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Research Article
Ameliorative Effects of Extract of *Carica papaya* Leaf and Metformin on Streptozotocin-Induced Diabetic Rats

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Abstract

Background and Objective: *Carica papaya* Linn has been used for the management of several ailments in African and Asian ethnomedicine. This study investigated the effects of aqueous extract of *Carica papaya* leaves and metformin on the pancreas of streptozotocin (STZ) induced diabetic Wistar rats. **Materials and Methods:** Forty-five Wistar rats consisting of Group A regarded as control while diabetes was induced in Group B, C, D and E with intraperitoneal administration of 60 mg kg^{-1} STZ. Group B served as diabetic control while Group C and D were treated with 1.0 g/100 mL and 3.0 g/100 mL of the extract administered as drinking water daily for six weeks, respectively. Group E was treated with 5000 mg kg^{-1} of metformin and animals were sacrificed processed for histological analysis. **Results:** The result of aqueous extract of *Carica papaya* leaf and metformin-treated rats showed a significant reduction in fasting blood sugar levels (FBS) in Group D and E ($p<0.05$) compared to Group A control and B diabetic group. Treatment with metformin and aqueous extract significantly decreased ($p<0.05$) the levels of serum biomarkers Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST) and Alkaline Phosphatase (ALP) in the diabetic treated groups compared to diabetic group. Administration of aqueous extract of *Carica papaya* leaves and metformin preserved the morphological architecture of the pancreas in Group D and E when compared to the diabetic group. **Conclusion:** This study concluded that aqueous extract of *Carica papaya* leaves and metformin ameliorated effects of STZ induced diabetes which improved metabolic disruptions and imbalances caused by diabetes in Wistar rats.

Key words: Diabetes, *Carica papaya*, metformin, streptozotocin, pancreas, amelioration, glucose

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Diabetes mellitus is known to be a chronic disease induced by inherited or acquired deficiency of insulin secretion or resistance to the action of the released insulin[1].

Studies have shown diabetes mellitus (DM) to be a common endocrine disorder that involves the loss of pancreatic β-cell function, this information is changing the focus of research into possible replacement therapy[2].

Diabetes is caused due by either the pancreas not producing enough insulin (type 1) or the cells of the body not responding properly to the insulin produced (type 2)[3].

Consequently, this results in an increased concentration of blood glucose level leading to organ damage. Besides, it has been observed that much of the increase in the incidence of diabetes worldwide occur in developing countries which may be associated with unhealthy diets, ageing, obesity and sedentary lifestyle, while malnutrition-related causes may be playing predominant roles[4].

The report has indicated that diabetes is a complex metabolic disorder that is associated with developing insulin resistance, impaired insulin signalling, abnormal glucose and β-cell dysfunction and lipid metabolism with Ub-clinical inflammation coupled with increased oxidative stress. Additionally, the metabolic disorders associated with diabetes invariably lead to long-term pathogenic conditions which may show the characteristic features of micro-and macro-vascular complications, retinopathy, nephropathy and neuropathy which ultimately results in a decrease in quality of life leading to an increase in the mortality rate[5]. Among the diet is the main modifiable factor The role of diet in the face of multiple risk factors underlining the incidence and progression of diabetes has been previously emphasized through experimental and epidemiological evidence indicating that consumption of vegetables rich in phenolic compounds with high antioxidant capacity has demonstrated an inverse relationship with the incidence, progression and prevalence of diabetes mellitus[6]. It has also been observed that dietary control remains one of the most dependable means in the prevention and management of chronic degenerative diseases such as cardiovascular diseases and diabetes mellitus Literature record has shown that various plants have been used in traditional medicine in the management of diabetes in Nigeria, However, the efficacy of these herbal remedies has not been validated appreciably[7].

It has been reported that *Carica papaya* belongs to the family of caricaceae and several species of caricaceae have an employed in various dimensions as a remedy against a variety of clinical disorders and diseases[8,9]. *C. papaya* has been reported to contain two important biologically active compounds known as chymopapain and papain that are widely used for the treatment of digestive disorders[10]. Other active compounds of *C. papaya* are lipase, a hydrolase that is tightly bonded to the water-insoluble fraction of crude papain and is thus considered as a "naturally immobilized" biocatalyst[11].

Papaya is a powerhouse of nutrients and is available throughout the year. It is a rich source of three powerful antioxidants vitamin C, vitamin A and vitamin E, the minerals, magnesium and potassium, the B vitamin pantothenic acid and folate and fibre. In addition to all these, it contains a digestive enzyme-papain that effectively treats causes of trauma, allergies and sports injuries. It also contains papain and chymopapain which are two industrially proteolytic enzymes. Phytochemical analysis of the leaf of *Carica papaya* revealed the presence of saponins, tannins, flavonoids, alkaloids, terpenoids, carbohydrates, anthraquinones and lacked steroids. The quantitative phytochemical analysis of the *Carica papaya* leaf extract showed that the concentration of alkaloids was the highest followed by flavonoids, tannins and saponins, which are known to exhibit pharmacological activities. The therapeutic potentials of plants have been linked with their antioxidant potentials[12,13]. Flavonoids are potent water-soluble antioxidants and free radical scavengers that prevent oxidative cell damage, have strong anticancer activity and protect against the different levels of carcinogenesis. Flavonoids have also been found to play a very important role in protection against oxidative stress[14].

It has been documented that metformin is known to be an oral Biguanide anti-hyperglycemic agent which belongs to the trade name Glucophage among others. Metformin is the first-line of medication for the management of type 2 diabetes[15], particularly in individuals known to be overweight Clinical evidence has indicated that metformin is generally well-tolerated in many individuals[16] which also tends a low risk of causing low blood sugar when administered. The drug has the principles of decreasing glucose production by the liver, through a mechanism resulting in increasing the insulin sensitivity of body tissues. Additionally, metformin has also been reported to exhibit an anorexiant effect in most people, thereby reducing caloric intake[17]. Metformin treatment ultimately decreases gluconeogenesis (glucose production) in the liver. Similarly, It also has been revealed from studies that metformin administration leads to insulin-sensitizing effect with multiple actions on various tissues including the adipose tissue, skeletal muscle, ovary, endothelium and liver[18].

Because of the previous reports and findings, this study investigated the ameliorative effects of an extract of *Carica papaya* leaf and metformin on streptozotocin-induced diabetic rats.

MATERIALS AND METHODS

Study area: The study was carried out at the Department of Anatomy Animal House and Laboratory from July, 2020-March, 2021.

Collection and identification of *Carica papaya* leaves: Freshly cut matured leaves of *Carica papaya* were collected from Ladoke Akintola University of Technology, Ogbomosho and were identified and authenticated in the Department of Pure and Applied Biology by Professor Ogunkunle, a Botanist. The leaves were rinsed severally with clean tap water to remove dust particles and debris and thereafter allowed to completely drain. The collected leaves were then chopped into bits on a chopping board and air-dried at room temperature 25-30°C for four weeks before taking to the experimental site.

Preparation of aqueous extract of *Carica papaya* leaves: The air-dried leaves were ground into powdery form. About 400 g of the powdered leaves were then taken to the Department of Food Science and Engineering (Lipid Room), Ladoke Akintola University of Technology, Ogbomosho for aqueous extraction. The aqueous extract was kept in the refrigerator until the time it was used for the study.

Preparation of metformin: One pack of metformin 500 mg containing ten sachets was bought at the Sumter Pharmacy, Sabo, Ogbomoso, Oyo state. It was pounded using a laboratory mortar and pestle at the Histology Laboratory of Ladoke Akintola University of Technology, Ogbomoso, Oyo State, Nigeria. The powdered form was mixed with 200 mL of distilled water.

Experimental design and grouping of experimental animals: Forty-five adult male Wistar rats were used for this study. They were separated into 5 groups namely:

Group A : 9 normal control
Group B : 9 diabetic-control
Group C : 9 diabetic treated with low dose (1.0 g/100 mL) aqueous extract of *Carica papaya* leaves
Group D : 9 diabetic treated with high dose (3.0 g/100 mL) aqueous extract of *Carica papaya* leaves
Group E : 9 diabetic treated with 5000 mg kg^{-1} b.wt., metformin

After grouping, the animals were tagged for easy recognition.

Weekly assessment of blood glucose level and body weight: The glucose level of the experimental animals was monitored using the "fine test auto-coding premium glucometer test kit" and the values were recorded. The blood glucose levels were taken during the period of acclimatization, after induction of diabetes (to confirm if they were diabetic) and during the period of administration of aqueous extract of *Carica papaya* leaves and metformin The body weights of the experimental animals were monitored and weighed once a week with a sensitive weighing scale and the values were recorded. The body weights were taken during acclimatization periods, during the period of administration of metformin and aqueous extract of *Carica papaya* leaves to observe the effect of diabetes on the body weight of the adult Wistar rats.

Induction of diabetes: After 4 weeks of acclimatization, diabetes was induced in the adult Wistar rats by intraperitoneal injection of 60 mg kg^{-1} streptozotocin. Hyperglycemia was confirmed 3 days after induction by measuring the tail vein blood glucose level with a glucometer. Only the animals with fasting blood glucose levels greater than 126 mg dL^{-1} were considered diabetic.

Administration of aqueous extract of *Carica papaya* leaves and metformin: To determine the hypoglycemic effect of *Carica papaya* leaves and metformin in diabetic rats, oral doses of *Carica papaya* aqueous extracts (1.0 g and 3.0 g/100 mL) were administered as drinking water and metformin 5000 mg kg^{-1} b.wt., was administered orally with the aid of a cannula.

Group A : Normal control group, animals were given feed and distilled water for six weeks
Group B : Diabetic control group, animals were given feed and distilled water for six weeks
Group C : Diabetic group treated with a low dose of aqueous extract of *Carica papaya* leaves, 1.0 g/100 mL of aqueous extract of *Carica papaya* leaves was administered as drinking water for six weeks
Group D : Diabetic group treated with a high dose of aqueous extract of *Carica papaya* leaves, 3.0 g/100 mL of aqueous extract of *Carica papaya* leaves was administered as drinking water for six weeks
Group E : Diabetic group treated with metformin, 5000 mg kg^{-1} b.wt., of metformin was administered orally with the aid of a cannula for six weeks

Assay for biochemical parameters: Serum levels of Aspartate Transaminase (AST), Alanine Transaminase (ALT) and Alkaline phosphatase (ALP)[19] were determined using colourimetric methods using Randox diagnostic kits from the US.

Statistical analysis: All data were expressed as Mean±S.E.M. The statistical analysis of the results obtained in this study was evaluated and tested for significance using student's t-test. If the p-value of the t-test was less than 0.05 ($p<0.05$), then the result was significant. If the p-value of the t-test was greater than 0.05 ($p>0.05$), then that means that the result is not significant.

Photomicrography: The digital micrographs of the pancreas sections were obtained to show the morphological changes that occurred in the treated groups as compared to the control groups. The photomicrographs were taken at the Department of Anatomy, Ladoke Akintola University of Technology, Ogbomosho, Oyo State, using a digital AmScope Microscope from the US.

RESULTS

Statistical evaluation: Group A (control) body weight increased from 166.7 g at week 0-184.3 g at week 6, Group B (diabetic control) body weight increased from 201.8 g at week 0-203.6 g at week 6, Group C (1.0 g/100 mL low dose of *C. papaya* leaves extract) body weight increased from 210.9 g at week 0-213.5 g at week 6, Group D (3.0 g/100 mL high dose of *C. papaya* leaves extract) body weight decreased from 254.9 g at week 0-237.3 g at week 6, Group E (5000 mg kg^{-1} b.wt., metformin) body weight increased from 177.3 g at week 0-202.7 g at week 6 as seen in Table 1. Group E (5000 mg kg^{-1} b.wt.) showed a significant increase in final weight when compared to Group A and B. Group D shows a significant decrease in final weight when compared to Group C.

Table 2 shows that there was a slight decrease in the pancreatic weight in Group C (1.0 g/100 mL aqueous extract of *C. papaya* leaves) when compared to Group A (control) and an increase in the pancreatic weight in Group B (diabetic control) and D (3.0 g/100 mL aqueous extract of *C. papaya* leaves) when compared to Group A. There was a significant increase in the pancreatic weight in Group E (5000 mg kg^{-1} b.wt., metformin) when compared to Group A.

Table 3 shows that the fasting blood sugar levels decreased significantly ($p<0.05$) in diabetic treated Wister rats from week 0-6 in Group C, D and E when compared to Group A (control) while it increased significantly ($p<0.05$) from week 0 to week 6 in Group B (diabetic control) when compared to Group A (control) and diabetic treated groups, Group C, D and E.

Table 4 shows an elevation of serum biomarkers Alanine transaminase (ALT), Aspartate transaminase (AST) and Alkaline phosphatase (ALP) in Group B (diabetic control), 34.19, 100.8 and 15.97, respectively when compared to Group A (control) 26.47, 93.40 and 12.71, respectively. Group C (low dose of *C. papaya* leaves extract) showed a slight reduction of ALT, AST and ALP, 24.95, 84.04 and 12.45, respectively when compared to Group A and B. Group D (High dose of *C. papaya* leaves extract) and Group E (metformin treated) showed a significant ($p<0.05$) reduction in the serum levels of ALT, AST and ALP when compared to Group A and B.

In Fig. 1a, histological analysis of the pancreas shows normal histology of the pancreas. The parenchyma of the pancreas shows normal serous acinar and zymogenic cells containing abundant granular eosinophilic cytoplasm. There is normal interlobular connective tissue and normal septa. There are normal islets of langerhans consisting of round to oval collections of endocrine cells.

In Fig. 1b, the histological analysis of the pancreas shows the very poor histological architecture. The parenchyma of the pancreas shows complete degenerated serous acinar and zymogenic cells. There is a loss of granular eosinophilic cytoplasm. The interlobular connective tissues are also highly fibrotic with heavy deposition of connective tissue. Also seen is the diffuse islet of langerhans with degenerated alpha and beta cells. The pancreatic tissue appeared distorted in thin sections.

In Fig. 1c, this group was treated with oral administration of 1.0 g/100 mL aqueous extract of *Carica papaya* leaf extract for six weeks. The histological analysis of the pancreas shows moderate histological features. The parenchyma of the pancreas shows mildly normal serous acinar and zymogenic cells containing abundant granular eosinophilic cytoplasm. The interlobular connective tissues however are highly fibrotic with heavy deposition of connective tissue. There are mildly normal islets of langerhans and some mild presence of red inflammatory cells. This group shows a little improvement in pancreatic morphology.

This group was treated with oral administration of 3.0 g/100 mL aqueous extract of *Carica papaya* leaf extract for six weeks. The histological analysis of the pancreas in Fig. 1d shows normal histology of the pancreas. The

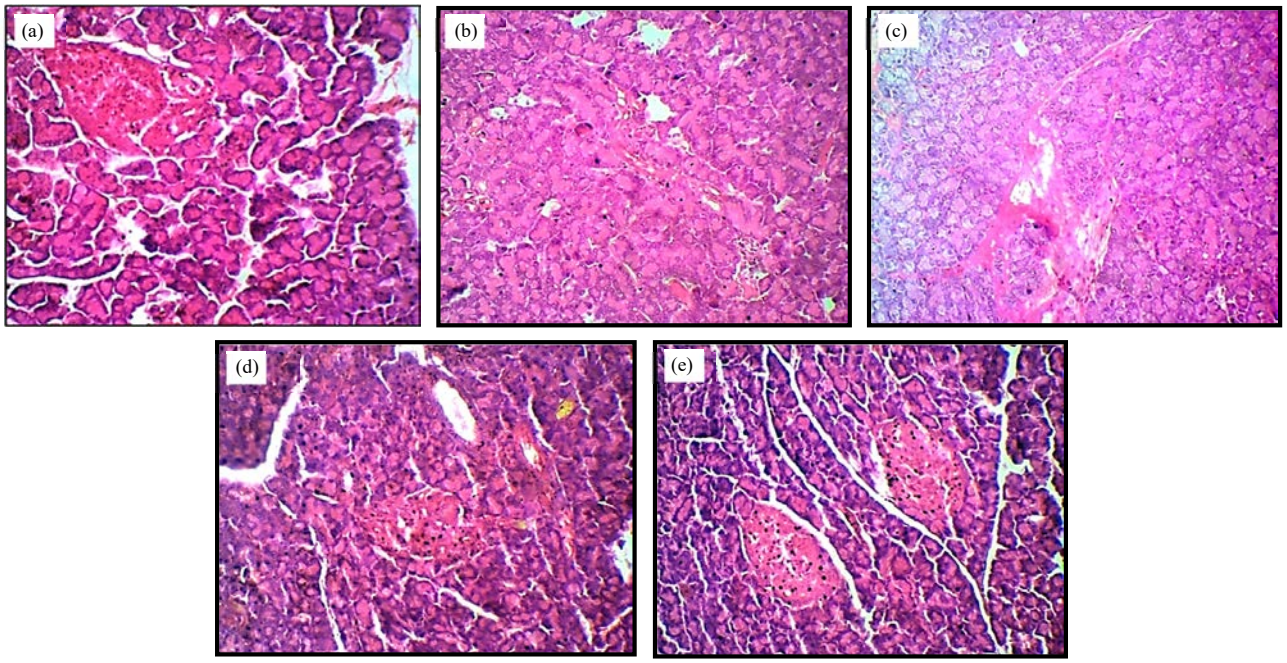

Fig. 1(a-e): Histological analysis of the pancreas shows histology of the pancreas, (a) Group A (control), (b) Group B (diabetic control), (c) Group C (low dose aqueous extract of *Carica papaya* leaf extract), (d) Group D (high dose aqueous extract of *Carica papaya* leaf extract) and (e) Group E (metformin)

Table 1: Means±S.E.M of the initial and final body weights (g) of adult Wistar rats before and after administration

Groups	Initial weight	Final weight	Weight gain or loss (%)
Group A (control)	166.7±10.01	184.3±7.932	+17.6
Group B (diabetic control)	201.8±2.57**	203.6±7.109	+1.8
Group C (1.0 g/100 mL low dose of *C. papaya* leaf extract)	210.9±3.96***	213.5±5.779**	+2.6
Group D (3.0 g/100 mL high dose of *C. papaya* leaf extract)	254.9±10.46***	237.3±6.839***	-17.6
Group E (5000 mg kg^{-1} b.wt., metformin)	177.3±5.65	202.7±11.10	+25.4

p<0.05, a value greater than 0.05 are considered insignificant while values less than 0.05 are considered significant (*) and values were expressed as Means±Standard error of the mean

Table 2: Means±S.E.M of pancreas weight of adult Wistar rats after administration of metformin and *Carica papaya* leaf extract to diabetic Wistar rats

Groups	Mean pancreatic weight Means±S.E.M (G)	Relative pancreatic weight (%)
Group A (control)	0.56±0.05	0.30
Group B (diabetic control)	0.57±0.07	0.28
Group C (1.0 g/100 mL low dose of *C. papaya* leaf extract)	0.44±0.04	0.21
Group D (3.0 g/100 mL high dose of *C. papaya* leaf extract)	0.56±0.04	0.24
Group E (5000 mg kg^{-1} b.wt., metformin)	0.82±0.05*	0.41

p<0.05, a value greater than 0.05 are considered insignificant while values less than 0.05 are considered significant (*) and values were expressed as Means±Standard error of the mean

Table 3: Means±S.E.M of the initial and final fasting blood sugar levels (mg dL^{-1}) of adult Wistar rats before and after administration

Groups	Initial fasting blood sugar	Final fasting blood sugar	Loss or gain (%)
Group A (control)	97.33±3.651	65.63±4.018	- 31.7
Group B (diabetic control)	79.44±5.075*	93.50±1.254***	+14.06
Group C (1.0 g/100 mL low dose of *C. papaya* leaf extract)	79.78±3.515**	50.75±2.469**	- 29.03
Group D (3.0 g/100 mL high dose of *C. papaya* leaf extract)	89.00±4.103	53.88±2.979*	-35.12
Group E (5000 mg kg^{-1} b.wt., metformin)	80.22±5.939*	62.33±8.353	-17.89

p<0.05, a value greater than 0.05 are considered insignificant while values less than 0.05 are considered significant (*) and values were expressed as Means±Standard error of the mean

Table 4: Means±S.E.M of serum level of ALT, AST and ALP of adult Wistar rats after treatment

Groups	ALT	AST	ALP
Group A (control)	26.47±1.751	93.40±1.174	12.71±0.2267
Group B (diabetic control)	34.19±1.979*	100.8±1.906**	15.97±0.3866***
Group C (1.0 g/100 mL low dose of *C. papaya* leaf extract)	24.95±1.015	84.04±0.7252***	12.45±0.4259
Group D (3.0 g/100 mL high dose of *C. papaya* leaf extract)	18.25±0.9443**	71.20±2.656***	12.44±0.3961
Group E (5000 mg kg^{-1} b.wt., metformin)	24.19±1.176	66.40±3.660***	11.96±0.4720

$p<0.05$, a value greater than 0.05 are considered insignificant while values less than 0.05 are considered significant (*) and values were expressed as Means±Standard error of the mean

parenchyma of the pancreas shows normal serous acinar and zymogenic cells containing abundant granular eosinophilic cytoplasm. There is normal interlobular connective tissue and normal septa. There are normal islets of Langerhans consisting of round to oval collections of endocrine cells. This group shows a considerable improvement in the pancreatic morphology with evidence of preserved pancreatic tissue.

This group was treated with oral administration of 5000 mg kg^{-1} b.wt., of metformin for six weeks. The histological analysis of the pancreas in Fig. 1e shows normal histology of the pancreas. The parenchyma of the pancreas shows normal serous acinar and zymogenic cells containing abundant granular eosinophilic cytoplasm. There is normal interlobular connective tissue and normal septa. There are normal islets of langerhans consisting of round to oval collections of endocrine cells. This group shows a considerable improvement in the pancreatic morphology with evidence of preserved pancreatic tissue similar to Group D.

DISCUSSION

This study shows that the intraperitoneal administration of streptozotocin (STZ) to adult Wistar rats significantly increased blood glucose levels after four days, thereby inducing diabetes, as well as decreased body weight. This result agrees with previous observations that have employed this model and also reported the loss of body weight[19]. Several reports suggest that this model of type 1 diabetes induced by STZ is adequate to evaluate the hypoglycemic effects of *Carica papaya* leaves. Weight loss is a main sign of diabetes but its mechanism is not clear. It could be due to many factors such as loss of appetite, increased muscle wasting and loss of tissue proteins[20]. Studies also have reported that medicinal plant extracts like *Carica papaya* contains flavonoids, saponins and polyphenols that increase the activity of anti-oxidants[14]. This antioxidant effect of plant extracts decreases the oxidative stress generated by diabetes, resulting in a reduced or delayed progression of endothelial degeneration, nephropathy and neuropathy[14]. Additionally, the antidiabetic effect of *Carica papaya* extract can be due to its content of phytochemicals responsible for antioxidant actions. This study showed that the administration of metformin and *Carica papaya* leaf aqueous extract significantly decreased blood glucose levels at $p<0.05$ as shown in Table 3 in diabetic adult Wistar rats. Moreover, a possible stimulatory mechanism on the few surviving beta cells has been considered, which could allow the release of more insulin.

The bodyweight of adult Wistar rats in Group A (control) considerably increased likewise those in the treated group (Group C, D and E) as seen in Table 1. Group B (diabetic control) suffered a loss of weight in the course of the study. Group C (diabetic low dose treated) were observed to be gradually regaining their weight as they were being treated with 1.0 g/100 mL aqueous extract of *Carica papaya* leaves. Group D (diabetic high dose treated) were observed to have a gradual loss in body weight as they were being treated with 3.0 g/100 mL aqueous extract of *Carica papaya* leaves as supported previously[14]. Group E (metformin treated) experienced a significant ($p<0.05$) increase in body weight as they were treated with 5000 mg kg^{-1} b.wt., metformin, which has been supported previously. In this present study, the administration of metformin and aqueous extract of *Carica papaya* leaves maintained the body weights of diabetic treated Wistar rats, Group C, Group D and Group E as shown in Table 1. Table 1 also showed a decrease in the body weights of adult Wistar rats in Group B during the experiment and it could be due to factors such as loss of appetite, increased muscle wasting and loss of tissue proteins about the previous report[21].

There was a slight decrease in pancreatic weight of Group C (treated with 1.0 g/100 mL aqueous extract of *Carica papaya* leaf extract for six weeks) when compared to Group A (control) and B (diabetic control) at $p<0.05$ and a significant ($p<0.05$) increase in pancreatic weight of Group E (treated with oral administration of 5000 mg kg^{-1} b.wt., of metformin for six weeks), when compared to Group A and B at $p<0.05$ as seen in Table 2. The pancreatic weight of Group D (treated with 3.0 g/100 mL aqueous extract of *Carica papaya* leaf for six weeks) remained the same as that of Group A. The pancreatic islets are preferentially affected in diabetes by the destruction of insulin-secreting beta cells, treatment with *Carica papaya* leaf extract and metformin may act by

stimulating the few remaining pancreatic islet beta cells with the subsequent release of more insulin, instead of pointing to the regeneration of beta cells of the islets may be responsible for the insulin increase in the treated rats as damage to islets in diabetic rats treated with *Carica papaya* extract and metformin was therefore greatly reduced in the treated rats.

In addition, the fasting blood sugar (FBS) level as shown in Table 3 increased significantly ($p<0.05$) in Group B (diabetic Wistar rats) when compared to Group A, C, D and E. Group C, D and E showed a significant ($p<0.05$) decrease in FBS when compared with Group A and B. This shows that treatment of diabetes with an aqueous extract of *Carica papaya* leaves and metformin significantly diminished FBS ($p<0.05$) in diabetic rats. This hypoglycemic effect may be explained in part either by decreasing intestinal absorption of glucose, by an increase in peripheral absorption of glucose utilization or by an increase in the catabolism of glucose due to its translocation to muscles and adipose tissues and also increased glucose tolerance.

More so, the elevation of serum biomarker enzymes (AST) Aspartate aminotransferase, (ALP) Alkaline phosphatase and (ALT) Alanine aminotransferase was observed in Group B (diabetic control) when compared to Group A at $p<0.05$ as seen in Table 4 suggesting damages done to the Islets of langerhans by hyperglycemia. ALT and AST are enzymes that are mostly found in the liver while ALP is found almost throughout all cells of the body. The treatment of diabetes in Group C, D and E greatly reduced the activities of ALT when compared to Group A and B at $p<0.05$. Therefore, treatment with metformin and *Carica papaya* leaves aqueous extract reversed the activities of the serum biomarkers AST, ALT and ALP by decreasing it near to normal levels which were induced by hyperglycemia in diabetic treated Wistar rats.

Histological analysis of the pancreas as seen in Fig. 3 showed normal histological architecture of the pancreas in diabetic treated Group D and E when compared to Group A and B at $p<0.05$. Group B (diabetic control) as shown in showed very poor pancreatic histological architecture when compared to Group A at $p<0.05$. Group C which was treated with 1.0/100 mL aqueous extract of *Carica papaya* leaf extract for six weeks showed a histological analysis of the pancreas with moderate histological features as the result shows that the pancreatic architecture was affected in this Group when compared to Group A and B at $p<0.05$.

CONCLUSION

This study concluded that the aqueous extract of *Carica papaya* leaves and Metformin possess an anti-diabetic effect. This study, therefore, supports that treatment with an aqueous extract of *Carica papaya* leaves and metformin ameliorates the effects of STZ induced diabetes. It also improved metabolic disruptions and imbalances caused by diabetes in adult Wistar rats investigated.

SIGNIFICANCE STATEMENT

This study discovers the higher efficacy and potency of extract of *Carica papaya* leaves compared with metformin as well as a possible synergistic and beneficial effect of the combination of the named substances. This study will be helpful in further studies to elucidate the role and application of an aqueous extract of *Carica papaya* leaves and metformin in health delivery and effective management of diabetes mellitus.

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