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Original Article

Cardioprotective Activity of Propionic Acid in High-Fat Diet/ Streptozotocin-Induced Cardiotoxicity in Diabetic Rats Model

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Abstract

Background: The healthcare sector is increasingly focusing on the discovery of toxic-free natural medicines to treat diabetes-related complications. The current study investigated the cardioprotective efficacy of propionic acid (PA) in a type 2 diabetic rat model. **Methods:** Twenty-five Wistar rats (200–300 g) were used. The rats were fed a high-fat diet for 8 weeks, and streptozotocin (30 mg/kg b.wt) was injected intraperitoneally to induce diabetes. The animals were divided into 5 groups (n = 5) and treated for 4 weeks. Group 1: normal control; Group 2: normal control + PA (60 mg/kg b.wt); Group 3: diabetic; Group 4: diabetic + PA (60 mg/kg b.wt); Group 5: diabetic + metformin (200 mg/kg b.wt). Serum and supernatant plasma retrieved from blood samples, along with heart tissue homogenate after centrifugation, were used to determine biochemical parameters. **Results:** Propionic acid administration significantly ($p < 0.05$) reduced serum insulin, fasting blood glucose, oral glucose tolerance, cardiac creatine kinase-myoglobin, troponin-I, Lactate dehydrogenase, brain natriuretic peptide, caspase-3, triglycerides, total cholesterol, low-density lipoprotein cholesterol, oxidative malondialdehyde, tumor necrosis factor-α, interleukin-1β, interleukin-6, heart rate, blood pressure, QT and QTc intervals, QRS interval, PR interval, and food and water intake. It also significantly increased cardiac B-cell lymphoma-2, superoxide dismutase, catalase, reduced glutathione, high-density lipoprotein cholesterol, P-wave, and body and heart weight in diabetic rats. **Conclusion:** Propionic acid lowered hyperglycemia and prevented cardiac injury by suppressing elevated cardiac injury markers, oxidative stress, and inflammation. Propionic acid may be useful as a natural medication for treating cardiac ailments in diabetes.

Keywords: *Cardiac; Diabetes Mellitus; Inflammation; Oxidative Stress; Propionic Acid*

Introduction

Diabetes mellitus (DM) is globally ranked as the fourth largest metabolic disease, and its prevalence continues to rise every year (Singh *et al.,* 2025). In 2019, DM was the eighth leading cause of death and disability (Ong *et al.,* 2023). Current estimates from the International Diabetes Federation predict that approximately 783 million adults will be living with diabetes by 2045 (Migdalis, 2024).

DM, a non-communicable metabolic disorder, is characterized by chronic hyperglycemia due to alterations in the metabolism of carbohydrates, fats, and proteins resulting from insulin secretion deficiency from pancreatic beta cells, insulin resistance, or both (Sini *et al.,* 2025). Chronic hyperglycemia affects multiple organs, leading to microvascular and macrovascular complications such

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as diabetic retinopathy, nephropathy, neuropathy, and cardiovascular diseases including atherosclerosis, myocardial infarction, and coronary artery disease (Wang *et al.,* 2024).

Cardiovascular disease (CVD) complications are a major cause of mortality in both type 1 and type 2 diabetes patients (Patsoukaki *et al*., 2025). Approximately 30–40% of diabetes patients develop cardiovascular-related complications (Marassi & Fadini, 2023). Persistent hyperglycemia disrupts the balance between oxidative stress and endogenous antioxidant defense, promoting the overproduction of reactive oxygen species (ROS), which exacerbates oxidative injury and triggers the release of inflammatory mediators, consequently damaging cardiac structure and impairing function (Hashiesh *et al.,* 2023).

The existing well-known conventional antidiabetic drugs exhibit suboptimal effectiveness, and adverse toxicity effects have driven growing interest in novel and alternative therapies (Ansari *et al.,* 2024). Scientists have increasingly focused on medicinal plants as potential sources of safe alternative treatments (Yedjou *et al.,* 2023). Recently, secondary metabolites from medicinal plants rich in antioxidants have been documented to effectively mitigate oxidative injury and ameliorate cellular function in DM patients (Sukhikh *et al.,* 2023). Among these plants, *Anacardium occidentale* (*A. occidentale*) has been recognized for its ethnomedicinal properties. All parts of the tree, including the leaves, bark, and nuts, are extensively used in traditional medicine to combat various diseases. One study documented cardiovascular therapeutic effects of *A. occidentale* in non-diabetic patients (Brito *et al.,* 2025). The nuts are rich in vitamins, dietary fiber, unsaturated fatty acids, and diverse bioactive compounds. They have been studied for their role in reducing inflammation, limiting oxidative damage, and preventing the progression of chronic metabolic diseases (Dias *et al.,* 2024). Furthermore, molecular docking research identified propionic acid (PA) from the nuts as an efficient bioactive compound with antidiabetic drug-likeness properties (Ajao *et al.,* 2023). However, there remains limited scientific experimental evidence on the in vivo effects of PA in mitigating organ damage in DM. The present research investigated the cardiopharmacological protective efficacy of PA in a T2DM rat model.

Methodology

Experimental Animal

Twenty-five mature Wistar Albino rats weighing between 200–300 g was obtained from the animal breeding house of the Physiology Department, Ladoke Akintola University of Technology (LAUTECH), Ogbomoso, Oyo State, Nigeria. The animals were housed in clean polypropylene cages and acclimatized for 2 weeks, with free access to standard pelletized feed and water *ad libitum*. They were maintained under hygienic environmental conditions with 40–50% humidity, a temperature range of 25–27 °C, and a 12:12 h light/dark cycle. All experimental procedures were conducted in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals.

High-Fat Diet and Diabetes Induction

The animals were initially divided into two groups. Five rats fed a normal diet served as the control group, and twenty rats fed a high-fat diet (carbohydrate: 30%, fat: 65%, protein: 5%) served as the group designated for diabetes induction. Each group was maintained on its respective diet for eight weeks. After this period, both the control and high-fat diet (HFD) groups were subjected to a 12-hour overnight fast. Animals in the HFD group were then intraperitoneally injected with a repeated dose of freshly prepared streptozotocin (STZ) (30 mg/kg b.wt) to induce diabetes. These animals received a 20% glucose solution to prevent STZ-induced hypoglycemic death. Diabetes induction was confirmed 72 hours after STZ injection using blood obtained from the tail vein and analyzed with a glucometer. Animals with fasting blood glucose (FBG) levels higher than 200 mg/dL were identified as diabetic and were selected as the DM group for the study.

Experimental Animal Grouping/Treatment

The rats were randomly assigned into five groups, with 5 rats per group. Animals in the control category were divided into two groups, while the DM animals were divided into three groups and treated with propionic acid (PA) or metformin (Met). The treatment lasted for 4 weeks and was organized as follows:

Group 1: Normal control (NC)

Group 2: NC + PA (60 mg/kg b.wt)

Group 3: DM (untreated)

Group 4: DM + PA (60 mg/kg b.wt)

Group 5: DM + Met (200 mg/kg b.wt)

During the treatment period, food intake and water intake were measured daily, and changes in body weight were recorded weekly.

Oral Glucose Tolerance Test (OGTT)

OGTT was performed on the animals during the treatment phase on days 1, 7, 14, 21, and 28. The animals were fasted overnight (12 h) and were then orally administered a 20% glucose solution. Blood glucose levels were measured at 0 min (before glucose ingestion) and at 30, 60, 90, and 120 min after glucose solution ingestion.

Electrocardiogram Recording

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured noninvasively using a tail-cuff sphygmomanometer. Electrocardiogram (ECG) recordings were obtained through non-invasive three-lead electrodes placed in a lead II configuration, sampled at 1 kHz. The R–R interval, P–R interval, P wave, QRS complex, Q–T interval, and heart rate were analyzed. QTc was calculated from the QT interval using the formula: $QTc = QT / (RR/f)^{1/2}$.

Biochemical Analysis

After the treatment, the animals were fasted overnight (12 h) and humanely sacrificed under anesthesia using ketamine (40 mg/kg b.wt) and xylazine (20 mg/kg b.wt). The abdominal–thoracic cavity was dissected to access the heart. Blood samples were collected from the apex beat of the heart, and the hearts were excised immediately after blood collection. The hearts were rinsed in normal saline to remove blood stains and homogenized in a cold phosphate-buffered solution. The blood samples were centrifuged at 3500 rpm for 15 min, and the heart tissue homogenates were centrifuged at 5000 rpm for 15 min at −4 °C using a cold Eppendorf centrifuge (5810R, Germany). After centrifugation, the retrieved serum and supernatant plasma were used for the estimation of biochemical parameters.

Fasting blood glucose was measured using the glucose oxidase/peroxidase method by placing a drop of pricked tail venous blood onto a glucometer (Acu-Chek). Serum insulin and glycated hemoglobin (HbA1c) levels were determined by the ELISA method using a specific rat ELISA kit.

Serum levels of creatine kinase–myoglobin (CK-MB), troponin I (cTn-I), and brain natriuretic peptide (BNP), as well as cardiac levels of tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), malondialdehyde (MDA), catalase (CAT), superoxide dismutase (SOD), and reduced glutathione (GSH), were quantified using the enzyme-linked immunosorbent assay (ELISA) method with assay kits specific to each parameter, following the manufacturers' protocols. In addition, cardiac lactate dehydrogenase, caspase-3, and B-cell lymphoma-2 were measured spectrophotometrically using commercial kits according to the manufacturers' guidelines.

The cardiac lipid profile—triglycerides (TG), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-cholesterol)—was determined using an enzymatic colorimetric method with commercially available assay kits. Low-density lipoprotein cholesterol (LDL-cholesterol) was calculated

using the formula of Friedewald *et al.*:
LDL-cholesterol = TC − (HDL-C + TG/5) (Friedewald *et al.*, 1972).

Statistical Analysis

Data were expressed as the mean ± SEM and analyzed using one-way analysis of variance (ANOVA) with GraphPad Prism (version 10.3 software), followed by a Bonferroni post hoc test for comparison of significant differences. Statistical significance was set at $p < 0.05$.

Ethical Consideration

The research obtained ethical clearance from the Faculty of Basic Medical Science Ethical Approval Committee of Ladoke Akintola University of Technology, Nigeria with reference number: ERCFBMSLAUTECH: 049/06/2024 in 2024.

Results

PA Effect on body and heart weight in HFD/STZ-Induced Diabetic Rats

HFD/STZ-induced diabetic rats exhibited significant ($p<0.05$) lower body and heart weight in comparison with controls. Diabetic rats administered with PA showed an improvement in body and heart weight compared to diabetic controls (Table 1)

PA Effect on Food and Water Intake in HFD/STZ-Induced Diabetic Rats

Food and water intake increased ($p<0.05$) significantly in diabetic rats compared with the control rats. PA reduced the intake of food and water in diabetic treated rats compared with the untreated (Table 1).

PA Effect on Serum OGTT, Insulin, FBG, and HbA1c in HFD/STZ-Induced Diabetic Rats

There was a significant ($p<0.05$) increase in serum OGTT, insulin, FBG and HbA1c in diabetic rats compared with normal controls. PA administration improves the OGTT and reduces the levels of insulin, FBG and HbA1c in diabetic rats compared to untreated diabetic rats (Figure 1: A-D).

PA Effect on Cardiac Biomarkers in HFD/STZ-Induced Diabetic Rats

Serum CK-MB, TnP-I, LDH and BNP were significantly ($p<0.05$) higher in diabetic rats in comparison with control rats. PA administration to the diabetic rats lowered the cardiac biomarker levels compared with non-treated diabetic rats (Figure 2: A-D).

PA Effect on HR, BP and ECG parameters in HFD/STZ-Induced Diabetic Rats

HR, systolic and diastolic BP, PR-interval, QRS-interval, QT-interval and QTc-interval increased ($p<0.05$) significantly, and P-wave reduced ($p<0.05$) significantly in diabetic rats in comparison with the control. Administration of PA reduced the HR, BP, and ECG intervals and raised the P-wave compared with untreated diabetic rats (Table 2).

PA Effect on Cardiac Lipid Profile in HFD/STZ-Induced Diabetic Rats

There was a significant ($p<0.05$) decrease in HDL-cholesterol. Triglycerides, TC, and LDL-cholesterol increased ($p<0.05$) significantly in diabetic rats compared to controls. PA administration to the diabetic rats increased cardiac HDL-cholesterol levels, and reduced the levels of triglycerides, TC and LDL-cholesterol compared with non-treated diabetic rats (Figure 2: E-H).

PA Effect on Cardiac Oxidative Stress in HFD/STZ-Induced Diabetic Rats

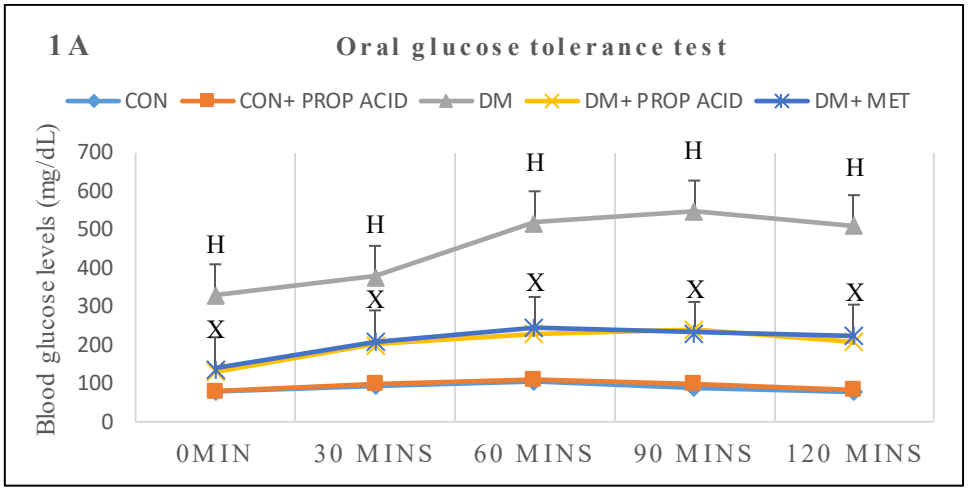
Cardiac malondialdehyde increased ($p<0.05$) significantly, and cardiac SOD, CAT and GSH were significantly ($p<0.05$) reduced in diabetic rats in comparison with controls. Malondialdehyde levels reduced and antioxidant levels increased in diabetic rats treated with PA compared with untreated (Figure 3: A-D).

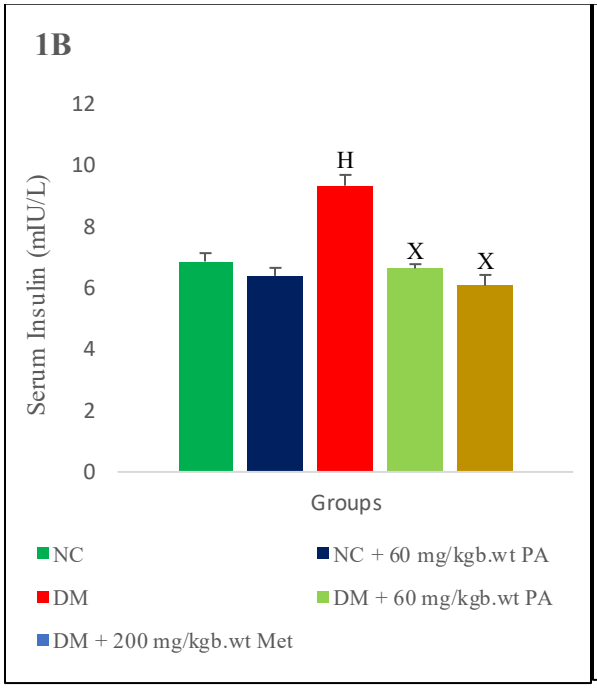
PA Effect on Cardiac Inflammatory Cytokines in HFD/STZ-Induced Diabetic Rats

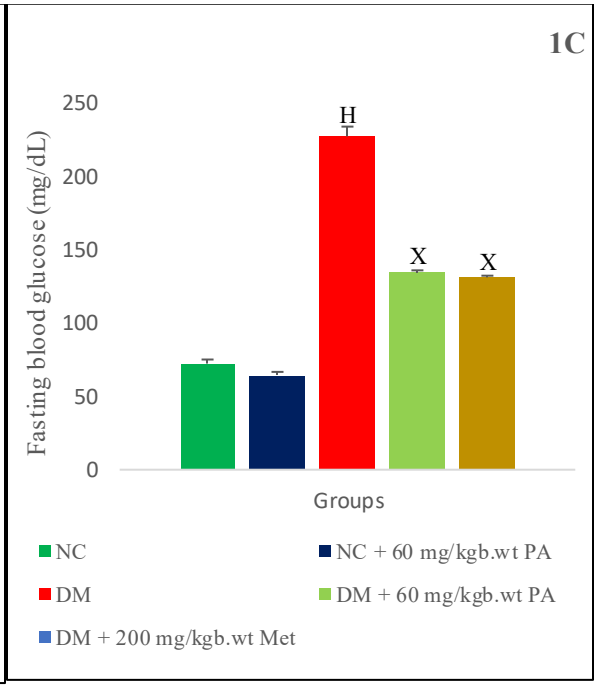
TNF-alpha, IL-1beta and IL-6 increased (p<0.05) significantly in the cardiac of diabetic rats compared with controls. PA administration reduced the inflammatory cytokines in the diabetic rat hearts compared with the non-treated (Figure 3: E-G).

PA Effect on Cardiac Apoptotic and Anti-apoptotic Markers HFD/STZ-Induced Diabetic Rats

Caspase-3 increased (p<0.05) significantly and B-cell lymphoma-2 decreased in the hearts of diabetic rats compared with controls. PA administration reduced the caspase-3 and elevated the B-cell lymphoma-2 in the diabetic rat hearts compared with the non-treated (Figure 3: H & I).







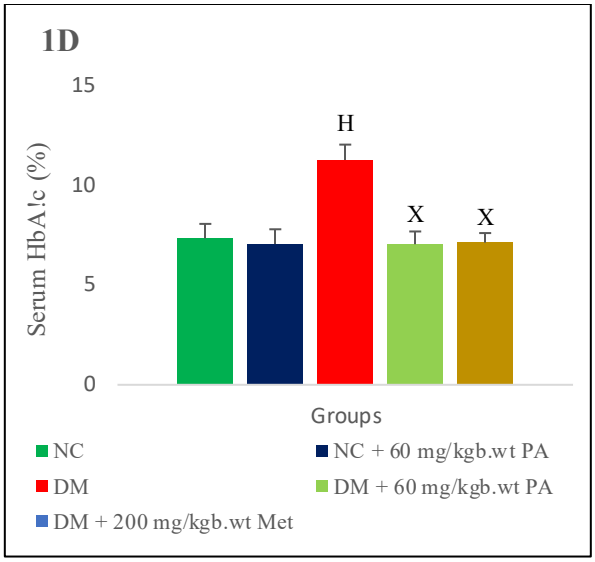
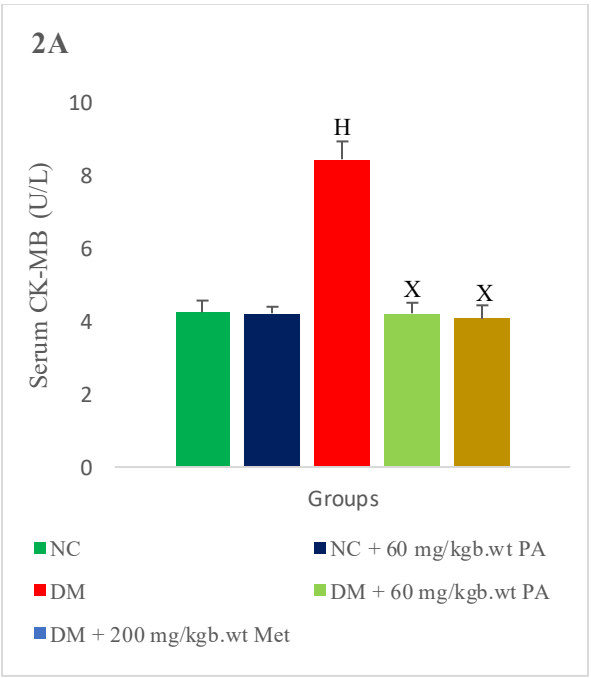


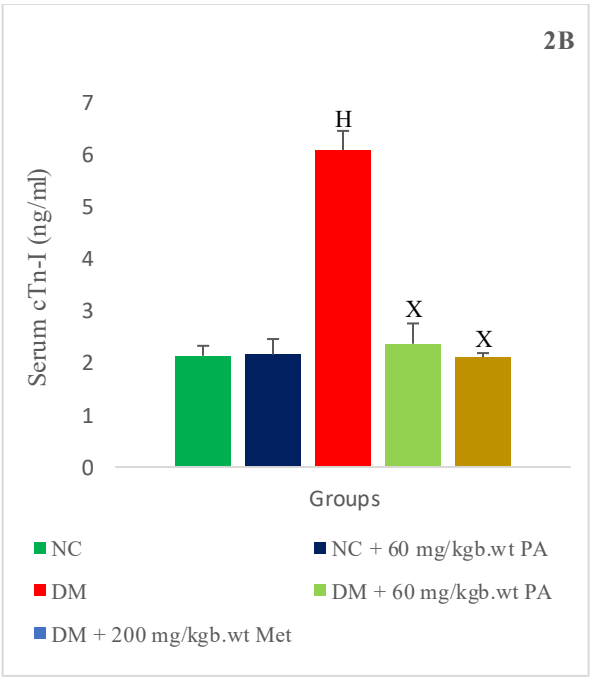
Figure 1: PA Effect on Serum (A) Oral Glucose Tolerance Test, (B) Insulin, (C) Fasting Blood Glucose, (D) HbA1c in HFD/Streptozotocin-Induced Diabetic Rats. Data Values Expressed as Standard Error of Mean (n=5). [H]significant at p<0.05 vs Control; [X]significant at p<0.05 vs Diabetic

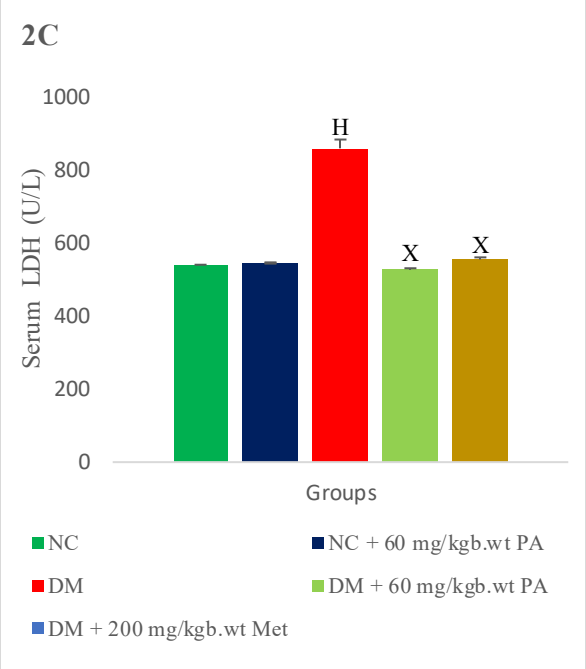
Table 1: PA Effect on Body Weight, Heart Weight, Food Intake and Water Intake HFD/STZ-Induced Diabetic Rats

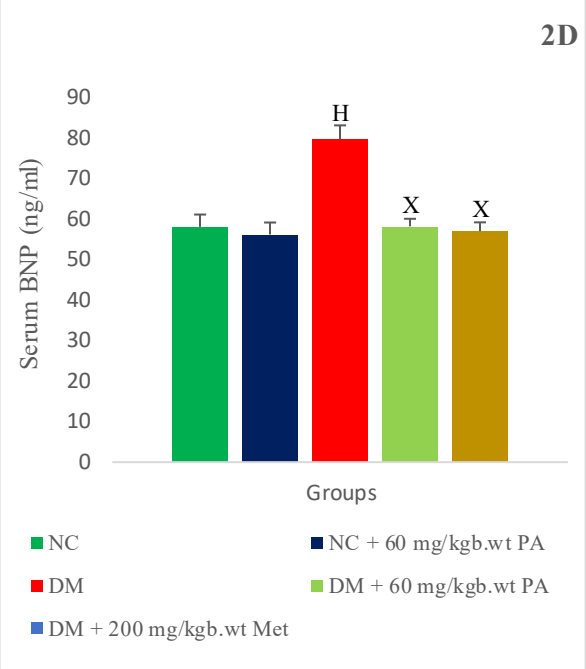
Parameters Groups	Body weight (g)	Heart weight (g)	Food intake/rat/day (g)	Water intake/rat/day (ml)
NC	299.20 ± 3.43	3.18 ± 0.05	29.60 ± 1.29	37.40 ± 1.54
NC + PA (60 mg/kgb.wt)	292.80 ± 2.63	3.07 ± 0.04	27.00 ± 0.71	36.80 ± 2.48
DM	190.20 ± 3.69^{H}	2.08 ± 0.07^{H}	40.60 ± 1.33^{H}	58.60 ± 1.17^{H}
DM + PA (60 mg/kgb.wt)	236.00 ± 3.30^{X}	2.67 ± 0.00^{X}	31.00 ± 0.71^{X}	37.80 ± 1.49^{X}
DM + Met (200 mg/kgb.wt)	251.20 ± 2.35^{X}	2.97 ± 0.09^{X}	32.00 ± 0.55^{X}	40.00 ± 1.41^{X}

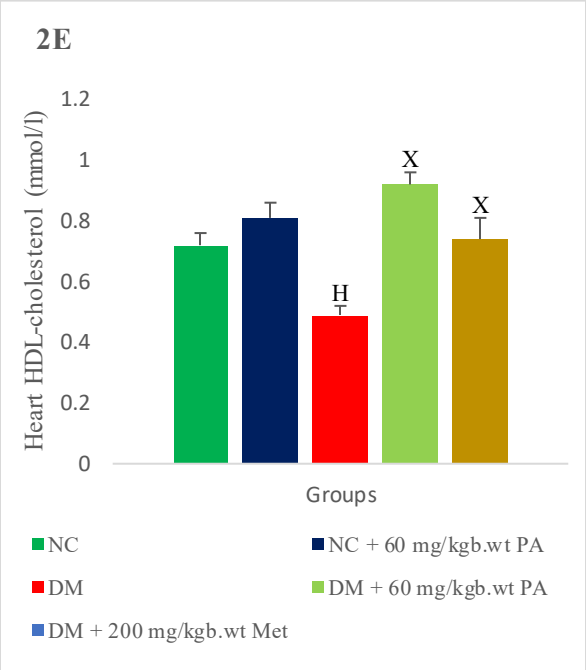
Data values expressed as standard error of mean (n=5). [H]significant at p<0.05 vs control; [X]significant at p<0.05 vs diabetic.

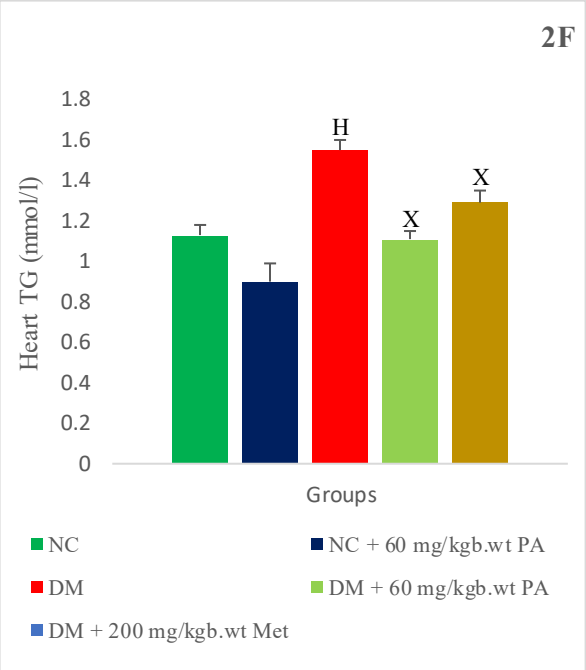


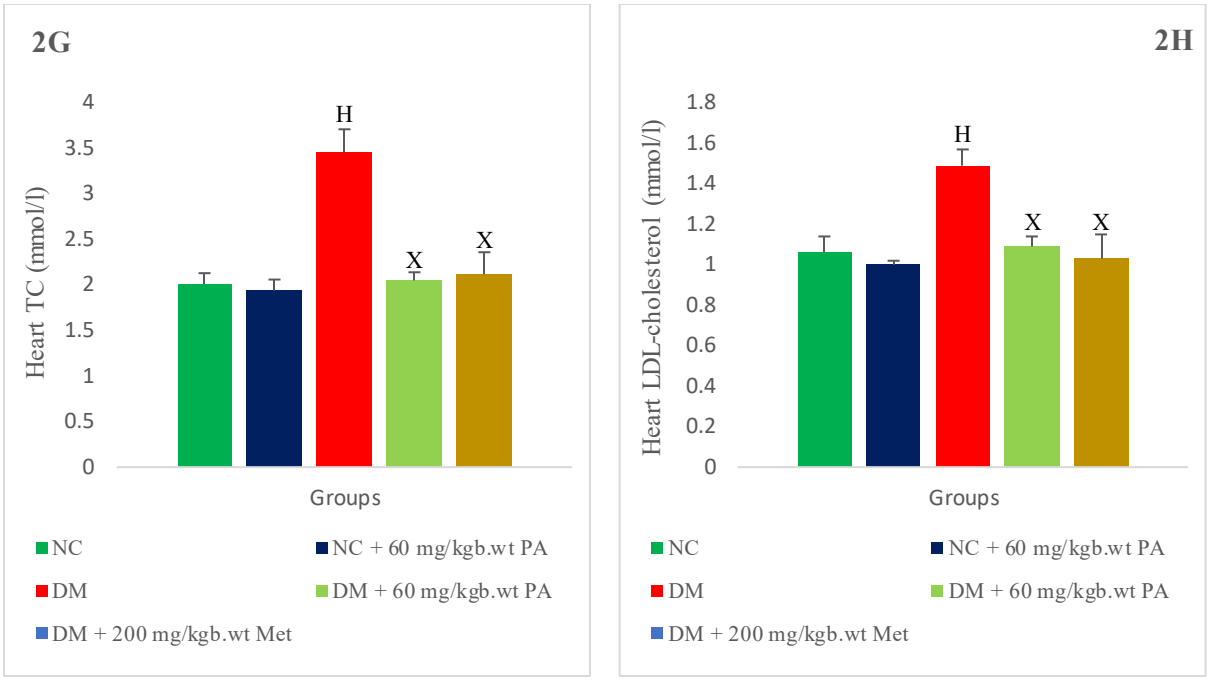



2C
Serum LDH (U/L)
1000
800
600
400
200
0
H
X
X
Groups
NC
NC + 60 mg/kgb.wt PA
DM
DM + 60 mg/kgb.wt PA
DM + 200 mg/kgb.wt Met


2D
Serum BNP (ng/ml)
90
80
70
60
50
40
30
20
10
0
H
X
X
Groups
NC
NC + 60 mg/kgb.wt PA
DM
DM + 60 mg/kgb.wt PA
DM + 200 mg/kgb.wt Met


2E
Heart HDL-cholesterol (mmol/l)
1.2
1
0.8
0.6
0.4
0.2
0
H
X
X
Groups
NC
NC + 60 mg/kgb.wt PA
DM
DM + 60 mg/kgb.wt PA
DM + 200 mg/kgb.wt Met


2F
Heart TG (mmol/l)
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
H
X
X
Groups
NC
NC + 60 mg/kgb.wt PA
DM
DM + 60 mg/kgb.wt PA
DM + 200 mg/kgb.wt Met



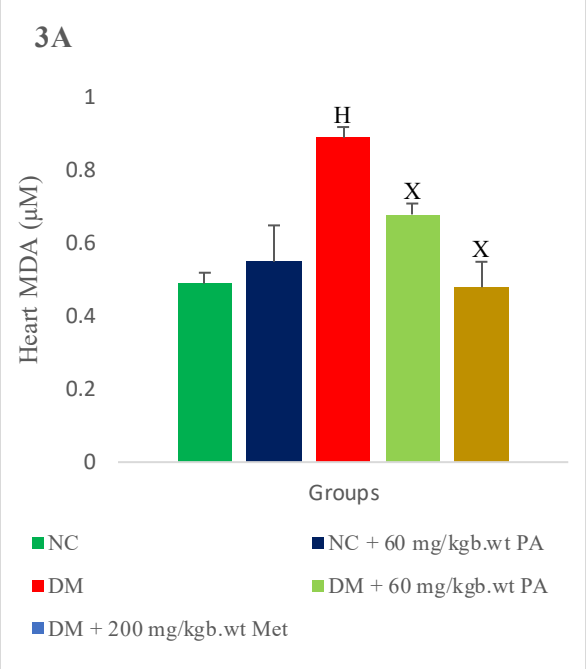
Data values expressed as standard error of mean (n=5). [H]significant at p<0.05 vs Control; [X]significant at p<0.05 vs diabetic.

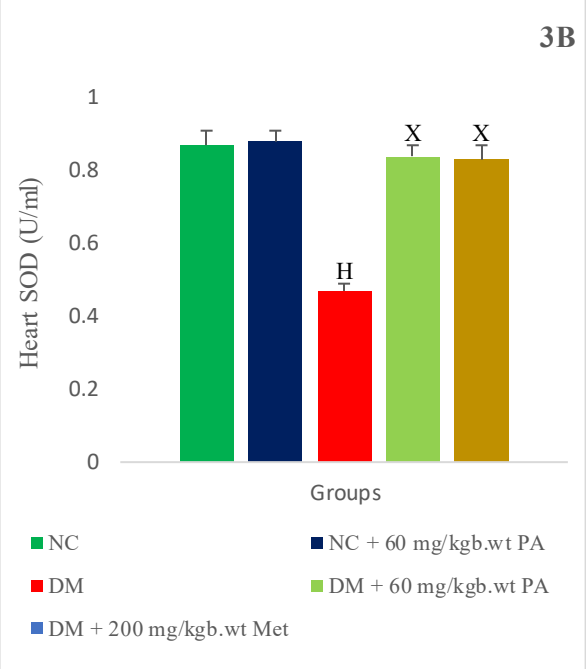
Figure 2: PA Effect on Heart (A) CK-MB, (B) cTn-I, (C) LDH, (D) BNP, (E) HDL-Cholesterol, (F) TG, (G) TC, (H) LDL-Cholesterol in HFD/Streptozotocin-Induced Diabetic Rats

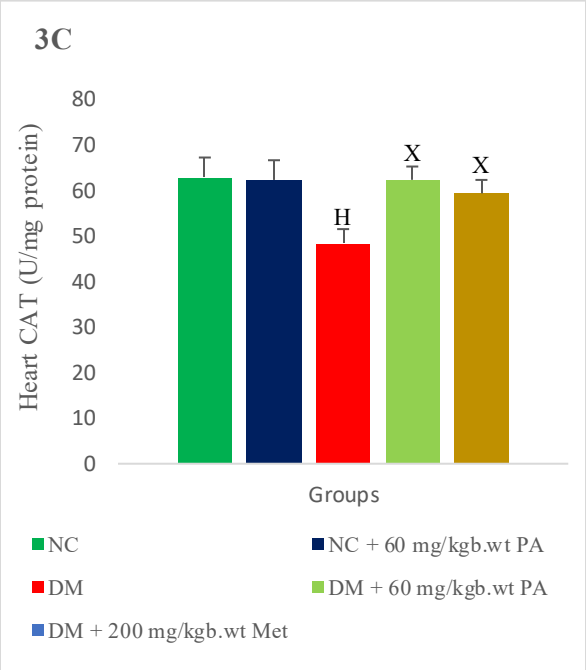
Table 2: PA Effect on Heart Rate, Blood Pressure, and Electrocardiograph Parameters in HFD/STZ-Induced Diabetic Rats

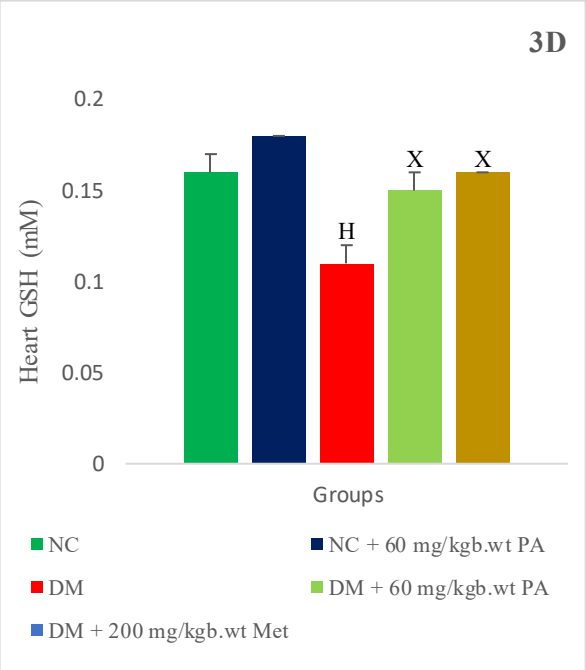
Groups Parameters	NC	NC + PA (60 mg/kgb.wt)	DM	DM + PA (60 mg/kgb.wt)	DM + Met (200 mg/kgb.wt)
Heart (BPM)	275.00 ± 1.84	278.00 ± 4.98	410.00 ± 6.52^{H}	333.00 ± 8.31^{X}	303.80 ± 6.32^{X}
SBP (mmHg)	123.60 ± 2.73	129.40 ± 2.69	178.60 ± 6.99^{H}	146.00 ± 2.98^{X}	143 40 ± 3.94^{X}
DBP (mmHg)	82.80 ± 3.15	82.00 ± 2.307	140.00 ± 1.70^{H}	109.44 ± 1.17^{X}	93.40 ± 3.53^{X}
P-wave (m)	26.00 ± 0.95	26.20 ± 1.16	15.00 ± 1.00^{H}	25.40 ± 0.93^{X}	25.00 ± 1.05^{X}
QT-interval (ms)	49.00 ± 1.22	53.00 ± 1.30	94.00 ± 3.30^{H}	57.60 ± 2.06^{X}	59.00 ± 2.83^{X}
QTc-interval (ms)	131.20 ± 8.21	134.20 ± 2.96	235.40 ± 8.74^{H}	170.00 ± 3.86	155.80 ±2.29^{X}
QRS-interval (ms)	24.40 ± 2.06	24.80 ± 1.77	39.00 ± 1.00^{H}	30.40 ± 1.36^{X}	30.80 ± 1.49^{X}
PR-interval (ms)	29.00 ± 0.89	26.40 ± 1.03	38.80 ± 1.02^{H}	32.60 ± 1.44^{X}	32.20 ± 2.35^{X}

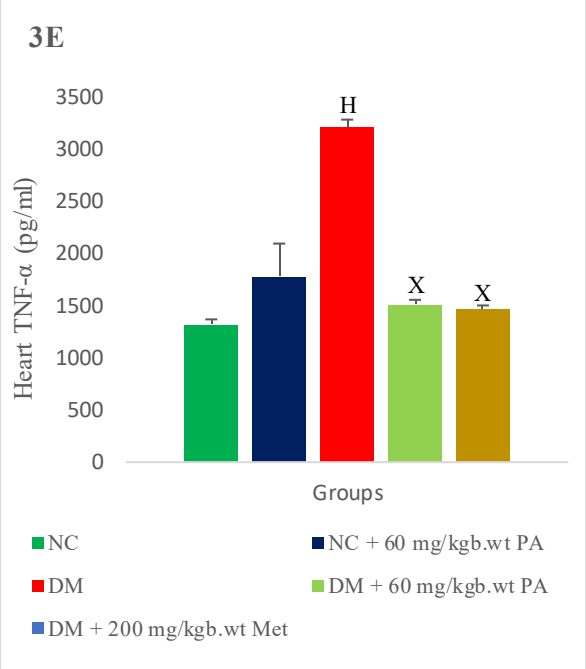
Data values expressed as standard error of mean (n=5). [H]significant at p<0.05 vs control; [X]significant at p<0.05 vs diabetic.

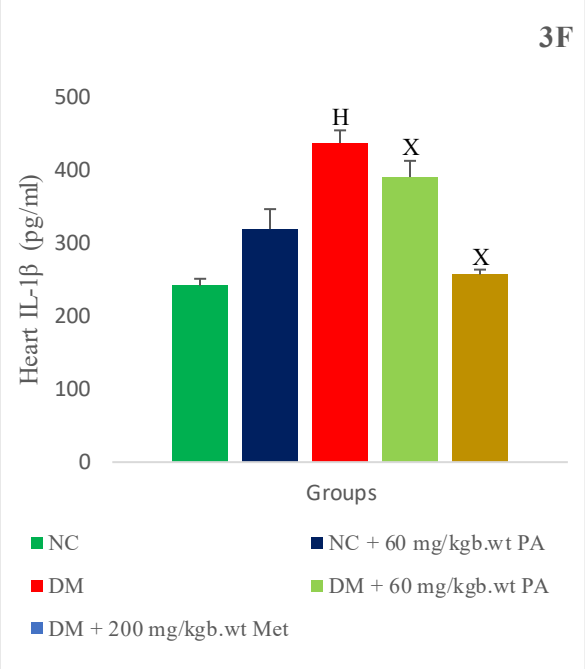

3A
Heart MDA (µM)
1
0.8
0.6
0.4
0.2
0
H
X
X
Groups
NC
NC + 60 mg/kgb.wt PA
DM
DM + 60 mg/kgb.wt PA
DM + 200 mg/kgb.wt Met

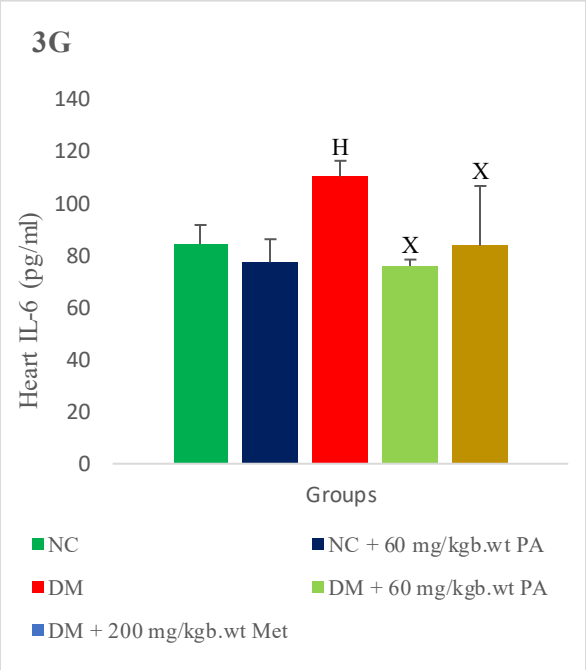

3B
Heart SOD (U/ml)
1
0.8
0.6
0.4
0.2
0
H
X
X
Groups
NC
NC + 60 mg/kgb.wt PA
DM
DM + 60 mg/kgb.wt PA
DM + 200 mg/kgb.wt Met

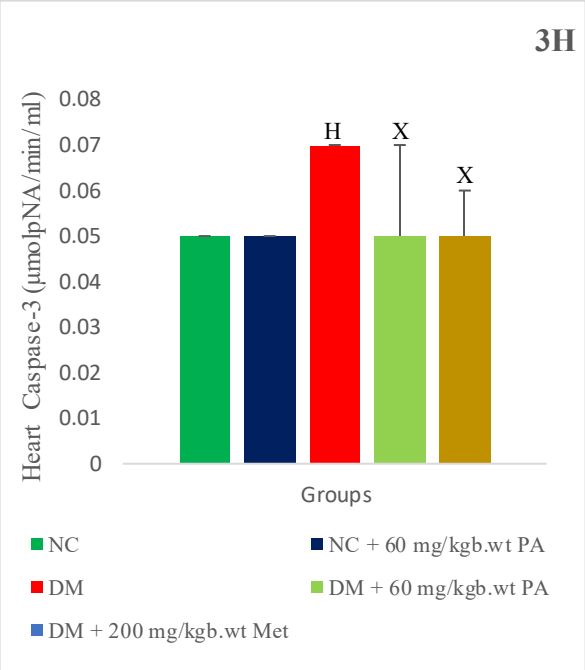

3C
Heart CAT (U/mg protein)
80
70
60
50
40
30
20
10
0
H
X
X
Groups
NC
NC + 60 mg/kgb.wt PA
DM
DM + 60 mg/kgb.wt PA
DM + 200 mg/kgb.wt Met

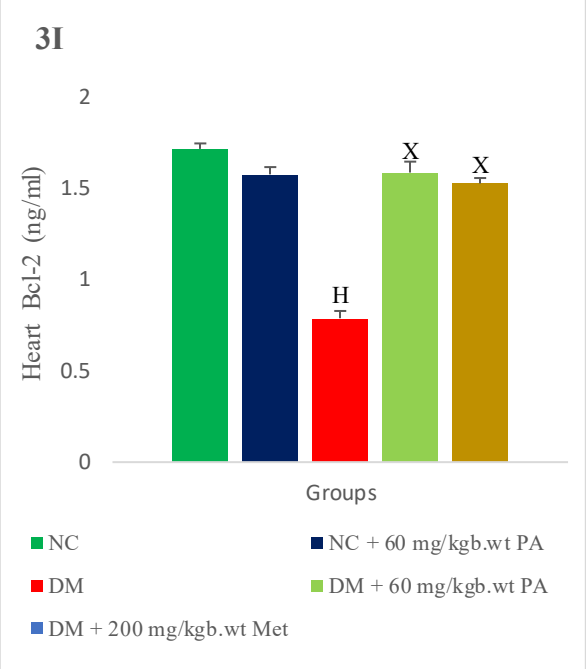

3D
Heart GSH (mM)
0.2
0.15
0.1
0.05
0
H
X
X
Groups
NC
NC + 60 mg/kgb.wt PA
DM
DM + 60 mg/kgb.wt PA
DM + 200 mg/kgb.wt Met


3E
Heart TNF-α (pg/ml)
3500
3000
2500
2000
1500
1000
500
0
H
X
X
Groups
NC
NC + 60 mg/kgb.wt PA
DM
DM + 60 mg/kgb.wt PA
DM + 200 mg/kgb.wt Met


3F
Heart IL-1β (pg/ml)
500
400
300
200
100
0
H
X
X
Groups
NC
NC + 60 mg/kgb.wt PA
DM
DM + 60 mg/kgb.wt PA
DM + 200 mg/kgb.wt Met


3G
Heart IL-6 (pg/ml)
140
120
100
80
60
40
20
0
H
X
X
Groups
NC
NC + 60 mg/kgb.wt PA
DM
DM + 60 mg/kgb.wt PA
DM + 200 mg/kgb.wt Met


3H
Heart Caspase-3 (µmolpNA/min/ml)
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
H
X
X
Groups
NC
NC + 60 mg/kgb.wt PA
DM
DM + 60 mg/kgb.wt PA
DM + 200 mg/kgb.wt Met



Data values expressed as standard error of mean (n=5). ^{H}*significant at p<0.05 vs control;* ^{X}*significant at p<0.05 vs diabetic*

Figure 3: PA Effect on Heart (A) MDA, (B) SOD, (C) CAT, (D) GSH, (E) TNF-α, (F) IL-1β, (G) IL-6, (H) Caspase-3, (I) Bcl-2 in HFD/Streptozotocin-Induced Diabetic Rats

Discussion

The prevalence of type-2 diabetes mellitus (T2DM) persistently increases and accounts for over 90% of DM incidence (Migdalis, 2024). T2DM patients are three times likely to develop cardiovascular diseases (Shah *et al.,* 2025) and CVDs emerged as the major causes of mortality (about 70%) in T2DM. Over the past decades, the use of medicinal plants' natural active compounds has been considered as less toxic and an alternative treatment option for DM and its related complications (Scarpa *et al.,* 2024). The current experiment investigates the cardiovascular protective effect of propionic acid, an active phytochemical of *A. occidentale* nuts in diabetic rats.

Diabetes symptoms include polyphagia, polydyspia, polyuria, and uncontrollable loss of body weight (Tegegne *et al.,* 2024). Insulin deficiency alters glucose use for energy, causing breakdown of fat and structural proteins in muscle, resulting in a remarkable loss of weight (Almalki, *et al.,* 2024). Similar increase in water intake, food intake and reduced body and heart weight was noticed in the diabetic rat model of the present finding, supporting the other literature (Barka *et al.,* 2024). Oral treatment of diabetic rats with PA alleviates these symptoms and improves body weight, as well as heart weight. The effect of PA could be linked to enhancing insulin sensitivity for glucose uptake, thereby preventing the breakdown of protein and fat in muscle for restoring body weight.

Diabetic patients are clinically diagnosed with sustained hyperglycemia and insulin resistance (Hurtado-Carneiro *et al.,* 2024). In T2DM, spontaneous release of insulin by pancreatic beta-cells is a compensatory mechanism to regulate sustained hyperglycemia and insensitivity of the targeted organs to insulin effects leads to hyperglycemia-hyperinsulinemia (Attanasio *et al*., 2024). Corroborating the findings of Racine *et al*. (2025), diabetic rats obviously exhibited the hallmark of T2DM in our study, as evidenced by elevated levels of blood glucose and insulin in serum. Active bioactive compounds in medicinal plants have been studied with ability to enhance insulin sensitivity and inhibit hepatic glycogenolysis (Horvath *et al.,* 2025). Supporting this report, the PA administration lowered the blood glucose and returned the insulin level to a desirable level. Scientifically, these results indicate that PA possesses the potential to inhibit glucose absorption in the intestinal tract, modulate insulin sensitivity at peripheral organs and tissues for glucose uptake, and regulate glucose-dependent insulin release.

Evidence from a previous study established that poorly managed chronic hyperglycemia affects cardiac electrophysiological patterns (El-Nasr *et al.,* 2025). Elongation in QT interval and abnormal repolarization patterns, are signs of risk of developing arrhythmias and sudden cardiac arrest in diabetes (Welten *et al.,* 2023). In consistent with El-Nasr *et al*. findings of El-Nasr *et al*. (2025), changes in ECG parameters, such as prolonged QTc-interval, QT-interval and reduced P-wave amplitudes, were noticed in the ECG record of the diabetic rats of this study. Conversely, PA administration exhibited a noteworthy cardioprotective efficacy in diabetic rats by reducing heart rate, QTc intervals, QT and improving the P-wave, highlighting PA potential as a treatment agent to alleviate diabetes-induced heart dysfunction, which aligns with the result of Sarker *et al.* (2024), on Astaxanthin enhanced heart rate variability and alleviated myocardial injury in diabetic rats, primarily through its ability to suppress oxidative stress and inflammation, key factors driving the development of cardiac disease in diabetes.

Chronic hyperglycemia in diabetes adversely damaged the cardiac structure, tissue integrity, and function independently of other cardiovascular risk factors, ultimately contributing to diabetic cardiomyopathy and heart failure (Akhtar *et al.,* 2023). Lactate dehydrogenase (LDH), a key enzyme involved in cellular energy metabolism, is released into circulation following tissue injury and therefore serves as a biomarker of cardiac damage (Zhang *et al.,* 2024). Similarly, creatine kinase (CK), a guanidino-kinase that catalyzes the reversible conversion of creatine to phosphocreatine, is predominantly expressed in skeletal muscle and myocardium. Among its isoenzymes, creatine kinase-MB (CK-MB) is widely used as a sensitive and specific indicator in evaluating the extent of myocardial damage (Li *et al.,* 2023). Due to cardiac muscle damage and ventricular dysfunction, serum LDH and CK-MB have been reported to increase in diabetic patients (Netala *et al.,* 2025). Over many decades, serum cardiac troponin-I (cTn-I) has been regarded as the typical biomarker for the diagnosis of acute myocardial necrosis. Also, brain natriuretic peptide (BNP) plays a significant role in cardiac homeostasis and has been noticed to be disrupted in clinical conditions (Liao *et al.,* 2025). In our findings, these biomarkers were elevated in the serum, suggesting cardiac damage in the diabetic rats, which accords with the previous reports of Welten *et al.* (2023). However, treatment with PA lessens these cardiac injury biomarkers and could be due to its antioxidant properties that attenuate oxidative damage, which supports the cardioprotective effect of this compound.

Dyslipidaemia is a key risk factor for cardiovascular disease progression in DM. The oxidizing of fatty acids by the liver produces fuel and mobilization of LDL-cholesterol to peripheral tissues (Barka *et al.,* 2024). Elevated cholesterol is the most common lipid anomaly in DM and is driven by increased cholesterol formation, impaired cholesterol absorption, and enhanced lipolysis. Insulin deficiency further accelerates the influx of fatty acids into the liver for excessive cholesterol synthesis (Rao *et al.,* 2025). Inactivation of the enzyme lipoprotein lipase to hydrolyze triglyceride due to insulin deficiency causes high triglyceride (Suzuki *et al.,* 2016), and a deficiency in cholesterol clearance from the peripheral tissue contributes to high triglyceride and diminished high-density lipoprotein-cholesterol (Diaz *et al.,* 2025). Hypertriglyceridemia, elevated total cholesterol and LDL-cholesterol, coupled with reduced HDL-cholesterol, was observed in the hearts of diabetic rats in our study. The lipid abnormalities observed in the cardiac tissue may be attributed to impaired insulin sensitivity for regulation of lipid metabolism, which is in line with a finding report of Barka *et al*. (2024). Nevertheless, the administration of PA reduced the cardiac triglyceride, total cholesterol, LDL-cholesterol and improved the HDL-cholesterol. The cardiac lipid-lowering potency of PA may be due to the restoration of insulin secretion, which regulates lipoprotein hydrolysis and its influx into peripheral tissues, supporting previous research reports on the anti-hyperlipidemic effects of Quercetin (Ozorowski *et al.,* 2025).

Myocardial damage in diabetes is influenced by hyperglycemia-induced oxidative stress and inflammation (Caturano, *et al.,* 2025). Long-term hyperglycemia affects oxidant balance, causing the production of high reactive oxygen species (ROS), and the endogenous antioxidant incapacity to eliminate free radicals majorly contributes to cellular damage (Caturano *et al*., 2023). A report showed cardiac oxidative stress marker malondialdehyde (MDA) elevation in diabetic rats (Li *et al.,* 2023). Corroborating this report, our study also observed a decrease in antioxidant activity of SOD, CAT and GSH, along with elevated malondialdehyde in the heart of diabetic rats. PA showed a remarkable anti-

oxidative effect by attenuating the marker of oxidative damage and up-regulating the cardiac antioxidant activity in diabetic rat hearts, which indicates PA cardiac therapeutic effect in diabetes and could be linked to its insulin secretion restoration for glycemic regulation. These results are in harmony with a study that reveals certain flavonoids prevent cardiac oxidative stress by activating nuclear factor erythroid 2-related factor 2 (NRF2), thereby enhancing antioxidant enzymes (Emeka *et al.,* 2024).

Hyperglycemia-induced oxidative stress is known to stimulate diverse inflammatory responses through the activation of nuclear factor kappa-B (NF-κB) cells, which facilitates the release of inflammatory cytokines such as TNF-α, interleukin-1β, and interleukin-6 in the diabetic heart. These inflammatory cytokines contribute to the progression of cardiac cell damage (Masenga *et al*., 2023). The present findings also detect an upsurge in the circulation of pro-inflammatory cytokines, especially TNF-α, as well as IL-1β and IL-6 in the hearts of diabetic rats, which aligns with findings of Zhang and Dhalla (2024). PA supplement potently reduced these pro-inflammatory cytokines in the diabetic rat hearts. In agreement with research findings that revealed the capability of phytochemicals in reducing cardiac inflammation (Deng *et al.,* 2024). PA could exert these anti-inflammatory properties through its anti-oxidative potency by scavenging free radical generation in the heart, further supporting the cardio-protective effects of this bioactive compound in diabetic conditions.

The unregulated oxidative stress and inflammatory cytokines activate cardiac apoptosis in diabetes (Li *et al.,* 2023). The expression of caspase-3, a pro-apoptotic marker, has been reported to increase in diabetic hearts with a reduction in anti-apoptotic marker, B-cell lymphoma-2 expression (Wang *et al.,* 2020). Similarly, up-regulation of caspase-3 and down-regulation of B-cell lymphoma-2 were observed in the hearts of diabetic rats. Chronic hyperglycemia has been documented to reduce activation of the AKT signalling network by excessive ROS, thereby promoting the activity of the forkhead box 3 (FOXO3) gene that favours apoptosis. Polyphenol compounds such as resveratrol have been recently reported to reduce FOXO3 to prevent cardiovascular damage by eliminating oxidants (Li *et al.,* 2023). In support of the report, PA administration lowered the pro-apoptotic marker and increased the anti-apoptotic marker level, which might result from its anti-oxidative efficacy in enhancing the activation of AKT signalling pathway to down-regulate the FOXO3 gene activity.

Conclusion

Treatment with propionic acid successfully prevents cardiac damage in diabetic rats. The supplementation of propionic acid alleviates the cardiac oxidative stress, inflammation and apoptosis. Propionic acid could be utilized as a new promising therapy for cardiac disease in diabetes. Clinical trial investigations to authenticate these efficacies in humans would provide a safer and alternative therapy approach to lessen diabetes-related cardiovascular mortality.

Conflict of Interest

The author(s) declare that there is no conflict of interest regarding the publication of this article.

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