VIA MEDICA

ORIGINAL ARTICLE

Folasade Omobolanle Ajao*, Oluwatobi Sunday Ajiroba, Marcus Olaoye Iyedupe, Noheem Olaoluwa Kalejaiye

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

Renoprotective effect of *Anacardium occidentale* nuts in high-fat diet/ /streptozotocin-induced diabetic rats via regulating oxidative stress and inflammatory response

Corresponding author:

Folasade O. Ajao
Department of Physiology,
Ladoke Akintola University
of Technology, P.M.B 4000,
Ogbomoso 210214, Nigeria
tel: +2348034659049
e-mail: foajao@lautech.edu.ng

Medical Research Journal 2024;
Volume 9, Number 4, 417–425
DOI: 10.5603/mrj.102180

ISSN 2451-2591
e-ISSN 2451-4101

ABSTRACT

Introduction: The undesirable effect of antidiabetic drugs prompted attention to discover novel medicines to manage hyperglycemia-associated complications. This study investigated the effectiveness of *Anacardium occidentale* nuts on kidney function in hyperglycemia diabetic rats.

Material and methods: Forty male matured rats weighing 200 ± 20 g were used. Diabetes was induced with a repeated dose (35 mg/kgb.wt) of freshly prepared streptozotocin injected intraperitoneally. The rats were grouped into 5 groups, 8 rats/group. Group I: control: Group II: Diabetic; Group III & IV: Diabetic + 100 mg/kgb.wt & 200 mg/kgb.wt *Anacardium occidentale* nuts; Group V: Diabetic + 200 mg/kgb.wt metformin. The rats were anesthetized and sacrificed after 21 days of treatment. Blood samples and kidney homogenates were used for biochemical assay.

Results: Insulin, fasting blood glucose (FBG), glycated hemoglobin (HbA1c), kidney potassium (K^+), chloride (Cl^-), bicarbonate (HCO_3^-), creatinine, blood urea nitrogen (BUN), triglycerides (TG), total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), malondialdehyde (MDA), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-1B (IL-1β) significantly ($p < 0.05$) increased in diabetic rats. Body weight, total protein (TP), kidney high-density lipoprotein-cholesterol (HDL-C), superoxide dismutase (SOD), catalase (CAT), and reduced glutathione (GSH) decreased significantly. *Anacardium occidentale* nuts administration reduced the insulin, FBG, HbA1c, kidney biomarkers, TG, TC, LDL-C, MDA, TNF-a, IL-6, & IL-1β levels and, improved the body weight, TP, HDL-C, SOD, CAT, and GSH levels.

Conclusion: *Anacardium occidentale* nuts mitigates hyperglycemia and restores kidney function via attenuation of oxidative stress and inflammation in the kidney. It could be used as a novel drug to manage diabetes-associated kidney complications.

Keywords: *Anacardium occidentale* nuts, hyperglycemia, kidney biomarkers, lipid profile, oxidative stress & inflammation

Med Res J 2024; 9 (4): 417–425

Introduction

The prevalence of diabetes mellitus in 2015 was approximately 415 million and was recently estimated to reach 330 million by 2030 and 642 million by 2040 [1].

Diabetes mellitus (DM) is a metabolic disorder characterized by elevated blood glucose as a result of inadequate insulin produced by pancreatic beta-cells (β-cells) or insensitivity to insulin action by peripheral tissues [2]. Chronic uncontrolled hyperglycemia causes macro-vascular and micro-vascular complications such as diabetic nephropathy in diabetic patients [3].

Approximately 40% of global diabetic patients suffer diabetic nephropathy [4]. Diabetic nephropathy

is a chronic condition that affects the structure and function of small blood vessels in diabetic people. Diabetic nephropathy is recognized as a major cause of glomerular dysfunction, hyper-filtration, and albuminuria which consequently leads to the progression of end-stage renal disease (ESRD) [5]. Also, diabetic nephropathy increases cardiovascular disease risk [6]. The mechanism involved in the initiation, pathogenesis, and progression of diabetic nephropathy involves the interaction between oxidative stress-induced inflammation and apoptotic in renal tissues [3]. The anti-diabetic medications used to manage diabetes display many harmful complications and are ineffective in curing the adverse effects [7]. However, there is a growing research interest in medicinal plants' benefits in managing diabetes and related complications [8].

Anacardium occidentale (*A. occidentale*) famously known as cashew, is a tropical plant that belongs to the family of *Anacardiaceae* [9]. *A. occidentale* parts include the leaves, bark, and nuts are used medicinally for several ailments, and evidence from numerous research studies showed that *A. occidentale* parts possess potent anti-diabetic, antioxidant, antibacterial, anti-diarrhea and anti-inflammatory properties [10]. Preliminary phytochemical analysis of *A. occidentale* proved the presence of bioactive compounds including saponins, glycosides, proteins, alkaloids, tannins, phenolics, and flavonoids with hypoglycemic properties [11]. Also, the nuts demonstrated lipid-lowering effects [12]. To date, the pharmacological effects of *A. occidentale* on improving kidney function in diabetes with chronic hyperglycemia remain elusive. Therefore, this study investigated the therapeutic properties of *A. occidentale* nuts on hyperglycemia-induced renal function impairment in diabetic rats.

Material and methods

Drugs and chemicals

Streptozotocin, citrate buffer, phosphate buffered saline, normal saline, metformin. All chemicals used are analytical grade.

Anacardium occidentale Nuts extraction

The *Anacardium occidentale* (*A. occidentale*) nuts were collected at the Ladoke Akintola University of Technology Agricultural Research Farm. The nuts were air-dried, the outer-coated layer was removed and the nuts were ground into a fine powder. 1 gram of the powdered form was extracted with 80% methanol in a Soxhlet apparatus. The solid extract obtained was placed into a rotary evaporator under reduced pressure to form a crude semi-solid and stored at –4°C till needed.

Experimental animals

Forty adult male Wistar rats weighing between 200 ± 20 g were utilized. The animals were purchased at the Physiology Department Animal House, Ladoke Akintola University of Technology, Ogbomoso, Oyo-State, Nigeria. During the two weeks of acclimatization, the rats were kept in a well-cleaned ventilated polypropylene cage and allowed to have access to feed and water *ad libitum* under a pathogen-free standard environment condition of temperature 25 ± 2°C, relative humidity 50 ± 5%, and 12:12 hours light/dark. All experimental procedures were carried out by the National Institutes of Health's (NIH) Guide for the Care and Use of Laboratory Animals guidelines and was given an Ethical approval number: ERCFBMSLAUTECH:021/01/2024 by Ladoke Akintola University of Technology Research Ethical Committee.

Diabetes induction

After acclimatization, the rats were fed a high-fat diet for six weeks before diabetes induction. The rats fasted overnight and intraperitoneal injected with a freshly prepared repeated dose (35 mg/kgb.wt) of streptozotocin (STZ) to induce diabetes. The animals were also administered with a 2% glucose solution to hinder drug-induced hypoglycemic death. The rats' blood samples were collected through the tail vein after 72 hours of STZ injection to check the fasting blood glucose levels using a glucometer. Rats with fasting blood glucose (FBS) levels ≥ 200 mg/dL were considered diabetic and selected for experimental.

Animals grouping

Eight non-diabetic rats served as control and thirty-two rats were rendered diabetic. The animals were randomly distributed into 5 groups, 8 rats/group as follows:

- Group I: control (non-diabetic);
- Group II: Diabetic (untreated);
- Group III: Diabetic + 100 mg/kgb.wt *A.occidentle* nuts (low dose);
- Group IV: Diabetic + 200 mg/kgb.wt *A.occidentle* nuts (high dose);
- Group V: Diabetic + 200 mg/kgb.wt metformin.

The treatment lasted for 21 days. Food intake and water intake were measured daily, and body weight and fasting blood glucose levels were determined weekly throughout the treatment period.

Determination of the nuts human dose

The human equivalent dose (HED) of the nuts for low dose and high dose is 16.2 mg/kg/day and 32.4 mg/kg/day. These were determined based on the established Food and Drug Administration formula [13]:

HED = Animal dose x correction factor (K_m).

Rat K_m = 0.162.

Biochemical assay

After administration of the last dose of the nuts extract, the animals were allowed to fast overnight (12 hours) and anesthetized with ketamine (40 mg/kgb.wt) and xylazine (20 mg/kgb.wt) doses to render the animals' unconsciousness. The animals were sacrificed by cervical dislocation and dissected inferior-superiorly. Blood samples were collected from the apex beat of the rats' hearts. The kidneys were isolated, rinsed in normal saline, and homogenized with cold phosphate-buffered saline. The blood samples and kidneys' homogenates were centrifuged separately at 3500 rpm for 15 minutes at –4°C respectively. The retrieved clear supernatant plasma was used for the biochemical assay parameter estimation.

Fasting blood glucose levels were measured with a glucometer using the glucose-oxidase/peroxidase (GOD-POD) method. Insulin and glycated hemoglobin (HbA1c) levels were using the enzyme-linked immunosorbent assay (ELISA) method with respective assay kits.

Total protein, kidney electrolytes and biomarkers K^+, Cl^-, HCO_3^-, creatinine, and blood urea nitrogen (BUN) 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. [14] equation: LDL-C = TC – (HDL-C + TG/5) [14]. Cardiovascular risk indices (CRI) were calculated as TG/HDL-C.

Atherogenic Coefficient (AC) and Castelli's Risk Index-1 (CRI) were calculated using the following formulas:

AC = (TC – HDL-C) / HDL-C

CRI = TC/ HDL-C.

Kidney oxidative stress marker malondialdehyde (MDA), antioxidant activities of catalase (CAT) and superoxide dismutase (SOD), and inflammatory cytokines' tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), were measured using ELISA with each specific assay kits following the manufacturer's protocol.

Renal histological examination

The small portions were cut from the rinsed kidneys and stored in 10% formalin. The kidneys were fixed in paraffin wax and 5μm of the tissue sections were stained with hematoxylin and eosin (H&E). The stained tissue sections were examined for any histological changes under a light microscope (400×).

Statistical analysis

Data were analyzed using GraphPad Prism. Results are presented as the mean ± standard error of the mean (SEM). Statistical significance was determined with analysis of variance (ANOVA) followed by Tukey's post hoc test. A $p < 0.05$ was considered statistically significant.

RESULTS

Effect of *Anacardium occidentale* nuts methanolic extract on body weight and total protein in HFD/STZ-induced diabetic rats

The body weight and total protein of diabetic rats reduced ($p < 0.05$) significantly compared with control. Supplementation of low dose (100 mg/kgb.wt) and high dose (200 mg/kgb.wt) *A. occidentale* nuts to the diabetic rats improved the body weight and total protein compared with untreated diabetic rats (Fig. 1A, B).

Effect of *Anacardium occidentale* nuts methanolic extract on food and water intake in HFD/STZ-induced diabetic rats

Food intake decreased and water intake increased ($p < 0.05$) significantly in the diabetic rats compared with control. The treatment of diabetic rats with low dose (100 mg/kgb.wt) and high dose (200 mg/kgb.wt) *A. occidentale* nuts significantly reduced water intake and no significant difference in food intake compared with the untreated diabetic rats. (Fig. 1C, D).

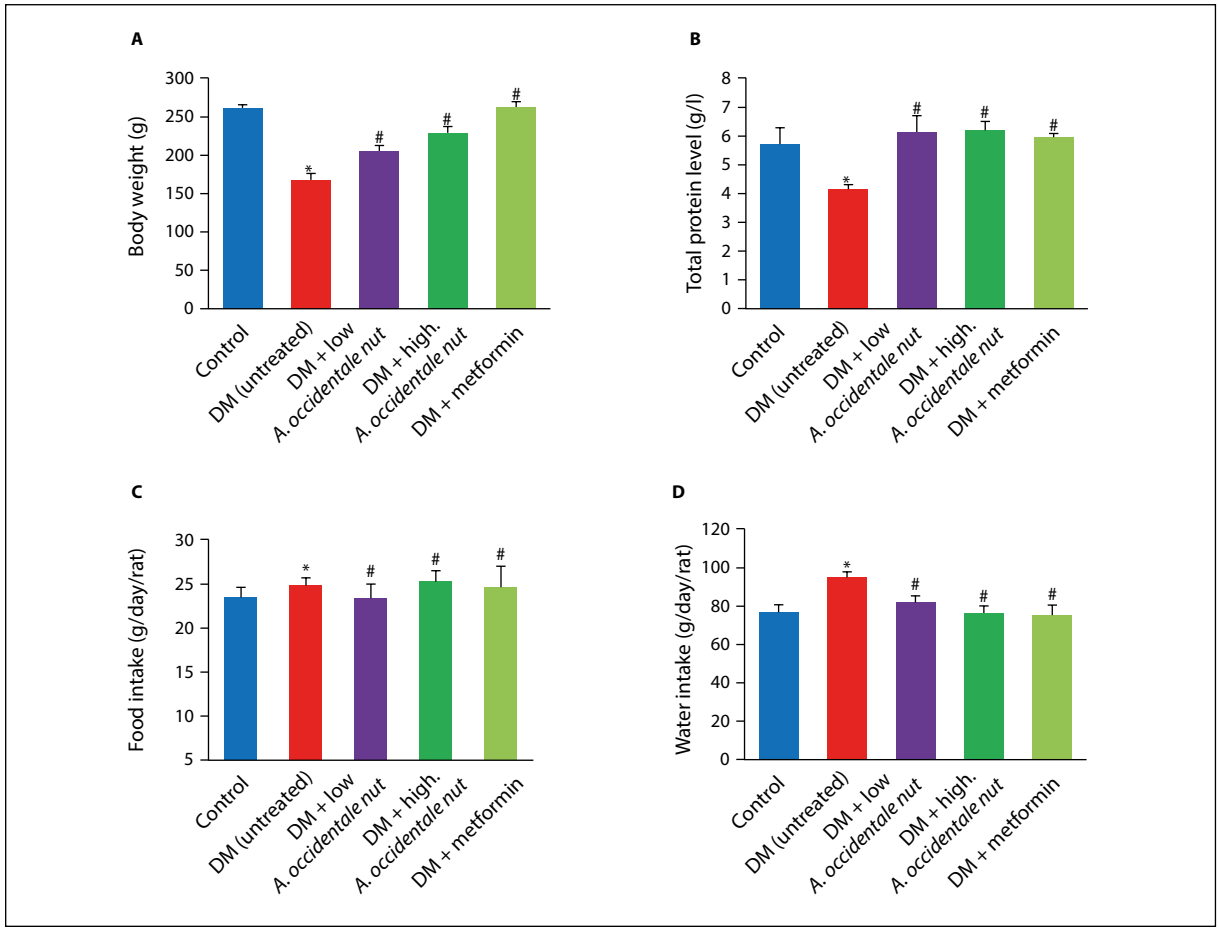

Figure 1. Effect of *A. occidentale* nuts methanolic extract on (A) body weight (B) total protein(C) food intake (D) water intake in HFD/STZ-induced diabetic rats. Values are expressed as mean ± SEM (n = 8)*;* *significant at $p < 0.05$ compared with the control; #significant at $p < 0.05$ compared with untreated diabetic group

Effect of *Anacardium occidentale* nuts methanolic extract on insulin, blood glucose, and glycated hemoglobin in HFD/STZ-induced diabetic rats

Diabetic rats showed a significant ($p < 0.05$) increase in the plasma insulin, FBG, and HbA1c levels compared with the control group. Administration of low dose (100 mg/kgb.wt) and high dose (200 mg/kgb.wt) *A. occidentale* nuts extract to the diabetic rats significantly decreased the insulin, FBG, and HbA1c levels compared to the untreated diabetic group (Figure 2A, B & C).

Effect of *Anacardium occidentale* nuts methanolic extract on kidney function biomarkers and renal in HFD/STZ-induced diabetic rats

The levels of renal HCO_3^-, Cl^-, and K^+ decreased ($p < 0.05$) significantly and BUN and CRT significantly increased in diabetic rats compared to the control group. Administration of low dose (100 mg/kgb.wt) and high dose (200 mg/kgb.wt) *A. occidentale* nuts extract to the diabetic rats significantly increased the HCO_3^-, Cl^-, K^+ and total protein levels and decreased the BUN and CRT levels in comparison to the untreated diabetic group (Table 1).

Effect of *Anacardium occidentale* nuts methanolic extract on kidney lipid profile in HFD/STZ-induced diabetic rats

Compared with the control rats, there was a significant ($p < 0.05$) increase in the levels of TG, TC, LDL, TG/HDL-c ratio, and Castelli's risk index in diabetic rats, and HDL levels were reduced significantly. Administration of low dose (100 mg/kgb.wt) and high dose (200 mg/kgb.wt) *A. occidentale* nuts extract to the diabetic rats significantly elevated the HDL levels and remarkably reduced TG, TC, LDL, TG/HDL-c ratio and Castelli's risk index levels compared to the untreated diabetic group (Table 2).

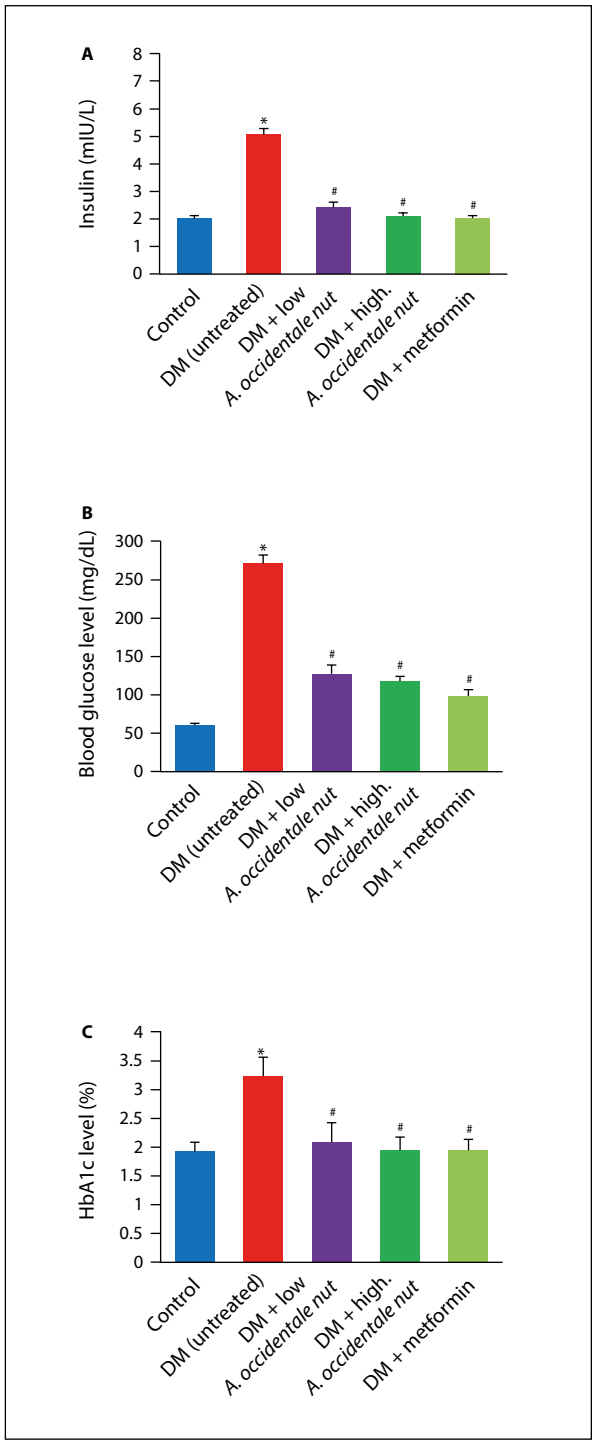

Figure 2. Effect of *A. occidentale* nuts methanolic extract on (A) insulin (B) fasting blood glucose (C) glycated hemoglobin in HFD/STZ-induced diabetic rats. Values are expressed as mean ± SEM (n = 8); *significant at $p < 0.05$ compared with the control; #significant at $p < 0.05$ compared with the untreated diabetic group

Effect of *Anacardium occidentale* nuts methanolic extract on kidney oxidative stress marker and antioxidants in HFD/STZ-induced diabetic rats

The marker of oxidative stress malondialdehyde (MDA) significantly ($p < 0.05$) increased and antioxidants SOD, CAT, and GSH diminished significantly in diabetic rats compared with the control group. Treatment of the diabetic rats with low dose (100 mg/kgb.wt) and high dose (200 mg/kgb.wt) *A. occidentale* nuts extract significantly raised the SOD, CAT, and GSH and lowered the MDA level in comparison to the untreated diabetic group (Table 2).

Effect of *Anacardium occidentale* nuts methanolic extract on kidney inflammatory cytokines in HFD/STZ-induced diabetic rats

The levels of inflammatory cytokines and tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), and interleukin-1β (IL-1β), in the diabetic rats were significantly ($p < 0.05$) high compared to the control group. Low dose (100 mg/kgb.wt) and high dose (200 mg/kgb.wt) *A. occidentale* nuts extract administration to the diabetic rats lessen the level of IL-6, IL-1β, and TNF-α compared to the untreated diabetic group (Table 2).

Discussion

Hyperglycemia considerably causes complications related to diabetes mellitus [15]. Diabetic renal disease which can later end in prolonged renal failure is a complication noticeable in diabetes patients with uncontrolled hyperglycemia [16]. This study investigates the treatment effectiveness of *A. occidentale* nuts on the harmful consequence of hyperglycemia on renal function in diabetic rats.

Body weight loss and elevated blood glucose are features and clinical diagnoses for diabetes. Body weight loss in diabetes occurs as a consequence of muscle wasting which has been linked to tissue structural and functional protein catabolism [17]. High blood glucose levels, polyphagia, polydipsia, and body weight loss with a concomitant decrease in total protein were obvious in the diabetic of this study, supporting the findings of Chike-Ekwughe et al. [18]. A decrease in total protein indicates spontaneous structural protein catabolism that leads to a reduction in body weight in

Table 1. Effect of *A. occidentale* nuts methanolic extract kidney function biomarkers in HFD/STZ-induced diabetic rats

Groups Parameters	Control	DM (untreated)	DM + low *A. occidentale* nuts dose	DM + high *A. occidentale* nuts dose	DM + metformin	P-value
BUN (mg/dL)	8.90 ± 1.10	18.24 ± 1.91	12.84 ± 0.56	9.90 ± 0.44	8.60 ± 3.56	0.041
Creatinine (mg/dL)	47.20 ± 1.57	78.94 ± 1.62	48.45 ± 1.46	47.72 ± 1.40	49.29 ± 1.90	0.012
K^+(mmol/L)	155 ± 3.60	133 ± 7.50	161.90 ± 6.87	156 ± 4.24	152.60 ± 3.66	0.003
Cl^- (mmol/L)	55.35 ± 30.93	45.72 ± 1.72	53.99 ± 4.43	56.02 ± 1.67	57.36 ± 2.24	0.044
HCO_3^- (mmol/L)	161.20 ± 6.23	128.00 ± 3.94	159.10 ± 7.74	159.00 ± 5.60	166.60 ± 2.61	0.031

Table 2. Effect of *A. occidentale* nuts methanolic extract on kidney lipid profile, oxidative stress marker, antioxidant and inflammatory cytokines in HFD/STZ-induced diabetic rats

Groups Parameters	Control	DM (untreated)	DM + low *A. occidentale* nuts dose	DM + high *A. occidentale* nuts dose	DM + metformin	P-value
TG (mg/dL)	178.79 ± 5.67	212.29 ± 4.96	163.86 ± 6.44	166.21 ± 2.75	169.39 ± 4.83	0.001
TC (mg/dL)	176.54 ± 4.49	251.73 ± 5.25	176.68 ± 5.53	166.21 ± 3.55	176.06 ± 4.84	0.024
LDL-C (mg/dL)	50.76 ± 3.66	136.93 ± 6.86	54.26 ± 4.31	49.54 ± 5.41	52.02 ± 6.65	0.001
HDL-C (mg/dL)	89.82 ± 5.29	72.34 ± 1.79	94.37 ± 8.82	91.61 ± 7.01	86.82 ± 3.68	0.044
TG/HDL-C ratio	2.04 ± 0.08	2.94 ± 0.06	1.79 ± 0.10	1.81 ± 0.11	2.08 ± 0.02	0.008
Atherogenic coefficient (AC)	1.05 ± 0.08	2.48 ± 0.08	1.03 ± 0.04	0.96 ± 0.05	1.09 ± 0.02	0.033
Castelli's risk index (CRI)	2.04 ± 0.05	3.48 ± 0.08	1.90 ± 0.08	2.13 ± 0.09	2.09 ± 0.07	0.031
MDA (μM)	1.16 ± 0.04	2.52 ± 0.06	1.41 ± 0.03	1.12 ± 0.07	1.18 ± 0.09	0.043
SOD (u/ml)	1.40 ± 0.05	0.85 ± 0.08	1.37 ± 0.05	1.33 ± 0.06	1.45 ± 0.04	0.004
CAT (u/mg)	23.12 ± 1.40	14.41 ± 1.12	20.24 ± 2.64	19.75 ± 1.02	24.04 ± 0.20	0.038
GSH (mM)	1.88 ± 0.06	0.96 ± 0.08	1.99 ± 008	1.84 ± 0.08	1.84 ± 0.11	0.002
TNF-α (pg/ml)	603.3 ± 30.93	750.2 ± 30.23	603.6 ± 35.65	613.5 ± 23.38	609.4 ± 19.07	0.001
IL-6 (pg/ml)	87 ± 7.70	151.6 ± 6.18	92.40 ± 5.40	87.78 ± 5 .38	89.59 ± 2.60	0.004
IL-1β (pg/ml)	7.35 ± 0.59	16.05 ± 1.51	8.78 ± 0.54	7.92 ± 0.35	7.45 ± 0.31	0.025

diabetic rats. However, LAOND and HAOND supplements lowered the blood glucose and improved the body weight of diabetic rats, which implies that the nuts increase tissue protein anabolic process for body weight recovery, inhibit hepatic glycogenolysis and stimulate the peripheral tissues to insulin action for glucose uptake, resulting in blood sugar lowering effect of the nuts and this support Sarmah and Roy findings [19].

Insulin is a crucial hormone that regulates the breakdown of carbohydrates, fats, and proteins through various pathways [20]. Contrary to diminished insulin secretion from beta-cells of the pancreas reported in diabetes [21], high insulin level was observed in the diabetic of this study and indicated a state of insulin resistance. LAOND and HAOND administration reverse the insulin level closely to the normal. This suggests that the nuts restore the pancreatic beta-cell integrity for normal insulin secretion and ameliorate insulin utilization by peripheral tissues.

Glycated hemoglobin (HbA1c) serves as the clinical marker for chronic glycemic control in diabetic patients [22]. Chronic hyperglycemia results in the glycosylation of amino groups on lysine residues in proteins [23]. This condition leads to a decrease in total hemoglobin levels and an increase in glycated hemoglobin, which is directly proportional to blood glucose levels [24]. Supporting the findings of Jiang [21], diabetic rats of the current study had elevated HbA1c levels. Treated of the rats with LAOND and HAOND decreased the HbA1c level, revealing the nuts efficiency in long-term glycemic regulatory effect.

In diabetes conditions, creatinine, blood urea nitrogen (BUN), and uric acid levels serve as valuable

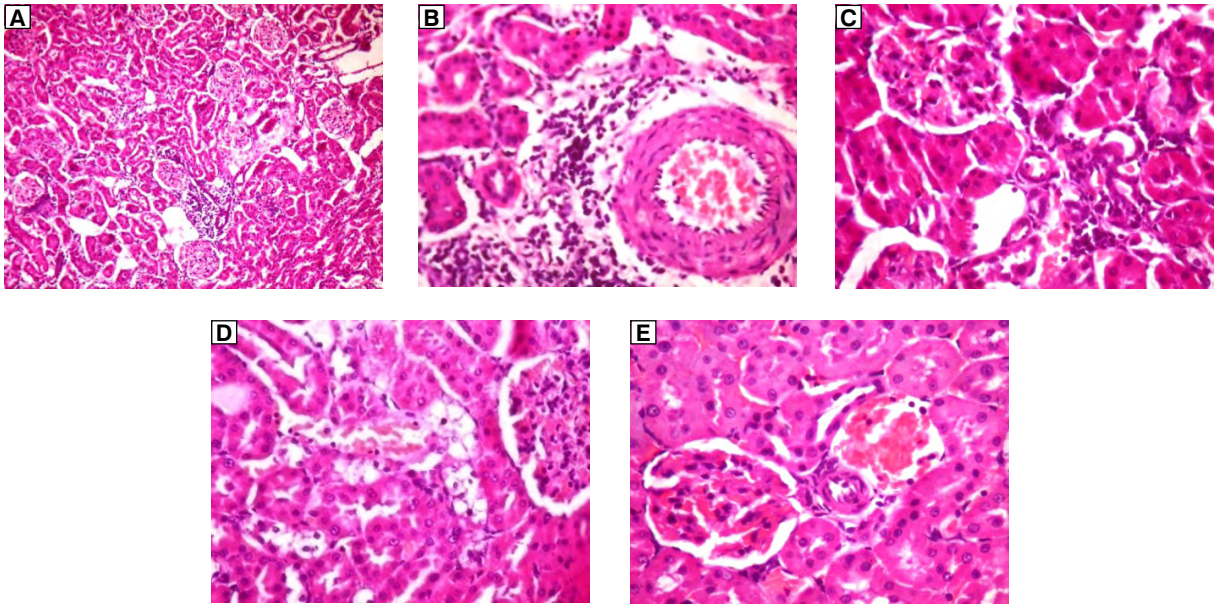

Figure 3. The photomicrograph histology of the kidney section (H & E staining, X400) (**A**) control, showed the normal architecture of renal cells (**B**) diabetic (untreated) rats showed distortion of bowman's corpuscle, the collapse of renal tubules and infiltration of inflammatory cells. **C**, **D** & **E** depicted restoration of the normal kidney cell architecture in diabetic rats treated with low and high doses of *A. occidentale* nuts and metformin

biomarkers for evaluating renal function [25]. An increase in BUN, creatinine, and uric acid signified a state of renal damage in diabetes [26]. Increased BUN and creatinine were observed in the diabetic rats of the present study, which harmonized with the report of Giribabu et al. [27]. However, these renal function biomarkers normalized upon administration of LAOND and HAOND doses, suggesting the efficacy of the nuts in restoring renal function and protecting the structural integrity of renal tissues which corroborates the findings of Kang et al. [28].

Renal regulation of body electrolytes deleteriously alters in chronic hyperglycemia during diabetes mellitus [29]. Lessening in the body potassium (K^+), chloride (Cl^-), and bicarbonate (HCO_3^-) has been reported in diabetic rats [30]. In support of the previous report, the present findings also discovered a reduction in K^+, Cl^-, and HCO_3^- in diabetic rats. Recently, findings revealed that plants possess abundant minerals including potassium, sodium, and bicarbonate with therapeutic properties [31]. Treated of the diabetic rats with LAOND and HAOND modulate the level of body electrolytes. This might be due to the existence of the aforementioned minerals in *A. occidentale* nuts with potent effectiveness in improving body electrolytes for renal function, this aligns with the report of Alatawi and Falshubaily [32].

Hyperglycemia is known as the etiology of dyslipidemia complications in diabetes [33]. Dyslipidemia, a typical rise in blood triglyceride (TG), total cholesterol, low-density lipoprotein-cholesterol (LDL-C), and low high-density lipoprotein-cholesterol (HDL-C) which reported to aggravate risks of macro-vascular complications such as cardiovascular disease in patients with diabetes [34]. Diabetic rats of the present study exhibited remarkably elevated kidney TG, TC, LDL-C, atherogenic coefficient (AC), atherogenic index (AI), and Castelli's risk index (CRI) accompanied with diminished HDL-C and are in line with the report of Aslam et al. [35]. LAOND and HAOND attenuate kidney dyslipidemia in the diabetic rats noticed by suppressing the TG, TG, LDL-C, AC, AI, and CRI levels and enhancing the HDL-C levels and, this indicates *A. occidentale* nuts hypolipidemic efficacy. Literature shows that plant bioactive compounds such as polyphenols possess hypolipidemic activity by adjusting the fatty acid and cholesterol synthesis pathway and improving insulin sensitivity [36–38]. The hypolipidemic of *A. occidentale* nuts could be attributed to this bioactive compound which could stimulate kidney cells to insulin action in mobilizing excessive fat deposition from the kidney and this parallels the findings of Eleazu [39].

Oxidative stress induced by uncontrolled hyperglycemia is positively linked to the pathogenesis and

progression of cellular complications related to diabetes via an imbalance in the oxidant and antioxidant systems [40]. Overproduction of reactive oxygen species and reduction in the antioxidant system contribute to renal injury [41]. Consistent with the findings of Giribabu et al. [42], the current study of diabetic rats displayed an increase in kidney oxidative stress marker malondialdehyde (MDA) and a decline in antioxidant superoxide dismutase (SOD), catalase (CAT), and reduced glutathione (GSH). Research evidence revealed the benefit of plant natural antioxidants in protecting against organ injury by scavenging free radicals induced by hyperglycemia [43]. Treatment of diabetic rats with LAOND and HAOND ameliorates the kidney antioxidant activities and suppresses the marker of oxidative stress, denoting that *A. occidentale* nuts possess anti-oxidative properties to eliminate free radical in the kidney, which is in agreement with Zhu et al. [44] report.

Hyperglycemia-induced oxidative stress subsequently triggers overexpression of pro-inflammatory, which play a vital role in the progression of tissue injury [45]. Overexpression of inflammatory biomarker tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β) reported in the kidney of diabetic rats [46, 47]. In the kidneys of diabetic rats of the present study, up-regulation of TNF-α, IL-6, and IL-1β observed, which is in accord with Al-Hussaini et al. [48] findings. Also, both LAOND and HAOND gavage to the diabetic rats reduced the expression of the pro-inflammatory biomarkers in the kidney, proving the anti-inflammatory effects of *A. occidentale* nuts and maybe link to the natural antioxidant in the nuts to suppress kidney oxidative stress, this is in concurrent with Yin et al. [49] findings, on suppression of pro-inflammatory overexpression in the kidney of diabetic by flavonoid.

Conclusions

A. occidentale nuts avert hyperglycemia considerably and improve kidney function by inhibiting oxidative stress and inflammatory damage in the kidney. The nuts could help prevent and manage renal complications of hyperglycemia.

Abbreviations

LAOND: low *Anacardium occidentale* nuts dose; HAOND: high *Anacardium occidentale* nuts dose

Article information

Ethics statement: *In the manuscript.*
Authors' contributions: *FO and OS conceived the original idea and designed and supervised the research. SO, NO, performed the experiments with the support of FO. OS, MO, and NO analyzed the data. OS, MO, prepared the manuscript. FO and MO reviewed the manuscript. All authors have read and approved the final manuscript.*
Conflict of interest: *The authors declare no conflict of interest.*
Funding: *None.*

References

1. Ogurtsova K, Fernandes JDd, Huang Y, et al. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Research and Clinical Practice. 2017; 128: 40–50, doi: 10.1016/j.diabres.2017.03.024.
2. Edgerton D, Kraft G, Smith M, et al. Insulin's direct hepatic effect explains the inhibition of glucose production caused by insulin secretion. JCI Insight. 2017; 2(6), doi: 10.1172/jci.insight.91863.
3. Eisa N, Khodir A, El-Sherbiny M, et al. RETRACTED: Phenethyl isothiocyanate attenuates diabetic nephropathy via modulation of glycative/oxidative/inflammatory signaling in diabetic rats. Biomedicine & Pharmacotherapy. 2021; 142: 111666, doi: 10.1016/j.biopha.2021.111666.
4. Alicic R, Rooney M, Tuttle K. Diabetic Kidney Disease. Clinical Journal of the American Society of Nephrology. 2017; 12(12): 2032–2045, doi: 10.2215/cjn.11491116.
5. Abdou H, Elkader HTA. The potential therapeutic effects of Trifolium alexandrinum extract, hesperetin and quercetin against diabetic nephropathy via attenuation of oxidative stress, inflammation, GSK-3β and apoptosis in male rats. Chemico-Biological Interactions. 2022; 352: 109781, doi: 10.1016/j.cbi.2021.109781.
6. Tan S, Snelson M, Østergaard J, et al. The Complement Pathway: New Insights into Immunometabolic Signaling in Diabetic Kidney Disease. Antioxidants & Redox Signaling. 2022; 37(10-12): 781–801, doi: 10.1089/ars.2021.0125.
7. Zhang D, Xie T, Leung P. Irisin Ameliorates Glucolipotoxicity-Associated β-Cell Dysfunction and Apoptosis via AMPK Signaling and Anti-Inflammatory Actions. Cellular Physiology and Biochemistry. 2018; 51(2): 924–937, doi: 10.1159/000495395.
8. Fuster VP, Pérez AP, Gómez JC, et al. Executive summary: Updates to the dietary treatment of prediabetes and type 2 diabetes mellitus. Endocrinología, Diabetes y Nutrición (English ed.). 2021; 68(4): 277–287, doi: 10.1016/j.endien.2020.10.008.
9. Lim TK. Anacardium occidentale. Edible Medicinal and Non-Medicinal Plants. 2011: 45–68, doi: 10.1007/978-90-481-8661-7_6.
10. Salehi B, Gültekin-Özgüven M, Kırkın C, et al. Plants: Chemical,Nutritional Composition and Biotechnological Applications. Biomolecules. 2019; 9(9), doi: 10.3390/biom9090465, indexed in Pubmed: 31505888.
11. Tedong L, Dimo T, Dzeufiet PD, et al. Antihyperglycemic and renal protective activities of *Anacardium occidentale* (anacardiaceae) leaves in streptozotocin induced diabetic rats. African Journal of Traditional, Complementary and Alternative Medicines. 2005; 3(1), doi: 10.4314/ajtcam.v3i1.31136.
12. 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, doi: 10.1371/journal.pone.0225736, indexed in Pubmed: 31830056.
13. USFDA. Guidance for Industry: Estimating the Maximum Safe Starting Dose in Adult Healthy Volunteer. Rockville, MD: US Food and Drug Administration. : 2005.
14. 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, indexed in Pubmed: 4337382.

15. Ohiagu F, Chikezie P, Chikezie C. Pathophysiology of diabetes mellitus complications: Metabolic events and control. Biomedical Research and Therapy. 2021; 8(3): 4243–4257, doi: 10.15419/bmrat.v8i3.663.
16. Khanra R, Bhattacharjee N, Dua TK, et al. Taraxerol, a pentacyclic triterpenoid, from Abroma augusta leaf attenuates diabetic nephropathy in type 2 diabetic rats. Biomed Pharmacother. 2017; 94: 726–741, doi: 10.1016/j.biopha.2017.07.112, indexed in Pubmed: 28802226.
17. Ghauri S, Raza SQ, Imran M, et al. Assessment of α-amylase and α-glucosidase inhibitory potential of peel extracts in hyperglycemic/hypoglycemic rats. 3 Biotech. 2021; 11(4): 167, doi: 10.1007/s13205-021-02717-8, indexed in Pubmed: 33816044.
18. Chike-Ekwughe A, John-Africa LB, Adebayo AH, et al. Antioxidative and anti-diabetic effects of Tapinanthus cordifolius leaf extract on high-fat diet and streptozotocin-induced type 2 diabetic rats. Biomed Pharmacother. 2024; 176: 116774, doi: 10.1016/j.biopha.2024.116774, indexed in Pubmed: 38820976.
19. Sarmah S, Roy AS. A review on prevention of glycation of proteins: Potential therapeutic substances to mitigate the severity of diabetes complications. Int J Biol Macromol. 2022; 195: 565–588, doi: 10.1016/j.ijbiomac.2021.12.041, indexed in Pubmed: 34920073.
20. Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. Nature. 2001; 414(6865): 799–806, doi: 10.1038/414799a, indexed in Pubmed: 11742412.
21. Jiang N, Zhang Y. Antidiabetic effects of nerolidol through promoting insulin receptor signaling in high-fat diet and low dose streptozotocin-induced type 2 diabetic rats. Hum Exp Toxicol. 2022; 41: 9603271221126487, doi: 10.1177/09603271221126487, indexed in Pubmed: 36169646.
22. Peterson CM, Jones RL, Koenig RJ, et al. Correlation of glucose regulation and hemoglobin Alc in diabetes mellitus. N Engl J Med. 1976; 295(8): 417–420, doi: 10.1056/NEJM197608192950804, indexed in Pubmed: 934240.
23. Asgary S, Naderi G, Sarrafzadegan N, et al. Anti-oxidant effect of flavonoids on hemoglobin glycosylation. Pharm Acta Helv. 1999; 73(5): 223–226, doi: 10.1016/s0031-6865(98)00025-9, indexed in Pubmed: 10085787.
24. ISHIHARA Y. Hemoglobin A_1 and Glucose Tolerance. Sangyo Igaku. 1981; 23(7): 722, doi: 10.1539/joh1959.23.7_722_1.
25. Nowak N, Skupien J, Smiles AM, et al. Markers of early progressive renal decline in type 2 diabetes suggest different implications for etiological studies and prognostic tests development. Kidney Int. 2018; 93(5): 1198–1206, doi: 10.1016/j.kint.2017.11.024, indexed in Pubmed: 29398132.
26. Nna VU, Abu Bakar AB, Zakaria Z, et al. Malaysian Propolis and Metformin Synergistically Mitigate Kidney Oxidative Stress and Inflammation in Streptozotocin-Induced Diabetic Rats. Molecules. 2021; 26(11), doi: 10.3390/molecules26113441, indexed in Pubmed: 34198937.
27. Giribabu N, Karim K, Kilari EK, et al. Phyllanthus niruri leaves aqueous extract improves kidney functions, ameliorates kidney oxidative stress, inflammation, fibrosis and apoptosis and enhances kidney cell proliferation in adult male rats with diabetes mellitus. J Ethnopharmacol. 2017; 205: 123–137, doi: 10.1016/j.jep.2017.05.002, indexed in Pubmed: 28483637.
28. Kang GG, Francis N, Hill R, et al. Dietary Polyphenols and Gene Expression in Molecular Pathways Associated with Type 2 Diabetes Mellitus: A Review. Int J Mol Sci. 2019; 21(1), doi: 10.3390/ijms21010140, indexed in Pubmed: 31878222.
29. Ngozi A, Christopher O, Ifeoma I, et al. Ameliorative Potentials of Methanol Fractions of on Some Hematological and Biochemical Parameters in Streptozotocin Diabetic Rats. Endocr Metab Immune Disord Drug Targets. 2018; 18(6): 637–645, doi: 10.2174/1871530318666180328112904, indexed in Pubmed: 29595116.
30. El Rabey HA, Al-Seeni MN, Bakhashwain AS. The Antidiabetic Activity of and Propolis on Streptozotocin-Induced Diabetes and Diabetic Nephropathy in Male Rats. Evid Based Complement Alternat Med. 2017; 2017: 5439645, doi: 10.1155/2017/5439645, indexed in Pubmed: 28298934.
31. Manivannan A, Bhardwaj R, Padmanabhan S, et al. Biochemical and nutritional characterization of coconut (Cocos nucifera L.) haustorium. Food Chem. 2018; 238: 153–159, doi: 10.1016/j.foodchem.2016.10.127, indexed in Pubmed: 28867086.
32. Alatawi K, Alshubaily F. Coconut products alleviate hyperglycaemic, hyperlipidimic and nephropathy indices in streptozotocin-induced diabetic wistar rats. Saudi Journal of Biological Sciences. 2021; 28(8): 4224–4231, doi: 10.1016/j.sjbs.2021.06.060.
33. Maliszewska K, Kretowski A. Brown Adipose Tissue and Its Role in Insulin and Glucose Homeostasis. Int J Mol Sci. 2021; 22(4), doi: 10.3390/ijms22041530, indexed in Pubmed: 33546400.
34. Beverly JK, Budoff MJ. Atherosclerosis: Pathophysiology of insulin resistance, hyperglycemia, hyperlipidemia, and inflammation. J Diabetes. 2020; 12(2): 102–104, doi: 10.1111/1753-0407.12970, indexed in Pubmed: 31411812.
35. Aslam B, Hussain A, Sindhu ZU, et al. Polyphenols-rich polyherbal mixture attenuates hepatorenal impairment, dyslipidaemia, oxidative stress and inflammation in alloxan-induced diabetic rats. Journal of Applied Animal Research. 2023; 51(1): 515–523, doi: 10.1080/09712119.2023.2230754.
36. Renganathan S, Pillai RG. Antioxidant activities of Dhanwantaram Kashayam -an Ayurvedic poly herbal formulation alleviates diabetic complications in rats. J Diabetes Metab Disord. 2020; 19(2): 1345–1355, doi: 10.1007/s40200-020-00655-5, indexed in Pubmed: 33553031.
37. Madić V, Petrović A, Jušković M, et al. 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, doi: 10.1016/j.jep.2020.113210, indexed in Pubmed: 32795501.
38. Hassan F, Aslam B, Muhammad F, et al. Hypoglycemic properties of Sphaeranthus indicus and Nigella sativa in alloxan-induced diabetes mellitus in rats; A new therapeutic horizon. Pak Vet J. 2022; 42(2): 141–146.
39. Eleazu C, Ekeleme CE, Famurewa A, et al. Modulation of the Lipid Profile, Hepatic and Renal Antioxidant Activities, and Markers of Hepatic and Renal Dysfunctions in Alloxan-Induced Diabetic Rats by Virgin Coconut Oil. Endocr Metab Immune Disord Drug Targets. 2019; 19(7): 1032–1040, doi: 10.2174/1871530319666190119101058, indexed in Pubmed: 30659555.
40. Giacco F, Brownlee M. Oxidative stress and diabetic complications. Circ Res. 2010; 107(9): 1058–1070, doi: 10.1161/CIRCRESAHA.110.223545, indexed in Pubmed: 21030723.
41. Fakhruddin S, Alanazi W, Jackson KE. Diabetes-Induced Reactive Oxygen Species: Mechanism of Their Generation and Role in Renal Injury. J Diabetes Res. 2017; 2017: 8379327, doi: 10.1155/2017/8379327, indexed in Pubmed: 28164134.
42. Giribabu N, Karim K, Kilari EK, et al. Phyllanthus niruri leaves aqueous extract improves kidney functions, ameliorates kidney oxidative stress, inflammation, fibrosis and apoptosis and enhances kidney cell proliferation in adult male rats with diabetes mellitus. J Ethnopharmacol. 2017; 205: 123–137, doi: 10.1016/j.jep.2017.05.002, indexed in Pubmed: 28483637.
43. 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.
44. Zhu W, Chen M, Shou Q, et al. Biological activities of chinese propolis and brazilian propolis on streptozotocin-induced type 1 diabetes mellitus in rats. Evid Based Complement Alternat Med. 2011; 2011: 468529, doi: 10.1093/ecam/neq025, indexed in Pubmed: 21785625.
45. Sierra-Mondragon E, Molina-Jijon E, Namorado-Tonix C, et al. All-trans retinoic acid ameliorates inflammatory response mediated by TLR4/NF-κB during initiation of diabetic nephropathy. J Nutr Biochem. 2018; 60: 47–60, doi: 10.1016/j.jnutbio.2018.06.002, indexed in Pubmed: 30193155.
46. Ajiboye BO, Ojo OA, Akuboh OS, et al. Anti-Hyperglycemic and Anti-Inflammatory Activities of Polyphenolic-Rich Extract of Syzygium cumini Linn Leaves in Alloxan-Induced Diabetic Rats. J Evid Based Integr Med. 2018; 23: 2515690X18770630, doi: 10.1177/2515690X18770630, indexed in Pubmed: 29756477.
47. Oguntibeju OO, Aboua GY, Omodanisi EI. Effects of Moringa oleifera on oxidative stress, apoptotic and inflammatory biomarkers in streptozotocin-induced diabetic animal model. South African Journal of Botany. 2020; 129: 354–365, doi: 10.1016/j.sajb.2019.08.039.
48. Al-Hussaini H, Kilarkaje N. Trans-resveratrol mitigates type 1 diabetes-induced oxidative DNA damage and accumulation of advanced glycation end products in glomeruli and tubules of rat kidneys. Toxicol Appl Pharmacol. 2018; 339: 97–109, doi: 10.1016/j.taap.2017.11.025, indexed in Pubmed: 29229234.
49. Yin M, Jiang N, Guo L, et al. Oleuropein suppresses oxidative, inflammatory, and apoptotic responses following glycerol-induced acute kidney injury in rats. Life Sci. 2019; 232: 116634, doi: 10.1016/j.lfs.2019.116634, indexed in Pubmed: 31279782.