Scientia Africana, Vol. 23 (No. 4), October, 2024. Pp 21-32
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ANTI-DIABETIC ACTIVITY OF HYDRO-ETHANOL EXTRACT OF MATURE (YELLOW) *CARICA PAPAYA* LEAF ON STREPTOZOTOCIN-INDUCED DIABETIC WISTAR RATS

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Received: 26-07-2024
Accepted: 17-08-2024

https://dx.doi.org/10.4314/sa.v23i4.2

Journal Homepage: http://www.scientia-african.uniportjournal.info
Publisher: *Faculty of Science, University of Port Harcourt.*

ABSTRACT

Diabetes is a metabolic disease, caused by significant abnormalities in insulin secretion or action on receptors. Many bioactive compounds from medical plants have demonstrated anti-diabetic efficacy with fewer side effects than synthetic medicines. This study was aimed at assessing the anti-diabetic effect of hydroethanol extract of mature (yellow) Carica papaya leaf on streptozotocin-induced diabetes. Forty-eight Wistar male rats were placed into six groups of eight animals per group: With the exception of Group A (normal control), all other groups were injected once intraperiotonially with streptozotocin, at a dose rate of 60 mg/kg body weight. Group B were untreated; Group C rats were treated with 100 mg/kg metformin, while Groups D, E, and F received 250 mg/kg, 500 mg/kg, and 750 mg/kg of the extracts, respectively, for 14 days. The rats' blood sugar levels were assayed as well as their body weight. Histopathological examination of tissue sections from the rats' pancreas was also conducted. The results showed a significant decrease in the blood sugar levels of animals treated with 250 and 750 mg/kg body weight, while animals treated with 500 mg/kg body weight of the extract reversed the hyperglycemic condition to normalglycemic; likewise, improvement in body weight was observed in the group treated with 500 mg/kg of the extracts. The result from the histological evaluation of the pancreas correlates with the biochemical findings. Treatment with various concentrations of the extracts led to a moderate preservation of the pancreatic beta-cells. This study suggests that; mature (yellow)Carica papaya leaf has hypoglycemic potentials.

Keywords: Diabetes, *Carica papaya*, Hydro-ethanol, Pancreas, Yellow leaf, Wistar rats.

INTRODUCTION

Diabetes mellitus is a metabolic syndrome and an endocrine disorder that is mostly attributed to an inability of insulin to function, secrete, or both to maintain glucose homeostasis Rehman et al. (2023). It is a multifactorial ailment that could be caused by an individual's genetic make-up, environmental factors, etc. Diabetes elevates the risk of other diseases in patients, such as hypertension, kidney failure, fatty liver, and many others (ADA, 2022). Diabetes is characterised by elevated plasma sugar levels in the body. Diabetic patients are unable to breakdown glucose for the body's utilisation due to a defect in insulin action or secretion (Quispe et al. 2023). This chronic metabolic disorder represents a significant threat to the health of the populace and life

outcomes (Roy et al., 2023). The terminal ailment has no socioeconomic, ethnic, or gender barrier. The factor that adds to the risk of the illness is poor dietary nutrients, inactivity, and genetics, being overweight and unhealthy habits. The World Health Organisation estimates that more than 180 million people around the globe are living with diabetes mellitus, and the number is projected to double by 2030 (Omonkhua et al., 2014). Categorically, this condition is listed as type-1 diabetes, type-2 diabetes, gestational diabetes, and others (Quispe et al., 2023). About 5% to 10% of all instances of diabetes include type-1 diabetes, also known as juvenile onset diabetes or insulin dependent diabetes mellitus. Up to 80% of patients have type-2 diabetes, commonly known as non-insulin-Dependent diabetes mellitus-onset diabetes (Nimenibo-Uadia and Nwachukwu, 2020). Regardless of socioeconomic or demographic origin, the number of people with type-2 diabetes, which currently affects more than half a billion people, have been rising quickly each year (Roy et al. (2023). Pregnancy-related gestational diabetes mellitus is a form of diabetes mellitus that usually develops in the middle or later stages of pregnancy. According to Zhao et al. (2015), the placenta produces chemicals that interfere with the correct function of insulin.

Medicinal plants are considered as significant sources of compounds with therapeutic potential for ages, and evidence-based research supports the therapeutic and pharmacological advantages of plant-derived substances (Wannes and Marzouk, 2016). Medicinal plants have been used since ancient times for the treatment and management of diabetic mellitus in the traditional medicine systems of many cultures throughout the globe. The World Health Organization (WHO) has recommended the extension of the scientific study of the anti-diabetic capabilities of various plant species and advised the use of medicinal plants for the management of diabetes (Yedjou et al., (2023). In comparison to contemporary synthetic medications, traditional medicine has demonstrated significantly superior results, fewer side effects, and lower costs in the treatment of diabetes mellitus (Prabhakar and Banerjee, 2020). The 25 plant species chosen for the study of diabetes came from an ethno-botanical assessment of medicinal plants used historically to treat inflammation and related illnesses like pain, arthritis, and stomach problems in southern Africa (Wannes and Marzouk, 2016). The research of natural compounds as prospective anti-diabetic drugs is currently receiving increased attention. The research of plants with anti-diabetic properties may provide fresh insight into diabetes mellitus treatment strategies (Yedjou et al., 2023). In order to find potential bioactive compounds for the finding and creating of new targeted anti-diabetic drugs that may control diabetes with the fewest side effects possible compared to conventional anti-diabetic medications, medicinal plants are becoming more and more popular among scientists, researchers, and pharmaceutical companies worldwide (Alam et al. (2023).

Carica papaya Linn., a member of the tiny family Caricaceae, has long been a popular herb used in folk medicine around the world to cure a variety of ailments Anita and Devendrasinh, (2017). Several studies have been done to ascertain the bioactivities of various parts of the *Carica papaya* plant, such as the shoots, leaves, fruits, seeds, roots, etc. The fresh (green) leaves of *Carica papaya* have been proven to contain many bioactive components with anti-oxidant, anti-anaemic, anti-diabetic, and anti-hyper-lipidemic activities (Sushmitha et al., 2018). Mature yellow leaves refer to leaves that have reached their full growth and development stage and have turned yellow naturally as part of their aging process (Igbashio et al., 2023). To date, in vivo studies has focused much on the antidiabeteic activities of the fresh (green) *Carica papaya* leaf, there is no in vivo study being conducted on the anti-diabetic effects of the mature (yellow) *Carica papaya* leaf. This has triggered the interest to carry out this

Scientia Africana, Vol. 23 (No. 4), October, 2024. Pp 21-32
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research work. The aim of this research is to determine the anti-diabetic activity of hydro-ethanol extract of mature (yellow) *Carica papaya* leaf on streptozotocin- induced diabetic Wistar rats.

MATERIALS AND METHODS

Plant Collection

The mature (yellow) *Carica papaya* leaves were harvested around the Ovia-North-East Local Government Area of Edo State.The leaves were verified at the Department of Plant Biology and Biotechnology, University of Benin. The herbarium specimen was deposited and voucher number given UBH-C505/2023 (*Carica papaya Linn.*).

Preparation and Extraction of Plant Extract

The leaves were thoroughly washed under running water to remove adhering dirt, shreded and air-dried for 14 days. Thereafter, the dried leaves were pulverised using an industrial blender and weighed. 1100g of the powdered extract was soaked in 5000 ml (30% water and 70% ethanol) for 72 hours with constant stirring. It was filtered using a 2-layer muslin cloth, after which it was filtered again using filter paper. The solvent was evaporated from the crude extract using a rotary evaporator, after which it was freeze-dried using a freeze-dryer and the percentage yield weighed.

Qualitative Test for Phytochemicals

The photochemical screening was conducted using standard procedures by Sofowora (1993); Trease, and Evans (1989); Odebiyi and Sofowora (1978).

Experimental Animals

A total of 48 male Wistar rats, weighing between 160 and 200 grams, were acquired from the Department of Anatomy's animal house, School of Basic Medical Sciences, College of Medical Sciences, University of Benin. For a period of 14 days, they were allowed to acclimatize with unrestricted access to food and water while being housed in polypropylene cages at room temperature and fed with pelleted chicken finisher's mash feed.

Ethical Clearance

Treatment of animals and all experimental procedures was done in accordance with the guidelines of National Research Council (2011). Ethical approval was given by the ethics committee, College of Medical Sciences, University of Benin with reference number CMS/REC/2023/490.

Animal Grouping

Table 1: Experimental design

Groups	Treatments
Group A (Normal Control):	Food and water only
Group B (Diabetic untreated):	Administered 60 mg/kg body weight Streptozotocin (STZ)
Group C (100mg/kg metformin):	Administered 60mg/kg body weight STZ and 100mg/kg metformin
Group D (250 mg/kg extract):	Administered 60 mg/kg body weight STZ and 250mg/kg extract
Group E (500 mg/kg extract):	Administered 60 mg/kg body weight STZ and 500mg/kg extract
Group F (750 mg/kg extract):	Administered 60 mg/kg body weight STZ and 750mg/kg extract

Induction -of Diabetes and Treatment

Diabetes was induced using the common diabetogenic agent streptozotocin (STZ), administered interperitoneally after fasting the rats overnight. Blood glucose level (FBS) and body weight of the rats was checked before induction of the diabetes. The STZ was freshly prepared by dissolving in 0.1 M cold citrate buffer, PH 4.5 and administered at a single dose of 60mg/kg body weight. Diabetes was confirmed after four days of induction. Only rats with fasting blood sugar levels equal or greater than 200mg/dL were considered diabetic and were used for the study. Treatment was commenced immediately after confirming diabetes and lasted for 14 days.

Determination of Body Weight

The body weight of the experimental animals was measured five times. Firstly, was on the first day of acclimatization (Day 1); secondly was on the last day of acclimatization (Day 14) before the induction; thirdly was on (day 18), four days after induction with STZ. The fourth time of measuring body weight was 7 days after treatment, which is (Day 25) and lastly, was 14 days after the commencement of treatment before the sacrifice (Day 32). The weight was taken using a digital weighing balance.

Determination of Fasting Blood Sugar (FBS) Level

Fasting blood sugar level was measured four times during the course of the study using fine test glucometer. Firstly, was before induction of diabetes with STZ on the 14^{th} day of acclimatization. Secondly, FBS was checked four days after induction of diabetes to confirm the disease condition on (Day18). Thirdly, FBS was measured after 7 days of administering treatment (Day 25) and lastly, 14 days after treatment before sacrifice (Day 32). At the end of 14 days of treatment, the rats were fasted overnight; then sacrificed. The blood glucose level were taken via tail vein puncture after sterilizing the tails of the animals with 10% alcohol, then allowing the blood to touch the test strip which was inserted into a calibrated glucose meter. This gave direct reading in mg/dl after the meter beep in 5 seconds.

Collection and Preparation of Tissue

At the end of 14 days of treatment, the rats were fasted overnight; FBS level and body weight was measured and then sacrificed; the pancreas were harvested and placed in 10% buffered formalin and was processed as described by Eze and Aideyan (2020), for histopathological evaluation.

Statistical Analysis

Statistical package for social sciences (SPSS) version 25.0was used to analyse the data obtained from the study. Results obtained were expressed as mean ± SEM (Standard Error of Mean). Differences among the means were determined by one-way analysis of variance (ANOVA). Values were deemed statistically significant at $P<0.05$.

RESULTS

Table 2: Qualitative Phytochemical Screening of Mature (Yellow) *Carica papaya* Leaf

Phytochemicals	Tests	Inference
Glycosides	General test	-
Saponins	Frothins	+ +
Phenolics	Ethanol/ferric chloride	+
Eugenols	Ethanol/ferric chloride	+
Terpenoids	Salkowski	+
Steroids	Acetic/H_2SO4	+

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Alkaloids	Wagner	+
Flavonoids	Lead acetate	+
Tannins	Ferric chloride	+

Key: +: Present; ++ Largely present; - Absent

Table 3: *Effect of Treatment on the Body Weight of Streptozotocin-induced Diabetic Wistar Rats*

	Day 1	Day 14	Day 18	Day 25	Day 32
Normal control	187.9±2.11	235.3±1.25[a]	252.50±5.47[a]	269.8±4.27[a]	291.9±2.79[a]
Diabetic untreated	200.4.1±5.21	254.3± 3.77[a]	230.6±5.46[a]	210.4±5.42[a]	186.0±4.74[a]
100mg/kg metformin	180.8±1.62	232.5±6.27[a]	210.57±6.41[b]	191.2±5.08[b]	165.0±4.16[b]
250mg/kg Extract	164.0±1.62	203.9±3.39[a]	192.50±4.79[b]	174.5±5.46[b]	154.0±1.47[b]
500mg/kg Extract	181.1±1.31	238.4±3.42[a]	224.86±2.73[a]	222.0±2.35[a]	222.83±2.58[a]
750 mg/kg Extract	175.3±.861	225.5±4.61[a]	209.33±4.77[b]	198.80±2.91[b]	184.20±5.16[b]

Values are expressed in mean ± SEM of 5 determinations. Alphabets represents different levels of statistical significance at ($p<0.05$) between groups and across days.

Table 4: Effect of Treatment on Fasting Blood Sugar (FBS) of Streptozotocin-induced Diabetic Wistar Rats

Groups	Day 14	Day 18	Day 25	Day 32
Normal control	91.0±3.10[b]	89.9±2.99[b]	96.8±2.64[b]	89.9±3.35[b]
Diabetic untreated	86.8±3.33[b]	466±21.65[a]	457±22.57[a]	421.0±18.23[a]
100mg/kg Metformin	91.4±2.86[b]	531±11.28[a]	455.17±19.94[a]	357.60±16.63[a]
250mg/kg Extract	92.8±5.00[b]	494.17±33.66[a]	375.80±86.11[a]	234.67±126.79[a]
500mg/kg Extract	88.0±2.46[b]	450.1±25.43[a]	113.63±19.77[a]	102.29±19.77[a]
750mg/kg Extract	91.00±4.49[b]	498.33±25.59[a]	373.60±70.03[a]	345.26±60[a]

Values are expressed in mean ± SEM of 5 determinations. Alphabets represents different levels of statistical significance at ($p<0.05$) between groups and across days.

Result of Histopathological Evaluation

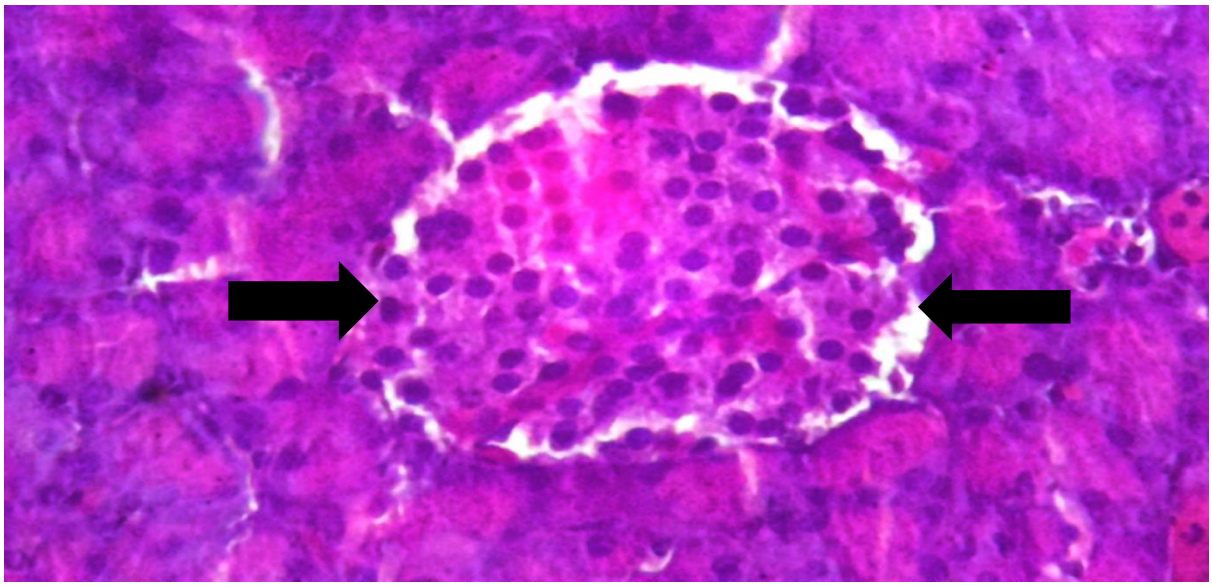

Plate 1: Photomicrograph of a section of the pancreas of normal control group showing normal histo-architecture with closely-parked acini and islets of Langerhans (H&E; 400X)**.**

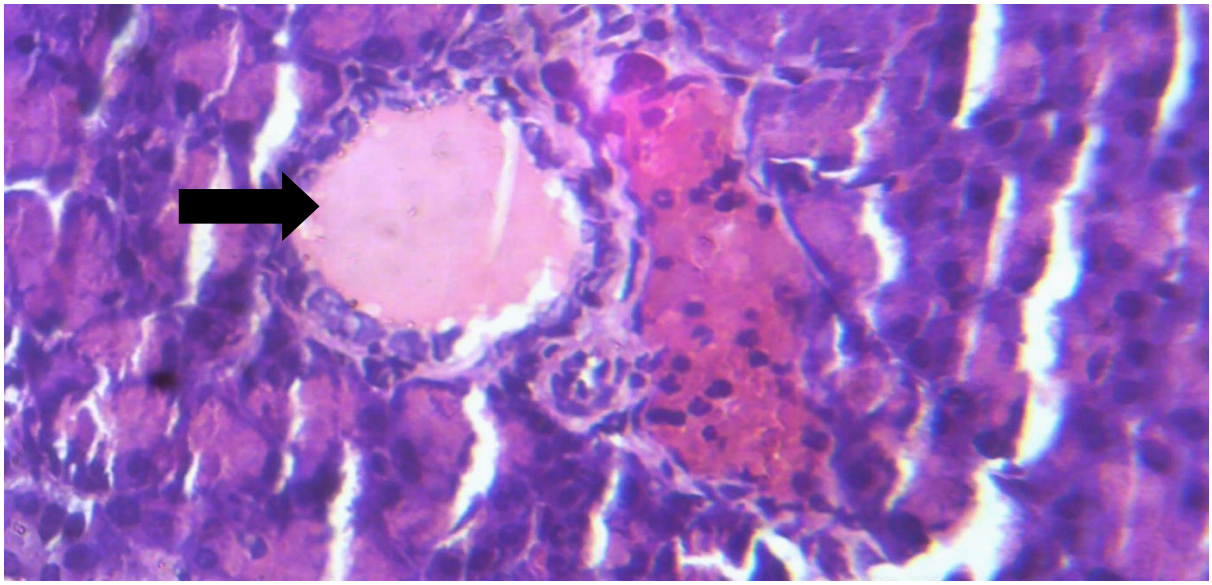

Plate 2: Photomicrograph of a section of the pancreas of the group of rats treated with only60mg/kg streptozotocin showed total destruction of beta cells in the Islet of Langerhans (H&E; 400X).

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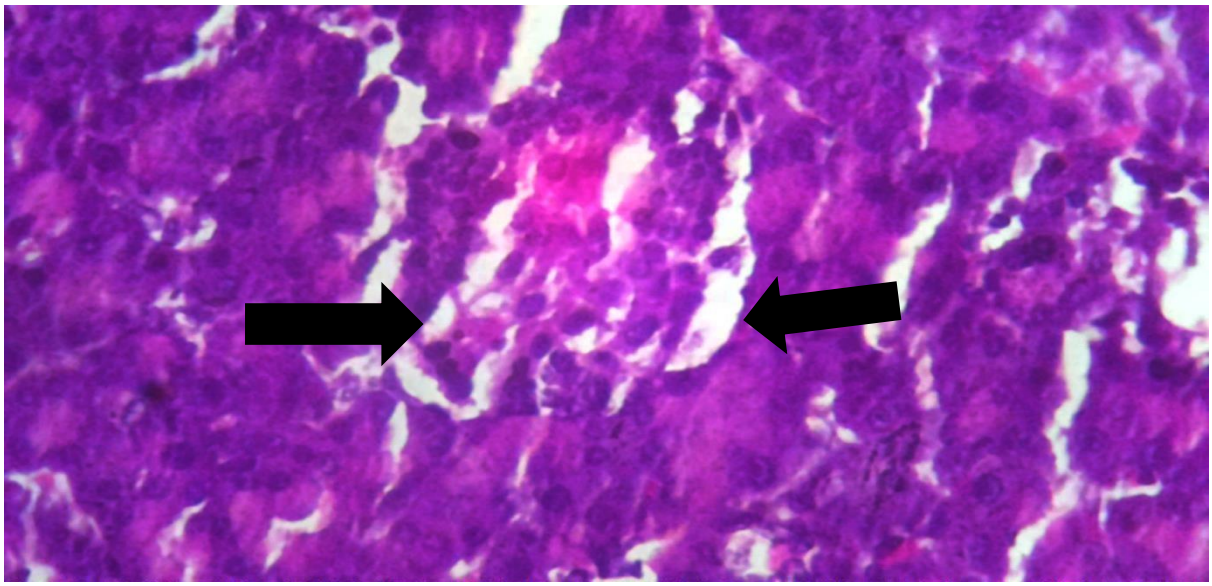

Plate 3: Photomicrograph of a section of the pancreas of the group of rats treated with 60 mg/kg streptozotocin and 100 mg/kg metformin showing very few preserved beta cells in the Islet of Langerhans (H&E; 400X).

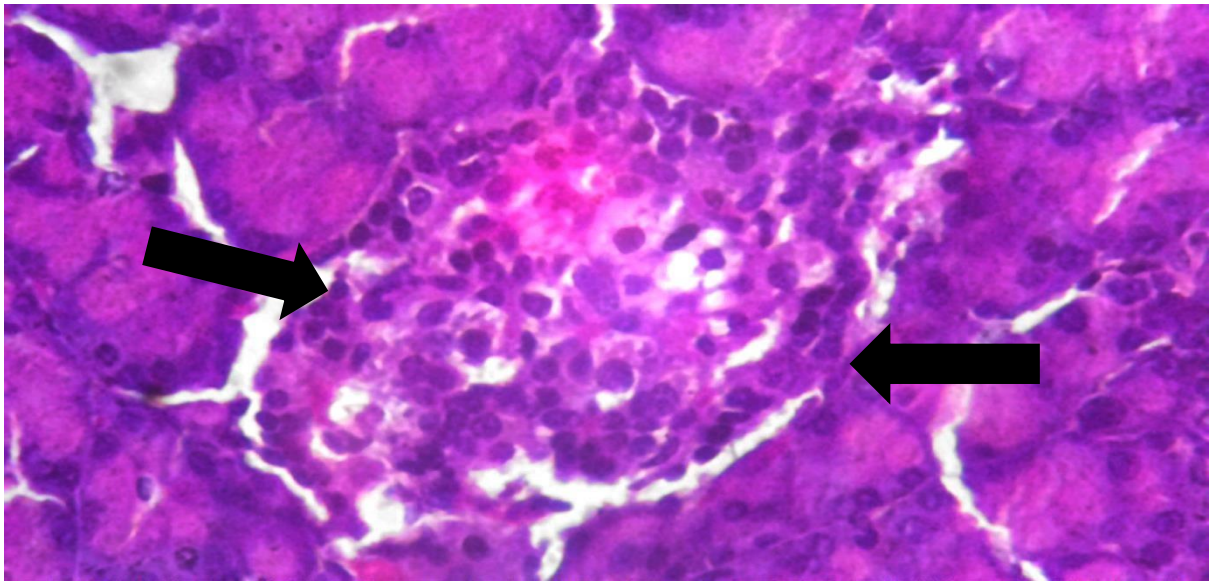

Plate 4: Photomicrograph of a section of the group of rats treated with 60 mg/kg streptozotocin and 250 mg/kg of the extract showing moderate preservation beta-cells in the Islet of Langerhans (H&E; 400X).

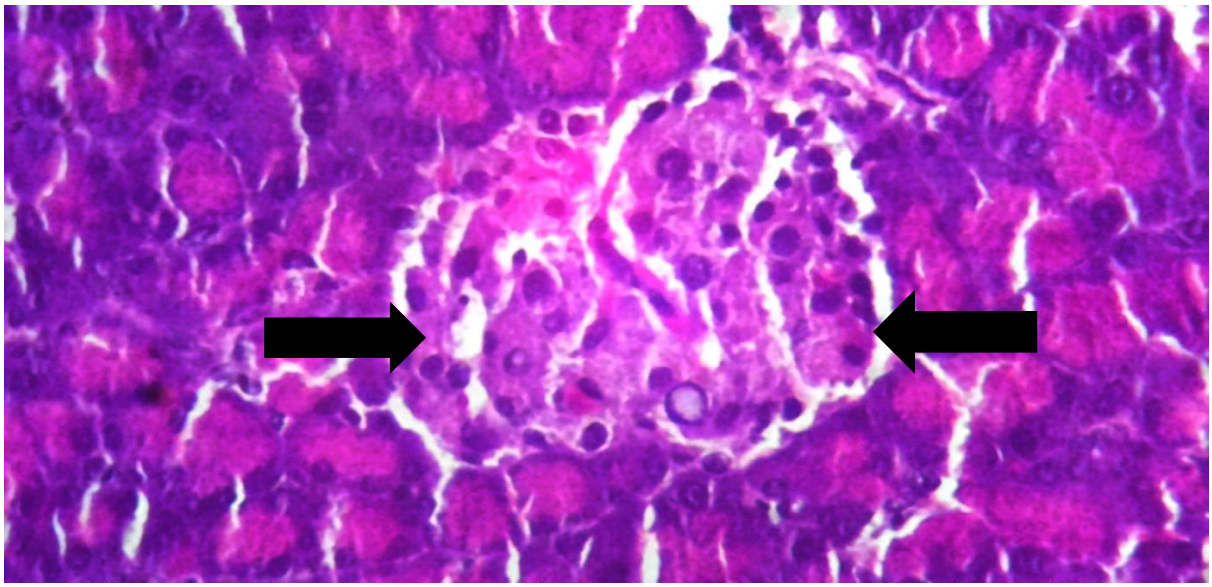

Plate 5: Photomicrograph of a section of the pancreas of the group of rats treated with 60mg/kg streptozotocin and 500 mg/kg of the extract showing moderate preservation beta cells in the Islet of Langerhans (H&E; 400X).

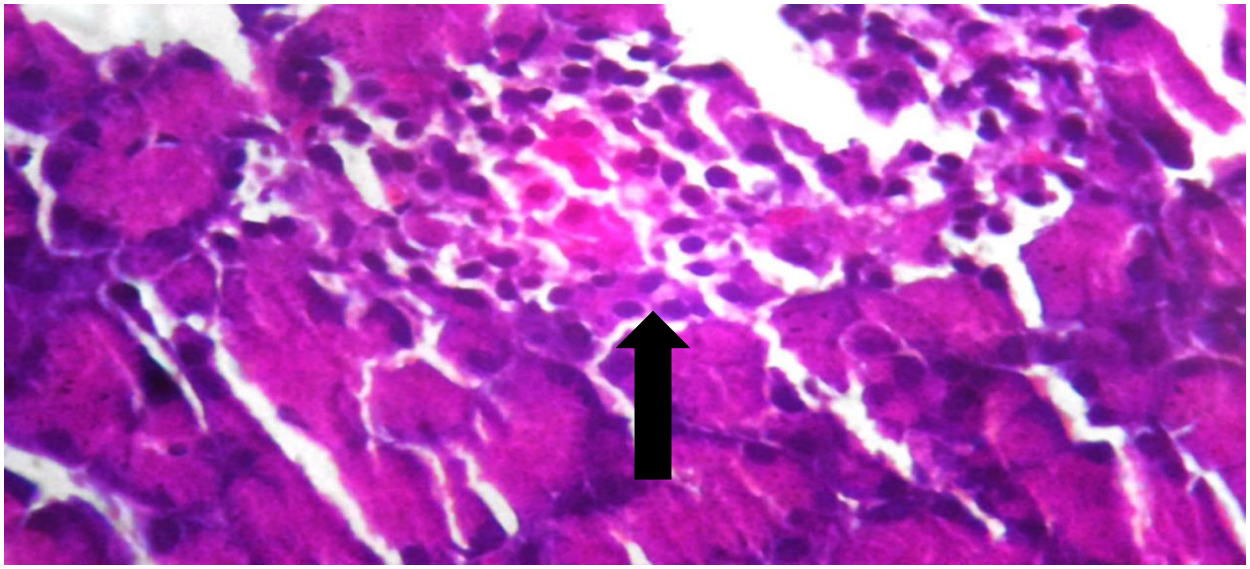

Plate 6: Photomicrograph of a section of the pancreas of the group of rats treated with 60 mg/kg streptozotocin and 750 mg/kg of the extract showing moderate preservation beta cells in the Islet of Langerhans (H&E; 400X)**.**

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DISCUSSION

The phytochemical screening of hydro-ethanol extract of mature (yellow) *Carica papaya* leaf (HEMYCPL) is presented in Table 2. The result showed that, alkanoids, eugenols, phenols, flavonoids, steroids, tannins, saponins, terpenoids, were present. Saponins were largely present while glycosides were absent. The handful of phytochemicals revealed in mature (yellow) *Carica papaya* leaf suggests that the plant would be relevant for medicinal purposes in treating and management of illnesses. *Carica papaya leaf* has long been used in terms of its medicinal uses and has been used in numerous Asian nations to treat a range of illnesses. They are used to treat corns, warts, constipation, weakness, amenorrhoea, menstrual issues, eczema, sinusitis, cutaneous tubercle, glandular tumours, diabetes, ulcers, hypertension, dengue, and other conditions due to the presence of the aforementioned significant phytochemicals (Sharma et al., 2022). Saponins have several potential health benefits, such as antioxidant, anti-inflammatory, anti-diabetic and anti-cancer properties (Peng and Biao, 2021). The anti-inflammatory and antioxidant properties of eugenol protect neuron cells and lessen illness caused by oxidative stress (Wang and Wu, 2018). It has been demonstrated that flavonoids support cardiovascular health by reducing blood pressure and cholesterol levels and preserving blood vessels; they may reduce the risk of heart disease Gogna et al. (2015). According to Gani et al. (2017), tannins have anti-inflammatory effects. Yadav and Agarwala (2011), reported that phenolic compounds have proven anti-aging, anticarcinogenic, antiaopotosis, antiarterosclerotic, and cardiovascular protection (Airaodion et al., 2019) reported that the presence of alkaloids, flavonoids, and phenolic compound in the leaf of *Carica papaya* is responsible for its hypoglycaemic effect and antioxidant activity.

Table 3 presents the effect of treatment on the body weight of streptozotocin-induced diabetic Wistar rats. During the experiment, STZ-induced diabetic rats exhibited a notable reduction of weight loss in comparism to the normal control rats. Omokhhua et al. (2014) reported that weight loss in STZ-diabetes may be due to loss of protein and muscle wasting. Weight loss is a symptom of diabetes attributed to the low utilization of energy by cells due to low insulin secretion. At the end of the 14-day treatment, there was no significant increase in body weight of rats treated with 100 mg/kg metformin, 250 mg/kg, and 750 mg/kg hydro-ethanol extract of mature yellow *Caricapapaya l*eaf except for group treated with 500 mg/kg body weight of the extract, which showed a significant increase in body weight. The weight loss in STZ-diabetic groups may be attributed to the observed excess urination (Polyuria) in the STZ-diabetic groups. Significant improvements in body weight in rats treated with 500 mg/kg suggest that the 500 mg/kg of extract had the best potential for improving body weight, and this shows that the plant could have potential for improving glucose uptake and utilization by cells.

Table 4 presents the effect of treatment on the fasting blood sugar levels of streptozotocin-induced diabetic Wistar rats. The increase in fasting blood sugar levels in streptozotocin-induced diabetic rats was due to the cytotoxic and disruptive nature of streptozotocin on the pancreas, which is involved in preserving the body's normal sugar homeostasis. In normal individuals, endogenous insulin is secreted from the pancreas in a pulsatile manner. Insulin secretion rates are less responsive to changes in glucose levels in diabetic patients compared to normal subjects. This is an indication of the loss of normal glucose homeostasis in diabetic patients (Quina and Badwan, 2015).

When the diabetic rats were treated with metformin (standard diabetic drug) and different concentrations of hydro ethanol extract of mature (yellow) *Carica papaya* leaf, there was a significant decrease in the FBS levels, this agrees with the work done by

Airarodion et al. (2019) on the antidiabetic effect of *Carica papaya* leaves in alloxan-induced diabetic rats. Although treatment with 500 mg/kg of the extract was able to reverse the hyperglycemic condition of the rats to normaglycemic condition, decreasing the FBS levels from 450.13 ±25.43 to 102.29 ±10.50 mg/dl. The antihyperglycemic effect of the extract may be due to the enhanced secretion of insulin from the beta cells of the pancreas or may be due to increased tissue uptake of glucose by enhancement of insulin sensitivity (Maniyar and Bhixavatimath et al., 2012). The characteristic reduction in fasting blood sugar in STZ-induced diabetes by the extract may be partly due to the plant's ability to improve sugar utilisation by the cells or increase insulin secretion by regenerating the pancreas. This may be because the plant contains anti-diabetic agents, which could control high sugar levels. The phytochemical analysis of mature *Caricapapaya* leaf extract as on Table 2 revealed that the plant contains bioactive compounds such as flavonoids, phenols, and alkaloids, which have been reported in previous literatures to possess hypoglycemic properties.

Finally, the microscopic examination of tissues sections from the rats' pancreas correlates with the biochemical findings as shown on plates 1-6. The pancreas of the normal control rats (plate 1) did not show any detectable change in colour or size, rather normal histo- architecture with closely-parked acini and islets of Langerhans was observed. Histological examination of the diabetic untreated rats showed total destruction of the β-cells in the pancreatic islet of Langerhans (plate 2) when compared to the normal control rats (plate1), this has led to a threshold of fasting blood glucose of these rats. However, treatment with metformin and various concentrations of the extracts led to regeneration and mitigated the situation as shown on plates 3-6.

CONCLUSION

This study has demonstrated that the hydro-ethanol extract of mature (yellow) *Carica papaya* leaf is a rich source of essential phytochemicals, and possesses anti-diabetic potential against streptozotocin-induced diabetes.

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