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Effect of Aqueous Leaf Extract of *Terminalia catappa* (Indian Almond) on the Liver of Alloxan-Induced Diabetic Wistar Rat

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Abstract: Different schools of thought believed the Indian almond has antidiabetic and hepatoprotective potentials, however, there is paucity of information on the ability of this plant to carry out its antidiabetic properties. This study therefore seeks to determine the effect of aqueous leaf extract of Indian almond on the liver of alloxan-induced diabetic Wistar rats. Three groups of Wistar rats were used in this study, a normal control, a diabetic control, and a treated group (5 per group). Rats in the normal group were administered distilled water orally per day, rats in the diabetic group were intraperitoneally injected with 150mg/kg body weight of alloxan and administered distilled water orally per day, while rats in the treated group were intraperitoneally injected with 150mg/kg of alloxan and treated orally with 600mg/kg body weight of aqueous leaf extract of Indian almond per day for 21days. Administration of aqueous leaf extract of Indian almond to the diabetic rats caused a significant decrease in the level of blood glucose, activities of alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP), total bilirubin and conjugated bilirubin ($p< 0.05$) and a significant increase in the level of total protein and albumin ($p< 0.05$) when compared with the control groups. The results obtained from this study suggested that the aqueous leaf extract of Indian almond possesses antidiabetic activity and could be used for the management of diabetes and liver damage associated with its metabolic consequences.

Keywords: Diabetes Mellitus, Liver, Hyperglycemia, *Terminalia catappa.*

I. Introduction

Diabetes mellitus (DM), commonly referred to as diabetes, has been one of the most devastating diseases known to man [1]. It is a major endocrine disorder that is on the rise [2]. Diabetes mellitus is a group of metabolic dysfunction characterized by an uncontrolled hyperglycemic state that results from defects in insulin secretion, action or both. Diabetes mellitus is one of the main threats to human health globally in the 21st century. As estimated by the World Health Organisation (WHO), in developing countries, the prevalence of diabetes is increasing with about 70 million people suffering from diabetes mellitus [3].

The liver plays a vital role in regulating glucose levels in physiological and pathological states such as DM. In type 1 DM, insulin deficiency upregulates hormone-sensitive lipase in the adipose tissues, subsequently leading to increased lipolysis and the circulation of free fatty acids, which subsequently accumulate in the liver. These processes enhance the hepatic uptake of very low-density lipoproteins and the synthesis of triglycerides [4]. Concurrently, elevated glucagon levels inhibit hepatic triglyceride output. Therefore, the accumulation of fat in the liver may be due to an imbalance in the uptake, synthesis, export and oxidation of free fatty acids in the liver [5]. Aside from abnormalities in lipoprotein metabolism, an accumulation of hepatic fat in DM may be due to either hyperglycaemia-induced activation of the transcription factor carbohydrate-responsive element-binding protein and sterol regulatory element- binding protein 1c, the upregulation of the glucose transporter 2 protein with subsequent intrahepatic fat synthesis or a combination of these mechanisms [6].

There are lots of chemical agents available to treat diabetic patients, but total recovery from diabetes has not yet been reported [7]. However, plants that are potential sources of hypoglycemic bioactive ingredients provide an alternative to synthetic agents [8]. Plants of medicinal value have been found to contain numerous bioactive compounds known as phytochemicals that can protect humans against diseases. Some of these phytochemicals possess pharmacological concomitant such as antioxidant activities, antidiabetic properties, anti-microbial activities and analgesic effects [9]. Presently, aside from the various types of oral hypoglycemic agents used in the management of diabetes mellitus, interests in the use of herbal remedies are on the rise due to the side effects associated with orthodox therapeutic agents. Therefore, there is need for the development of new oral antidiabetic therapy with minimal side effects. Most medicinal plants exert their antidiabetic effects through different mechanisms such as stimulation of insulin release from pancreatic beta cells, alteration of some glucose metabolizing enzymes, reduction of glucose intake or both [10].

Indian almond is a large tropical tree in the Leadwood tree family, Combretaceae that grows mainly in the tropical regions of Asia, Africa, and Australia [11]. The generic name originates from the Latin word “terminalis,” referring to the leaves teeming at the ends

ISSN No. 231-2705 | DOI: 10.51244/IJRSI | Volume X Issue V May 2023

of the shoots. It is commonly referred to as Indian almond, tropical almond and false kamani. It's also found in many parts of Southern Nigeria and it is often referred to as *Ẹbẹlẹbọ* among the Ẹdo people of the South-South geopolitical zone of Nigeria. The tree grows to about 35 m in height, with an upright, symmetrical crown and branches that are horizontal and arranged in tiers. The leaves are large in size, ovoid in shape, leathery and glossy dark green in appearance. The mature leaves measure about 15-25 cm long and 9-15 cm broad. The trees are monoecious, having distinct male and female flowers on the same tree. The flowers are about 1 cm in diameter, greenish-white in appearance and inconspicuous with no petals. The fruit is a drupe that contains a single seed, it is about 5-6 cm long and 3-6cm broad, it is green at first and red when ripens. The seed within the fruit is edible when fully ripe tasting almost like an almond [12].

The phytochemical constituent of the leaves of *T. catappa* includes 1-degalloyl-eugeniin, 2,3-(4,4',5,5',6,6'-hexahydroxy-diphenoyl)-glucose, chebulagic acid, gentisic acid, corilagin, geraniin, granatin B, kaempferol, punicalagin, punicalin, quercetin, tercatain, tergallagin, terflavin A, and terflavin B [12]. These phytochemical constituents may be responsible for the traditional use of this plant.

The aim of this study therefore, is to determine the effect of aqueous leaf extract of Indian almond on the liver of alloxan-induced diabetic Wistar rat.

II. Materials and Methods

A. Plant Specimen Collection and Authentication

The leaves of Indian almonds were collected from a growing tree inside the University of Benin, Benin City, Nigeria, on June 2018. It was identified and authenticated by Dr. Akinobosun A.O. (Plant Taxonomist), of the Department of Plant Biology and Biotechnology (PBB), University of Benin, Benin City.

B. Aqueous Extract Preparation

The leaves were shade dried at room temperature. The dried leaves were subjected to size reduction to a coarse powder using a dry grinder and passed through sieve nos 40. The powder of Indian almond leaves was packed in a Soxhlet apparatus and extracted with distilled water for 18 hours. The obtained extract was dried at 45°C in a hot air oven till semisolid mass was obtained.

Fig. 1: Indian almond.

C. Animals Used

Wistar albino rats (150-300 g) of the male sex were procured from the Department of Human Anatomy animal house of the University of Benin. The Wister rats used were strictly males because it was reported that female sex hormones (17-βestradiol) have a lowering effect on the plasma cholesterol concentration [13]. Before and during the experiment rats were fed with standard diet. After randomization to various groups and before initiation of the experiment, the rats were acclimatized for a period of 7 days under standard environmental conditions of temperature, relative humidity, and dark/light cycle. Animals described as fasting were deprived of food and water for 16 hours ad libitum.

D. Experimental Design

The rats were randomly divided into cross-sectional three groups comprising of 5 animals in each group as follows:

Group A: Normal control + distilled water per day.

Group B: Diabetic control + distilled water per day.

Group C: Diabetic rat + 600mg/kg of aqueous leaf extract Indian almond per day.

ISSN No. 231-2705 | DOI: 10.51244/IJRSI | Volume X Issue V May 2023

Preliminary oral LD_{50} (median lethal dose) doses of aqueous extract of Indian almond in rats were found to be above 3000mg/kg as gotten from an acute toxicity study [14]. Group C was treated with one-fifth of LD_{50} dose of aqueous extract (600mg/kg per day per oral) [15].

E. Induction of Type 1 Diabetes Mellitus Using Alloxan

One gram of Alloxan was weighed and dissolved in 10 ml of distilled water in a beaker and shaken thoroughly. The Alloxan solution dosage of 150 mg/kg body weight was administered to the Wistar rats to achieve type 1 diabetes [13].

Fasting blood glucose of animals were observed 2 days after induction to ensured type 1 diabetes has been ensured. Animals with blood glucose level above 220mg/dL were used for this study.

F. Collection of Blood Sample

Fasting blood glucose estimation and body weight measurement were done on day 1, 7 and 21 of the study. Blood samples were collected by tail snip method and blood glucose levels were estimated using an electronic glucometer (Miles Inc., USA).

On day 21 the rats were sacrificed under diethyl ether anesthesia, 24 hours after the last treatment. Blood specimens were collected from the animals by cardiac puncture into Lithium heparin and EDTA bottles. Blood specimens in lithium heparin bottles were separated and analyzed for ALT and AST activities [16], ALP activity [17], Total protein [18], Albumin [19] and Bilirubin [20], while blood specimens in the EDTA were analyzed for full blood count using CELL-DYN emerald hematology system by Abbot.

The liver and pancreas of each rat were harvested and placed in 10% formalin solution for immediate histological studies using haematoxylin and eosin staining techniques. The photomicrographs of histological studies are presented in Fig. 2 (A-C) and Fig. 3 (A-C).

G. Statistical Analysis

Data collected were analyzed using statistical package for social sciences programme (SPSS) version 21.0 (IBM, ICN, USA). The analysis of variance (ANOVA) was used to compare means, and means were expressed as mean ± SEM. Post Hoc analysis were used to detect sources of difference between the groups. A P-value of <0.05 was considered statistically significant.

III. Results

Table 1. Body Weights (g) of Wistar Rats in Control Groups and Treated Group

Parameters Measured	Diabetic control (n=4)	Normal control (n=4)	Treated group (n=4)
Day1 body weight (g)	220.00^{a}±25.73	196.25^{c}±14.34	202.50^{b}±20.66
Day 7 body weight (g)	210.00^{a}±27.38	203.75^{b}±13.28	195.00^{c}±19.25
Day 14 body weight (g)	195.00^{b}±19.47	212.50^{a}±12.33	190.00^{c}±19.25
Day 21 body weight (g)	197.50^{b}±26.65	223.75^{a}±10.28	195.00^{c}±17.25

Key: n=Number of rats in each group

P=2-tail probability at $\alpha=0.05$

All values expressed in mean ± SEM (standard error of the mean). Superscript show posthoc analysis with a highest value, c lowest value, Mean which share the same superscript symbol(s) are not statistically different, while mean with different superscript symbol(s) indicate statistically difference.

Table 2. Fasting Blood Glucose of Wistar Rats in Control Groups and Treated Group

Parameters measured	Diabetic control (n=4)	Normal control(n=4)	Treated group (n=4)
Basal FBG (mg/dL)	75.75^{a}±6.83	60.50^{b}±3.47	59.25^{c}±4.71
Day 1 FBG (mg/dL)	269.50^{b}±10.91	67.00^{c}±10.35	437.75^{a}±14.00
Day 7 FBG (mg/dL)	341.50^{a}±9.40	65.00^{b}±2.48	357.00^{a}±7.62
Day 14 FBG (mg/dL)	423.75^{a}±7.12	65.75^{c}±4.64	295.50^{b}±5.20
Day 21 FBG (mg/dL)	491.00^{a}±3.18	65.75^{c}±4.30	186.25^{b}±4.90

Key: FBG=Fasting blood glucose

ISSN No. 231-2705 | DOI: 10.51244/IJRSI | Volume X Issue V May 2023

n=Number of rats in each group

P=2-tail probability at α=0.05

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Table 3. Liver Function Indices of Wistar Rats in Control Groups and Treated Group

Parameters measured	Diabetic control(n=4)	Normal control(n=4)	Treated group(n=4)
ALT(U/L)	38.75^{a}±1.49	14.00^{c}±0.81	20.25^{b}±0.47
AST(U/L)	55.25^{a}±2.49	18.75^{c}±0.47	25.00^{b}±0.70
ALP(U/L)	200.50^{a}±2.10	136.00^{c}±0.91	145.00^{b}±1.41
AST/ALT	1.42^{a}±0.04	1.34^{b}±0.05	1.20^{b}±0.06
Albumin (g/L)	26.77^{c}±1.14	43.17^{a}±1.54	35.50^{b}±0.92
Globulin (g/L)	28.17^{b}±2.18	34.77^{a}±1.21	27.20^{b}±1.00
T.Protein (g/L)	54.95^{c}±1.79	77.95^{a}±1.08	62.70^{b}±1.26
T.Bilirubin (mg/dL)	1.75^{a}±0.86	0.77^{c}±0.04	1.06^{b}±0.07
CON.Bilirubin(mg/dL)	0.82^{a}±0.04	0.29^{b}±0.00	0.41^{b}±0.04
UNC.Bilirubin(mg/dL)	0.93^{a}±0.04	0.47^{c}±0.04	0.65^{b}±0.03

Key: ALT= Alanine amino transferase, AST= Aspartate amino transferase, ALP= Alkaline phosphatase, T.protein = Total Protein, T.bilirubin= Total Bilirubin, CON.Bilirubin= Conjugated Bilirubin, UNC.Bilirubin= Unconjugated Bilirubin.

n=Number of rats in each group

P=2-tail probability at α =0.05

All values expressed in mean ± SEM (standard error of the mean).

Superscript show posthoc analysis with a highest value, c lowest value, Mean which share the same superscript symbol(s) are not statistically different, while mean with different superscript symbol(s) are statistically difference.

Table 4. Haematological Parameters of Wistar Rats in Control Groups and Treated Group

Parameters measured	Diabetic control(n=4)	Normal control(n=4)	Treated group(n=4)
WBC($\times10^{3}$µl)	10.87^{a}±0.25	9.72^{a}±0.52	8.32^{b}±0.29
RBC($\times10^{6}$µl)	6.85^{b}±0.46	9.50^{a}±0.12	7.42^{b}±0.18
Haemoglobin (g/dL)	13.77^{b}±0.77	16.05^{a}±0.32	14.15^{b}±0.27
PCV (%)	43.90^{b}±2.71	52.97^{a}±1.15	42.37^{b}±1.44
PLT ($\times10^{3}$µl)	263.50^{c}±70.40	1228.00^{a}±81.30	720.75^{b}±106.81

Key: WBC= White blood cells, RBC=Red blood cells, PCV=Packed cell volume, PLT=Platelets

n=Number of rats in each group

P=2-tail probability at α=0.05

All values expressed in mean ± SEM (standard error of the mean).

Superscript show posthoc analysis with a highest value, c lowest value, Mean which share the same superscript symbol(s) are not statistically different, while mean with different superscript symbol(s) indicate statistically difference.

IV. Discussion

Normal control Wistar rats were found to be stable in their body weight while diabetic rats showed a non-significant reduction in body weight for 21 days. Alloxan caused weight reduction due to disorder in glucose metabolism thus, leading to protein breakdown

ISSN No. 231-2705 | DOI: 10.51244/IJRSI | Volume X Issue V May 2023

and mobilization of body fat which was reversed by aqueous leaf extracts Indian almond after 21days of treatment in the treated group.

In light of this study, basal fasting blood glucose in the diabetic control and treated group show no significant difference when compared to the normal control, prior to induction and treatment of diabetes mellitus, this signifies that all animals in diabetic control and treated group had basal blood glucose level before induction. After 21days, fasting blood glucose concentration in diabetic control shows a significant increase when compared to normal control. This is due to lack of management of diabetes mellitus, thus, leading to the increase blood glucose over time. On the other hand, the treated group shows a significant reduction in fasting blood glucose after 21days when compared to diabetic control, this finding agrees with the result obtained by Ahmed, [21], whose previous study showed that aqueous and cold extract of fresh and tender leaf of Indian almond has the capacity to decrease the high blood glucose level and lipids in alloxan-induced animal models. This anti-hyperglycemic action may be due to insulin potentiating effect via stimulation of the undamaged or residual pancreatic islets to release insulin by the aqueous extract or probably regeneration of beta cells by the aqueous extract.

Liver function indices after a period 21days shows that diabetic control had a significant increase in liver enzyme markers, when compared to normal control. The levels of AST, ALT and ALP in this study significantly increased in diabetic induced Wistar rats, this was in line with the result of Ohaeri and Eluwa, [22]. Previous research has proven that a decrease in SOD and CAT activities within an hyperglycaemic state leads to an increase in ROS, which eventually contributes to oxidation- induced liver damage [23], thus, resulting in the leakage of AST, ALT and ALP from the liver cytosol into the blood stream, which gives an indication of the hepatotoxic effect of diabetogenic agent. Increase in serum activities of AST shows hepatic injuries similar to viral hepatitis, infarction, and muscle damages. ALT, which mediates conversion of alanine to pyruvate and glutamate, is specific for the liver and is a suitable indicator of hepatic injuries. In addition, ALP is membrane bound and its alteration is likely to affect membrane permeability and produces derangement in the transport of metabolites.

Treated group shows a significant decrease in liver enzyme markers from serum, this may be due to the prevention of intracellular and tissue enzyme leakage resulting from cell membrane stability or cellular regeneration which correlates with Lin *et al.,* [24]. They found that treatment with the aqueous extracts of Indian almonds exhibited antihepatotoxic activity against carbon tetrachloride (CCl4)-induced toxicity in the rat. Chakkalakal *et al.,* [25] stated that the multiple antioxidant effects of the tannin components from Indian almonds have the capability to prevent lipid peroxidation (LPO), and formation of superoxide. Punicalin and punicalagin are the most copious phyto constituents and have the effective antioxidant activity of *T. catappa*. Chung *et al.,* [26] isolated 2alpha, 3beta, 23-trihydroxyursane -12 -en-28-oic acid (DHUA) from Indian almond leaf and evaluated the superoxide radicals scavenging activity and antimitochondrial swelling activity by in vitro. DHUA (50-500 µmol/L) inhibits Ca^{2+} induced mitochondrial swelling and also shows superoxide radicals scavenging activity in a dose-dependent manner, thus buttressing the hepatoprotective activity of almond leaf. In addition, AST/ALT ratio in the treated group shows significant reduction to basal level, after 21days when compared to diabetic control, this may be due to the effect of aqueous leaf extract on AST and ALT as seen above. AST/ALT ratio in diabetic group shows a significant increase when compared to negative control, this further buttresses the fact that there was hepatotoxicity, which might have been caused by diabetogens or complications of diabetes mellitus. Similarly total protein and albumin shows significant increase after 21days when compared with diabetic control, this might be due to the plants ability to restore the synthetic ability of the liver or potentiate albumin synthesis, and this is in line with Luka et *al.,* [13]. Diabetic control shows a significant decrease in serum protein, albumin, and globulin, this may be due to decrease synthesis of plasma protein by the liver due to damage done to the hepatocytes, which correlates with previous work done by Liu *et al.,* [27]. However, in the treated group, globulins shows no significant difference after 21days when compared to diabetic control. Furthermore, the conjugated and unconjugated fraction of bilirubin in diabetic treated shows a significant decrease after 21days when compared to diabetic control, this may be due to the ability of aqueous leaf extract to restore proper bilirubin metabolism by repairing hepatocellular damage caused by the diabetogen or complications of diabetes, this result is in line with Luka et *al.,* [13]. Furthermore, diabetic control shows a significant increase in both conjugated and unconjugated fractions of bilirubin, which may occur due to hepatocellular injury or destruction.

The examination of blood has been described as a good way of accessing the health status of animals, because it plays an important role in the physiological, nutritional and pathological status of organisms [28]. Haematological parameters provide information regarding the status of bone marrow activities and haemolysis [29]. It has been revealed in this study that selected haematological parameters in diabetic control showed significant reduction when compared to normal control, this abnormalities correlates with the results of Uluışık and Keskin, [30]. This might be due to the destruction of matured red blood cells leading to low haemoglobin count (Hb) (due to the non-emzymatic glycosylation of excess glucose with the haemoglobin) with decrease in red blood cell (RBC) (an indication of imbalance between its synthesis and destruction) and packed cell volume (PCV) normally being affected by Latent autoimmune induced diabetes in adults (LADA-induced diabetes), an indication of anaemia [A and B could not stimulate the formation or secretion of erythropoietin, which stimulates stem cells in the bone marrow to produce red blood cells, in contrary to

ISSN No. 231-2705 | DOI: 10.51244/IJRSI | Volume X Issue V May 2023

Ohlsson and Aher, [32]. on the other hand, WBC in the diabetic control was higher, but show no statistical difference when compared to normal control, this increase might be as a result of release of cytokines, such as TNF-α, transforming growth factor-1, superoxide, nuclear factor κB (NF-κB), monocyte chemo attractant protein 1, interleukin-1β, and others to participate in the pathogenesis of diabetic micro- and macrovascular complications. On the other hand, WBC in the treated group shows a significant decrease when compared to diabetic control, which may suggest the anti-inflammatory properties of Indian almonds. The various polyphenolic compounds, triterpenoids, and other chemical compounds found in the plants may be responsible for the anti-inflammatory activities.

Photomicrograph of Liver histology of normal control shows a distinct centriole and hepatocytes with pyknotic nucleus and a well fenestrated sinusoids, when compared to the diabetic control, which reveals focal lymphocytic infiltrates with prominent disseminated stenosis and hepatocytes that do not appear distinct indicating hepatocellular damage. Photomicrograph of Liver of treated group when compared to diabetic group, shows more distinct centriole with lesser inflammatory cells, the hepatocytes also reveals lightly vacuolated nucleus indicating signs of regeneration of hepatocytes by the aqueous leaf extract of Indian almonds.

Photomicrograph of pancreatic cells of normal control reveals prominent bulky lobules with visible intra lobular duct at low power and at high power magnification, there are slightly stained polygonal islet cells arranged in cords. Pancreatic cells of diabetic control reveals slightly coarse deeply stained polygonal islet cells arranged in cords at high power magnification with some slight congestion. On the other hand, pancreatic cells of treated group reveals bulky lobules with mild fatty changes and indistinct boundary between the endocrine and exocrine part at low power magnification. Some scanty inflammatory cells at high magnification are seen infiltrating through the tissue septae, islet area and around the duct. This effect may be due to β-carotene, the beneficial role of β-carotene in reducing diabetic complications like glycosylation in alloxan-induced diabetic rats [33], had been reported previously. Photomicrographical data in our studies confirms healing of pancreas by Indian almond leaf extracts, as a plausible mechanism of their antidiabetic activity.

V. Conclusion

Liver damage is one of the complications in patients with uncontrolled diabetes mellitus. Insulin deficiency has been known to induce complex cascades of abnormalities in lipoprotein metabolism, activation of the transcription factor carbohydrate-responsive element-binding protein and sterol regulatory element- binding protein 1c, and the upregulation of the glucose transporter 2 protein, thus, resulting in Type I diabetes-induced liver damage. The antioxidants, anti-diabetic and anti-inflammatory properties of aqueous leaf extract of *T. catappa* makes it a potential therapy in the treatment and management of diabetes mellitus and its associated liver complications. It's recommended that more studies be carried out to fully understand the Immunomodulatory mechanisms behind the hepatoprotective, regenerative and antidiabetic properties of this potential therapy.

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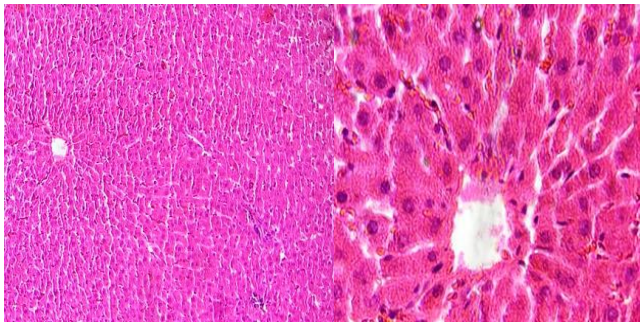
APPENDIX



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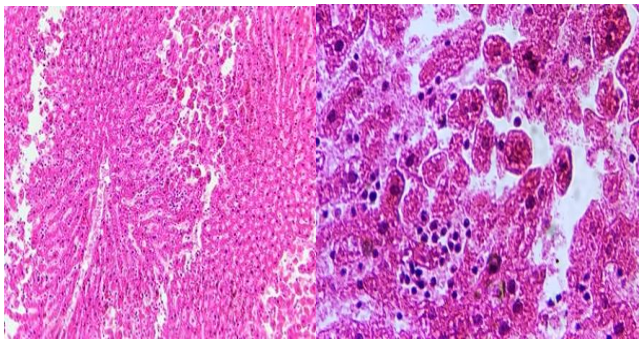

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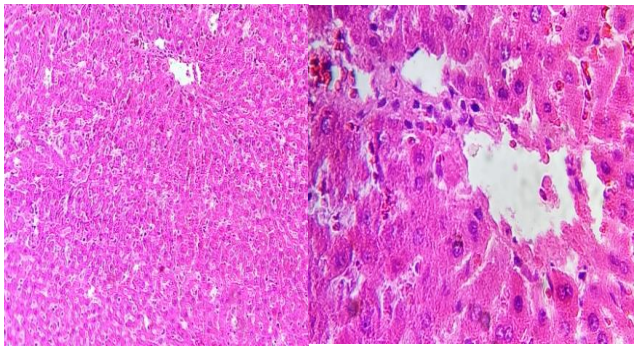
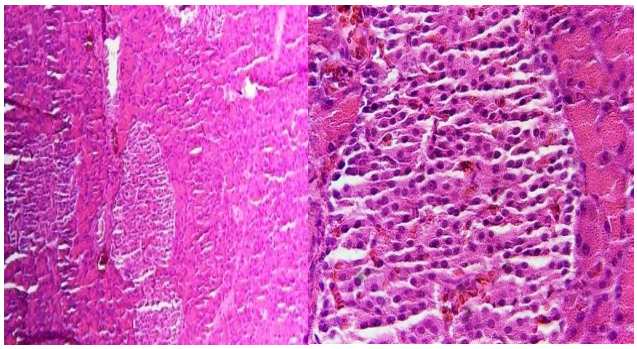


C

Fig. 2. Shows the photomicrograph of 100x and 400x magnification of the Liver (A) Normal control + distilled water per day (B) Diabetic control + distilled water per day (C) Diabetic rat + 600mg/kg of aqueous leaf extract Indian almond per day.



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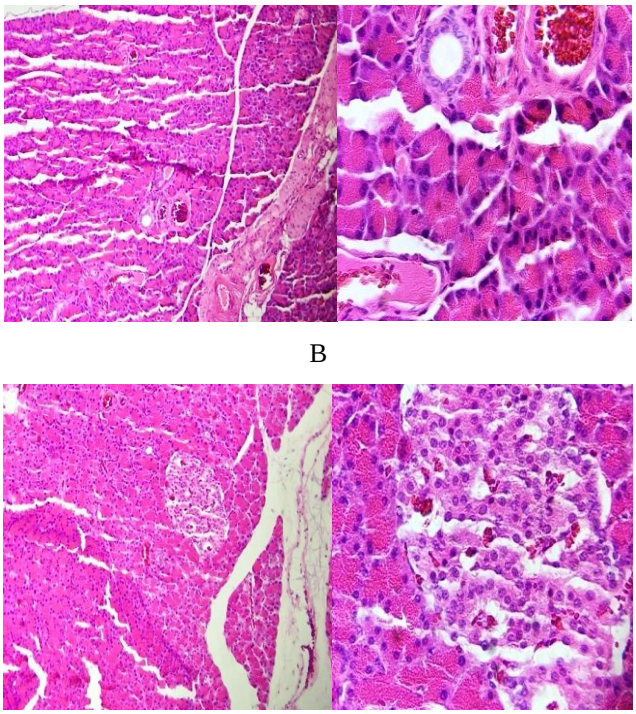

B

C

Fig. 3. Shows the photomicrograph of 100x and 400x magnification of the pancreas (A) Normal control + distilled water per day (B) Diabetic control + distilled water per day (C) Diabetic rat + 600mg/kg of aqueous leaf extract Indian almond per day.