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Evaluation of the Antihyperglycemic and Antioxidant Effects of Methanol Crude Extract of Unripe Pulp of *Carica papaya* on Diabetic Male Albino Rats Induced by Alloxan

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

This study investigated the effects of the methanol extract of *Carica papaya* leaves on anti-diabetic and antioxidant effects in alloxan-induced diabetic rats. *Carica papaya* leaves were extracted using 80% methanol. 40 healthy rats weighing 110–150 g was grouped into eight (8) groups of five rats each: Group 1 (normal control), Group 2 (negative control), and Group 3 (positive control); Group 4 (200 mg/kg) of extract; Group 5 (400 mg/kg) of extract; Group 6 (600 mg/kg) of extract; Group 7 (800 mg/kg) of extract; and Group 8 (1000 mg/kg) of extract. Diabetes was induced by a single intraperitoneal administration of 120 mg/kg body weight of alloxan. Groups 1-3 served as normal, negative (untreated), and positive (standard drug) controls, respectively; groups 4–8 were treated groups. Administration was done orally for twenty-eight (28) days, and fasting blood glucose levels were obtained at a seven-day interval. After treatments, the rats were anaesthetized, and blood was collected by cardiac puncture for determination of redox status using standard analytical procedures. Diabetic rats treated with *Carica papaya* leaf extract significantly reduced ($p < 0.05$) their glucose level when compared with the positive control and the negative control. The reduction in fasting blood glucose levels of the extract-treated groups was consistently observable in groups 7 and 8, respectively, which were treated with high doses. The serum glutathione peroxidase, reduced glutathione, catalase, and superoxide dismutase catalase activities of rats treated with extracts showed a significant increase ($p<0.05$) when compared with the diabetic untreated (negative) control. There was a significant reduction in malondialdehyde levels in all the groups treated with the extract when compared with the diabetic untreated (negative) control. The non-enzymatic antioxidants (Vitamin C and E) increased significantly in some of the treated groups when compared with the negative control. The present study showed that the methanol extract of *Carica papaya* leaves offered a significant hypoglycemic effect and antioxidant effect in alloxan-induced diabetic rats, which can be a result of the presence of certain phytochemicals responsible for the increase in the antioxidant enzyme activity of the experimental animals.

Keywords: Alloxan monohydrate; Carica papaya leaves; antioxidants; diabetes mellitus.

1. INTRODUCTION

"Diabetes mellitus (DM) is a chronic metabolic disorder that is characterized by hyperglycemia (blood sugar levels that are much higher than normal) and varying degrees of impairment in carbohydrate, lipid, and protein metabolism due to reduced insulin production (type-1), a poor response to insulin, and/or beta cell dysfunction. (type-2)" [1,2]. "The increasing nature of the disorder requires constant reassessment of hyperglycemic control in persons with diabetes and proper adjustment of curative regimens. When hyperglycemic control is not managed with a single agent, the addition of a second or third drug is always comparatively more effective than switching to another single agent" [3]. "In spite of the fact that researchers have established that oral medications such as metformin, sulfonylurea, and some exogenous insulin serve as therapies for the treatment of diabetes [4], a recent discovery has it that these oral medications have various adverse effects when taken, including gastrointestinal adverse effects, body fluid accumulation, and heart disease. As a result, there is a need to search for highly efficacious, safe, and harmless oral sugar level drug formulations that will be free from adverse effects" [5].

Herbal remedies have been used for a long time to treat many different kinds of illnesses because they contain a lot of phytochemicals. They are considered to be all-natural, risk-free, and very efficient [6]. Herbal medications for diabetes control and treatment have been shown to be superior to synthetic alternatives owing to their greater availability, cheaper cost, fewer challenges, and fewer adverse reactions. Herbal drugs decrease blood sugar in a number of ways, including by lowering insulin resistance, increasing insulin production, protecting pancreatic beta cells, and so on [7]. More than 800 plant species have been found to display antidiabetic properties, and hundreds more have been utilized medicinally throughout the years as integrated therapies for a wide range of ailments [8].

Carica papaya (Linnaeus family Caricaceae) is a medicinal plant that may be found growing in tropical or subtropical regions all over the globe. Due to the *papaya's* medicinal qualities, various portions of the fruit, particularly the leaves, are often put into infusions for therapeutic purposes.

Numerous bioactive metabolites, including glutaminyl-cyclase, chitinase, and cysteine [9], as well as alkaloid compounds, such as pseudo-carpaine, dehydro-carpaine-I, and dehydro-carpaine-II, as well as other significant active substances, such as flavonoids, papain, ascorbic acid, chymo-papain, tocopherol, cystatin. [10]. Papain, a proteolytic enzyme found in *C. papaya*, helps break down proteins [11]. Additionally, it has been used to reduce a number of irritable bowel syndrome (IBS) symptoms, including bloating and constipation [12]. *Papaya* leaf has been used therapeutically to cure a variety of illnesses, including dengue fever and malaria, according to studies [13]. Some research has also noted *papaya's* anti-tumour, anti-microbial, and anti-inflammatory properties [14]. Some of the beneficial and necessary substances found in *papaya* protect the organism from oxidative stress by acting as antioxidants and scavenging free radicals [15]. *Papaya's* antioxidants may stave off a number of degenerative illnesses, including leukaemia, heart attacks, and early ageing.

An imbalance between the generation and removal of free radicals leads to oxidative stress, a harmful condition. It is important to note that oxidative damage, which accumulates over the course of a person's life and has been linked to ageing and age-related diseases like cancer, heart disease, and neurodegenerative disorders, among others, can be caused if the production of free radicals exceeds the protective effects of antioxidants. [16]. According to research, long-term diabetes changes the balance between the production of reactive oxygen species and the total antioxidant state [17]. However, further research is required to determine the status of each antioxidant enzyme in diabetes, especially in the early stages of the illness. Hence, this study was set up to evaluate the potency of the leaf extract on induced diabetic rats. Specifically, the study aimed to evaluate the antihyperglycemic and antioxidant effects of a methanol crude extract of unripe pulp of *Carica papaya* on diabetic male albino rats induced by alloxan. This work is important because biochemical changes are major observable clinical and pathological features common with diabetes.

2. MATERIALS AND METHODS

2.1 Plant Materials

C. papaya leaves were collected from pawpaw trees in Lodu Ndume, Umuahia North Local Government Area of Abia State, Nigeria. The leaves were identified and authenticated by a plant taxonomist (Dr Ibe K. Ndukwe) from the forestry department, College of Natural Resources and Environment Management (CNREM), and Michael Okpara University of Agriculture Umudike, where a voucher specimen (IHF 26123) was deposited in the departmental herbarium. The leaves were collected, washed, and dried under shade at room temperature 25^{o}C, then weighed and milled into powder. The leaves powder were soaked in 80:20 v:v of methanol:distilled water for three days with occasional shaking, filtered by using Whatman filter paper No.1, the solvent was evaporated by rotary evaporator under reduced pressure at 40^{o}C.

2.2 Phytochemicals and Toxicity of Methanolic Extract of *Carica papaya*

“Phytochemical screening was performed for the presence of alkaloids, carbohydrates, amino acids, glycosides, protein, phenolic compounds, and tannins in different organic solvents such as hexane, ethyl acetate, methanol, and ethanol, according to standard procedure” [18,19]. “Acute oral toxicity (LD50) was performed by the method of Lorke” [20]. “Three groups of rats each comprising of three rats each were administered with 500, 800 and 1000 mg/kg of herbal formulation by mouth and examined for mortality within 24 hours. Following the results of mortality in each group, another set of three groups of rats were administered higher doses of the test drug, to achieve the least and most toxic value and LD50 was calculated by geometric mean of the mortality values. LD50was calculated as: LD50 = [M0 + M1] ÷ 2, where M0 = highest dose of test substance that gave no mortality and M1= lowest dose of test substance that gave mortality” [20].

2.3 Ethical Adherence and Experimental Animals and Design

The study adhered strictly to the ethical guidelines on animal use as stipulated by the National Research Council, NRC, USA (2011). Forty (40) healthy adult wistar rats (110-150g) procured from College of Veterinary Medicine, Michael Okpara University of Agriculture, Umudike, Abia State was used for the study. All animals were allowed free access to food and water and were housed in aluminum cages maintained under standard laboratory conditions with light and dark cycles of 12 h each and room temperature of 25 ºC. Acclimatized adult male

albino rats (110-150g) were randomly allotted to eight groups of 5 rats each. Group 1 rats received normal saline (1 ml). Group 2 (induced with diabetes but not treated), and Group 3 (induced with diabetes and treated with standard drug (Glibenclamide, 2 mg/kg bw)); Group 4 (200 mg/kg) of extract; Group 5 (400 mg/kg) of extract; Group 6 (600 mg/kg) of extract; Group 7 (800 mg/kg) of extract; and Group 8 (1000 mg/kg) of extract. At the end of acclimatization, the animals were allowed to fast and then diabetes was induced by intra-peritoneal (IP) injection of 120mg/kg body weight of alloxan monohydrate solution by the method of Yanardag and Colak [21]. Rats with elevated blood glucose concentration above 150mg/dl were considered diabetic after 4 days of induction using fasting blood sugar test and were used for the study. Experimental administration was orally by gavage and daily for 28 days. At the end of 28 days experimental period, the animals were sacrificed by cervical dislocation, and blood samples were collected by cardiac puncture into plain bottles (to obtain clotted blood). The blood thus collected was allowed to clot after standing for 10 minutes at ambient temperature. Thereafter, the respective serum was separated by centrifuging the coagulated blood samples at 3000 × g for 15 minutes and used for the determination of fasting blood glucose (FBG), of superoxide dismutase (SOD), catalase activity (CAT), Malondialdehyde (MDA), reduced glutathione (GSH), and glutathione peroxidase (GPx). The serum indicators level of antioxidant parameters (MDA, GSH, GPx SOD, CAT) was respectively determined with Randox commercial Kits.

2.4 Estimation of Blood Glucose Concentration

The blood glucose levels of the animals were determined using a Glucometer Acu-check (Tyson Bio Evolve glucometer, Tyson Bioresearch Inc., Hangzhou, China) and subsequently on a weekly basis at days 0, 7, 14, 21 and 28 throughout the period of treatment with standard drug and extract.

2.5 Determination of Antioxidant Activity

2.5.1 Determination of superoxide dismutase (SOD)

Superoxide dismutase was determined using the method Aebi [22]. Adrenaline (10 mg) was dissolved in 17 mL of distilled water to make adrenaline solution. Serum sample (0.1 mL) was added to 2.5 mL of phosphate buffer (pH 7.8). Adrenaline solution (0.3 mL) was added, mixed well and absorbance was read at 450 nm at 30 seconds interval for 5 times.

2.5.2 Determination of catalase activity

Determination of catalase activity was according to the method of Obi and Egbuonu [23].

2.5.3 Determination of reduced glutathione

Glutathione concentration was determined according to the method of Ellman [24].

2.5.4 Determination of glutathione peroxidase

“The activity of reduced glutathione peroxidase was determined using the method of Paglia and Valentine” [25].

2.5.5 Determination of peroxidase activity

“The activity of reduced glutathione peroxidase was determined using the method of Paglia and Valentine” [25].

2.5.6 Malondialdehyde (MDA) level Determination

Lipid peroxidation was determined spectrophotometrically by measuring the level of lipid peroxidation product, malondialdehyde (MDA), as described by Onkawa et al. [26]. Malondialdehyde reacts with thiobarbituric acid (TBA) to form a red or pink coloured complex that absorbs maximally in acid solution at 532 nm.

2.5.7 Vitamin C Determination

Vitamin C level was determined using the method of Omaye et al. [27].

2.5.8 Vitamin E Determination

“Vitamin E level was determined using the method of Rosemberg” [28].

2.6 Statistical Analysis

Data obtained from the experiments were analyzed using one-way analysis of variance (ANOVA). Statistical package for social sciences (SPSS) version 20.0. The analysis data was

reported as mean ± standard error of mean (SEM). Significant difference using Tukey's Post Hoc test was accepted at 95% confidence level of probability i.e., at $p < 0.05$.

3. RESULTS

The result of the phytochemical assay, revealed the presence of important bioactive compounds such as Alkaloid, Carbohydrate, Amino acid, Glycoside, Phenols, tannin, Proteins, Saponin, Quinine, Oxalate, Anthocyanin (Table 1).

The result of the acute toxicity study indicated that the *Carica papaya* leaf extract does not have any acute toxicity since no mortality was recorded at the highest dose of 1000 mg/kg (Table 2).

The results for the effect of *Carica papaya* leaf extracts on GSH, GPx, SOD, MDA, and CAT in diabetic animals, as presented in Table 4, showed that glutathione was significantly (P 0.05) reduced in the diabetic control animals compared to the normal control animals. Glutathione concentration significantly increased back to normal in the *Carica papaya* leaf extract-treated groups compared to the diabetic control animals. Glutathione depletion was also reversed in the glibenclamide group. The diabetic control group showed a significant decrease in SOD and CAT expression compared to the normal animals. SOD and CAT levels also increased significantly in the *Carica papaya* leaf extract treatment group at 200, 400, 600, 800, and 1000 mg/kg compared to the diabetic control and normal animals. Expression of the MDA was significantly elevated in the diabetic control animals compared to the normal animals, and treatment with *Carica papaya* leaf extracts was able to significantly reverse the expression of the MDA to normal.

4. DISCUSSION

C. papaya is a potential therapeutic plant rich in phytochemicals that include glycosides, saponins, flavonoids, and phytosterols. Due to the pharmacological efficacy of these bioactive components, they play a variety of vital functions in human existence. It's interesting to note that the *C. papaya* has shown to be one of the best digestive aids for breaking down gluten, the metabolic trigger for celiac disease. Plant extracts must be subjected to acute toxicity testing in order to establish the proper dosage range for later application and evaluate any possible side effects.

C. papaya leaf extracts were discovered to be risk-free with a wide therapeutic range, as the acute toxicity result showed no evidence of toxicity and there was no incidence of fatality up to a very high dosage. A crude methanol extract of the unripe pulp of *C. papaya* was thus used in this investigation to assess its antihyperglycemic and antioxidant properties on diabetic male albino rats that had been induced by alloxan.

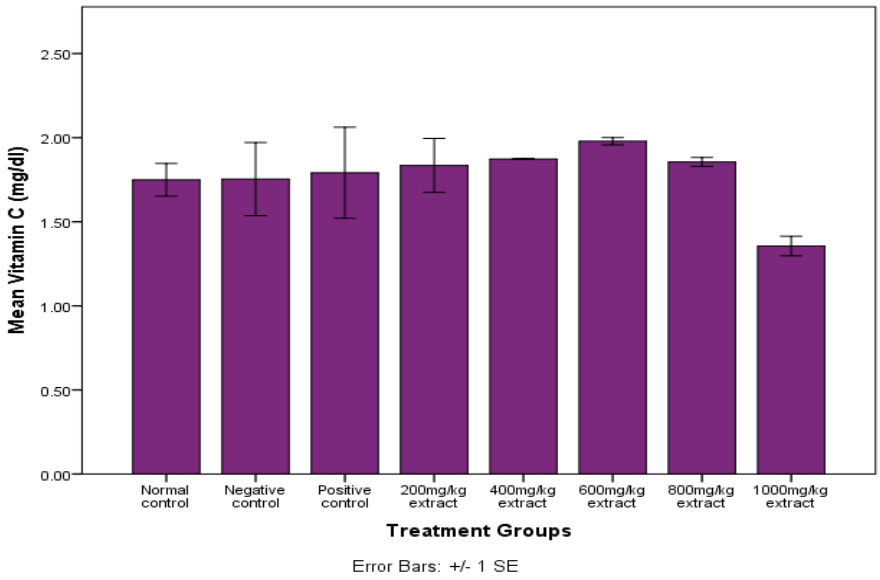

Fig. 1. Vitamin C concentration in diabetic rats treated with extracts of C*arica papaya* leaves

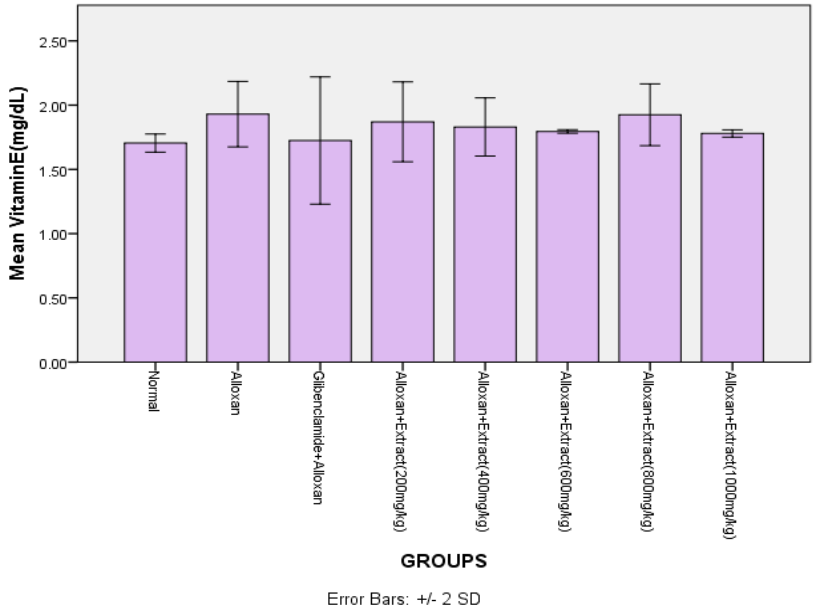

Fig. 2. Vitamin E concentration in diabetic rats treated with extracts of C*arica papaya* leaves

Table 1. Qualitative analysis of *Carica papaya* leaves extract: phytochemical screening

S. No.	Sample	Alkaloid	Carbohydrate	Amino acid	Glycoside	Phenols tannin	Proteins	Saponin	Quinine	Oxalate	Anthocyanin
1.	Methanol	+	+	+	+	+	−	+	+	+	−

Table 2. Acute toxicity of methanolic extract of *Carica papaya* leaves

Groups	Concentration (mg/kg)	Mortality
Group 1 (Control)	-	Nil
Group 2	400mg/kg	Nil
Group 3	600 mg/kg	Nil
Group 4	800 mg/kg	Nil
Group 5	1000 mg/kg	Nil

Table 3. Comparison of mean glucose level in the *C. papaya* leaves extract in normal control, negative and positive (Glibenclamide) for 28 days

Groups/Days	DAY 0	DAY 7	DAY 14	DAY 21	DAY 28
Group A (Normal control): received distilled water only	65.0±1.02	64.3±0.02	66.0±0.12	63.0±1.11	62.2±0.05
Group B (Negative control): were diabetic but not treated	356.2±0.12	350.1±0.10	352.3±0.12	364.0±0.12	378.0±1.05
Group C (Positive control) were diabetic and treated with Glibenclamide	325.1±0.01	269.2±0.13*	240.6±1.11*	190.3±0.14*	174.2±1.13*
Group D: were diabetic and treated with 200mg/Kg B. WT of *C. papaya* leaves	303.5±1.00	232.4±1.05*	211.2±1.01*	179.1±0.10*	149.0±0.13*
Group E: were diabetic and treated with 400mg/Kg B. WT of *C. papaya* leaves	307.2±1.04	265.2±2.02*	256.2±1.03*	160.2±1.11*	100.2±0.02*
Group F: were diabetic and treated with 600mg/Kg B. WT of *C. papaya* leaves	302.5±1.11	270.4±1.02*	243.1±1.14*	136.2±1.15*	94.2±1.11*
Group G: were diabetic and treated with 800mg/Kg B. WT of *C. papaya* leaves	315.2±0.15	250.3±0.10*	232.1±1.10*	112.2±1.05*	94.2±0.14*
Group H: were diabetic and treated with 1000mg/Kg B. WT of *C. papaya* leaves	306.2±1.12	262.1±1.11*	226.2±1.13*	100.1±1.02*	85.0±1.03*

*Values are mean ± SD; n=5, values are statistically diabetic but not treated, Group C (Positive control) were significant *(p<0.05). Group A (Normal control): received diabetic and treated with Glibenclamide, Group D: were distilled water only, Group B (Negative control): were diabetic and treated with 200mg of C. papaya leaves, Group*

Table 4. Mean±SE of the antioxidant's parameters in groups of animals under investigation

Antioxidant Enzymes	Group 1 Normal Control	Group 2 Negative Control	Group 3 Positive Control	Group 4 200 mg/kg extract	Group 5 400 mg/kg extract	Group 6 600 mg/kg extract	Group 7 800 mg/kg extract	Group 8 1000 mg/kg extract
GPx (iu/l)	24.27±1.10*	15.50±0.51	27.80±1.00*	28.22 ± 0.14*	30.19±1.21*	31.59±1.38*	32.00±0.05*	35.63±0.32*
GSH (mg/dl)	5.35± 0.06*	3.90±3.09	4.98±0404*	4.75±0.02*	5.00±0.05*	5.56±0.10*	5.42±0.12*	5.59±0.10*
CAT (iu/l)	2.85± 0.05*	2.22±0.11	3.58± 0.52*	3.89±0.14*	4.52±0.12*	5.01±0.07*	5.27±0.00*	5.98±0.80*
SOD (iu/l)	3.09± 0.02*	2.10±0.00	3.12± 0.12*	4.14±0.00*	4.15±0.04*	5.15±0.32*	5.16± 0.02*	5.17±0.00*
MDA (nmol/ml)	3.01± 0.05	4.97±0.14	3.34±0.04	3.02±0.04	3.18±0.05	3.00±0.02	2.96±0.01	2.63±0.04

Result is expressed as mean ± Standard Deviation (n=5). Mean values (*) are significantly different from the negative control group at p<0.05

Significantly lowered fasting blood glucose levels were achieved by the aqueous extract of *C. papaya* leaves ($p<0.05$). When compared to glibenclamide, the usual medication for treating diabetes, our results showed that extracts on dosages of 200, 400, 600, 800, and 1000 mg/kg body weight of *C. papaya* leaves decreased blood glucose as much or more. This outcome demonstrated how potent the leaves of the *C. papaya* leaf may be as a diabetic therapy. It is recommended to use *C. papaya* to prevent and control diabetes since it has fewer side effects—or none at all—than conventional medications, such as glibenclamide, which has negative health impacts. In addition, the hyperglycemia caused by alloxan was mitigated by the extract. The findings of this research agree with those of the earlier study by Airaodionet al. [29] "on the effect of oral intake of African locust bean on fasting blood sugar and lipid profiles of albino rats". It also corresponds with another report by Airaodion et al. [30], who studied "the effect of a methanolic extract of *Corchorus olitorius* leaves on hypoglycemic and hypolipidemic activities in albino rats". In addition, the extract mitigated the complications of alloxan-induced diabetes; after 28 days, there were no ($p<0.05$) differences between the fasting blood sugar of animals treated with 200, 400, 600, 800, and 1000 mg/kg of body weight of crude extract of *C. papaya* leaves and the fasting blood sugar of non-diabetic animals serving as a normal control. "Several other plants and extracts have also been reported to have an antihyperglycemic and an insulin-stimulatory effect" [31]. "Most of the plants with hypoglycemic properties have been found to contain metabolites such as glycosides, alkaloids, and flavonoids" [32].

In diabetes, free radicals are produced as a result of the oxidation of glucose, nonenzymatic protein glycation, and the oxidative breakdown of glycated proteins that follows. Increased lipid peroxidation, insulin resistance, and cellular organelles and enzyme damage may all result from abnormally high quantities of free radicals and the loss of antioxidant defence systems. The risk of complications from diabetes mellitus may rise as a result of these oxidative stress effects [33].

The results of the antioxidant enzyme activities are shown in Table 4. The activities of all groups treated with *C. papaya* extract at varied doses significantly (p 0.05) increased when compared with the untreated negative (diabetic group) control. The extract at a dose of 1000 mg/kg body weight also showed a significant ($p<0.05$) increase in the activity of some antioxidant enzymes like glutathione peroxidase, reduced glutathione, catalase, and superoxide dismutase when compared with the negative control group. There was no significant ($p<0.05$) difference in the mean values of MAD in the treated group when compared with the negative control group. This result was in line with the findings of Ukpabi-Ugo et al. [34], who reported that "a significant rise in activity of antioxidant enzymes protects the cell from oxidative damage caused by reactive oxygen species". Also, Raghavan and Krishnakumari [35] reported that "the decrease in the activities of the superoxide dismutase enzyme resulted in the involvement of deleterious oxidative changes and also insufficient availability of MAD".

Administration of a methanol extract of pawpaw (*Carica papaya*) leaves elicited an effective reverse of the alloxan-induced oxidative stress. This antioxidant effect of pawpaw leaves is due to its phytochemical constituents, which include polyphenols, vitamins, and minerals, as reported by Nwangwa and Ekhoye [36] and Ezekwe et al. [37].

Non-enzymatic antioxidants (Vitamin C and E) levels showed no significant difference ($p > 0.05$) in the untreated diabetic rats when compared with the normal control. This result was in line with the findings of Ukpabi-Ugo et al. [34], who reported similar levels of no significant difference in vitamin E and D levels in the untreated diabetic rats.

5. CONCLUSION

The present study showed that the methanol extract of *Carica papaya* leaves offered a significant hypoglycemic effect and antioxidant effect in alloxan induced diabetic rats. These properties of extract may be attributed to its constituents which are mainly polyphenolic compounds with its antioxidant properties. *Carica papaya* leaves can be used in the management of diabetes whose pathogenesis and progression are known to be influenced by oxidant species.

CONSENT

It's not applicable.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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