

**ORIGINAL ARTICLE** 

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

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#### **Keywords**

- ⇒ Diabetes mellitus
- ⇒ Propionic Acid
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- Oxidative stress
- ⇒ Inflammation

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#### 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- $\alpha$  (TNF- $\alpha$ ), transformation-growth-factor-beta (TGF- $\beta$ ), 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.

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#### 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 ( $\beta$ -cells and  $\alpha$ -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 chromatographymass 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 druginduced 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<sup>+</sup>) potassium (K<sup>+</sup>), Chloride (Cl<sup>-</sup>), bicarbonate (HCO3<sup>-</sup>) 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- $\alpha$ ), 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  $\pm$  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- $\alpha$ ), transforming growth factor beta (TGF- $\beta$ ) 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

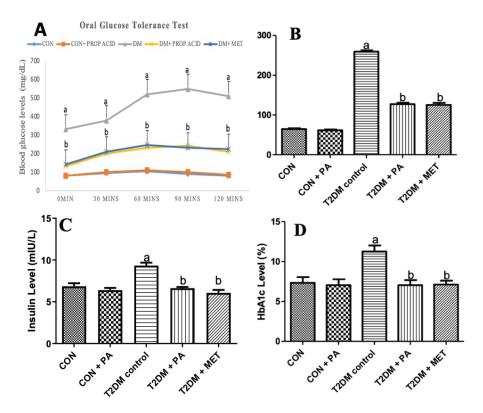
Parameters	CON	CON + PA	T2DM control	<b>T2DM + P</b> A	T2DM + MET
Food Intake (g/day/ rat)	34.86±1.38	29.76±0.65	37.36±0.67ª	29.48±1.17 <sup>b</sup>	38.24±0.50 <sup>b</sup>
Water Intake (ml/day/rat)	35.02±1.1 <b>0</b>	36.12±1.26	53.07±0.84ª	34.55±1.65 <sup>b</sup>	35.60±1.53 <sup>b</sup>
Body Weight (g)	262.75±7.36	254.75±5.78	179.00±7.46ª	224.75±6.49b	227±6.70 <sup>b</sup>
Relative Kidney Weight (g)	0.65±0.01	0.64±0.01	0.77±0.02ª	0.79±0.03b	0.73±0.04 <sup>b</sup>

Values are expressed as mean  $\pm$  SEM (n=10). <sup>a</sup>represents significant at p<0.001 vs CON, <sup>b</sup>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±0.01ª	0.54±0.03 <sup>b</sup>	0.53±0.03 <sup>b</sup>		
TC (mmol/l)	2.19±0.07	2.00±0.26	3.23±0.15°	2.11±0.06 <sup>b</sup>	2.17±0.05 <sup>b</sup>		
LDL (mmol/l)	1.50±0.10	1.35±0.25	2.86±0.15°	1.45±0.09 <sup>b</sup>	1.48±0.02 <sup>b</sup>		
HDL (mmol/l)	0.58±0.03	0.54±0.00	0.18±0.01ª	0.56±0.04 <sup>b</sup>	0.58±0.05 <sup>b</sup>		
GSH (mM)	0.74±0.03	0.78±0.07	0.20±0.01 <sup>a</sup>	0.78±0.05 <sup>b</sup>	0.76±0.03 <sup>b</sup>		
CAT (U/mg protein)	7.68±0.43	7.74±0.30	3.81±0.24°	8.30±1.13 <sup>b</sup>	7.91±0.67 <sup>b</sup>		
SOD (U/ml)	1.39±0.04	1.36±0.07	1.25±0.03°	0.78±0.06 <sup>b</sup>	1.11±0.05b		
MDA (µM)	1.02±0.02	1.11±0.01	1.91±0.02°	1.22±0.12 <sup>b</sup>	1.10±0.12 <sup>b</sup>		

Values are expressed as mean  $\pm$  SEM (n=10). <sup>a</sup>represents significant at p<0.001 vs CON, <sup>b</sup>represents significant at p<0.001 vs diabetic rats. CON: Control, PA: Propionic acid

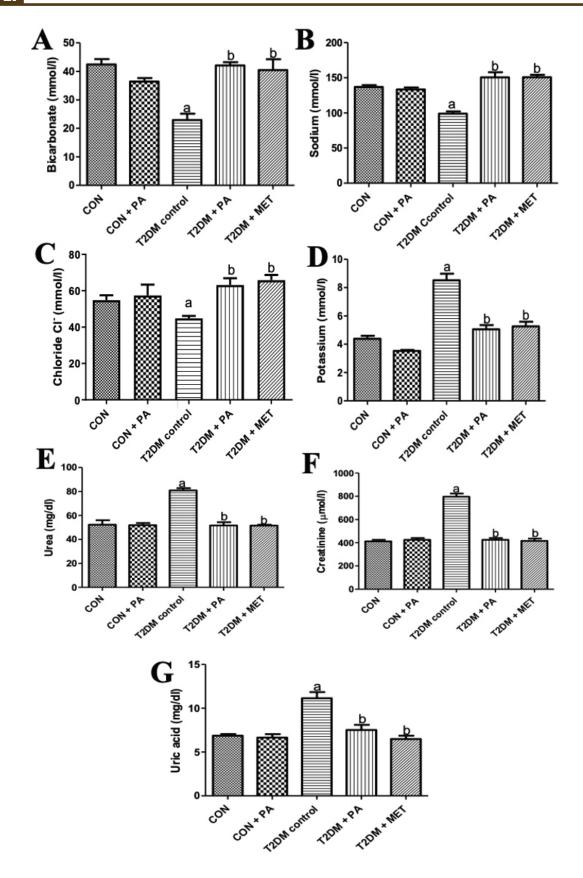


**Figure 1:** Effect of Propionic acid on (A) OGTT, (B) FBG, (C) Insulin, (D) HbA1c in HFD/STZ-induced diabetic rats. Values are expressed as mean  $\pm$  SEM (n=10). <sup>a</sup>represents significant at p<0.001 vs control, <sup>b</sup>represents significant at p<0.001 vs diabetic rats.

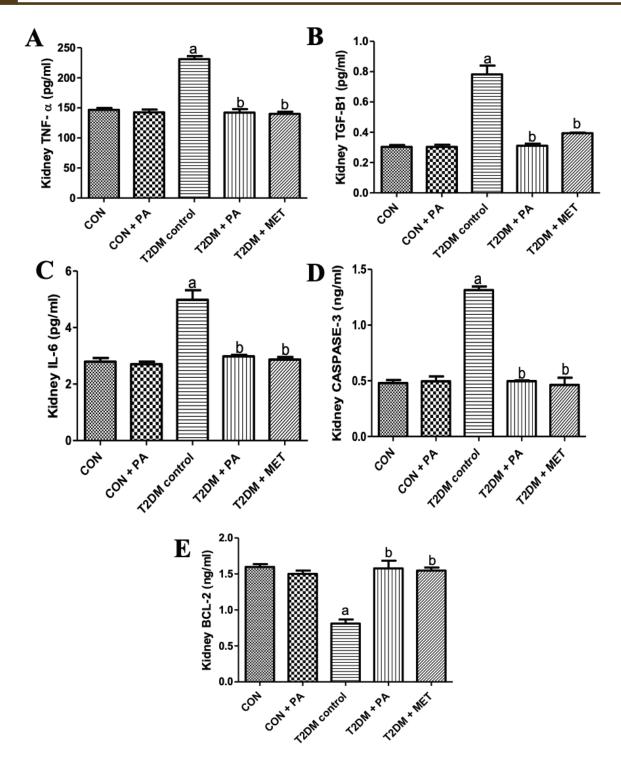
#### **Discussion**

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  $\alpha$ -glucosidase and  $\alpha$ -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*  $\pm$  *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- $\alpha$ , (B) TGF- $\beta$ , (C) IL-6, (D) Caspase-3, (E) Bcl-2 levels in HFD/STZ-induced diabetic rats. *Values are expressed as mean*  $\pm$  *SEM* (n=10). <sup>a</sup>represents significant at p<0.001 vs control, <sup>b</sup>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- $\alpha$ , TGF- $\beta$  and IL-6 levels was observed in the diabetic rats, which agrees with Ahmad et al Studies involving natural products (53) findings. 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

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**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

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