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Antidiabetic effect of aqueous extract of ripe *Carica papaya* Linnaeus seed in alloxan-induced diabetic albino rats

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This research was carried out to evaluate the antidiabetic effect of aqueous extract of ripe *Carica papaya* L. seed in alloxan-induced diabetic albino rats. Diabetes is a metabolic disease associated with sustained hyperglycaemia. Diabetes has become a global threat because its incidence is increasing on daily basis. Pathogenesis of diabetes mellitus and the possibility of its management by therapeutic agents without any side effects have triggered great interest in scientific research. So, World Health Organization has recommended and encouraged the use of alternative therapy especially in countries where access to the conventional treatment of diabetes is inadequate. Ripe pawpaw fruits were collected from a farm, washed, sliced and the seeds were removed. The seeds were air-dried, ground, sieved and the aqueous extract was prepared by dissolving 10 g of the powder in 40 ml of distilled water. Twenty albino rats were used for this research. The animals were divided into four groups, each group containing five animals. Groups 1 and 2 rats were diabetic and treated with 1200 and 400 mg/kg of aqueous extract of ripe *C. papaya* L. seed respectively, group 3 involves diabetic untreated rats, and group 4 the control rats. Fasting blood glucose, lipid profile, serum proteins and some electrolytes were measured. Results of this experiment showed a significant decrease ($P<0.05$) in the fasting blood glucose. There was also a significant increase in the level of serum protein and some electrolytes toward the basal level. Concentrations of lipid profile were reduced in diabetic untreated rats. Effect of ripe *C. papaya* L. seed is duration-dependent and it has been shown from this research that aqueous extract of ripe *C. papaya* L. seed has an antidiabetic effect.

Key words: Ripe *Carica papaya* L. seed, metabolic disease, albino rats, blood glucose, serum protein, electrolytes, lipid profile.

INTRODUCTION

Diabetes is a heterogenous disease that is characterized by hyperglycaemia, lipoprotein abnormalities and altered intermediary metabolism of main food substances (Scoppola et al., 2001). Chronic hyperglycaemia during diabetes causes glycation of body proteins that in turn leads to secondary complications affecting eyes, kidneys, nerves and arteries (Kameswara et al., 1999). Along with hyperglycaemia, diabetes is associated with microvascular

and macrovascular complications which are the major causes of morbidity and death in diabetic subjects (Virella, 2003). Diabetes case in North America and Europe is about 10% of their population, about 50% in Africa and about 27% in Nigeria (Rother, 2007). Diabetes mellitus can be diagnosed by demonstrating any of the following: fasting plasma glucose level at or above 126 mg/dl (7 mmol/l), plasma glucose at or above 200 mg/dl (11.1 mmol/l) 2 h after 75 g oral glucose load as in a glucose tolerance test, random plasma glucose at or above 200 mg/dl (Sacks et al., 2011).

There is an elevated serum lipids in diabetes. Lipids play an important role in the pathogenesis of diabetes mellitus (Mironava et al., 2007). Serum protein concentration is decreased in diabetes also electrolyte concentrations such as sodium and chloride ions are reduced due to excessive loss of electrolyte in urine (polyuria associated with diabetes). Diabetes can be managed by exercise, diet and pharmaceutical drugs which are either too expensive or have undesirable side effects or contraindications (Seuring, 2015). The search for more effective and safer hypoglycaemic agents therefore has continued to be an area of research (Krishna et al., 2004). Also, the pathogenesis of diabetes mellitus and the possibility of its management by therapeutic agents without any side effects have stimulated great interest in scientific research, so, management of diabetes without any side effects is still a challenge for the medical system. The World Health Organization has recommended and encouraged the use of alternative therapy especially in countries where access to the conventional treatment of diabetes is not adequate (WHO, 1980).

The aim of this study is to investigate the antidiabetic effect of aqueous extract of ripe *Carica papaya* L. seed in alloxan-induced diabetic albino rats.

MATERIALS AND METHODS

Collection and preparation of ripe *C. papaya* seeds

Ripe pawpaw fruits were collected from Ologundudu farm in Oke-Ogun area of Oyo State, Nigeria. The fruits were washed, sliced and the seeds were removed. The seeds were air-dried and ground into powdery form using mortar and pestle and sieved. Ten grams of the powder was dissolved in 40 ml of distilled water as crude extract.

Animals

Albino rats weighing 60 to 125 g were used. The animals were maintained under laboratory conditions of humidity, temperature (23 to 25°C) and light 12 h light-dark cycle in the animal house of to 25°C) and light 12 h light-dark cycle in the animal house of Department of Physiology, Ladoke Akintola University of Technology, Ogbomoso, Nigeria and allowed free access to grower's mash and water *ad libitum*. The animals were acclimatized for two weeks. The experiment was carried out according to the guideline procedures of the animal house.

Induction of diabetes

After fasting the animals for 12 h over the night, the animals were given a single dose of intraperitoneal injection of freshly prepared alloxan solution of 120 mg/kg body weight (Bahnak and Gold, 1982). The diabetic state was ascertained in terms of high blood glucose level within 48 h of induction.

Experimental design

Twenty albino rats were used but the animals were divided into four groups, each group containing five animals (n=5):

Group 1: Ddiabetic rats treated with 12000 mg/kg of aqueous extract of *C. papaya* L. seed
Group 2: Diabetic rats treated with 400 mg/kg of aqueous extract of *C. papaya* L. seed
Group 3: Diabetic untreated rats
Group 4: Control rats

Determination of fasting blood glucose level

Fasting blood glucose levels were determined by using glucometer (Accu-chek Active) and test strips by glucose oxidase method.

Duration of treatment

Treatment began on the day the diabetic state was ascertained. Blood glucose level was determined weekly for three weeks throughout the period of the experiment.

Analysis

The animals were then sacrificed through cervical dislocation and blood samples were collected through cardiac puncture for the biochemical analysis.

Biochemical analysis

Determination of lipid profile

Triglycerides (TG), total cholesterol (T-ch) and high density lipoprotein cholesterol (HDL-c) concentrations were measured by using spectrophotometer with the aid of commercial kits (France). LDL-c level was estimated using Shertzer's formula (Shertzer et al., 2011).

LDL-c = T-ch- (TG/5) - (HDL-c)

Determination of total protein

Colorimetric assay (Biuret): In an alkaline medium, divalent copper reacts with protein peptide bonds forming a purple-colored

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Table 1. Effect of aqueous extract of *Carica papaya* L. seed on fasting blood glucose level (FBG) (mg/dl).

Group	FBG prior Alloxan induction	FBG after alloxan induction	FBG after 7 days of treament	FBG after 14 days of treatment	FBG after 21 days of treatment
1. Diabetic rats+1200 mg/kg of Aq. Extract of *Carica papaya* L. seed	83.20 ± 1.26*	320.2 ± 6.44*	202.2 ± 4.40*	134.8 ± 4.96*	99.6 ± 4.03*
2. Diabetic rats + 400 mg/kg of Aq. Extract of *Carica papaya* L. seed	64.80 ± 0.98*	370.6 ± 7.45*	249.2 ± 5.42*	184.8 ± 6.81*	98.00 ± 3.97*

Fasting blood glucose levels were increased significantly (P<0.05) 48 h after the induction of diabetes. But the fasting blood glucose levels were reduced toward the basal level by the aqueous extract of ripe *Carica papaya* L. seed significantly (P<0.05). Values are given as Mean ± SEM (n=5: number of rats per group); Significant difference *P<0.05.

Table 2. Effect of aqueous extract of ripe *Carica papaya* L. seed on lipid profile (mg/100 ml).

Group	Cholesterol	Triglyceride	HDL	LDL
1. Diabetic rats +1200 mg/kg of Aq. Extract of *Carica papaya* L. seed	39.40 ± 1.73*	86.40 ± 3.80*	16.58 ± 0.73*	13.90 ± 0.61*
2. Diabetic rats + 400 mg/kg of Aq. Extract of *Carica papaya* L. seed	63.60 ± 3.76*	165.00 ± 9.77**	14.84 ± 0.88*	15.76 ± 0.93*
3. Diabetic untreated rats	43.40 ± 1.73*	74.00 ± 2.94*	11.50 ± 0.46*	17.10 ± 0.68*
4. Control rats	65.60 ± 2.22	125.80 ± 4.24	100.70 ± 3.41	22.50 ± 0.76

*Represent significant decrease at P<0.05 compared to control rats. **Represent significant increase at P<0.05 compared to control rats. Values are given as Mean ± SEM (n=5: number of rats per group).

biuret complex that is measured photometrically. The color intensity generated by this complex is directly proportional to the total protein concentration. Reaction is as follows:

Protein + Cu^{2+} $\xrightarrow{\text{alkaline solution}}$ Cu-protein complex

Units of measurement: Total protein concentration is measured in g/dL (conventional units) and g/L (SI units). The conversion formula is as follows:

g/dL × 10 = g/L

Determination of sodium ion

Sodium ion was determined by flame emission photometry.

Determination of chloride ion

Chloride ion was determined by measurement colometrically.

Statistical analysis

All values were expressed as Mean ± standard error of mean (SEM). The differences were compared using one-way analysis of variance (ANOVA) followed by student t-test. P values < 0.05 were considered as significant. (Table 1 to 4)

RESULTS AND DISCUSSION

Alloxan monohydrate induces diabetes by damaging the insulin secreting cells of the pancreas leading to hyperglycaemia (Cnop et al., 2005). Diabetes mellitus is a metabolic disease linked to impaired glucose metabolism (Tallroth et al., 1990). Three main types of diabetes mellitus (DM) exist. Type 1 diabetes mellitus results from the failure of the body to produce insulin and is required of the individual to inject insulin or wear an insulin pump (Amed and Oram, 2016). This type was formerly called insulin-dependent diabetes mellitus. Type 2 diabetes mellitus results from insulin resistance, a situation where the cells of the body cannot access insulin. This was formerly called non-insulin dependent diabetes mellitus. The third major type of diabetes mellitus is gestational diabetes; it happens when pregnant women who have no past history of diabetes begin developing high level of blood sugar. Other forms of diabetes mellitus include congenital diabetes, which is due to genetic defects of insulin secretion, cystic fibrosis-related diabetes, steroid diabetes induced by high doses of glucocorticoids, and several forms of monogenic diabetes. The prevalence of diabetes is about 8.3% affecting about 387 million people worldwide in 2013 with many cases of diabetes undiagnosed in Africa (Guariguata et al., 2014). The incidence of diabetes is increasing daily and has become a

Table 3. Effect of aqueous extract of ripe *Carica papaya* L. seed on serum protein concentration (g/l).

Group	Albumin	Globulin
1. Diabetic rats +1200 mg/kg of Aq. Extract of *Carica papaya* L. seed	24.40 ± 1.75*	23.00 ± 1.64
2. Diabetic rats + 400 mg/kg of Aq. Extract of *Carica papaya* L. seed	26.60 ± 1.97*	26.2 ± 1.94*
3. Diabetic untreated rats	27.20 ± 1.83*	22.00 ± 1.48*
4. Control rats	27.80 ± 1.84	28.60 ± 1.89

Albumin and globulin levels were increased significantly (P<0.05) in diabetic rats treated with the aqueous extract of ripe *Carica papaya* L. seed toward the basal level. Values are given as Mean ± SEM (n=5: number of rats per group); Significant difference *P<0.05.

Table 4. Effect of aqueous extract of ripe *Carica papaya* L. seed on electrolyte concentration (mmol/l).

Group	Na^+	Cl^-
1. Diabetic rats +1200 mg/kg of Aq. Extract of *Carica papaya* L. seed	126.8 ± 2.94**	100.20 ± 2.32*
2. Diabetic rats + 400 mg/kg of Aq. Extract of *Carica papaya* L. seed	126.00 ± 2.08**	103.80 ± 1.71*
3. Diabetic untreated rats	119.80 ± 1.93*	99.40 ± 1.61*
4. Control rats	122.60 ± 1.44	107.4 ± 1.27

Sodium ion concentration increased significantly (P<0.05) in diabetic rats treated with the aqueous extract of ripe *Carica papaya* **L.** seed when compared with the control rats. Chloride ion concentration increased significantly toward the basal level by the aqueous extract of ripe *Carica papaya* **L.** seed. Values are expressed as Mean ± SEM (n=5, number of rats per group).

treat globally.

An observation in this study correlates with the previous research finding in that the blood glucose levels significantly increased in alloxan-induced diabetic rats. However, the glucose levels were reduced toward the basal level significantly (P<0.05) after the treatment with the aqueous extract of ripe *C. papaya* L. seed for three consecutive weeks.

One of the symptoms of diabetes is polyuria, that is, excessive elimination of urine resulting to loss of electrolytes such as sodium and chloride ions (Rother, 2007). This study also observed a decrease in sodium and chloride ions concentrations in the diabetic rats which were increased significantly (P<0.05) after the three weeks of treatment with the aqueous extract of ripe *C. papaya* L. seed.

In this study, decrease in the concentrations of albumin and globulin was also observed. These concentrations however, increased significantly toward the basal level after the three weeks of treatment with the aqueous extract of ripe *C. papaya* L. seed.

The levels of lipid profile in this study were significantly reduced when compared with the control rats. This observation could be as a result of the longer duration of the experiment.

Conclusion

The possible mechanism by which aqueous extract of ripe *C. papaya* L. seed brings about its hypoglycaemic action may be by potentiating the insulin effect either by increasing the pancreatic secretion of insulin from the cells of Islets of Langerhans or its release from bound insulin.

This finding indicates that aqueous extract of ripe *C. papaya* L. seed has antidiabetic effect and could also normalize other symptoms associated with the disease. Further study can be done to find out the active ingredients responsible for this action.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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