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Assessment of Fertility Effect and Hypolipidemic Activity of *Carica papaya* (Linn) Leaf Methanol Extract in Male Diabetic Rats

Opeyemi O. Ayodele[1*], Ifeoluwa M. Dada[1] and Rotimi K. Adekunle[1]

[1]Department of Biological Sciences, College of Basic and Applied Sciences, Mountain Top University, Nigeria.

Authors' contributions

This work was carried out in collaboration among all authors. Author OOA developed the research concept and design, and wrote the first draft of the manuscript. Authors IMD and RKA carried out the experiments and performed the statistical analysis. All authors read and approved the final manuscript.

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ABSTRACT

Aim: Diabetes mellitus (DM) is a prevalent metabolic disorder that leads to other microvascular and macrovascular complications. Diabetes affects fertility and blood clotting, and also cause impaired lipid profile thus leading to increased atherogenic risks and coronary diseases. This research investigates the effects of *Carica papaya* leaf methanol extract on fertility indices and lipid profile of male diabetic rats.

Methodology: Male Wistar albino rats were randomly divided into five groups of six rats each. Diabetes was induced in the rats by a single intraperitoneal injection of streptozotocin (55 mg/kg). Diabetic rats were treated orally with 100 and 200 mg/kg *C. papaya* methanol extract for 14 days. At the end of administration, the plasma glucose concentration and lipid profile were assayed by spectrophotometric methods; seminal analysis was carried out for evaluation of morphology, motility and sperm count under the microscope. The bleeding and clotting times of the rats were also determined.

Results: *C. papaya* leaf methanol extract caused significant (p = 0.05) reduction in plasma glucose, total cholesterol, triglycerides, VLDL-C, LDL-C, bleeding and clotting times of diabetic treated rats, while the HDL-C of treated groups were significantly (p = 0.05) elevated compared to

**Corresponding author: Email: opeige@yahoo.com, ooayodele@mtu.edu.ng;*

the diabetic control. Percentage normal cells were lower in diabetic control rats (41.4±4.4%) and *C. papaya* treated groups (50.0±8.5% for 100 mg/kg; 47.5±9.1% for 200 mg/kg) compared with the normal control group (69.5±5.6%). Similar results were recorded for sperm count. The qualitative phytochemical screening showed the presence of steroids, anthraquinone, tannin, and other bioactive compounds.

Conclusion: findings from this study indicated that *C. papaya* leaf methanol extract could possess hypoglycemic and hypolipidemic activities. Thus, could be considered as a potential source of bio pharmacological agent for management and control of DM and its complications. Prolonged administration of C. papaya leaves may negatively affect male fertility.

Keywords: Diabetes mellitus; Carica papaya; fertility; lipid profile; seminal analysis.

1. INTRODUCTION

Diabetes mellitus (DM) is a potentially morbid disease that is comparatively common all over the world [1]. DM results from unusual high concentration of glucose in the blood which might be a direct implication of insulin deficiency [2]. It is a complicated disorder characterized by hyperglycaemia, causing malfunction in the secretion of insulin or insulin action. Diabetes mellitus is perhaps the world's prevailing increasing metabolic sicknesses affecting hundreds of millions of people [3].

DM can lead to other microvascular and macrovascular complication, affecting both men and women. It has thus been discovered to have an adverse effect on the fertility of men as a result of diabetic induced oxidative stress, which damages the sperm cell [4]. The state is accompanied with range of complications that affects the structural and functional properties of biomolecules [5-6]. Reports have indicated that male diabetic patients are prone to infertility [6-7].

Dyslipidemia has been reported as a significant risk factor that predisposes to cardiovascular disease in DM. This is because diabetes is usually accompanied by impaired lipid profile, which can lead to increased atherogenic index and coronary heart disease [8]. Several lipid defects are correlated with DM; emerging proof confirms the crucial position of hyperlipidemia, primarily high blood cholesterol, especially Low-density lipoprotein cholesterol (LDL-C) and Very low-density lipoprotein (VLDL-C) in atherosclerosis and cardiovascular diseases [9]. There are significant defects in lipid metabolism and lipoproteins in diabetes, which can be determined by the extent of insulin deficiency, insulin resistance, diet, obesity, and the attendant main and secondary causes of hyperlipidemia [10]. Elevated lipoproteins and other lipids in diabetic dyslipidemia results increased interaction of these lipids with free radicals, causing increased lipid peroxidation in the plasma, tissues and membranes. This ultimately affects tissues and organs functions. Lipid peroxidation is well established source of free radicals that play an important part in the pathogenesis of diabetes its complications [9].

Over the years, there is increased research focus on medicinal plants which may possess active compounds that can negate some of these complications associated with DM because herbal drugs generally have low toxic effects. *Carica papaya* L. Caricaceae also known as pawpaw with potential medicinal properties, is cultivated in most tropical countries [11]. It is a well-known medicinal plant with the stem, root, leaves, fruit and even the seed having tremendous health benefits [12]. Papaya is a powerhouse of nutrients and it is always available all through the seasons. It is a rich source of the three powerful antioxidant vitamins A, C, and E; minerals, magnesium, and potassium [13].

Papaya has been used in folklore and traditional medicine in Nigeria, Africa and other continents to treat different health conditions such as asthma, abdominal discomfort, diabetes, drug poisonings, fever, pain, hypertension, infections, malaria, and obesity. The plant is rich in phytochemicals such as flavonoids which have capability to inhibit the action of free radicals hence reduce oxidative stress [12]. Unripe papaya fruit has been reported to have an abortifacient effect on pregnant rats, and chloroform extract from papaya was reported to cause azoospermia in male rats [12,14]. *C. papaya* was also reported to be very useful in treating protozoal infections, bacterial infections, fungal infections, inflammation, and tumors because of its richness in antioxidants [15].

Papaya leaf juice is used in increasing platelets count, relieve of menstrual pain and nausea because of the richness in antioxidants contents [15]. The therapeutical potential of *C. papaya* on dengue and malaria, and the anti-inflammatory effect were reported [16-18]. In view of these reports, we found it essential to investigate the acclaimed anti-hyperglycemic effect of *C. papaya* leaves and the effects on lipid profile, blood clotting and fertility indices of male diabetic rats.

2. MATERIALS AND METHODS

2.1 Plant Material

Fresh papaya leaves were obtained from a local farm Ayobo Ipaja, Lagos State, Nigeria ((N 6° 36' 47.052", E 3° 15' 57.2652") in January 2019. The plant was identified and authenticated in the herbarium of the Department of Botany, University of Lagos, Lagos, Nigeria and a voucher specimen number 8787 was deposited for future reference.

2.1.1 Preparation of extract

The leaves were separated from the stem, cut into smaller pieces and oven-dried at 40^{o}C. The dried leaves were ground into powder using a mechanical blender. A 70 g of the C. papaya powder was macerated in 70% methanol (ratio 8:1 w/v) with intermittent shaking at room temperature for 72hours. The macerate was then filtered using muslin cloth, followed by Whatman no 4-filter paper. Subsequently, the solvent was evaporated under reduced pressure at a temperature of 40^{o}C using a rotary evaporator. The concentrate (methanol extract) was then stored in a refrigerator at 4°C.

2.1.2 Qualitative phytochemical screening

The methanolic extract was tested for the presence of certain phytochemicals using standard methods described by Sofowora [19], Harbone [20], and Trease and Evans [21] with slight modifications.

2.2 Experimental Animals

Male Wistar albino rats weighing (150-230 g) were purchased from the Animal facility of the Babcock University, Ilisan-remo, Nigeria. The animals were allowed to acclimatize for 14 days under controlled conditions of 12 hours light/dark cycle in the animal facility of the Department of Biological Sciences, Mountain Top University, Nigeria. They were maintained on standard feed and water *ad libitum*. All experiments on rats were carried out in absolute compliance with the National Institute of Health (NIH) animal care guidelines and approval was given by Institutional animal ethics committee.

2.3 Acute Toxicity Study

The acute toxicity study for the methanol extract of *C. papaya* leaves was performed according to the Organization for Economic Cooperation and Development (OECD) guideline 423 [22]. No mortality or abnormal behavior was observed up to 2000mg/kg for the methanol extract; thus, the dose was considered safe and doses of 100–200 mg/kg body weight were adopted for further pharmacological study.

2.4 Induction of Experimental Diabetes

Thirty (30) male albino rats (Wistar strain) weighing between 150-230 g were randomly grouped into 5 different well-ventilated cages of 6 rats per cage. The animals were weighed, and their fasting glucose levels were determined before inducing diabetes. A single intraperitoneal injection of streptozotocin (55 mg/kg b.w) dissolved in 0.1M citrate buffer (pH 4.5) for injection was administered after fasting. Control animals (group I) received distilled water as placebo while group II-V received 5% glucose solution for the next 12 hours to overcome STZ-induced hypoglycemia. The fasting blood glucose of the experimental rats were checked 72 hours (post induction) to confirm successful induction of diabetes. Hyperglycemia was confirmed three days after STZ injection in animals with blood glucose > 200 mg/dL, thus regarded as diabetic.

2.5 Experimental Design

The rats were divided as normal and hyperglycemia groups. The hyperglycemic rats were divided into 4 groups consisting of six animals each; the groups and doses administered were summarized below:

Group I– Normal Control (given distilled water)
Group II – STZ-Induced Diabetic rats given distilled water
Group III – Diabetic rats administered with 100 mg/kg body weight of *C. papaya* leaf methanol extract.
Group IV – Diabetic rats administered with 200 mg/kg body weight of *C. papaya* leaf methanol extract.

Group V – Diabetic rats administered with 100 mg/kg body weight metformin (standard drug).

Plant extract administration was done orally, once daily for 2 weeks. After which blood samples for Fasting blood glucose (FBG) determination were collected through a slight incision on the lateral tail vein using a surgical blade. The measurements were done in duplicate to ascertain the reliability of the glucometer readings. At the end of administration, the rats were sacrificed under anesthesia by cervical dislocation. Blood samples were collected through ocular and cardiac puncture into Lithium heparin bottles and centrifuged at 2500 rpm for 15mins. The obtained plasma was refrigerated at 4^{o}C for biochemical assays. Semen samples were collected from the epididymis into a clean plain tube, the liver was excised and washed in cold 0.9% NaCl, homogenized cold, and centrifuged at 12,000 rpm for 10mins. The supernatant was separated and frozen for assays.

2.6 Assays for Blood Glucose and Lipid Profile

Analysis of fasting blood sugar on plasma was done using Randox glucose (GOD-PAP) reagent. Plasma and liver lipid profile (total cholesterol, triglycerides and HDL-cholesterol) of the experimental rats were determined using standard assay kits from Randox laboratories, UK. The low-density lipoprotein cholesterol (LDL-C) and very low-density lipoprotein cholesterol (VLDL-C) concentrations were calculated using formula stated below:

$$\text{Concentration of VLDL-C (mg/dL)} = \frac{\text{Triglycerides conc.}}{5}$$

Concentration of LDL-C (mg/mL) = Total cholesterol - VLDL-cholesterol - HDL-cholesterol [23].

2.6.1 Determination of blood clotting and bleeding times of experimental rats

The clotting time was determined using Ivy's method as reported [24]. A drop of blood from the proximal tail of the rat was placed on a clean glass slide and a stopwatch began at the same time. A pin was passed across once every 15seconds. As soon as a thread of fibrin was seen, the stopwatch was stopped and the time was recorded as the blood clotting time of the rat.

The bleeding time was determined according to the method by reported by Raoof et al. [25]. The rat's tail was cut using a surgical blade 1-2cm proximal from the end (transection technique). A stop watch began immediately to observe till bleeding stop. Spots were made with the bleeding tail on a filter paper every 15seconds until the paper was no longer stained with blood. The time was recorded as the bleeding time of the rat.

2.6.2 Determination of sperm count and morphology of the experimental rats

The sperm count and morphology of the experimental rats were determined according to the method by Cheesbrough, [26].

To estimate the sperm count, a drop of liquefied semen was placed on the hemocytometer and covered with a cover glass to charge the hemocytometer. The charged hemocytometer was then placed under the microscope at 10X objective lens. Sperm cells that were seen in 5 squares that are diagonal to one another in the large square that contained 25 smaller squares were counted. Total number of cells counted was then multiplied by a factor 50,000.

For sperm morphology, a thin smear of the sample was made on a clean, grease-free slide, and fixed in 95% Ethanol. This was air dried and then stained with sodium bicarbonate-formalin for 1 minute. The fluid was washed away with equal volume of water, and the smear was flooded with carbol-fuchsin for 5 minutes, then rinsed with equal volume of water. The smear was counter stained using methylene blue for 2 minutes, rinsed with water again and air dry. The stained smear was then examined under the 10X objective lens under the microscope to count the number of sperm cells with good morphology in a total of 100 sperm cells counted. The spermatozoa were assigned normal or abnormal based on the sperm morphology criteria; the sperms assigned normal have smooth, oval head, well-defined acrosome, and no abnormality of midpiece (curved mid-piece) or tail.

2.7 Statistical Analysis

All values are presented as mean ± standard deviation. Variation within a set of data was analyzed by one-way analysis of variance (ANOVA) followed by Tukey's post hoc using the Graph Pad Prism Software (GPPS 7.0). P value less than 0.05 ($p < 0.05$) were considered significant.

3. RESULTS

3.1 Components of *C. papaya* leaf Methanol Extract

The phytochemical screening of the *C. Papaya* leaf methanol extract indicates the presence of some bioactive compounds including alkaloids, anthraquinone, flavonoids, glycosides, phenols, saponins, steroids, and tannins (Table 1).

3.1.1 Effects of methanol extract of *C. papaya* leaves on plasma glucose concentration of STZ- induced diabetic rats

A significant increase ($p < 0.001$) of plasma glucose concentration of diabetic control compared to the normal control was observed. Administration of the two tested concentrations (100 mg/dL and 200 mg/dL) of the plant extract significantly ($p < 0.001$) reduced the plasma blood glucose in the diabetic-treated rats (Fig. 1).

3.1.2 Effects of administration of methanol extract of *C. papaya* leaves on plasma lipid profile of STZ induced diabetic rats

The plasma total cholesterol, triglycerides and VLDL-C were significantly ($p = 0.05$) increased in diabetic control group compared with the normal rats. Administration of *C. papaya* leaf extract to diabetic rats significantly reduced ($p = 0.05$) the elevated lipid parameters in concentration dependent manner with the 200 mg/kg extract treated group recording the most significant reduction in all instance (Figs. 2 &3). Furthermore, the plasma HDL-C concentration was significantly reduced ($p < 0.01$) in diabetic control compared with the normal control; the concentrations were significantly increased in the diabetic treated groups compared with diabetic control (Fig.3).

3.1.3 Effects of administration of methanol extract of *C. papaya* leaves on bleeding and Clotting times of STZ induced diabetic rats

The bleeding and clotting times were reduced in diabetic control rats (2.19 ± 0.59 and 1.40 ± 0.16 mins, respectively) compared with the normal rats (3.12 ± 1.13 and 2.56 ± 0.16, respectively). Administration of plant extract to the diabetic rats further reduced the bleeding time. Similar reductions were observed in the diabetic treated groups compared with the normal control. However, there were no differences in the bleeding and clotting times of treatment groups compared with the diabetic control, with the exception of bleeding time for diabetic group given 100 mg/kg extract which recorded shorter time of 1.44 ± 0.44 mins.

3.1.4 Effects of administration of methanol extract of *C. papaya* leaves on some fertility indices of male diabetic rats

3.1.4.1 Sperm count

Sperm count was significantly ($p < 0.001$) reduced in the diabetic control and treated groups compared with the normal control rats. Administration of plant extract recorded no significant difference in the sperm counts of the diabetic treated groups compared with the diabetic control; however, a significantly higher counts was recorded with metformin (Fig. 5).

Table 1. Qualitative phytochemical constituents of *C. papaya* leaf extract

Phytochemical test	Observation	Results
Alkaloids	A yellow precipitate	++
Carbohydrates	Benedict's Test: Mild formation of orange precipitation Molisch's Test: Mild formation of dark-purple coloration	+
Glycosides	Appearance of pink color	+
Saponin	Formation of 1-2cm of foam above the solution after shaking	++
Terpenoids	Golden yellow coloration	++
Polyphenol	Green-Blue color observed	+
Flavonoids	Intense yellow color which becomes colorless after the addition of diluted acid	++
Tannins	Blue-green coloration formed	++
Protein	Violet/blue pigmentation	++
Phytosterol	Deep violet-blue coloration	++
Anthraquinone	Pink-red coloration	+
Lipids	Oil stain observed	+
Phenol	Formation of a bluish black colour	++

+ detected, ++ highly detected

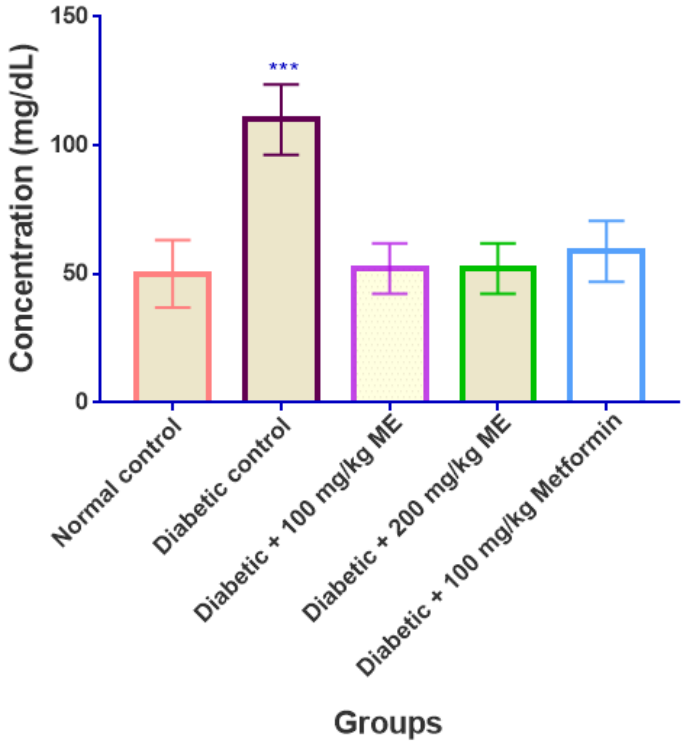

Fig. 1. Effects of different concentrations of *C. papaya* leaf methanol extract on plasma glucose concentrations of diabetic rats

*Data are presented as mean ± SD of replicate determinations; n=5; *** p < 0.001; ME- Methanol extract*

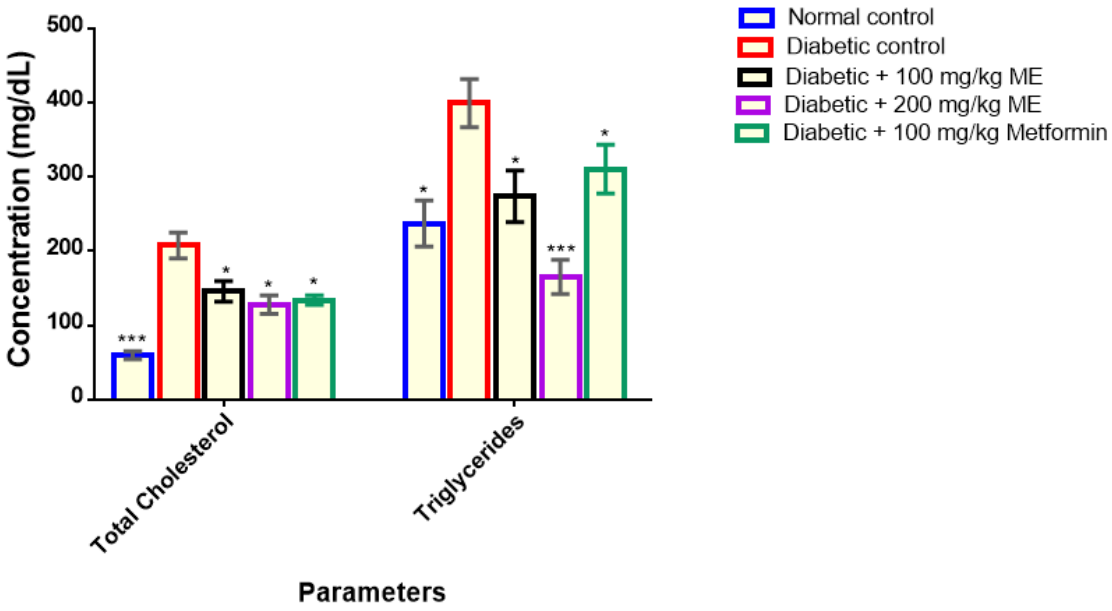

Fig. 2. Effects of different concentrations of *C. papaya* leaf methanol extract on plasma total cholesterol and triglycerides of diabetic rats

*Data are presented as mean ± SD of replicate determinations; n=5; *** p < 0.001, * p = 0.05 compared with diabetic control within each parameter; ME- Methanol extract*

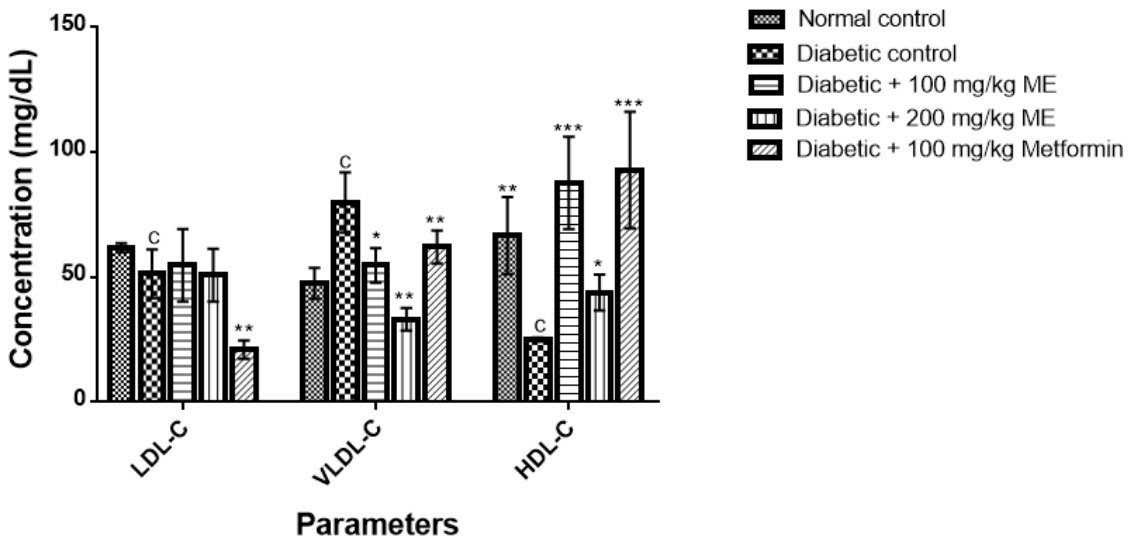

Fig. 3. Effects of different concentrations of *C. papaya* leaf methanol extract on LDL-C, VLDL-C, and HDL-C of diabetic rats

*Data are presented as mean ± SD of replicate determinations; n=5; *** p < 0.001, **p < 0.01, * p = 0.05 compared with diabetic control (c) within each parameter; ME- Methanol extract, LDL-C: low-density lipoprotein cholesterol: VLDL-C: very low-density lipoprotein cholesterol, HDL-C: high density lipoprotein cholesterol*

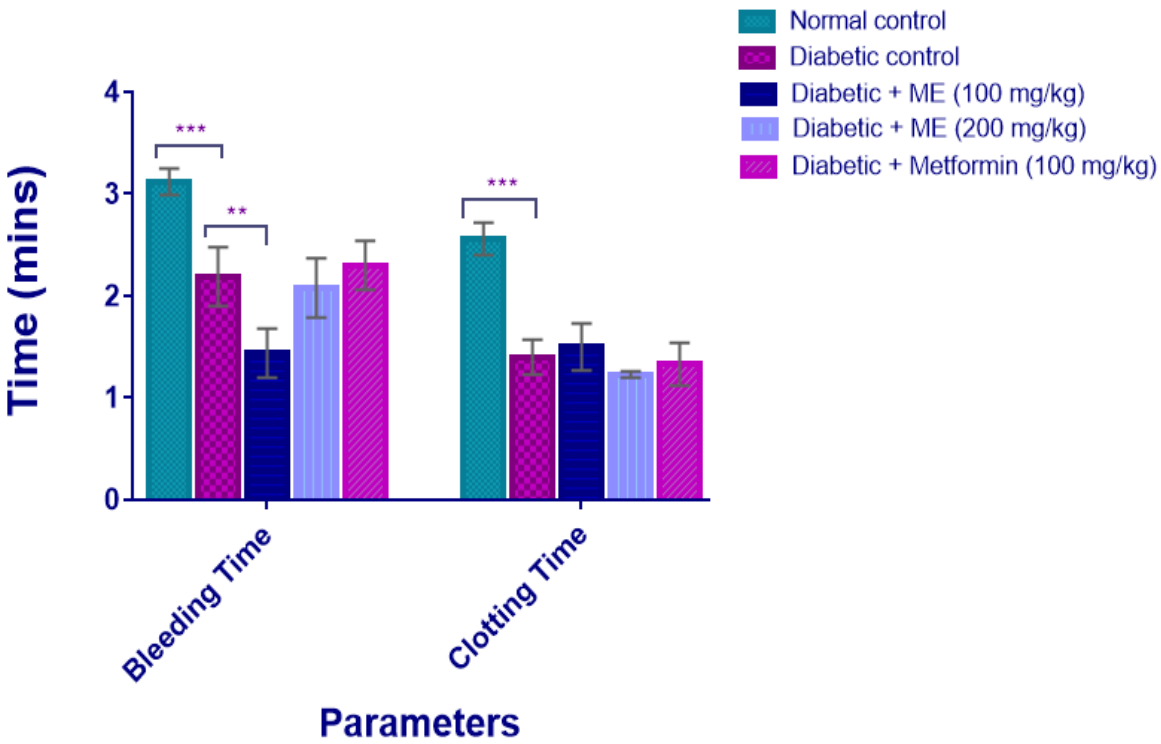

Fig. 4. Effects of different concentrations of *C. papaya* leaf methanol extract on Bleeding and Clotting times of diabetic rats

*Data are presented as mean ± SD of replicate determinations; n=5.; *** p < 0.001, **p < 0.01 compared with diabetic control within each parameter; ME- Methanol extract, mins: minutes.*

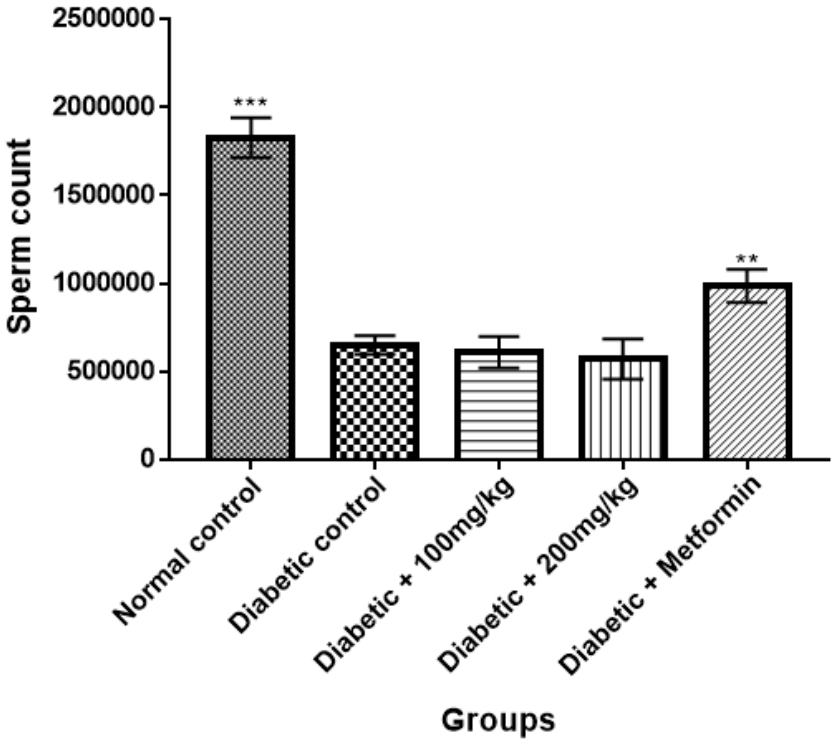

Fig. 5. Effects of different concentrations of *C. papaya* leaf methanol extract on sperm count of male diabetic rats

*Data are presented as mean ± SD of replicate determinations; n=5; *** p < 0.001, * p = 0.05 compared with diabetic control; ME- Methanol extract*

3.1.4.2 Sperm morphology

Result reveals that the percentage normal cells were reduced in diabetic control group and *C. papaya* treated groups compared with the normal control group. The percentage of abnormal cells were significantly (*p = 0.05*) increased in the treatment groups as well as diabetic control in comparison with the normal control group. There were no differences in the percentage of normal and abnormal sperm cells in the groups administered with 100 mg/kg and 200 mg/kg body weight of extract (Fig. 6).

3.1.4.3 Sperm motility

The diabetic control group recorded a significantly (*p = 0.05*) lower percentage of motile cell, and higher percentage of non-motile compared with the normal control group. There was a significant increase in percentage of non-motile cells in diabetic control, and diabetic rats treated with *C. papaya* leaf extract compared with the normal control group. The metformin-treated group recorded significantly higher percentage of motile cells in comparison to the diabetic control (Table 2).

Table 2. Sperm motility of normal control and diabetic rats treated with different concentrations of *C. papaya* leaf methanol extract

Groups	Motile cells (%)	Non-motile cells (%)	Sluggish (%)
Normal control	65.41 ± 4.40^{b}	11.95 ± 2.86^{a}	22.60 ± 0.71^{c}
Diabetic control	30.30 ± 2.50^{a}	57.60 ± 4.90^{b}	12.10 ± 0.90^{a}
Diabetic + 100mg/kg ME	23.81 ± 4.00^{a}	59.52 ± 10.50^{b}	16.67 ± 0.50^{b}
Diabetic + 200mg/kg ME	33.10 ± 5.50^{a}	51.50 ± 0.50^{b}	15.40 ± 2.00^{b}
Diabetic + Metformin	67.20 ± 14.2^{b}	18.60 ± 0.50^{a}	14.40 ± 2.10^{b}

Values are mean ± SD of replicate determinations; n=5. Mean values followed by different superscript letters are significantly different within group. ME- methanol extract

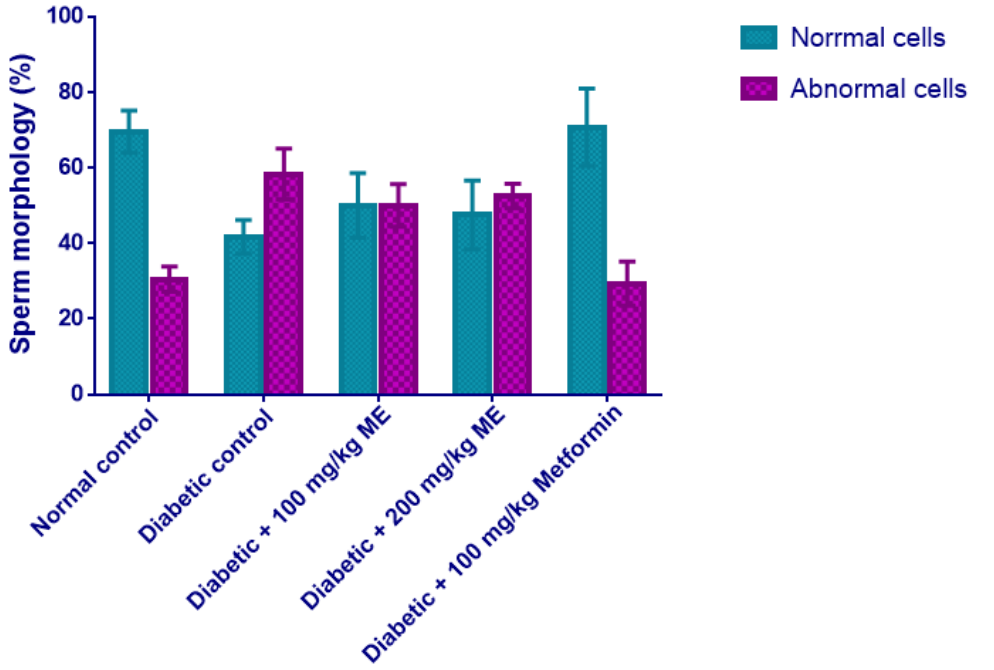

Fig. 6. Effects of different concentrations of *C. papaya* leaf methanol extract on Spermatozoa morphology of diabetic rats

Data are presented as mean ± SD of replicate determinations; n=5. ME- Methanol extract

4. DISCUSSION

Proper regulation of glucose in the body by the action of insulin and glucagon is impaired in DM. This is indicated in the study results in which the plasma glucose levels were significantly increased in diabetic rats compared to the normal control rats. Administration of *C. papaya* leaf methanol extract decreased the plasma glucose concentrations in diabetic treated rats similarly with metformin. This indicates that *C. papaya* leaves maybe beneficial like metformin in the regulation of the blood glucose concentration. This agrees with the report that *C. papaya* leaf aqueous extract significantly lowered blood glucose concentrations in diabetic rats [27]. The blood glucose-lowering effect of *C. papaya* may partly be explained by either a decrease in the rate of intestinal glucose absorption or an increase in peripheral glucose utilization by increasing insulin production [28-29].

The observed significant decrease of plasma total cholesterol, triglycerides, LDL-C and VLDL-C in diabetic rats treated with varied concentrations of C. papaya leaf methanol extract compared with the diabetic control rats corroborates the report of Juarez- Rojop*, et al.* [27] that triglycerides and cholesterol levels were reduced in diabetic rats upon the administration of *C. papaya* aqueous extract. Diabetes-related hyperlipidemia may occur as a result of an accelerated biosynthesis of hepatic triglycerides. The plasma cholesterol, TAG, LDL-C and VLDL-C lowering effect of *C. papaya* may be attributed to its ability to ameliorate hyperlipidemia by decreasing the activities of cholesterol biosynthesis enzymes and/or lowering the rate of lipolysis as regulated by insulin action [30].

HDL-C in this present study was decreased significantly (p = 0.05) in diabetic control rats compared with the normal rats. Significant increases were recorded in diabetic rats treated with plant extract and metformin compared with the diabetic control rats. This may be as a result of the hypolipidemic effect of *C. papaya* which could cause a rise in HDL-C level; a good cholesterol for the prevention of cardiovascular diseases [31]. Similar increase in HDL-C concentration as reported on the serum cholesterol lowering effect of *Ficus exasperate.* This was attributed to the plant's ability to increase the excretion of cholesterol [32]. Thus, suggesting that *C. papaya* leaves could be used as anti-atherogenic agent for the management of atherosclerosis and hyperlipidemia.

The present study showed a decrease in bleeding time and clotting time in diabetic control rats compared to the normal rats. *C. papaya* leaf methanol extract (100 mg/kg) further reduced the bleeding time of the diabetic-treated rats. The observed marked reduction in blood clotting parameters tested in diabetic rats may be due to the hyper-coagulation state reported in DM [33]. Ability of *C. papaya* leaves to further decrease or sustain the shorter bleeding and clotting times despite amelioration of hyperglycemia indicate the procoagulant tendency of the plant which may be attributed to reported pro-platelet activity of *C. papaya*.

The bleeding time assesses the vascular and platelets reactions associated with blood coagulation, while the clotting time evaluates the proteases of the intrinsic coagulation pathway (Factors I, II, V, VIII, IX, X, XI, and XII). The bleeding time examines the vasoconstrictive effects of the blood vessels, formation of hemostatic plug, and the activity of the platelets [25]. The reduced bleeding and clotting times observed with *C. papaya* administration thus indicate that the plant may possibly elicit its activity by improving the integrity of the blood vessel, enhancing the formation of platelet plug, and increasing the synthesis or activation of the proteins of the intrinsic coagulation pathway.

Reports have indicated that male diabetic patients are prone to infertility [5-6]. Although hormonal fluctuations also may lead to infertility, the efficiency of the reproductive cell (spermatozoa) is affected majorly by the morphological integrity of the cell [34]. The present study showed significant decreases in the tested fertility indices of diabetic rats compared with the normal rats, indicative of diabetic-associated infertility. The observed seemingly improved sperm morphology with no marked reduction in sperm count in the diabetic-treated rats compared with the diabetic control may be as a result of the anti-hyperglycemic activity of the *C. papaya* leaves, thus confounding the anti-fertility activity reports of the plants. No marked reduction in sperm morphology was recorded in the treatment groups compared to the diabetic control possibly because of the antidiabetic properties of papaya. Another possible reason for no marked difference in results could be duration of plant administration. Administration in previous studies reporting anti-fertility of *C. papaya* were done for longer days [35-37]. Therefore, further study for clarification is required.

The qualitative phytochemical screening of *C. papaya* leaves revealed that the methanol extract contains a great proportion of alkaloids, anthraquinones, flavonoids, phenols, tannins, and other bioactive compounds. Some of these phytochemicals could be responsible for the observed hypoglycemic, hypolipidemic and pro-coagulation effects. Previous phytochemical screening of aqueous extract and hexane fraction of *C. papaya* leaves showed that the plant contains steroids, tannin, and glycosides among others [27].

4. CONCLUSION

C. papaya leaves possess hypoglycemic and hypolipidemic activities, and thus could be a source of novel hypoglycemic and hypolipidemic agent in pharmaceutical drug development. Findings in this study indicate that *C. papaya* leaf extract may have health benefits to diabetic patients in the management and prevention of diabetic complications through dyslipidemia improvement. Prolonged administration of *C. papaya* leaves may negatively affect male fertility.

CONSENT

It is not applicable.

ETHICAL APPROVAL

All experiments on rats were carried out in absolute compliance with the National Institute of Health (NIH) laboratory animal care guidelines (NIH publication No. 85-23, revised 1985), and approval was given by Institutional animal ethics committee.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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