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Research Article

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Hypoglycaemic, Hypolipidemic and Hepatoprotective Activities of Ripe and Unripe Carica Papaya Methanol Extracts in Streptozotocin-Induced Diabetic Male Albino Rats

Adetayo Modupe Olusola*

Department of Biochemistry, Babcock University, Surgana, Ogun, Nigeria

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ABSTRACT

Diabetes mellitus is associated with elevated plasma glucose levels, hyperlipidaemia and hepatic dysfunction. Traditional plant treatment has shown a surging interest in the last few decades. The purpose of this study was to determine the effect of ripe and unripe Carica Papaya Methanol Extract (CPME) on blood glucose levels, lipid profile, liver function biomarker enzymes and plasma total protein in Streptozotocin-Induced (STZ) diabetic albino rats. Thirty male albino rats were randomly divided into six groups. Diabetes was induced in groups 4 to 6 Treated groups (2, 3, 5 and 6) were given 500mg/kg body weight ripe or unripe CPME, as appropriate, for 21 days. Blood glucose was measured on days 0, 7, 14 and 21 after which animals were sacrificed and blood samples collected for estimation of biochemical parameters. Ripe and unripe CPME significantly reduced plasma glucose, total cholesterol, triglyceride, low density, very low-density lipoprotein and liver function biomarker enzyme levels and significantly increased high density lipoprotein levels of the treated animals while the total protein levels, were within the normal range. Ripe and unripe C. papaya methanol extracts showed hypoglycaemic, hypolipidemic and hepatoprotective activities in STZ-induced diabetic albino rats with the unripe fruit being more effective.

Keywords: *Diabetes*; *Carica papaya; Hypoglycemic; Hepatoprotective*

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by the presence of hyperglycaemia due to defect in insulin secretion, action or both. The World Health Organization estimates that about 422 million people worldwide have diabetes, with 1.6 million deaths being directly attributed to diabetes each year. Both the number of cases and the prevalence of diabetes have been steadily increasing over the past few decades with diabetes being the seventh leading cause of death. The chronic hyperglycaemia of diabetes is associated with relatively specific long-term microvascular complications affecting the eyes, kidney and nerves, as well as increased risk of cardiovascular diseases [1]. The abnormalities in carbohydrate, fat, and protein metabolism that are found in diabetes are due to deficient action of insulin on target issues. Management of diabetes remains elusive with modalities targeting just the reduction of associated complications to some level. However, strategies involving the use of plant materials

have shown a more promising result in not only the reduction of these complications but also the adverse effects of using the traditional drugs in this condition.

Carica papaya, commonly known as Pawpaw, is a tropical fruit belonging to the plant family Caricaceae and the genus Carica native to Mexico and Central America, it is the most economically important fruit in the Caricaceae family, and is currently cultivated in tropical areas world-wide with Nigeria being the third largest producer globally, it is cultivated for its large, sweet melon-like fruits. C. papaya is well known for its exceptional nutritional and medicinal properties throughout the world. The whole C. papaya including its leaves, seeds, fruits and juice, is used as a traditional medicine. C. papaya has been considered as a nutraceutical fruit due to its versatile medicinal properties such as anti-fertility, diuretic, anti-hypertensive, hypolipidemic, anti-bacterial, anti-fungal, anti-diabetic, anti-tumour and free radical scavenging activities [2]. Chloroform, aqueous and ethanol extracts of C. papaya leaf have been reported to exhibit hypoglycaemic and hypolipidemic activities. Also, aqueous extract of unripe C. papaya fruit has been shown to possess hypoglycaemic activity. Despite numerous researches on the hypoglycaemic and hypolipidemic activities of C. papaya, there is insufficient information on the effect of ripening on these activities. The present study therefore purposed to examine the hypoglycaemic, hypolipidemic and hepatoprotective activities of ripe and unripe C. papaya fruit methanol extract in streptozotocin-induced diabetic albino rats.

LITERATURE REVIEW

Experimental Section

All chemicals used in the study were of analytical grade and procured from standard chemical dealers. Chemicals and reagents were stored based on the storage instructions indicated for each.

Identification of plant Material and Preparation of Extract

Fresh ripe and unripe C. papaya Linn fruit were collected directly from the C. papaya tree located in a garden around the New Market area of Ilishan-Remo, Ogun State, Nigeria. Thereafter, authentication of the fruit was done at the Forest Herbarium, Ibadan, Oyo State, by Mr Egunjoibi, AJ. and it was given a voucher specimen number of FHI. The fruits were peeled and the seeds inside were removed, the fruit pulps were then washed with distilled water. The fruits were diced and soaked separately in 80% methanol at room temperature, for 24 hours [3]. This was filtered with filter paper the filtrate was collected and concentrated to dryness using a rotary evaporator (RE-1050, Shanghai Yuhua Instrument Equipment CO., China) to obtain the ripe and unripe Carica Papaya Methanol Extract (CPME).

Experimental Animals

Thirty male albino rats aged 4 weeks and weighing between 80-100 g were purchased from the animal facility, University of Ibadan, Ibadan, Oyo State. The animals were housed in clean, well aerated and well illuminated battery cages and were fed commercial rat chow and water ad libitum. The rats were acclimatized for a period of two weeks. The animals thereafter were divided into six groups of five animals each, as follows;

- Group 1: Normal rats with no treatment (normal control)
- Group 2: Normal rats treated with 500mg/kg body weight ripe CPME
- Group 3: Normal rats treated with 500mg/kg body weight unripe CPME
- Group 4: DM-induced rats with no treatment (diabetic control)
- Group 5: DM-induced rats treated with 500mg/kg body weight ripe CPME
- Group 6: DM-induced rats treated with 500mg/kg body weight unripe CPME

Induction of Diabetes

Diabetes was induced, in groups 4, 5 and 6, by intraperitoneal injection of streptozotocin 65 mg/kg body weight in 0.1 M cold citrate buffer pH 4.5. Animals in the control group received the vehicle alone. Blood was extracted from the tail vein, after 48 hours, for glucose analysis using the Accuchek™ Glucometer, model 35NZ (Roche Diabetes Care, Mannheim, Germany). Rats with fasting blood glucose of 200 mg/dL and above were considered diabetic.

Sacrificing of Experimental Animals

At the end of 21 days treatment, the rats were allowed to fast overnight for 10-12 hours. Blood samples were collected from the experimental animals through ocular puncture into lithium heparin bottles using syringe after which the rats were sacrificed through pelvic dislocation.

Measurement of Blood Glucose Level

Blood samples were collected from the tip of the tail to determine the fasting blood glucose level which was measured using Accuchek™ Glucometer based on the glucose oxidase method. This was done on days 0, 7, 14 and 21.

Biochemical Parameters

Plasma total cholesterol, triglyceride, low density lipoprotein, high density lipoprotein, aspartate aminotransferase, alanine amino transferase and total protein were determined by the kit method with the use of Randox Kit. The assay procedures were carried out based on the instructions provided on the kit.

Statistical Analysis

Data obtained from this study were expressed as Mean ± Standard Error of Mean (SEM). Statistical analysis of the data was carried out by means of one-way analysis of variance. Post-hoc test was done using Duncan Multiple-Range Test (DMRT). Graphs were constructed using GraphPad Prism 6. $P<0.05$ was considered statistically significant.

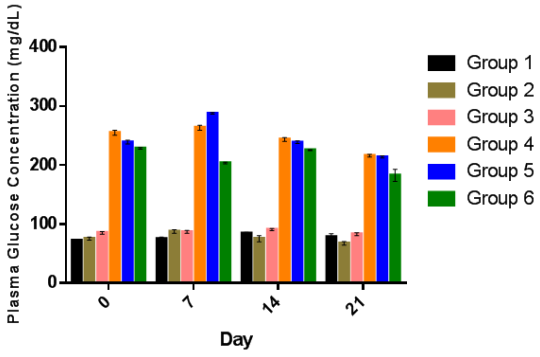

Figure 1: Effect of ripe and unripe *C. papaya* methanol extract on blood glucose levels of streptozotocin-induced diabetic albino rats

Ethical Consideration

Ethical approval (Number: BUHREC 308/19) was obtained from the Babcock University Research and Ethics Committee prior to commencement of the study.

RESULTS AND DISCUSSION

Effect of ripe and unripe C. papaya methanol extract on blood glucose levels of streptozotocin-induced diabetic albino rats.

The effect of ripe and unripe CPME on changes in blood glucose levels of experimental animals. The ripe and unripe CPME significantly ($p < 0.05$) reduced the blood glucose levels of animals in the treated groups, with the unripe CPME being more effective on days 14 and 21. The non-diabetic treated animals also had lowered blood glucose levels but was not significantly ($p > 0.05$) different from the untreated animals, with values falling within the normoglycemic range. The elevated blood glucose levels of diabetic animals on day 0 showed that they were hyperglycaemic and after treatment with the ripe and unripe CPME, there was a reduction in the blood glucose levels, to the normal range [4]. This show the potential of ripe and unripe CPME in bringing about hypoglycaemic effect however, the unripe CPME was observed to be more effective than the ripe CPME in reducing blood glucose levels of the animals. This is similar to findings from previous studies which reported that aqueous extract of unripe C. papaya fruit helped to reduce blood glucose levels of diabetic rats. Thus, the unripe pulp of Carica papaya may probably contain active substances that possess blood glucose lowering activities.

Group 1: Normal rats with no treatment (normal control); Group 2: Normal rats treated with 500 mg/kg body weight ripe CPME; Group 3: Normal rats treated with 500 mg/kg body weight unripe CPME; Group 4: Type 1 DM-induced rats with no treatment (diabetic control), Group 5: Type 1 DM-induced rats treated with 500 mg/kg body weight ripe CPME; Group 6: Type 1 DM-induced rats treated with 500 mg/kg body weight unripe CPME.

Table 1 shows the effect of ripe and unripe CPME on lipid profile of experimental animals. The ripe and unripe CPME significantly ($p < 0.05$) reduced the plasma total cholesterol, triglyceride, low density lipoprotein, very low-density lipoprotein and significantly increased ($p < 0.05$) the high-density lipoprotein levels of animals in the treated groups. Unripe CPME was more effective than the ripe CPME in regulating the lipid profile parameters of the animals within a healthy range [5]. The groups treated with unripe CPME was found to have better lipid profile levels compared to the groups treated with ripe CPME. This suggests that methanol extract of unripe C. papaya has a more effective hypolipidemic action than the methanol extract of ripe C. papaya extract. All lipid profile parameters were within the normal range in the groups treated with unripe CPME. This suggests that unripe C. papaya fruit may be an excellent nutraceutical for prevention of cardiovascular diseases which may result from improper metabolism of fat in diabetic conditions.

This finding is in congruence with that of a previous research on the effect of feeding ripe and unripe papaya fruit pulps on blood lipid profile of normal male adult albino rabbits. It was revealed that both ripe and fruit pulps resulted in consistent lowering of serum cholesterol, low density lipoprotein cholesterol and triglycerides and elevation in phospholipids and high-density lipoprotein cholesterol levels at 1,3 and 6 weeks of fruit pulp feeding. Values are expressed in mean ± SEM. Values in the same column having the same superscript alphabets have no statistically significant difference at $p < 0.05$. Group 1: Normal rats with no treatment (normal control); Group 2: Normal rats treated with 500mg/kg body weight ripe CPME; Group 3: Normal rats treated with 500mg/kg body weight unripe CPME; Group 4: Type 1 DM-induced rats with no treatment (diabetic control), Group 5: Type 1 DM-induced rats treated with 500mg/kg body weight ripe CPME; Group 6: Type 1 DM-induced rats treated with 500mg/kg body weight unripe CPME (Table 2).

Table 1 : Effect of ripe and unripe C. papaya methanol extract on lipid profile of streptozotocin-induced diabetic albino rats

Group	Parameter				
	TC (mg/dL)	**TG (mg/dL)**	**LDL (mg/dL)**	**VLDL (mg/dL)**	**HDL (mg/dL)**
1	102.22 ± 3.02^{b}	108.54 ± 2.43^{b}	29.80 ± 4.49^{a}	24.17 ± 3.16^{a}	57.85 ± 4.01^{e}
2	104.22 ± 2.32^{b}	116.70 ± 1.14^{c}	25.99 ± 0.13^{a}	22.48 ± 4.34^{a}	51.24 ± 4.56^{d}
3	84.44 ± 3.10^{a}	101.63 ± 2.08^{a}	32.03 ± 4.22^{a}	20.10 ± 5.19^{a}	58.65 ± 3.26^{e}
4	120.22 ± 1.6^{d}	237.92 ± 5.62^{f}	75.97 ± 0.06^{d}	47.37 ± 2.59^{c}	20.04 ± 5.03^{a}
5	119.78 ± 2.67^{d}	164.79 ± 6.19^{e}	54.71 ± 3.24^{c}	30.80 ± 2.79^{b}	39.72 ± 4.26^{c}
6	113.11 ± 2.51^{c}	135.79 ± 4.44^{d}	44.70 ± 2.89^{b}	28.86 ± 2.28^{b}	31.44 ± 8.56^{b}

- TC – Total cholesterol; TG – Triglyceride; LDL – Low density lipoprotein cholesterol;
- VLDL – Very low-density lipoprotein cholesterol; High density lipoprotein cholesterol.

Table 2: Effect of ripe and unripe C. papaya methanol extract on liver function biomarker enzymes and total protein of streptozotocin-induced diabetic albino rats

Group	AST (U/L)	ALT (U/L)	TP (g/dL)
1	31.00 ± 1.08^{a}	32.67 ± 0.62^{a}	7.06 ± 0.02^{b}
2	44.67 ± 5.57^{b}	51.00 ± 4.14^{b}	7.52 ± 0.32^{d}
3	41.33 ± 5.15^{b}	45.00 ± 6.14^{b}	7.22 ± 0.19^{c}
4	84.67 ± 2.39^{d}	69.00 ± 4.55^{d}	4.56 ± 0.04^{a}
5	60.67 ± 3.79^{c}	56.33 ± 9.57^{c}	7.02 ± 0.23^{b}
6	58.33 ± 1.14^{c}	56.00 ± 8.37^{c}	6.85 ± 0.30^{b}

Values are expressed in mean ± SEM. Values in the same column having the same superscript alphabets have no statistically significant difference at $p < 0.05$.

- Group 1: Normal rats with no treatment (normal control)
- Group 2: Normal rats treated with 500 mg/kg body weight ripe CPME;
- Group 3: Normal rats treated with 500 mg/kg body weight unripe CPME;
- Group 4: DM-induced rats with no treatment (diabetic control),
- Group 5: DM-induced rats treated with 500 mg/kg body weight ripe CPME;

- Group 6: DM-induced rats treated with 500 mg/kg body weight unripe CPME.

AST – Aspartate Transaminase; ALT – Alanine Transaminase; TP – Total Protein

The effect of ripe and unripe CPME on liver function biomarker enzymes and total protein concentration of experimental animals. The ripe and unripe CPME significantly ($p < 0.05$) reduced the plasma AST and ALT levels of treated animals with the unripe CPME being most effective among the treated groups while the total protein levels of all groups had no significant ($p < 0.05$) difference and were within the normal range except for the diabetic control (untreated) group which was lower than normal. There was a decrease in the levels of AST and ALT in the groups treated with both the ripe and unripe methanol extract of C. papaya for the diabetic groups. However, the unripe C. papaya methanol extract was more effective in decreasing the AST levels of the treated animals compared to the ripe C. papaya methanol extract. These results showed that the extracts may have hepatoprotective properties. This reduction of AST and ALT to their normal levels indicate that the extracts hat a protective effect on the liver as high levels indicate damage to the liver. This finding is similar to previous report which showed that chloroform extracts of unripe C. papaya fruit caused a decrease in AST and ALT levels of experimental animals compared to the diabetic control. The total protein concentration of all study groups was found to have no significant difference. This shows that ripe and unripe CPME helped to maintain the total protein levels of plasma within the normal range. The diabetic untreated group had lower levels of total protein, below the normal range, confirming the uncontrolled breakdown of protein associated with the disease condition when it is not properly managed.

CONCLUSION

It can be concluded from the findings of the study that methanol extract of ripe and unripe C. papaya possesses hypoglycaemic, hypolipidemic and hepatoprotective properties with the unripe CPME being more effective. C. papaya may therefore be a promising fruit containing potential antidiabetic nutraceuticals for the management of diabetes and its complications.

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