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Research Article

Phytochemical Profiling and Antidiabetic Potential of Aqueous Fruit Extract of *Carissa carandas* in Streptozotocin-Induced Diabetic Rats: Evaluation of Hepato-Renal Biomarkers

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Abstract

The present study aimed to evaluate the antidiabetic and hepato-renal protective potential of an aqueous fruit extract of *Carissa carandas* in streptozotocin (STZ)-induced diabetic rats. Diabetes was induced using STZ, and experimental animals were treated with graded doses of the extract or glibenclamide as a standard drug. Both acute and sub-chronic studies were conducted to assess fasting blood glucose levels, body weight, liver function enzymes (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), and renal function markers (urea, uric acid, and creatinine). Diabetic control rats exhibited a significant elevation in fasting blood glucose levels compared to normal controls. Acute administration of *C. carandas* extract produced a significant time-dependent antihyperglycemic effect, with maximal activity observed at the 5th hour post-treatment. Among the tested doses, 1000 mg/kg body weight demonstrated the highest efficacy. In the sub-chronic study, 21-day administration of the extract significantly reduced fasting blood glucose levels in diabetic rats, bringing them closer to near-normal values, comparable to glibenclamide treatment. The extract also exhibited mild hypoglycemic activity in normoglycemic rats. Furthermore, treatment effectively prevented diabetes-induced body weight loss. STZ-induced diabetes resulted in significant elevations in hepatic (AST, ALT) and renal biomarkers (urea, uric acid, and creatinine), indicating organ dysfunction. Treatment with *C. carandas* extract significantly normalized these altered biochemical parameters, with effects comparable to the standard drug. Overall, the findings demonstrate that the aqueous fruit extract of *Carissa carandas* possesses potent antihyperglycemic activity and provides significant hepato-renal protection in experimental diabetes, suggesting its potential as a promising therapeutic agent for the management of diabetes and its associated complications.

Keywords: *Carissa carandas*, Aqueous fruit extract, STZ-induced diabetes, Antihyperglycemic activity, Hepato-renal biomarkers

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Introduction

Diabetes mellitus is a multifactorial metabolic disease characterized by persistent elevation of blood glucose levels resulting from inadequate insulin secretion, impaired insulin action, or a combination of both factors. Over the past few decades, the incidence and prevalence of diabetes have increased dramatically across both developed and developing countries, making it one of the most serious global health concerns (1, 2). Prolonged hyperglycaemia is associated with disturbances in carbohydrate, lipid, and protein metabolism, which ultimately lead to structural and functional damage in several organs. Among the organs most affected are the liver and kidneys, where chronic diabetic complications frequently manifest as hepatopathy and nephropathy (3, 4).

Streptozotocin (STZ)-induced diabetes in experimental rodents is widely employed as a reliable model for studying the pathogenesis of diabetes and evaluating the efficacy of potential antidiabetic agents. This model reproduces several characteristic features of human diabetes, including sustained hyperglycaemia, reduction in body weight, and impairment of hepatic and renal functions (5, 6). The liver is a key organ involved in maintaining glucose

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metabolism, and diabetes-related hepatic dysfunction is often accompanied by increased serum activities of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) (7). Similarly, diabetic nephropathy is associated with alterations in renal function markers such as urea, uric acid, and creatinine, which are commonly used to assess the extent of kidney damage and functional impairment in diabetic conditions (4, 8).

Despite the availability of several synthetic antidiabetic agents, long-term therapy is often associated with adverse effects and limited efficacy in preventing secondary complications. Therefore, there is a growing interest in the exploration of plant-based therapeutic agents that are effective, safe, and economically viable for long-term management of diabetes (9, 10). Medicinal plants rich in bioactive phytoconstituents such as flavonoids, phenolics, and alkaloids have been extensively reported to exhibit significant antihyperglycemic, antioxidant, and organ-protective properties in experimental models of diabetes (11, 10).

Carissa carandas L. (family: Apocynaceae) is an important medicinal plant widely used in traditional South Asian medicine for the treatment of diabetes, liver disorders, and renal ailments. Previous phytochemical and pharmacological studies have demonstrated that *C. carandas* fruits are rich in phenolics, flavonoids, and other bioactive compounds with notable antioxidant and antidiabetic potential (12, 13). However, comprehensive experimental evidence evaluating its antihyperglycemic efficacy along with hepato-renal protective effects in STZ-induced diabetic models remains limited.

Therefore, the present study was designed to systematically evaluate the antidiabetic efficacy and hepato-renal protective potential of the aqueous fruit extract of *Carissa carandas* in streptozotocin-induced diabetic rats. The study specifically aimed to assess its effects on fasting blood glucose levels, body weight, and key biochemical markers of liver and kidney function, including AST, ALT, urea, uric acid, and creatinine.

Materials and Methods

Experimental Animals

Male Wistar albino rats (aged 3–4 months; body weight 180–200 g) were used for the present study. The animals were maintained under standard laboratory conditions, with free access to a standard pellet diet and water ad libitum. They were housed in clean, dry polypropylene cages under a well-ventilated environment with a controlled 12 h light/12 h dark cycle. All experimental procedures were conducted between 08:00 and 10:00 h to minimize circadian variations.

Ethical Approval

All experimental protocols were reviewed and approved by the Institutional Animal Ethics Committee (IAEC) of Dravidian University, Andhra Pradesh, India (Approval No.: DU/IAEC/SRR/0003/2022). All procedures were carried out in accordance with standard ethical guidelines for the care and use of laboratory animals

Chemicals

Streptozotocin (STZ) was procured from Sigma-Aldrich (St. Louis, MO, USA). All other chemicals and reagents used in the study were of analytical grade and obtained from standard suppliers including SRL, Merck, SD Fine, and HiMedia (India). Organic solvents of the highest purity were used throughout the study. Glibenclamide, a standard oral hypoglycemic agent, was procured from a licensed local pharmacy.

Collection and Authentication of Plant Material

Fresh fruits of *Carissa carandas* were collected from the Mosali Madugu forest area, Chittoor District, Andhra Pradesh, India, during the fruiting season (September–October). The plant material was taxonomically identified, and a voucher specimen was deposited in the herbarium of the Department of Biotechnology, Dravidian University, Kuppam, for future reference. The collected fruits were washed, shade-dried at room temperature, and coarsely powdered using a mechanical grinder.

Preparation of Aqueous Extract

The dried fruit powder (500 g) of *Carissa carandas* was subjected to aqueous extraction using distilled water in a 1:4 (w/v) ratio. The extraction was carried out in successive stages to ensure maximum recovery of phytoconstituents. The extract was filtered through muslin cloth followed by Whatman No. 1 filter paper to remove particulate matter.

The filtrate was then concentrated under reduced pressure using a rotary evaporator to remove excess solvent. The concentrated extract was further dried in a hot air oven at 60°C for 10–12 hours to obtain a semi-solid crude extract. The dried extract was collected, weighed, and stored in an airtight container at 4°C until further use**.**

Induction of Diabetes

Experimental diabetes was induced in overnight-fasted (12–15 h) male Wistar albino rats (180–200 g) by a single intraperitoneal injection of freshly prepared streptozotocin (STZ) at a dose of 45 mg/kg body weight. STZ was dissolved in ice-cold 0.1 M citrate buffer (pH 4.5) immediately before administration **(14)**. Since STZ can induce acute hypoglycemia due to rapid pancreatic β-cell destruction and subsequent insulin release, the animals were provided with 15% glucose solution for 24 h after 8 h of STZ administration to prevent hypoglycemic shock. Diabetes was confirmed 48 h after STZ injection by measuring fasting blood glucose levels. After one week, when stable hyperglycemia was established, rats with fasting blood glucose levels ≥ 250 mg/dL were considered diabetic and selected for further experimental studies.

Phytochemical Screening of Aqueous Extract

Preliminary phytochemical screening of the aqueous extract of *Carissa carandas* was carried out using standard qualitative methods to identify major classes of bioactive constituents.

The phytochemical screening was limited to major classes of secondary metabolites that are commonly reported in *Carissa carandas* and are relevant to its biological activity. Detailed phytochemical characterization using advanced analytical techniques was beyond the scope of the present study. The following tests were performed:

Saponins: Frothing test

Tannins: Ferric chloride ($FeCl_3$) test

Flavonoids: Shinoda test

Alkaloids: Standard acid–base test

Triterpenes: Sulfuric acid test

These tests were conducted to qualitatively assess the presence of major phytochemical groups in the extract.

Detailed Phytochemical Analysis of Aqueous Extract

Qualitative phytochemical analysis of the aqueous fruit extract of *Carissa carandas* was carried out using standard procedures as described below:

1. Test for Saponins (Frothing Test): Approximately 300 mg of the plant extract was mixed with 5 mL of distilled water and boiled for 2 minutes. The mixture was cooled and vigorously shaken for 3 minutes. The formation of a stable froth indicated the presence of saponins.

2. Test for Tannins (Ferric Chloride Test): To 1 mL of the extract, 1 mL of 0.008 M potassium ferricyanide and 1 mL of 0.02 M ferric chloride ($FeCl_3$) in 0.1 N hydrochloric acid were added. The development of a blue or green coloration indicated the presence of tannins.

3. Test for Triterpenes: About 300 mg of the extract was dissolved in 5 mL of chloroform and heated at 80°C for 30 minutes. After cooling, a few drops of concentrated sulfuric acid (H_2SO_4) were added carefully. The appearance of a reddish-brown coloration indicated the presence of triterpenes.

4. Test for Alkaloids: Approximately 300 mg of the extract was treated with 2 M hydrochloric acid and filtered. The acidic filtrate was then mixed with amyl alcohol. The formation of a colored layer indicated the presence of alkaloids.

5. Test for Flavonoids (Shinoda Test): To 1 mL of the extract, 8–10 drops of concentrated hydrochloric acid (HCl) and a small quantity of magnesium powder were added. The mixture was heated for 10–15 minutes and then cooled. The development of a pink or red coloration indicated the presence of flavonoids.

Acute Toxicity Study

An acute toxicity study was conducted to evaluate the safety profile of the aqueous fruit extract of *Carissa carandas*. The animals were fasted overnight (12 h) prior to the experiment and randomly divided into four groups, each consisting of three rats. The test groups received the extract orally at doses of 500, 1000, and 1500 mg/kg body weight, respectively, while the control group received an equivalent volume of distilled water. Following administration, the animals were allowed free access to food and water. All animals were closely observed for 24 hours for any signs of acute toxicity, including behavioral changes such as irritation, restlessness, respiratory distress, abnormal locomotion, and catalepsy. Mortality, if any, was recorded during the observation period.

Acute Antidiabetic Study (Determination of Effective Dose)

A total of 24 Wistar albino rats were used and divided into two batches (n = 12 each): diabetic and normal.

Batch I (Diabetic Rats):

Diabetes was induced by a single intraperitoneal injection of streptozotocin (STZ), as described earlier. The diabetic rats were further divided into four groups (n = 3 per group):

Group I (DC): Diabetic control rats received distilled water orally

Group II (Cc-500): Diabetic rats treated with *C. carandas* extract (500 mg/kg body weight)

Group III (Cc-1000): Diabetic rats treated with *C. carandas* extract (1000 mg/kg body weight)

Group IV (Cc-1500): Diabetic rats treated with *C. carandas* extract (1500 mg/kg body weight)

Batch II (Normal Rats):

Normal (non-diabetic) rats were also divided into four groups (n = 3 per group) following the same treatment protocol as Batch I, except that diabetes was not induced.

Assessment of Antidiabetic Activity

The acute antihyperglycemic effect of the extract was evaluated after a single oral administration. Fasting blood glucose (FBG) levels were measured at 0 (baseline), 1, 3, and 5 hours post-treatment in both normal and diabetic rats.

Sub-Chronic Study (21-Day Treatment Protocol)

For the sub-chronic study, experimental animals were randomly divided into five groups, each consisting of six rats (n = 6):

Group I (Normal Control, NC): Normal rats administered normal saline (0.9%, p.o.) once daily for 21 days

Group II (Diabetic Control, DC): Streptozotocin-induced diabetic rats administered normal saline (0.9%, p.o.) once daily for 21 days

Group III (D + Cc1000): Diabetic rats treated with aqueous fruit extract of Carissa carandas (1000 mg/kg body weight, p.o.) once daily for 21 days

Group IV (N + Cc1000): Normal rats treated with aqueous fruit extract of Carissa carandas (1000 mg/kg body weight, p.o.) once daily for 21 days

Group V (D + Glb): Diabetic rats treated with glibenclamide (10 mg/kg body weight, p.o.) once daily for 21 days

Biochemical Analysis of Serum Parameters

Blood samples were collected in EDTA-coated tubes, and serum was separated immediately by centrifugation. The serum samples were stored at −20°C until further biochemical analysis.

Estimation of Blood Glucose

Fasting blood glucose levels were measured using dextrostix based on the glucose oxidase–peroxidase (GOD–POD) method with a digital glucometer (Accu-Chek, Roche Diagnostics).

Estimation of Serum Urea

Serum urea levels were estimated using the diacetyl monoxime–thiosemicarbazone (DAM–TSC) colorimetric method (**15**). Briefly, serum samples and urea standards were treated with DAM–TSC reagent under acidic conditions and heated in a boiling water bath for color development. After cooling, the absorbance of the pink chromogen was measured at 540 nm against a reagent blank. Urea concentration was calculated using a standard calibration curve and expressed as mg/dL.

Estimation of Serum Uric Acid

Serum uric acid levels were determined by the phosphotungstic acid method (16). Serum samples were treated with phosphotungstic acid reagent in an alkaline medium to produce a blue-colored complex. The absorbance was measured at 660 nm, and uric acid levels were calculated from a standard curve and expressed as mg/dL.

Estimation of Serum Creatinine

Serum creatinine was estimated using Jaffe's colorimetric method (17). Serum samples were reacted with alkaline picrate reagent, and the absorbance of the colored complex was measured at 520 nm. Creatinine concentration was calculated from a standard calibration curve and expressed as mg/dL.

Estimation of Aspartate Aminotransferase (AST)

Serum AST activity was determined by the method of Reitman and Frankel (18). The assay is based on the formation of oxaloacetate, which subsequently reacts to form a colored complex. The absorbance was measured at 540 nm, and enzyme activity was expressed as U/L.

Estimation of Alanine Aminotransferase (ALT)

Serum ALT activity was estimated using the Reitman and Frankel (18) method. The assay is based on the formation of pyruvate, which reacts to form a colored complex. The absorbance was recorded at 540 nm, and enzyme activity was expressed as U/L.

Statistical Analysis

All experimental data were expressed as mean ± standard deviation (SD) (n = 6). Statistical analysis was performed using one-way analysis of variance (ANOVA), followed by Tukey's Honestly Significant Difference (HSD) test and Duncan's Multiple Range Test (DMRT) using SPSS software (version 16.0; SPSS Inc., Chicago, IL, USA). Differences were considered statistically significant at $p < 0.05$ and $p < 0.01$.

Results

Phytochemical Analysis of Aqueous Fruit Extract of *Carissa carandas*

Preliminary phytochemical screening of the aqueous fruit extract of *Carissa carandas* revealed the presence of several important bioactive constituents, including saponins, tannins, triterpenes, alkaloids, and flavonoids.

The qualitative tests demonstrated the formation of characteristic color changes and reactions specific to each phytochemical group. Stable frothing confirmed the presence of saponins, while the development of a blue-colored solution indicated tannins. The appearance of a reddish coloration suggested the presence of triterpenes. Similarly, the formation of a pink-colored layer confirmed alkaloids, and the development of a red coloration indicated the presence of flavonoids. The present phytochemical screening was preliminary in nature and employed one standard qualitative test for each metabolite class. Further confirmation using additional phytochemical tests and advanced analytical methods is recommended in future investigations

These results indicate that the aqueous extract of *Carissa carandas* is rich in diverse phytoconstituents that may contribute to its observed biological activities**.**

Acute Toxicity Study

Oral administration of graded doses of the aqueous extract of *Carissa carandas* (CcAq.e) at 500, 1000, and 1500 mg/kg body weight did not produce any observable signs of toxicity in normal healthy rats. No behavioral abnormalities, including irritation, restlessness, respiratory distress, abnormal locomotion, or catalepsy, were observed during the 24-hour monitoring period.

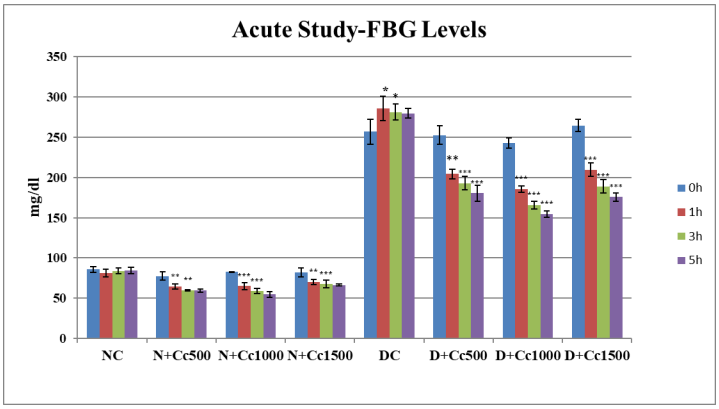
Furthermore, no mortality or lethality was recorded in any of the treated groups throughout the study duration. These findings indicate that the aqueous extract of *Carissa carandas* is safe and non-toxic at the tested dose levels.

Table 1: Qualitative Phytochemical Analysis of *Carissa carandas* Extract

S. No.	Phytochemical Test	Observation	Inference
1	Saponins (Frothing test)	Stable froth formation	Present
2	Tannins ($FeCl_3$ test)	Blue coloration	Present
3	Triterpenes	Reddish coloration	Present
4	Alkaloids	Pink-colored layer formation	Present
5	Flavonoids (Shinoda test)	Red coloration	Present

Acute Antidiabetic Activity of *Carissa carandas* Extract

Figure 1: Dose-dependent effect of oral administration of aqueous extract of *Carissa carandas* on fasting blood glucose levels in normal and streptozotocin-induced diabetic rats. Each bar represents mean ± standard deviation (SD) (n = 3). Statistical significance was determined relative to the corresponding zero-time value; *P≤0.05, **P≤0.01 ***P≤0.001



The effect of graded doses of *Carissa carandas* aqueous extract on fasting blood glucose (FBG) levels in both normal and streptozotocin-induced diabetic rats is presented in Figure 1. The diabetic control (DC) group exhibited significantly elevated fasting blood glucose levels compared to the normal control group. In contrast, treatment with *C. carandas* extract produced a significant, time-dependent reduction in blood glucose levels in diabetic rats over the study period.

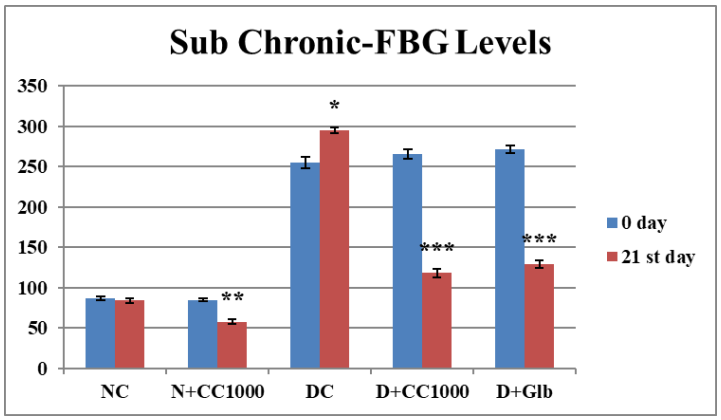
The antihyperglycemic effect was evident as early as 1-hour post-administration and reached a maximum at the 5th hour. At the 5th hour, all tested doses (500, 1000, and 1500 mg/kg body weight) significantly ($p < 0.01$) reduced blood glucose levels compared to the diabetic control group. Among these, the 1000 mg/kg dose exhibited the most pronounced antihyperglycemic effect ($p < 0.001$), reducing blood glucose levels from 242.66 ± 6.11 mg/dL to 154.66 ± 4.04 mg/dL.

In contrast, the diabetic control group, which received only distilled water, showed no significant reduction in fasting blood glucose levels throughout the observation period. In normoglycemic rats, administration of the extract also resulted in a significant reduction in blood glucose levels, indicating mild hypoglycemic activity. Notably, the 1000 mg/kg dose produced the maximum hypoglycemic effect at the 5th hour (54.66 ± 3.21 mg/dL), compared to the other tested doses.

Overall, the results demonstrate that *Carissa carandas* extract exhibits a significant dose-dependent antihyperglycemic effect, with the 1000 mg/kg dose showing optimal efficacy.

Effect of *Carissa carandas* on Fasting Blood Glucose Levels (Sub-Chronic Study)

Figure 2: Effect of oral administration of aqueous extract of *Carissa carandas* on fasting blood glucose levels in normal and streptozotocin-induced diabetic rats during the 21-day treatment period. Each bar represents mean ± standard deviation (SD). Statistical significance was determined relative to the corresponding zero-time value; *P≤0.05, **P≤0.01 ***P≤0.001



The effect of *Carissa carandas* aqueous extract (1000 mg/kg body weight) on fasting blood glucose levels in normal and streptozotocin-induced diabetic rats over a 21-day treatment period is presented in Figure 2.

Streptozotocin-induced diabetic rats exhibited a sustained and significant elevation in blood glucose levels throughout the experimental period compared to normal control rats, confirming the establishment of persistent hyperglycemia.

Treatment with *C. carandas* extract resulted in a significant reduction in fasting blood glucose levels in diabetic rats. The antihyperglycemic effect observed was comparable to that of the standard drug glibenclamide.

In addition, administration of the extract to normal rats resulted in a moderate but significant reduction in blood glucose levels, indicating mild hypoglycemic activity.

Overall, these findings demonstrate that *Carissa carandas* exhibits both antihyperglycemic activity in diabetic rats and hypoglycemic activity in normoglycemic rats, highlighting its potential role in glucose regulation.

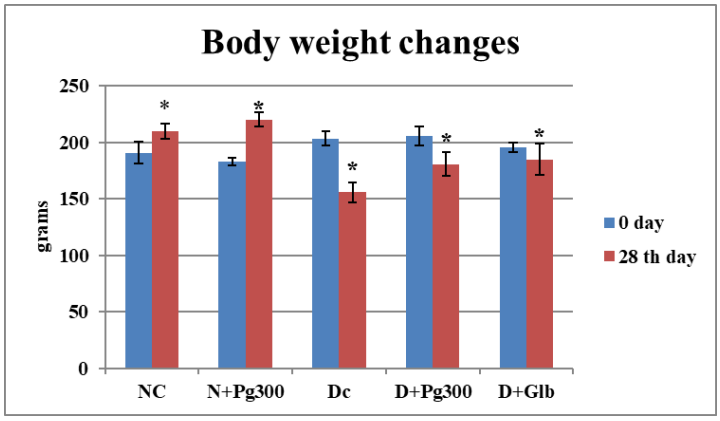
In the present study, streptozotocin-induced diabetic rats exhibited a significant decrease in body weight during the experimental period ($p < 0.01$) compared to normal control rats.

However, treatment with the aqueous extract of *Carissa carandas* for 21 days effectively prevented this body weight loss in diabetic rats, with treated animals showing a significant improvement in body weight compared to the diabetic control group (Figure 3).

In contrast, normal rats treated with *C. carandas* extract did not show any significant changes in body weight throughout the study period, indicating that the extract does not adversely affect normal growth.

Effect of *Carissa carandas* on Body Weight

Figure 3: Effect of oral administration of aqueous extract of *Carissa carandas* on body weight changes in normal and streptozotocin-induced diabetic rats during the 21-day treatment period. Each bar represents mean ± standard deviation (SD). Statistical significance was determined relative to the corresponding zero-day value; *P≤0.01



Effect of *Carissa carandas* on Renal Function Markers

Serum Urea, Uric Acid, and Creatinine

Streptozotocin-induced diabetic rats exhibited a significant elevation in renal function markers, including serum urea, uric acid, and creatinine levels, compared to normal control rats, indicating impaired kidney function.

Treatment with aqueous extract of *Carissa carandas* (1000 mg/kg body weight) for 21 days significantly ameliorated these alterations and restored the levels toward near-normal values, comparable to the standard drug glibenclamide.

Specifically, serum urea levels were markedly increased in diabetic rats compared to normal controls and were significantly reduced following *C. carandas* treatment, similar to glibenclamide-treated rats (Figure 4).

Similarly, serum uric acid levels were significantly elevated in diabetic rats compared to normal controls. Treatment with *C. carandas* extract significantly reduced uric acid levels, approaching normal values and comparable to glibenclamide (Figure 5).

Serum creatinine levels were also significantly increased in diabetic rats compared to normal controls. Administration of *C. carandas* extract significantly reduced creatinine levels, with effects comparable to glibenclamide treatment (Figure 6).

Overall, these findings indicate that *Carissa carandas* extract exerts a protective effect against diabetes-induced renal dysfunction.

Effect of *Carissa carandas* on Liver Function Markers

Serum AST and ALT Activities

Streptozotocin-induced diabetic rats showed a significant increase in liver function enzymes, including aspartate aminotransferase (AST) and alanine aminotransferase (ALT), compared to normal control rats, indicating hepatic damage.

The activity of AST was significantly elevated in diabetic rats (105.83 ± 3.06 U/L) compared to normal controls (73.50 ± 3.56 U/L). Treatment with *C. carandas* extract for 21 days significantly

reduced AST levels (78.50 ± 1.04 U/L), which was comparable to glibenclamide-treated rats (76.00 ± 1.26 U/L) (Figure 7).

A similar trend was observed for ALT activity, where elevated enzyme levels in diabetic rats were significantly reduced following treatment with *C. carandas* extract (Figure 8).

These results demonstrate that *Carissa carandas* effectively attenuates diabetes-induced hepatic injury and restores liver function.

Figure 4. Effect of oral administration of aqueous extract of *Carissa carandas* on serum urea levels in normal and streptozotocin-induced diabetic rats. Each bar represents mean ± SD (n = 6). Bars sharing the same letter are not significantly different at $p < 0.01$.

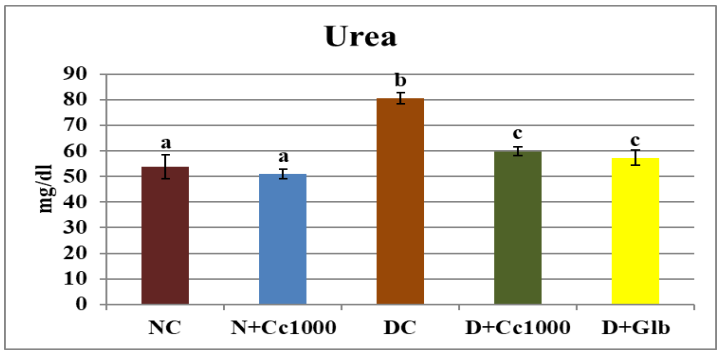


Figure 5: Effect of oral administration of aqueous extract of *Carissa carandas* on serum uric acid levels in normal and streptozotocin-induced diabetic rats. Each bar represents mean ± SD (n = 6). Bars sharing the same letter are not significantly different at p < 0.01.

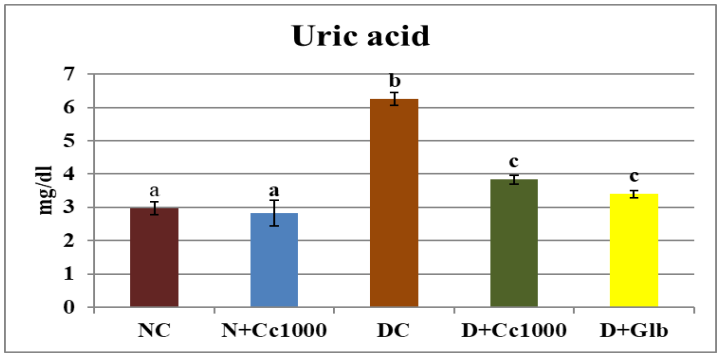


Figure 6:. Effect of oral administration of aqueous extract of *Carissa carandas* on serum creatinine levels in normal and streptozotocin-induced diabetic rats. Each bar represents mean ± SD (n = 6). Bars sharing the same letter are not significantly different at p < 0.01.

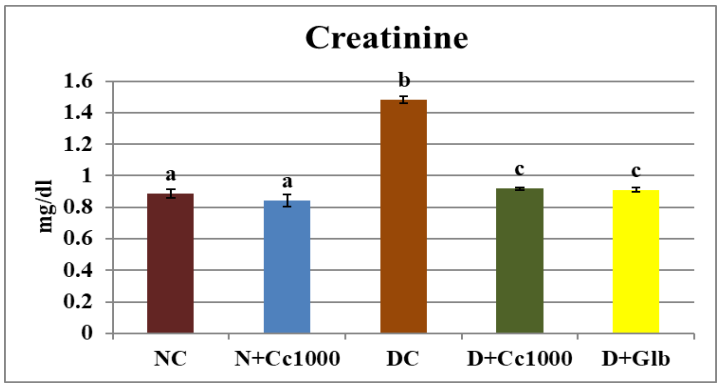


Figure 7: Effect of oral administration of aqueous extract of Carissa carandas on serum AST activity in normal and streptozotocin-induced diabetic rats. Each bar represents mean ± SD (n = 6). Bars sharing the same letter are not significantly different at p < 0.01.

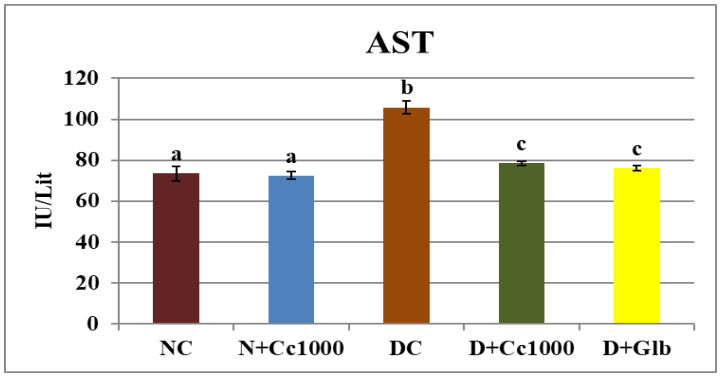
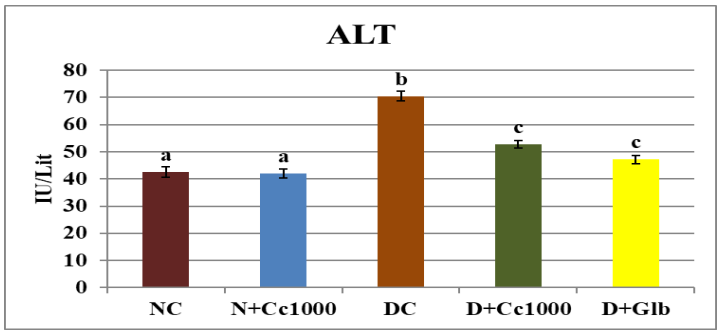


Figure 8: Effect of oral administration of aqueous extract of Carissa carandas on serum ALT activity in normal and streptozotocin-induced diabetic rats. Each bar represents mean ± standard error (SE) (n = 6). Bars sharing the same letter are not significantly different at p < 0.01.



Discussion

The fundamental mechanism underlying hyperglycemia in diabetes mellitus involves excessive hepatic glucose production through glycogenolysis and gluconeogenesis, along with reduced peripheral utilization of glucose (19). The results of the present study confirm that administration of the aqueous fruit extract of *Carissa carandas* exhibits significant antidiabetic activity in streptozotocin (STZ)-induced diabetic rats.

The observed antihyperglycemic effect may be attributed to insulin-like activity of the extract, possibly through enhanced peripheral glucose uptake, stimulation of residual pancreatic β-cells, or inhibition of hepatic gluconeogenesis. Glibenclamide, a sulfonylurea drug, is effective in moderate diabetic conditions by stimulating insulin secretion from functional β-cells but becomes less effective in severe diabetes where β-cell destruction is extensive (20).

Medicinal plants are gaining increasing attention as potential sources of bioactive compounds for diabetes management due to their efficacy and safety.

Despite the availability of several therapeutic options for diabetes management, there remains a need for agents capable of controlling hyperglycaemia while simultaneously protecting against diabetes-associated complications. Chronic diabetic conditions are frequently accompanied by pathological changes such as nephropathy, hepatic dysfunction, oxidative stress, and disturbances in lipid metabolism, which contribute significantly to

disease progression and morbidity. The streptozotocin (STZ)-induced diabetic rat model employed in the present investigation closely mimics several metabolic and pathological features observed in human diabetes, including renal enlargement, hepatic injury, enhanced oxidative stress, and hypercholesterolemia (21, 22, 23).

The present findings demonstrate that *Carissa carandas* extract (1000 mg/kg body weight) significantly reduces fasting blood glucose levels in diabetic rats. Fasting blood glucose is an important parameter for monitoring diabetes progression (24).

The hypoglycemic and antihyperglycemic effects observed in this study may be attributed to stimulation of residual pancreatic β-cells, regeneration or protection of pancreatic tissue, potentiation of insulin secretion, and enhanced peripheral glucose utilization (25, 26).

Elevated levels of serum urea observed in diabetic rats may be due to increased protein catabolism and altered nitrogen metabolism (27). Alterations in nitrogen homeostasis can lead to increased hepatic urea synthesis and release of nitrogenous waste products into circulation.

Uric acid, an end product of purine metabolism, is often elevated in diabetic conditions and is associated with oxidative stress and increased xanthine oxidase activity (28, 29, 30). Increased serum uric acid levels may result from either enhanced production or reduced excretion (31). Elevated uric acid levels are also linked to increased free radical generation and oxidative stress (32).

Interestingly, uric acid may also act as an antioxidant under certain conditions by preventing oxidative damage to endothelial enzymes (33).

Creatinine, a metabolic byproduct of muscle metabolism, is widely used as a reliable indicator of renal function. Elevated creatinine levels in diabetic rats indicate impaired kidney function (34). In the present study, the reduction of creatinine levels following treatment with *Carissa carandas* extract suggests improved renal function and protective effects against diabetic nephropathy (35).

The kidneys are essential organs responsible for maintaining physiological and metabolic balance through the excretion of nitrogenous waste products, including urea, uric acid, and creatinine. In diabetic conditions, elevated serum concentrations of these biomarkers are commonly regarded as indicators of impaired renal function and progressive kidney damage (36). Such biochemical abnormalities are frequently linked to enhanced oxidative stress, increased lipid peroxidation, and disturbances in normal metabolic processes, all of which contribute to the development of diabetic complications (29, 30).

Aminotransferases such as AST and ALT are key indicators of liver function and hepatocellular integrity. Elevated levels of these enzymes in serum reflect liver damage due to leakage from hepatocytes into the bloodstream (37, 38). Increased AST and ALT levels are also considered predictors of metabolic dysfunction, including diabetes (39).

Consistent with previous reports, streptozotocin-induced diabetic rats in the present study exhibited marked elevations in serum AST and ALT activities, reflecting diabetes-associated hepatic damage. Administration of the aqueous extract of *Carissa carandas* for 21 days significantly lowered the levels of these hepatic enzymes, indicating improvement in liver function and reduced hepatocellular injury. The observed hepatoprotective activity may be associated with the presence of bioactive phytoconstituents possessing antioxidant properties, which could protect hepatocytes from oxidative stress and help maintain cellular membrane integrity (40, 41)

Overall, the findings of the present study indicate that *Carissa carandas* extract exerts significant antihyperglycemic, renoprotective, and hepatoprotective effects in STZ-induced diabetic rats, thereby addressing both primary and secondary complications of diabetes.

Conclusion

The present study demonstrates that the aqueous fruit extract of *Carissa carandas* possesses significant antidiabetic activity in streptozotocin (STZ)-induced diabetic rats. The extract exhibited a clear dose-dependent antihyperglycemic effect, with the 1000 mg/kg body weight dose showing optimal efficacy.

In the sub-chronic model, treatment with *C. carandas* extract significantly reduced fasting blood glucose levels and effectively prevented diabetes-associated body weight loss. The extract also exhibited mild hypoglycemic activity in normoglycemic rats, indicating its glucose-regulatory potential.

Treatment with the aqueous extract of *Carissa carandas* produced significant protective effects on renal function, as demonstrated by the reduction in serum urea, uric acid, and creatinine concentrations toward normal values. In addition, the extract effectively attenuated diabetes-induced elevations in hepatic biomarkers, namely alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The normalization of these biochemical parameters indicates that the extract possesses both renoprotective and hepatoprotective properties, thereby contributing to the overall improvement of organ function in diabetic animals.

Overall, the findings suggest that *Carissa carandas* extract exerts antihyperglycemic, renoprotective, and hepatoprotective effects, comparable to the standard drug glibenclamide. These results highlight its potential as a promising natural therapeutic agent for the management of diabetes and its associated complications. However, further studies are required to elucidate the underlying molecular mechanisms and to establish its clinical applicability.

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