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Hypoglycaemic and hypolipidemic effect of different solvents extract of unripe *Carica papaya* seed in streptozotocin-induced diabetic rats

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Abstract

Background and Objective: The increasing number of diabetes coupled with some serious side effects from synthetic drugs has led to the ever-increasing search for alternatives. This study investigated the anti-diabetic and hypolipidemic potentials of unripe *Carica papaya* (UCP) seed extract in diabetic rats using three different solvents.

Materials and Methods: Thirty adult male Wistar rats were used. Twenty-five out of thirty were induced diabetes following an overnight fast, by a single intravenous injection of 60 mg/kg STZ. The rats were grouped into six groups (n=5):NC: normal control, DC: diabetic control, DSTD: diabetic and treated with glibenclaimide, DAUCP, DMUCP and DPEUCP rats were induced but treated with 200 mg of aqueous, methanol and petroleum ether extract of UCP seed extract respectively. The extracts were administered to the animals orally for 21 days.

Results: The animals administered with different extracts showed significant decrease ($P<0.05$) in blood sugar level, total cholesterol, triglycerides, LDL-C and an increase level in HDL-C when compared to the diabetic control group.

Conclusion: The observed improvement in blood glucose and lipid parameters in the streptozotocin induced diabetic rats; following the treatment with the extracts suggest valuable hypoglycaemic and hypolipidemic potentials of the plant. This implies that unripe *C. papaya* seed can be effectively used in the management of diabetes.

Keywords: Diabetes; *Carica papaya*; Wistar rat; Hyperglycaemia; Hyperlipidaemia

1. Introduction

Diabetes mellitus (DM) is a chronic disease that is characterized by a relative or absolute lack of insulin, resulting in hyperglycaemia. It has emerged as a public healthcare problem with sustained hyperglycaemia which has been linked to many complications such as neuropathy, nephropathy and retinopathy and increased risk of cardiovascular disease [1-4]. The International Diabetes Federation estimates that there are approximately 425 million adults (20-79 years) who were living with diabetes in 2017 with a projected increase of 629 million by 2045 [5-7]. Globally, 45.8% of all diabetes cases, or 174.8 million people, are estimated to have undiagnosed diabetes mellitus (UDM) in 2013[8]. In Nigeria, about 5 million people are still living with diabetes, while1.56 million cases were recorded in 2015 with 105,091 deaths documented as of 2014[6,9].

Diabetes mellitus can be prevented by regulating the blood sugar level with various types of medicines and practicing different exercise or diet plan[10-12]. Currently available therapies for diabetes mellitus are insulin treatment for type 1 diabetes mellitus and other oral hypoglycemic drugs such as sulphonylureas, thiazolidinediones, peptide analogs for

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treatment of type 2 diabetes mellitus [13-14]. These therapies act by improving insulin secretion, decreasing glucose release from the liver or reducing gastrointestinal absorption of sugars[15-16]. However, while insulin and other commonly administered drugs do not provide absolute cure, they also predispose the patients to a wide range of serious complications, such as heart and kidney diseases and blindness [17-18]. Alternatively, exogenous sources of surrogateβ-cells, such as adult human pancreases donated after death, fetal pancreas, pluripotent and multipotent stem cells have also been propagated, but not much success has been recorded so far[19].

Treatment of diabetes mellitus without any adverse effects is still the biggest question in medicine. According to world ethnobotanical 800 medicinal plants are used for the prevention of diabetes mellitus[11]. Most of which are not clinically proven to possess anti-diabetic properties. Synthetic drugs which are used for treatment of diabetes are associated with various adverse effects such as vomiting, dysentery, migraine, swelling, weight increase, malignant anemia, faintness and other serious complications. In order to meet up with the current challenge, there is a need to search for effective and safe alternative sources of treatment through herbal therapy, to provide improved treatment for diabetes and associated complications[19-20]. Herbal drugs are proved to be a better choice over synthetic drugs because of less side effects and adverse effects[21]. Several medicinal plants and herbs have been proved to have anti-diabetic activity[1-2,22]. Various clinical studies confirmed that medicinal plant extracts show antidiabetic activity and restoring the action of pancreatic *β*- cells [23-28].

Carica papaya linn (family caricaceae), commonly called pawpaw (English), Ibepe (Yoruba-Nigeria) or Okroegbe (Igbo-Nigeria), is a tree-like herbaceous plant, widely cultivated for its edible fruits. It originated from Southern Mexico and Costa Rica[29-30]. The *C. papaya* is a fast growing, erect and typically unbranched herbaceous tree, with hollow trunk of about 20-30 cm in diameter[31-32]. Traditional uses of papaya in some developing countries are being investigated; papaya may provide an alternative to standard treatments for a variety of ailments. There is no data on the effect of unripe *C. papaya* seed on glycaemic control and dyslipidaemia using solvents of different polarities. In this study, we investigated the hypoglycaemic and hypolipidemic potentials of aqueous, methanol and petroleum ether extracts of unripe *Carica papaya* seed in streptozotocin-induced diabetic rats and comparison of these different extracts to ascertain the most potent in the management of diabetes.

2. Material and methods

2.1. Chemicals/Reagents

All chemicals and reagents used in this research were of analytical grade. Streptozotocin (STZ) was purchased from Sigma chemicals, (St. Louis, USA), others were obtained from Merck., while Kits for different enzyme assays were purchased from Biosystems S.A., Mexico.

2.2. Plant material

Unripe fruits of *Carica papaya* were harvested from local farm at Okuku Yala Local Government Area of Cross River State, Nigeria. The plant was identified and authenticated by Dr. Michael Eko, a botanist in the Department of Biological Sciences, University of Calabar and a voucher specimens number 73 was deposited in the Herbarium, Department of Botany, University of Calabar, Nigeria. The fruits were cut into pieces and the seeds removed and thoroughly washed and dried at room temperature. Dried seeds were crushed and ground to powder using a domestic mixer grinder (model: binatone BLG-450).

2.3. Extraction using aqueous and organic solvents

The aqueous extraction was performed by soaking 400 g of powdered *C. papaya* seed in 1 L of distilled water over 48 hours. The extract was filtered with Whatman filter paper no 1 (24 cm) and dried at 40 °C. The extract was kept frozen at -20 °C for use. It was reconstituted in distilled water for administration.

The methanol and petroleum ether extraction were performed each by wrapping 400 g powder sample of *C. papaya* seeds in a thimble and placed in a 1000 cm^3 Soxhlet extractor (M&G Scientific Co., England). The samples were Soxhlet extracted following standard analytical laboratory method at 60 °C for 72 h. The extract was evaporated to dryness at 40 °C. The extract was kept frozen at -20 °C for use. It was reconstituted in Tween 80 for administration.

2.4. Animals

Thirty male Wistar rats weighing 130 to 160 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 Department of Medical

Biochemistry, Cross River University of Technology, Okuku Campus and allowed free access to grower's mash and water *ad libitum*. The animals were acclimatized for two weeks. The experiment which lasted for 21 days was carried out according to the guideline procedures of the Animal House. The rats were maintained in accordance with the principles of laboratory animal care[33] guidelines. The experiment protocol was designed according to the Departmental Animal Ethics Committee guidelines.

2.5. Induction of Diabetes

Overnight-fasted rats were induced with diabetes by a single intraperitoneal injection of 60 mg/kg body weight of streptozotocin (STZ) freshly dissolved in citrate buffer (0.01 M, pH 4.5). Control animals received 0.9 % sterile saline. Hyperglycemia was confirmed 3 days after injection by measuring the tail vein blood glucose level with an Accu-Chek Active (Roche Diabetes Care GmbH, Mannheim, Germany. Animals with fasting blood glucose levels ≥ 200 mg/dL and ≤ 450 mg/dL were considered diabetic and used for the study.

2.6. Experimental Design

Thirty male Wistar rats were used but the animals were divided into six groups, each group containing five animals (n=5).

- NC: Normal Control
- DC: Diabetic Control
- DAUCP: Diabetic and 200 mg Aqueous Extract of unripe *C. papaya* seed
- DMUCP: Diabetic and 200 mg Methanol Extract of unripe *C. papaya* seed
- DPEUCP: Diabetic and 200 mg Petroleum Ether Extractof unripe *C. papaya* seed
- DSTD: Diabetic and standard Drug (glibenclamide)

2.7. Duration of Treatment

Treatment began on the day the diabetic state was ascertained. Blood glucose level and body weight were determined weekly for three weeks throughout the period of the experiment. On the 21stday treatment the animals were fasted overnight, anesthetized and sacrificed by humane decapitation.

2.8. Collection of blood sample

Blood was collected directly through cardiac puncture. Three (3) mL were put into plain tube and were centrifuged at 3000 g for 10 min to obtain serum for biochemical analysis.

2.9. 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. This was done weekly for three weeks.

2.10. Determination of Body Weight

The rats were weighed weekly for three weeks.

2.11. Determination of Biochemical Parameters

Serum was used for the evaluation of biochemical parameters, including serum's total cholesterol, triglyceride, and high-density lipoprotein (HDL) were measured by the enzymatic colorimetric method using Randox kits. The concentration of low density lipoprotein (LDL) cholesterol was calculated using the formula of Friedwald[34].

2.12. Statistical Analysis

Data obtained was analysed using the SPSS statistical package, version 23 with one-way analysis of variance (ANOVA) and statistical significance established at $P< 0.05$. Data is expressed as the mean ± SD.

3. Results

Results of the effect of daily treatment of streptozotocin-induced diabetic rats with various extracts of unripe *Carica papaya* seed and glibenclamide are presented below.

3.1. Weekly blood glucose levels of streptozotocin-induced diabetic rats treated with various extracts of Unripe *Carica papaya* seed

Figure 1 shows the mean fasting blood glucose of experimental rats treated with the aqueous, methanol, petroleum ether extracts and glibenclamide. On day 0 there was a significant difference ($P<0.05$) between the normal control and other groups. Other groups except normal control exhibited hyperglycemia showing that induction of diabetics was successful. After the experimental period (3-week), STZ-diabetic rats exhibited significant ($P<0.05$) hyperglycemia compared with the control rats. The extracts and glibenclamide decreased blood glucose level in the diabetic rats compared to the untreated diabetic rats ($P<0.05$). On day 7 the glucose level of DC group increase when compared to the day 0 while in the treated groups it reduced. On day 21 the reduction in glucose level of DMUCP and DSTD were significant ($P<0.05$) when compared to DAUCP and DPEUCP. The reduction in glucose level of DMUCP and DSTD were statistically similar. Among the extracts, DMUCP seems to be more potent in the reduction of glucose.

3.2. Weekly bodyweight of streptozotocin-induced diabetic rats treated with various extracts of Unripe *Carica papaya* seed.

In Figure 2 diabetic control (DC) group exhibited significant loss in body weight. In the normal control group and treated rats there was significant ($P> 0.05$), increase in body weight. This indicates that action of the extracts and glibenclamide improved body weight. On the day 21 DMUCP seems to have improved the body weight more than other treated groups.

3.3. Lipid profile of streptozotocin-induced diabetic rats treated with various extracts of unripe *Carica papaya* seed.

The diabetic control group showed elevated levels of TC, TG and LDL-C with lowered levels of HDL-C (Table 1). Serum levels of LDL-C and VDL-C were significantly reduced ($P<0.05$) with a corresponding increase in HDL-C in treated rats. TC, TG and HDL-C levels in DMUCP and DSTD were statistically similar. Reduction in the levels of TC, TG and LDL-C were highest in DMUCP when compared with other extracts treated groups. Specifically, the reduction in the level of LDL-C was highest in DMUCP when compared to all the treated groups. HDL-C levels in NC, DMUCP and DSTD were statistically similar. Furthermore, the increase in the level of HDL-C was highest in DMUCP when compared with other extracts treated groups. This is followed by DPEUCP. Data on lipid profile indicates that methanol extract is the most active in ameliorating the alteration in lipid metabolism observed due to induction of diabetes.

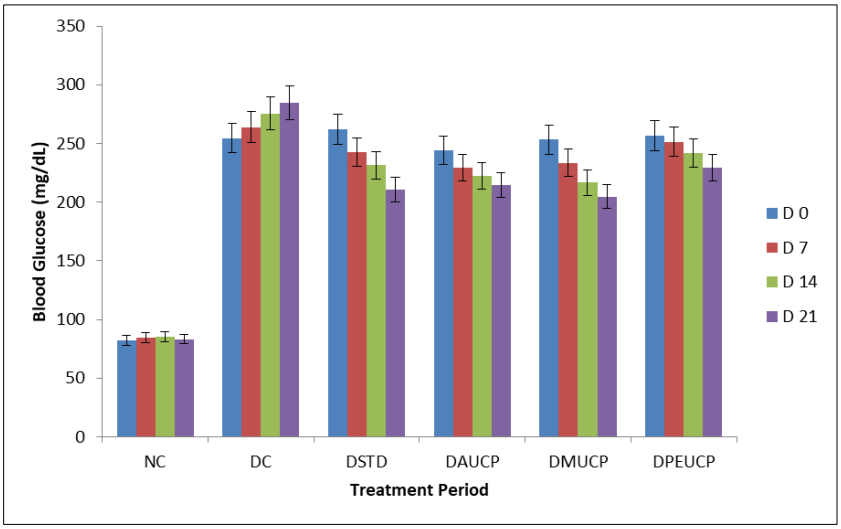

Figure 1 Weekly Blood Glucose Level of Rats treated with Aqueous, Methanol, Petroleum Ether extracts and Glibenclamide

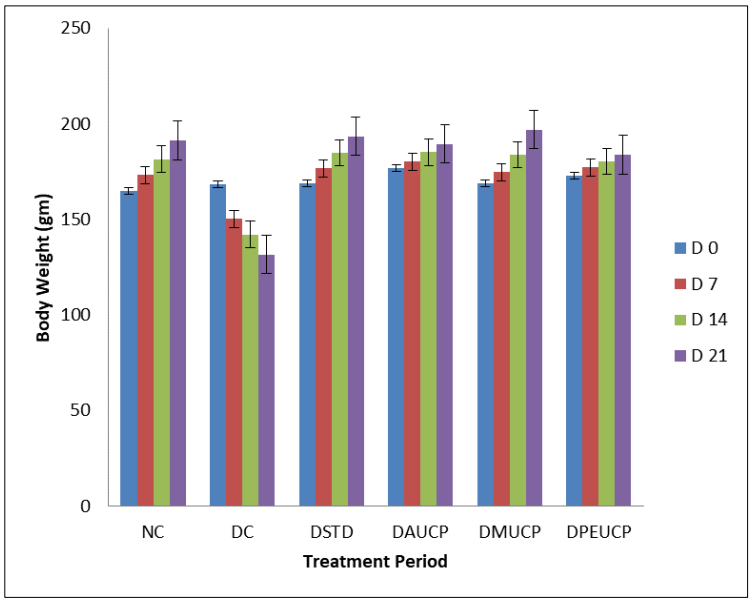

Figure 2 Weekly bodyweight of streptozotocin-induced diabetic rats treated with various extracts of Unripe *Carica papaya* seed

Table 1 Lipid profile of streptozotocin-induced diabetic rats treated with various extracts of Unripe *Carica papaya* seed

GROUP	TC (mg/dL)	TG (mg/dL)	HDL-C (mg/dL)	LDL-C (mg/dL)
NC	98.60±0.82^{a}	91.15±0.48^{a}	76.32±0.43^{d}	14.92±0.56^{a}
DC	198.29±0.51^{e}	417.54±2.86^{d}	25.85±0.45^{a}	53.68±0.80^{e}
DSTD	122.77±0.50^{b}	114.95±1.11^{b}	58.60±0.52^{d}	38.50±0.24^{c}
DAUCP	130.96±0.47^{c}	120.12±1.17^{c}	56.77±0.44^{b}	39.68±0.66^{d}
DMUCP	122.81±0.26^{b}	114.23±2.07^{b}	58.80±0.65^{d}	37.67±0.60^{b}
DPEUCP	132.49±0.49^{d}	119.26±0.71^{c}	57.53±0.19^{c}	39.09±0.59^{cd}

Values are mean ±SD (n=5). Values with different superscript (a, b, c, d, e) on the same row are statistically different (P<0.05).NC: Normal Control; DC: Diabetic Control; DSTD: Diabetic + 0.1 mg glibenclamide; DAUCP: Diabetic + 200 mg Aqueous Extract of unripe *C. papaya* seed; DMUCP: Diabetic + 200 mg Methanol Extract of unripe *C. papaya* seed; DPEUCP: Diabetic + 200 mg Petroleum Ether Extract of unripe *C. papaya* seed

4. Discussion

Several studies have reported that continuous glucose monitoring is a technique which appears to be highly useful in diabetes patients[35]. Hence, continuous glucose monitoring (CGM) has been demonstrated to be clinically valuable, reducing risks of hypoglycemia and hyperglycemia, and improving patient quality of life for a wide range of patient populations and clinical indications[35-36]. Many metabolic disturbances were associated with hyperglycemia in diabetic human[37]. So, it is very important to look for new drugs with safe, cheap, and high efficiency properties for DM control instead of the current hypoglycemic drugs which associated with the side effects[38].

Several drugs are used to control DM, however, perfect glucose control is rarely achieved[39-40], use of medicinal plants as alternative remedies has been necessitated due to the elevation of medication cost, synthetic medicine side influences, and lack of full recovery of diabetic patients treated with chemical hypoglycemic agents[41]. Traditional therapies originated from medicinal plants have proved a vital role in the control of DM[42]. The present study was designed to investigate the effect of aqueous, methanol and petroleum ether extracts of unripe *Carica papaya* seed on STZ-induced DM in Wistar male rats.

STZ is widely used in studies investigating DM, as it specifically targets β-cells and reduces blood insulin levels, leading to hyperglycemia and mimicking DM pathology[43-44]. In this study, it was observed that streptozotocin caused significant hyperglycaemia in the rats as evidenced by the spike in blood glucose. This is in accordance with other previous findings [45-46] where glucose level increased after induction of diabetes. It was further observed that oral administration of aqueous, methanol and petroleum ether extracts of unripe *Carica papaya* seed respectively (once a day for 3 weeks) at a dosage of 200 mg/kg bodyweight resulted in significant reduction of blood glucose levels in streptozotocin-induced diabetic Wistar rats. This is in agreement with other reports[1,47]. The reduction in glucose level might have mimicked the peripheral action similar to that of insulin or it might be that the extracts stimulate increased glucose utilization and glucose tolerance through body tissues of the diabetic rats which can be attributed to the bioactive molecules present in the seeds. The extracts might have the ability to regenerate*β*-cells of the pancreas and which was supported by the decrease in blood glucose levels. However, the result of this study showed that methanol extract of *C. papaya* was most effective, as it showed a highest potential of reducing the fasting blood glucose of experimental rats. This suggests that methanol extract has some active components which made it most among the three extracts.

Weight loss is one of the symptoms of diabetes mellitus occurring especially when there is persistent hyperglycaemia. From the present study, it is noted that there was a significant increase in body weight following administration of the extracts. Conversely, significant decrease in body weight was recorded in diabetic rats without treatment which is similar to previous findings by Zafar & Naeem-Ul-Hassan[45]. Studies have equally reported significant weight reduction in untreated diabetic rats[48]. The decrease in bodyweight associated with diabetes mellitus has been attributed to the gluconeogenesis giving rise to increased muscle wasting and loss of proteins in tissues[49-50], and this could account for the loss of weight seen in the diabetic control group. This observed increase in body weight might be as a result of improvement in the body physiology that facilitated increase in appetite and appropriate utilization of food.

Hyperlipidaemia is a kind of metabolic disorder which involves an abnormally high level of blood lipids and lipoproteins. Lipids play a vital role in the pathogenesis of diabetic mellitus. Diabetic is associated with profound alterations in the plasma lipid, triglycerides and lipoprotein profile and with an increased risk of arteriosclerosis, coronary heart disease, cerebral stroke, myocardial infarction and renal failure[51-53]. The most common lipid abnormalities in diabetes are hypertriglyceridemia and hypercholesterolemia.

The significantly higher serum lipids level observed in the STZ-induced diabetic control rats when compared to normal control might be as a result of disturbance in the regulation of the activity of the hormone-sensitive enzyme, lipase, by insulin due to its deficiency or absence, caused by the STZ-induced destruction of beta islet cells. Lipase is known to convert triglycerides to free fatty acids and glycerol. Insulin inhibits the hormone -sensitive lipase in adipose tissue and in the absence of insulin, the plasma level of free fatty acids increases. In liver, the free fatty acids are catabolized to acetyl CoA, and the excess acetyl CoA is converted to cholesterol, triglyceride and ketone bodies resulting in ketosis[54]. The abnormally high concentration of serum lipoprotein in the diabetic control rats may also be due to increase in the mobilization of free fatty acids from the peripheral fat depots by glucagons in the absence of insulin[55]. Excess of fatty acids in plasma produced by the STZ-induced diabetes promotes the liver conversion of some fatty acids into triacylglycerol, phospholipids and cholesterol which may be discharged into the blood as lipoproteins[56]. The increase in the levels of serum lipids such as cholesterol and triglycerides in the diabetic rats as noted in this study may be due to the fact that under normal circumstances, insulin activates lipoprotein lipase and hydrolyses of triglycerides. Insulin increases uptake of fatty acids into adipose tissue and increases triglyceride synthesis.

Moreover, insulin inhibits lipolysis. In case of insulin deficiency, lipolysis is not inhibited but an increased lipolysis which finally leads to hyperlipidemia. In diabetic condition, the concentration of serum free acids is elevated as a result of free fatty acid outflow from fat deposited, where the balance of the free fatty acid esterification-triglyceride lipolysis cycle is displaced in favour of lipolysis[57].

High density lipoprotein (HDL) is an anti-atherogenic lipoprotein. It transports cholesterol from peripheral tissues into the liver and thereby acts as a protective factor against coronary heart disease. In this present study the level of HDL-cholesterol increased after administration of the extracts. This might be due to increase in the activity of lecithin cholesterol acyl transferase (LCAT), which may contribute to the regulation of blood lipids[58]. Administration of the extracts lowered cholesterol, triglycerides and LDL cholesterol levels. Significant lowering of total cholesterol, triglycerides, low density lipoprotein, (LDL)-cholesterol and rise in HDL-cholesterol is a very desirable biochemical state for prevention of atherosclerosis and ischaemic conditions[59-60].

The three extracts significantly reduced in TC, TG and LDL as compared to the diabetic control whilst HDL levels were significantly increased. One explanation for this could be that increased utilization of glucose (reflected by a drop in glucose levels) led to the inhibition of lipid peroxidation and control of lipolytic hormones. A number of plants have

been reported to have anti-hyperlipidemic effects in such a manner[61-63]. The common factors that lead to the development of atherosclerosis and coronary heart disease in diabetes are hypertriglyceridemia, hypercholesterolemia and elevated LDL levels[64]. Therefore, lowering of serum lipid levels with elevation of HDL through drug therapy seems to be associated with a decrease in the risk of cardiovascular disease and related complications[65].

The significant hypolipidemic activities shown by the extracts administered orally when compared to diabetic control might be due to ability of the extracts of UCP to cause regeneration of the β-cells of the pancreas and potentiation of insulin secretion from surviving β-cells. The increase in insulin secretion and the consequent decrease in blood glucose level may lead to stimulation of fatty acid biosynthesis (Insulin stimulates lipid synthesizing enzymes (fatty acid synthase, acetyl-CoA carboxylase) and also the incorporation of fatty acids into triglycerides in the liver and adipose tissue). In the presence of insulin, the hormone-sensitive lipase will be inhibited in the adipose tissue, and mobilization of fatty acid from adipose tissue by glucagons will also be inhibited and therefore leading to the observed decrease plasma level of free fatty acids[66-67].

The plasma concentration of lipoprotein (LDL) will reduce since there is no elevated level of fatty acids (from lipolysis and from breakdown of triacylglycerol by the hormone-sensitive lipase) that will be converted to acetyl CoA in the liver. Elevated acetyl CoA are converted to cholesterol, triacylglycerol, phospholipids and ketone bodies. The principal lipids carried by lipoprotein are triacylglycerol and cholesterol. Absence of elevated cholesterol and triacylglycerol in the liver will lead to decreased synthesis of lipoproteins. The cholesterol and triacylglyceride that will be transported will be from diet and *de novo* synthesis[56]. Therefore, it is notable that the reductions in plasma cholesterol levels observed in the treated groups were accompanied by significantly higher HDL level when compared to that of diabetic group. High levels of HDL have been reported to be inversely related to the incidence of coronary heart disease[68-69].

High density lipoprotein (HDL) may foster the removal of cholesterol from peripheral tissue to the liver for catabolism and excretion. Also, high levels of HDL may compete with LDL receptor sites on arterial smooth muscle cells and thus partially inhibit uptake and degradation of LDL. HDL plays a role in lipid metabolism, complement regulation and the immune response, it is also thought to carry excess cholesterol back to liver where it is converted to bile acids and excreted into the small intestine; because of this, HDL is often referred to as 'Good Cholesterol' with high levels associated with a decreased risk of myocardial infarction. HDL removes cholesterol from non-hepatic tissues to liver through the process known as reverse cholesterol transport[68]. Studies by Khan et al.[68] have associated reduction in plasma HDL cholesterol in diabetic rats and diabetic patients to defect in reverse cholesterol transport. Among the three extracts, methanol proved the most potent in normalising the alteration observed in the lipid metabolism.

5. Conclusion

Findings from the present work indicate that the extracts possess hypoglycaemic and hypolipidemic properties which may explain the traditional use of this plant for management of diabetes mellitus and its complications.

Compliance with ethical standards

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Statement of ethical approval

The ethical approval is obtained from Faculty of Basic Medical Sciences, Cross River University of Technology, Okuku, Cross River State, Nigeria Animal Researches Ethic Committee in the session held on 24.01.2022 (decision number 2022.08.12).

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