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ORIGINAL RESEARCH ARTICLE

Antihyperglycemic and Pancreatic Antioxidant Effects of *Carica papaya* Leaf Extract in Streptozotocin-Induced Diabetic Rat

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ABSTRACT
Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia and progressive pancreatic β-cell damage, often exacerbated by oxidative stress. This study evaluates the antihyperglycemic, insulinotropic, antioxidant, and pancreatic cytoprotective effects of *C. papaya* leaf crude extract in streptozotocin (STZ)-induced diabetic rats. Thirty-six male Wistar rats were randomly and equally assigned into six groups: normal control, diabetic control, metformin-treated (100 mg/kg), crude *Carica papaya* extract-treated (200 mg/kg and 400 mg/kg), and n-hexane fraction-treated (200 mg/kg). Diabetes was induced using a single intraperitoneal injection of STZ (60 mg/kg). Over 21 days, fasting blood glucose, serum insulin levels, HOMA-IR and HOMA-β indices were assessed. Oxidative stress biomarkers, including superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), and malondialdehyde (MDA), were measured in pancreatic tissues. Histological analysis of the pancreas was conducted to evaluate tissue integrity. One-Way ANOVA was used to compare means, and $p<0.05$ was considered statistically significant. The 200 mg/kg crude extract (CECP200) significantly reduced fasting blood glucose and improved insulin levels, HOMA-β, and HOMA-IR compared to the diabetic and metformin-treated groups ($p < 0.05$). CECP200 also restored antioxidant enzyme activities (SOD, CAT, GSH) and significantly reduced MDA levels, indicating protection against oxidative damage. Histopathological findings revealed partial preservation of islet architecture and reduced pancreatic necrosis in CECP200-treated rats, whereas the n-hexane fraction group showed less consistent histological recovery and mild inflammatory changes. *C. papaya* leaf crude extract shows strong antihyperglycemic, antioxidant, and pancreatic protective effects in diabetic rats, highlighting its potential as a complementary diabetes prevention and management, pending further investigation.

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hyperglycemia, *Carica papaya*, oxidative stress, pancreas, diabetes

INTRODUCTION
Diabetes mellitus (DM) is widely recognized as one of the most prevalent and complex non-communicable diseases of the 21st century (Ogurtsova et al., 2022; Verma et al., 2021). It is defined by sustained hyperglycemia resulting from impaired insulin secretion, insulin resistance, or a combination of both, and is closely linked to progressive metabolic disturbances and severe microvascular and macrovascular complications (Islam et al., 2025). As reported by International Diabetes Federation, an estimated 537 million adults globally were affected by diabetes in 2021, with projections indicating an increase to 643 million by 2030 (International Diabetes Federation, 2021). This upward trend is largely attributed to global demographic shifts and increasingly sedentary lifestyles (Aschner et al., 2021). Notably, the disease exerts a particularly heavy toll on low- and middle-income countries, where limited access to healthcare services and therapeutic options contributes to heightened levels of morbidity and mortality (Flood et al., 2021).

Type 1 and Type 2 diabetes exhibit overlapping pathophysiological mechanisms, notably persistent hyperglycemia, elevated reactive oxygen species (ROS) production, and oxidative stress-mediated damage to pancreatic β-cells (Bhatti et al., 2022; Eguchi et al., 2021). Oxidative stress is particularly significant in the onset and progression of diabetes and its complications, as it impairs insulin secretion, induces β-cell apoptosis, and disrupts overall glucose regulation (Dinić et al., 2022). The pancreas—especially the insulin-secreting islets of Langerhans—is particularly vulnerable to oxidative injury due to its inherently low levels of antioxidant enzymes (Arunachalam et al., 2022). Consequently, therapeutic interventions for diabetes aim not only to achieve

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glycaemic control but also to mitigate oxidative stress and safeguard pancreatic function (Papachristoforou et al., 2020).

Although conventional antidiabetic agents such as insulin, sulfonylureas, biguanides, and thiazolidinediones are effective in regulating blood glucose levels, their use is frequently constrained by adverse effects, including hypoglycemia, gastrointestinal discomfort, weight gain, and a progressive decline in therapeutic efficacy (Giglio et al., 2022; Mathu et al., 2021; Tomlinson et al., 2022). These challenges have prompted growing interest in alternative and complementary treatment modalities, particularly those based on medicinal plants, which have long been employed in traditional medical systems for diabetes management (Ghorat et al., 2024). Medicinal plants possess a broad spectrum of pharmacological activities, including antihyperglycemic, antioxidant, anti-inflammatory, and cytoprotective properties, positioning them as promising candidates for integrative approaches to diabetes care (Ansari et al., 2025; Clemente-Suárez et al., 2025; Tran et al., 2020).

Among the numerous medicinal plants explored for antidiabetic potential, *Carica papaya* L. (family: Caricaceae), commonly known as papaya, has gained considerable attention due to its longstanding ethnomedicinal use and wide-ranging pharmacological attributes (Agada et al., 2021). Indigenous to tropical and subtropical regions, *Carica papaya* (*C. papaya*) has traditionally been employed in folk medicine to manage various conditions, including fever, infections, gastrointestinal disturbances, and diabetes (Ogunlakin et al., 2023). Notably, the leaf of *C. papaya* has emerged as a focal point of scientific interest, owing to its rich array of bioactive compounds—such as flavonoids, alkaloids, saponins, tannins, and phenolics—which exhibit significant antioxidant and hypoglycemic effects (Babalola et al., 2024; Hariono et al., 2021).

Previous in vivo and in vitro investigations have demonstrated that *C. papaya* leaf extracts can effectively reduce blood glucose levels, improve insulin sensitivity, and ameliorate dyslipidaemia in experimental diabetic models (Nxumalo et al., 2024; Nyakundi et al., 2024). Furthermore, the antioxidant activity of the plant has been linked to its capacity to scavenge reactive oxygen species, enhance endogenous antioxidant defence systems, and attenuate oxidative damage in metabolically important organs such as the pancreas, liver, and kidneys (Sharma et al., 2022). However, despite these encouraging findings, most available studies have focused predominantly on crude leaf extracts, providing limited information regarding the relative contributions of individual solvent fractions to the overall antidiabetic activity. Consequently, the specific phytochemical fractions responsible for pancreatic protection and antioxidant modulation remain inadequately characterized.

In addition, although several studies have reported improvements in glycaemic indices following treatment with *C. papaya* extracts, comparatively few have comprehensively evaluated pancreatic antioxidant status alongside histopathological evidence of tissue preservation or regeneration. Understanding whether specific fractions confer superior protection against oxidative stress-induced β-cell injury is essential for identifying the bioactive constituents that may contribute to the therapeutic potential of the plant. Addressing these gaps may facilitate the development of more targeted phytotherapeutic interventions for diabetes management. Therefore, the present study was designed to comparatively evaluate the antihyperglycaemic, insulin-sensitizing, antioxidant, and pancreatic histoprotective effects of crude ethanolic extract and solvent-partitioned fractions of *C. papaya* leaves in streptozotocin-induced diabetic rats.

MATERIALS AND METHODS

Preparation of *C. papaya* Leaf Extract

Fresh, mature leaves of *C. papaya* were harvested from the farmland of the Forestry Research Institute of Nigeria (FRIN) in Ibadan, Oyo State. Botanical authentication was conducted by a taxonomist at the Department of Botany, University of Jos, and the specimen was assigned a herbarium voucher number [FHI 1142134]. The collected leaves were thoroughly washed, air-dried at ambient temperature, and subsequently ground into a fine powder. The powdered plant material was subjected to maceration in 70% ethanol for 72 hours with intermittent agitation. The resulting mixture was filtered using Whatman No. 1 filter paper, and the filtrate was concentrated under reduced pressure using a rotary evaporator (PEC MEDICAL, RE52A, China) to obtain the crude ethanol extract. The extract was then stored at 4°C until further use.

Acute oral toxicity of the crude ethanolic extract and n-hexane fraction of *C. papaya* leaves was evaluated in accordance with OECD Guideline 423 (OECD, 2002). Following an overnight fast, rats received a single oral administration of the extract at a limit dose of 2000 mg/kg body weight and were observed continuously during the first 24 h and daily thereafter for 14 days for signs of toxicity, behavioural changes, and mortality. No mortality or treatment-related adverse effects were observed during the observation period. Consequently, treatment doses of 200 mg/kg and 400 mg/kg, representing approximately one-tenth and one-fifth of the limit dose, respectively, were selected for the efficacy study.

Fractionation

The crude ethanolic extract of *Carica papaya* leaves was subjected to solvent–solvent partitioning using n-hexane, chloroform, and ethyl acetate according to the method described by Soib et al. (2020), with slight modifications to accommodate a larger quantity of extract. Fractionation was carried out in the Postgraduate Research Laboratory, Department of Biochemistry, Bingham University, Karu. Following concentration of the respective fractions, percentage yields were determined. The n-hexane fraction yielded 17.15% (w/w), while the crude ethanolic extract yielded 20.72% (w/w). Based on preliminary phytochemical screening and yield considerations, the n-hexane fraction was selected for further biological

evaluation in the animal experiment, whereas the chloroform and ethyl acetate fractions were not investigated further.

Animals and Acclimatization

A total of 36 adult male Wistar rats (weighing between 160–200 g) were obtained at ten weeks of age from the Animal House, Faculty of Basic Medical Sciences, University of Ibadan. The animals were housed in standard polypropylene cages under controlled environmental conditions, including a 12-hour light/dark cycle, ambient temperature of 22 ± 2 °C, and relative humidity of 50–60%, within the Animal Care Unit of the Faculty of Basic Medical Sciences, Bingham University, Karu, Nasarawa State, Nigeria. All rats were provided unrestricted access to standard rodent feed and clean water. Prior to experimentation, the animals were acclimatized for two weeks to reduce stress-related variability. Experimental procedures were conducted in accordance with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals (NIH Publication No. 85-23), and the study protocol received ethical approval from the Institutional Animal Ethics Committee (Reg. No. NHREC/21/05/2005/01523).

Sample Size Determination

Sample size was determined a priori using the G*Power software (version 3.1.9.7, Heinrich-Heine University, Düsseldorf, Germany). Assuming a large effect size (f = 0.40), a significance level (α) of 0.05, and a statistical power (1−β) of 0.80 for one-way analysis of variance (ANOVA), a minimum sample size of 30 animals was required. To account for potential losses following streptozotocin administration and to maintain adequate statistical power, 36 rats (n = 6 per group) were included in the study.

Experimental Design

Following confirmation of diabetes induction, animals were randomly allocated to the experimental groups. To minimize observer bias, serum samples and pancreatic tissue specimens were coded prior to biochemical and histopathological analyses. Investigators responsible for laboratory assays and microscopic evaluation were blinded to treatment allocation until completion of data analysis. The animals were randomly assigned into six groups as follows:

- Group 1: (Normal Control): Non-diabetic rats given normal saline (2 mL/kg/day, orally).
- Group 2 (Diabetic Control): STZ-induced diabetic rats given normal saline (2 mL/kg/day, orally).
- Group 4: (Metformin Group): Diabetic rats treated with Metformin (dose: 100 mg/kg/day, orally).
- Group 3: (n-Hexane Fraction): Diabetic rats treated with *C. papaya* leaf n-hexane fraction (dose: 200 mg/kg/day, orally).
- Group 5: (Low-Dose Extract): Diabetic rats treated with *C. papaya* ethanol extract (dose: 200 mg/kg/day, orally).
- Group 6 (High-Dose Extract): Diabetic rats treated with *C. papaya* ethanol extract (dose: 400 mg/kg/day, orally).

The crude ethanol extract, n-hexane fraction, and metformin were freshly suspended in normal saline immediately prior to administration. Normal saline served as the vehicle for all treatments and was administered orally to the control groups at an equivalent volume (2 mL/kg body weight/day). The treatment was maintained for a continuous period of 21 days.

Induction of Diabetes Mellitus

Diabetes was induced by administering a single intraperitoneal injection of streptozotocin (STZ) at a dosage of 60 mg/kg body weight, prepared freshly in 0.1 M cold citrate buffer (pH 4.5). Seventy-two hours post-injection, fasting blood glucose levels were assessed using a glucometer (Accu-Chek®, Roche Diagnostics). Rats exhibiting fasting blood glucose concentrations equal to or exceeding 250 mg/dL were classified as diabetic and subsequently enrolled in the study.

Preparation and administration of metformin

A 500 mg tablet of metformin hydrochloride was dissolved in 10 mL of double-distilled water to obtain a working solution with a concentration of 50 mg/mL. The solution was administered to the rats orally at a dosage of 100 mg/kg body weight, adjusted according to individual animal weight (Lekshmi et al., 2015). Metformin was chosen for this study due to its well-established status as the standard first-line pharmacological therapy in the treatment of T2DM (Ekeuku et al., 2022).

Preparation of serum and tissue supernatants

Blood samples were collected from overnight-fasted rats on days 0, 7, 14, and 21 of the experimental period for the determination of blood glucose levels. At the end of the treatment phase, the animals were fasted overnight, and blood was obtained via cardiac puncture under deep anaesthesia induced by diethyl ether. Diethyl ether was used in accordance with institutional animal care protocols available at the time of the study. Serum and pancreatic tissue supernatants were prepared following standard procedure (Olszowy-Tomczyk et al., 2022). After centrifugation at 894 × g for 15 minutes, the serum was carefully aspirated using a Pasteur pipette. The pancreas was excised, blotted, weighed, and homogenized in 0.25 M sucrose solution at a 1:5 (w/v).(Akanji & Yakubu, 2000). The pancreatic homogenates were then centrifuged at 1398 × g for 20 minutes, and the resulting supernatants were stored at −20°C for 24 hours prior to biochemical analysis.

Determination of biochemical parameters

Standard analytical procedures were employed for the assessment of fasting blood glucose (Siregar et al., 2020),

insulin (Bürgi et al., 1988), HOMA-IR and HOMA-β (Yoon et al., 2016), catalase (Tan et al., 2020), superoxide dismutase (Campos-Shimada et al., 2020), glutathione (Nwogueze et al., 2021), and malondialdehyde (Sagita et al., 2022), as previously described by respective authors.

Histopathological Examination

The pancreas was excised and fixed in 10% neutral-buffered formalin, followed by dehydration, paraffin embedding, and sectioning at a thickness of 5 µm. The tissue sections were stained with Hematoxylin and Eosin (H&E) for general histopathological evaluation. Microscopic analysis, conducted under light microscopy at varying magnifications, focused on assessing the structural integrity of the islets of Langerhans, as well as the presence of cellular infiltration, necrosis, and vacuolation. Histological sections were coded and evaluated independently by a pathologist who was blinded to treatment allocation. Pancreatic injury was assessed based on the degree of acinar degeneration, inflammatory cell infiltration, fibrosis, vascular congestion, and islet alterations.

Statistical Analysis

Data are expressed as mean values (n = 6) ± standard error of the mean (SEM). Statistical comparisons among group means were carried out using Duncan's Multiple Range Test (DMRT), with significance established at $P \leq 0.05$. All analyses were performed using IBM SPSS Statistics version 20 and GraphPad Prism version 8.0.1 (GraphPad Software Inc., USA).

RESULT

Impact of *C. papaya* Leaf Crude Extract and Fractions on Blood Glucose Levels

Table 1 shows that streptozotocin (STZ) administration induced persistent hyperglycaemia throughout the 21-day study, with blood glucose concentrations remaining significantly higher than those of the control group at all time points ($p < 0.05$). Metformin treatment progressively reduced blood glucose by 27.8% from baseline after 21 days. Greater reductions were observed following treatment with *C. papaya* preparations, with the n-hexane fraction, CECP200, and CECP400 producing reductions of 52.1%, 53.7%, and 37.0%, respectively, over the treatment period. In contrast, untreated diabetic rats exhibited a slight increase (3.9%) in blood glucose from baseline. By Day 21, rats treated with the n-hexane fraction (7.66 ± 0.25 mmol/L) and CECP200 (7.11 ± 1.47 mmol/L) exhibited significantly lower blood glucose concentrations than both the untreated diabetic and metformin-treated groups ($p < 0.05$), whereas CECP400 also significantly reduced glucose levels relative to the untreated diabetic group.

Effect of *C. papaya* Leaf Crude Extract and Fractions on Fasting Blood Glucose, Insulin Levels, HOMA-IR, and HOMA-β Indices

Fig 1 reveals that STZ-induced diabetes significantly reduced insulin levels (5.33 ± 1.24 mlU/L), HOMA-β (9.56 ± 2.87), and increased HOMA-IR (3.62 ± 0.17) compared to the control group (21.63 ± 2.13 mlU/L, 184.32 ± 2.15, and 4.64 ± 0.15, respectively; $p<0.05$), indicating β-cell dysfunction and insulin resistance. Treatment with metformin improved these parameters, but crude extracts and the n-hexane fraction of *C. papaya* showed greater enhancements. Notably, CECP200 and CECP400 significantly increased insulin levels (15.82 ± 0.36 and 19.81 ± 1.23 mlU/L, respectively) and HOMA-β (74.64 ± 2.32 and 70.93 ± 1.55), while also modulating HOMA-IR values. CECP200 yielded a lower HOMA-IR (5.00 ± 0.11) than metformin (6.50 ± 0.17), suggesting improved insulin sensitivity. These findings suggest that *C. papaya* leaf extract, particularly at 200 mg/kg, enhances pancreatic β-cell function and insulin sensitivity more effectively than metformin.

Table 1: Effect of crude extract and fractions of *C. papaya* leaf on Glucose level

	Glucose level (mmol/L)			
	Day 0	**Day 7**	**Day 14**	**Day 21**
Control	4.83 ± 0.21	4.83 ± 0.21	4.83 ± 0.21	4.83 ± 0.21
STZ	14.69 ± 0.49*	14.68 ± 0.42*	15.60 ± 0.58*	15.26 ± 0.33*
Diabetic + Metformin	14.48 ± 0.26*	13.20 ± 0.92*	12.21 ± 0.14*^{a}	10.45 ± 0.67*$^{+}$
Diabetic + n-Hexane	15.98 ± 0.54*	12.48 ± 0.26*	9.30 ± 0.17*$^{ab+}$	7.66 ± 0.25^{a+}
Diabetic + CECP200	15.37 ± 0.27*	12.26 ± 0.25*	9.36 ± 0.27*$^{ab+}$	7.11 ± 1.47^{a+}
Diabetic + CECP400	13.87 ± 0.42*^{ab}	10.29 ± 0.25*^{ab}	9.51 ± 0.26*$^{ab+}$	8.74 ± 1.60^{a+}

Values are expressed as mean ± SEM (n = 6). (*) = $p<0.05$ when compared to Control; (a) = $p<0.05$ when compared to STZ; (b) = $p<0.05$ when compared to Diabetic + Metformin; (+) = $p<0.05$ when compared to Day 0. STZ = 60 mg/kg body weight of Streptozotocin induced Diabetes; Diabetic + Metformin = 100 mg/kg body weight of Metformin in diabetic rats ; Diabetic + n-Hexane = 200 mg/kg body weight of aqueous fraction n-Hexane in diabetic rats; Diabetic + CECP200 = 200 mg/kg body weight of crude extract *C. papaya* in diabetic rats; Diabetic + CECP400 = 400 mg/kg body weight of crude extract *C. papaya* in diabetic rats

Influence of *C. papaya* Leaf Crude Extract and Fractions on Pancreatic Antioxidant Enzyme Activities and Oxidative Stress Markers

Fig 2 shows that STZ-induced diabetes significantly impaired pancreatic antioxidant defenses, as indicated by reduced levels of SOD (53.30 ± 1.44 u/mL), CAT (33.95 ± 1.08 u/mg), and GSH (1.36 ± 0.14 mM), alongside a marked increase in MDA (21.48 ± 0.86 µM), a marker of lipid peroxidation ($p<0.05$ vs. control). Treatment with metformin partially restored antioxidant levels and reduced oxidative stress, but *C. papaya* extracts showed

stronger effects. CECP400 restored SOD (77.58 ± 3.34) close to control values and significantly reduced MDA (8.68 ± 0.81), while CECP200 and the n-hexane fraction also improved antioxidant enzyme activities and glutathione levels. Notably, the n-hexane group exhibited the highest CAT (45.67 ± 0.60) and GSH (9.57 ± 0.87) levels among treated groups, suggesting potent free radical scavenging capacity.

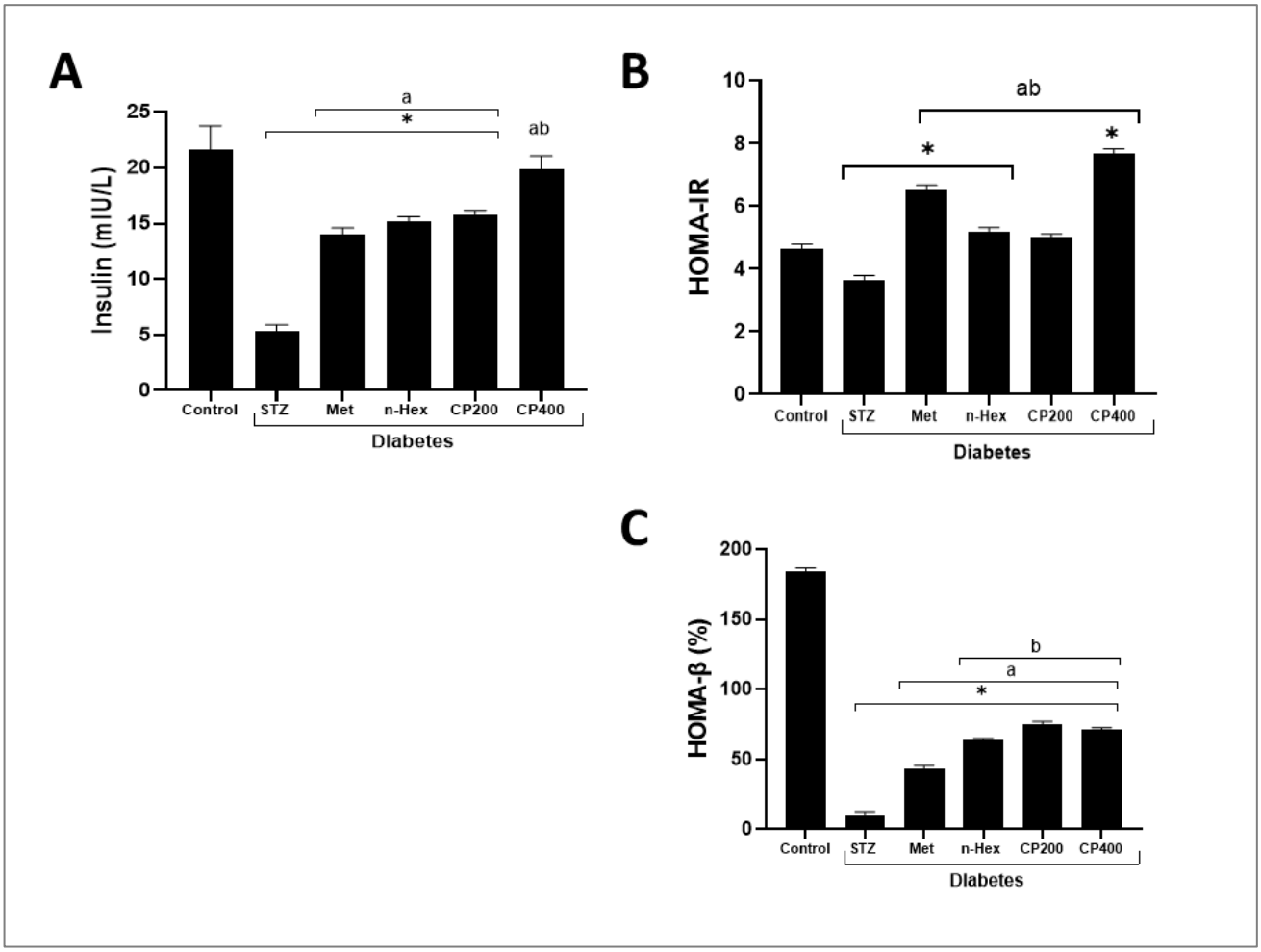

Fig 1: Effect of crude extract and fractions of *C. papaya* leaf on fasting glucose and insulin concentration, HOMA-IR and HOMA-β

Values are expressed as mean ± SEM (n = 6). (*) = p<0.05 when compared to Control; (a) = p<0.05 when compared to STZ; (b) = p<0.05 when compared to Diabetic + Metformin; STZ = 60 mg/kg body weight of Streptozotocin induced Diabetes; Diabetic + Metformin = 100 mg/kg body weight of Metformin in diabetic rats; Diabetic + n-Hexane = 200 mg/kg body weight of aqueous fraction n-Hexane in diabetic rats; Diabetic + CP200 = 200 mg/kg body weight of crude extract *C. papaya* in diabetic rats; Diabetic + CP400 = 400 mg/kg body weight of crude extract *C. papaya* in diabetic rats; A – Insulin; B - HOMA-IR- Homeostatic Model Assessment of Insulin Resistance; C - HOMA- β - Homeostatic Model Assessment of Beta-cell Function

Histology of the Pancreas

Histopathological analysis of the pancreas (Fig. 3) revealed that control rats exhibited normal pancreatic architecture, with well-preserved serous acinar and zymogenic cells containing abundant granular eosinophilic cytoplasm, normal interlobular connective tissue, and intact islets of Langerhans. Histological examination of the STZ-treated group revealed vacuolation of acinar cells and disruption of interlobular connective tissue, whereas overt structural damage to the islets of Langerhans was not readily apparent at the level of examination employed. Treatment with metformin restored normal pancreatic structure, resembling that of the control group. Rats treated with 200 mg/kg of the n-hexane fraction displayed normal acinar and zymogenic cells but showed moderate fibrosis of the interlobular connective tissue, collagen deposition in ducts, and mild interstitial fluid accumulation. Both 200 mg/kg and 400 mg/kg doses of the crude extract preserved normal pancreatic architecture, though mild inflammatory infiltration was observed in the interlobular connective tissue, with no alteration in the islets of Langerhans.

DISCUSSION

The findings of this study demonstrate that *C. papaya* (*C. papaya*) leaf crude extract and its n-hexane fraction possess significant antihyperglycemic, insulinotropic, antioxidant, and pancreatic cytoprotective effects in STZ-induced diabetic rats.. These results are consistent with several previous studies reporting hypoglycemic activity of *C. papaya* leaf extract, yet they also diverge from others where minimal or no significant antidiabetic effects were observed.

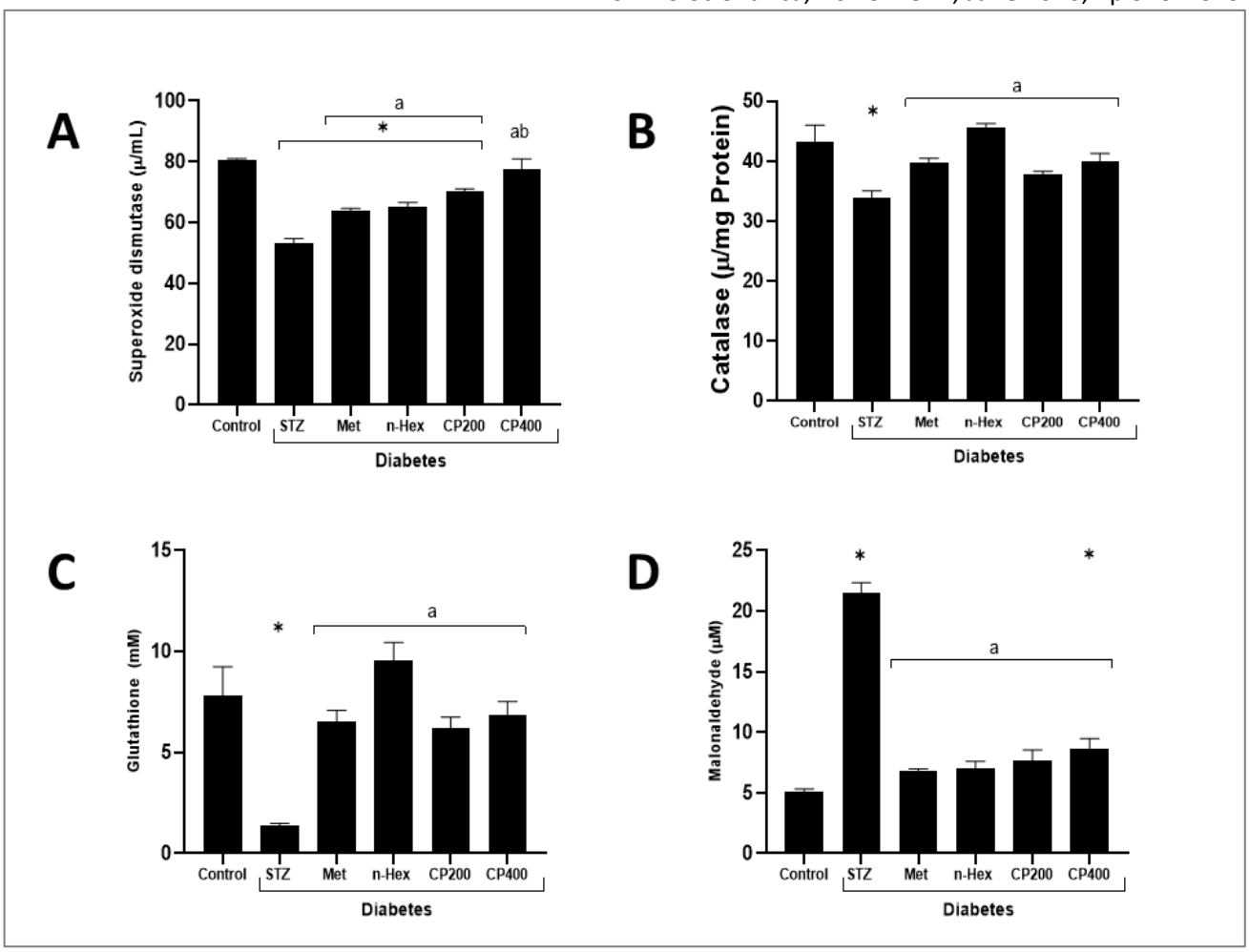

Fig 2: Effect of crude extract and fractions of *C. papaya* leaf on pancreatic antioxidant activities and oxidative stress marker

Values are expressed as mean ± SEM (n = 6). (*) = $p<0.05$ when compared to Control; (a) = $p<0.05$ when compared to STZ; (b) = $p<0.05$ when compared to Diabetic + Metformin; STZ = 60 mg/kg body weight of Streptozotocin induced Diabetes; Diabetic + Metformin = 100 mg/kg body weight of Metformin in diabetic rats; Diabetic + n-Hexane = 200 mg/kg body weight of aqueous fraction n-Hexane in diabetic rats; Diabetic + CP200 = 200 mg/kg body weight of crude extract *C. papaya* in diabetic rats; Diabetic + CP400 = 400 mg/kg body weight of crude extract *C. papaya* in diabetic rats; A - SOD-superoxide dismutase, B - CAT-catalase, C - GSH-glutathione, D - MDA-malondialdehyde

The observed reduction in blood glucose levels following treatment with 200mg/Kg.bw *C. papaya* and the n-hexane fraction is consistent with earlier findings, which reported significant reductions in fasting glucose in alloxan-induced diabetic rats treated with aqueous *C. papaya* extract (Morolahun et al., 2019). Similarly, documented glucose-lowering and insulin-enhancing effects of *C. papaya* in diabetic rodents, attributing the effects to the presence of flavonoids and alkaloids that enhance peripheral glucose uptake and have been associated with preservation of β-cell integrity and insulin secretory capacity (Kumari Sinha et al., 2018). In this study, 200mg/Kg.bw *C. papaya* and the n-hexane fraction led to significantly lower glucose levels by Day 21 compared to metformin, indicating greater reductions in fasting blood glucose than those observed in the metformin-treated group under the conditions of the present study. However, the underlying mechanisms responsible for this effect were not investigated and therefore should be interpreted cautiously. This aligns with a study that reported that plant-derived bioactives with antioxidant properties often act through multiple mechanisms, including inhibition of intestinal glucose absorption, stimulation of insulin secretion, and improved indices associated with glucose homeostasis (Unuofin & Lebelo, 2020). Contrastingly, some studies have failed to observe significant antidiabetic effects of *C. papaya*. For example, aqueous extracts of *C. papaya* produced only marginal effects on fasting glucose and antioxidant parameters in diabetic rats, an outcome differing markedly from the present study (Solikhah et al., 2020).

Although HOMA-IR and HOMA-β were originally developed for human studies, they have been widely employed in experimental diabetic rodent models as surrogate indicators of insulin sensitivity and β-cell function. The results should therefore be interpreted cautiously and in conjunction with fasting insulin concentrations, glycaemic indices, oxidative stress markers, and histopathological findings. In evaluating insulin dynamics, the present study demonstrated that both 200mg/Kg.bw and 400mg/Kg.bw. of *C. papaya* significantly improved serum insulin levels and HOMA-β, suggesting a partial restoration of pancreatic β-cell function. This therapeutic effect, as previously reported, demonstrated that polyphenol-rich plant extracts protected β-cells and enhanced insulin secretion by mitigating oxidative stress and inflammatory pathways—

mechanisms also implicated in *C. papaya*'s bioactivity (Roy et al., 2023). Similarly, treatment with flavonoid-rich plant extracts significantly increased insulin secretion and preserved β-cell mass in streptozotocin-induced diabetic rats, supporting the view that phytochemicals can exert insulinotropic effects via both direct β-cell stimulation and antioxidative modulation (Nyakundi et al., 2024). However, contrasting results observed that despite elevated insulin levels following administration of high-dose flavonoid-rich plant extracts, insulin sensitivity indices such as HOMA-IR remained unimproved or worsened, a pattern mirrored in the current study's 400mg/Kg.bw. of *C. papaya* group (Nyakundi & Yang, 2023). The differing responses observed between the two extract doses may reflect dose-dependent biological effects of the phytochemical constituents. However, the mechanisms underlying these differences remain unclear because molecular markers of insulin signaling and glucose transport were not assessed in the present study..

From the perspective of oxidative stress, the results show significant restoration of antioxidant enzymes (SOD, CAT, GSH) and reduction in MDA levels in groups treated with 200mg/Kg.bw and 400mg/Kg.bw. of *C. papaya*, and n-hexane, further corroborating the hypothesis that oxidative stress plays a pivotal role in diabetes pathogenesis. This outcome is consistent with other findings reported that *C. papaya* extracts rich in flavonoids and phenolic compounds significantly improved antioxidant status and suppressed lipid peroxidation in streptozotocin-induced diabetic rats, thereby supporting the notion that plant-derived phytochemicals can modulate redox homeostasis in diabetic conditions (Omiyale et al., 2024). Similarly, methanolic extracts of *C. papaya* leaves of previous study enhanced SOD and CAT activities and reduced MDA concentration in diabetic rats, suggesting that the antioxidative mechanisms may be mediated by the extract's capacity to scavenge free radicals and upregulate endogenous antioxidant systems (Nxumalo et al., 2024). However, conflicting evidence has been provided, finding no significant changes in oxidative stress markers following administration of *C. papaya* extract in diabetic rats, a discrepancy that may stem from differences in extraction methods, plant part used, dosage, or treatment duration (Amin, 2021).

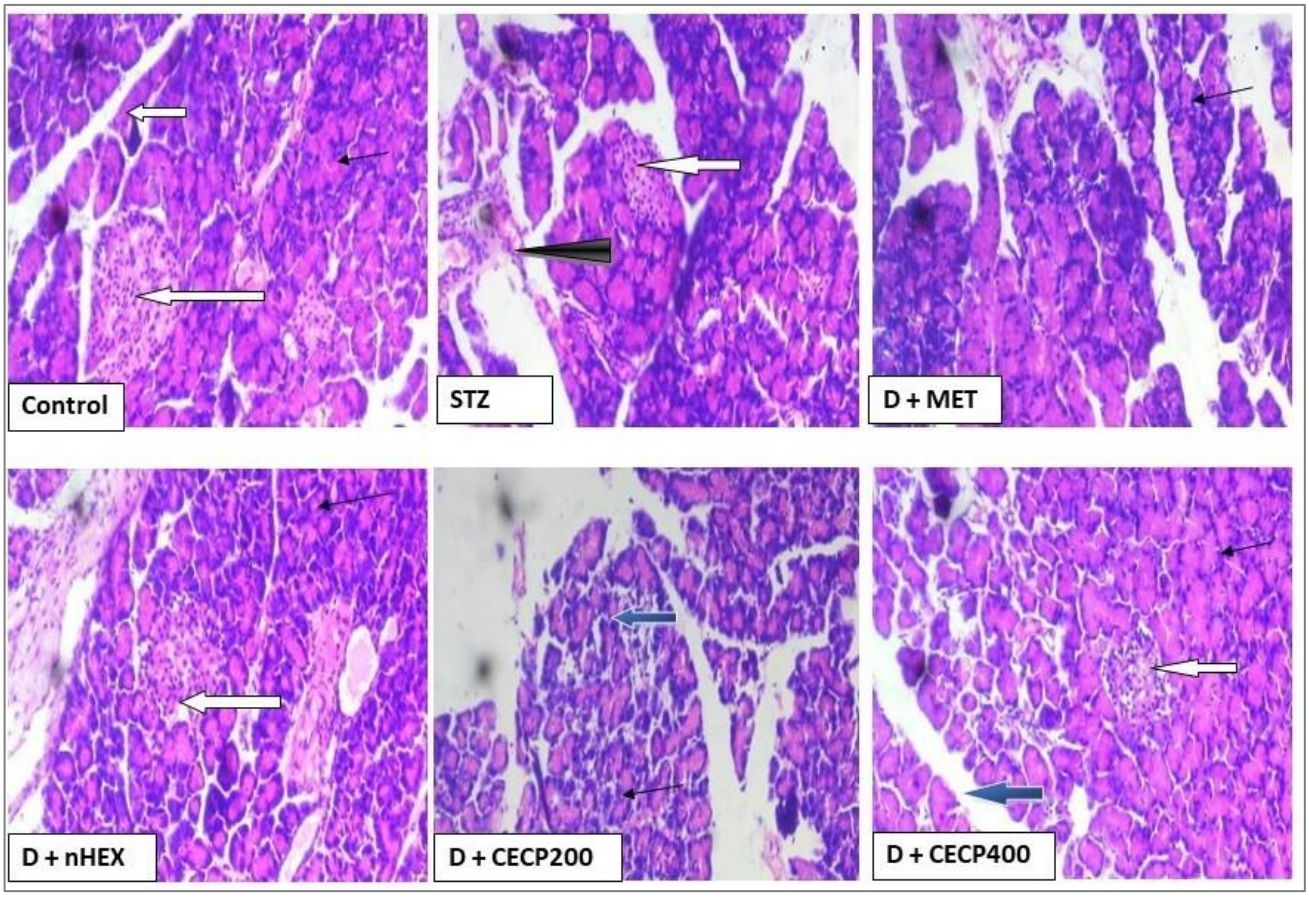

Fig 3. Pancreas Histology (x100)

Control: The pancreas of the control group shows normal architecture (slender arrow), with intact serous acinar and zymogenic cells, normal interlobular connective tissue (blue arrow), and well-preserved islets of Langerhans (white arrow). **STZ**: Streptozotocin-induced diabetic rats, the pancreas shows vacuolated acinar cells (slender arrow), abnormal interlobular connective tissue (blue arrow), and intact islets of Langerhans (white arrow). **D + MET:** metformin-treated diabetic rats, the pancreas shows normal architecture with intact acinar cells, normal connective tissue (green arrow) and ducts, and preserved islets (white arrow). **D + nHEX**: Diabetic rats treated with 200 mg/kg n-hexane extract, the pancreas shows normal acinar cells, moderate fibrosis, collagen in ducts, mild fluid buildup, and intact islets. **D + CECP200:** Diabetic rats treated with 200 mg/kg *C. papaya* extract, the pancreas shows normal structure, mild interlobular inflammation, and intact islets (blue arrow). **D + CECP400:** Diabetic rats treated with 400 mg/kg *C. papaya* extract, the pancreas shows normal acinar cells (slender arrow), normal interlobular tissue (blue arrow), and vacuolated islets of Langerhans (white arrow).

This antioxidant restoration at the biochemical level appears to translate into structural benefits as well, as shown in the histological assessments of pancreatic tissues. Both 200mg/Kg.bw and 400mg/Kg.bw. of *C. papaya* preserved islet architecture and reduced signs of pancreatic degeneration, supporting the biochemical evidence of improved insulin production. This outcome is in line with another study that proved structural regeneration of islets following *C. papaya* administration in diabetic models (Ebifa et al., 2021). Interestingly, the n-hexane fraction, while biochemically effective, revealed moderate fibrosis and interstitial infiltration, suggesting that functional recovery may precede structural remodeling or that lipophilic extracts, although potent in glycemic control, may lack certain hydrophilic anti-inflammatory agents critical for complete tissue repair. Resolution of inflammation and restoration of tissue integrity often require both lipophilic and hydrophilic compounds acting synergistically (Sitompul et al., 2024). This underscores the potential advantage of crude extracts over isolated fractions, as the former may offer a broader spectrum of therapeutic phytochemicals that act on multiple cellular targets.

Several limitations should be considered when interpreting the present findings. First, the STZ-induced diabetic rat model predominantly reflects pancreatic β-cell injury and therefore does not fully replicate the complex pathophysiology of human diabetes, particularly Type 2 diabetes characterized by progressive insulin resistance. Second, although HOMA-IR and HOMA-β were used as surrogate indicators of insulin sensitivity and β-cell function, these indices were originally developed for human studies and may have reduced validity in STZ-treated animals. Third, the phytochemical constituents responsible for the observed biological effects were not quantitatively characterized or standardized, limiting identification of the specific bioactive compounds involved. Furthermore, mechanistic biomarkers such as GLUT4 expression, insulin receptor signaling pathways, inflammatory mediators, and pancreatic insulin immunostaining were not evaluated, restricting conclusions regarding the precise mechanisms of action. Finally, the study was limited to a 21-day treatment period and did not include sub-chronic or chronic toxicity assessments; therefore, the long-term safety profile of the extract and its fractions remains to be established.

CONCLUSION

This study provides preliminary experimental evidence that *Carica papaya* leaf crude extract and its n-hexane fraction possess antihyperglycaemic, insulin-modulatory, antioxidant, and pancreatic protective properties in streptozotocin-induced diabetic rats. The 200 mg/kg crude extract exhibited the most pronounced effects on glycaemic control, insulin levels, and HOMA indices, whereas the 400 mg/kg crude extract and n-hexane fraction demonstrated comparatively stronger effects on selected antioxidant parameters. Histopathological findings further indicated partial preservation of pancreatic architecture following treatment, although mild residual tissue alterations persisted, particularly in the n-hexane fraction-treated group. Collectively, these findings suggest that *C. papaya* leaf preparations may have beneficial effects against diabetes-associated metabolic and oxidative disturbances; however, the results should be interpreted as preliminary evidence from an experimental animal model. Further studies are required to identify the active bioactive constituents, elucidate the underlying mechanisms of action, and establish long-term safety and efficacy.

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