

HYPOGLYCEMIC AND ANTIHYPERLIPIDEMIC EFFECTS OF ETHANOLIC FRUIT PEEL EXTRACT OF *Carica papaya* (pawpaw) IN AN ALLOXAN-INDUCED DIABETIC RATS

ORIGINAL RESEARCH ARTICLE

Background: Diabetes mellitus is a severe health concern that is usually linked to a person's lifestyle and genetic variables. Its frequency of occurrence is alarming. Anti-diabetics drugs are costly and come with adverse effects. This study aims to evaluate the phytochemical, toxicity profile, antidiabetic and antihyperlipidemic effects of ethanolic fruit peel extract of *Carica papaya* in alloxan-induced diabetic rats.

Methods: The qualitative phytochemicals and Acute toxicity (LD₅₀, oral, rats) were evaluated. Diabetes was induced in rats by intraperitoneal administration of alloxan monohydrate (120 mg/kg) while fasting. The rats were divided into 6 groups of 6 albino rats. Group 1 as normal control, group 2 as test control, and group 3 as standard (administrated with 0.1 mg/kg/day of glibenclamide). The ethanolic fruit peel extract of *Carica papaya* was administered to groups 4-6 at doses of 100, 200, and 500 mg/kg. 2-6 were induced with diabetes. Blood glucose levels were measured at 0, 3, 6, and 9 hrs, 1, 3, 7, 14, 21, and 28 days, and the serum lipid profile was evaluated at the last 28 days.

Results: The ethanolic fruit peel extract of *Carica papaya* shows the presence of tannins, saponins, alkaloids, flavonoids, cardiac glycosides, terpenoids, and anthraquinones. The acute toxicity indicated that the fruit peel of *Carica papaya* is practically non-toxic to the experimental rats and its LD₅₀ was found to be greater than 5000 mg/kg. There was a significant reduction in body weight from day 3 to day 28. The decreases in body weight were found in group 5. The extract of *Carica papaya* showed a significant ($p < 0.05$) reduction of blood glucose levels from day 3 to 28. Similarly, oral administration of fruit peel extract of *Carica papaya* at 100, 200, and 500 mg/kg showed significant decreases in serum cholesterol, triglycerides, and low density lipoprotein (LDL-C) with increases in serum high density lipoprotein (HDL-C).

Conclusion: The ethanolic fruit peel extract of *Carica papaya* exhibited potent hypoglycemic and antihyperlipidemic potential in alloxan-induced diabetic rats.

Keywords: Diabetics, Hypoglycemic, *Carica papaya*, Acute Toxicity, Phytochemicals, Antihyperlipidemic

1. INTRODUCTION

Diabetes mellitus is a global health problems, Its rate of occurrence is threatening and commonly associated with individual's lifestyle and genetic factors. People in the developing countries are more prone to the disease due to their exposure to the predisposing factors. Diabetes mellitus is a metabolic condition characterised by chronic hyperglycemia and a metabolic imbalance of carbohydrate, protein, and fat. Insulin secretion insufficiency is one of the symptoms [1]. Further metabolic problems such as dyslipidemia, weight loss, atherosclerosis, gangrene, retinopathy, renal disease, neuropathy, and coma may arise as a result of the diabetic state [2]. Diabetic patients and healthcare providers face a significant health and socioeconomic burden as a result of diabetes mellitus. According to the International Diabetes Federation (IDF), Africa's diabetes population is 19.8 million, with a projected growth to 41.5 million by 2035 [3]. Anti-diabetic or hypoglycaemic drugs are highly available, but are often expensive and unaffordable due to poverty and usually present side effects. As a result, natural products are thought to be safer because they are more compatible with biological systems.

Phytochemicals: These are bioactive nutrient found in plant, fruits and vegetables, also called phytonutrients which served as antioxidants that prevent cell damages. For example the carotenoids which are found in carrots and many fruits, the polyphenols which are abundant in grapes and certain

types of teas, the allyl sulfides found in garlic, onions, and leeks. Other phytochemicals like iso-flavones which are found in soy products which prevent the cell damage and fight free radical in the body [4].

Carica papaya is a tropical herbaceous plant with prominent leaves (20-60 cm long) native to Mexico, Central America, and northern South America, and a member of the Caricaceae family. *C. papaya* grows widely throughout the tropics and subtropics, where it is widely farmed. Chitinase, glutaminyl cyclase, and cysteine endopeptidases of class II and III from *Carica latex*[5]; linalool in fruit pulp, and alkaloids such as carpaine, pseudocarpaine, dehydrocarpaine I and II [6] and kaempferol and quercetin[7] from the leaves are among the metabolites identified.

There are claims that *C. papaya* leaf is anti-inflammatory and has a therapeutic impact on dengue and malaria [8]. According to other studies, a fermented papaya preparation lowers plasma glucose levels in both healthy people and people with type 2 diabetes. The hypoglycemic activities of *Carica papaya* have been previously described for its fruit and leaves [10], nevertheless, the available information regarding the fruit peel is deficient [11]. The present study was designed to perform phytochemical analyses of *Carica papaya* fruit peel, toxicity study and to evaluate its hypoglycemic and antihyperlipidemic effects in an alloxan induced diabetic rats.

2. METHODS

Collection and Identification Plant sample

The *carica papaya* fruit peel was collected from Wudil Local government, Kano state, Nigeria. It was authenticated at Biological Sciences Department, Kano University of Science and technology, Wudil, Kano, Nigeria with a butcher NO KUSTBIO-01122022.

Preparation of Extract.

The fruits peel was washed with clean water and dried at room temperature, after which it was pulverized to coarse powder using mechanical grinder. *Carica papaya* fruit peel ethanolic extract was prepared according to Gafna *et al.*,[12] method. One thousand grams (1000g) of the powder *Carica papaya* fruit peel was mixed and soaked in 2000cm³ ethanol in a 2 litres conical flask, the content of the flask was mixed vigorously. The mixture was shaken and top covered with aluminum foil and kept for 48 hours. The ethanolic extract was obtained by filtration using whatman No1 filter paper and concentrated using vacuum evaporator at 60°C in water bath (OSL200 water bath and shaker Grand instrument, Cambridge). At 40°C, the filtrate was evaporated to dry, yielding a brown colour solid residue (yield: 35% w/w). The residue was weighed and stored in air and water proof containers, kept in refrigerator at 4°C. Fresh preparation was created from this stock whenever it was needed.

Percentage yield(% w/w) =
$$\frac{\text{Weight of the sample extract obtained (g)}}{\text{Weight of the powdered sampled used (g)}} \times 100$$

Qualitative Phytochemicals Screening of *Carica papaya* peel extracts

The extract obtained was subjected to various qualitative tests for identification of the constituents such as alkaloids, tannins, saponins, glycosides, steroids/triterpenoids, flavonoids and Anthraquinones, by using simple and standard qualitative methods described by Trease and Evans [13].

Experimental Animals

Healthy male Wistar albino rats weighing about 150–200 g were used. The animals were housed in poly propylene cages, maintained under standard conditions and fed with standard diet and water *ad-libitum* (12:12 h light:dark cycle; 25 ± 2°C, 35%–60% humidity).

Acute Toxicity Study evaluation of *Carica papaya* peel extracts

The LD₅₀(Oral, rats) were determined according to Abdulmumin *et al.*,[14] in the first phase the rats were divided into three groups of three rats each and were administered with 10, 100, and 1000mg/kg of the ethanolic fruit peel extract of *Carica papaya* orally. The rats were observed for mortality and

general behavior. In the second phase, the rats were group into five group of one rat each and were administered with ethanolic fruit peel extract of *Carica papaya* at varying dose of 1250, 2000, 2750, 3750 and 5000 mg/kg. The rats were observed for 24hrs for mortality and other signs of toxicity.

Collection of Blood Samples

Blood samples were taken from overnight fasting rats under light ether anaesthesia using the retro orbital plexus puncture procedure. Induction of diabetes using alloxan monohydrate.

After overnight fasting, rats were given a single dosage (120 mg/kg, b.w., i.p.) of alloxan monohydrate (Sigma Ltd., USA) dissolved in normal saline to induce type 2 diabetes. The animals were provided regular food and water ad libitum after 1 hour of alloxan administration. After a week of stabilisation, animals with blood glucose levels greater than 250 mg/dl were chosen for the investigation. Experimental design

A total of thirty (30) wister rats were used in this study. And were randomly selected and grouped into 6 of 5 rats each. Group 1 served as normal control and was given water and standard diet *ad-libitum*. Group 2- 6 were allowed to fast for 12 hrs and induced with a single dose alloxan monohydrate (120 mg/kg, *i.p*) which was dissolved in normal saline as a vehicle. Group 2 served as negative control while group 3 were treated with standard drug (0.1 mg/kg/day of glibenclamide.), finally group 4-6 were administered orally with low, medium and high dose of 100, 200 and 500 mg/kg/day of *Carica papaya* ethanolic fruit peel extract respectively. Fasting blood glucose was determined at 0, 3, 6, and 9 hrs after administration. Treatment was continued for 28 consecutive days. Fasting blood glucose levels were estimated at 0, 3, 6, 9 hrs 1, 3, 7, 14 and 28 days.

Determination of blood Glucose level

Blood glucose levels were determined using Accu-Check Active® glucose strips and a test metre equipment (Accu-Chek Extra Care, Roche Diagnostics India Pvt. Ltd), which uses the GOD-POD method (glucose oxidase-peroxidase method) to assess blood glucose levels[16].

Serum lipids profile determination

On day 28, blood was collected from overnight fasted rats under ether anesthesia by retro orbital plexus puncture method and was kept aside for 30 mins for clotting. By centrifuging the same sample at 6000 rpm for 20 mins, the serum was separated and was analyzed for cholesterol by CHOD-PAP method (Cholesteroloxidase-Phenol+aminophenazone)[17] and triglycerides by GPO (Glycerol-3-phosphate oxidase) method, VLDL, VHDL [18].

Statistical Analysis

The data was statistically analyzed at P-value ($p < 0.05$) significantly accepted and a comparison between the groups was performed using one-way analysis of variance (ANOVA), followed by Turkey's test to compare the differences between treatments. All the values were expressed as mean \pm SEM

3. RESULTS AND DISCUSSION

Qualitative Phytochemicals Screening of Ethanolic Fruit Peel Extract of *Carica papaya*

The presence of tannins, saponins, alkaloids, flavonoids, cardiac glycosides, terpenoids, and anthraquinones was discovered in an ethanolic fruit peel extract of *Carica papaya* (Table 1). Tannins have long been known for their therapeutic qualities and for their physiological action as potent anti-microbials [19]. Saponins are used as expectorants and emulsifiers, and they also have antifungal properties. Alkaloids have been proven to have antibacterial and anti-inflammatory properties. Flavonoids and glycosides are widely utilized in herbal medicine for the treatment of a variety of disorders [20]. Terpenoids have been shown to have antibacterial, anti-hyperglycemic, and

immunomodulatory properties [19], while anthraquinones are widely employed to protect plants from a variety of diseases and have high antimicrobial properties [20].

Table 1 Qualitative Phytochemicals Screening of Ethanolic Fruit Peel Extract of *Carica papaya*

S/No	Phytochemical	Ethanol extract
1.	Tannins	+++
2.	Saponins	+
3.	Alkaloids	+
4.	Flavonoids	++
5.	Cardiac Glycosides	+++
6.	Terpenoids	+
7.	Anthraquinones	+++

Key: +=Trace, ++=Moderate, +++= High,++++=Very High,- =Absent

Acute Toxicity Evaluation of Ethanolic Fruit Peel Extract of *Carica papaya*

The acute lethal study of ethanolic fruit peel extract of *Carica papaya* (Table 2.) shows that no any mortality within 24 hrs oral administration of the extract in both phase 1 and 2 respectively and the LD50 oral rats was found to be greater than 5000 mg/kg body weight.

Table 2: First Phase LD₅₀ (Oral, rat) of Ethanolic Fruit Peel Extract of *Carica papaya*

Doses in (mg/kg)	Ethanol extract	
	No: of Rat	Mortality
PHASE I		
10	3	0/3
100	3	0/3
1000	3	0/3
PHASE II		
1250	1	0/1
2000	1	0/1
2750	1	0/1
3750	1	0/1
5000	1	0/1

LD₅₀ Oral, rats of ethanolic fruit peel extract of *Carica papaya* > 5000mg/kg body weight of rats.

The liver is the major site of detoxification in the body for drugs and toxins [21]. The LD₅₀ of a chemical is essentially the amount that may be predicted to kill half (i.e., 50%) of a group of animals, usually rats or mice. It is commonly reported as the amount of chemical given (in milligrammes) per 100 grammes (for small animals) or per kilogramme (for larger animals) of the test animal's body weight [22]. The LD50 obtained at the end of the study is reported in relation to the route of administration of the test substance, e.g., LD₅₀ (oral), LD₅₀ (dermal) etc. The most frequently performed lethal study is the oral LD₅₀. Results obtained from oral studies are important for drugs, food and accidental domestic poisonings. Generally, the

smaller the LD₅₀ value, the more toxic the substance is and vice versa. LD₅₀ values can be compared to other values using a toxicity scale [22].

Effects of Ethanolic Fruit Peel Extract of *Carica Papaya* on Weight of The Rats In An Induced Diabetes Rats

The effect of ethanolic fruit peel extract of *Carica papaya* on the weight of rats in an alloxan-induced diabetes study was evaluated for 0–14 days at intervals of 3 days, 7 days, and 14 days at doses of 100 mg/kg, 200 mg/kg, and 500 mg/kg in groups 2–5, while groups 1 and 2 served as normal and test control, respectively, and group 3 was given 0.1 mg/kg/day glibenclamide as the standard drug (table 3). Body weight gain in the normal group varied from 3 to 14 days. A significant reduction ($p < 0.05$) was also found in the diabetic rats when compared with normal control. However, from day 3 to 14, there was a considerable decline in body weight. Body weight loss was observed in group 5, which received 500 mg/kg of ethanolic fruit peel extract of *Carica papaya* (Table 3). After 14 days, there was a significant decrease in body weight in alloxan-induced diabetic rats. Similarly, the same findings were made in a number of experimental studies on diabetes [23, 24]. The rise in body weight seen in diabetic-induced rats demonstrated that anabolic effects had outweighed catabolic activities. And the weight loss indicated that catabolism had persisted. In the diabetic state, beta-cell death and insulin secretion dysfunction generate physio-metabolic abnormalities such as a decrease in body weight growth. The diabetic rats induced by alloxan were presented with these changes [25].

Table 3: Effect of Ethanolic Fruit Peel Extract of *Carica Papaya* On Weight Of The Rats In An Alloxan Induced Diabetes Rats

Group/doses	Weight of the rats in (g)			
	0 days	Day 3	Day 7	Day 14
Group 1 Normal control	150.75±19.62	153.0±19.30	154.5±10.24	156.5±20.24
Group 2 Test control induced with 120 mg/kg of alloxan	125.5±1.43*	122.33±1.53*	120.20±1.73*	110.0±1.33*
Group 3 Induced +0.1 mg/kg/day of glibenclamide	120.25±5.22 ^a	121.0±19.30 ^b	124.5±20.24 ^c	132.0±1.73 ^d
Group 4 Low dose of 100mg/kg of EFPECP	121.75±1.71 ^a	124.0±2.16 ^b	128.5±2.12 ^c	130.5±3.12 ^d
Group 5 Low dose of 200mg/kg of EFPECP	127.25±1.7 ^a	132.25±1.71 ^b	134.5±2.12 ^c	143.5±4.12 ^d
Group 6 High dose of 500 mg/kg of EFPECP	125.0±1.83 ^a	138.25±1.26 ^b	142.5±2.13 ^c	151.5±2.22 ^d

Results are expressed as mean ±S.E.M, n = 5

Values with asterisks are significantly different at $p < 0.05$ when compared with the normal rats.

Values in the same column and row with the same superscript are significantly different at $p < 0.05$ when compared with the test control. EFPECP= ethanolic fruit peel extract of *Carica papaya*

Effect of Ethanolic Fruit Peel Extract of *Carica papaya* on Blood Glucose Level In An Alloxan Induced Diabetes Rats.

The effects of ethanolic fruit peel extract of *Carica papaya* were evaluated in alloxan-induced diabetic rats. There was a significant rise ($p < 0.05$) in serum blood glucose levels in group 2 when compared to the normal control group. This suggests that alloxan causes diabetes by damaging the pancreas' incretin β -

cells, resulting in β -cell necrosis mediated by reactive oxygen species (ROS) with increases in calcium concentration, which leads to β -cell destruction [26]. Thus, at 120mg/kg, alloxan caused partial death of β -cells, despite the fact that the animal could become irreversibly diabetic with the possibility of regeneration [27]. The injection of 0.1 mg/kg/day glibenclamide resulted in a significant reduction in serum blood glucose levels in group 2 from 3–28 days (Table 4).

Glibenclamide showed its antihyperglycemic effect by stimulating insulin release from pancreatic β -cells, which reduced hepatic clearance and suppressed the secretion of glucagon. It is the second generation sulfonylurea that inhibits the process of gluconeogenesis [28]. Similarly, acute and chronic administration of ethanolic fruit peel extract of *Carica Papaya* at the doses of 100, 200, and 500 mg/kg for a period of 28 days showed that there was a significant ($P < 0.05$) reduction in the elevated blood glucose level when compared with the test control group. The decrease is in line with that of group 3 administered with standard drugs. Groups 4 and 5, on the other hand, showed a significant decrease in blood glucose levels after chronic administration of 100 and 200 mcg/kg for 28 days, but no significant changes at 3–14 days (Table 4).

Table 4: Effect of Ethanolic Fruit Peel Extract of *Carica papaya* on Blood Glucose Level In An Alloxan Induced Diabetes Rats

Groups/Doses	Blood Glucose Level Concentration (mg/dl)								
	0 hr	3 hrs	6 hrs	9 hrs	Day 1	Day 3	Day 7	Day 14	Day 28
Group 1 Normal control	87.5 ± 1.6	87.6 ± 1.3	87.9 ± 1.9	88.2 ± 1.5	88.3 ± 1.5	88.8 ± 1.3	89.7 ± 1.9	90.4 ± 1.3	89.9 ± 2.3
Group 2 Test control induced with 120 mg/kg alloxan	202.3 ± 4.3*	206.4 ± 3.1*	209.3 ± 3.7*	211.4 ± 3.1*	216.5 ± 2.7*	221.3 ± 1.2*	228 ± 2.2*	243.2 ± 7.6*	289.4 ± 8.8*
Group 3 Induced +0.1 mg/kg/day of glibenclamide	225.3 ± 5.4 ^a	219.3 ± 1.3 ^a	208.3 ± 2.2 ^a	211. ± 1.2 ^a	192.1 ± 3.6 ^a	154.2 ± 4.2 ^{ba}	120.7 ± 2.2 ^b	95.5 ± 1.4 ^a	85.5 ± 2.4 ^a
Group 4 Low dose of 100mg/kg of EFPECP	232.3 ± 2.6 ^a	230.7 ± 3.5 ^a	226.7 ± 5.4 ^b	222.3 ± 5.8 ^b	218.7 ± 5.5 ^a	214 ± 5.2 ^a	210 ± 5.2 ^a	178.3 ± 4.9 ^b	157.3 ± 3.4 ^b
Group 5 Low dose of 200mg/kg of EFPECP	240.2 ± 4.5 ^a	235.2 ± 5.1 ^a	229.4 ± 7.3 ^b	226.2 ± 6.6 ^b	220.8 ± 6.4 ^a	219.4 ± 4.8 ^a	210.6 ± 4.2 ^a	190.4 ± 3.3 ^c	145.4 ± 3.3 ^b
Group 6 High dose of 500 mg/kg of EFPECP	245.3 ± 11.8 ^a	210.1 ± 10.4 ^a	195.3 ± 6.1 ^d	185.3 ± 2.5 ^c	170.2 ± 10.2 ^b	150.4 ± 7.7 ^c	130.5 ± 3.8 ^c	110.4 ± 2.3 ^d	88.4 ± 3.3 ^c

Results are expressed as mean ± S.E.M, n = 5

Values with asterisks are significantly different at $p < 0.05$ when compared with the normal rats.

Values in the same column with the same superscript are statistically similar at $p < 0.05$ when compared with the test control.

Values in the same column with the different superscript are significantly different at $p < 0.05$ when compared with test control,

EFPECP= ethanolic fruit peel extract of *Carica papaya*

The improvements in high blood glucose levels shown with ethanolic fruit peel extract after administration of *Carica papaya* fruit peel to an alloxan-induced diabetic rat could be attributed to a decrease in the rate of intestinal glucose absorption or an increase in peripheral glucose utilization [29]. Translocation of GLUT4 to the plasma membrane in muscle and brown adipose cells, as well as overexpression of the uncoupling protein-1 in brown adipose tissue and hepatic gluconeogenesis, may all play a role in increased glucose

catabolism and hyperinsulinemia [30]. Furthermore, the ethanolic fruits peel extract of *Carica papaya* may act by stimulating the remaining β -cells with the release of more insulin, which is a possible mechanism for the β -cells that survived the effect of alloxan [32], while the ethanolic fruits peel extract of *Carica papaya* may act by stimulating the remaining β -cells with the release of more insulin. The ethanolic fruit peel extract of *Carica papaya* decreased the damage produced by alloxan on islets in this investigation, implying that the fruit peel extract is capable of cell regeneration [33].

Effect of Ethanolic Fruit Peel Extract of *Carica papaya* on Serum Lipids Profile In An Alloxan Induced Diabetes Rats.

After 28 days of oral treatment with ethanolic fruit peel extract of *Carica papaya* Linn, the serum lipid profile of alloxan-induced diabetic rats was examined. When compared to the normal group, blood cholesterol, triglycerides, and low density lipoprotein (LDL-C) levels were considerably higher ($p < 0.05$), whereas serum high density lipoprotein (HDL-C) levels were significantly lower ($p < 0.05$) (Table 5). When comparing group 5 to group 2 test control, the decreases and increases in serum lipid profile were shown to be statistically different ($p < 0.05$).

The increase in blood triglycerides, cholesterol, and LDL-C, as well as the decrease in serum HDL-C, indicated that lipid and protein metabolism were disrupted in diabetic rats [34,35]. Insulin shortage as a result of alloxan damage to the pancreatic cell leads to fat buildup in the bloodstream. Similarly, insulin secretion dysfunction may be linked to lipid metabolism in adipose tissue discharged into the bloodstream [36]. However, oral treatment of *Carica papaya* linn fruit peel extract at a dose of 500mg/kg resulted in significant reductions in serum cholesterol, triglycerides, and low density lipoprotein (LDL-C), as well as increases in serum HDL-C. ($p < 0.05$). *Carica papaya* fruit peel extract has hypoglycemic and antihyperlipidemic properties due to biochemical constituents such as tannins, saponins, alkaloids, flavonoids, cardiac glycosides, terpenoids, and anthraquinones.. And they have been implicated in ameliorating clinical disorders and diseases related to oxidative stress [37].

Many plant extracts, particularly those discovered in *Carica papaya* linn fruit peel extract, have hypoglycemic and anti-hyperlipidemic properties through altering the activity of enzymes involved in antioxidant, glucose, and lipid metabolism [38]. These compounds inhibit intestinal-glucosidase, pancreatic lipase, and cholesterol esterase activities [40], stimulate insulin secretion, and improve hepatic glutathione levels [39]. They also inhibit intestinal glucosidase, pancreatic lipases, and cholesterol esterase activities. As previously reported [40], disarrangement in serum lipids caused by lipemia in rats was readjusted and returned to normal by the activity of these phytochemicals.

Table 5: Effect of ethanolic fruit peel extract of carica papaya on serum lipids profile in an alloxan induced diabetes rats

Groups/Doses	Total cholesterol (mg/dl)	Triacylglycerol (mg/dl)	High density lipoprotein (mg/dl)	Low density lipoprotein (mg/dl)
Group 1 Normal control	63.61±2.24	86.14±11.4	31.18±1.31	25.12±1.10
Group 2 Test control induced with 120 mg/kg alloxan	95.62 ±2.9 [*]	232.1±17.3 [*]	21.25±2.09 [*]	34.15±1.06 [*]
Group 3 Induced +0.1 mg/kg/day of glibenclamide	60.31±2.34 ^a	81.23±10.2 ^b	29.28±1.21 ^c	21.11±1.03 ^d
Group 4 Administered with Low dose of 100mg/kg of EFPECP	70.22 ±2.3 ^a	190.11±12.3 ^b	27.15±1.11 ^c	27.25±1.16 ^d

Group 5 Administered with Medium dose of 200mg/kg of EFPECP	68.42 ±3.1 ^a	120.20±11.2 ^b	30.17±1.22 ^c	26.05±1.02 ^d
Group 6 Administered with High dose of 500 mg/kg of EFPECP	62.21±2.24 ^a	90.13±11.1 ^b	32.81±1.31 ^c	20.51±1.44 ^d

Results are expressed as mean ±S.E.M, n = 5

Values with asterisks are significantly different at p<0.05 when compared with the normal rats.

Values in the same column with the same superscript are significantly different at p<0.05 when compared with the test control. EFPECP= ethanolic fruit peel extract of *carica papaya*

4. CONCLUSION

The ethanolic fruit peel extract of *Carica papaya* exhibited potent hypoglycemic and antihyperlipidemic potential in an alloxan induced diabetic rats.

ETHICAL APPROVAL

The ethical approval was obtained from research and ethic committee of the Kano University of Science and Technology, Wudil.Kano.

ACKNOWLEDGEMENT

The authors wish to acknowledged the support of Tertiary Education Trust fund (TETFUND) Nigeria and Kano University of Science and Technology Wudil, Kano, Nigeria for sponsoring the Research under Institutional Based Research Grant (TETFUND/DR&D/UNI/WUDIL/RG/2018/VOL.I)

COMPETING INTERESTS

No competing interests exist between the authors of this study.

REFERENCES

- [1]. International Diabetes Federation. Diabetes Atlas, 6th Edition, Brussels, Belgium, 2013.
- [2]. Scott AIR, Clarke, BE, Healy H, D'Emden M, Bell SC. Microvascular complications in cystic fibrosis - related diabetes mellitus; a case report. *J Pancreas*, 2000; 1(4): 208-210.
- [3]. Yagi N, Komiya I, Arai K, Oishi M, Fukumoto Y, Shirabe S, Yokoyama H, Yamazaki K, Sugimoto H, Maegawa H; Japan Diabetes Clinical Data Management Study Group (JDDM study group),. Current status of oral antidiabetic drug prescribing patterns based on the body mass index for Japanese type 2 diabetes mellitus patients and yearly changes in diabetologists' prescribing patterns from 2002 to 2019 (JDDM61). *J Diabetes Investig*. 2022 Jan;13(1):65-73. doi: 10.1111/jdi.13621.
- [4]. Milugo TK, Omosa LK, Ochanda JO, Antagonistic effect of alkaloids and saponins on bioactivity in the quinine tree (*Rauvolfia caffrasond*): further evidence to support biotechnology in traditional medicinal plants. *BMC Compl Altern Med*. 2013;13:285.
- [5]. Azarkan, M., Garcia-Pino, A., Dibiani, R., Wyns, L., Loris, R., Baeyens-Volant, D., Crystallization and preliminary X-ray analysis of a protease inhibitor from the latex of *Carica papaya*. *Acta Crystallogr. Sect. F. Struct. Biol. Cryst. Commun*. 2006. 62, 1239-1242.
- [6]. Lim, T.K., *Carica papaya*. In: *Edible Medicinal and Non- Medicinal Plants*. Springer; 2012. 1:693-717.
- [7]. Miean, K.H., Mohamed, S.,. Flavonoid (myricetin, quercetin, kaempferol, luteolin, and apigenin) content of edible tropical plants. *J. Agric. Food Chem*. 2001:49, 3106-3112.
- [8]. Ahmad, N., Fazal, H., Ayaz, M., Abbasi, B.H., Mohammad, I., Fazal, L.. Dengue fever treatment with *Carica papaya* leaves extracts. *Asian Pac. J. Trop. Biomed*. 201:1, 330-333.
- [9]. Owoyele, B.V., Adebukola, O.M., Funmilayo, A.A., Soladoye, A.O., Anti-inflammatory activities of ethanolic extract of *Carica papaya* leaves. *Inflammopharmacol*. 2008. 16, 168-173.

- [10]. Aruoma, O.I., Hayashi, Y., Marotta, F., Mantello, P., Rachmilewitz, E., Montagnier, L., Applications and bioefficacy of the functional food supplement fermented papaya preparation. *Toxicology*. 2010. 278, 6-16.
- [11]. Sasidharan, S., Sumathi, V., Jegathambigai, N.R., Latha, L.Y.,. Antihyperglycaemic effects of ethanol extracts of *Carica papaya* and *Pandanus amaryfollius* leaf in streptozotocin-induced diabetic mice. *Nat. Prod. Res.* 2011; 20, 1982-1987.
- [12]. Krupa J, Sureshkumar J, Silambarasan R, Priyadarshini K, Ayyanar M. Integration of traditional herbal medicines among the indigenous communities in Iruvarur district of Tamil Nadu, India. *Journal of Ayurveda and Integrative Medicine.* 2018;10(1):32–37.
- [13]. Trease GE, Evans WC. London: Bailliere Tindall and Company Publishers; A Text book of Pharmacognosy; 1983. pp. 343–83. [[Google Scholar](#)]
- [14]. Abdulmumin Y, Abdulmumin. T. M., Muhammad I. A., Murtala M., Dalhatu1 M. M., Amina1 L. A., Bichi S. A and Sarki S. I. Bioassay Guided Fractionation, Phytochemicals and Toxicity Evaluation of *Eucalyptus camaldulensis* Leave Extracts. *South Asian Research Journal of Natural Products* 2021;4(2): 36-43
- [15]. Maniyar Y, Bhixavatimath P. Antihyperglycemic and hypolipidemic activities of aqueous extract of *Carica papaya* Linn. leaves in alloxan-induced diabetic rats. *J Ayurveda Integr Med* 2012;3:70-4.
- [16]. Ibegbulem CO, Chikezie PC. Hypoglycemic properties of ethanolic extracts of *Gongronema latifolium*, *Aloe perryi*, *Viscum album* and *Allium sativum* administered to alloxan-induced diabetic albino rats (*Rattus norvegicus*). *Pharmacog Commun.* 2013;3:12e16.
- [17]. Elbandy MA, Ashoush IS. Phytochemicals in pomegranate seeds and their effect as hypolipidemic agent in hypercholesterolemic rats. *World J Dairy Food Sci.* 2012;7:85e92.
- [18]. Elekofehintia OO, Kamdemb JP, Kadec IJ, Rochab JBT, Adanlawod IG. Hypoglycemic, antiperoxidative and antihyperlipidemic effects of saponins from *Solanum anguivi* Lam. fruits in alloxan-induced diabetic rats. *South Afr J Bot.* 2013;88:56e61.
- [19]. Silva GO, Abeyundara AT, Aponso MM. Extraction methods, qualitative and quantitative techniques for screening of phytochemicals from plants. *American Journal of Essential Oils and Natural Products.* 2017;5(2):29-32.
- [20]. Auwal MS, Saka S, Mairiga IA, Sanda KA, Shuaibu A, Ibrahim A. Preliminary phytochemical and elemental analysis of aqueous and fractionated pod extracts of *Acacia nilotica* (Thorn mimosa). *Veterinary Research Forum.* 2014;5(2):95-100.
- [21]. Liju VB, Jeena K, Kuttan R. Acute and subchronic toxicity as well as mutagenic evaluation of essential oil from turmeric (*Curcuma longa* L). *Food Chem Toxicol.* 2013;53:52-61.
- [22]. Mohammed A., Wudil A. M, Alhassan A. J., I. U. Muhammad., Idi A. and . Abdulmumin Y. Acute and Subchronic Toxicity Studies of Aqueous, Methanolic and n-Hexane Root Extracts of *Curcuma longa* L. on Albino Rats. *British Journal of Pharmaceutical Research* 2016;14(2): 1-8, 2016
- [23]. Jayaprasad, B., Sharavanan, P.S., Sivaraj, R.,. Effect of Chloroxylon swietenia Dc bark extracts on STZ induced diabetic rats with special attention to its glycoprotein levels. *Der Pharmacia Lett.* 2015;7, 414–418.
- [24]. Zhang, Y., Feng, F., Chen, T., Li, Z., Shen, Q.W., Antidiabetic and antihyperlipidemic activities of *Forsythia suspensa* (Thunb.) Vahl (fruit) in streptozotocin-induced diabetes mice. *J. Ethnopharmacol.* 2016. 192, 256–263.
- [25]. Kang, K.S., Kim, H.Y., Yamabe, N., Nagai, R., Yokozawa, T., Protective effect of sun ginseng against diabetic renal damage. *Biol. Pharm. Bull.* 2006. 29, 1678–1684.
- [26]. Prince SM, Menon VP. Hypoglycemic and other related actions of *Tinospora cardifolia* roots in alloxan induced diabetic rats. *J Ethnopharmacol* 2000;70:9-15.
- [27]. Szkudelski T. The mechanism of alloxan and streptozotocin action in beta cells of the rat pancreas. *Physiol Res* 2001;50:537-46.
- [28]. Davis SN, Granner DK. Insulin, oral agents and the pharmacology of endocrine pancreas. Goodman and Gillman's The Pharmacological Basis of Therapeutics. Hardman JG, Limbard LE, Gillman AG, editors. New York: Mc Graw Hill Co. Incorp.; 2001. p. 1679-714.
- [29]. Gupta R, Sharma AK, Sharma MC, Gupta RS: Antioxidant activity and protection of pancreatic β -cells by Embelin in streptozotocin-induced diabetes. *J Diabetes* 2012, 4:248–256.

- [30]. Bera TK, De D, Chatterjee K, Ali KM, Ghosh D: Effect of Diashis, a polyherbal formulation, in streptozotocin-induced diabetic male albino rats. *Int J Ayurveda Res* 2010, 1:18–24.
- [31]. Abeywickrama KR, Ratnasooriya WD, Amarakoon AM: Oral hypoglycaemic, antihyperglycaemic and antidiabetic activities of Sri Lankan broken orange pekoe fannings (BOPF) grade black tea (*Camellia sinensis* L.) in rats. *J Ethnopharmacol* 2011, 135:278–286.
- [32]. Cumaoğlu A, Ari N, Kartal M, Karasu Ç: Polyphenolic extracts from *Olea europea* L. protect against cytokine-induced β -cell damage through maintenance of redox homeostasis. *Rejuvenation Res* 2011, 14:325–334.
- [33]. Kondeti VK, Badri KR, Maddirala DR, Thur SK, Fatima SS, Kasetti RB, Rao CA: Effect of *Pterocarpus santalinus* bark, on blood glucose, serum lipids, plasma insulin and hepatic carbohydrate metabolic enzymes in streptozotocin -induced diabetic rats. *Food Chem Toxicol* 2010, 48:1281–1287.
- [34]. Kalaiselvi, A., Reddy, G.A., Ramalingam, V. Ameliorating effect of ginger extract (*Zingiber officinale* Roscoe) on liver marker enzymes, lipid profile in aluminium chloride induced male rats. *Int. J. Pharm. Sci. Drug Res.* 2015;7, 52–58.
- [35]. Al-Attar, A.M.,. Physiological and biochemical alterations in Sprague-Dawley female rats subjected to high fat diet and intermittent fasting. *J. Appl. Sci. Res.* 2010;6, 2096–2104.
- [36]. Rajalingam, R., Srinivasan, N., Govindarajulu, P., 1993. Effect of alloxan induced diabetes on lipid profiles in renal cortex and medulla of mature albino rats. *Indian J. Exp. Biol.* 31, 577–579.
- [37]. Jung M, Park M, Lee HC, Kang YH, Kang ES, Kim SK. Anti-diabetic agents from medicinal plants. *Curr Med Chem.* 2006;13:1203e1218.
- [38]. Jung UJ, Park YB, Kim SR, Choi M-S. Supplementation of persimmon leaf ameliorates hyperglycemia, and hepatic fat accumulation in type 2 diabetic mice. *PLoS One.* 2012;7(11):e49030.
- [39]. Shah NA, Khan MR. Antidiabetic effect of *Sida cordata* in alloxan induced diabetic rats. *Biomed Res Int.* 2014;2014:671294.
- [40]. Toma A, Makonnen E, Mekonnen Y, Debella A, Addisakwattana S. Intestinal α -glucosidase and some pancreatic enzymes inhibitory effect of hydroalcoholic extract of *Moringa stenopetala* leaves. *BMC Compl Altern Med.* 2014;14:180.