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Aqueous Extract of Carica papaya Leaves Protects Against Streptozotocin-Induced Renal Oxidative Stress and Dysfunction

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Abstract

Background: Diabetes mellitus is a global health challenge frequently complicated by oxidative stress–mediated nephropathy, and the nephroprotective potential of *Carica papaya* leaves remains underexplored. This study investigated the renoprotective potential of aqueous extract and fractions of *Carica papaya* leaves in streptozotocin (STZ)-induced diabetic Wistar rats.
Methods: Thirty-six male Wistar rats were divided into six groups: normal control, STZ-diabetic control, metformin (200 mg/kg), n-hexane fraction (400 mg/kg), aqueous extract (200 mg/kg), and aqueous extract of *Carica papaya* (400 mg/kg). Diabetes was induced with streptozotocin (50 mg/kg, i.p.), and treatments were administered orally for 42 days. Body weight, fasting glucose, insulin, renal function indices, oxidative stress markers, and renal histology were evaluated.
Results: STZ-diabetic rats exhibited hyperglycaemia (16.93 ± 0.52 mmol/L), insulin depletion (5.33 ± 1.24 mIU/L), and renal impairment with elevated creatinine (94.89 ± 10.95 µmol/L) and urea (104.87 ± 13.92 mg/dL). Treatment with *Carica papaya* significantly ($p \leq 0.05$) improved these parameters. The aqueous extract of *Carica papaya* (400 mg/kg) reduced glucose (4.93 ± 1.11 mmol/L), increased insulin (11.24 ± 0.56 mIU/L), and lowered creatinine (55.54 ± 0.76 µmol/L) and urea (54.86 ± 1.19 mg/dL). The n-hexane fraction produced the strongest antioxidant effect, restoring Superoxide dismutase (65.00 ± 1.57 U/mL), Catalase (45.67 ± 0.60 U/mg protein), and Gluthatione (9.57 ± 0.87 mM), while reducing Malonaldehyde (7.00 ± 0.62 µM). Histology showed that while untreated diabetic rats exhibited severe renal damage, metformin and *Carica papaya* leaf fractions offered varying degrees of nephroprotection
Conclusion: *Carica papaya* leaf extract, especially at higher doses and in its n-hexane fraction, protects against diabetic renal injury by improving glycaemic control, enhancing antioxidant status, and preserving kidney function.

Keywords: antioxidant, anti-diabetes, *Carica papaya*, n-hexane, metformin

Introduction

Type 2 diabetes mellitus represents the most prevalent form of diabetes.[1] Although its etiology is complex and influenced by multiple factors, modifiable determinants such as physical inactivity and inadequate dietary practices are strongly implicated in its onset.[2] Current global estimates indicate that one in ten adults is affected, accounting for approximately 537 million individuals; this figure is projected to rise to 643 million by 2030 and 783 million by 2045.[3] Moreover, diabetes and its associated complications constitute a major global cause of

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mortality, with approximately 6.7 million deaths recorded in individuals aged 20–79 years in 2021, one-third of which occurred among those younger than 60 years.[4]

Approximately 30–40% of individuals with diabetes develop diabetic nephropathy, a frequent and serious complication that contributes substantially to the burden of chronic kidney disease (CKD) and renal failure.[5] Diabetic nephropathy, a form of diabetic microangiopathy, is characterized by progressive glomerular injury driven by prolonged hyperglycemia, hypertension, microcirculatory dysfunction, and a prothrombotic state.[6,7] Current therapeutic strategies emphasize strict glycemic regulation alongside antihypertensive and lipid-lowering interventions; nevertheless, these measures often prove insufficient in halting disease progression in a considerable proportion of patients.[8] Consequently, many individuals with advanced CKD depend on renal replacement therapies such as dialysis, a renal replacement intervention, or kidney transplantation to sustain kidney function.[9,10]

In recent years, natural products have attracted considerable attention as complementary or alternative therapeutic options for diabetes and its associated complications.[11] Bioactive compounds derived from plants, particularly polyphenols, flavonoids, alkaloids, and terpenoids, are recognized for their strong antioxidant, anti-inflammatory, and antihyperglycaemic properties.[12,13] *Carica papaya* (family *Caricaceae*), commonly referred to as pawpaw, is a tropical fruit-bearing plant widely utilized in ethnomedicine.[14] Its leaves, in particular, have a long history of traditional use in Africa, Asia, and South America for the treatment of malaria, infectious diseases, and various inflammatory conditions. Phytochemical investigations of *Carica papaya* leaves have identified a diverse spectrum of bioactive constituents, including flavonoids (e.g., quercetin and kaempferol), alkaloids, phenolic acids, tannins, and saponins, many of which exhibit significant antioxidant activity.[15,16] Notably, aqueous leaf extracts have been shown to exert hypoglycaemic effects, enhance lipid metabolism, and modulate oxidative stress markers in experimental models of diabetes.[17–19]

Although emerging evidence highlights the therapeutic potential of *Carica papaya* leaf extract, systematic investigations into its nephroprotective efficacy in the context of diabetes-induced renal injury remain limited. The majority of existing research has centered on its antihyperglycaemic and hepatoprotective activities, while its capacity to preserve renal architecture and function under conditions of hyperglycaemia-induced oxidative stress has received comparatively little attention. Given that aqueous preparations represent the most common mode of traditional use, rigorous evaluation of the aqueous extract in experimental models of diabetic nephropathy is both scientifically pertinent and translationally valuable. Elucidating whether *Carica papaya* leaves can attenuate oxidative renal injury could provide novel insights into the development of affordable, accessible, and plant-derived interventions for diabetes-associated kidney complications. Accordingly, the present study investigated the protective effects of aqueous *Carica papaya* leaf extract on renal oxidative stress and dysfunction in streptozotocin (STZ)-induced diabetic Wistar rats. It was hypothesized that, owing to its phytochemically rich antioxidant profile, the extract would mitigate oxidative damage, enhance endogenous antioxidant enzyme activities, and preserve both renal function and histological integrity under diabetic conditions.

Methodology

Plant Material Collection and Authentication

Fresh, mature leaves of *Carica papaya* were harvested from cultivated fields in Forestry Research Institute Nigeria (FRIN, Ibadan, Oyo State) farmland during the raining season in the month of June, 2025. The leaves were taxonomically identified and authenticated by a plant taxonomist in the Department of Botany, Bingham University, Karu, Nigeria, and a voucher specimen (specimen number: FHI 1142134) was deposited in the institutional herbarium for reference.

Preparation of Aqueous Extract and Fraction

The harvested leaves were rinsed with distilled water to remove debris and air-dried under shade at room temperature (25–28 °C) for 10–14 days to preserve thermolabile phytochemicals. The dried

leaves were pulverized into coarse powder using an electric grinder. For aqueous extraction, 200 g of powdered leaves were macerated in 1 L of distilled water with continuous agitation at 40°C for 48 h under controlled laboratory conditions. The mixture was filtered sequentially through muslin cloth and Whatman No. 1 filter paper. The filtrate was concentrated under reduced pressure at 45°C using a rotary evaporator and subsequently lyophilized to dryness. The yield was recorded, and the dried extract stored in airtight containers at –20°C until use. In addition, a portion of the crude extract was partitioned with n-Hexane to obtain a non-polar fraction for comparative evaluation, as reported in previous phytochemical studies of *Carica papaya*.
Note: Preliminary phytochemical screening of both aqueous and hexane fractions was conducted to confirm the presence of secondary metabolites, and results were used to justify dose selection.

Experimental Animals
Thirty-six (36) healthy male Wistar rats (8–10 weeks old; 150–180 g) were kept in the Animal Care Unit of the Faculty of Basic Medical Sciences, Bingham University, Karu, Nasarawa State, Nigeria. Animals were housed in standard polypropylene cages under controlled conditions (temperature: 22 ± 2°C; relative humidity: 55 ± 5%; 12h light/dark cycle) and acclimatized for two weeks with free access to a standard pellet diet and water ad libitum. All animal procedures complied with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals (8th Edition, 2011) and were approved by the Institutional Animal Care and Use Committee (IACUC) of Bingham University(approval number: NHREC/21/05/2005/01523). Only male rats were used to minimize the confounding influence of hormonal variations observed in females; however, this is recognized as a limitation.

Induction of Experimental Diabetes
Experimental diabetes was induced by a single intraperitoneal injection of freshly prepared streptozotocin (STZ; Sigma-Aldrich, USA) at 50 mg/kg body weight, dissolved in 0.1 M cold citrate buffer (pH 4.5). To prevent acute hypoglycemia, rats received 5% glucose solution orally for 24 h post-injection. Seventy-two hours after STZ administration, fasting blood glucose levels were determined from tail vein blood using a glucometer. Rats with blood glucose ≥ 200 mg/dL were considered diabetic and included in the study. Treatment commenced immediately after confirmation of diabetes.

Experimental Design
Rats were randomly allocated into six experimental groups (n = 6 per group): (I) non-diabetic control, distilled water; (II) diabetic control (STZ-induced), distilled water; (III) STZ-diabetic, metformin (200 mg/kg/day, orally); (IV) STZ-diabetic, *Carica papaya* n-hexane fraction (400 mg/kg/day, orally); (V) STZ-diabetic, aqueous *C. papaya* extract (200 mg/kg/day, orally); and (VI) STZ-diabetic, aqueous *C. papaya* extract (400 mg/kg/day, orally). Treatments were administered once daily by oral gavage for 42 days.

Body Weight Measurement
Body weight of rats was measured at baseline (prior to induction of diabetes), after confirmation of hyperglycemia, and weekly throughout the 42-day treatment period using a digital weighing balance. Weight changes were recorded to monitor the effect of treatments on diabetes-associated weight loss.

Assessment of Renal Function
At the end of the experimental period, animals were fasted overnight, anesthetized with ketamine (50 mg/kg, intraperitoneally), and sacrificed. Blood samples were collected by cardiac puncture into heparinized tubes and centrifuged at 3000 rpm for 15 minutes (min) to obtain plasma. Serum creatinine, urea, and uric acid levels were quantified using commercial diagnostic kits (Randox Laboratories, UK) following the manufacturer's instructions.

Oxidative Stress Biomarkers
Kidney tissues were rinsed in ice-cold saline, blotted dry, homogenized in phosphate-buffered saline (0.1 M, pH 7.4), and centrifuged at 10,000 rpm for 15 min at 4°C, with the supernatants used for biochemical assays. Antioxidant and oxidative stress parameters were determined as follows: superoxide dismutase (SOD, U/mL)[20], catalase (CAT, U/mg protein)[21], reduced glutathione (GSH,

mM)[22], and malondialdehyde (MDA, μM; TBARS assay).

Serum Insulin Assay

Serum insulin levels were quantified using a rat-specific ELISA kit (e.g., DRG International, USA; catalog no. EIA-2048). Absorbance was measured at 450 nm with a microplate reader, and concentrations calculated against a standard curve. The assay sensitivity and intra-/inter-assay coefficients of variation were within the manufacturer's specifications.

Histopathological Examination

Kidney tissues were fixed in 10% neutral-buffered formalin for 48h, dehydrated through ascending grades of ethanol, embedded in paraffin, and sectioned at 5 μm thickness. Sections were stained with hematoxylin and eosin (H&E) for general histology and examined under a light microscope at ×100 magnification. Photomicrographs were taken for histopathological documentation. Although H&E was primarily used, the absence of additional staining methods (e.g., PAS or Masson's Trichrome) is acknowledged as a limitation.

Statistical Analysis

Data were expressed as mean ± standard error of the mean (SEM). Statistical analysis was performed using GraphPad Prism version 6.03. One-way analysis of variance (ANOVA) followed by Tukey's post hoc test was used to determine differences among groups. Prior to ANOVA, assumptions of normality (Shapiro–Wilk test) and homogeneity of variances (Levene's test) were confirmed. Statistical significance was set at $p \leq 0.05$.

Results

As presented in Fig. 1, STZ-induced diabetic rats demonstrated significant metabolic derangements characterised by marked reductions ($p \leq 0.05$) in body weight (98.61 ± 17.20 g) and serum insulin concentration (5.33 ± 1.24 mIU/L), accompanied by a substantial elevation in blood glucose level (16.93 ± 0.52 mmol/L) relative to the normal control group. Treatment with metformin significantly ameliorated these alterations, evidenced by restoration of body weight (272.61 ± 14.70 g), increased insulin concentration (14.02 ± 0.59 mIU/L), and a pronounced reduction in glycaemia (7.11 ± 0.31 mmol/L) compared with the untreated diabetic group. Similarly, administration of the n-hexane fraction at 400 mg/kg produced significant antidiabetic effects, as reflected by improved body weight (225.51 ± 20.55 g), elevated insulin level (15.19 ± 0.40 mIU/L), and marked glucose reduction (5.00 ± 0.89 mmol/L), with responses comparable to those observed in the metformin-treated group. The aqueous fraction at 400 mg/kg also significantly improved insulin secretion (11.24 ± 0.56 mIU/L) and glycaemic status (4.93 ± 1.11 mmol/L), although the associated increase in body weight (188.23 ± 34.80 g) was comparatively moderate. In contrast, treatment with the aqueous fraction at 200 mg/kg resulted in only partial metabolic recovery, with body weight (157.87 ± 30.94 g), insulin concentration (9.98 ± 0.55 mIU/L), and glucose level (8.75 ± 0.15 mmol/L) remaining significantly altered relative to the normal control group.

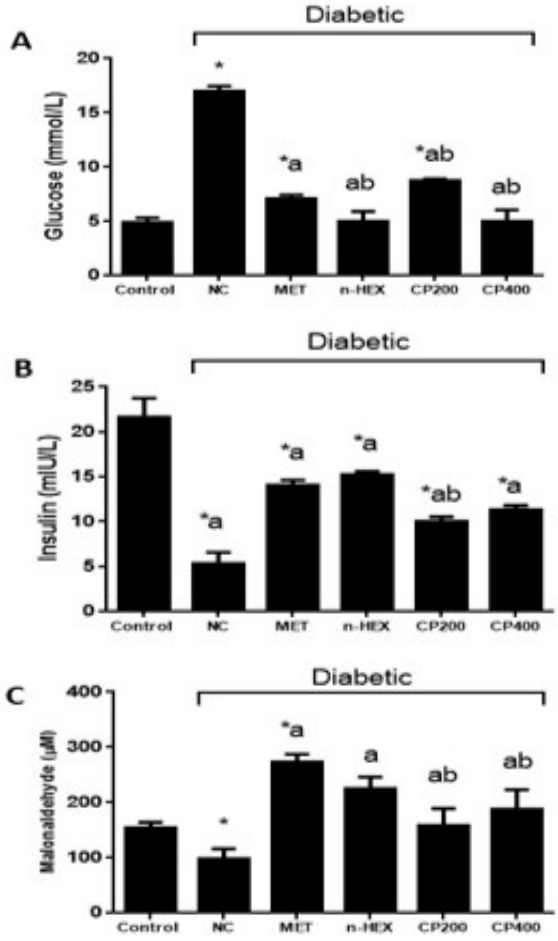


Fig 1: Effect of extract and fractions of *C. papaya* leaf on Glucose (A), Insulin level (B), and Body weight (C). *: $p \leq 0.05$ vs. normal control; a: $p \leq 0.05$ vs. STZ control; b: $p \leq 0.05$ vs. normal control. NC = Negative Control. MET = Metformin. n-HEX = 400 mg/kg of n-Hexane fractions. CP200 = Aqueous extract of 200mg/Kg *Carica papaya*. CP400 = Aqueous extract of 400mg/Kg *Carica papaya*.

Fig 2 shows the effect of *Carica papaya* leaf extract and fractions on renal function indices in STZ-induced diabetic rats. The STZ control group demonstrated significant renal impairment, with elevated serum creatinine (94.89 ± 10.95 µmol/L), urea (104.87 ± 13.92 mg/dL), and uric acid (10.12 ± 0.57 mg/dL) compared with the normal control ($p \leq 0.05$). Treatment with metformin significantly reduced these parameters, yielding values of 40.69 ± 7.90 µmol/L (creatinine), 51.71 ± 1.18 mg/dL (urea), and 7.49 ± 0.71 mg/dL (uric acid), which were comparable to those of the normal control ($p \leq 0.05$ vs. STZ control). Similarly, the n-hexane fraction (400 mg/kg) markedly restored renal function, as indicated by reduced creatinine (38.49 ± 2.71 µmol/L), urea (40.32 ± 2.90 mg/dL), and uric acid (5.92 ± 1.55 mg/dL), all of which were significantly lower than the STZ control ($p \leq 0.05$). The aqueous fraction at both 200 mg/kg and 400 mg/kg also demonstrated renoprotective activity, with significant reductions in creatinine (51.77 ± 1.02 and 55.54 ± 0.76 µmol/L, respectively), urea (54.11 ± 1.97 and 54.86 ± 1.19 mg/dL), and uric acid (4.84 ± 0.16 and 5.38 ± 0.41 mg/dL) compared with the STZ control ($p \leq 0.05$).

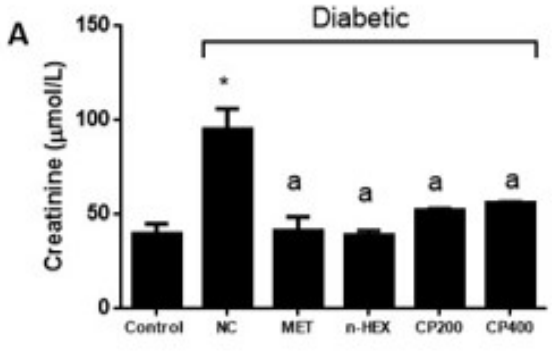
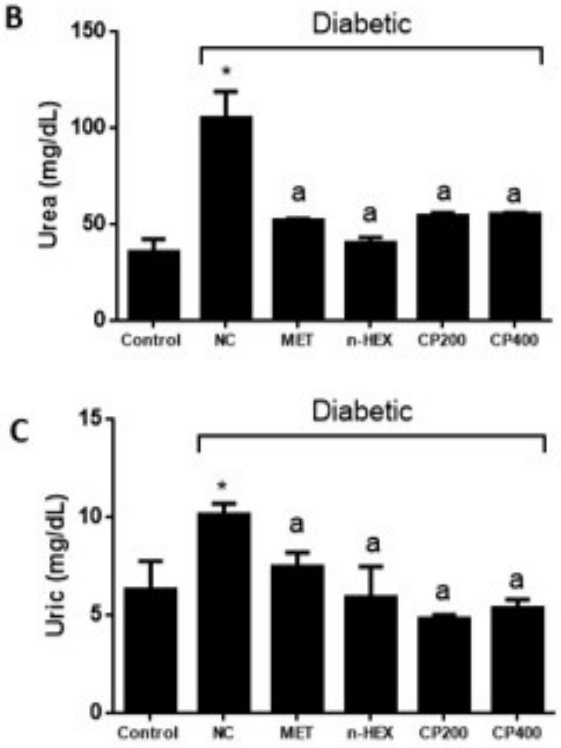


Fig 2. Effect of extract and fractions of *C. papaya* leaf on kidney function, Creatinine (A), Urea (B), Uric (C). *: $p \leq 0.05$ vs. normal control; a: $p \leq 0.05$ vs. STZ control. NC = Negative Control. MET = Metformin. n-HEX = 400 mg/kg of n-Hexane fractions. CP200 = Aqueous extract of 200mg/Kg *Carica papaya*. CP400 = Aqueous extract of 400mg/Kg *Carica papaya*.



As presented in Fig 3, STZ-induced diabetic rats showed significant oxidative stress, characterized by reduced activities of antioxidant enzymes SOD (53.30 ± 1.44 u/mL) and CAT (33.95 ± 1.08 u/mg protein), along with marked depletion of GSH (1.36 ± 0.14 mM) and elevated MDA levels (21.48 ± 0.86 µM) compared with the normal control ($p \leq 0.05$). Treatment with metformin significantly improved antioxidant defense, with increased SOD (63.78 ± 0.84 u/mL), CAT (39.81 ± 0.68 u/mg protein), and GSH (6.54 ± 0.54 mM), alongside a marked reduction in MDA (6.80 ± 0.17 µM) relative to the STZ control ($p \leq 0.05$). The n-hexane fraction (400 mg/kg) demonstrated the most pronounced antioxidant effect, with significant increases in SOD (65.00 ± 1.57 u/mL), CAT (45.67 ± 0.60 u/mg protein), and GSH (9.57 ± 0.87 mM), accompanied by a reduction in MDA (7.00 ± 0.62 µM) compared with the STZ group ($p \leq 0.05$). The aqueous fraction at 200 mg/kg produced moderate improvements in SOD (57.72 ± 0.29 u/mL), CAT (36.45 ± 0.85 u/mg protein), and GSH (3.85 ± 0.32 mM), with partial reduction of MDA (12.44 ± 0.30 µM), though values

remained significantly different from the normal control ($p \leq 0.05$). The aqueous fraction at 400 mg/kg also improved SOD (62.07 ± 0.62 u/mL), CAT (38.08 ± 0.21 u/mg protein), and GSH (4.85 ± 0.34 mM), with a corresponding decrease in MDA (13.74 ± 0.88 µM), but the effect was less pronounced than the n-hexane fraction.

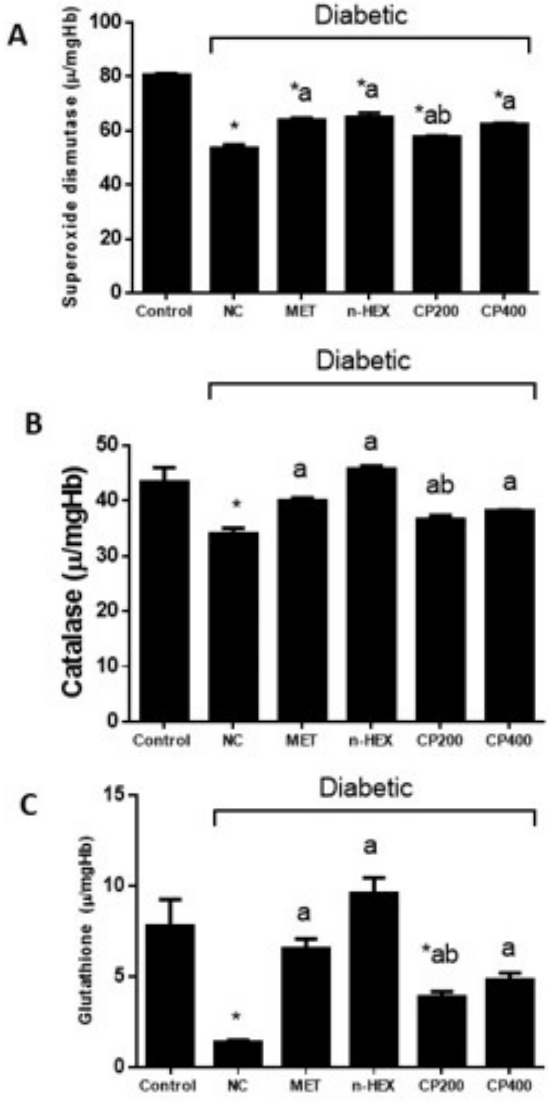
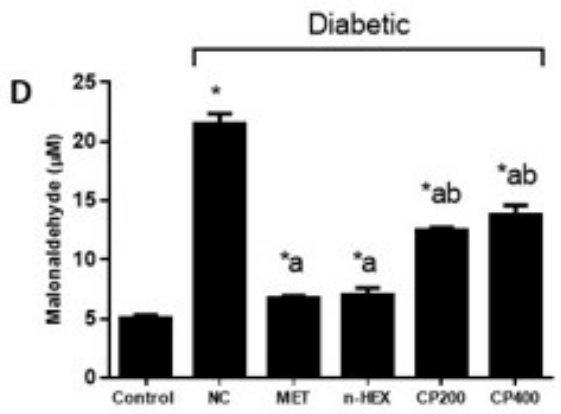


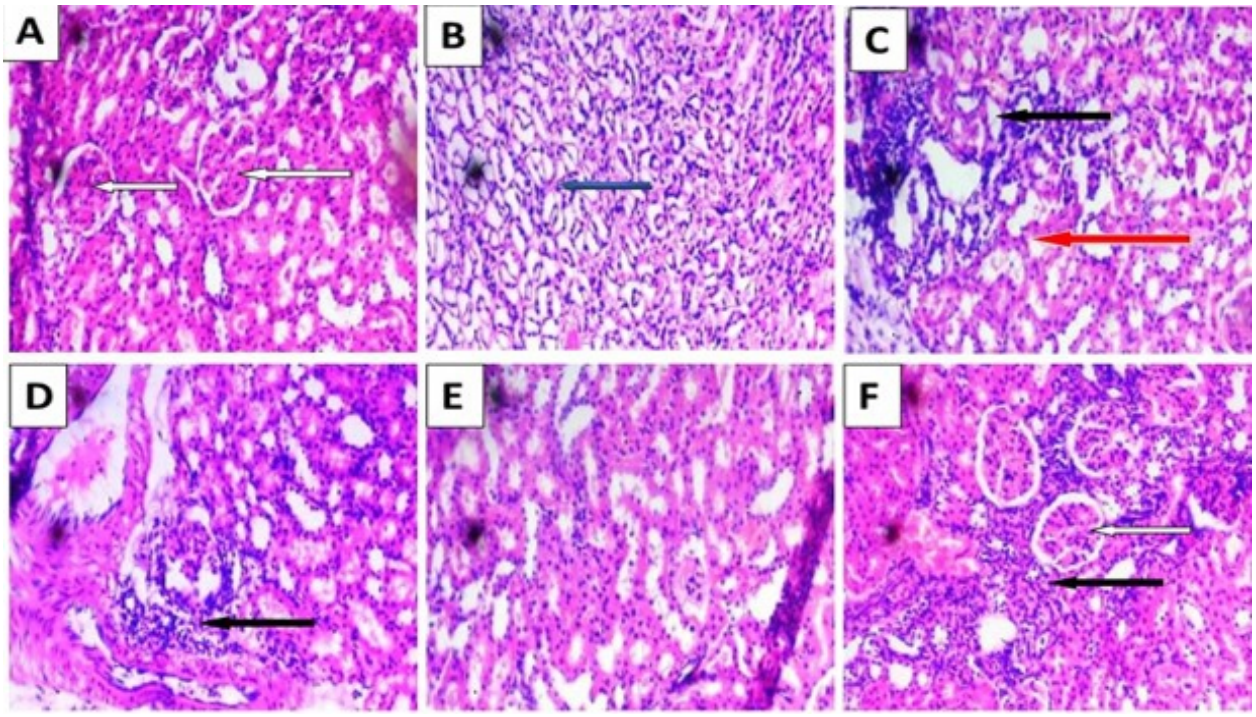
Fig 3. Effect of extract and fractions of *C. papaya* leaf on antioxidant parameters. Superoxide dismutase (A), Catalase (B), Reduced Glutathione (C), Malondialdehyde (D).

*: $p \leq 0.05$ vs. normal control; a: $p \leq 0.05$ vs. STZ control; b: $p \leq 0.05$ vs. normal control. NC = Negative Control. MET = Metformin. n-HEX = 400 mg/kg of n-Hexane fractions. CP200 = Aqueous extract of 200mg/Kg *Carica papaya*. CP400 = Aqueous extract of 400mg/Kg *Carica papaya*.



Histological examination revealed that control rats had normal renal architecture with intact glomeruli, renal tubules, and interstitial spaces. Untreated diabetic rats, however, showed severe renal damage characterized by glomerular degeneration and necrosis, tubular collapse and necrosis, and chronic inflammatory infiltration. Treatment with metformin largely restored renal structure, with normal glomeruli and tubules, though mild inflammatory infiltration and moderate tubular desquamation persisted. The 400 mg/kg n-hexane fraction provided partial protection, preserving glomeruli but showing tubular degeneration with vacuolation, epithelial hyperplasia, and moderate interstitial inflammation. The 200 mg/kg aqueous *Carica papaya* offered mild nephroprotection, with mostly normal glomeruli and tubules but some peripheral infiltrates and degeneration, while the 400 mg/kg aqueous *Carica papaya* demonstrated mesangial hyperplasia, epithelial desquamation, and focal moderate-to-severe inflammatory infiltration, indicating dose-dependent but incomplete renal protection.

Fig 3. Effect of extract and fractions of *C. papaya* leaf on antioxidant parameters. Superoxide dismutase (A), Catalase (B), Reduced Glutathione (C), Malondialdehyde (D)Fig 4. Photomicrograph section of kidney tissue from a representative Wistar rat; stained using hematoxylin and eosin (H & E) staining technique; using a magnification of 100× objective. Plate A (Control): Normal glomeruli and tubules with mild vascular congestion, no inflammatory infiltrates. Plate B (STZ): Severely distorted renal architecture with glomerular degeneration and necrosis, tubular collapse with severe necrosis, and chronic interstitial



inflammation. Plate C (STZ + Metformin): Renal cortex with normal glomeruli and tubules, mild interstitial inflammation, and moderate collecting tubule desquamation. Plate D (STZ + n-Hexane): Renal cortex with abnormal glomeruli, preserved tubules, and severe interstitial inflammatory infiltration. Plate E (STZ + Aq. 200mg/kg CP): Renal cortex with mostly normal glomeruli showing mild peripheral infiltrates and focal degeneration, intact tubules, and normal interstitium. Plate E (STZ + Aq. 400mg/kg CP): Renal cortex with glomerular mesangial hyperplasia, intact and desquamated tubules, and focal moderate to severe interstitial inflammation.

Discussion

The present study evaluated the renoprotective potential of aqueous extract and solvent fractions of *Carica papaya* leaves in streptozotocin (STZ)-induced diabetic Wistar rats, with emphasis on glycemic control, renal function, oxidative stress biomarkers, and histopathological alterations. The findings demonstrated that both the crude aqueous extract and solvent fractions significantly improved glycemic regulation, ameliorated oxidative stress, and preserved renal architecture, with varying degrees of efficacy across treatment groups. These results are consistent with the primary hypothesis that *Carica papaya* exerts nephroprotective effects through antioxidant and anti-inflammatory mechanisms, yet they also raise important questions when compared with prior literature.

With respect to glycemic control, the reduction in fasting blood glucose levels observed in rats treated with the crude extract and fractions corroborates earlier findings that *Carica papaya* leaf extract possesses hypoglycemic activity. Supporting studies by Juarez-Rojop et al.[23], Jimoh-Abdulghaffaar et al.[24], and Igbashio et al.[25] reported significant reductions in hyperglycemia in STZ-induced diabetic rats treated with papaya leaf extract, attributing this to the presence of flavonoids and alkaloids that enhance glucose uptake and insulin sensitivity. However, contrasting evidence exists: Solikhah et al.[26] found minimal to no hypoglycemic effect of *Carica papaya* in similar diabetic models, suggesting that differences in extraction method, dosage, or phytochemical profile might account for the discrepancies. For example, ethanolic extracts tend to yield more potent hypoglycemic effects compared to aqueous extracts, and regional variation in plant phytochemistry can influence outcomes.

Improvements in body weight among treated diabetic rats in this study further suggest a reversal of catabolic processes associated with insulin

deficiency. This aligns with the findings of Ezekwe et al.[27] and Venkateshwarlu et al.[28], who reported improved weight profiles following papaya leaf treatment. In contrast, Ezekwe et al.[29] demonstrated no significant impact of papaya extract on body weight, highlighting variability in responses. The differences may arise from treatment duration and the severity of diabetes induction.

Regarding insulin secretion and β-cell protection, the improvement in insulin levels among Carica papaya aqueous extract-treated rats indicates a possible protective effect against STZ-induced pancreatic toxicity. This is in line with the studies by Nxumalo et al.[17], Miranda-Osorio et al.[30], and Airaodion et al.[31], which documented β-cell regeneration and restoration of insulin secretion with papaya treatment. Conversely, studies by Ezekwe & Chikezie[29] and Omonkhua[32] did not observe such protective effects, attributing the discrepancy to the irreversible β-cell destruction induced by high-dose STZ. These opposing findings suggest that the extent of β-cell protection by papaya may depend on the severity of pancreatic damage and treatment initiation relative to disease onset.

Analysis of renal function biomarkers revealed significant reductions in serum creatinine, urea, and uric acid in papaya-treated groups, indicating improved renal clearance and reduced nephropathy. This outcome may be attributed to nephroprotective phytochemicals such as flavonoids, particularly quercetin in *Carica papaya*, which exert antioxidant effects, reduce lipid peroxidation, and preserve glomerular integrity. These findings are supported by comparable studies from Madinah et al.[33] and Igbinovia et al.[34], which demonstrated amelioration of renal dysfunction following papaya extract administration. On the contrary, Orororo et al.[35] and Rahman et al.[36] reported no significant nephroprotective effect in their models, which could be attributed to differences in dose regimen or renal insult severity. Such inconsistencies highlight the need for standardized dosing and extraction protocols to determine reproducibility and clinical relevance.

Antioxidant defense and oxidative stress markers provided further insights into the mechanism of action. Treatment with papaya extracts enhanced antioxidant enzymes (SOD, CAT, GSH) and reduced lipid peroxidation marker MDA, consistent with studies by Luiz et al.[37], El-Nekeety et al.[38] and Orororo et al.[35], which attributed these effects to flavonoids, phenols, and vitamins present in papaya leaves. This effect may be attributed to flavonoids such as quercetin, which scavenge free radicals, upregulate endogenous antioxidant defenses, and inhibit membrane lipid peroxidation. In contradiction, Anjum et al.[39] reported no significant modulation of antioxidant enzymes following papaya administration despite amelioration of oxidative stress level. This difference in outcome could be aligned to extract potency and phytochemical bioavailability. Variability in extraction solvents and plant maturity at harvest may explain such divergent results.

Histopathological findings in this study revealed severe renal damage in untreated diabetic rats, including tubular necrosis, glomerular degeneration, and chronic inflammatory infiltration. Conversely, papaya-treated rats exhibited markedly preserved renal architecture, ranging from normal glomeruli and tubules to moderate epithelial desquamation and inflammatory cell infiltration, depending on dose and fraction. These results support prior reports by Ukwa et al.[40] and Saad et al.[41] who observed structural renal protection with papaya therapy. The preservation observed in this study may be attributed to quercetin and other bioactive flavonoids in papaya, which stabilize cellular membranes, suppress inflammatory responses, and attenuate histopathological damage in renal tissues.

Despite the encouraging outcomes, this study has limitations. First, the focus was limited to biochemical and histological markers without exploring detailed molecular mechanisms such as gene expression or signaling pathways involved in oxidative stress modulation. Second, the experimental period may not fully capture the long-term effects of papaya treatment on chronic diabetic nephropathy. Third, variations in phytochemical content due to plant source, maturity, and extraction methods pose challenges for reproducibility and translation to human studies. Future investigations should incorporate molecular studies, standardized phytochemical profiling, and controlled clinical trials to confirm translational relevance.

Conclusion

The present study demonstrates that *Carica papaya* leaf extract and fractions exert significant nephroprotective effects in STZ-induced diabetic rats, manifested through glycemic regulation, restoration of renal function, antioxidant defense enhancement, and preservation of renal histoarchitecture. While these findings align with several supportive studies, discrepancies with opposing reports underscore the need for standardized methodologies and further mechanistic research. Collectively, these results reinforce the potential of *Carica papaya* as a complementary therapeutic agent for managing diabetic nephropathy, albeit with cautious optimism until validated by human clinical studies.

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Conflict of interest: The authors declare that they have no conflict of interests.

Authors' contributions: Conceptualization: Egesie G; Data curation: Adebayo OF; Formal analysis: Egesie G and Odeh OS; Funding acquisition: Adebayo OF; 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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