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ANTIDIABETIC ACTIVITY OF HEARTWOOD OF *TECOMELLA UNDULATA* SEEM. AND HISTOLOGY OF ORGANS IN STREPTOZOTOCIN-NICOTINAMIDE INDUCED DIABETES MELLITUS IN EXPERIMENTAL RATS

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ABSTRACT: Objective: The main objective of the present work was to analyze the therapeutic potential of various fractions of ethanolic extract of *Tecomella undulata* Seem. heartwood in streptozotocin - nicotinamide (STZ-NA) induced diabetes in experimental rats. **Materials and methods:** Diabetes was induced in the experimental rats by injecting nicotinamide and streptozotocin intraperitonealy at an interval of 15 minutes. The diabetic rats were then treated with standard drug; metformin and different fractions of 70% ethanolic extract of heartwood of *Tecomella undulata* for the 21 days. The animals were estimated for the different biochemical parameters which included liver function test, kidney function test and total lipid profile of experimental animals. Histopathological studies were also carried out on the liver and pancreas tissue sections. **Results:** All the fractions exhibited a reduced blood glucose level but the best results were revealed by acetone fraction as is indicated by statistical data. All fractions depicted a positive approach to normalize the altered biochemical parameters of kidney, liver and heart organs of diabetic animals. Thus it indicats that all the fractions of heartwood of *Tecomella undulata* can protect β cells of the pancreas and hepatocytes of liver from STZ-NA induced damage which is further confirmed through histopathological studies. **Conclusion:** The present study shows the potential hypoglycemic effect of the various fraction of ethanolic extract of *Tecomella undulata* and metformin in STZ-NA induced diabetes which may be due to the systematic effect on hepatocytic and pancreatic mechanism.

INTRODUCTION: Diabetes mellitus is a non insulin dependent disease characterized by an increased level of glucose in blood. This may be due to the insufficient production of insulin by the pancreas or the improper use of the insulin by the body [1].

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Today more than 415 million adults are diagnosed with diabetes mellitus and this may exceed to 642 million by 2040. In India itself there is an explosive increase in diabetic patients as reported by International Diabetes Federation which accounts to about 69 million diabetic patients in 2015 [2].

Presently, India holds the second position with people suffering with diabetes [3]. Since ages, India has a history of using herbs or herbal extracts for the treatment of various ailments and disease as these natural remedies are comparatively safer, economic, and have lesser side effects to allopathic medicines mainly because of their natural origin [4].

Tecomella undulata (family: Bignoniaceae) commonly known as Rugtrora in hindi and Ragat Rohido in Gujrati is well known for its medicinal value both in classical and folklore medicines [5]. It is used for planting out shelterbelt plantations and in agro-forestry in both arid and semi-arid areas for the production of high quality timber in addition to its use as fuel, wood and fodder [6]. The bark and leaves of *Tecomella undulata* have been reported to show potential effect in the treatment of various diseases including diabetes [7 - 8].

In spite of the widespread wealth and long-established use of this home-grown plant no legitimate study in appropriate amount has been done to validate its acclaimed anti-diabetic property on the heartwood part of plant. So, the present studies were conducted to explore the anti-diabetic potential of different fractions of 70% ethanolic extract of heartwood of *Tecomella undulata* plant on STZ-NA induced diabetes.

MATERIALS AND METHODS:

Plant Material and Authentication: Heartwood of *Tecomella undulata* Seem was procured from Bhiwani district (Haryana) in April 2013. Authentication of collected part was done by Dr. H.B. Singh Chief Scientist and Head, Raw Materials Herbarium and Museum NISCAR, New Delhi. The voucher specimen (Ref. No NISCAIR/ RHMD/ Consult/2011-2012/1975/275) is deposited in Department of Pharmaceutical Sciences, Maharshi Dayanand University Rohtak.

Preparation of Fractions: Shade dried heartwood of *Tecomella undulata* Seem was coarsely powdered and extracted using 70% ethanol by cold maceration. The filtered and concentrated crude extract was further fractionated into petroleum-ether, chloroform, acetone and hydro-alcoholic fractions. Each fraction was dried under vacuum and kept for future use in a tightly packed container. The percentage yield (w/w) was also calculated.

Chemicals: Metformin (MF) was procured from Ranbaxy laboratories limited, Gurgaon while streptozotocin and nicotinamide were purchased from Sisco research laboratories private limited, Mumbai (India). The other chemicals were arranged from the Loba. S.D. fine chemicals limited (India). All the solvents used were of LR grade obtained from E. Merck (India). Standard bio-diagnostic kits were procured for biochemical parameters.

Experimental Animals: Healthy Swiss albino rats of either sex weighing 150 - 200 g were used for experimental work. The animals were kept in well-ventilated area with optimum condition (temperature 25+2 ˚C, humidity: 60-65%, natural light and dark cycle of 12 hours each). They were acclimatized to animal house conditions and permitted free access of commercial pellet rat feed and water. The experimental protocol adopted was duly approved by Institutional Animal Ethics Committe (IAEC) of Maharshi Dayanand University Rohtak, India [Reg. No./date: 1767/RE /S/14/CPSCEA, 18/07/2014] as per the guidance of CPCSEA, Ministry of Social Justice and Experiment, Government of India with approved protocol no.: MDU/CAH/151-67, dated March 30, 2015.

Toxicity Studies: The acute toxicity study was conducted on albino rats as per the Organization for Economic Cooperation and Development (OECD) guidelines 423 [9]. All fractions and standard drug were administered orally in single dose of 2.0 g/kg and noticed for behavioral changes and mortality, if any, for first 24 hours and a total of 14 days.

Induction of Diabetes: For induction of diabetes; all the experimental animals were fasted for 18 hours and divided into seven groups of six animals each. After that 120 mg/kg body weight of nicotinamide injection; freshly prepared in saline solution was injected intra-peritoneally to animals. Subsequently 60 mg/kg body weight of streptozotocin injection; freshly prepared in citrate buffer at pH 4.5 was injected for the induction of diabetes [10]. The glucose solution (2%) was given to animals to protect them against the irreversible diabetogenic effect of streptozotocin [11]. Normal controlled rats were given citrate buffer alone. After 72 hours of injections, fasting sugar level was monitored, and animals with the blood glucose level above 250 mg/dl were considered diabetic with stable hyperglycemia [12].

Protocol for Anti-Diabetic Activity: After induction of diabetes; all the animals were again

grouped depending on the level of plasma glucose monitored. The selected rats were fasted for approximately 16 to 18 hours. The rats were subdivided into seven groups comprising six rats in each group [13].

Group 1: was normal control and orally treated with carboxymethyl cellulose 1% w/v.

Group 2: was reference controlled and were orally administered Metformin (100 mg/kg body weight/day).

Group 3: the animals were untreated diabetic controlled; also given carboxymethyl cellulose 1% w/v. For the oral delivery of fractions carboxymethyl cellulose 1% w/v was used as a vehicle.

Group 4 - 7: the animals were treated with test fractions (200 mg/kg body weight/day) by oral route respectively. During the treatment period, animals had free access to liquid water and feed. Nevertheless, feed was withdrawn about 16 hours prior to sampling for the glucose estimation of blood. The blood glucose level of the animals in all groups was checked at start of experiment and then at 7, 14 and 21 days of treatment time. The blood glucose was withdrawn from the tail vein of rats and analysed with the help of glucometer (Accu-Chek, Roche products (Private) Ltd., India).

Isolation of Tissue Section from Organs: The animals were fasted for 12 hours and then humanely sacrificed and the neck area was rapidly cleared of fleece before the jugular vein was piercingly cut [12]. The whole pancreas and liver were isolated. At the same time the blood (2ml) was collected.

Estimation of Biochemical Parameters: Glycosylated hemoglobin was estimated using whole blood. For biochemical parameters study automatic technique; Erbachem - 7, (Transasia) biochemistry analyser was used. Total protein in the serum was calculated using bovine serum albumin as standard. The biochemical parameters were identified using Erba and Coral Assay kits.

Histopathological Studies: Physiological saline solution (ice-cold) was used for washing the isolated tissue sections. 10% formal saline solution was used to fix the tissue sections for a minimum of 48 hours and then processed routinely and entrenched in paraffin wax. Approximately 5 - 6µm of tissue sections were cut thinly and stained with hematoxylin and eosin (HE) dye and subjected to microscopical examination [14].

Statistical Analysis: Statistical analysis was performed by one-way analysis of variance (ANOVA) followed by Dunnett's test using graph pad prism 7.0 and 6.0 versions. The Mean ± SEM for all values was calculated. ($P<0.05$) was considered as significant value.

RESULTS: The percentage yield of the ethanol extract of heartwood of *Tecomella undulata* was calculated to be 5.2%. After fractionation the percentage yield obtained for all fractions were: petroleum ether (15%), chloroform (24%), acetone (37%) and the remaining hydro-alcoholic fraction (13%).

Acute Toxicity Study Effect: At selected dose, no toxic effect was observed. So, one-tenth of this dose i.e. 200 mg/kg body weight was preferred for the *in-vivo* studies.

Effect on Blood Serum Glucose Level and Glycosylated Hemoglobin: In **Table 1**, the blood serum glucose levels in animals treated with fractions and metformin showed significant ($p < 0.01$) difference compared to normal animals during the treatment period of 0, 7, 14 and 21 days. Serum glucose levels in acetone fraction has shown significant ($p < 0.001$) decrease in elevated serum glucose level.

The acetone fraction has maximum reduction as compared to normal control animals within 21 days of treatment time. The glycosylated hemoglobin level for diabetic control has increased at a significant ($p < 0.0001$) level when compared to normal rats. The best results were shown by acetone fraction ($p < 0.0001$) and remaining fractions at a significance level of ($p < 0.001$, $p < 0.01$). When all fractions and standard drug were orally given to diabetic rats reversed the both altered parameter to about normal.

Effect on Body Weight and Feed Intake: Throughout the experimental period it was observed that, in comparison to normal control rats and treated rats, the untreated diabetic rats have consumed higher amount of feed due to their

polyphagic stage. In spite of this, there was a considerable reduction in weight gain in diabetic rats. But, treatment with all the fractions and standard drug, the weight loss was reversed gain at a significance value of ($p < 0.01$, $p < 0.05$) in third week of treatment. Data is represented in **Table 2.**

TABLE 1: EFFECT OF FRACTIONS ON AVERAGE BLOOD GLUCOSE LEVEL AND GLYCOSYLATED HAEMOGLOBIN IN STZ-NA INDUCED DIABETES IN RATS

Group No.	Treatment/ dose	Blood glucose level (mg/dl) (mean ± SEM)	Glycosylated hemoglobin (mmol/mol) (mean ± SEM)
1	Normal control	84 ± 2.27	37.8 ± 0.307
2	Reference control	214 ± 31.3[c]	41.5 ± 0.764[c]
3	Diabetic control	321 ± 5.75[a]	46 ± 0.730[a]
4	Petroleum ether control	202 ± 29.2[c]	42.2 ± 0.477[b]
5	Chloroform control	212 ± 32.4[c]	41.7 ± 0.76[b]
6	Acetone control	234 ± 17.2[b]	43 ± 0.731[a]
7	Remaining hydro-alcoholic control	205 ± 23.2[c]	41.5 ± 0.428[c]

All the values are expressed as mean ± SEM; n=6. The "a" represents the ****P < 0.0001, "b" as *** p < 0.001, "c" as ** p < 0.01 and "d" as * p < 0.05 as compared to normal control rats. The significant figure taken was upto 4. Statistical analysis was done by one-way ANNOVA with Dunnett test

TABLE 2: EFFECT OF ALL FRACTIONS AND STANDARD DRUG ON AVERAGE BODY WEIGHT AND FEED INTAKE ON STZ-NA INDUCED DIABETES IN EXPERIMENTAL ANIMALS

Group No.	Treatment/ dose	Feed Intake (g) (mean ± SEM)	Average body weight (g) (mean ± SEM)
1	Normal control	16.3 ± 1.89	201 ± 3.25
2	Reference control	23.8 ± 1.93	139 ± 8.2[b]
3	Diabetic control	39.9± 6.06[a]	158 ± 18.2[d]
4	Petroleum ether control	29.7 ± 1.09[d]	152 ± 8.93[c]
5	Chloroform control	26.1 ± 2.09	151 ± 6.36[c]
6	Acetone control	32.3 ± 1.62[c]	151 ± 6.61[c]
7	Remaining hydro-alcoholic control	33.6 ± 1.81[c]	146 ± 3.42[c]

All the values are expressed as mean ± SEM; n=6. The "a" represents the ****P < 0.0001, "b" as *** p < 0.001, "c" as ** p < 0.01 and "d" as * p < 0.05 as compared to normal control rats. The significant figure taken was upto 4. Statistical analysis was done by one-way ANNOVA with Dunnett test.

Effect on Kidney Function Parameters: Oral administration of all the fractions and standard drug in diabetic rats considerably normalized the abnormal kidney function parameters as compared to diabetic control rats. Administration of different fractions resulted in significant increases in the levels of total protein, albumin and globulin and decrease in the levels of blood urea, serum creatinine and serum uric acid at a significance ($p < 0.001$, $p < 0.01$, $p < 0.05$) as compared to diabetic control group. The reference drug and the acetone fraction showed the positive effect on all the altered parameters of a maximum significance ($p < 0.0001$) on total protein, albumin level. All the results are depicted in **Table 3**.

TABLE 3: EFFECT OF ALL FRACTIONS AND STANDARD DRUG ON KIDNEY FUNCTION PARAMETERS OF STZ-NA INDUCED DIABETIC ANIMALS

Test name	Normal control	Reference control	Diabetic control	Petroleum ether control	Chloroform control	Acetone control	Remaining hydro-alcoholic control
Blood urea (mg/dl)	7.88 ± 0.517[a]	10.9 ± 0.345[a]	15.4 ± 0.316	13.8 ± 0.678	11.6 ± 0.439[c]	12.2 ± 0.631[c]	13.4 ± 0.876
Serum creatinine (mg/dl)	0.821 ± 0.027	1.063 ± 0.011[c]	1.57 ± 0.144	1.48 ± 0.151	1.42 ± 0.162	1.13 ± 0.034[d]	1.66 ± 0.102
Serum uric acid (mg/dl)	4.78 ± 0.201[a]	4.43 ± 0.231[a]	13.1 ± 0.695	9.19 ± 0.664[c]	10.9 ± 0.540	9.74 ± 0.937[c]	11.3 ± 0.665
Total protein (g/dl)	7.193 ± 0.333[a]	8.3 ± 0.177[a]	4.23 ± 0.161	6.13 ± 0.514[c]	5.78 ± 0.321[d]	7.05 ± 0.365[a]	5.67± 0.375[d]
Albumin (g/dl)	2.6 ± 0.248	4.7 ± 0.158[c]	2.47 ± 0.197	3.25 ± 0.579	3.94 ± 0.629	6.03 ± 0.25[a]	4.78 ± 0.455[c]
Globulin (g/dl)	3.70 ± 0.338[b]	4.92 ± 0.411[a]	1.52 ± 0.201	3.63 ± 0.114[b]	3.09 ± 0.260[c]	2.15 ± 0.332	3.57 ± 0.419[b]

Effect of all fractions and standard drug on kidney function parameters of experimental animals: Data are shown as mean ± SEM, n=6. The value "a" represents the ****p < 0.0001, "b" represents the *** p < 0.001, "c" as ** p < 0.01 and "d" as * p < 0.05 as compared to diabetic control rats. Statistical analysis was done by way ANNOVA with Dunnet test

Effect on Liver Function Parameters: The effect of different fractions of ethanolic extract of heartwood of *Tecomella undulata* on liver function parameters was evaluated in all the groups. The treatment with separate fractions and reference drug reduced the elevated bilirubin, SGOT and SGPT parameters as compared to diabetic control group. Plant fractions have significantly ($p<0.001$) lowered the enhanced levels of liver function maker enzyme ALP. The plant fractions caused a significant ($p<0.0001$, $p < 0.001$, $p < 0.01$ and $p<0.05$) increase in the level of total protein albumin and globulin as compared to diabetic control group. Results are shown in **Table 4**.

TABLE 4: EFFECT OF ALL FRACTIONS AND STANDARD DRUG ON LIVER FUNCTION PARAMETERS OF STZ-NA INDUCED DIABETIC ANIMALS

Test Name	Normal control	Reference control	Diabetic control	Petroleum Ether control	Chloroform control	Acetone control	Remaining hydro-Alcoholic control
Bilirubin total (mg/dl)	0.847 ±0.037[a]	0.94 ± 0.137[a]	1.72 ± 0.206	1.17 ± 0.032[c]	1.22 ± 0.055[d]	1.3 ± 0.069[c]	1.4 ± 0.081[d]
SGOT (IU/L)	27.1 ± 1.930[a]	37.22 ± 1.963[a]	52.5 ± 1.478	39 ± 0.894[b]	45.8 ± 1.66	42.2 ± 2.85[c]	44.2 ± 2.87[d]
SGPT (IU/L)	31 ± 0.95[a]	38 ± 2.8[a]	52 ± 1.528	42 ± 0.95[c]	41 ± 1.424[a]	44 ± 1.6d	44 ± 2.5[d]
Alkaline Phosphate (IU/L)	51.5 ± 2.38[a]	112 ± 7.01[a]	146 ± 5.58	127 ± 3.63[d]	122 ± 2.79[c]	120 ± 3.05[b]	129 ± 4.23[d]
Total Protein (g/dl)	7.28 ± 0.3177[b]	8.55 ± 0.290[a]	4.46 ± 0.180	8.78± 0.32[a]	9.06 ± 0.183[d]	8.63 ± 0.430[c]	6.88 ± 0.612[d]
Albumin (g/dl)	3.77 ± 0.249	4.85 ± 0.416[c]	2.98 ± 0.224	4.97 ± 0.543[c]	3.29 ± 0.302	4.47 ± 0.211	4.27 ± 0.302
Globulin (g/dl)	3.52 ± 0.133	4.22 ± 0.552[c]	1.87 ± 0.230	3.8 ± 0.614[d]	3.967± 0.514[d]	3 ± 0.848[d]	4.02 ± 0.218[d]

Effect of all fractions and standard drug on liver function parameters of experimental animals: Data are shown as mean ± SEM, n=6. The value "a" indicates the ****$p < 0.0001$, "b" represents the *** $p < 0.001$, "c" as ** $p < 0.01$ and "d" as * $p < 0.05$ as compared to diabetic rats. Statistical analysis was done by one-way ANNOVA with Dunnett test

Effect on Total Lipid Profile: Treatment with all fractions and standard drug metformin showed positive effect on elevated triglycerides level, serum bad cholesterol (VLDL, LDL) and good cholesterol (HDL). The fractions as well as the standard drug decreased the increased levels of triglycerides, VLDL and LDL and enhanced the good cholesterol level near to normal at a significant ($p<0.0001$, $p < 0.001$, $p < 0.01$ and $p<0.05$) values as compared to diabetic animals. Out of all fractions, the best results were shown by acetone fraction with a significance of ($p< 0.001$) and reference drug on all parameters as is shown in **Table 5**.

TABLE 5: EFFECT OF ALL FRACTIONS AND STANDARD DRUG ON TOTAL LIPID PROFILE PARAMETERS OF STZ-NA INDUCED DIABETIC ANIMALS

Test name	Normal control	Reference control	Diabetic control	Petroleum ether control	Chloroform control	Acetone control	Remaining hydro-alcoholic control
Total cholesterol (mg/dl)	94± 3.24[a]	124 ± 5.41[b]	156 ± 3.93	139 ± 6.72	134 ± 4.09[d]	119± 5.65[b]	136 ± 3.03[d]
Triglycerides (mg/dl)	83.3± 2.84[a]	141 ± 1.83[a]	186 ± 4.42	159 ± 6.2[c]	165 ± 4.82[d]	157± 3.17[b]	170 ± 5.49
HDL cholesterol (mg/dl)	46.6± 2.58[c]	56.3 ± 0.854[a]	22.9± 0.415	32.3 ± 0.629[d]	33 ± 2.61[d]	34.8± 4.27[c]	34.8 ± 1.49[c]
VLDL (mg/dl)	13.71± 0.298[a]	27.5 ± 2.5[c]	40 ± 1.981	38 ± 1.77	31.3 ± 3.26	30.7± 1.61[d]	30.3 ± 3.72[d]
LDL(mg/dl)	61 ± 2.46[d]	129 ± 3.24[a]	153 ± 3.45	140 ± 4.17[d]	152 ± 2.7	131 ± 2.74[b]	138 ± 4.06[d]

Effect of all fractions and standard drug on total lipid profile: Data are shown as mean ± SEM, n=6. The value "a" represents the ****$p < 0.0001$, "b" represents the *** $p < 0.001$, "c" as ** $p < 0.01$ and "d" as * $p < 0.05$ as compared to diabetic control rats. Statistical analysis was done by one-way ANNOVA with Dunnett test

Histopathological Studies:

Histoarchitecture of Pancreas: The histological results from pancreas tissue section of one animal from each group are given in **Fig. 1**. Slide A1 (normal control) yellow arrow indicates unremarkable pancreatic tissue with preserved islet cells with no pancreatitis. Slide A2 (reference control) shows the preserved islet cells with unremarkable endocrine pancreases with moderate islet cell hyperplasia.

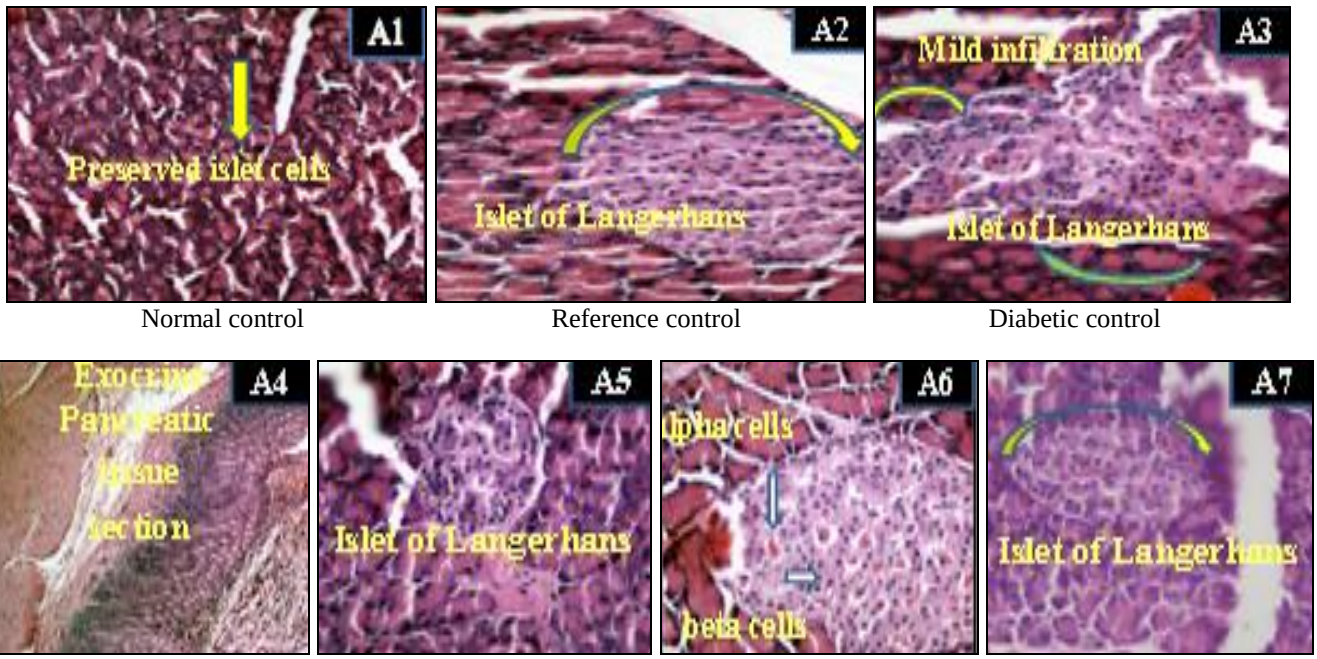
The yellow arrow is indicating the fully preserved boundaries of islet cells. Slide A3 (diabetic control) shows focal mild infiltration (indicated by the yellow arrow) by mononuclear cells. The green color arrow is indicating no defined boundaries of islets of langerhans. Slides A4 to A7 shows the pancreatic sections treated with fractions showing the unremarkable pancreatic tissue with preserved islet cells.

The slide A4 indicates the exocrine pancreatic section. The light stained area in the pancreas tissue section is islets of langerhans. Within that area, the red colored spots are of alpha cells (white arrow) while blue colored spots (white arrow) are the beta cells as seen in Slide A6. There is little evidence of pancreatitis or inflammation in all the sections treated with fractions.

Histoarchitecture of Liver: The histology results of liver section in normal rats (slide B1) showed mild patchy chronic portal triaditis composed of lymphocytes, plasma cells and admixed eosinophils with clear hepatocytes (white arrow), sinusoidal and kupffer cells (yellow arrow). No proofs of presence of granuloma osteatosis or cholestasis were seen. The rats treated with Metformin (Slide B2) showed moderate chronic portal triaditis with admixed eosinophils. Moderate central vein and sinusoidal dilation were also present. No granuloma or steatosis or cholestasis is considered in its histological section.

While in diabetic rat (slide B3) histological section there is moderate central vein and sinusoidal congestion with mild hepatocyte degeneration and minimal fatty change. In histological sections of liver of all the fractions (slide B4 to B7) mild chronic portal triaditis with several admixed eosinophils is seen. There is no sign of granuloma. Moderate central vein and sinusoidal dilation are present in the slides. All results are presented in **Fig. 1**.

Pancreatic tissue section



Normal control | Reference control | Diabetic control

Petroleum ether | Chloroform control | Acetone control | Remaining hydro-alcoholic control

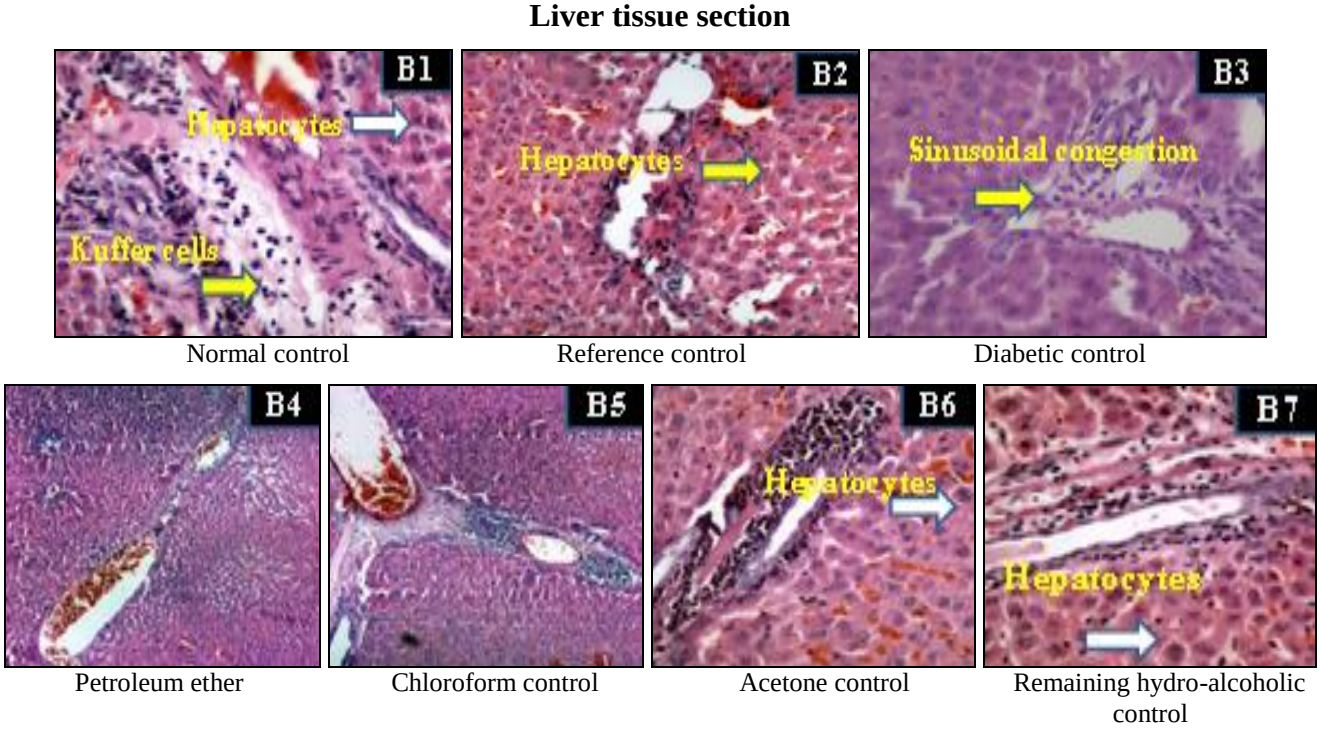


FIG. 1: HISTOLOGICAL FEATURES OF PANCREATIC AND LIVER TISSUE SECTIONS IN NORMAL, REFERENCE DRUG AND ALL FRACTIONS OF 70% ETHANOLIC EXTRACT OF HEARTWOOD OF *TECOMELLA UNDULATA* SEEM.

DISUCSSION: Streptozotocin is the most prominent diabetes inducing chemical entity used by many researchers due to its property of production of diabetes similar to human diabetes mellitus [15]. In the pancreatic cells, it produces free alkylating radicals by fragmenting the DNA molecule. The formation of these free radicals results in the decrease in nucleotides of cells and related compounds, especially NAD+ leading to oxidative stress on cells and cause cell necrosis. Nicotinamide was given in addition to streptozotocin to prevent the episodes of oxidative stress in diabetic animals because of its antioxidant properties [16].

The anti-hyperglycemic activity exhibited by all fractions of hydro-alcoholic extract of heartwood of *Tecomella undulata* and maximum activity shown by the acetone fraction in comparison to diabetic animals may be attributed due to a single or multiple mechanisms. This may include; blocking the absorption by inhibiting the carbohydrate metabolism enzymes [17], augmentation of insulin activity [18] with the help of glycogen synthetase, conversion of glucose to glycogen [19] *etc*. The oral administration of different fraction of heartwood of *Tecomella undulata* for 21 days significantly reduced the increased plasma glucose level. The hypoglycemic property of fractions may be the result of single or combination of more mechanisms.

From the biochemical profile studies, it was concluded that in diabetes, the enforced water loss through kidneys combined with the hyper osmolarity results from depreciating into intracellular water, activating the osmoreceptor of the thirst centre of the brain and condition of polydipsia which leads to increase in water intake (UKPDS, 1998) [20]. The catabolic effects then succeed, resulting in weight loss. The reference drug and fractions have significantly reversed the reduced weight of diabetic animals by controlling the biochemical parameters of kidneys.

Glycosylated haemoglobin content is the index of blood glucose control, the situation of diabetes mellitus due to binding of glucose to haemoglobin [21]. The rise in plasma glucose level causes structural and functional changes in the protein molecule like haemoglobin. Because of altered properties of haemoglobin, microvascular and macrovascular complications develop. Hence firm control of glucose in plasma causes a succeeding

reduction in haemoglobin level. Reference drug, metformin and all fractions showed a significant effect on the reduction of glycosylated haemoglobin thus confirming the antidiabetic behaviour of selected fractions.

Diabetes mellitus includes high levels of cholesterol, triglycerides, very low density and low density lipoproteins and reduction in high density lipoprotein.

This high level of these parameters may be due to rise in the draft of free fatty acids from their respective peripheral depots [22]. All the fractions and standard drug reversed the situation to normal level. Glycemic control may be the possible mechanism in the selected plant fractions [23].

Increased level of SGOT and SGPT results in increased glucose levels. After treatments with fractions and standard drug, levels of both serum enzymes were brought back to normal suggesting the regeneration process [24]. In the pathological conditions of liver the alkaline phosphatase level goes up in serum [25]. The level of ALP has been reported to be increased in diabetes mellitus. Biochemical studies of all fractions and standard drug significantly reduced elevated levels of ALP resulting in improvement of hepatic functions. In diabetic control group, there were a considerable decrease in total serum protein, albumin and A/G ratio while an increase was observed in serum globulin as compared to other treated groups. The results indicate that diabetic animals have to face severe malnutrition and over hydration situation [26].

Microscopic examination of liver section of all fractions treated animals especially slide B6 treated with acetone fraction showed a clear indication of preserved hepatocytes without any sign of congestion when compared to slide B3 of the diabetic group. In diabetic group slide, the arrow indicates the congestion with mild heaptocyte degradation. All other fractions and reference drug have also showed the positive effect on hepatocyte preservation.

From histopathological studies of pancreas of diabetic rat; it was found that focal mild infiltration by mononuclear cells in the exocrine pancreas section is shown by yellow arrow and undefined boundaries of islet of beta cells of langerhans are shown by white arrow. The pancreatic histology sections of both standard drug and all the fractions of plant showed the normal structure of both endocrine and exocrine sections with especially clear β-cells preservation by the acetone fraction in slide A6. In normal pancreatic section; islet cells are fully preserved and no pancreatitis is seen. So, the results obtained confirm that different fractions of heartwood of plant are safe and may be used as a potent hypoglycemic agent.

These fractions are also proficient to put on a normal footing biochemical parameters and morphological structure of affected tissues. It can thus be safely prescribed as the main therapy and also as an adjunct to dietary therapy for treatment of diabetes mellitus.

CONCLUSION: The present study shows the potential hypoglycemic effect of the various fraction of ethanolic extract of *Tecomella undulata* and metformin in STZ-NA induced diabetes which may be due to the systematic effect on hepatocytic and pancreatic mechanism.

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CONFLICT OF INTEREST: The authors declare no conflict of interest in this study.

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