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ANTIDIABETIC EFFECT OF ETHANOLIC LEAVES EXTRACTS OF *AZIMA TETRACANTHA* LAM. IN STREPTOZOTOCIN INDUCED DIABETIC RATS

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Keywords:

Azima tetracantha Lam., Antidiabetic, Antihyperglycemic, Antihyperlipidemic, Streptozotocin, Histology

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ABSTRACT: Objective: The goal of the present examination was to investigate anti-diabetic activity of *Azima tetracantha* Lam. leaves in streptozotocin-induced diabetic rats. **Materials and Method:** At a regular interval of an experimental protocol, blood glucose, insulin, glycogen, HDL, LDL, VLDL, FFA, PL, and TC and organs to bodyweight proportion were assessed in streptozotocin-induced diabetic rats. Histology of the pancreas and liver was also studied. The statistical analysis of streptozotocin-induced diabetic rats was observed in accordance to 4, 15, 30, 45, 60 days. **Results:** A significant decrease in blood glucose and a significant increase in insulin and glycogen were observed in diabetic rats treated with *A. tetracantha* Lam. treatment resulted in a significant reduction of LDL, VLDL, FFA, TC while increased HDL content is observed. Histology of diabetic rats treated with *A. tetracantha* Lam. showed the pancreatic β-cells regeneration. **Conclusion:** These findings suggest that *A. tetracantha* Lam. has potent anti-diabetic activity in streptozotocin-induced diabetic rats.

INTRODUCTION: Diabetes is defined as a state in which homeostasis of carbohydrate, protein, and lipid metabolism is improperly regulated as a consequence of a relative or absolute deficiency of insulin secretion, resistance to insulin action, or both at one or more points in the complex pathways of hormone action [1]. It is a hereditary or acquired incapability to transport sugar from the bloodstream into the cells. Devoid of sufficient insulin, the body cells cannot absorb adequate glucose from the blood; thus, blood glucose levels enhance, which is known as hyperglycemia. Hyperglycemia can damage some important body organs, for example, the kidneys, liver, eyes, nerves, heart, and blood vessels [2].

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The basic physiological function of insulin is promoting the synthesis of carbohydrates, proteins, lipids, and nucleic acids. The effects of insulin on carbohydrate metabolism include stimulation of glucose transport across muscle and adipocyte cell membranes, regulation of hepatic glycogen synthesis, and inhibition of glycogenolysis and gluconeogenesis [3, 4]. A decrease in either insulin secretion or sensitivity can cause diabetes that leads to deregulate the synthesis of carbohydrates, lipids, proteins, and nucleic acids [5]. Plants have always been an exemplary source of drugs and herbal drugs, which have been investigated all over the world to treat diabetes [6, 7].

Till today more than 1 200 species of plants have been screened for activity on the basis of traditional knowledge [8]. However, the ultimate objective of their use is that they should interact directly with our body chemistry without side effects [9, 10]. Synthetic hypoglycemic agents that are capable of reducing blood sugar levels possessed the most worrying side effects.

Most of the related side effects of synthetic drugs are metallic taste, gastrointestinal discomfort, and nausea. Therefore, finding other anti-diabetes agents, especially those made from natural sources, is desired [11]. *Azima tetracantha* Lam. (Family: Salvadoraceae) locally known as "Mulsangu", is a rambling spinous shrub flowering throughout the year found in Peninsular India, West Bengal, Orissa, African Countries and extends through Arabia to tropical Asia [12]. *Azima tetracantha* Lam. has been mentioned to be therapeutically used as antimicrobial, antifungal, anti-inflammatory, analgesic, antioxidant, antipyretic, antiulcer, anti-cancer, anti-snake venom, diuretic, and hepato-protective activities [13-17]. The present study was undertaken to study the effect of ethanol extract of *Azima tetracantha* Lam. on anti-oxidant, anti-diabetic, and anti-microbial activity.

MATERIALS AND METHODS:

Preparation of Plant Extracts: The fresh leaves were washed with running tap water and rinsed with distilled water to remove dust. The cleaned leaves were shade dried, and the shade dried leaves were coarsely powdered in an electric grinder and stored in an airtight glass container until further use. The leaves were identified by Dr. S. John Britto, Director, Rapinat herbarium, St. Joseph College, Tiruchirapalli, Tamil Nadu. The voucher specimen number (RHT.63874). Powdered leaves (100 mg) were extracted with different solvents of varying polarity (aqueous, ethanol, and hexane) in a ratio of 1:2 (w/v) by hot continuous percolation method in a Soxhlet apparatus (Harborne, 1973). The residue was again extracted with the same solvent twice. Extracts were filtered and concentrated using a rotary evaporator. The extracts free dried leaves samples were stored at -20 ºC.

Animal Model: Healthy adult male Wistar albino (180-200g) rats 8-10 weeks old rats were used in this study. The rats were housed in polypropylene cages and maintained under suitable nutritional and environmental conditions throughout the experiment. The Institutional animals' ethics committee approved all the experimental protocols SAC/IAEC/BC/2016/Ph.D-006)

Induction of Diabetes: After overnight fasting, diabetes was induced by intraperitoneal injection of Streptozotocin (STZ) (Sigma, St. Louis, MO) dissolved in normal saline, at a dose of 60 mg/kg. The control rats received the vehicle (Gum Acacia) alone. After 2 weeks of time for the development of diabetes, the rats with moderate diabetes having glycosuria and hyperglycemia (blood glucose range of above 220 mg/dL) were considered as diabetic rats and used for the experiment.

Experimental Design: The rats were divided into seven groups of 6 animals each as follows: Group I: Normal rats administered with 2% Gum Acacia as a vehicle; Group II: Diabetic control- Rats induced with Streptozotocin in normal saline at a dose of 60 mg/kg body weight; Group III: Rats induced with Streptozotocin and treated with ethanolic extract of *A. tetracantha* Lam. (100 mg/kg bw); Group IV: diabetic rats administered with ethanolic extract of *A. tetracantha* Lam. (200 mg/kg bw); Group V: diabetic rats administered with ethanolic extract of *A. tetracantha* Lam. (300 mg/kg bw); Group VI: Normal rats administered orally with ethanolic extract of *A. tetracantha* Lam. (300 mg/kg bw); Group VII: Diabetic rats administered with glibenclamide (1 mg/kg bw / oral) after 3 days of Streptozotocin induction **Fig. 1**.

FIG. 1: *IN-VIVO* ANTIDIABETIC ACTIVITY OF *AZIMA TETRACANTHA* LAM. LEAVES (GROUP 1: NORMAL, GROUP II: DIABETIC CONTROL, GROUP III: DIABETIC + A. TETRACANTHA LAM (100 mg/kg BW), GROUP IV: DIABETIC + *A. TETRACANTHA* LAM (200 mg/kg BW), GROUP V: DIABETIC + *A. TETRACANTHA* LAM (300 mg/kg BW), GROUP VI: NORMAL + *A. TETRACANTHA* LAM (300 mg/kg BW), GROUP VII: NORMAL + GLIBENCLAMIDE (100 mg/kg BW).

Histopathological Study: For the histopathological study, the tissues were fixed in Bouin's fluid for about 24 h and processed. Inadequately dehydrated tissues cannot be filtered with paraffin; in this condition, sectioning will be a problem. In order to avoid this, tissues were treated with ethanol. The tissues were kept in the xylol a clearing agent, till they become transparent. During impregnation, the clearing agent xylol was replaced by paraffin wax. The paraffin wax is also used for embedding with an optimum melting point of about 56 °C to 58 °C. Fixed tissues were cut at 5 µm and stained with hematoxylin and eosin. The sections were examined under Euromex microscope, and photo-micrographs were taken.

Estimation of Bio-chemical Parameters: The fasting blood glucose was measured on 4,15,30,45 and 60 days, and the effect of ethanolic leaves extract of *Azima tetracantha* Lam. was recorded for the following biochemical parameters.

Glucose Homeostasis Tests (Estimation of glucose, insulin, liver glycogen), Plasma Lipid Profile (Estimation of total cholesterol, triglyceride, phospholipids, Assay of HDL cholesterol and estimation of free fatty acid) [2, 7, 11, 17].

Statistical Analysis: Values are expressed as Mean ± SD for six rats. Mean values within a graph followed by different letters are significantly different from each other at P <0.05 level comparison by Duncan's multiple range test (DMRT).

RESULTS AND DISCUSSION:

Effect of Ethanolic Leaves Extract on Glucose, Glycogen and Insulin of Experimental Animals: Plasma glucose levels was measured in normal and experimental rats on 0^{th}, 3^{rd}, 7^{th}, 15^{th}, $30^{th,}$ and 60^{th} days of treatment with the ethanol extract of *Azima tetracantha* Lam. leaves are given in **Table 1** and **Fig. 2**. Administration of different doses (100, 200 and 300 mg/kg) of ethanolic leaf extract of *Azima tetracantha* Lam. and Glibenclamide to diabetic rats decreased the glucose level in a dose-dependent manner. Present study agreement with Nargis Begum *et al*. studies who reported the hypoglycemic and antihyperlipidemic activity of ethanolic leaves to extract of *Azima tetracantha* Lam. on alloxan-induced diabetic rats [16]. Glycogen and insulin level was estimated in normal and experimental rats represented in **Table 1** and **Fig. 2** Administration of different doses (100, 200, and 300 mgkg) of ethanolic leaf extract of *Azima tetracantha* Lam. and Glibenclamide to diabetic rats increased the glycogen and insulin level. The increased level of glycogen and insulin was observed directly proportional to the concentration of the *Azima tetracantha* Lam. leaves extract. Insulin lowers the concentration of glucose in the blood by inhibiting hepatic glucose production and by stimulating the uptake and metabolism of glucose by muscle and adipose tissue [18].

It has been reported that an increase of glucose uptake may be due to the extrapancreatic effect resemble insulin [19]. In the present study of the estimation of glycogen, there is a significant decrease in the glycogen levels of diabetic treated animals. Hence, it may be because of feedback regulation of the glycogen synthetase system to impair the normal capacity of the liver to synthesis glycogen [20]. The glycogen level significantly decreased in diabetic rats when compared to the treated with *Azima tetracantha* Lam. It resulted in a significant enhancement in the glycogen content. A similar result was observed in other studies [21, 22].

TABLE 1: EFFECT OF ETHANOLIC LEAVES EXTRACT ON GLUCOSE (MG/DL), INSULIN (µU/ML) AND GLYCOGEN (MG/G) OF EXPERIMENTAL ANIMALS

Groups	Glucose (mg/dl)					Insulin (µU/ml)	Glycogen (mg/ g Tissue)
	4^{th} day	15^{th} day	30^{th} day	45^{th} day	60^{th} day		
Group I	106.40±1.62 [a]	103.60±0.68 [a]	103.75±0.66 [a]	103.75±0.66 [a]	104.00±0.66 [a]	14.78±0.57 [a]	40.82±8.24 [a]
Group II	178.00±4.43 [b]	222.60±0.47 [b]	225.60±0.47 [b]	228.60±0.47 [b]	231.60±0.47 [b]	6.34±0.53 [b]	17.75±1.60 [b]
Group III	151.00±5.85 [c]	212.45±0.34 [c]	207.45±0.34 [c]	202.45±0.34 [c]	197.45±0.34 [c]	8.66±0.47 [c]	27.67±4.15 [c]
Group IV	142.00±2.33 [c]	207.95±0.34 [c]	199.95±0.34 [c]	191.95±0.34 [c]	183.95±0.34 [c]	9.64±0.36 [c]	34.06±5.04 [c]
Group V	114.00±2.71 [a]	103.95±0.34 [a]	102.70±0.34 [a]	117.70±0.34 [a]	118.70±0.34 [a]	13.54±0.53 [a]	39.97±6.01 [a]
Group VI	107.60±1.57 [a]	103.45±0.68 [a]	103.60±0.66 [a]	104.23±0.66 [a]	104.35±0.66 [a]	14.35±0.47 [a]	40.43±7.30 [a]
Group VII	106.40±1.62 [a]	108.35±0.34 [a]	106.45±0.34 [a]	114.45±0.34 [a]	122.45±0.34 [a]	14.78±0.57 [a]	40.04±8.03 [a]

Values are expressed as Mean ± SD for six rats. Mean values within a graph followed by different letters are significantly different from each other at P <0.05 level comparison by Duncan's multiple range test (DMRT).

The present study could have been due possibly to stimulation of insulin release from beta cells. The glycogen content is increased in the liver muscle of diabetic rats [23]. It may be due to the activation of the glycogen synthase system by *Azima tetracantha* Lam.

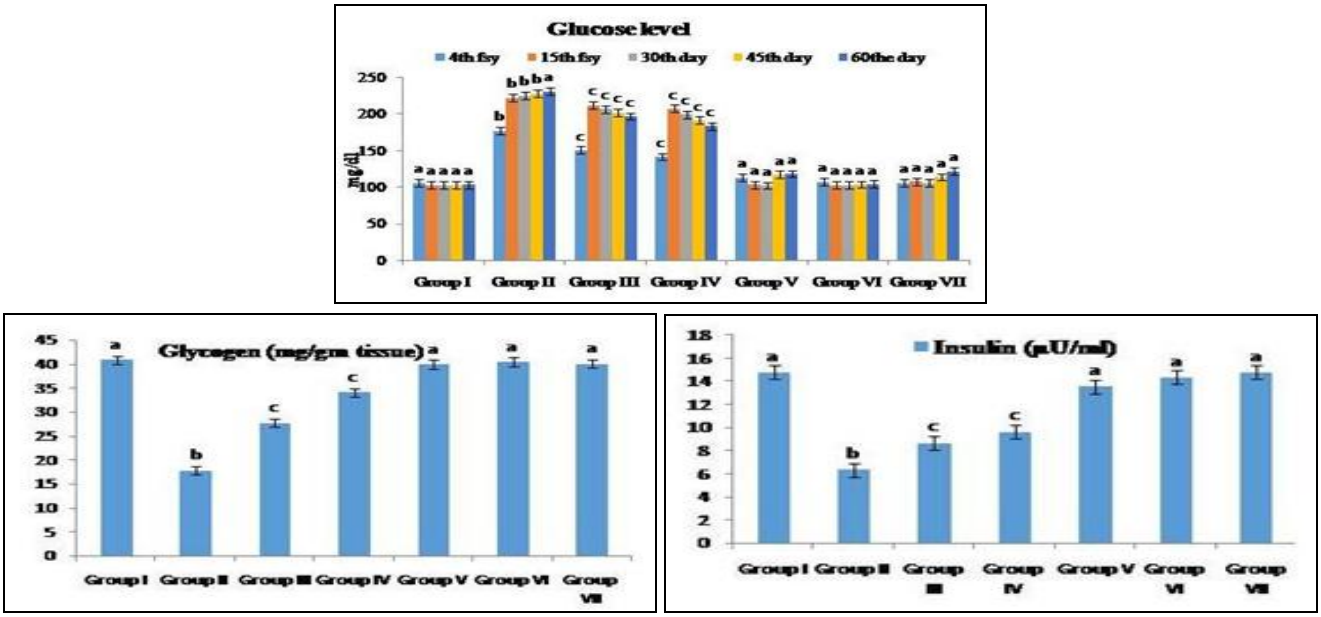

FIG. 2: EFFECT OF ETHANOLIC LEAVES EXTRACT ON GLUCOSE (mg/dl) GLYCOGEN (mg/g) AND INSULIN (µu/ml) OF EXPERIMENTAL ANIMALS. EFFECT OF *AZIMA TETRACANTHA* LAMS ETHANOLIC LEAVES EXTRACT ON HDL, LDL, VLDL, FFA, PL AND TC OF EXPERIMENTAL ANIMALS

In the present study, supplementation of different doses (100, 200 and 300 mgkg) of ethanolic leaves extract of *Azima tetracantha* Lam. decreased content in LDL, TC, VLDL, FFA, PL, TC and increased HDL content was observed in dose dependent manner. Among the various doses, the highest dose (300 mg/kg) of ethanolic leaves extract of *Azima tetracantha* Lam. showed significantly (p>0.05) restored the LDL), TG), VLDL), FFA, PL, TC and increased HDL content to normal rats. The standard treated group also decreased LDL, VLDL, FFA, TC while increased HDL content. *Azima tetracantha* Lam. alone (300 mg/kg) treated rats did not show any significant variation in lipid profile throughout the experimental period **Table 2** and **Fig. 3**. As reported elsewhere, the presence of an increased level of saturated free fatty acids in diabetes mellitus raises the serum cholesterol levels [24]. The total cholesterol is reflected by its fractions like VLDL, LDL & HDL. Terpestra reported that the increase in total serum cholesterol was mainly reflected in the LDL & VLDL fractions, whereas in the HDL fractions, there were only relatively mirror images [25]. In our study, we noticed significantly increased levels of serum total cholesterol, phospholipids, free fatty acid, triglycerides, and LDL Cholesterol but markedly decreased level of serum HDL cholesterol in STZ induced diabetic rats. These results are similar to those obtained by Bolkent *et al.* and Ravi *et al.*, [26, 27].

TABLE 2: EFFECT OF *AZIMA TETRACANTHA* LAM. ETHANOLIC LEAVES EXTRACT ON HDL, TG, LDL, VLDL, FFA, PL AND TC OF EXPERIMENTAL ANIMALS

Groups	Total Cholesterol (mg/g)	Phospholipids (mg/g)	Triglycerides (mg/g)	Free fatty acids (mg./g)	HDL (mg/dl)	LDL (mg/dl)	VLDL (mg/dl)
Group I	136.40±1.65 [a]	1.32±0.27 [a]	62.00±0.65 [a]	1.34±0.27 [a]	77.20±0.93 [a]	39.00±7.87 [a]	10.33±2.07 [a]
Group II	392.00±1.12 [b]	1.96±0.39 [b]	353.60±1.31 [b]	2.77±0.55 [b]	26.60±0.98 [b]	245.57±49.12 [b]	78.93±11.79 [b]
Group III	327.60±1.02 [c]	1.73±0.35 [c]	312.60±0.80 [c]	1.86±0.37 [c]	46.31±0.74 [c]	213.90±42.81 [c]	62.10±10.42 [c]
Group IV	230.00±1.55 [d]	1.54±0.31 [d]	262.60±0.94 [d]	1.55±0.31 [d]	54.80±0.79 [d]	143.90±28.83 [d]	43.77±8.75 [d]
Group V	140.54±0.98 [a]	1.41±0.28 [a]	73.60±1.10 [a]	1.43±0.29 [a]	70.80±0.67 [a]	89.90±18.02 [a]	23.93±4.79 [a]
Group VI	138.60±1.77 [a]	1.33±0.27 [a]	80.21±0.94 [a]	1.38±0.28 [a]	77.80±0.79 [a]	68.73±13.90 [a]	20.27±4.06 [a]
Group VII	144.00±1.98 [a]	1.26±0.25 [a]	72.80±5.10 [a]	1.33±0.27 [a]	81.80±0.34 [a]	44.70±9.15 [a]	7.13±1.69 [a]

Values are expressed as Mean ± SD for six rats. Mean values within a graph followed by different letters are significantly different from each other at P <0.05 level comparison by Duncan's multiple range test (DMRT).

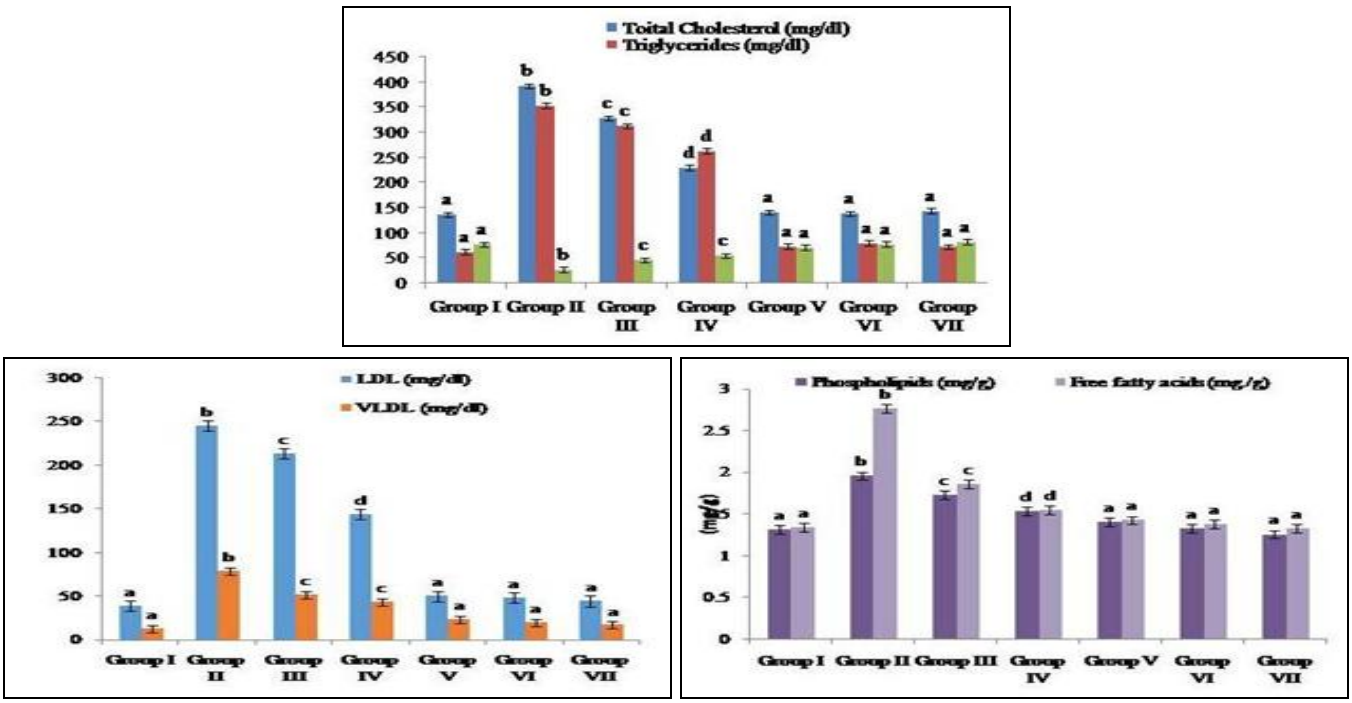

FIG. 3: EFFECT OF *AZIMA TETRACANTHA* LAM ETHANOLIC LEAVES EXTRACT ON HDL, TG, LDL, VLDL, FFA, PL AND TC OF EXPERIMENTAL ANIMALS

Histology of Liver and Pancreas: Photomicrographs of the normal liver showed well-visualized architecture with the predominant nucleus. Liver sections of streptozotocin-induced diabetic rats showed marked structural alterations in the liver. The major alteration was periportal fatty infiltration, necrosis of hepatocytes. This damage was reversed, and regeneration of parenchyma cells by the ethanolic leaf extract of *Azima tetracantha* Lam. (300 mg/ bw) and Glibenclamide treatments **Fig. 4**.

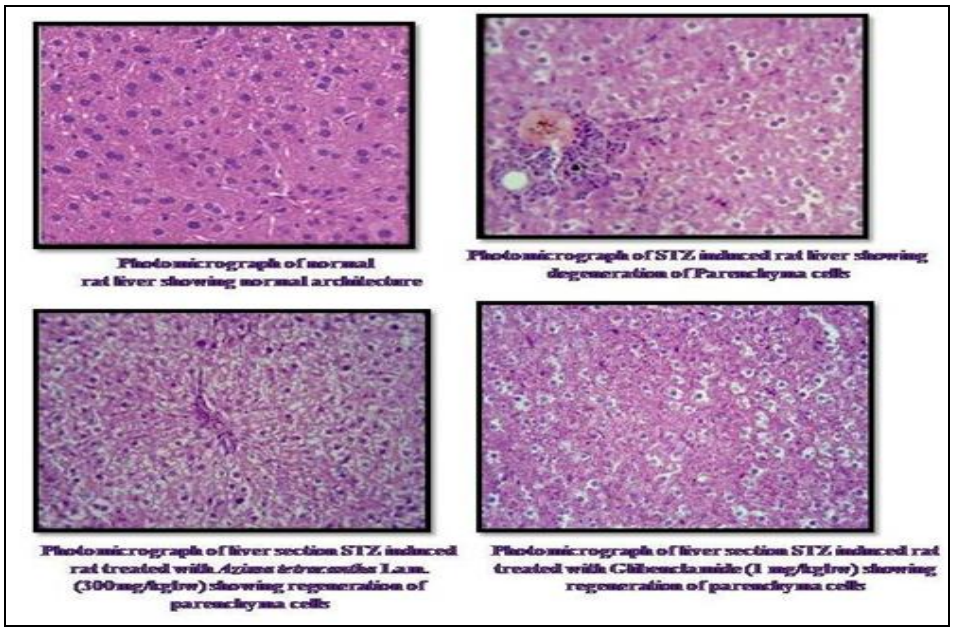

FIG. 4: HISTOLOGY OF LIVER IN NORMAL AND EXPERIMENTAL RATS (40X MAGNIFICATION)

Photomicrographs of the pancreas showed normal acini and normal cellular population in the islets of Langerhans in the pancreas of control rats. Pancreas sections of Streptozotocin-induced diabetic rats showed extensive damage to the islets of Langerhans and reduced dimensions of islets. Photomicrograph of Pancreatic Islets of Streptozotocin-induced rat treated with *Azima*

tetracantha Lam. (300 mg/kg) and Glibenclamide (1 mg/kg bw) showing regeneration of Islets of Langerhans, blood vessels and acinus **Fig. 5**. The present study revealed that the immediate action of Streptozotocin induced diabetes by destroying ß-cells. The ultra-structure of streptozotocin-diabetic pancreas showed considerable reduction in the islet langerhans and depleted islets [28]. The diabetic rats showed pancreatic islet regeneration. The regenerative effect of the pancreatic cells by *Azima tetracantha* Lam. ethanolic extract *via* exocrine cells of the pancreas may enlighten the positive effect of these agents on the production of insulin. The present finding is in agreement with Monday and Uzoma *et al*. study [29]. The role of *Azima tetracantha* Lam. ethanolic extracts in reversing the diabetic state at the cellular level besides the metabolic normalization further proves its potential as an antidiabetic assert [30-32]. So, the *Azima tetracantha* Lam. ethanolic extract was found to be effectively improving the liver and pancreas function and reduced the lesions associated with the diabetic state in Streptozotocin-induced diabetic rats [33-35].

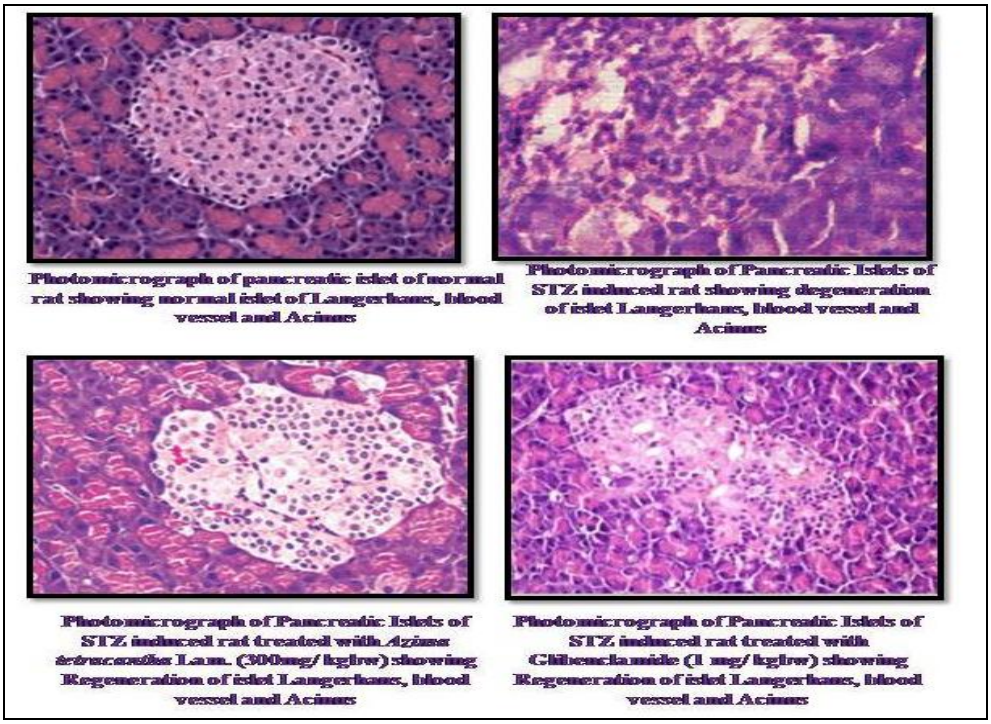

FIG. 5: HISTOLOGY OF PANCREAS IN NORMAL AND EXPERIMENTAL RATS (40X MAGNIFICATION)

CONCLUSION: STZ induced diabetic rats are one of the animal models of type 1 diabetes mellitus. It is well known for its selective pancreatic islet beta-cell cytotoxicity and has been extensively used to induce type 1 diabetes in an experimental rat model. Glibenclamide is often used as a standard antidiabetic drug in STZ induced diabetes to compare the efficacy of a variety of hypoglycemic drugs. The restoration of normal levels of plasma glucose, insulin, and glycogen and restoration of normal body and organ weight by *Azima tetracantha* Lam. leaves extract treatment which showed that *Azima tetracantha* Lam. ethanolic leaves extract causes antihyperglycemic effect. Likewise, the degenerative changes in the histology of the liver was found to be reversed by the *Azima tetracantha* Lam. ethanolic leaves extract treatment in Streptozotocin diabetic rats. The regeneration of β-cells and restoration of the normal architecture of pancreatic islets of Langerhans and acini in diabetic rats has observed due to *Azima tetracantha* Lam. ethanolic leaves extract treatment.

The antihyperlipidemic activity of *Azima tetracantha* Lam. ethanolic leaves extract was proved by the restoration of altered lipid profile. Overall, the experimental studies suggest that *Azima tetracantha* Lam. ethanolic leaves extract has potential antidiabetic activity.

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Author Contribution: All authors contributed equally to this manuscript.

CONFLICTS OF INTEREST: The authors declare that they have no conflicts of interest. It has not been published elsewhere. That it has not been simultaneously submitted for publication elsewhere, all authors agree to the submission to the Journal.

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