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Long Term Anti-Diabetic, Anti-Hyperlipidaemic and Anti-Atherogenic Effects of *Carica papaya* Leaves in Streptozotocin Diabetic Rats

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Authors' contributions

This work was carried out in collaboration between all authors. Authors OAA and OIO designed the study and wrote the protocol. Author OAA performed the statistical analysis and wrote the first draft of the manuscript. Authors OAA, AAF, ALO and AAR managed the analyses of the study. All authors read and approved the final manuscript.

Research Article

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ABSTRACT

Aim: To evaluate the long term (24 weeks) anti-diabetic, anti-hyperlipidaemic and anti-atherogenic effects of aqueous leaf extract of *Carica papaya* in streptozotocin (STZ) diabetic rats.
Study Design: The effect of daily oral administration of *C. papaya* aqueous leaf extract in streptozotocin diabetic rats was monitored for 24 weeks by assessing fasting blood sugar and serum lipid profile.
Place and Duration of Study: Department of Biochemistry Laboratory and Central Research Laboratory, Adekunle Ajasin University, Akungba-Akoko, Ondo State, Nigeria. March to October, 2009.
Methodology: 24 rats in three groups, normal control (group 1), diabetic control (group 2) and *C. papaya* treated diabetic rats, TDR (group 3) were used for this study. Body weight,

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fasting blood sugar (FBS), total cholesterol, total triglycerides, LDL-cholesterol and HDL-cholestrol, as well as atherogenic index (AI) and coronary risk index (CRI), were assessed periodically in the serum for 24 weeks.
Results: Treatment of STZ diabetic rats with *C. papaya* leaf extract produced significant (*P*<.05) reductions in FBS from week 2 of treatment. Normoglycaemia was attained in week 8 and sustained till week 24. Significant (*P*<.05) reductions in serum total cholesterol and LDL-cholesterol concentrations were also observed for most of the points monitored while HDL-cholesterol was significantly (*P*<.05) increased. The high AI and CRI caused by STZ diabetes was significantly (*P*<.05) reduced in the *C. papaya* treated diabetic rats.
Conclusion: The findings from this study substantiate the long term potential and traditional usage of *C. papaya* for antidiabetic and antihyperlipidaemic effects.

Keywords: Carica papaya; antidiabetic; anti-hyperlipidaemic; anti-atherogenic; medicinal plant.

1. INTRODUCTION

Diabetes and its complications remain a major public health problem world wide [1]. It is even more disturbing to note that regions where the disease was previously uncommon have become endemic in diabetes, particularly type 2 diabetes [2]. Over the past few decades, the understanding of the pathogenesis of diabetes has improved significantly and this has increased treatment options. The drugs currently used to treat diabetes mostly target the lowering of blood glucose concentrations to normal levels [3]. However, the side effects of these various forms of treatments, as well as, the seemingly unabated increase in the incidence of diabetes and its complications, has prompted research into alternative means of treating this disease. There is growing evidence that the different aspects of diabetes pathogenesis must be targeted to offer a holistic approach to its treatment [4]. Long term complications arising from diabetes are major causes of diabetes morbidity and mortality. The alteration of the serum lipid profile by diabetes mellitus is a particularly bothersome effect of the disease. This leads to increased risk of cardiovascular diseases in diabetics [5]. The reversal of diabetes dyslipidaemia is thus a major strategy in diabetes treatment. The use of plant based extracts to treat diabetes in tradtional societies is well documented. Many researchers believe that medicinal plant preparations, which contain different phytochemicals, may combat diabetes at multiple points producing faster and perhaps better resolution of diabetes symptoms [4]. *Carica papaya* is used extensively in traditional societies, including Africa, to treat diabetes [6,7,8]. The antidiabetic and hypolipidaemic effects of *C. papaya* is also documented [1,9,10]. Since the antidiabetic and anti-hyperlipidaemic effects of *C. papaya* have been established in short term studies, it is imperative to assess these parameters in long term studies since most diabetics who use this plant extracts consume them for long periods of time. Previous studies have shown that *C. papaya* leaves possess long term (24 weeks) hypoglycaemic effects in normal rabbits [11].

This study was therefore designed to assess the long term (24 weeks) antidiabetic, antihyperlipidaemic, as well as possible anti-atherogenic effects of aqueous leaf extract of *C. papaya*.

2. MATERIALS AND METHODS

2.1 Reagents

Assay kits for glucose, total cholesterol, total triglycerides and HDL-Cholesterol were products of Randox Laboratory Ltd, Ardmore, Diamond Road, Crumlin, Co. Anrtim, United Kingdom. Streptozotocin (Sigma, London) and other analytical grade chemicals were used for this study.

2.2 Plant Extract Preparation

C. papaya leaves were collected from a farm in Akungba-Akoko, Ondo State, Nigeria. Herbarium specimen, with voucher number UIH 22288 was deposited at the Herbarium of the University of Ibadan, Nigeria.

A modification of Onoagbe et al. [12] method was used to prepare the extract. Briefly, the shade dried leaves were crushed and then soaked in distilled water for 72 hours in a plastic container and covered with cheesecloth. The contents were stirred several times a day and at the end of the third day the contents were filtered through two layers of cheesecloth. The extract was quantified by drying 1 ml of the homogeneous filtrate (by controlled heating i.e. in an oven kept at 40ºC) in a pre-weighed watch glass; this was done in triplicates and the average determined. The average yield of extract obtained was 54 mg/ml. The extract was kept in the freezer until use, when it was allowed to thaw at room temperature.

2.3 Animal Management and Experimental Design

Twenty-four (24) adult male and female Wistar rats (average weight 228.7g) were obtained from the Animal Unit of the University of Ibadan Teaching Hospital (UCH), Ibadan, Nigeria. The rats were kept in a well-ventilated room, with 12h light and 12h dark cycles. They were given free access to food (standard pelleted feed) and water and allowed to acclimatize for three weeks before the commencement of the study. Treatment of the animals conformed to the guidelines in the Principles of Laboratory Animal Care (NIH Publication 85-23, revised 1985) and was approved by the local Institutional Review Board (IRB).

Three groups of eight rats each were used for this study, namely:

Group 1: normal control rats given water for 24 weeks; Group 2: diabetic control rats given water for 24 weeks and Group 3: *C. papaya* treated diabetic rats (TDR), orally given 200 mg/kg body weight of *C. papaya* aqueous leaf extract daily for 24 weeks. This dose was chosen from a pilot dose-response study; it reflects a balance between the toxic and therapeutic dose of the extract. The rats were weighed weekly.

2.4 Induction of Diabetes

Streptozotocin, dissolved in acidified (pH 4.5) normal saline, was administered to the rats, by intra-peritoneal injection, at a dose of 65mg/kg body weight after a 12-hour fast. Diabetes was confirmed after seven (7) days of STZ administration by measuring fasting blood sugar (FBS). Only rats with glucosuria and FBS higher than 8.2 mmol/l were used.

2.5 Blood Collection

Blood was drawn from the tail vein of each rat before the administration of streptozotocin to obtain the basal levels of all parameters. After the administration of STZ and the commencement of treatment, FBS was assessed at week 2 and week 4; and thereafter, once every four weeks. Other parameters were assessed once every four weeks. At the end of the monitoring phase, the rats were sacrificed; blood was obtained through heart puncture. Blood for glucose assays was collected in fluoride bottles while that for serum lipid profile was collected in plain bottles. Blood samples for glucose and other biochemical assays were allowed to clot on ice and centrifuged at 1,000 X g for 5 minutes; the serum was then separated for analysis.

2.6 Biochemical Analyses

Glucose, serum total triglycerides, serum total cholesterol and serum HDL-cholesterol concentrations were analyzed by the methods of Barham and Trinder [13], Tietz [14], Richmond [15] and Lopes-Virella et al. [16] respectively. Serum LDL-cholesterol levels were calculated by the Friedewald et al. [17] method, as described in the manual of the Randox HDL-cholesterol kit. Atherogenic index and coronary risk index (CRI) were calculated by the formula shown below:

Atherogenic Index (AI) = LDL-cholesterol/HDL-cholesterol [18]

Coronary Risk Index (CRI) = Total cholesterol/HDL-cholesterol [19]

2.7 Statistical Analysis

The differences among groups were analyzed by the one-way analysis of variance (ANOVA). The Duncan's Post Hoc test was used to assess the significant difference between means. $P<.05$ was accepted as significant The SPSS 11.0, SPSS Inc., Chicago, Illinois, USA, was used for this analysis.

3. RESULTS AND DISCUSSION

The administration of STZ to rats in this study produced classic diabetes symptoms such as weight loss, hyperglycaemia and hyperlipidaemia. For the untreated diabetic rats, these symptoms remained for the duration of the study.

3.1 Body Weight and Organ Body Weight Ratio

The body weight of STZ diabetic rats were reduced when compared to normal control (not statistically significant). From week 14, the body weight of *C. papaya* TDR was slightly higher than diabetic control but lower than normal control (Fig. 1)

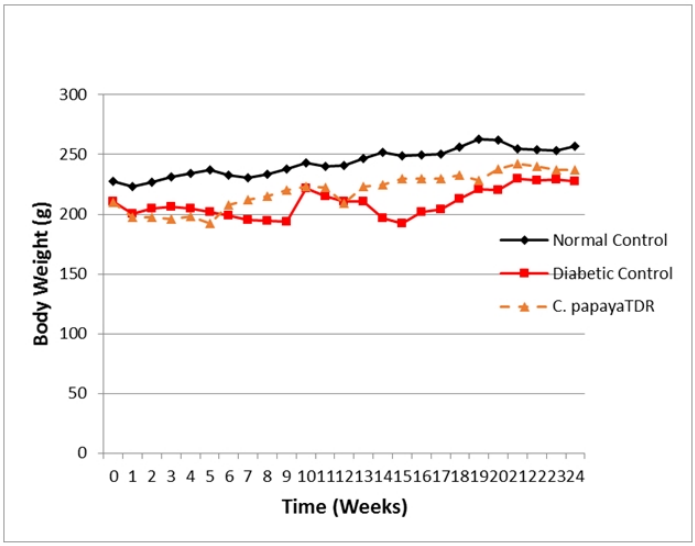

Fig. 1. Effect of long-term administration of *C. papaya* on body weight (g) of STZ-induced diabetic rats. Data were obtained weekly and are means of 4-8 determinations ± standard error of mean (SEM). Error bars were less than 15% of mean values and are removed for clarity

STZ diabetes increased the relative liver, heart (insignificantly), kidney and pancreas (significantly) weights (Fig. 2). Treatment with *C. papaya* brought the liver- and pancreas-body weight ratio to normal control values but did not restore the kidney- and heart-body weight ratio to normal.

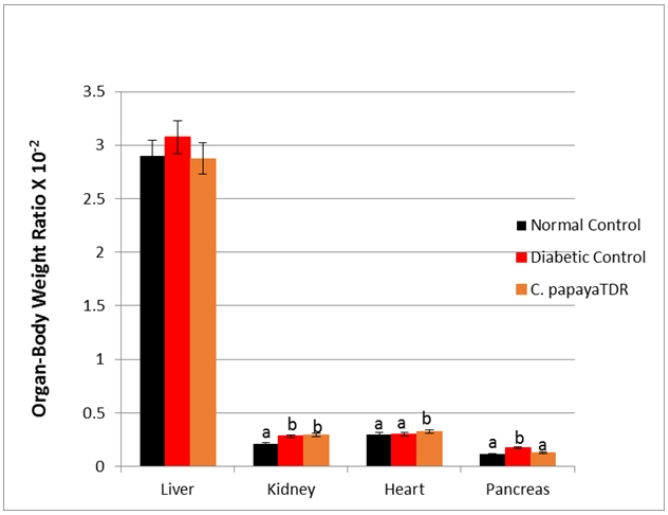

Fig. 2. Effect of long-term administration of *C. papaya* on organ-body weight ratio of STZ-induced diabetic rats. Data were obtained from excised tissues at the end of 24 weeks of monitoring and are expressed as mean ± S.E.M; n=4-8. ANOVA followed by Duncan's test ($p < 0.05$). [a]statistically similar to normal control; [b]statistically different from normal control

Weight loss caused by diabetes could be attributed to the general negative caloric effect of the disease. Though the actual body weight of the STZ diabetic rats increased from week 10 to 24; throughout this study, there was a reduction in body weight gain of this group when compared to normal control. The body weight gain of the treated diabetic rats improved from week 6 when compared to untreated diabetic control. Howarth et al. [20] reported that long term (24 weeks) evaluation of the effect of STZ on the body weight of rats showed a reduction in the body weight gain of rats even though the actual body weight of STZ diabetic rats increased. The amelioration of the weight loss in STZ diabetic rats treated with *C. papaya* implies that the extract was able to modulate the symptoms of the disease to the extent of improving caloric utilization. The ability of the plant extract to restore liver and pancreas relative weights may also be seen as a beneficial effect.

3.2 Fasting Blood Sugar

STZ diabetes caused significant increases in FBS concentration from the point of STZ administration to the end of the study (24 weeks) (Fig. 3). Treatment of STZ diabetic rats with *C. papaya* extract caused significant ($P<.05$) lowering of FBS after 2 weeks. By week 4, a further reduction in FBS concentration was observed in the *C. papaya* TDR; this reduction was significantly ($P<.05$) lower than diabetic control and nearly similar to normal control. From week 8 to the end of the study, the FBS concentration of the treated diabetic rats was statistically indistinguishable from normal control but significantly ($P<.05$) lower than diabetic control.

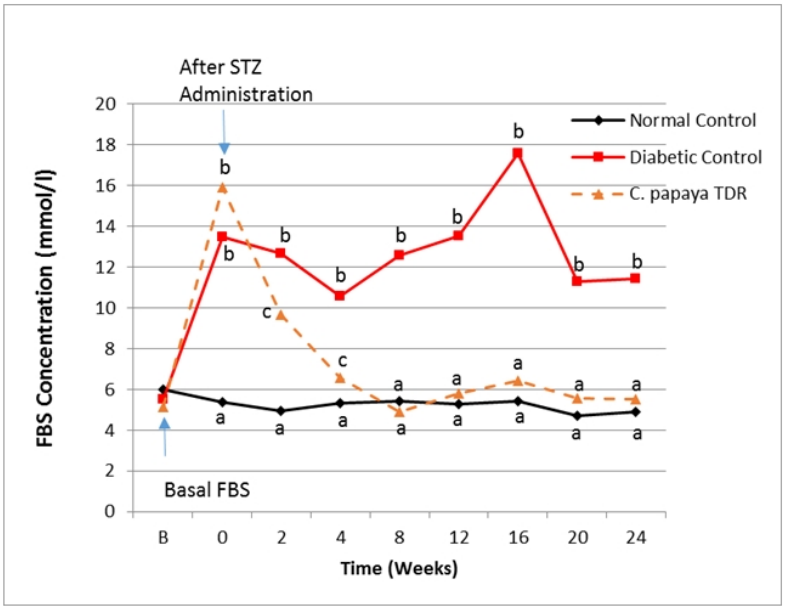

Fig. 3. Effect of long-term administration of *C. papaya* on fasting blood sugar (FBS) concentration (mmol/l) of STZ-induced diabetic rats. Data were obtained from serum at pre-determined intervals and are expressed as mean ± S.E.M; n=4-8. ANOVA followed by Duncan's test ($p< 0.05$). [a]statistically similar to normal control; [b]statistically different from normal control; [c]statistically different from normal and diabetic controls

The reduction in fasting blood sugar observed in the *C. papaya* TDR in this study is a further confirmation of the antidiabetic effects that have been reported for this plant [1,9,10]. This study also revealed for the first time, that the antidiabetic effect of aqueous *C. papaya* leaf extract is sustained for a long period of time (24 weeks). *C. papaya* leaves have been shown to contain fibre and nearly 60% carbohydrates [21], as well as phytochemicals such as saponins, tannins [21] and flavonoids [22]. Plant carbohydrates and fibre, as well as phytochemicals like saponins, tannins and flavonoids, are believed to exert their antidiabetic effects by several mechanisms including slowing down digestion [23,24], inhibiting α-amylase and α-glucosidase [25] and regulating intestinal brush border transport of glucose [26]. Some phytochemicals, such as saponins and flavonoids found in *C. papaya*, are reported to cause β-cell regeneration [27,28]. It is therefore possible that one of the mechanisms by which *C. papaya* extract exerts its anti-diabetic effect is the restoration of pancreatic islet cell function. This suggestion is supported by the report of Juárez-Rojop et al. [10] of the regeneration of pancreatic islet cells of STZ diabetic rats treated with *C. papaya* leaf extract for four weeks. The presence of these different components in *C. papaya* leaves may act together to counter STZ-induced hyperglycaemia.

3.3 Serum Lipid Profile, Atherogenic and Cardiovascular Risk Indices

Significantly (*P*<.05) higher serum total triglyceride levels in the untreated diabetic group were recorded in weeks 8 and 12, with insignificantly higher values in week 24 compared to normal control (Table 1). Compared to diabetic control, the *C. papaya* TDR had significantly higher serum triglyceride values in week 12 and lower values were recorded at weeks 8 and 24.

Table 1. Effect of long-term administration of *C. papaya* on serum total triglyceride concentration (mmol/l) of STZ-induced diabetic rats

Weeks	Normal Control	Diabetic Control	*Carica papaya* TDR
0	4.04 ± 1.23	4.81 ± 1.03	2.48 ± 0.18
4	1.08 ± 0.08	0.84 ± 0.2	0.86 ± 0.3
8	0.63 ± 0.21[a]	2.51 ± 0.73[b]	0.83 ± 0.29[a]
12	2.27 ± 0.48[a]	2.68 ± 0.24[a]	3.61 ± 1.12[b]
16	0.41 ± 0.1	0.34 ± 0.08	0.5 ± 0.14
20	0.71 ± 0.14	0.73 ± 0.13	1.27 ± 0.19
24	0.9 ± 0.1	1.28 ± 0.25	0.83 ± 0.07

Data are expressed as mean ± S.E.M; n=4-8. ANOVA followed by Duncan's test (p< 0.05). [a]statistically similar to normal control; [b]statistically different from normal control.

Table 2 shows that the serum total cholesterol levels of the untreated diabetic rats were significantly (*P*<.05) higher than normal control at weeks 4, 12 and 20. For the *C. papaya* TDR, serum cholesterol levels were mostly lower (statistically significant at weeks 4 and 12) than diabetic control values.

Table 2. Effect of long-term administration of *C. papaya* on serum total cholesterol concentration (mmol/l) of STZ-induced diabetic rats

Weeks	Normal Control	Diabetic Control	*Carica papaya* TDR
0	2.83 ± 0.46	2.62 ± 0.54	2.72 ± 0.46
4	3.42 ± 0.46[a]	3.85 ± 0.5[b]	3.43 ± 0.53[a]
8	2.72 ± 0.3	3.26 ± 0.96	2.31 ± 0.25
12	2.86 ± 0.4[a]	5.97 ± 0.75[b]	4.91 ± 1.35[c]
16	2.8 ± 0.26	3.67 ± 0.71	2.61 ± 0.21
20	2.9 ± 0.35	3.07 ± 0.61	3.45 ± 0.48
24	4.68 ± 0.23[a]	4.01 ± 0.75[b]	3.71 ± 0.38[b]

Data are expressed as mean ± S.E.M; n=4-8. ANOVA followed by Duncan's test (p< 0.05). [a]statistically similar to normal control; [b]statistically different from normal control; [c]statistically different from normal and diabetic controls.

The serum LDL-cholesterol levels of the untreated diabetic rats were significantly (*P*<.05) higher than normal control in weeks 12, 16 and 20 and insignificantly higher for other weeks except week 24 (Table 3). All serum LDL- cholesterol levels of the *C. papaya* TDR were lower (significant at weeks 12, 16 and 20) than diabetic control values. Taking all the LDL-cholesterol results together, none of the increases recorded for the treated diabetic group was as high as the untreated diabetic group.

Table 3. Effect of long-term administration of *C. papaya* on serum LDL-cholesterol concentration (mmol/l) of STZ-induced diabetic rats

Weeks	Normal Control	Diabetic Control	*Carica papaya* TDR
0	1.07 ± 0.37	1.2 ± 0.23	1.44 ± 0.27
4	1.68 ± 0.56	2.44 ± 0.43	1.18 ± 0.44
8	1.04 ± 0.41	1.32 ± 0.7	0.94 ± 0.4
12	0.79 ± 0.14[a]	3.63 ± 0.77[b]	1.96 ± 0.95[a]
16	0.91 ± 0.26[a]	2.72 ± 0.85[b]	1.27 ± 0.25[c]
20	1.37 ± 0.26[a]	1.9 ± 0.63[b]	1.49 ± 0.32[a]
24	3.26 ± 0.23	2.48 ± 0.69	2.34 ± 0.41

Data are expressed as mean ± S.E.M; n=4-8. ANOVA followed by Duncan's test (p< 0.05). [a]statistically similar to normal control; [b]statistically different from normal control; [c]statistically different from normal and diabetic controls.

The serum HDL-cholesterol of the diabetic control rats were consistently lower than normal control with significant values seen in weeks 4 and 16. At week 4, the serum HDL-cholesterol levels of the treated diabetic rats were significantly (*P*<.05) higher than normal and diabetic controls (Table 4). Thereafter, the HDL-cholesterol levels of the *C. papaya* TDR was lower than normal control but higher than diabetic control.

Table 4. Effect of long-term administration of *C. papaya* on serum HDL-cholesterol concentration (mmol/l) of STZ-induced diabetic rats

Weeks	Normal Control	Diabetic Control	*Carica papaya* TDR
0	1.28 ± 0.11	1.84 ± 0.22	1.85 ± 0.13
4	1.25 0.31[a]	1.03 ± 0.26[b]	1.86 ± 0.22 [a]
8	1.74 ± 0.23	0.93 ± 0.26	1.12 ± 0.3
12	1.49 ± 0.28	1.12 ± 0.22	1.35 ± 0.32
16	1.71 ± 0.27[a]	0.8 ± 0.18[b]	1.12 ± 0.08[c]
20	1.21 ± 0.32	0.84 ± 0.25	1.38 ± 0.26
24	1.01 ± 0.06	0.94 ± 0.09	0.99 ± 0.06

Data are expressed as mean ± S.E.M; n=4-8. ANOVA followed by Duncan's test (p< 0.05). [a]statistically similar to normal control; [b]statistically different from normal control; [c]statistically different from normal and diabetic controls.

From week 4 to 20, the atherogenic index of the untreated diabetic rats significantly (*P*<.05) increased compared to normal control (Table 5). Treatment of diabetic rats with *C. papaya* leaf extract significantly (*P*<.05) reduced (weeks 4, 12, 16 and 20) their atherogenic index compared to diabetic control.

Table 5. Effect of long-term administration of *C. papaya* on the atherogenic index (AI) of STZ-induced diabetic rats

Weeks	Normal Control	Diabetic Control	*Carica papaya* TDR
0	0.80 ± 0.28	0.75 ± 0.16	0.79 ± 0.14
4	1.69 ± 0.51[a]	3.42 ± 1.67[b]	0.64 ± 0.24[c]
8	1.04 ± 0.63	2.17 ± 1.15	1.26 ± 0.72
12	0.59 ± 0.14[a]	4.11 ± 1.53 [b]	2.40 ± 1.78[c]
16	0.73 ± 0.34[a]	4.82 ± 1.73[b]	1.18 ± 0.31[a]
20	1.68 ± 0.45[a]	2.89 ± 0.89[b]	1.09 ± 0.21[a]
24	3.32 ± 0.33	2.69 ± 0.76	2.40 ± 0.44

Data are expressed as mean ± S.E.M; n=4-8. ANOVA followed by Duncan's test (p< 0.05). [a]statistically similar to normal control; [b]statistically different from normal control; [c]statistically different from normal and diabetic controls.

The coronary risk index (CRI) of the diabetic control group was higher than normal control from week 4 to 20 (Table 6). The CRI of the *C. papaya* TDR were lower than the untreated groups at all points of assessment, significant (*P*<.05) at weeks 4, 8, 12, 16 and 20.

Long term dyslipidaemia from diabetes mellitus increases the risk of development of cardiovascular diseases (CVD) [5] The risk of CVD was assessed by monitoring the serum lipid profile, comparing the total cholesterol to HDL-c ratio [29] and assessing the atherogenic lipoprotein profile of serum (LDL-c to HDL-c ratio) [30]. The most apparent evidence of the antihyperlipidaemic effects of *C. papaya* leaf extract were the reductions in serum total cholesterol and LDL-cholesterol concentrations, as well as the increases in HDL-cholesterol, in the treated STZ diabetic rats compared to the untreated diabetic control. Several components of *C. papaya* leaf extract, such as fibre [31], saponins [32] and flavonoids [33], are reported to have antihyperlipidaemic effects. These factors significantly

reduced the atherogenic and coronary risk indices of the treated diabetic rats, thus potentially protecting them from cardiovascular diseases.

Table 6. Effect of long-term administration of *C. papaya* on the coronary risk index (CRI) of STZ-induced diabetic rats

Weeks	Normal Control	Diabetic Control	*Carica papaya* TDR
0	2.23 ± 0.33	1.39 ± 0.23	1.59 ± 0.33
4	3.15 ± 0.53[a]	5.01 ± 1.37[b]	1.85 ± 0.23[c]
8	2.03 ± 0.66[a]	4.66 ± 1.78[b]	2.53 ± 0.76[a]
12	2.16 ± 0.41[a]	6.37 ± 1.76[b]	5.28 ± 2.99[c]
16	1.85 ± 0.35[a]	6.04 ± 1.76[b]	2.39 ± 0.34[a]
20	3.10 ± 0.52[a]	4.36 ± 0.97[a]	2.58 ± 0.18[b]
24	4.74 ± 0.39	4.35 ± 0.89	3.79 ± 0.44

Data are expressed as mean ± S.E.M; n=4-8. ANOVA followed by Duncan's test ($p< 0.05$).
[a]statistically similar to normal control; [b]statistically different from normal control; [c]statistically different from normal and diabetic controls.

4. CONCLUSION

C. papaya is used extensively in traditional societies to treat diseases including diabetes. The finding from this study that aqueous leaf extract of *C. papaya* possess long term antidiabetic and antihyperlipidaemic, as well as anti-atherogenic effects, is a further demonstration of the enormous medicinal value of this plant.

CONSENT

Not applicable.

ETHICAL APPROVAL

All authors hereby declare that "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed, as well as specific national laws where applicable. All experiments have been examined and approved by the appropriate ethics committee.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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