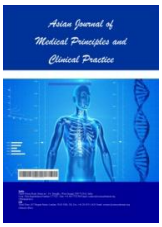

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Comparative effects of *Carica Papaya*, Avocado Pear and Ginger Extracts on the Histological Structure of the Pancreas of Streptozotocin-induced Diabetic Rats

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Authors' contributions

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

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ABSTRACT

Introduction: The increasing global prevalence of diabetes mellitus requires a holistic approach for its management. This study was carried out to compare the effects of *Carica papaya* (Pawpaw) leaves, *Persea americana* (Avocado pear) and *Zingiber officinale* (Ginger) on the histological structure of the pancreas of Streptozotocin (STZ)-induced diabetic wistar rats.
Methodology: Fifty (50) male wistar rats with weights ranging from 170-250g were used for this study. They were divided into five groups (I, II, III, IV, and V) of 10 rats each. Groups II, III, IV and V were given 50 mg/kg STZ freshly dissolved in 0.1M citrate buffer (P^H 4.5) in a volume of 1ml/kg body weight intraperitoneally to induce diabetes mellitus while Group A served as non-diabetic controls while Group B served positive controls. Group C, D, and E were given 3g/100ml body weight of freshly prepared of aqueous extract of *Carica papaya* leaves, Avocado Pear and Ginger respectively. The treatment continued for 28 days, then rats were anesthetized, and their pancreas

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were extirpated and processed for light microscopic examinations. The blood glucose levels were determined, and the weights were also taken at baseline and during the treatment.
Results: The STZ-induced rats exhibited hyperglycemia accompanied with increases in glucose and loss in body weight. Aqueous extract of *Carica papaya* leaves, Avocado Pear and Ginger were found effective in lowering serum glucose and returned the weight of treated diabetic rats to almost original values. Microscopic examination of the pancreatic sections of diabetic rats treated with aqueous extract of *Carica papaya* leaves, Avocado Pear and Ginger revealed regeneration of islet of langerhans compared with the untreated diabetic group. Although the three plants have regenerative abilities on islets of Langerhans, *Carica papaya* has more regenerative potentials than the other two plants.
Conclusion: Results from this study showed that treatment with aqueous extracts from *Carica papaya*, Avocado Pear, and Ginger were effective in lowering hyperglycemia Spreptozotocin-induced diabetic Wistar rats.
Recommendation: The herbal plants used for this study should be used as candidate substances for the development of regimens for the management and treatment of diabetes mellitus.

Keywords: Diabetes mellitus; avocado; carica papaya; ginger; hyperglycemia; medicinal plants.

1. INTRODUCTION

Diabetes mellitus is a metabolic disease resulting from insulin deficiency, leading to high blood glucose levels and hyperglycemia [1]. Hyperglycemia resulting from defects in insulin action or insulin production leads to a number of complications [2] The changes in biochemical parameters such as formation of advanced glycation end products (AGEs) have increased the expression of pro-inflammatory cytokine genes [3]. Diabetic complications have demonstrated that the production of excess reactive oxygen species (ROS) leads to tissue injury or apoptosis, and reduction of antioxidant enzyme activities and tissue glutathione (GSH) levels has been reported in diabetes mellitus [3]. Both oxidative stress and inflammation play a major role in the development of tissue insulin resistance [4]

Diabetes is a disease that affects many people in the 21st century and is known as the fifth leading cause of death [5]. High prevalence, variable pathogenesis, progressive process and complications of diabetes all highlight the urgent need for effective treatments. Nowadays, different treatments, such as insulin therapy, pharmacotherapy, and diet therapy, are available to control diabetes. There are several types of glucose-lowering drugs that exert anti-diabetic effects through different mechanisms. These mechanisms include stimulation of insulin secretion by sulfonylurea and meglitinides drugs, increasing of peripheral absorption of glucose by biguanides and thiazolidinediones [6], delay in the absorption of carbohydrates from the intestine by alpha-glucosidase, and reduction of hepatic gluconeogenesis by biguanides [7]. In the past three decades, despite the significant progress made in the treatment and management of diabetes, the results of such efforts in patients is still far from perfect. These treatments have some disadvantages, including drug resistance (reduction of efficiency), side effects, and even toxicity. For example, sulfonylureas lose their effectiveness after 6 years of treatment in 44% of patients. It is also said that the glucose-lowering drugs are not able to control hyperlipidemia [8].

Today, many treatments that involve the use of medicinal plants are recommended. Most plants contain carotenoids, flavonoids, terpenoids, alkaloids, glycosides and can often have anti-diabetic effects [8]. The anti-hyperglycemic effects that result from treatment with plants are often due to their ability to improve the performance of pancreatic tissue, which is done by increasing insulin secretions or reducing the intestinal absorption of glucose [8].

The management of type 2 diabetes mellitus is possible with drug that can lower the blood sugar level on the one hand and restore the liver glycogen level on the other hand. In modern system of medicine, there is no drug, which is reported to possess both of the properties [9]. However, the hypoglycemic effect of some herbal extracts have been confirmed in human and animal models of type 2 diabetes and conventional drugs have been derived from the active molecule of these medicinal plants. Metformin, a less toxic biguanide and potent oral glucose lowering agents, was developed from

Galega officinalis and used to treat diabetes mellitus [10].

This study was carried out to assess and compare the effects of *Carica papaya* leave, *Persea americana* (Avocado pear) and *Zingiber officinale* (Ginger) on the structure of the pancreas of streptozotocin-induced diabetic wistar rats.

2. MATERIALS AND METHODS

2.1 Experimental Animals

Fifty (50) male sex wistar rats with weights ranging from 170-250g were procured from the Laboratory Animal House, College of Medicine, Ambrose Alli University Ekpoma, Edo State and transferred to the Experimental Laboratory Health Affairs Ventures, Ekpoma, where they were allowed one (1) week for acclimatization. During the period of acclimatization, the rats were fed with growers' mash and water *ad libitum.*

The research was conducted in accordance with the internationally accepted principles for laboratory animal use and care as found in the European Community guidelines (EEC Directive of 1986; 86/609/EEC).

2.2 Plant Materials

Carica papaya leaves, *Persea americana* (Avocado pear) and *Zingiber officinale* (Ginger) were freshly collected from plants in a local garden in Emuhi-Ekpoma, Edo State, Nigeria. The leaves were botanically identified and authenticated at the Herbarium of the Botany Department, Ambrose Alli University, Ekpoma. They were cut into pieces and oven-dried at 40^0c for 10days and then made into a fine powder for extraction.

2.3 Experimental Design

The rats were randomly divided into five groups of ten (10) animals each as follows:

Group I: Non diabetic rats receiving distilled water and normal feed only (negative control).

Group II: Diabetic rats receiving distilled water and normal feed only (positive control).

Group III: Diabetic rat receiving 3g/100ml carica papapya extract and normal feed only

Group IV: Diabetic rats receiving 3g/100ml avocado pear extract and normal feed only

Group V: Diabetic rats receiving 3g/100ml ginger extract and normal feed only

2.4 Induction of Diabetes in Rats

Experimental diabetes was induced following an overnight fast by a single intraperitoneal injection of 50 mg/kg STZ that was freshly dissolved in 0.1M citrate buffer (P^H 4.5) in a volume of 1ml/kg body weight. Control animals received 0.9% sterile saline. Hyperglycemia was confirmed three days after injection by measuring the tail vein blood glucose level with an Accu-Check Sensor Comfort glucometer. Only the animals with fasting blood glucose levels ≥250 mg/dl were used for this study.

2.5 Animal Sacrifice and Sample Collection

The animals were sacrificed after being anesthetized with chloroform. They were laid down on the dissection board in a supine position and their anterior thoraco-abdominal cavities were carefully dissected in the midline to expose the organs of interest (Pancreas). The pancreas were transferred into 10% formol saline before further histological protocol and analysis was performed. Body weights were also measured at baseline and before animals were sacrificed.
Blood samples were also collected into Fluoride-Oxalate bottles for the determination of glucose.

2.6 Biochemical And Histopathological Analyses

Plasma glucose was analyzed spectrophotometrically using Enzymatic Endpoint method (GOD/PAP) described by Barham and Trinder, (1972). Commercially available test kits, products of Randox laboratories, U.K. was used.

General tissue morphology of pancreas was done using H&E.

2.7 Data Analysis

Data obtained were analyzed using SPSS version 20 statistical software package. Results generated were expressed as mean ± SD and a P-value of <0.05 were considered significant. The significance difference among the groups was assessed by repeated-measures analysis of

variance (ANOVA). The photomicrography of pancreas tissue morphology was also displayed.

3. RESULTS

Table 1 shows the weights of animals. At baseline, there was no significant difference ($p>0.05$) in the body weight of animals among all the groups. At week 1, there was significant decrease ($p<0.05$) in the body weight of diabetic rat groups (Group II-V) when compared with non-diabetic control groups. At week 2-4, there was a significant increase ($p<0.05$) in the body weights of treated diabetic groups (III-V) when compared with diabetic untreated group (group II).

Table 2 shows the blood glucose level of animals. There was significant reduction ($p<0.05$) in the blood glucose of diabetic treated groups when compared with diabetic untreated group.

4. DISCUSSION

This study was carried out to compare anti-diabetic effects of *Carica papaya* leave, *Persea americana* (Avocado pear) and *Zingiber officinale* (Ginger) on the pancreas of streptozotocin-induced diabetic wistar rats. The results show that the intraperitoneal administration of STZ to rats significantly increased glucose blood levels four days after injection, as well as decreased body weight. In addition, other diabetes-related signs were observed. These results agree with previous observations by an earlier research finding [11], that have employed this model and that also report loss of body weight. Several reports suggest that this model of type 1 diabetes induced by STZ is adequate to evaluate the properties of leaves or fruits from different plants [12].

From this study, there was significant weight loss in diabetic rats when compared with controls. This is in agreement with the work of another research [13] who had reported significant weight loss in diabetic induced rats. 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 waste and loss of tissue proteins [14]

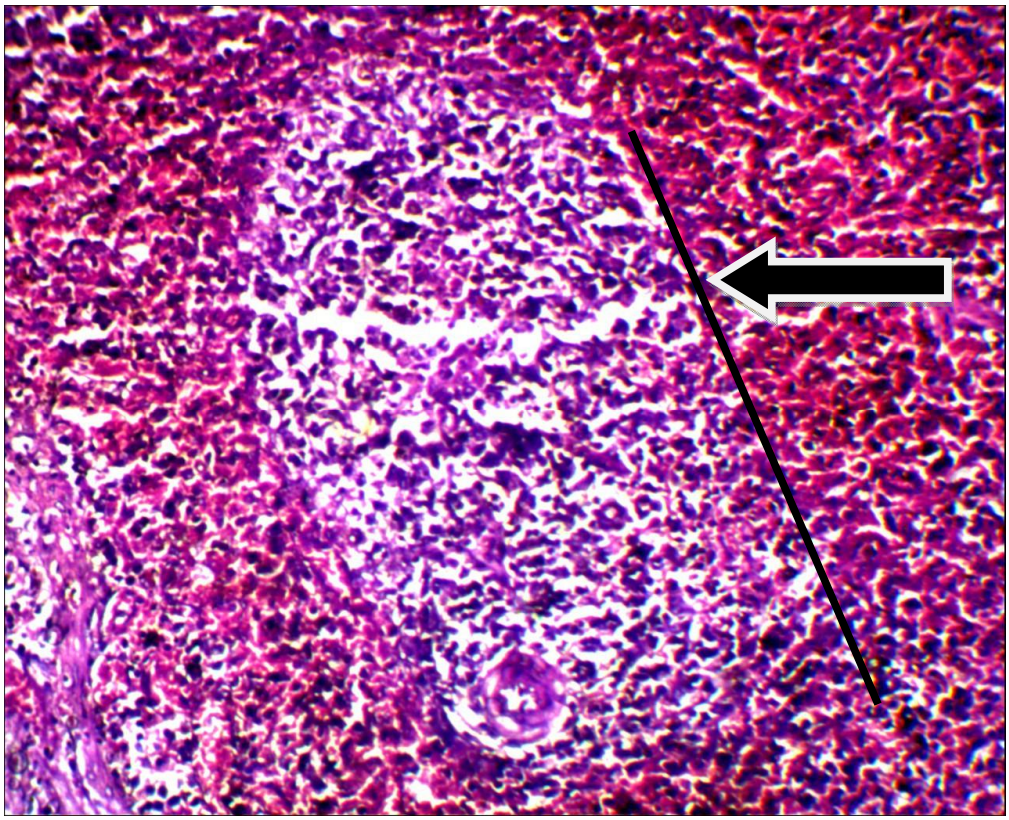

Fig. 1. Normal control- showing a wide area of islet-containing beta cells of about 7microns.(H&E X400)

Table 1. Effects of Carica Papaya, Avocado Pea and Ginger on Body Weights of Diabetic Rats

Period	GROUP I Mean±SD N=10	GROUP II Mean±SD N=10	GROUP III Mean±SD N=10	GROUP IV Mean±SD N=10	GROUP V Mean±SD N=10	F-value	p-value
Baseline	223.40±9.61[a]	226.70±6.52[a]	223.80±7.87[a]	226.50±5.72[a]	225.40±6.96[a]	0.413	0.799
Week 1	227.00±7.42[a]	174.10±9.86[b]	176.00±25.06[b]	185.30±7.76[c]	182.90±4.23[c]	27.461	<0.001
Week 2	230.80±6.60[a]	165.00±7.96[b]	182.20±25.36[c]	188.20±7.44[d]	186.40±4.33[d]	35.876	<0.001
Week 3	232.60±6.19[a]	156.60±7.07[b]	187.30±25.90[c]	191.30±6.46[c]	189.20±4.37[c]	45.813	<0.001
Week 4	236.40±5.79[a]	146.20±6.29[b]	193.10±25.33[c]	195.70±5.12[c]	193.00±4.74[c]	66.819	<0.001

KEYS: values with different superscripts are statistically different at p<0.05
GROUP I=Normal Control Rats
GROUP II= Diabetic Control Rat
GROUP III=Diabetic Rat + 3g/100ml Aqeous Extract of Carica papaya
GROUP IV= Diabetic Rat + 3g/100ml Aqeous Extract of Avocado Pear
GROUP V= Diabetic Rat + 3g/100ml Aqeous Extract of Ginger

Table 2. Effects of Carica Papaya, Avocado Pea and Ginger on Blood Glucose Level (mg/dl) of Diabetic Rats

Period	GROUP I Mean±SD N=10	GROUP II Mean±SD N=10	GROUP III Mean±SD N=10	GROUP IV Mean±SD N=10	GROUP V Mean±SD N=10	F-value	p-value
Baseline	83.80±7.77[a]	280.80±21.26[b]	269.00±15.91[b]	272.00±19.92[b]	278.70±14.45[b]	275.558	<0.01
Final	83.50±4.55[a]	422.20±12.70[b]	115.30±14.66[c]	120.30±9.52[c]	120.70±9.34[c]	309.235	<0.01

KEYS: values with different superscript are statistically different at p<0.05
GROUP I=NORMAL CONTROL RATS,
GROUP II= DIABETIC CONTROL RAT,
GROUP III=DIABETIC RAT + 3g/100ml AQEOUS EXTRACT OF CARICA PAPAYA
GROUP IV= DIABETIC RAT + 3/100ml AQEOUS EXTRACT OF AVOCADO PEAR
GROUP V= DIABETIC RAT + 3.0g/100ml AQEOUS EXTRACT OF GINGER

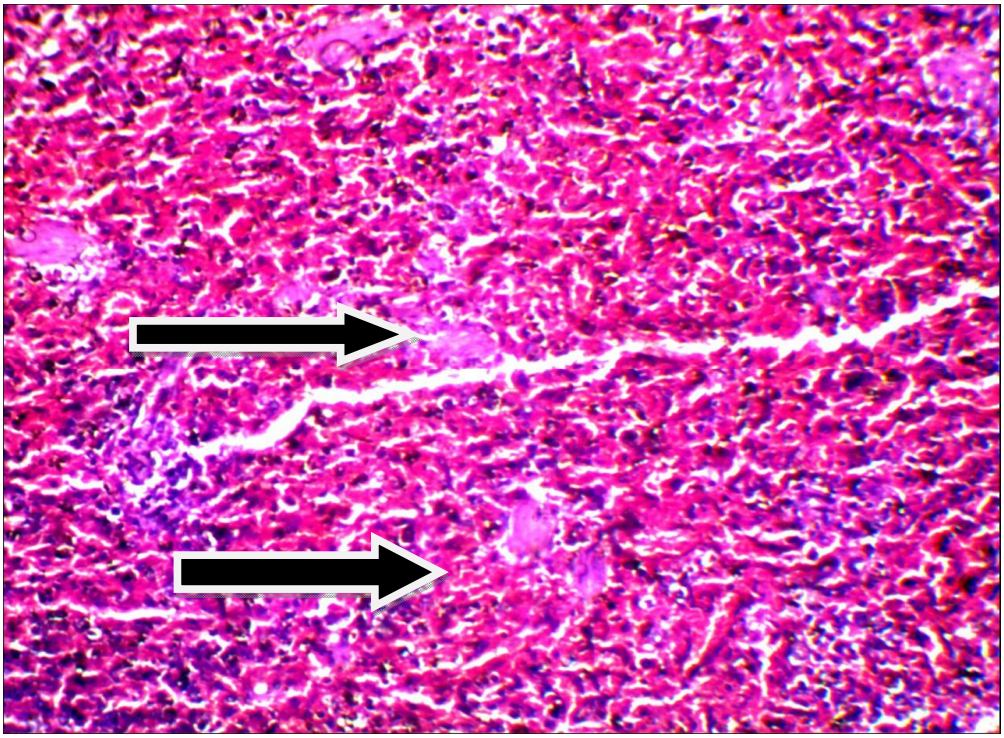

Fig. 2. Diabetic control rat- Showing scanty remains/ patches (black arrow) of degenerated islets of langerhams.(H&E X400)

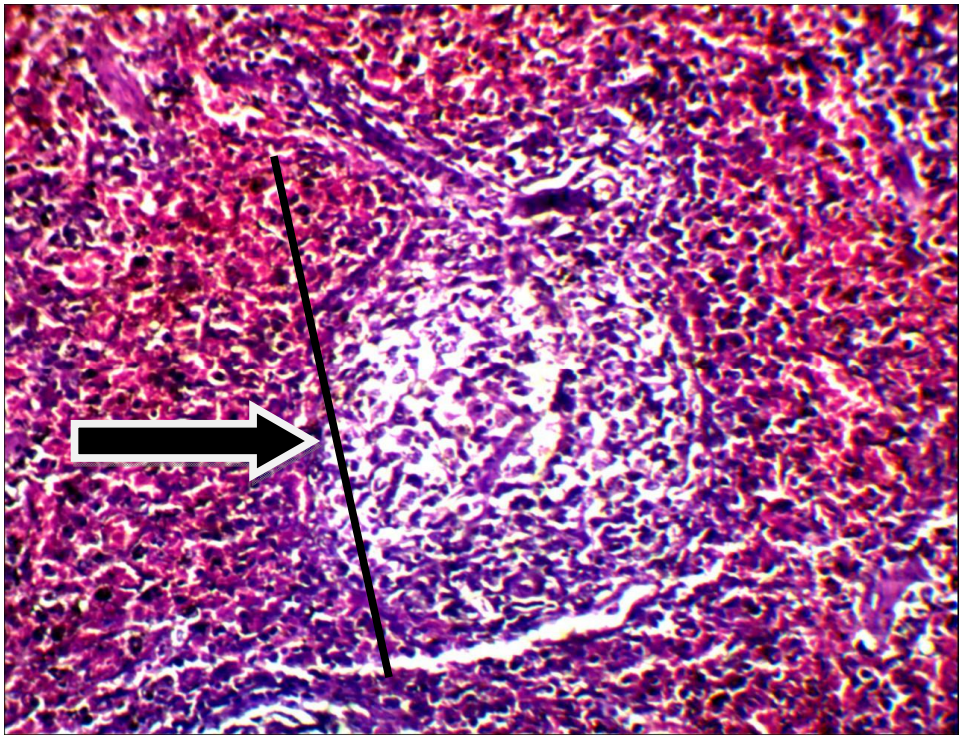

Fig. 3. Diabetic rat treated with 3g /100ml Carica papaya-Showing regeneration of islet Cells to 5microns (H&E X400)

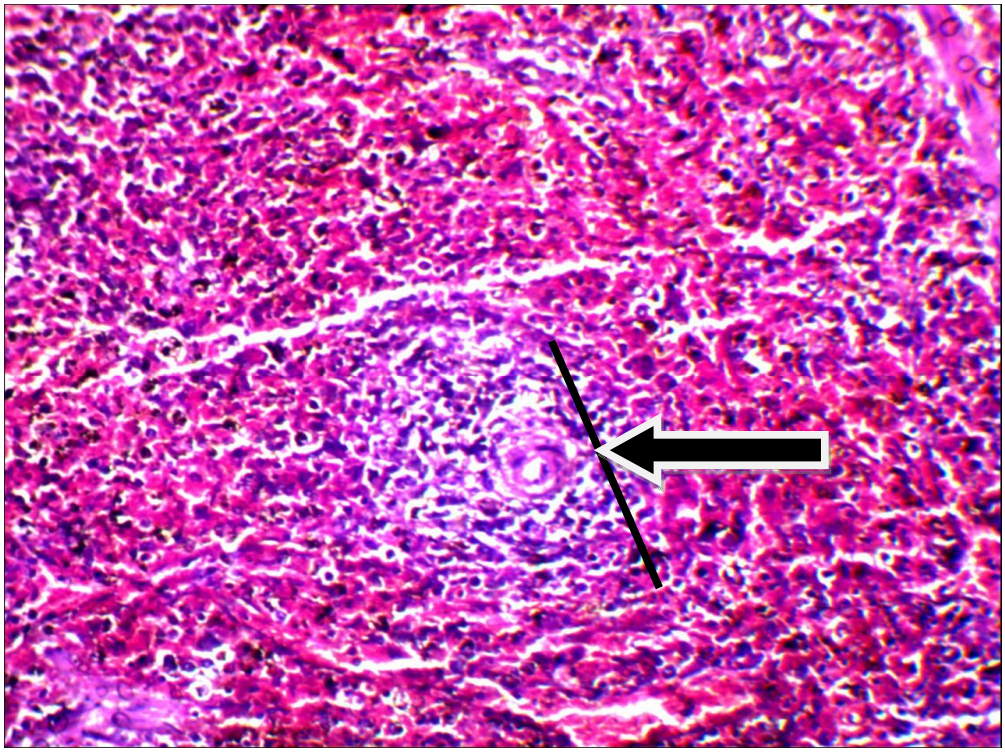

Fig. 4. Diabetic rats treated with 3g/100ml of aqueous extract of AVOCADO-Showing regeneration of islet to 3microns(H&E X400)

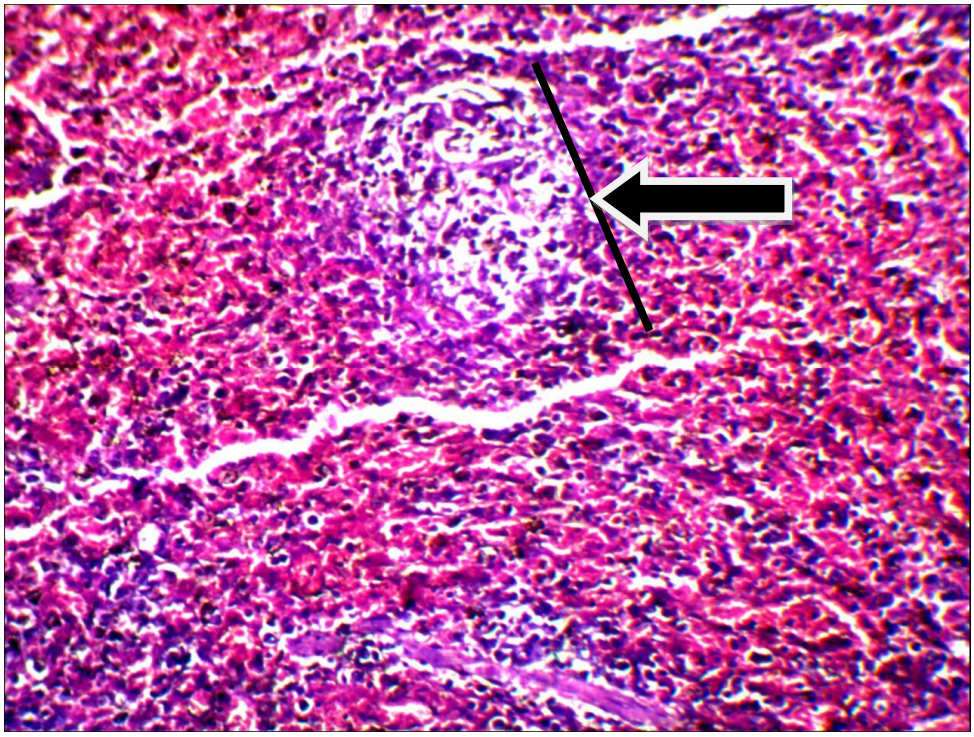

Fig. 5. Diabetic rat treated with 3g/100ml of aqueous extract of ginger showing regeneration of islet to 3microns (H&E X400)

This present study showed that the aqueous extract of C. *papaya* leaf significantly diminished blood glucose levels ($p<0.05$) in diabetic treated rats when compared with diabetic control rats. This finding agrees with some other earlier works [12,13]. This hypoglycemic effect may be explained in part by either a decrease in the rate of intestinal glucose absorption [15,16] or an increase in peripheral glucose utilization [16]. This may be due to increased catabolism of glucose due to GLUT4 translocation to the plasma membrane in muscle and brown adipose cells [14,17] with upregulation of the uncoupling protein-1 in brown adipose tissue and hepatic gluconeogenesis [16,18], causing as a resultant hyperinsulinemia or enhancement of peripheral glucose utilization [19,20]. Moreover, a possible stimulatory mechanism on the few surviving β-cells has been considered, which could allow the release of more insulin [21]. Our results suggest that the aqueous C. papaya leaf extract may act by stimulating the few remaining β-cells with the subsequent release of more insulin, instead of pointing to the regeneration of β-cells of the islets as responsible for the insulin increase.

In the present study, ginger administration to diabetic rats showed remarkable decrease in glucose levels compared to the non-treated group. However, blood glucose did not decrease to normal level. This is in agreement with another work [22] who in their various studies have reported that ginger has anti-hyperglycemic effect by reducing glucose levels. This probably due to the ability of the aqueous extract to increase glucose uptake and glycogen synthesis and to increase phosphorylation of the insulin receptor [23]. Furthermore, another author [24] stated that ginger promoted glucose clearances in insulin-responsive peripheral tissues and augmented insulin release, which maintained blood glucose homeostasis. The same authors added that ginger extract and its gingerol active ingredient enhanced glucose uptake in cultured rat skeletal muscle cells. STZ-induced oxidative stress was prevented by ginger administration based on its ability to inhibit lipid peroxidation and hence protect β-cells from diabetic free radicals damaging effect [25].

The present study showed that the aqueous extract of avocado pear significantly reduced blood glucose level in diabetic treated rats when compared with non-treated rats. This is in agreement with the another finding [26]. The anti-diabetic effects of avocado extracts indicate the presence of hypoglycaemic agents in the avocado pear. Hypoglycemic effect of the avocado pear extract may probably be due to contents of elements such as calcium, magnesium, potassium, sodium, zinc, chromium [26]. These elements play role in blood glucose homeostasis by regulating the key enzymes involved in gluconeogenesis in the liver e.g. glucose-6-phosphatase, fruitcose-1,6-bisphosphatatase and phosphoenolpyruvate-carboxykinase, thereby blocking gluconeogenesis and enhancing glucose utilization in the body [27]. Avocado pear may contain certain hypoglycemic agents such as phytochemicals like tannins. It might also contain insulin stimulatory substances such as insulin receptors substrate (IRS), glycogen synthase, the b3 adrenergic receptor, glucose dependent insulinotrophic polypeptide (GIP) receptor [26]. However, the mechanism by which the extract lowered the blood glucose level in STZ induced diabetic rats is not clearly understood, but It could be by stimulating peripheral utilization of glucose by inhibiting absorption in the gastrointestinal tract (GIT), increasing glucose metabolism, or regenerating the pancreatic tissue or potentiating the insulin secretion by the surviving B- cells [26].

Histopathological studies of diabetic control rats showed degeneration of pancreatic islet cells when compared to non-diabetic control rats. This is in agreement with another research finding [28,29]. This phenotype most likely gave rise to insulin deficiency. Insulin deficiency (or diabetes mellitus) causes excessive elevation and poor utilization of blood glucose and leads to hyperglycemia [29].

In this study, histopathological study of diabetic-treated groups indicated an increased volume density of islets and probably increased percentage of beta cells in diabetic rats that received the extracts of *Carica papaya*, ginger and avocado pear which may be a sign of regeneration. Signs of regeneration of β-cells, the potentiation of insulin secretion from surviving β-cells of the islets of Langerhans and a decrease in blood glucose levels have been reported to occur after consuming some plant extracts [30]. The extract of these substances may have some chemical components that exert regenerative effects on β-cells, stimulate these cells to produce more insulin (pancreatotrophic action) or have some insulin-like substances. The tissue-protective effect of plants can be observed by its ability to restore and reverse the already damaged tissues of STZ induced rats, and the observed effect is in agreement with what other researchers have reported. Other

researchers [31] have reported that *Terminalia arjuna* stem bark reversed pathological lesions that were evoked in cells of alloxan-induced diabetic rats.

Another study [32] investigated the anti-diabetic mechanism of combined *Vernonia amydalina* and *Azadirrachta indica* extracts by evaluating their effects on the histology of the pancreas and livers of normal and diabetic rats. The findings indicated a recovery/reversal of liver and pancreatic damage in streptozotocin-induced diabetic rats. A Study [33] had suggested the restorative effect of *P. americana* extracts on the pancreatic islet cells of alloxan induced diabetic rats.

In the current study, our results showed significant increase in weight of diabetic treated rat when compare with non-treated diabetic rats. This observation agrees with another study [26]. The increase in weight could be due to certain compounds and or mineral elements that may stimulate effective utilization of nutrients. In addition, the extract from these substances may contain nutrients such as protein and fat this coupled with their effective utilization, may be responsible for the weight gain.

5. CONCLUSION

The levels of blood glucose which were raised in STZ-induced diabetic rats can be lowered by aqueous extracts of *Carica papaya*, Avocado Pear and Ginger. Histopathological investigation of pancreatic sections of diabetic rats treated with *Carica papaya*, Avocado Pear and Ginger revealed approximately normal structure of islets of Langerhans, compared with the diabetic untreated group. Although the three plants have regenerative potentials on islets of Langerhans, *Carica papaya* has more regenerative potentials than other two plants. Overall, it can be concluded that aqueous extract of *Carica papaya*, Avocado Pear and Ginger possess hypoglycemic in STZ-induced diabetic rats.

6. RECOMMENDATION

We therefore recommend that the medicinal plants used in this study should be considered excellent candidates for future studies on the management of diabetes mellitus.

7. STUDY SIGNIFICANCE

This study has re-emphasized the importance of using herbs as therapeutic tools in managing and controlling diabetes. This study has shown that some medicinal plants have regenerative powers and can be used in treatment of damage tissues.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It's not applicable.

ETHICAL APPROVAL

Animal Ethic committee approval has been taken to carry out this study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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