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Hypoglycemic, hypolipidemic and body weight effects of unripe pulp of *Carica papaya* using diabetic Albino rat model.

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ABSTRACT

The present study was designed to evaluate some selected biochemical effects of unripe pulp of *Carica papaya* on alloxan induced diabetes in rats. Animals weighing (160-200 g) were divided into three (3) groups of 10 animals each; Group I (normal control), Group II (diabetic control) and Group III (test control). Diabetes was induced in albino rats by intraperitoneal injection of alloxan monohydrate at a single dose of 120 mg/kg body weight into groups II and III respectively. Animals in groups I and II received normal rat feeds while animals in group III were fed with unripe pulp of *Carica papaya* for a period of 28 days. Body weight and glucose levels were measured on days 0, 7, 14, 21, and day 28. It was observed in this study that there was a significant reduction of Glycated hemoglobin in the test group when compared with the induced control (diabetic rats) and normal control group ($P<0.05$). The unripe pulp of *Carica papaya* elicited significant ($P<0.05$) reduction of blood glucose, lipid profile parameters except high density lipoprotein cholesterol (HDL-C) which significantly increased ($p<0.05$). Result also showed significant ($P<0.05$) reduction in body weight. These action is believed to be due to the bioactive constituents of the plant. Unripe pulp of *Carica papaya* exhibits proven potentials in the parameters evaluated to become of important medicinal and pharmacological interest.

Keywords: *Carica papaya*, unripe pulp, hypoglycemia, hypolipidemia.

1. Introduction

Plants have been used by mankind as remedies from the beginning of civilization. The uses of medicinal plants as traditional medicine are well known. This is mainly due to the presence of bioactive metabolite in plants which formed the basis of herbal medication [1]. Medicinal herbs used in indigenous medicines for the management of diabetes mellitus contain both organic and inorganic constituents [1]. Some of these inorganic trace elements possess antidiabetic properties, which accounts for the activity of medicinal herbs [2]. *Carica papaya* linn [family Caricaceae] is a widely grown, perennial tropical tree which grows up to 5 to 10 meters tall with an erect and branchless trunk, its leaves are large, 50–70 cm in diameter deeply palmately lobed with 7 lobes [3]. Its melon - like fruit [papaya] is known by different names in different parts of the world. Ethno-botanical survey conducted by some researchers have indicated the seeds are reputed for the management of various human and veterinary diseases including abdominal discomfort, pain, malaria, diabetes, obesity, infections and oral drug poisonings by the Yoruba herbalists South West Nigeria [4]. In spite of the presence of known anti-diabetics in the pharmaceutical market, remedies from medicinal plants are used with success to treat this disease [5]. Treatment imposes economic burden [6] and the documented incidence is quite ambiguous. Different parts of the plant are attributed with different medicinal values, for example in African traditional medicine, the boiled green leaves of papaya, combined with leaves of *Azadirachta indica*, *Cymbopogon citratus*, *Psidium guajava*, and stem bark of *Alstonia boonei* boiled together and the hot infusion is drank as one wine glass full thrice daily in the treatment of malaria [4]. Its fresh leaves are also efficacious in the treatment of gonorrhea, syphilis and amoebic dysentery [7].

The milky juice of the unripe fruit is a powerful abortificant and antihelmentic for round worms, stomach disorders and enlargement of the liver and spleen, the seeds are also effective as a vermifuge and in the treatment of hypertension, diabetes and hypercholesterolemia [8]. This study seeks to evaluate the effect of unripe pulp of *Carica papaya* in glycemic control, hypolipidemic and body weight effect, considering the fact that diabetes mellitus is associated with increased mortality and morbidity, and drugs for the management of diabetes are rather expensive and associated with some side effects, it is therefore necessary to examine unripe pulp of *Carica. papaya* on alloxan induced diabetes in rats and consequently make recommendations for its use in the management of diabetic conditions in humans.

2. Materials and Methods

2.1. Laboratory Animals and Experimental Design

Thirty (30) weaned male albino rats (about 8-9 weeks) were obtained from the animal farm of the University of Nigeria, Nsukka. The animals were taken to the laboratory where they were housed in a plastic cage and placed on commercial feeds [growers marsh/rat chow] bought from the local market as produced by, Vital feed Nigeria Ltd and allowed to drink water freely [*ad libitum*] till the end of the acclimatization for two weeks. The animals weighed between 160-200 g.

2.2 Grouping of Animals:

The animals were divided into three (3) groups of ten (10) rats each.

Group I and Group II were fed with normal rat chow and allowed free access to water *ad libitum* while Group III were fed with grated unripe pulp of *Carica papaya* and allowed free access to water *ad libitum*. Diabetes was induced into rats in Groups II and III.

GROUP I [Normal Control] no diabetes, eat rat chow and water
GROUP II [Induced Control] diabetes, eat rat chow and water
GROUP III [Test Control] diabetes, eat *Carica papaya* and water

Treatment of laboratory animals was in accordance with the principles of laboratory animal care.

2.3 Plant Materials

Unripe pulp of *Carica papaya* was obtained from a local farm in Emii, Owerri North Local Government Area of Imo State and was authenticated by a botanist before use.

2.4 Induction of Diabetes

Diabetes mellitus was induced by a single intraperitoneal injection of 120 mg/kg body weight of alloxan monohydrate [Sigma Aldrich, MO USA], Alloxan was dissolved in 0.9% normal saline as vehicle. Animals with blood glucose greater than 200 mg/dl were considered diabetic after 2 days of induction and were used for the experiment.

2.5 Blood Glucose Determination

Blood glucose was determined on days 0, 7, 14, 21, and 28. One touch Accucheck glucometer [Roche Diagnostics, Germany] was used to determine the glucose level by collecting 2 ml of blood from the tails (tail prick) after mild anaesthesia using ether. Animals were fasted for 16-18 hours prior to blood collection.

2.6 Measurement of Body Weight

Body weight was measured on days 0, 7, 14, 21, and 28. Body weight noted was expressed as mean body weight [g].

2.7 Determination Lipid Profile. Total Plasma Cholesterol [TC], Triglyceride [TG] and High density lipoprotein cholesterol [HDL-C] was estimated by enzymatic assay method using analytical kits [Biolab SA Maizy, France]. While VLDL-C and LDL –C are based on calculations;-

VLDL-C =TG/5 . and LDL-C = TC-(VLDL-C+HDL-C).

2.8 Statistical Analysis

Result were expressed as mean ± SEM [standard error of mean]. Statistical analysis were performed using One Way Analysis of Variance [ANOVA]. And values of $P<0.05$ at 95% level of significance was used to assess significant difference between control and treated groups.

3. Result and Discussion

Table 1: Effects of unripe pulp of *Carica papaya* on blood glucose (mg/dl) and glycated hemoglobin level (%) in normal and alloxan induced diabetes in male albino rats

Days	0	7	14	21	28	Glycated Haemoglobin (%) on day 28.
Group I	97.00±1.14^{c}	102.00±1.30^{c}	97.80±0.66^{c}	100.40±0.67^{c}	100.80±1.06^{c}	3.83±0.09^{c}
Group II	270.80±0.66^{a}	190.00±0.89^{a}	160.60±0.60^{a}	157.00±0.89^{a}	157.20±0.73^{a}	9.56±0.42^{a}
Group III	265.60±1.77^{b}	160.20±0.58^{b}	132.60±0.74^{b}	130.20±0.73^{b}	120.20±0.37^{b}	5.34±0.37^{b}

Data are expressed as mean± standard error of mean (SEM). n=10 and statistically significant by analysis of variance (ANOVA) at $P<0.05$.Means with the same letter in the same column are not significantly different

Table 2: Effects of unripe pulp of *Carica papaya* on lipid profile (mg/dl) in normal and alloxan induced diabetes in male albino rats (day 28)

	LDL	HDL	VLDL	TG	TC
Group I	33.20±3.69^{b}	31.80±0.35^{c}	10.23±0.49^{b}	51.15±2.48^{b}	69.93±1.07^{b}
Group II	103.49±4.28^{a}	37.31±0.60^{b}	30.94±0.99^{a}	154.73±4.96^{a}	171.75±3.85^{a}
Group III	17.13±1.82^{c}	45.50±0.47^{a}	12.50±1.15^{b}	62.51±5.78^{b}	75.14±0.79^{b}

Data are expressed as mean ± standard error of mean (SEM). n=10 and statistically significant by analysis of varience (ANOVA) at $P<0.05$. Means with the same letter in the same column are not significantly different

Table 3. Effects of unripe pulp of *Carica papaya* on body weights (g) in normal and alloxan induced diabetes in male albino rats

Days	0	7	14	21	28
Group I	181.00±4.00^{c}	182.20±4.56^{b}	192.20±4.97^{a}	206.40±6.81^{a}	219.60±7.25^{a}
Group II	196.60±5.41^{a}	190.80±4.80^{a}	184.60±5.04^{b}	182.40±4.47^{b}	179.00±3.88^{b}
Group III	190.00±5.24^{b}	167.60±3.50^{c}	150.40±7.96^{c}	142.00±10.71^{c}	136.00±12.08^{c}

Data are expressed as mean ± standard error of mean (SEM). n=10 and statistically significant by analysis of variance (ANOVA) at P<0.05. Means with the same letter in the same column are not significantly different.

4. Discussion:

Apart from hyperglycemia, diabetes mellitus is accompanied by hypercholesterolemia, hyperlipidemia and hepatic steatosis [8]. From table 1 there is significant decrease in blood glucose of the test group(Group III) when compared with the induced diabetic control (GroupII) and normal control group(Group I) at a significant level of P<0.05. There was an obvious reduction in plasma glucose for the test group that was fed on unripe pulp of *Carica papaya*, when compared to the induced control group (diabetic group) and the normal control group (P<0.05). From this study, it shows that diabetic albino rat fed with unripe pawpaw (*Carica papaya*) for as long as 4 weeks led to hypoglycemia (P<0.05). Arul *et al*. [9], demonstrated similar hypoglycemic effect using *Semecarpus anacardium* Linn. on streptozotocin induced diabetes in rats. Also the table shows a significant decrease of glycated hemoglobin level of the test diabetic group (Group III) when compared with induced diabetic control (Group II) and normal control (Group I) at a significant level of P<0.05. Diabetic hyperglycemia results in an increase in free-radical production by a mechanism involving glucose oxidation followed by protein glycation and oxidative degeneration [10]. Glycation (non enzymatic glycosylation) involves the condensation of glucose with the N-amino group of lysine, the α-amino group of an N- terminal amino acid or the amines of nucleic acids [11]. The first reaction is the formation of an unstable Schiff base, which reaches a steady state within hours and is reversible. Rearrangement of the Schiff base into an Amadori product reaches a steady state in approximately 28 days and is also reversible. When molecules have slow turnover rates, these Amadori products undergo multiple dehydration reactions and rearrangements to irreversibly form Advanced Glycation End Products. Thus, the unripe pulp of *Carica papaya* may probably contain active substances that possess blood glucose lowering activities [12, 13]. This study is further supported by Baustista [14] who used *Urena lobata* Linn to demonstrate hypoglycemia.

It was also observed in this study that there was a significant reduction of Glycated hemoglobin in the test group when compared with the induced control(diabetic rats) and normal control group at (P<0.05). It is therefore possible that the unripe pulp of *Carica papaya* may possess active substances which scavenges the free radicals of glucose oxidation, protein glycation and oxidative degeneration or probably an improvement in insulin secretion. This study is however supported by Gupta *et al*. [15] when they demonstrated that IND01 (Fenugreek seeds) showed improved glycemic control (significant decrease in HBA1c) on day 28 of treatment as compared with n-STZ control rats

Table 2 shows the effect of unripe pulp of *Carica papaya* on lipid parameters. There was significant decrease on the LDL, VLDL, TG and TC of test diabetic group (Group III) when compared with diabetic control (Group II) (P<0.05) levels. However there is no significant difference between Groups III and Groups I for TC and TG levels, and between Groups III and Group I for VLDL levels .But there is marked increase in the level of HDL of test induced (Group III) when compared to groups II and 1 (P<0.05) significance. This can substantiate the cardioprotective effect of *Carica papaya.* The present study also showed a decrease in LDL, VLDL, TG, and TC in the test group (Group III) when compared with the induced group (Group II) (P<0.05). However there was a significant increase in HDL in the test group when compared with the diabetic rats (P<0.05). A significant increase in serum cholesterol and triglycerides observed in this experiment is in agreement with the findings of the [1]. The marked hyperlipidemia that characterizes the diabetic state may therefore be regarded as a consequence of the uninhibited actions of lipolytic hormones on the fat depots. *Carica papaya* treatment to the rats elicited a hypolipidemic activity. All the lipid components viz; Total cholesterol, LDL-C, VLDL and triglycerides were reduced significantly (P<0.05) for the test animals when compared to the diabetic control and normal control animals. The more prominent effect being reduction in LDL-C which is a known triggering factor for coronary occlusion or its block

Table 3 shows result of body weight as affected by unripe pulp of *Carica papaya* .There was a gradual decrease in body weight of alloxan diabetic group fed on *Carica papaya*, the plant showed a weight reducing effect on the test group (Group III) when compared with the induced control (Group II) and normal control (Group I) P<0.05 significance. This is in accordance with the findings of [2] who examined the Effect of *Irvingia grandifolia*, *Urena lobata* and *Carica papaya* on the oxidative status of normal rabbit.

4.1 Conclusion

From this study, it was observed that there was a general reduction in body weight between the test induced groups (Group III) when compared to the animals in both Groups II and Groups (P<0.05). The test group lost more weight due to the effect of the unripe pulp of *Carica papaya* they were fed with. While the induced group had a normal gradual weight loss most probably because they were diabetic. The study also demonstrated the hypolipidemic effects of papaya by reducing the levels of TC, TG, VLDL and LDL. These combined effects can subsequently play a vital role in preventing the incidences of premature occurrence of coronary heart diseases, this is further strengthened by the increase in the levels of high density lipoprotein cholesterol (HDL). The study however demonstrated the weight reducing effects of papaya which may have a role to play in trying to improve the sensitivity of insulin in cases of overweight type 2 diabetics.

4.2 Graphical illustration of Results obtained.

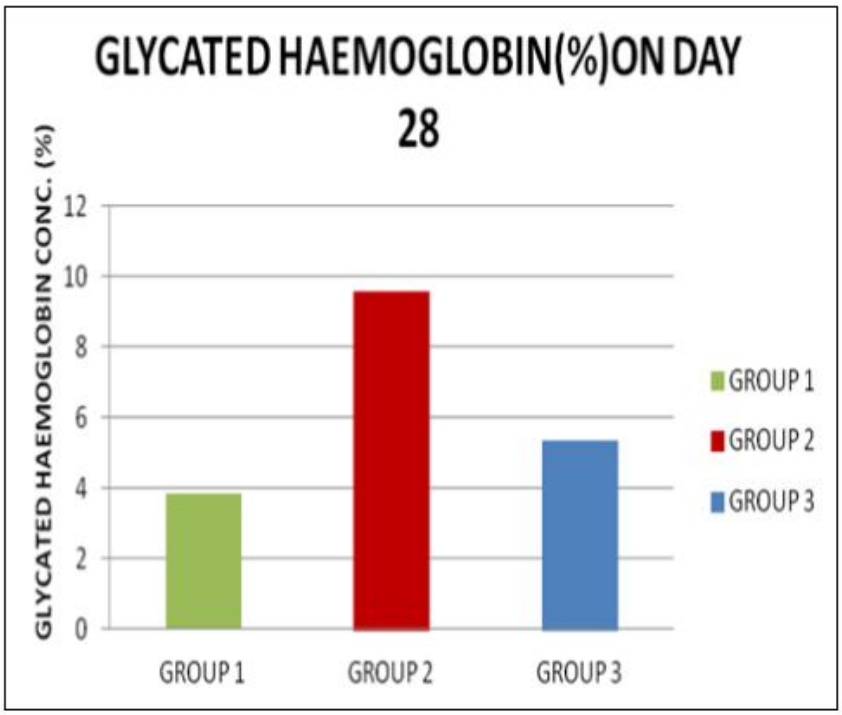

Fig 1: Showing the effects of unripe pulp of *Carica papaya* on Glycated hemoglobin levels

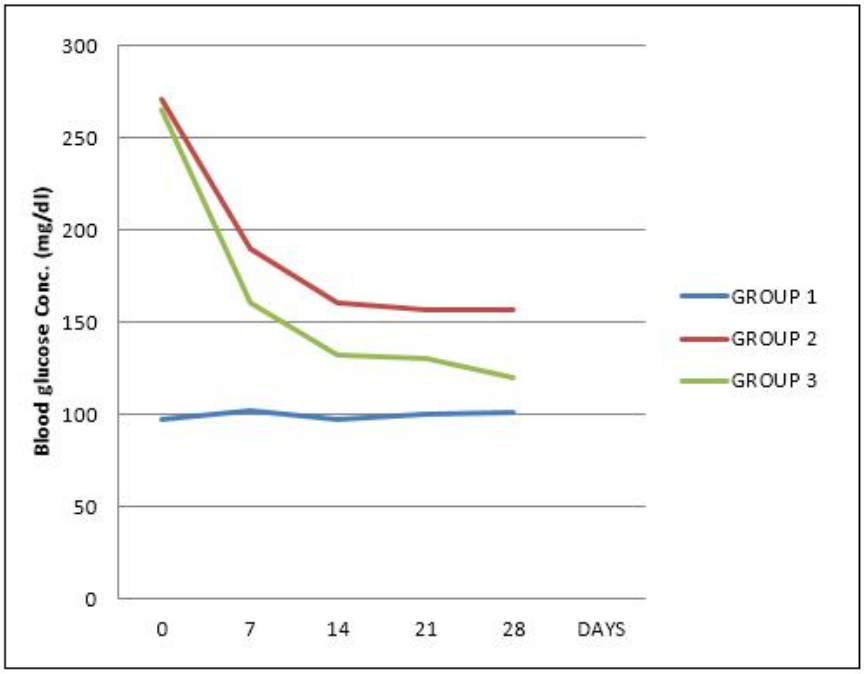

Fig 2: Showing the effects of unripe pulp of *Carica papaya* on blood glucose level

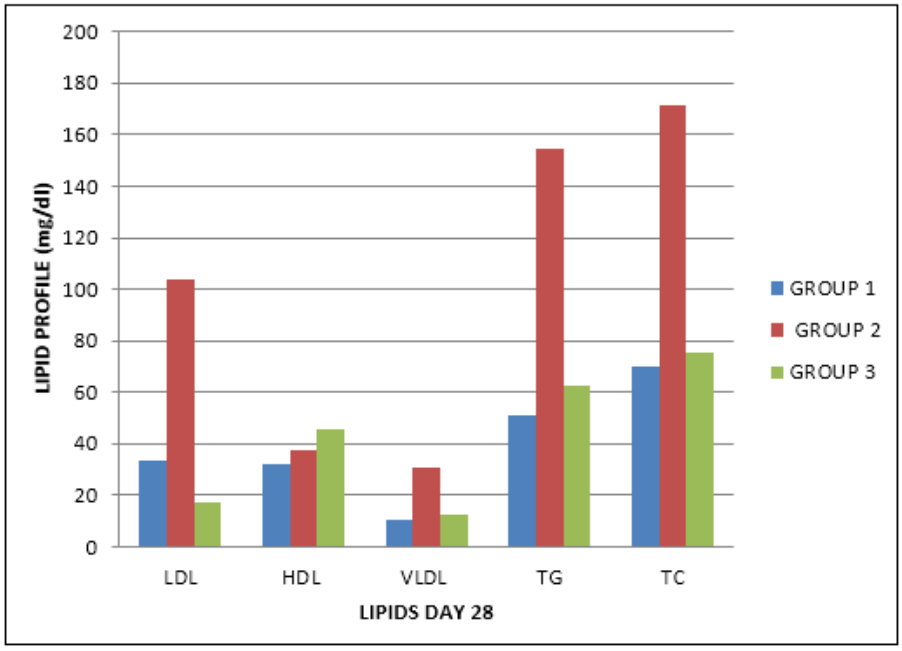

Fig 3: shows effect of unripe pulp of *Carica papaya* on lipid parameters.

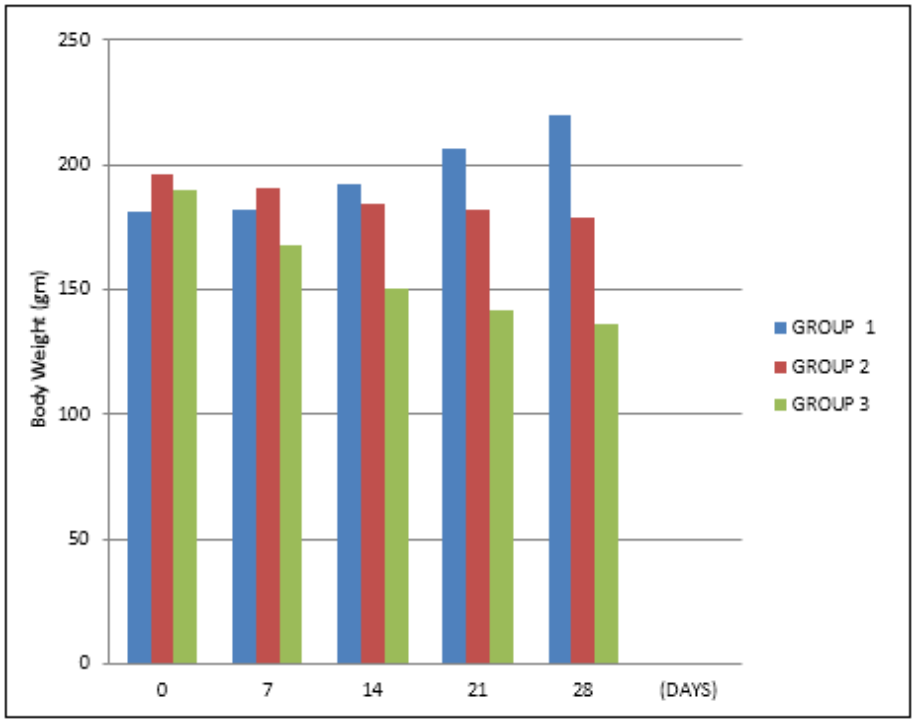

Fig 4: Bar chart showing effects of unripe pulp of *Carica papaya* on body weight.

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