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## **Effect of Methonolic Pericarp Extract of *Feronia limonia* on Hypoglycemic and Antihyperglycemic Activities in Normal and Streptozotocin Induced Diabetic Rats**

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### **ABSTRACT**

Diabetes mellitus is a chronic metabolic disorder characterized by raise in blood glucose levels known as hyperglycemia. In the present study, the methonolic pericarp extract of *Feronia limonia* (MPFL) was evaluated for hypoglycemia and its antihyperglycemic activity in streptozotocin-induced diabetic rats. The percentage inhibition of blood glucose levels in hypoglycemic activity of MPFL 150 and 300 mg kg<sup>-1</sup> were found to be 26.91±0.53 (3 h) and 34.67±0.93 (6 h) and 22.53±0.32 (3 h) and 25.24±0.78 (6 h) hypoglycaemic normal rats. The antihyperglycemic activity of MPFL with 150 and 300 mg kg<sup>-1</sup> in STZ induced diabetic rats were found to be 31.38±0.77 and 35.42±0.71 at 6 h, respectively. The biphasic reduction was observed in both in normal and diabetic rats might be due to biphasic absorption or biliary secretion of the active principle present in MPFL. Further the samples from diabetic rats were estimated for lipid profile. The lipid profile parameters were significantly brought back to near normal by the treatment if MPFL for 12 weeks. At the end of 12 weeks study period the serum parameters like bilirubin, creatinine, total protein, albumin, uric acid and urea were found to be increased in diabetic rats and treatment with MPFL there is a significant reduction in all the parameters. So, the MPFL found to have significant antihyperglycemic, antihyperlipedemia activity and significant protection against the damage to kidney. Which might be due to antioxidant potential present in the MPFL.

**Key words:** Diabetes mellitus, antihyperglycemic activity, *Feronia limonia*

### **INTRODUCTION**

Diabetes mellitus the most common endocrine disorder of carbohydrate metabolism is affecting approximately 8.3% of the population worldwide (IDF, 2013). Thomas (1998) added the word 'Mellitus' to the disease, a word from Latin meaning 'Honey' a reference to the sweet taste of the urine (Chopra *et al.*, 1956). Diabetes mellitus is not a single disease entity but rather a group of metabolic disorders sharing a common underlying feature of hyperglycemia. Hyperglycemia in diabetes, results from defects in insulin secretion, insulin action or most commonly both (Robbins and Cotran, 2004). Chronic elevation of blood glucose level leads to damage of blood vessels (angiopathy). The endothelial cells lining the blood vessels take in more glucose than normal, since they don't depend on insulin. They then form more surface glycoproteins than normal

and cause the basement membrane to grow thicker and weaker. In diabetes, the resulting problems are grouped under “Microvascular disease” (due to damage to small blood vessels) like retinopathy, nephropathy and neuropathy and “Macrovascular disease” (due to damage to the arteries) like cardiomyopathy.

Different groups of oral hypoglycemic agents are currently available with characteristic profiles of side effects (Holman and Turner, 1991; Williams and Pickup, 1991; Kameswara *et al.*, 1997). The search for antidiabetic agents with little or no side effects is continuous processes. The plant kingdom is a wide field to look for effective oral hypoglycemic agents. More than 300 species have been reported to display hypoglycemic activity (Rahman and Zaman, 1989) but only few of them have been investigated despite the World Health Organization (WHO) recommendation that traditional plant remedy for diabetics warrant further evaluation (WHO, 1980).

Effective control of blood glucose level is a key step in preventing or reversing diabetic complications and improving the quality of life in both type 1 and type II diabetic patients (Xie *et al.*, 2005). In the history of Unani, Ayurveda, Siddha or Homeopathic has been well documented that illness can be managed purely by herbal preparations, thus the diabetic individual could lead a healthy life as non-diabetics. Experiments and clinical trials conducted worldwide have provided dependable evidences on the effects of various herbal formulations in the maintenance of normal blood sugar level. These invaluable findings are now conclusively processed in the backdrop of Ayurveda, Unani and Siddha system (Ameen Syed *et al.*, 2005).

The fruit pericarp extract of *Feronia limonia* (Rutaceae) consists of 2, 6-dimethoxy benzoquinone and osthenol and three volatile flavour components like methyl hexanoate, ethyl-3-hydroxyhexanoate and butanoic acid. Free fatty acids like palmitic, oleic, linoleic, linolenic acid, palmitoleic and stearic acids;  $\beta$ -sitosterol,  $\beta$ -amyrin (Saima *et al.*, 2000), unsaponifiable matter like lupeol and stigmasterol (MacLeod and Pieris, 1981).

## **MATERIALS AND METHODS**

**Chemicals:** Streptozotocin was purchased from SIGMA Aldrich, St. LOUIS, MO, USA. All other chemicals used for this study were of analytical grade.

**Plant materials:** The ripened wood apples (*Feronia limonia*) were obtained from local market. The pericarps were manually separated and shade dried. The pericarps were powdered in a grinder to get 40-mesh size powder. The moisture content of pericarp powder was found to be 13.5%. The powder was suspended in 2% gum acacia and used in the experimental studies.

**Animals:** Animals were obtained from the Tina laboratories, Hyderabad. Albino Wistar rats (180-200 g) of male were used in the present study. The animals were housed under standard environmental conditions ( $23\pm 1^\circ\text{C}$ ) with relative humidity of  $50\pm 10\%$  and maintain 12:12 dark and light cycle, maintained with free access to water and *ad libitum* standard laboratory diet (70% carbohydrates, 25% proteins, 5% lipids (Hindustan liver Bangalore). After randomization before the experiment, the rats were acclimatized for a period of two weeks. The animal housing and handling were in accordance with CPCSEA guidelines. Our college was approved by CPCSEA for conducting animal experiments with the registration No. 516/01/A/CPCSEA. The prior permission for the study was obtained from our Institutional Animal Ethics Committee (IAEC).

**Induction of diabetes:** The rats were fasted for 18 h prior to the experiment with water *ad libitum*. The rats were injected intraperitoneally with nicotinamide 100 mg kg<sup>-1</sup>. After 15 min streptozotocin (STZ) were administered. STZ dissolved in citrate buffer at a dose of 55 mg kg<sup>-1</sup> body weight. Animals were treated with 10% glucose to combat the early phase of hypoglycemia. Blood samples were collected after 72 h of STZ treatment and the induction of diabetes mellitus was confirmed by estimation of fasting Blood Glucose Levels (FBG). Only those rats with blood glucose levels  $\geq 250$  mg dL<sup>-1</sup> were included in the study (Day 0).

**Experimental procedures:** Control group was administered with distilled water, Methonolic Pericarp Extract of *Feronia limonia* (MPFL) at 150 and 300 mg kg<sup>-1</sup> of rat body weight to group-1 and group-2, respectively. Blood samples were withdrawn at 0, 1, 2, 3, 4, 6, 8, 10 and 12 h intervals by Retro-orbital Puncture Method and were analyzed for blood glucose by GOD/POD method using SCREEN MASTER 3000 autoanalyser.

After the induction of diabetes, the rats were grouped in to eleven different groups of each containing six animals. Group 1 contains control rats received distilled water and fed on normal diet, group 2 as diabetic control received vehicle only, group 3 contains diabetic rats treated with gliclazide at a dose of 1 mg kg<sup>-1</sup> body weight, group 4 contains diabetic rats received MPFL at a dose of 150 mg kg<sup>-1</sup> body weight, group 5 contains diabetic rats received MPFL at a dose of 300 mg kg<sup>-1</sup> body weight for 12 weeks. Treatment with drugs was started after 72 h of STZ treatment (i.e., Day 1) and was continued for 12 weeks. All drugs were given orally as a single oral dose. Blood glucose was measured before starting the treatment (day 0) and 4 weekly thereafter upto the end of the treatment and estimated fasting blood glucose by glucose-oxidase-peroxidase (GOD-POD) method. All the treatment groups were compared with diabetic control group.

**Biochemical assays:** At the end of the 12 week study period, rats were fasted overnight and blood samples were withdrawn through the retroorbital plexus using glass capillary. Blood was allowed to clot and serum was separated by centrifugation at 4000 rpm for 10 min. Serum glucose levels were estimated at 0, 1, 2, 3, 4, 6 and 8 h intervals. Serum glycosylated haemoglobin, triglycerides, total cholesterol, HDL, LDL, VLDL, bilirubin, creatinine, albumin, total protein, urea, uric acid and BUN levels were estimated. Serum glucose levels were estimated by GOD/POD method. Triglyceride, total cholesterol, HDL was measured by commercially available kits (Bucolo and David, 1973; Nader *et al.*, 2001). Bilirubin (Jendrassik and Grof, 1938), creatinine (Bowers and Wong, 1980), total protein (Tietz, 1996), albumin (Doumas *et al.*, 1972), uric acid (Thomas, 1998), urea (Fossati *et al.*, 1980). At the end of the study all the rats were dissected and pancreas was used for histopathological studies.

**Statistical analysis:** All the data was expressed as SEM. Statistical analysis was carried out using one way ANOVA followed by Dunnet's multiple comparison test.

## RESULTS AND DISCUSSION

The WHO Expert Committee recommended the importance to investigate and explore hypoglycemic agents from plant origin because plants used in the traditional medicine have fewer side effects than synthetic drugs (Alarcon-Aguilara *et al.*, 1998). So in the present study discussed about the hypoglycemic and antihyperglycemic effects of MPFL. The doses of selected fruit pericarp extracts were fixed basing on their acute toxicity study in mice and preliminary hypoglycemic studies in Wistar albino rats. The doses that produce optimal and dose dependent reduction in blood glucose levels were selected for hypoglycemic and antihyperglycemic studies.

Some medicinal plants with hypoglycemic properties are known to increase circulating insulin level (pancreatic mechanism) in normoglycemic rats (Lamela *et al.*, 1985). Another possible mechanism of action is that the extracts might stimulate residual pancreatic mechanism (extra pancreatic), probably increasing peripheral utilization of glucose as postulated by Erah *et al.* (1996). The MPFL were shown significant hypoglycaemic activity with biphasic effect. The biphasic effect might be due to biphasic absorption or enterohepatic recirculation. We hypothesized that MPFL could have a sulfonylurea-like mechanism since they significantly decreased the blood glucose levels in normoglycaemic rats. Sulfonylurea compounds lower blood glucose in normal and in diabetic animals by stimulating insulin release from pancreatic  $\beta$  cells and by peripheral utilization of glucose. The MPFL shown to have better hypoglycemic activity compared to standard Gliclazide in normal rats (Table 1).

Streptozotocin (STZ) is used to induce diabetes mellitus in albino Wistar rats, a poly ADP ribose inhibitor, nicotinamide was administered after 15 min of STZ administration to offer partial protection against the action of STZ in rats. So, in the present study we used the Streptozotocin-nicotinamide model to prevent the excessive damage to the pancreas of diabetic rats. In this study, treatment with the MPFL significantly reduced the elevated plasma glucose levels in STZ induced diabetic rats. The MPFL shown delayed absorption in diabetic animals compared to normoglycemic animals, this might be due to delayed gastric absorption and motility in diabetic condition as diabetes affecting the digestive processes, the motility and nervous control of the entire system of gastrointestinal tract. The effect of diabetes on digestive system can also cause malabsorption (Bener *et al.*, 2012). The MPFL shown to have better antihyperglycemic activity compared to standard gliclazide in STZ induced diabetic rats (Table 2).

Table 1: Effect of MPFL on hypoglycemic activity in normal rats during twelve hours

Groups	Time (h)							
	1	2	3	4	6	8	10	12
Control	0.00±0.00	0.15±0.38	1.24±0.30	1.53±0.57	1.57±0.18	1.91±0.52	3.18±0.23	2.99±0.26
Gliclazide	33.00±2.80	24.90±4.40	15.90±6.00	13.60±4.84	14.70±5.15	26.60±4.84	12.40±3.72	12.30±3.70
MPFL (150 mg kg <sup>-1</sup> )	4.42±0.53	10.30±0.91	26.91±0.53	9.16±0.95	22.53±0.32	9.20±0.64	3.20±0.51	2.83±0.80
MPFL (300 mg kg <sup>-1</sup> )	6.02±0.96	11.30±1.21	34.67±0.93	13.80±1.35	25.24±0.78	10.71±1.27	3.95±1.41	3.38±0.96

Table 2: Effect of MPFL on antihyperglycemic activity in STZ induced diabetic rats

Groups	Time (h)						
	0	1	2	4	6	8	
Control	0.00±0.00ns	0.96±0.35ns	2.10±0.39ns	2.95±0.28ns	3.91±0.28ns	5.20±0.30*	
D. control	0.00±0.00ns	0.28±0.07	0.36±0.12	0.69±0.06	0.80±0.07	1.27±0.05	
Gliclazide	0.00±0.00ns	2.39±1.42ns	13.22±2.01 <sup>§</sup>	32.00±1.03 <sup>§</sup>	25.02±0.70 <sup>§</sup>	20.59±0.94 <sup>§</sup>	
MPFL (150 mg kg <sup>-1</sup> )	0.00±0.00ns	4.89±0.240*	10.86±0.46 <sup>§</sup>	17.85±1.03 <sup>§</sup>	31.38±0.77 <sup>§</sup>	19.29±1.41 <sup>§</sup>	
MPFL (300 mg kg <sup>-1</sup> )	0.00±0.00ns	5.03±0.650 <sup>§</sup>	12.28±1.06 <sup>§</sup>	20.17±2.07 <sup>§</sup>	35.42±0.71 <sup>§</sup>	25.83±1.62 <sup>§</sup>	

ns: Not significant, \*<sup>§</sup>Significant at p<0.05, p<0.01 and p<0.001 level, respectively, Significance followed by one way ANOVA followed by Dunnet's multiple comparison test when compared with disease control group

Streptozotocin (STZ) induced diabetic rats enhanced the level of glycated hemoglobin (HbA1c) due to raise in levels of glucose in blood which further react with hemoglobin and produce the glycated hemoglobin formation (Pari and Saravanan, 2004). The MPFL significantly lowered the blood glucose which lead to the decrease in the levels of glycated hemoglobin (Table 3).

The levels of serum lipids are usually elevated in diabetes mellitus (Pushparaj *et al.*, 2000). This abnormal high level of serum lipids is mainly due to the uninhibited actions of lipolytic hormones on the fat depots. It is reported that hypercholesterolemia (increased levels of total cholesterol) and hypertriglyceridemia (increased levels of triglycerides) occurs in STZ-induced diabetic rats (Pushparaj *et al.*, 2000, 2001). Under normal circumstances, insulin activates the enzyme lipoprotein lipase which hydrolyses triglycerides (Taskinen, 1987). However, in diabetic state lipoprotein lipase is not activated due to insulin deficiency resulting in hypertriglyceridemia. The MPFL significantly reduced the levels of total cholesterol, triglycerides, LDL and VLDL and increased the levels of HDL. The MPFL shown to have better antihyperlipidemic activity compared to standard gliclazide in STZ induced diabetic rats (Table 4).

The serum bilirubin levels were found to be increased in STZ induced diabetic rats. Rana *et al.* (1996) reported that the increase in serum bilirubin (hyper-bilirubenimia) in STZ induced diabetic rats, may be resulted from the decrease of liver uptake, conjugation or increase total bilirubin, direct bilirubin production from hemolysis. The elevation in serum bilirubin indicates liver damage. The MPFL shown to have better hepatoprotective activity than standard gliclazide (Table 3). The estimation of total protein is useful for measuring gross changes in protein levels caused by various disease states. In diabetic conditions the circulating protein binds with free reducing sugars leads to formation amadori products. The MPFL able to increase the protein levels may be by breaking the link between the reducing sugars and amino acids of proteins. Urea is the major nitrogen containing metabolic product of protein metabolism, uric acid is the major product of purine nucleotides, adenosine and guanosine creatinine is endogenously produced and released into body fluids and its clearance measured as an indicator of glomerular filtration rate (Burtis and Ashwood, 1996). The metabolism of protein is found to be increased in the diabetic rats as indicated by

Table 3: Effect of different concentrations of MPFL on kidney parameters on normal and Streptozotocin induced diabetic and normal rats

Groups	HbA1c	T. bilirubin	D. bilirubin	Creatinine	Total protein	Albumin	Uric acid	BUN
Control	4.37±0.64*	0.75±0.018*	0.69±0.019 <sup>§</sup>	0.69±0.02*	6.15±0.17*	3.72±0.10*	3.63±0.17*	21.95±0.45*
D. control	11.68±0.41	1.75±0.055	1.22±0.013	1.90±0.03	3.95±0.23	7.20±0.10	8.14±0.21	36.20±0.20
Standard	3.88±0.34*	0.72±0.025*	0.69±0.021 <sup>§</sup>	0.78±0.02*	5.87±0.67*	4.10±0.06*	4.13±0.11*	22.44±0.33*
MPFL (150 mg kg <sup>-1</sup> )	5.96±0.54*	0.91±0.010*	0.81±0.028 <sup>ns</sup>	0.94±0.03*	7.49±0.16*	4.45±0.09*	5.16±0.18*	27.40±0.34*
MPFL (300 mg kg <sup>-1</sup> )	4.67±0.29*	0.76±0.022*	0.69±0.026 <sup>§</sup>	0.84±0.05*	7.92±0.15*	4.04±0.11*	3.96±0.14*	24.71±0.25*

ns: Not significant, \*<sup>§</sup>significant at p<0.001, p<0.01 and p<0.05 level, respectively, two way ANNOVA followed by Bonferroni post test when compared with toxicant group

Table 4: Effect of MPFL on lipid profile of STZ induced diabetic rats

Groups	Triglycerides (mg dL <sup>-1</sup> )	Total cholesterol (mg dL <sup>-1</sup> )	HDL (mg dL <sup>-1</sup> )	LDL (mg dL <sup>-1</sup> )	VLDL (mg dL <sup>-1</sup> )
Control	80.3±1.8*	127.8±2.0*	62.0±1.9*	49.5±2.90*	16.0±0.3*
Diabetic control	132.5±3.0	241.8±4.6	36.3±1.3	179.0±4.90	26.5±0.6
Standard	82.5±2.6*	130.6±3.1*	58.0±2.0*	56.16±4.9*	16.5±0.5*
MPFL (150 mg kg <sup>-1</sup> )	105.0±2.5*	144.8±4.0 <sup>§</sup>	51.5±1.1*	73.1±3.10*	21.0±0.5*
MPFL (300 mg kg <sup>-1</sup> )	85.3±1.7 <sup>§</sup>	138.3±2.8*	60.3±1.4*	60.9±3.60*	17.0±0.3*

ns: Not significant, \*<sup>§</sup>significant at p>0.001 and p>0.05 level, respectively, two way ANNOVA followed by Bonferroni post test when compared with toxicant group

increase in the levels of serum urea, uric acid and decreased levels of proteins as explained above. The MPFL shown to decrease the levels of urea and uric acid probably by decreasing the metabolism of proteins (Table 3).

The treatment with the MPFL found to be useful in reducing the damage caused due to hyperglycaemia induced by STZ. The MPFL was shown to have better and comparable antihyperglycaemic activity with standard gliclazide. Serum creatinine and serum BUN levels measurement is taken as an index of altered GFR in diabetic nephropathy (Sugimoto *et al.*, 1997). The present results showed that the level of serum creatinine and BUN levels was significantly elevated in diabetic animals. The treatment with MPFL for 12 weeks shown significant reduction in the creatinine and BUN (Table 3).

The light microscopic examination of pancreatic section of control group revealed that the normal structure of the exocrine and endocrine parts of the pancreas (Fig. 1). Previous studies reported similar findings and added that the pancreas had a rich capillary network essential for the secretary process (Junqueira *et al.*, 2005). The light microscopic examination of endocrine part of pancreas of disease control group revealed the altered structure of both the exocrine and endocrine portions with significant decrease in the number of secretary cells (Fig. 2). The treatment with the

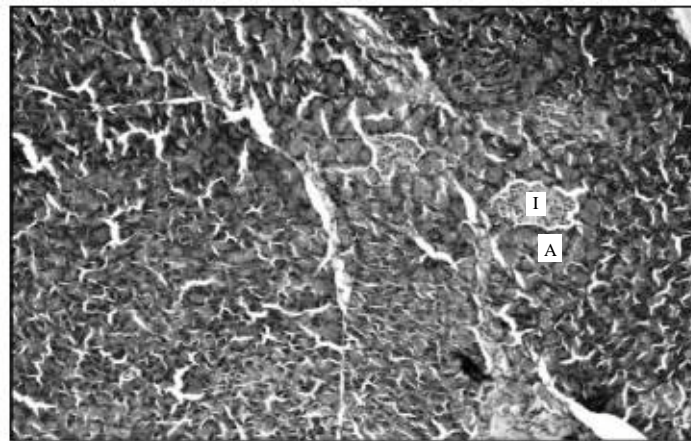


Fig. 1: Histopathological study of pancreas in normal rats

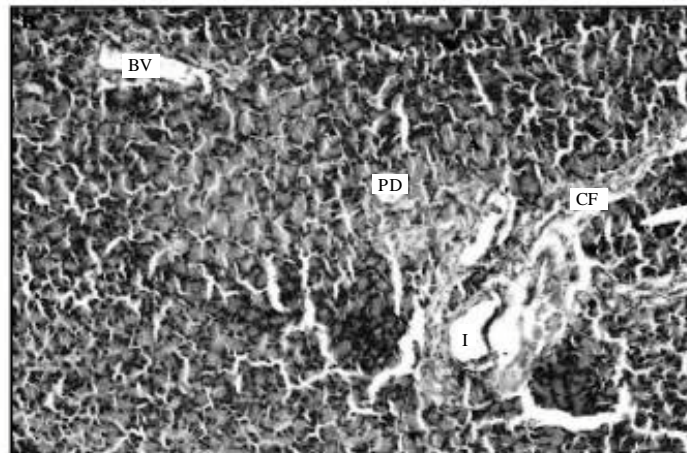


Fig. 2: Histopathological study of pancreas in disease control rats, BV: Blood vessels, PD: Pancreatic duct, I: Islet of langerhans and CF: Collegen fibres

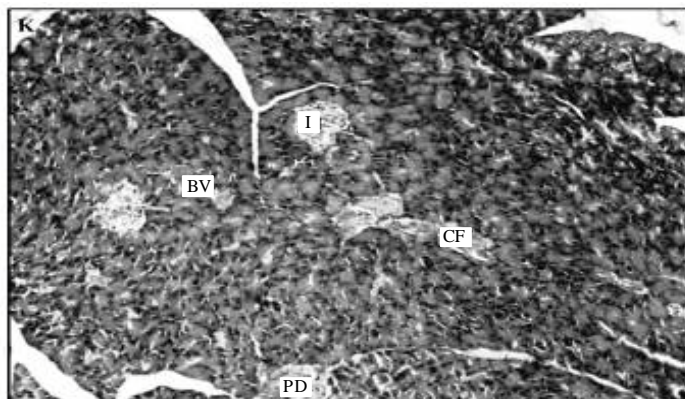


Fig. 3: Histopathological study of pancreas in Gliclazide treated rats, BV: Blood vessels, PD: Pancreatic duct, CF: Collegen fibres and I: Islet of langerhans

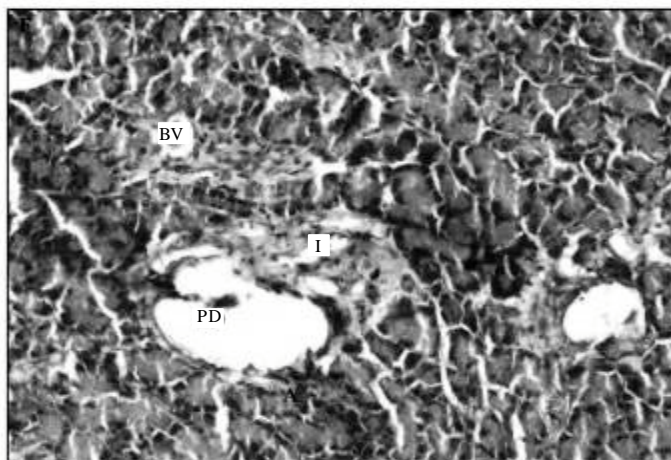


Fig. 4: Histopathological study of pancreas in MPFL (150 mg kg<sup>-1</sup>) treated rats, BV: Blood vessels, PD: Pancreatic duct and I: Islet of langerhans

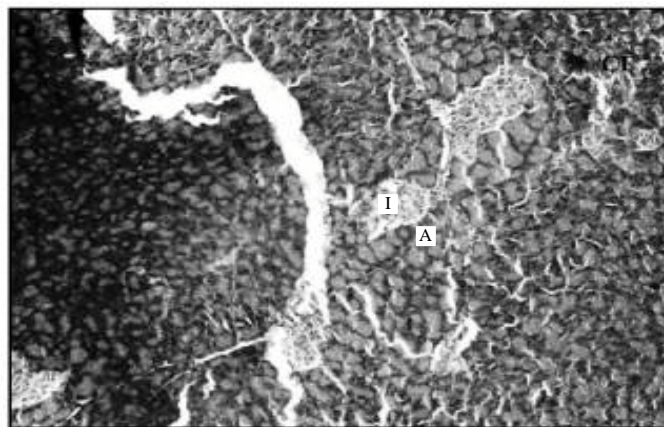


Fig. 5: Histopathological study of pancreas in MPFL (300 mg kg<sup>-1</sup>) treated rats, I: Islet of langerhans and A: Acini



gliclazide for 12 weeks found to prevent the degenerative changes in STZ induced diabetic rats (Fig. 3). In MPFL (150 mg kg<sup>-1</sup>) treatment group shown pancreatic duct, collagen fibers and dilated blood vessels (Fig. 4). The treatment with MPFL (300 mg kg<sup>-1</sup>) shown dilated duct with flattened epithelium and collagen fibers (Fig. 5).

## CONCLUSION

It is concluded that, the methonolic pericarp extract of *Feronia limonia* showed better hypoglycemic and antihyperglycemic activity against STZ induced diabetic rats. All the activities might be due to high levels of volatile flavours, flavonoids and free fatty acids in methonolic pericarp extract of *Feronia limonia*.

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