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Research Article

Protective Effects of *Carica papaya* Leaf Ethanolic Extract against Dyslipidaemia and Oxidative Stress in Streptozotocin-Induced Rats Fed a High Fat Diet: A Dose Response Study

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ABSTRACT
Diabetes mellitus, linked to dyslipidaemia and oxidative stress, often resists complete management by conventional therapies, whereas *Carica papaya* leaves offer potential adjunctive benefits. This study evaluated the protective effects of *C. papaya* leaf ethanolic extract against dyslipidaemia in streptozotocin (STZ)-induced diabetic rats fed a high-fat diet. Thirty male Wistar rats were divided into five groups (n = 6): normal control, STZ-induced diabetic control, STZ + metformin (25 mg/kg), and STZ + *C. papaya* ethanolic extract (200 mg/kg and 400 mg/kg). Diabetes was induced by a high-fat diet followed by a single intraperitoneal injection of STZ (40 mg/kg). Treatments were administered orally for 28 days. Fasting blood glucose, serum lipid profile (TC, TG, LDL-C, HDL-C), antioxidant enzyme activities (SOD, CAT, GSH), malondialdehyde (MDA) levels, and atherogenic indices were determined using standard biochemical assays. Data were analysed using one-way ANOVA followed by Tukey's post hoc test at $p < 0.05$. *Carica papaya* extract produced a significant, dose-dependent reduction in fasting blood glucose and MDA levels, while enhancing SOD, CAT, and GSH activities. Lipid abnormalities induced by STZ and high-fat diet were ameliorated, with marked reductions in TC, TG, and LDL-C, and elevation of HDL-C. Atherogenic indices were significantly reduced, indicating an improved cardiovascular risk profile. The 400 mg/kg dose exhibited near-normal biochemical values comparable to those of metformin. The ethanolic leaf extract of *Carica papaya* exhibits dose-dependent antihyperglycaemic, antioxidant, and hypolipidaemic effects in diabetic rats.

Keywords: Antioxidants; Diabetes; Lipid profile; Metformin; Streptozotocin

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INTRODUCTION

Diabetes mellitus (DM) is a multifactorial metabolic disorder characterized by chronic hyperglycaemia resulting from impaired insulin secretion, insulin resistance, or both (Alam *et al*., 2021). Its global prevalence exceeds 530 million adults and is projected to surpass 780 million by 2045 (Laraeni *et al*., 2021). Beyond hyperglycaemia, dyslipidaemia and oxidative stress are major contributors to diabetic complications, particularly cardiovascular disease, which accounts for more than half of diabetes-related deaths (Caturano *et al*., 2025). Diabetic dyslipidaemia is characterized by elevated triglycerides, total cholesterol, and low-density lipoprotein cholesterol (LDL-C), with reduced high-density lipoprotein cholesterol (HDL-C) (Hirano *et al*., 2022). Persistent

hyperglycaemia further promotes oxidative stress through excessive generation of reactive oxygen species and glycoxidation products, leading to lipid peroxidation, endothelial dysfunction, and metabolic impairment (Papachristoforou *et al*., 2020).

Although insulin, oral hypoglycaemic agents, statins, and fibrates remain central to diabetes management, their long-term use is limited by adverse effects, cost, and incomplete correction of oxidative and lipid abnormalities (Kosmas *et al*., 2018). Consequently, attention has shifted toward plant-derived therapeutics with multitarget metabolic actions. Phytochemicals such as flavonoids and phenolic acids have demonstrated beneficial effects on oxidative stress and lipid metabolism through modulation of peroxisome proliferator-activated receptors and AMP-activated protein kinase pathways (Fakhri *et al*., 2024).

Carica papaya L. leaves contain bioactive compounds including quercetin, kaempferol, caffeic acid, and saponins, which possess antioxidant, anti-inflammatory, and hypolipidaemic properties (Akanda *et al*., 2025; Alara *et al*., 2022; Koul *et al*., 2022; Sancho *et al*., 2011). Previous studies have reported improvements in glycaemic control, pancreatic β-cell preservation, and reduced lipid peroxidation in diabetic models (Miranda-Osorio *et al*., 2016; Roy *et al*., 2022). However, limited evidence exists regarding their effects on atherogenic indices and oxidative stress biomarkers in high-fat diet/streptozotocin-induced diabetes, particularly in comparison with metformin. Therefore, this study investigated the dose-dependent effects of C. papaya leaf ethanolic extract on lipid profiles, atherogenic indices, and oxidative stress biomarkers in diabetic rats, hypothesising that the extract would ameliorate dyslipidaemia and oxidative imbalance through modulation of antioxidant and lipid-regulatory pathways.

MATERIALS AND METHODS

Plant Material Collection and Authentication

Fresh leaves of *C. papaya* L. (family Caricaceae) were collected in May 2025 from the Forestry Research Institute of Nigeria (FRIN), Ibadan, Oyo State (7°23'N, 3°55'E). The plant was authenticated by a taxonomist at the FRIN Herbarium, and a voucher specimen (FHI 1142134) was deposited for reference. The leaves were rinsed with distilled water, air-dried under shade at 25–28 °C for 15 days, and milled into coarse powder (1 mm mesh) using a stainless-steel grinder. The powdered material was stored in airtight amber containers at 4 °C and extracted within four weeks to minimize oxidative degradation.

Preparation of Crude Ethanolic Extract

Powdered *C. papaya* leaves (6 kg) were extracted by maceration in 10 L of absolute ethanol (Sigma-Aldrich, Germany) for 72 h at ambient temperature with intermittent agitation to ensure optimal solvent penetration. The mixture was filtered successively through muslin cloth and Whatman No. 1 filter paper, and the combined filtrate was concentrated under reduced pressure at 60 °C using a rotary evaporator (RE52A, PEC Medical, China) to obtain a dark-green viscous crude ethanolic extract with a yield of 9.8% (w/w). The extract was stored in airtight amber bottles at 4 °C until further use to minimize oxidative degradation and preserve phytochemical integrity.

Experimental Animals and Ethical Considerations

Thirty male albino Wistar rats (10 weeks old, 165–178 g) were obtained from the Animal House, Faculty of Basic Medical Sciences, University of Ibadan, Nigeria. Animals were housed in polypropylene cages (five rats per cage) under controlled conditions (22 ± 2 °C, 55 ± 5% humidity, 12 h light/dark cycle) with free access to standard rat chow (Vital Feeds, Nigeria) and water ad libitum. Bedding was replaced every two days, and animals were acclimatized for 14 days prior to the experiment.

All procedures were approved by the Health Research Ethics Committee of Bingham University Teaching Hospital (approval number: NHREC/21/05/2005/01523) and conducted in accordance with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals (8th edition, 2011) and ARRIVE 2.0 guidelines. Randomization was performed using a computer-generated sequence, and investigators conducting biochemical assays were blinded to treatment allocation. Only male rats were used to minimize hormonal variation effects.

Induction of Type 2 Diabetes Mellitus

Type 2 diabetes mellitus was induced following an eight-week high-fat diet (42.4% fat, 33.5% carbohydrate, 13.9% protein; UAC Feeds, Nigeria) to promote insulin resistance, after which rats received a single intraperitoneal injection of streptozotocin (STZ; 40 mg/kg; Sigma-Aldrich, USA) freshly prepared in cold citrate buffer (0.1 M, pH 4.5). Control rats received an equivalent volume of citrate buffer. Seventy-two hours post-injection, fasting blood glucose levels were measured from tail vein blood using a glucometer (Accu-Chek Active, Roche Diagnostics, Germany. Rats exhibiting fasting blood glucose levels ≥ 11.1 mmol/L were classified as

diabetic, and those with total cholesterol > 4.7 mmol/L and triglycerides > 1.7 mmol/L, accompanied by elevated LDL-C and/or reduced HDL-C, were identified as dyslipidaemic; only animals meeting these criteria were enrolled for treatment, which commenced on day 4 following STZ administration (Gideon & Owhonda, 2024).

Experimental Design

Diabetic and control rats (n = 6 per group; total = 30) were randomly divided into five groups and treated orally once daily for 28 days as follows: Group 1 served as the normal control and received only the vehicle (1 mL/kg of 0.5% carboxymethylcellulose solution); Group 2 was the diabetic control, administered STZ only; Group 3, the positive control, received STZ plus Metformin (25 mg/kg); Groups 4 and 5 were treated with STZ plus crude ethanolic extract of *C. papaya* leaves at doses of 200 mg/kg and 400 mg/kg, respectively.

All treatments were administered via oral gavage each morning (08:00–09:00 h) to minimize circadian variability. Dose selection was guided by prior literature and preliminary toxicity data indicating optimal efficacy within the 200–400 mg/kg range (Timothy *et al*., 2022). Fasting blood glucose was recorded weekly throughout the study.

Acute Oral Toxicity Study

Acute oral toxicity was assessed according to OECD Guideline 425 (OECD, 2008). Male Wistar rats (200 ± 10 g) were fasted overnight and sequentially administered the ethanolic extract at 300 mg/kg and 2000 mg/kg body weight. Animals were observed continuously for 24 h and daily for 14 days for behavioural changes (tremors, convulsions, salivation, lethargy) or mortality. Food intake was monitored daily. No mortality or abnormal behaviour was observed, suggesting an oral LD_{50} > 2000 mg/kg.

Sample Collection

At the end of the 28-day treatment period, rats were fasted overnight and anaesthetized using intraperitoneal ketamine (80 mg/kg) and xylazine (10 mg/kg). Blood samples were collected by cardiac puncture into plain tubes, allowed to clot at room temperature, and centrifuged at 3000 rpm for 15 min at 4 °C. Serum was aliquoted into labelled vials and stored at −20 °C until biochemical and oxidative stress analyses.

Determination of Serum Lipid Profile

Serum total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) were quantified using enzymatic colorimetric kits (Randox Laboratories, Crumlin, UK; Cat. Nos. CH200, TR210, CH203) according to manufacturer instructions. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula [LDL-C = TC − HDL-C − (TG/5)] (Harnafi *et al*., 2008). Absorbance was read at 500–550 nm using a UV–Vis spectrophotometer (Shimadzu UV-1800, Japan). All analyses were performed in duplicate, and quality control sera were included in each run.

Evaluation of Lipid-Derived Atherogenic Indices

The potential for atherogenic risk was assessed through the computation of established lipid-derived indices, including the atherogenic index (Joerin *et al*., 2014), the HDL-to-LDL cholesterol ratio (Adám-Vizi & Seregi, 1982), and the coronary risk index (Singh *et al*., 2016).

Assessment of Oxidative Stress Biomarkers

Antioxidant enzyme activities were determined in serum using validated spectrophotometric methods. Catalase (CAT) activity was measured by the decomposition rate of hydrogen peroxide at 240 nm (Aebi, 1984), superoxide dismutase (SOD) by inhibition of nitroblue tetrazolium reduction at 560 nm (Marklund & Marklund, 1974), and glutathione (GSH) by the rate of NADPH oxidation at 340 nm (Rotruck *et al*., 1973). Lipid peroxidation was quantified as malondialdehyde (MDA) via thiobarbituric acid reactive substances (TBARS) with absorbance read at 532 nm (Yagi, 1994). Protein concentration was determined using the Bradford (1976) method, and all enzyme activities were normalized to total protein and expressed as U/Ml

Data Analysis

Data are presented as mean ± standard error of the mean (SEM). Normality and homogeneity of variance were assessed using the Shapiro–Wilk and Levene tests, respectively. Group differences were analyzed by one-way ANOVA followed by Tukey's post hoc test, with outliers identified using the Grubbs test. Statistical significance was set at $p < 0.05$. A priori sample size estimation using G*Power 3.1.9.7 (four-group one-way ANOVA, Cohen's f = 0.40, $\alpha = 0.05$, power = 80%) indicated a minimum sample size of 24 animals (n = 6/group). Analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA), and graphs were generated with GraphPad Prism version 9.0 (GraphPad Software, San Diego, CA, USA).

RESULTS

Effect of *C. papaya* Leaf Ethanolic Extract on Fasting Blood Glucose Levels of **STZ-induced rats fed a high fat diet**

Table 1 shows that following STZ administration, diabetic rats exhibited significantly elevated fasting

blood glucose levels at baseline, confirming successful diabetes induction. This hyperglycaemia persisted throughout the study in untreated animals, indicating sustained glycaemic dysregulation. Treatment with metformin resulted in a progressive and significant reduction in glucose levels, demonstrating effective glycaemic control. Similarly, administration of the ethanolic extract of *C. papaya* leaves at both 200 mg/kg and 400 mg/kg produced a significant, time- and dose-dependent decline in fasting glucose. By Day 28, glucose levels in extract-treated rats were significantly lower than in untreated diabetics and approached near-normal values, indicating potent antihyperglycaemic efficacy comparable to metformin, with the 200 mg/kg dose showing a slightly greater effect.

Effect of ethanolic extracts of *C. papaya* leaf on serum antioxidant activities and Malondialdehyde content of **STZ-induced rats fed a high fat diet**

After 28 days of STZ administration, *C. papaya* treatment markedly improved serum antioxidant activity and reduced lipid peroxidation (Fig 1). Compared with the control group, STZ-treated rats showed significant ($p < 0.05$) decreases in SOD (5766.54 ± 397.0 vs. 1973.72 ± 241.0 U/mL), CAT (3180 ± 162.0 vs. 1252.20 ± 142.0 U/mL), and GSH (7.88 ± 1.24 vs. 1.39 ± 0.14 mM), with a corresponding increase in MDA (4.76 ± 0.29 vs. 21.06 ± 0.68 µM), indicating enhanced oxidative stress. Metformin (STZ + MET) treatment significantly ($p < 0.05$) restored antioxidant enzyme activities and reduced MDA levels relative to the STZ group. Similarly, *C. papaya* leaf extract improved oxidative stress markers in a dose-dependent manner: at 200 mg/kg, SOD, CAT, and GSH increased to 6619.48 ± 163.0 U/mL, 3636.86 ± 90.0 U/mL, and 6.11 ± 0.41 mM, respectively, while MDA decreased to 7.61 ± 0.63 µM; at 400 mg/kg, antioxidant enzyme activities approached control values. Nonetheless, MDA levels remained slightly but significantly ($p < 0.05$) elevated compared with control rats.

Effect of extract and fraction of *C. papaya* leaf on lipid profile of **STZ-induced rats fed a high fat diet**

Fig 2 shows the improvement in lipid profile of STZ induced diabetic rats fed with HFD. STZ-treated rats exhibited a marked ($p < 0.05$) increase in total cholesterol (TC: 4.91 ± 0.33 vs. 2.94 ± 0.64 mmol/L), triglycerides (TG: 7.57 ± 0.62 vs. 1.42 ± 0.16 mmol/L), and low-density lipoprotein cholesterol (LDL-C: 2.36 ± 0.25 vs. 1.75 ± 0.61 mmol/L), accompanied by a significant ($p < 0.05$) decrease in high-density lipoprotein cholesterol (HDL-C: 0.78 ± 0.13 vs. 1.08 ± 0.17 mmol/L). Treatment with metformin (STZ + MET) significantly ($p < 0.05$) ameliorated these dyslipidemic changes, reducing TC (2.81 ± 0.25 mmol/L), TG (3.40 ± 0.62 mmol/L), and LDL-C (0.69 ± 0.13 mmol/L) levels compared to the STZ group. Similarly, administration of the ethanolic extract of *C. papaya* leaf improved the STZ-induced lipid abnormalities in a dose-dependent manner. At 200 mg/kg, the extract significantly ($p < 0.05$) decreased TG (2.52 ± 0.08 mmol/L) and increased HDL-C (1.01 ± 0.06 mmol/L), while the 400 mg/kg dose produced a more pronounced effect, further reducing TG (2.09 ± 0.13 mmol/L) and elevating HDL-C (1.26 ± 0.12 mmol/L), approaching the values observed in the normal control group.

Table 1: Effect of ethanolic extracts of *C. papaya* leaf on fasting glucose level of Streptozotocin -induced rats fed a high fat diet

	Fasting Glucose level (mmol/L)				
Group	Day 0	Day 7	Day 14	Day 21	Day 28
Control	5.58 ± 0.16	4.81 ± 0.19	4.73 ± 0.24	4.66 ± 0.27	4.61 ± 0.22
STZ	14.89 ± 0.47*	15.02 ± 0.42*	15.83 ± 0.56*	15.28 ± 0.48*	15.11 ± 0.51*
STZ + MET	14.70 ± 0.34*	13.11 ± 0.78*	12.04 ± 0.25*^{a}	10.24 ± 0.68*$^{+}$	8.97 ± 0.44*$^{a+}$
STZ + CP200	13.82 ± 0.27*	12.09 ± 0.36*	9.41 ± 0.37*$^{ab+}$	6.97 ± 1.38^{a+}	5.91 ± 0.72^{a+}
STZ + CP400	13.35 ± 0.41*^{ab}	10.11 ± 0.31*^{ab}	9.29 ± 0.25*$^{ab+}$	8.52 ± 1.48^{a+}	6.73 ± 0.65^{a+}

Data are expressed as mean ± SEM. n = 6 rats per group. *$p < 0.05$, compared to normal control group. $^{a}p < 0.05$, compared to STZ group. $^{b}p < 0.05$, compared to normal control group. $^{+}p < 0.05$, compared to Day 0. STZ-Streptozotocin, MET - Metformin, CP- ethanolic extract of *C. papaya*

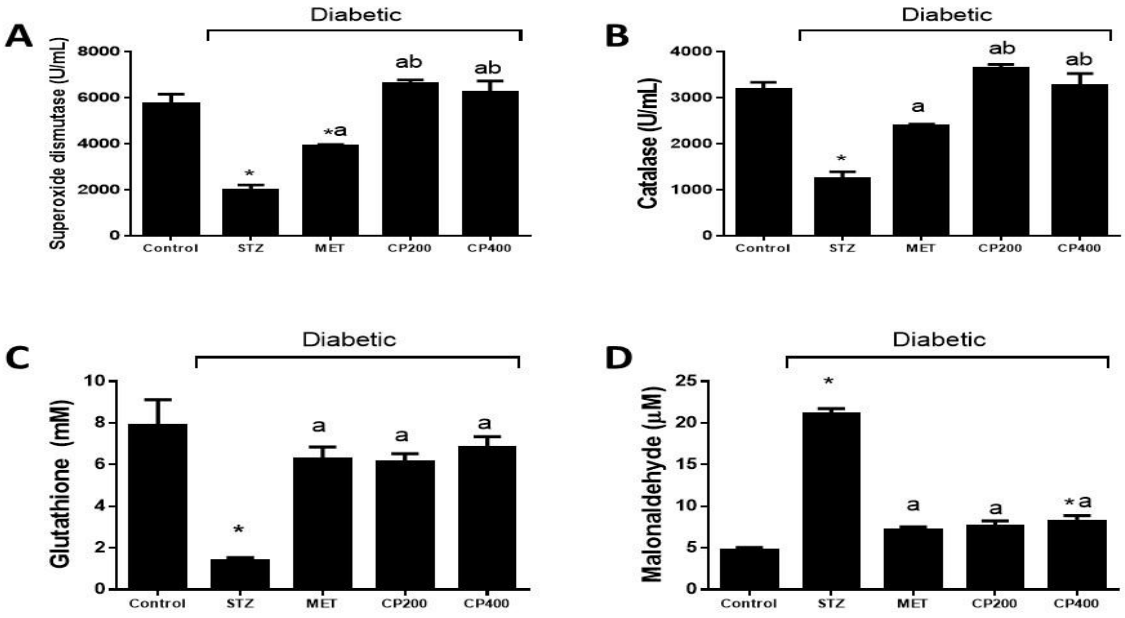

Fig 1. Effect of ethanolic extracts of *C. papaya* leaf on serum antioxidant activities and Malondialdehyde content of Streptozotocin-induced rats fed a high fat diet

Data are expressed as mean ± SEM (n = 6). * $p < 0.05$, compared to normal control group. [a] $p < 0.05$, compared to STZ group. [b]$p < 0.05$, compared to normal control group. STZ- Streptozotocin, MET - Metformin, CP- ethanolic extract of *C. papaya*. A - Superoxide dismutase, B - catalase, C - glutathione, D - malondialdehyde

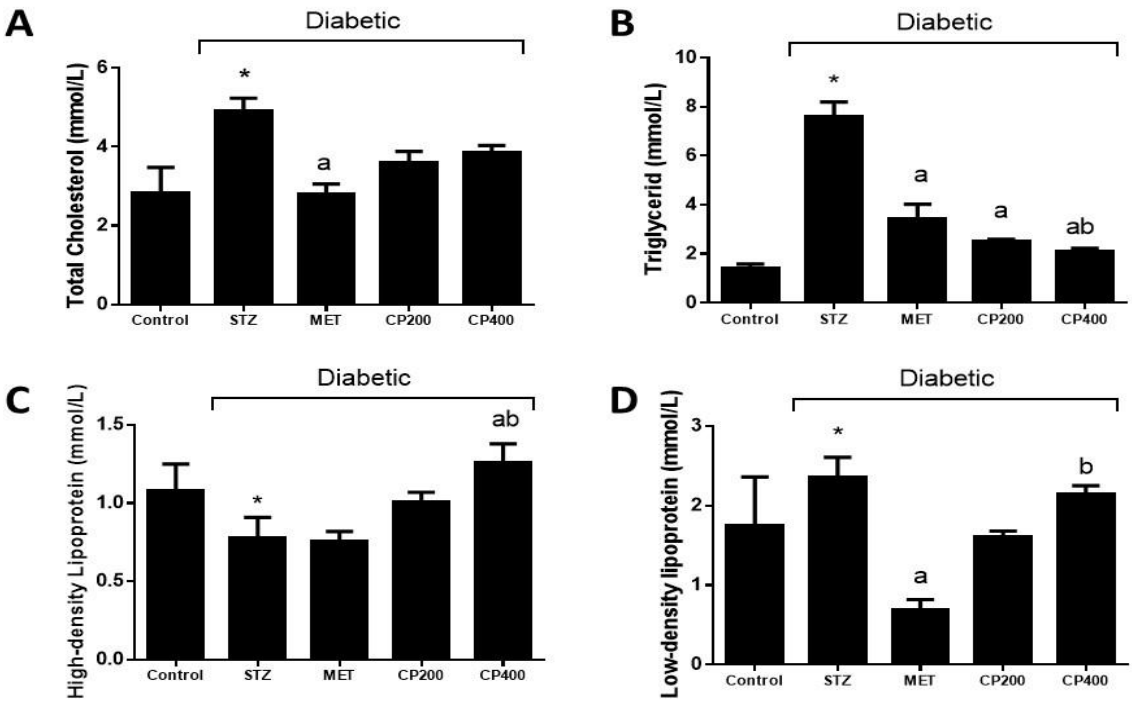

Fig 2. Effect of extract and Fraction of *C. papaya* leaf on lipid profile of Streptozotocin-induced rats fed a high fat diet

Data are expressed as mean ± SEM (n = 6). *p < 0.05, compared to normal control group. [a]p < 0.05, compared to STZ group. [b]p < 0.05, compared to normal control group. STZ- Streptozotocin, MET - Metformin, CP- ethanolic extract of *C. papaya*. A - Total cholesterol, B - Triglycerides, C – High-density lipoprotein cholesterol, D - Low density lipoprotein cholesterol.

Effect of *C. papaya* Leaf Extract and Its Fraction on Atherogenic Indices of STZ-induced rats fed a high fat diet

Figure 3 illustrates the amelioration of atherogenic indices in STZ-induced diabetic rats maintained on a HFD. The STZ-treated rats showed a significant (p<0.05) elevation in the atherogenic index of plasma (AIP; 0.99 ± 0.07 vs. 0.12 ± 0.08), a significant (p<0.05) reduction in the HDL/LDL ratio (0.33 ± 0.07 vs. 0.62 ± 0.26), and a significant (p<0.05) increase in coronary risk index (6.30 ± 0.59 vs. 2.72 ± 0.67,). Treatment with metformin (STZ + MET) significantly (p < 0.05) improved these indices relative to the STZ group. Similarly, administration of the ethanolic extract of *C. papaya* leaf elicited a dose-dependent improvement in lipid-related risk parameters. At 200 mg/kg, the extract significantly (p < 0.05) lowered AIP (0.40 ± 0.06), increased the HDL/LDL ratio (0.63 ± 0.05), and reduced CRI (3.57 ± 0.33) compared with the STZ group (p < 0.05), while the 400 mg/kg dose produced a statistically significant (p < 0.05) pronounced effect, with AIP (0.22 ± 0.05), HDL/LDL ratio (0.59 ± 0.07), and CRI (3.06 ± 0.21) values approaching those of the normal control.

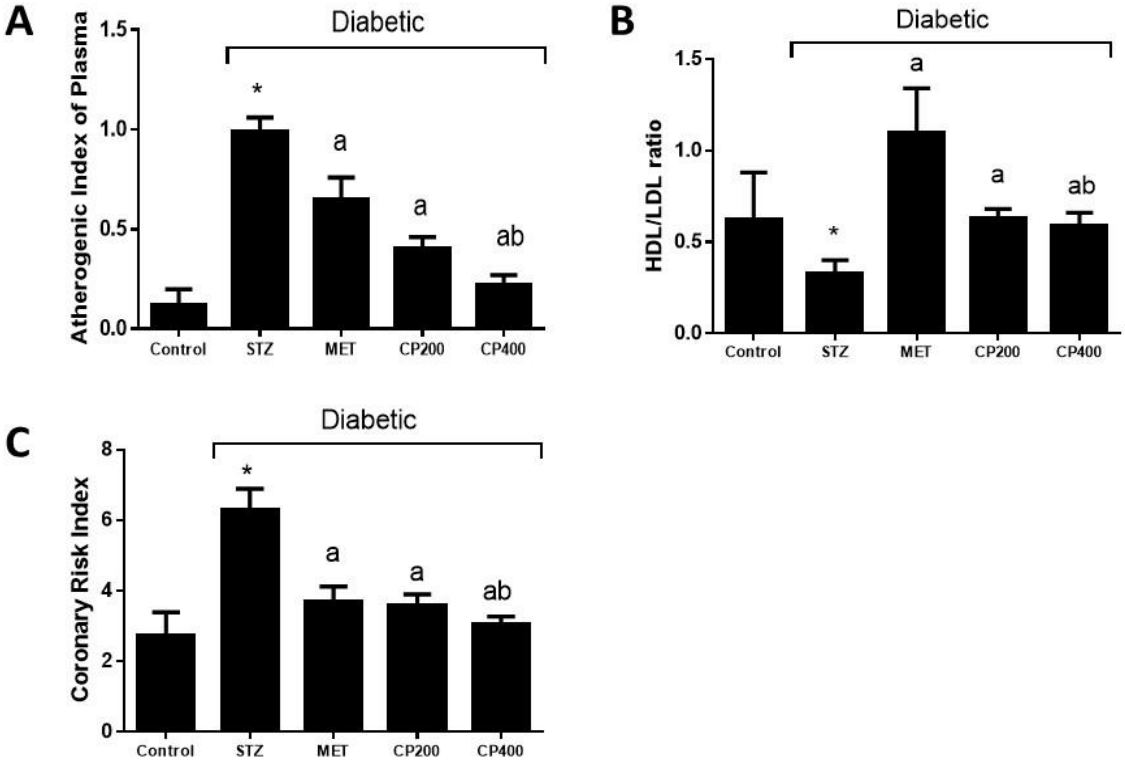

Fig 3. **Effect of *C. papaya* Leaf Extract on Atherogenic Indices of Streptozotocin-induced rats fed a high fat diet**

Data are expressed as mean ± SEM (n = 6). *p < 0.05, compared to normal control group. ap < 0.05, compared to STZ group. bp < 0.05, compared to normal control group. STZ- Streptozotocin, MET - Metformin, CP- ethanolic extract of *C. papaya*. A – Atherogenic Index of Plasma, B – HDL/LDL ratio, C – Coronary Risk Index

DISCUSSION

The present study demonstrates that the ethanolic leaf extract of *Carica papaya* possesses significant antihyperglycaemic, antioxidant, hypolipidaemic, and cardioprotective activities in STZ-induced diabetic rats fed a HFD. The combined use of STZ and HFD provides a suitable experimental model that mimics key metabolic abnormalities observed in diabetes

mellitus, including hyperglycaemia, oxidative stress, and dyslipidaemia. The observed therapeutic effects of *C. papaya* suggest that the plant may target multiple pathological pathways involved in the progression of diabetic complications.

The persistent hyperglycaemia observed following STZ administration is consistent with the well-established diabetogenic action of STZ, which selectively damages pancreatic β-cells through DNA alkylation, mitochondrial dysfunction, and excessive generation of reactive oxygen species (ROS), resulting in impaired insulin secretion and glucose dysregulation (Dinić *et al*., 2022; Eguchi *et al*., 2021). The substantial improvement in glycaemic control observed with C. papaya extract suggests not only a glucose-lowering effect but also a potential ability to disrupt the interconnected pathways of oxidative stress, inflammation, and metabolic dysfunction that drive diabetes progression. Previous studies by Juárez-Rojop *et al*. (2012) and Airaodion (2019) similarly reported antihyperglycaemic effects of *C. papaya* extracts, supporting the reproducibility of this biological activity across different experimental models.

Interestingly, the 200 mg/kg dose produced slightly greater glycaemic improvement than 400 mg/kg, suggesting a non-linear dose–response relationship for C. papaya. Similar patterns have been reported for other phytotherapeutics, where maximal efficacy occurs within an optimal range, while higher doses may reduce bioavailability, alter phytochemical interactions, or trigger compensatory physiological responses. Although the underlying mechanisms remain unclear, this finding underscores the importance of dose optimisation and indicates that increased dosage does not necessarily enhance therapeutic benefit. The antihyperglycaemic effects of C. papaya are likely related to its phytochemical constituents, including flavonoids, alkaloids, and saponins, which have been shown to enhance insulin secretion, improve insulin sensitivity, stimulate peripheral glucose uptake, and inhibit intestinal glucose absorption (Kong *et al*., 2021).

Oxidative stress is a key mechanism linking hyperglycaemia to diabetic complications, as excess ROS drives lipid, protein, and DNA damage as well as β-cell dysfunction, making restoration of antioxidant defences a critical therapeutic target in diabetes management. The ability of *C. papaya* treatment to improve antioxidant status suggests that its protective effects may extend beyond direct free-radical scavenging. Enhanced activities of endogenous antioxidant systems imply preservation of cellular redox balance, which is critical for maintaining pancreatic integrity and normal metabolic function. Similar antioxidant effects have been reported by Shaban *et al*. (2021) and Luiz *et al*. (2020), who demonstrated that *C. papaya* leaf extracts possess substantial free-radical scavenging capacity and can inhibit oxidative damage in experimental disease models.

The observed reduction in oxidative stress markers further supports the antioxidant potential of *C. papaya*. STZ-induced diabetes caused a significant decline in key enzymatic antioxidants such as SOD, CAT and GSH, with a concomitant rise in MDA, indicating enhanced lipid peroxidation and oxidative damage. This outcome aligns with Gilani *et al*. (2021) study that reported that STZ increased oxidative stress via decrease in serum antioxidant activities and elevation of lipid peroxidation leading to histopathological deterioration of tissues. Findings from this study further show that treatment with *C. papaya* ethanolic extract significantly restored antioxidant enzyme activities and reduced MDA levels in a dose-dependent manner, with values approaching those of the normal control. This suggests that the extract mitigates oxidative damage by scavenging ROS and enhancing endogenous antioxidant defense systems. These findings are in agreement with those of Shaban *et al*. (2021) and Luiz *et al*. (2020), who demonstrated that *C. papaya* leaf extract possesses strong free radical–scavenging and lipid peroxidation–inhibiting properties. Orororo *et al*. (2024) previously suggested that alkaloids and flavonoids are specific phytochemical constituents of *C. papaya* that possess antioxidant properties, which mitigate free radical activity and thereby sustain the functional efficiency of endogenous antioxidant systems. The ability of *C. papaya* to improve antioxidant status may play a key role in protecting β-cells from oxidative injury, thereby supporting insulin secretion and glucose homeostasis (Fazal *et al*., 2022).

Dyslipidaemia is another hallmark of diabetes and represents a major contributor to cardiovascular morbidity and mortality. Insulin deficiency and insulin resistance promote increased lipolysis, hepatic triglyceride synthesis, and abnormal lipoprotein metabolism, resulting in elevated concentrations of atherogenic lipids and reduced cardioprotective HDL cholesterol (Hermans & Valensi, 2018; Komolafe *et al*., 2008). The ability of *C. papaya* extract to improve lipid homeostasis therefore has important clinical implications. Rather than merely correcting lipid abnormalities, the observed effects suggest a broader

influence on metabolic regulation. Improvement in lipid metabolism may reduce lipid accumulation within tissues, decrease oxidative modification of lipoproteins, and limit the progression of vascular dysfunction associated with diabetes.

The hypolipidaemic activity observed in this study is consistent with previous reports demonstrating beneficial effects of *C. papaya* on lipid metabolism. Matsuane *et al*. (2023) and Ebo *et al*. (2021) reported reductions in LDL cholesterol and improvements in overall lipid profiles following administration of *C. papaya* extracts in experimental models of metabolic dysfunction. The mechanisms underlying these effects may involve suppression of hepatic cholesterol synthesis, enhancement of lipid clearance pathways, and improved reverse cholesterol transport. Abdel-Halim *et al*. (2021) further suggested that the antioxidant constituents of *C. papaya* contribute to improved hepatic lipid metabolism, indicating that the hypolipidaemic and antioxidant properties of the extract may operate through interconnected pathways. This interaction is biologically plausible because oxidative stress is known to impair lipid metabolism and promote the formation of oxidized LDL, a key mediator of atherosclerotic plaque development.

The improvement in atherogenic indices further strengthens the evidence for the cardioprotective potential of *C. papaya*. Atherogenic indices are increasingly regarded as sensitive predictors of cardiovascular risk because they reflect the balance between protective and atherogenic lipoproteins. This was also in accordance to the findings of Nimmanapalli *et al*. (2017) demonstrated that these atherogenic indices contribute significantly to the estimation of CVD risk in type 2 diabetes mellitus patients. *C. papaya* ethanolic extract treatment significantly improved these indices, with values approaching those of the normal control group The favourable modulation of these indices observed following *C. papaya* treatment suggests that the extract may reduce cardiovascular risk beyond its effects on glucose metabolism alone. Given that cardiovascular disease remains the leading cause of mortality among diabetic patients, this finding has considerable therapeutic relevance. The cardioprotective effects of *C. papaya* may arise from multiple complementary mechanisms, including reduction of oxidative stress, improvement of lipid metabolism, preservation of vascular integrity, and attenuation of lipid peroxidation. Similar observations were reported by Sasongko *et al*. (2022), who demonstrated that *C. papaya* leaf extract improved lipid homeostasis and reduced markers of cardiovascular risk in hyperglycaemic conditions. Collectively, these findings suggest that the extract exerts a multifaceted protective effect capable of simultaneously targeting several metabolic abnormalities associated with diabetes. Such multitarget activity is particularly advantageous because diabetes is a complex disorder involving numerous interconnected pathological pathways.

Importantly, this study provides a more integrated evaluation of *C. papaya* by combining GC–MS-based phytochemical profiling with detailed metabolic, antioxidant, lipid, and cardiovascular risk assessments in an HFD/STZ model that closely resembles human type 2 diabetes. The inclusion of atherogenic indices adds a clinically relevant cardiovascular dimension that is often absent in phytopharmacological studies. Furthermore, the comparative dose analysis revealed a non-linear dose–response relationship, identifying 200 mg/kg as more effective than 400 mg/kg, thereby emphasizing the importance of defining an optimal therapeutic window for phytomedicines. The GC–MS findings further strengthen the mechanistic basis of the observed effects by demonstrating a chemically diverse phytochemical profile that supports a multi-target mode of action.

A major strength of this study lies in its comprehensive and ethically rigorous design, integrating metabolic and oxidative parameters to elucidate the protective effects of *C. papaya* leaf ethanolic extract in a well-established diabetic–dyslipidaemic rat model. The dose–response approach (200 mg/kg and 400 mg/kg) and inclusion of both diabetic and metformin-treated controls enhanced the reliability of findings, while the simultaneous assessment of glycaemic, lipid, and antioxidant markers provided a multidimensional evaluation of therapeutic efficacy. However, the study's limitations include its restriction to male Wistar rats, lack of histopathological and molecular analyses, and absence of phytochemical quantification of individual bioactive compounds. Moreover, the 28-day duration may not reflect long-term outcomes, and the findings, though promising, cannot yet be extrapolated to human settings without further pharmacokinetic and clinical investigations.

CONCLUSION

This study demonstrates that the ethanolic leaf extract of *C. papaya* exerts dose-dependent protective effects against dyslipidaemia and oxidative

stress in STZ-induced diabetic rats fed a high-fat diet. The extract significantly improved fasting blood glucose, restored antioxidant enzyme activities, reduced lipid peroxidation, and normalized lipid parameters, resulting in lower atherogenic indices and potential cardioprotective benefits. The findings highlight *C. papaya* as a promising source of plant-based antioxidants with therapeutic potential for managing oxidative and metabolic disturbances in diabetes, warranting further studies to isolate active compounds, clarify molecular mechanisms, and assess long-term safety and efficacy.

Authors' contributions: Conceptualization: Egesie G; Data curation: Adebayo OF; Formal analysis: Egesie G and Odeh OS; Investigation: Adebayo OF and Odeh OS; Methodology: Adebayo OF, Egesie G, and Odeh OS; Project administration: Adebayo OF; Software: Adebayo OF; Supervision: Egesie G, and Odeh OS; Validation: Adebayo OF, Egesie G, and Odeh OS; Visualization: Adebayo OF, Egesie G, and Odeh OS; Original Draft Writing: Adebayo OF; Writing–Review and Editing: Adebayo OF and Egesie G

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Conflicts of Interest Statement
The authors declare no conflict of interest.

REFERENCES

Abdel-Halim, S., Ibrahim, M., Abdel Mohsen, M., Abou-Setta, L., Sleem, A., & El-Missiry, M. (2021). The influence of the extraction method on polyphenols, flavonoids composition and anti-hyperlipidemic properties of papaya leaves (*Carica papaya* Linn.). *Bulletin of the National Research Centre*, *45*(1), 85.

Adám-Vizi, V., & Seregi, A. (1982). Receptor independent stimulatory effect of noradrenaline on Na,K-ATPase in rat brain homogenate. Role of lipid peroxidation. *Biochemical Pharmacology*, *31*(13), 2231–2236. https://doi.org/10.1016/0006-2952(82)90106-x

Aebi, H. (1984). Catalase in vitro. *Methods in Enzymology*, *105*, 121–126. https://doi.org/10.1016/s0076-6879(84)05016-3

Akanda, M. K. M., Hasan, A. H. M. N., Mehjabin, S., Parvez, G. M. M., Yasmin, S., Akhtar, M. S., Anjum, S., Ashique, S., Sulatana, R., & Ansari, M. Y. (2025). *Carica papaya* in health and disease: a review of its bioactive compounds for treating various disease conditions, including anti-inflammatory and anti-arthritic activities. *Inflammopharmacology*, 1–34.

Alam, S., Hasan, M. K., Neaz, S., Hussain, N., Hossain, M. F., & Rahman, T. (2021). Diabetes Mellitus: insights from epidemiology, biochemistry, risk factors, diagnosis, complications and comprehensive management. *Diabetology*, *2*(2), 36–50.

Alara, O. R., Abdurahman, N. H., & Alara, J. A. (2022). *Carica papaya*: comprehensive overview of the nutritional values, phytochemicals and pharmacological activities. *Advances in Traditional Medicine*, *22*(1), 17–47.

Bradford, M. M. (1976). A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. *Analytical Biochemistry*, *72*, 248–254. https://doi.org/10.1016/0003-2697(76)90527-3

Caturano, A., Rocco, M., Tagliaferri, G., Piacevole, A., Nilo, D., Di Lorenzo, G., Iadicicco, I., Donnarumma, M., Galiero, R., Acierno, C., Sardu, C., Russo, V., Vetrano, E., Conte, C., Marfella, R., Rinaldi, L., & Sasso, F. C. (2025). Oxidative Stress and Cardiovascular Complications in Type 2 Diabetes: From Pathophysiology to Lifestyle Modifications. In *Antioxidants* (Vol. 14, Issue 1). https://doi.org/10.3390/antiox14010072

Dinić, S., Arambašić Jovanović, J., Uskoković, A., Mihailović, M., Grdović, N., Tolić, A., Rajić, J., Đorđević, M., & Vidaković, M. (2022). Oxidative stress-mediated beta cell death and dysfunction as a target for diabetes management. *Frontiers in Endocrinology*, *13*, 1006376.

Ebo, O. E., Ighodaro, C. N., Silas, W. J., ALOAMAKA, O. E., & CHIME, A. O. (2021). Anti-Hypercholesterolemic and Hepatoprotective Effect of Aqueous Seed Extract of *Carica papaya* in Rats Fed with Thermoxidized Palm Oil Diet. *Am. J. Biomed. Sci*, *13*(1), 44–50.

Eguchi, N., Vaziri, N. D., Dafoe, D. C., & Ichii, H. (2021). The Role of Oxidative Stress in Pancreatic β Cell Dysfunction in Diabetes. *International Journal of Molecular Sciences*, *22*(4). https://doi.org/10.3390/ijms22041509

Fakhri, S., Moradi, S. Z., Moradi, S. Y., Piri, S., Shiri Varnamkhasti, B., Piri, S., Khirehgesh, M. R., Bishayee, A., Casarcia, N., & Bishayee, A. (2024). Phytochemicals regulate cancer metabolism through modulation of the AMPK/PGC-1α signaling pathway. *BMC Cancer*, *24*(1), 1079.

Fazal, J., Naz, L., Sohail, S., Yasmeen, G., Khan, N. I., & Zehra, N. (2022). Anti-diabetic activity of *Carica papaya* Linn in Alloxan-Induced diabetic rats. *Int. J. Endorsing Health Sci. Res*, *10*, 42–48.

Gideon, E., & Owhonda, G. (2024). Investigating the Effects of Costus lucanucianus on Lipid Profile and Oxidative Stress in Diabetic and Dyslipidaemic Male

Wistar Rats. *Article in Greener Journal of Medical Sciences*, *14*(2), 181–188. https://www.researchgate.net/publication/385939027

Gilani, S. J., Bin-Jumah, M. N., Al-Abbasi, F. A., Nadeem, M. S., Afzal, M., Sayyed, N., & Kazmi, I. (2021). Fustin ameliorates hyperglycemia in streptozotocin induced type-2 diabetes via modulating glutathione/Superoxide dismutase/Catalase expressions, suppress lipid peroxidation and regulates histopathological changes. *Saudi Journal of Biological Sciences*, *28*(12), 6963–6971.

Harnafi, H., Caid, H. S., el Houda Bouanani, N., Aziz, M., & Amrani, S. (2008). Hypolipemic activity of polyphenol-rich extracts from Ocimum basilicum in Triton WR-1339-induced hyperlipidemic mice. *Food Chemistry*, *108*(1), 205–212.

Hermans, M. P., & Valensi, P. (2018). Elevated triglycerides and low high-density lipoprotein cholesterol level as marker of very high risk in type 2 diabetes. *Current Opinion in Endocrinology, Diabetes, and Obesity*, *25*(2), 118–129. https://doi.org/10.1097/MED.0000000000000398

Hirano, T., Kodera, R., Hirashima, T., Suzuki, N., Aoki, E., Hosoya, M., Oshima, T., Hayashi, T., Koba, S., & Ohta, M. (2022). Metabolic properties of lowdensity lipoprotein (LDL) triglycerides in patients with type 2 diabetes, comparison with small dense LDL-cholesterol. *Journal of Atherosclerosis and Thrombosis*, *29*(5), 762–774.

I Airaodion, A. (2019). Antidiabetic Effect of Ethanolic Extract of *Carica papaya* Leaves in Alloxan-Induced Diabetic Rats. *American Journal of Biomedical Science & Research*, *5*(3), 227–234. https://doi.org/10.34297/ajbsr.2019.05.000917

Joerin, L., Kauschka, M., Bonnländer, B., Pischel, I., Benedek, B., & Butterweck, V. (2014). Ficus carica leaf extract modulates the lipid profile of rats fed with a high-fat diet through an increase of HDL-C. *Phytotherapy Research: PTR*, *28*(2), 261–267. https://doi.org/10.1002/ptr.4994

Juárez-Rojop, I. E., Díaz-Zagoya, J. C., Ble-Castillo, J. L., Miranda-Osorio, P. H., Castell-Rodríguez, A. E., Tovilla-Zárate, C. A., Rodríguez-Hernández, A., Aguilar-Mariscal, H., Ramón-Frías, T., & Bermúdez-Ocaña, D. Y. (2012). Hypoglycemic effect of *Carica papaya* leaves in streptozotocin-induced diabetic rats. *BMC Complementary and Alternative Medicine*, *12*, 236. https://doi.org/10.1186/1472-6882-12-236

Komolafe, O., Adeyemi, D., Adewole, S., & Obuotor, E. M. (2008). Streptozotocin-induced diabetes alters the serum lipid profiles of adult Wistar rats. *Internet Journal of Cardiovascular Research*, *7*. https://doi.org/10.5580/2251

Kong, Y. R., Jong, Y. X., Balakrishnan, M., Bok, Z. K., Weng, J. K. K., Tay, K. C., Goh, B. H., Ong, Y. S., Chan, K. G., & Lee, L. H. (2021). Beneficial role of *Carica papaya* extracts and phytochemicals on oxidative stress and related diseases: a mini review. *Biology*, *10*(4), 287.

Kosmas, C. E., Silverio, D., Sourlas, A., Garcia, F., Montan, P. D., & Guzman, E. (2018). Impact of lipid-lowering therapy on glycemic control and the risk for new-onset diabetes mellitus. *Drugs in Context*, *7*, 212562. https://doi.org/10.7573/dic.212562

Koul, B., Pudhuvai, B., Sharma, C., Kumar, A., Sharma, V., Yadav, D., & Jin, J.-O. (2022). *Carica papaya* L.: A Tropical Fruit with Benefits beyond the Tropics. In *Diversity* (Vol. 14, Issue 8). https://doi.org/10.3390/d14080683

Laraeni, Y., Danuyanti, I. G. A. N., Resnhaleksmana, E., Pauzi, I., Mataram, I. K. A., & Agustini, N. P. (2021). High antioxidant level in cajanus sajan reduces blood glucose level and improves blood lipid profile of rats as diabetes mellitus models. *International Journal of Health Sciences*, *5*(1), 29–37.

Luiz, T. C., da Cunha, A. P. S., Aguiar, D. H., Sugui, M. M., de Campos Bicudo, R., Sinhorin, A. P., & Sinhorin, V. D. G. (2020). Antioxidant potential of *Carica papaya* Linn (Caricaceae) leaf extract in mice with cyclophosphamide induced oxidative stress. *Scientia Medica*, *30*(1), 16.

Marklund, S., & Marklund, G. (1974). Involvement of the Superoxide Anion Radical in the Autoxidation of Pyrogallol and a Convenient Assay for Superoxide Dismutase. *European Journal of Biochemistry*, *47*(3), 469–474. https://doi.org/https://doi.org/10.1111/j.1432-1033.1974.tb03714.x

Matsuane, C., Kiage, B. N., Karanja, J., Kavoo, A. M., & Rimberia, F. K. (2023). Hypolipidaemic effects of papaya (*Carica papaya* L.) juice on rats fed on a high fat and fructose diet. *Journal of Nutritional Science*, *12*, e76.

Miranda-Osorio, P. H., Castell-Rodríguez, A. E., Vargas-Mancilla, J., Tovilla-Zárate, C. A., Ble-Castillo, J. L., Aguilar-Domínguez, D. E., Juárez-Rojop, I. E., & Díaz-Zagoya, J. C. (2016). Protective action of *Carica papaya* on β-cells in streptozotocin-induced diabetic rats. *International Journal of Environmental Research and Public Health*, *13*(5), 446.

Nimmanapalli, H. D., Kasi, A. D., Devapatla, P. kumar, & Nuttakki, V. (2017). Lipid ratios, atherogenic coefficient and atherogenic index of plasma as parameters in assessing cardiovascular risk in type 2

diabetes mellitus. *International Journal of Research in Medical Sciences*, *4*(7 SE-Original Research Articles), 2863–2869. https://doi.org/10.18203/2320-6012.ijrms20161966

Orororo, O. C., Efekemo, O., Odeghe, O. B., Clark, P. D., Awhin, E. P., Egbune, E. O., & Efejene, I. O. (2024). Phytochemical Screening, in vitro antoxidant capacity and Nephro-protective effects of combined extract of Psidium guajava and *Carica papaya* leaves in rats intoxicated with cadmium. *Asian Journal of Medicine and Health*, *22*(8), 86–97.

Papachristoforou, E., Lambadiari, V., Maratou, E., & Makrilakis, K. (2020). Association of glycemic indices (hyperglycemia, glucose variability, and hypoglycemia) with oxidative stress and diabetic complications. *Journal of Diabetes Research*, *2020*(1), 7489795.

Rotruck, J. T., Pope, A. L., Ganther, H. E., Swanson, A. B., Hafeman, D. G., & Hoekstra, W. G. (1973). Selenium: biochemical role as a component of glutathione peroxidase. *Science (New York, N.Y.)*, *179*(4073), 588–590. https://doi.org/10.1126/science.179.4073.588

Roy, J. R., Janaki, C. S., Jayaraman, S., Periyasamy, V., Balaji, T., Vijayamalathi, M., & Veeraraghavan, V. P. (2022). *Carica papaya* reduces muscle insulin resistance via IR/GLUT4 mediated signaling mechanisms in high fat diet and streptozotocin-induced type-2 diabetic rats. *Antioxidants*, *11*(10), 2081.

Sancho, L. E. G.-G., Yahia, E. M., & González-Aguilar, G. A. (2011). Identification and quantification of phenols, carotenoids, and vitamin C from papaya (*Carica papaya* L., cv. Maradol) fruit determined by HPLC-DAD-MS/MS-ESI. *Food Research International*, *44*(5), 1284–1291.

Sasongko, H., Lestari, R. G., Indasari, R. D., Wulandari, R. D., & Musta'ani, S. (2022). The Hypolipidemic Effect of Mountain Papaya and Bitter Melon Fruit Ethanolic Extract in Diabetic Rats. *Journal of Tropical Biodiversity and Biotechnology*, *7*(3), 1–13. https://doi.org/10.22146/jtbb.75349

Shaban, N. Z., El-Kot, S. M., Awad, O. M., Hafez, A. M., & Fouad, G. M. (2021). The antioxidant and anti-inflammatory effects of *Carica papaya* Linn. seeds extract on CCl4-induced liver injury in male rats. *BMC Complementary Medicine and Therapies*, *21*(1), 302.

Singh, S. V., Shrivastava, A., Jyotshna, Chaturvedi, U., Singh, S. C., Shanker, K., Saxena, J. K., Bhatia, G., & Pal, A. (2016). A mechanism-based pharmacological evaluation of efficacy of Flacourtia indica in management of dyslipidemia and oxidative stress in hyperlipidemic rats. *Journal of Basic and Clinical Physiology and Pharmacology*, *27*(2), 121–129. https://doi.org/10.1515/jbcpp-2015-0017

Timothy, O., Okpakpor, E. E., & Iniaghe, L. O. (2022). Biosafety evaluation of *Carica papaya* aqueous leaf extract on haematological parameters and organ/body weight ratio in Wistar rats. *Dutse Journal of Pure and Applied Sciences*, *8*(1b), 90–96. https://doi.org/10.4314/dujopas.v8i1b.11

Yagi, K. (1994). Lipid peroxides and related radicals in clinical medicine. *Advances in Experimental Medicine and Biology*, *366*, 1–15. https://doi.org/10.1007/978-1-4615-1833-4_1