is a physio-biological process necessary for the maintenance of cellular homeostasis. Hyperglycemia alter the apoptotic process by increasing the pro-apoptotic protein caspase-3 and decreasing the anti-apoptotic protein Bcl-2 (21). In this study, increase in caspase-3 levels with a concurrent decrease in Bcl-2 levels (anti-was observed in the diabetic rats, which corroborates the findings of Yang *et al.* (55). Administration of propionic acid reduces caspase-3 levels and improves Bcl-2 levels. These showed that propionic acid had anti-apoptotic potential by alleviating caspase-3 levels, these findings is in concordance with the previous report of Wang *et al* on the kidney (56). The efficacy of propionic acid to suppress anti-apoptotic markers might result from the attenuation of oxidative stress, equilibration of the antioxidant defense system and inhibition of inflammatory cytokine overexpression.

Conclusions

The present study demonstrates that propionic acid has anti-diabetic, antioxidant, and renoprotective effects by alleviating kidney inflammation and oxidative stress. Therefore, propionic acid could help in managing renal damage and renal function deterioration in T2DM. Furthermore, consumption of the *Anacardium occidentale* nuts could be a natural source of propionic acid supplement to the diet in preventing the development of T2DM and related complications.

Conflict of interest: The authors report no conflict of interest.

Funding source: No funding was required.

Ethical approval: All procedures were strictly followed the guidelines of National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals. Ethical approval for the study was obtained from the Ethical Research Committee of the Faculty of Basic Medical Sciences, LAUTECH, Ogbomoso, Oyo State, Nigeria with approval number: ERCFBMSLAUTECH: 049/06/2024.

Informed consent: Not applicable

Acknowledgments: None

Peer-review: Externally. Evaluated by independent reviewers working in at least two different institutions appointed by the field editor.

Data availability: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Contributions

Research concept and design: FOA, KSO, OO, NOK

Data analysis and interpretation: OO, FOA, KSO, NOK, MOI

Collection and/or assembly of data: OO, FOA, KSO, NOK, MOI

Writing the article: MOI, OO

Critical revision of the article: OO, MOI, FOA

Final approval of the article: OO, FOA, KSO, NOK, MOI

All authors read and approved the final version of the manuscript.

References

1. Joseph A, Thirupathamma M, Mathews E, Alagu M. Genetics of type 2 diabetes mellitus in Indian and Global Population: A Review. Egypt J Med Hum Genet. 2022;23:135.
2. International Diabetes Federation. IDF Diabetes Atlas Tenth Edition. (cited 10 September 2022). Available from: https://diabetesatlas.org/
3. Ojo OA, Ibrahim HS, Rotimi DE, Ogunlakin AD, Ojo AB. Diabetes mellitus: From molecular mechanism to pathophysiology and pharmacology. Med Novel Technol Devices. 2023;19:100247.
4. DeFronzo RA, Tripathy D. Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. Diabetes Care. 2009;32 Suppl 2:S157–63.
5. Aghaei Zarch SM, Dehghan Tezerjani M, Talebi M, Vahidi Mehrjardi MY. Molecular biomarkers in diabetes mellitus (DM). Med J Islam Repub Iran. 2020;34:28.
6. Halim M, Halim A. The effects of inflammation, aging and oxidative stress on the pathogenesis of diabetes mellitus (type 2 diabetes). Diabetes Metab Syndr. 2019;13:1165-72.
7. Asmat U, Abad K, Ismail K. Diabetes mellitus and oxidative stress: A concise review. Saudi Pharm J. 2016;24:547-53.
8. Dludla PV, Mabhida SE, Ziqubu K, Nkambule BB, Mazibuko-Mbeje SE, Hanser S, et al. Pancreatic β-cell dysfunction in type 2 diabetes: Implications of inflammation and oxidative stress. World J Diabetes. 2023;14(3):130-46.

9. Berbudi A, Rahmadika N, Tjahjadi AI, Ruslami R. Type 2 Diabetes and its impact on the immune system. Curr Diabetes Rev. 2020;16:442-9.

10. Pillai A, Fulmali D. A narrative review of new treatment options for diabetic nephropathy. Cureus. 2023;15(1):e33235.

11. Kostovska I, Trajkovska KT, Topuzovska S, Cekovska S, Labudovic D, Kostovski O, et al. Nephrinuria and podocytopathies. Adv Clin Chem. 2022;108:1-36.

12. Zhou Z, Luo R, Wan Z, Kuang H, Lyu J. Advances in the role of autoantibodies in diabetic nephropathy: review (Article in Chinese). Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi. 2020;36:175-9.

13. Warren AM, Knudsen ST, Cooper ME. Diabetic nephropathy: an insight into molecular mechanisms and emerging therapies. Expert Opin Ther Targets. 2019;23:579-91.

14. Maiti AK. Development of biomarkers and molecular therapy based on inflammatory genes in diabetic nephropathy. Int J Mol Sci. 2021;22:9985.

15. Li Q, Wang X, Guo A, Zheng W, Bi J, He Y, et al. The curative effect of metformin and linagliptin in newly-diagnosed type 2 diabetes patients with nonalcoholic fatty liver disease. Int J Clin Exp Med. 2021;14(1):391-8.

16. Okur ME, Ozbek H, Polat DC, Yılmaz S, Arslan R. Hypoglycemic activity of Capparis ovata desf. var. palaestina zoh. methanol extract. Braz J Pharm Sci. 2018;54.

17. Rahman MM, Dhar PS, Anika SF, Ahmed L, Islam MR, Sultana NA, et al. Exploring the plant-derived bioactive substances as anti-diabetic agent: An extensive review. Biomed Pharmacother. 2022;152:113217.

18. Siracusa R, Fusco R, Peritore AF, Cordaro M, D'Amico R. The antioxidant and anti-inflammatory properties of Anacardium occidentale L. cashew nuts in a mouse model of colitis. Nutrients. 2020;12:834.

19. Ajao FO, Akanmu O, Iyedupe MO. Comparative effects of cashew nut, leaf and stem bark (Anacardium occidentale L.) on hyperglycemia and associated abnormalities in streptozotocin-induced diabetic rats. J Drug Deliv Ther. 2022;12(4):47-55.

20. Dias CCQ, Madruga MS, Pintado MM, et al. Cashew nuts (Anacardium occidentale L.) decrease visceral fat, yet augment glucose in dyslipidemic rats. PLoS One. 2019;14(12):e0225736.

21. Cordaro M, Siracusa R, Fusco R, D'Amico R, Peritore AF. Cashew (Anacardium occidentale L.) nuts counteract oxidative stress and inflammation in an acute experimental model of carrageenan-induced paw edema. Antioxidants. 2020;9:660.

22. Ajao FO, Iyedupe MO, Akanmu O, Kalejaiye NO, Adegoke AL. Anti-oxidative, anti-inflammatory and anti-apoptotic efficacy of Anacardium occidentale nuts methanolic extract in pancreas of high-fat diet/streptozotocin-induced diabetic rats. Int J Diabetes Clin Res. 2023;10:177.

23. Tan Y, Zhang Z, Zheng C, Wintergerst KA, Keller BB, Cai L. Mechanisms of diabetic cardiomyopathy and potential therapeutic strategies: preclinical and clinical evidence. Nat Rev Cardiol. 2020;1-23.

24. Salahuddin M, Jalalpure SS. Antidiabetic activity of aqueous fruit extract of Cucumis trigonus Roxb. in streptozotocin-induced diabetic rats. J Ethnopharmacol. 2010;127:565–7.

25. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18(6):499–502.

26. Natrus LV, Osadchuk YS, Lisakovska OO, Labudzinskyi DO, Klys YG, Chaikovsky YB. Effect of propionic acid on diabetes-induced impairment of unfolded protein response signaling and astrocyte/microglia crosstalk in rat ventromedial nucleus of the hypothalamus. Neural Plast. 2022;2022:6404964.

27. Boonphang O, Ontawong A, Pasachan T, Phatsara M, Duangjai A, Amornlerdpison D, et al. Antidiabetic and renoprotective effects of Coffea arabica pulp aqueous extract through preserving organic cation transport system mediated oxidative stress pathway in experimental type 2 diabetic rats. Molecules. 2021;26:1907.

28. Iheagwam FN, Iheagwam OT, Onuoha MK, Ogunlana OO, Chinedu SN. Terminalia catappa aqueous leaf extract reverses insulin resistance, improves glucose transport and activates PI3K/AKT signalling in high fat/streptozotocin-induced diabetic rats. Sci Rep. 2022;12:10711.

29. Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, et al. Pathophysiology of type 2 diabetes mellitus. Int J Mol Sci. 2020;21(17):6275.

30. Omoboyowa DA, Afolabi FO, Aribigbola TC. Pharmacological potential of methanol extract of Anacardium occidentale stem bark on alloxan-induced diabetic rats. Biomed Res Ther. 2018;5(7):2440-54.

31. Adoga JO, Channa ML, Nadar A. Kolaviron attenuates cardiovascular injury in fructose-streptozotocin induced type-2 diabetic male rats by reducing oxidative stress, inflammation, and improving cardiovascular risk markers. Biomed Pharmacother. 2021;144:112323.

32. Ahmed AA, Alsalmi W. Disturbance of electrolytes (Na, K and Cl) homeostasis among patients with type II diabetes mellitus. Libyan J Med Res. 2022;16(2):153-60.

33. Lagat JK, Ng'wena AGM, Mwaniki DM. Effects of Achyranthes aspera, Bidens pilosa and Ajuga remota leaf extracts on serum glucose and electrolyte

levels in alloxan treated male goats. Afr J Health Sci. 2021;34(4):537-49.

34. Ojiako OA, Chikezie PC. Blood Na+/K+ and Cl- levels of hyperglycemic rats administered with traditional herbal formulations. Pharmacogn Commun. 2015;5(2):140-4.

35. Obafemi TO. Gallic and hesperidin ameliorate electrolyte imbalances in AlCl3-induced nephrotoxicity in Wistar rats. Biochem Res Int. 2022;2022:1-10.

36. Olorunnisola OS, Adetutu A, Popoola RB, Owoade AO, Adegbola P, Adesina BT. Nephroprotective effect of ethanolic leaf extract of Thaumatococcus danielli (Benth.) in streptozotocin induced diabetic rats. Funct Foods Health Dis. 2017;7(12):923-35.

37. He J, Wan Y, Fan X, Yu H, Qin Y, Su J, et al. Associations between kidney function with all-cause and cause-specific mortality in type 2 diabetes mellitus patients: a prospective cohort study in China. J Health Popul Nutr. 2025;44(1):77.

38. Laville SM, Couturier A, Lambert O, Metzger M, Mansencal N, et al. Urea levels and cardiovascular disease in patients with chronic kidney disease. Nephrol Dial Transplant. 2022;38(1):184-92.

39. Tang X, Xu L, Meng RG, Du YQ, Liu SJ, et al. Association between serum uric acid and the early marker of kidney function decline among Chinese middle-aged and older population: evidence from the China health and retirement longitudinal study. Biomed Environ Sci. 2023;36(3):231-40.

40. Ife AV, Abah MA, Moranyo AE. Effect of Cucumis callosus fruit extract on the liver function of DMBA-induced mammary cancer in female albino Wistar rats. Int J Complement Altern Med. 2024;17(6):255-61.

41. Soji-Omoniwa O, Falegan MP, Omoniwa BP, Olundegun WM, Jugu TY. Effect of co-administration of metformin and aqueous leaf extract of Bryophyllum pinnatum on kidney function indices in diabetic rats. Sci World J. 2024;19(4).

42. Almatroodi SA, Alnuqaydan AM, Babiker AY, Almogbel MA, Khan AA, Rahmani AH. 6-Gingerol, a bioactive compound of ginger attenuates renal damage in streptozotocin-induced diabetic rats by regulating the oxidative stress and inflammation. Pharmaceutics. 2021;13:317.

43. Beverly JK, Budoff MJ. Atherosclerosis: Pathophysiology of insulin resistance, hyperglycemia, hyperlipidemia, and inflammation. J Diabetes. 2020;12(2):102-4.

44. Adelakuna SA, Akomaye AJ, Omotoso OD, Arowosegbe OA. Anti-hepatopathy and anti-nephropathy activities of Taraxacum officinale in a rat model of streptozotocin diabetes-induced hepatorenal toxicity and dyslipidemia via attenuation of oxidative stress, inflammation, apoptosis, electrolyte imbalances, and mitochondrial dysfunction. Aspects Mol Med. 2024;3:100034.

45. Abdelazeim SA, Shehata NI, Aly HF, Shams SGE. Amelioration of oxidative stress-mediated apoptosis in copper oxide nanoparticles-induced liver injury in rats by potent antioxidants. Sci Rep. 2020;10(1):1-14.

46. Madić V, Petrović A, Jušković M. Polyherbal mixture ameliorates hyperglycemia, hyperlipidemia and histopathological changes of pancreas, kidney and liver in a rat model of type 1 diabetes. J Ethnopharmacol. 2021;265:113210.

47. Omiyale BO, Ekundayo BE, Mathenjwa-Goqo MS, Ajiboye BO, Oyinloye BE. Protective effect of phenolic-rich extract of Annona muricata Linn leaf on renal oxidative stress and inflammation in streptozotocin-induced diabetes in diabetic rats. Sci Afr. 2025;27:02515.

48. Murtaza S, Khan JA, Aslam B, et al. Pomegranate peel extract and quercetin possess antioxidant and hepatoprotective activity against concanavalin A-induced liver injury in mice. Pak Vet J. 2021;41:197-202.

49. Petsouki E, Cabrera SNS, Heiss EH. AMPK and NRF2: Interactive players in the same team for cellular homeostasis? Free Radic Biol Med. 2022;190:75-93.

50. Naidoo K, Khathi A. Investigating the effects of gossypetin on liver health in diet-induced pre-diabetic male Sprague Dawley rats. Molecules. 2025;30:1834.

51. Amorim RG, Guedes GDS, Vasconcelos SMDL, Santos JCDF. Kidney disease in diabetes mellitus: cross-linking between hyperglycemia, redox imbalance and inflammation. Arq Bras Cardiol. 2019;112:577-87.

52. Chen TL, Xu EL, Lu HJ, Xu H, Wang SF, et al. The influence of diabetes-enhanced inflammation on cell apoptosis and periodontitis. Adv Biosci Biotechnol. 2021;3:712-9.

53. Ahmad MF, Naseem N, Rahman I, Imam N, Younus H, Pandey SK, et al. Naringin attenuates the diabetic neuropathy in STZ-induced type 2 diabetic Wistar rats. Life. 2022;12:2111.

54. Dare A, Channa ML, Nada A. L-Ergothioneine and its combination with metformin attenuates renal dysfunction in type-2 diabetic rat model by activating Nrf2 antioxidant pathway. Biomed Pharmacother. 2021;141:111921.

55. Yang F, Zhang Z, Zhang L. Bisacurone attenuates diabetic nephropathy by ameliorating oxidative stress, inflammation and apoptosis in rats. Hum Exp Toxicol. 2022;41:1-14.

56. Wang G, Qu FZ, Li L, Lv JC, Sun B. Necroptosis: a potential, promising target and switch in acute pancreatitis. Apoptosis. 2021;21:121-9.