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Anti Hyperglycemic Activity of *Elytraria Acaulis* Lind. on Streptozotocin-Induced Diabetic Rats

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Abstract

Aim of the present work is to evaluate the Anti-hyperglycemic activity of *Elytraria acaulis* Lind. on streptozotocin-induced diabetic rats. *Elytraria acaulis* Lind. belongs to family Acanthaceae which is a small shrub, that grows in shady dry places. The whole plant is used for medicinal purposes. Diabetes was induced in rats by administering streptozotocin (60 mg/kg) intraperitonially. Animals were divided into five groups (n=6) receiving different treatments: Group I: vehicle (Control), Group II: diabetic (control), Groups III and IV: *Elytraria acaulis* Lind. extract treated (200 and 400 mg/kg, orally respectively) and Group V: standard anti diabetic drug glibenclamide (500 mcg/kg, orally). Blood serum was analyzed for the following biochemical parameters like blood glucose level, oral glucose tolerate test, body weight and liver glycogen & glycated hemoglobin levels. Histopathological study of pancreas, liver and kidney was examined. The *Elytraria acaulis* Lind. extracts were effective in decreasing blood glucose level, increases oral glucose tolerance test, moderately alteration in body weight and there was a marked reduction in the liver glycogen levels and reduction in glycated hemoglobin levels. Histopathological study, showing improvement with nearly normal islets of langerhans, showing marked improvement with normal architecture with mild hepatocytes degeneration and showing acid significantly inhibited glomerular hypertrophy, glomerulosclerosis. It is concluded that, the anti-hyperglycemic effect of methanolic extracts of *Elytraria acaulis* Lind. may be due to both reductions in glucose level and improvement in Histopathological studies. The methanolic extract of *Elytraria acaulis* Lind. at the dose level of 400 mg/kg produced more significant reduction in glucose level when compare with low dose 200 mg/kg. Hence, it is proved that *Elytraria acaulis* Lind. is having anti diabetic activity in streptozotocin induced diabetic rats.

Keywords: *Elytraria acaulis* Lind; Streptozotocin; Hyperglycemia.

Introduction

Diabetes Mellitus (DM) is a major health problem all over the world. Globally, the number of people that have been diagnosed with diabetes has exploded in the past two decades. In 2000, 151 million, in 2010, about 221 million people are diabetic and it has been predicted that 324 million will be diabetic by 2025 [1]. Several approaches were made to reduce the hyperglycemia, the hallmark of diabetes mellitus, with treatment such as sulfonylurea which stimulates pancreatic islet cells to secrete insulin; metformin, which act to reduce hepatic glucose production; glycosidase inhibitors, which interfere with glucose absorption and insulin itself, which suppresses glucose production and augment glucose utilization [2]. The growing public interest and awareness of natural products have led pharmaceutical industry and academic researchers to pay more attention to medicinal plants [3]. The apparent reversal from western to herbal medicine is partly due to the fact that synthetic drug have always shown adverse reactions and other undesirable side effects. This has led. on the belief that natural products are safer because they are more harmonious with biological system. In addition, the cost of administering modern anti-diabetic drugs is beyond the reach of low income and those living in rural areas [4]. Nigeria People use hundreds of traditional plants for the management of diabetes mellitus. To date, however, only a few of this medicinal plants have received scientific scrutiny, despite the fact that the world Health Organization has recommended that medical and scientific examination of such plant should be undertaken [5]. *Elytraria acaulis* Lind. belongs to the family Acanthaceae which is a small shrub, that grows in shady dry places. The whole shrub is used for medicinal purposes [6]. *Elytraria acaulis* Lind. is frequently being used, the leaves decoction of this plant is prescribed in fever, venereal diseases and root is used in mammary tumor, abscesses, pneumonia and infantile diarrhea as well as traditional medicine for long days [7]. Leaves are used for treating wounds infected with worms [8]. Locally in Tamilnadu (Tirunelvelli Dist) it is used as anti-diabetic. The present investigation was therefore carried out to study anti hyperglycemic activity of *Elytraria acaulis* Lind. on streptozotocin-induced diabetic rats

Materials and Methods

Animals

Wistar strains of albino rats of either sex weighing 150-200 g were used as the experimental models. The animals were kept in well ventilated cages and were fed with the commercial pelleted rat chow and water *ad-libitum*. Animals were maintained in standard animal house.

Preparation of plant extract

The whole shrub of *Elytraria acaulis* Lind. were dried and powdered in a mechanical grinder. The powdered material was extracted with methanol using soxhlet apparatus. This extract was filtered and concentrated in vacuum evaporator and kept in vacuum desiccators for complete removal of solvent. The yield was 150 g with respect to 2 Kg of dried powder and used for oral administration.

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Treatment	Dose (mg/kg)	Blood Glucose at different hours after the treatment			
		0h	1h	2h	3h
Control (normal saline)	2 ml/kg	90.5 ± 1.6	86.9 ± 1.2	87.6 ± 2.1	91.3 ± 1.3
Methanol Extract of EA	200	86.4 ± 2.0	82.3 ± 1.4	85.5 ± 1.3	83.7 ± 2.2
	400	83.6 ± 1.2	81.8 ± 1.6	84.0 ± 1.5	82.7 ± 1.8
Glibenclamide	500 µg	85.2 ± 1.6	80. ± 1.5	74.6 ± 1.9* (12.44%)	65.9 ± 1.7** (22.65%)

N=6 animals in each group; Values are expressed as mean ± SEM
*P<0.01; ** P< 0.001 compared with initial level of blood glucose (0 h) in the respective group
Data were analyzed by one way ANOVA followed by Tukey multiple comparison analysis

Table 1: Effect of methanol extract of *Elytraria acaulis* Lind. extract on Fasting Blood Glucose Levels (mg %) of Normal Rats

Chemicals

Streptozotocin and glibenclamide was purchased from Sigma Chemicals Co (St. Louis, MO, USA). Glucometer and glucometer strips obtained from Roche Diagnostic, USA), 1-chloro2,4-dinitro benzoic acid (CDNB), 5,5-dithio-bis-2-nitro benzoic acid (DTNB), Oxidized glutathione, reduced glutathione (GSH), α-Tocopherol acetate and ascorbic acid were supplied by Sisco Research Laboratories Pvt. Ltd., Mumbai, India. Thiobarbituric acid was purchased from E-Merck, India. All other chemicals used were of analytical grade.

Induction of diabetes

Diabetes was induced in rats by streptozotocin (60 mg/kg) which was dissolved in citrate buffer; pH 4.5, and was injected by a single intra peritoneal injection in rats previously fasted for 16 h [9]. Animals with post-prandial glycemia over 250 mg/kg, 5 days after streptozotocin administration, were considered diabetic. To prevent the hypo glycemia which occurred during the first 24 h following the streptozotocin administration, 5% glucose solution was orally given to the diabetic rats.

Hypoglycemic activity

The hypoglycemic test was performed in overnight fasted (18 h) normal rats. Rats were divided into 5 groups (n=6), where group I were administered normal saline (2 ml/kg), group II were diabetic control, the groups III & IV were given extract of *Elytraria acaulis* Lind. at a dose of 200 and 400 mg/kg by orally and group V were given orally glibenclamide (500 mcg/kg). Blood was withdrawn from the tail vein at 0, 1, 2 and 3 hrs and glucose levels were estimated using a glucose oxidase–peroxidase reactive strips and a glucometer (Accu-chek, Roche Diagnostics, USA).

Experimental design

The rats were divided into five groups, each consisting of six rats.

Group I : Normal control received orally distilled water alone for 28 days.

Group II : Diabetic control received orally distilled water alone for 28 days

Group III: Received methanol extract of *Elytraria acaulis* Lind. orally at dose of 200 mg/kg body weight for 28 days

Group IV: Received methanol extract of *Elytraria acaulis* Lind. orally at dose of 400 mg/kg body weight for 28 days.

Group V : Received glibenclamide orally at dose of 500 mcg/kg for 28 days.

Body weight of rats was taken on pre and post treatment i.e. day 0, 1st, 2nd, 3rd and 4th weeks of post treatment. Fasting blood glucose level of rats were taken pre and post treatment i.e. 0, 1st, 2nd, 3rd and 4th weeks of post treatment. Glucose levels were estimated using a glucose oxidase–peroxidase reactive strips and a glucometer (Accu-chek, Roche Diagnostics, USA).

At the end of experimental period, all the rats were sacrificed by cervicalde capitation. Blood samples were collected, allowed to clot. Serum was separated by centrifuging at 2500 rpm for 15 min and analyzed for various biochemical parameters [9].

Oral glucose tolerance test (OGTT) [10]

The oral glucose tolerance test was performed in overnight fasted (18 h) normal rats. Rats were divided into 4 groups (*n*=6), group I were administered normal saline (2 ml/kg), group II were given orally glibenclamide (500 mcg/kg), the groups III & IV were given extract of *Elytraria acaulis* Lind. at a dose of 200 & 400 mg/kg by orally. Glucose (2 g/kg) was fed 30 min after the administration of extract. Blood was withdrawn from the tail vein at 30, 60, 120 min of glucose administration and glucose levels were estimated using a glucose oxidase–peroxidase reactive strips and a glucometer (Accu-chek, Roche Diagnostics, USA).

Biochemical analysis

Blood glucose level, Oral glucose tolerate test, body weight and liver glycogen and glycated haemoglobin were estimated by standard techniques and Histopathological studies were examined .

Statistical analysis

All values were expressed as mean ± standard error mean (SEM). The differences were compared using one-way analysis of variance (ANOVA). P values < 0.05 were considered to be significant.

Results

Effect of the *Elytraria acaulis* Lind. on blood glucose levels of normoglycaemic rats

The effect of various doses of *Elytraria acaulis* Lind. extract obtained from blood glucose levels in normoglycaemic rats are shown in Table 1**.** The glucose levels were compared to the values obtained from initial (0 hr). As shown in table 1, the extract at 200 & 400 mg/kg doses did not show any significant reduction on blood glucose levels in normoglycaemic rats. Glibenclamide (500 mcg/kg) induced significant reduction in blood glucose level of 22.65% (3 h) when compared to the 0 h of respective group.

Effect of the Elytraria *acaulis* Lind. extract on Oral Glucose Tolerance Test (OGTT)

The blood glucose levels of different doses of the *Elytraria acaulis* Lind. Extract glibenclamide and vehicle treated rats after oral administration of glucose (2 g/kg) were summarized in Table 2**.** The

Treatment	Dose (mg/kg)	Blood Glucose at different hours after the treatment			
		0h	0.5h	1h	2h
Control (normal saline)	2 ml/kg	83.4± 1.7	101.8 ± 1.2	169.5 ± 2.1	96.3 ± 1.8
Methanol Extract of EA	200	85.5 ± 2.0	103.6 ± 1.4	126.0 ± 1.2	101.5± 1.5 [b]
	400	84.6 ± 1.4	98.8 ± 1.6[a,b]	114. 6± 1.1 [a,c]	93.4 ±1.9 [a,b]
Glibenclamide	500 µg	82.2 ± 1.8	96.5 ± 1.3	105.8 ± 2.0	67.6 ± 1.6

N=6 animals in each group; Values are expressed as mean ± SEM
[a]P<0.001 Vs Control
[b]P<0.001; [c]P<0.01 Vs Glibenclamide
Data were analyzed by one way ANOVA followed by Tukey multiple comparison analysis

Table 2: Effect of methanol extract of Elytraria acaulis Lind. extract on Oral Glucose Tolerance Test (mg %) of Normal Rats.

Treatment	Dose (mg/kg)	Blood Glucose (mg %)					
		0 Day	After streptozotocin induced	1st week after Treatment	2nd Week	3rd week	4th week
Control	--	88.47 ±1.69	86.20 ±1.23	84.61 ±1.17	85.72 ± 1.26	92.20 ± 1.50	89.26 ± 1.08
Diabetic Control	--	91.15 ±1.56	362.27 ± 2.79[a]	387.52 ± 3.29 [a]	390.18 ± 3.14 [a]	375.05 ±4.76 [a]	381.34 ±2.54 [a,b]
Methanol Extract of EA	200	94.34 ± 1.42	378.65 ± 3.04 [a]	293.35±2.07 [a,b §]	258.63± 2.10 [a,b,§]	210.14 ± 2.34 [a,b§]	196.45 ±1.47 [a,b§]
	400	90.72 ± 1.69	389.24 ± 2.16 [a]	241.43 ± 2.10 [a,b§]	203.72 ± 1.92 [a,b,§]	180.26 ±2.15 [a,b§]	152.12 ±1.31 [a,b§] (60.91%)
Glibencla-mide	500 µg	92.83 ± 1.31	367.18 ± 2.17 [a]	180.26 ± 1.74 [a,b§]	165.59 ± 1.23 [a,b§]	147.26 ± 1.31 [a,b§]	134. 92 ±1.56 [a,b§] (63.25%)

N=6 animals in each group; Values are expressed as mean ± SEM
[a]P<0.001 Vs Control; [b]P<0.001 Vs Diabetic control
[§]P<0.001 Vs after STREPTOZOTOCIN induction in the corresponding group.
Data were analyzed by one way ANOVA followed by Tukey multiple comparison analysis

Table 3: Effect of *Elytraria acaulis Lind*. extract on blood glucose levels in streptozotocin induced diabetic rats.

Treatment	Dose (mg/kg)	O day	1st week	2nd week	3rd week	4th week	Body weight gain (g)
Control	--	225.3 ± 1.5	234.4 ± 1.7*	245.6 ± 1.4*	250.2 ± 1.3*	258.8 ± 1.7*	+ 33.5
Diabetic control	--	230.6 ± 2.3	221.4 ± 2.1[$]	210.9 ± 1.6*[$]	196.7 ± 2.4*[$]	185.1 ± 2.0*[$]	- 45.5
Methanol Extract of EA	200	224.5 ± 1.6	228.3 ± 1.4	235.7 ± 1.9*	240.3 ± 1.2	245.6 ± 1.5*	+ 24.0
	400	226.4 ± 1.4	231.4 ± 1.8	237.5 ± 1.5*	243.8 ± 1.6*	250.7 ± 1.8*	+ 27.7
Glibenclamide	500 µg	228.5 ± 1.2	239.7 ± 1.7	245.8 ± 1.8*	252.4 ± 1.1*	259.9 ± 1.7*	+ 31.4

N=6 animals in each group; Values are expressed as mean ± SEM
*P<0.01compared with initial level of body weight (0 day) in the respective group.
[$] P<0.01 Vs Control

Table 4: Effect of *Elytraria acaulis Lind*. extract on body weight changes (g) in streptozotocin induced diabetic rats.

blood glucose levels of the normoglycaemic rats reached a peak at 1 h after the oral administration of glucose and gradually decreased to the pre-glucose load level. The extract of *Elytraria acaulis* Lind. at doses of 200 & 400 mg/kg showed a significant (P<0.001) effect, with blood glucose levels dropping to 101.5 & 93.4 mg %, respectively from that of corresponding group, after 2 h of glucose administration. It therefore appears that 400 mg/kg of the extract of *Elytraria acaulis* Lind. is the most effective dose on OGTT of normoglycaemic rats. It was considered that *Elytraria acaulis* Lind. 400 mg/kg may be the ceiling dose for its inhibitory effect. Glibenclamide prevented the drastic increase of blood glucose 1 h after the glucose loading and reduced the level even below the normal values 2 h after the glucose loading.

Effect of the *Elytraria acaulis* Lind. extract on blood glucose levels and body weight changes in streptozotocin-induced diabetic rats

In order to determine the anti-hyperglycemic effects, two doses of the *Elytraria acaulis* Lind. extract were administered throughout 4 weeks consecutively. The blood glucose level of each animal was monitored on 0 day, 1st, 2nd, 3rd, and 4th week, after the administration of the *Elytraria acaulis* Lind. extract. As shown in Table 3**,** the blood glucose levels of diabetic control rats were significantly (P<0.001) higher than those of the control rats during the experiment period.

The observed effect with a dose of 400 mg/kg of the *Elytraria acaulis* Lind. extract was more potent (60.91%) than that of the other dose of 200 mg/kg of the extract (48.11%) on the 4th week. The highest reduction in blood glucose was observed on the 4th week for 400 mg/kg and glibenclamide 500 mcg/kg dose hit the highest (63.25%) and even nearly equivalent effect was found.

During the 4 week administration, rats treated with various doses of the *Elytraria acaulis* Lind. extract and glibenclamide were also monitored for changes in body weight, (Table 4). Streptozotocin administration caused a significant (*P*<0.001) weight loss by -45.5 g, whereas rats in the normal group continued to put on weight (+33.5 g). Treatment with 200 & 400 mg/kg of *Elytraria acaulis* Lind. recovered the weight loss of animals found to be + 24 g and 27.7 g respectively.

Liver glycogen and glycated haemoglobin

Streptozotocin diabetic rats showed significant (P<0.001) alteration in the glycosylated hemoglobin levels and liver glycogen levels in comparison to normal rats. Administration of *Elytraria acaulis* Lind. (200 & 400 mg/kg) and glibenclamide restored the above parameters significantly towards normal.

There was a marked reduction in the liver glycogen levels of streptozotocin diabetic rats from 10.97 g/100 g tissue (in normal control rats) to 4.65 mg/100g tissue. *Elytraria acaulis* Lind. extract (200 mg/kg) treatment showed 6.54 mg/100 g increase, while at 400 mg/kg there was

Treatment	Dose (mg/kg)	Liver glycogen (mg/g)	Glycated haemoglobin (%)
Control	-	10.97 ± 0.56	2.56 ± 0.08
Diabetic control	-	4.65 ± 0.32[a]	7.19 ± 0.21[a]
Elytraria acaulis Lind. extract	200	6.54 ± 0.29[a,e]	6.03 ± 0.17[a,d]
	400	8.76 ± 0.12[a,d]	3.84 ± 0.10[a,d]
Glibenclamide	500 µg	9.48 ± 0.27[a,d]	2.93 ± 0.15[d]

N=6 animals in each group; Values are expressed as mean ± SEM
[a]P<0.001; [b]P<0.01; [c]P<0.05 Vs Control
[d]P<0.001; [e]P<0.01 Vs Diabetic control
Data were analyzed by one way ANOVA followed by Tukey multiple comparison analysis

Table 5: Effect of *Elytraria acaulis* Lind. extract on liver glycogen & glycated hemoglobin levels in streptozotocin induced diabetic rats

8.76 mg/100 g increase in liver glycogen levels as compared with the untreated diabetic rats. Glibenclamide treatment elicited 9.48 mg/100 g increase in liver glycogen levels when compared to the untreated diabetic rats (Table 5)

Treatment with *Elytraria acaulis* Lind. reduced glycated haemoglobin percent levels from 7.19% (in diabetic control) to 6.03% and 3.84% in rats treated with 200 mg/kg and 400 mg/kg doses respectively. The glycated haemoglobin levels were found to be 2.93% in glibenclamide 500 mcg/kg treated rats (Table 5).

Histopathological study of the pancreas of streptozotocin induced diabetic rats

The normal control rats showed no architectural changes in the histology of the pancreas [Figure1]. In the streptozotocin diabetic untreated rats, the islets of langerhans showed diffused necrotic changes of moderate to marked degree as a result of which they were significantly reduced in size and number. Only occasional presence of the islets could be detected in a few rats. The group of rats treated with glibenclamide showed diffused necrotic changes of mild to moderate degree in the pancreas. There was a mild reduction in the size and number of the islets in this group. The effect of *Elytraria acaulis* Lind. extract (400 mg/kg) on streptozotocin diabetic rats was comparable with that of glibenclamide. The *Elytraria acaulis* Lind. extract (200 mg/kg) treated group of rats showed moderate degree of necrosis of the islets of langerhans. The pancreatic damage observed in glibenclamide and *Elytraria acaulis* Lind. extract (400 mg/kg) treated diabetic animals was milder than that found in the untreated diabetic control group.

Morphological changes in hepatocytes

The streptozotocin induced diabetic rats exhibited a higher hepatic lipid droplets compared to the normal rats (Figure 2). The supplementation of *Elytraria acaulis* Lind. extract lowered (200 and 400 mg/kg) the hepatic lipid droplets accumulation size compared to the control.

Morphological changes in kidney

Figure 3 shows, sections of kidney from the diabetic (group II) and diabetic treated rats had clearly shown the protective effect of the *Elytraria acaulis* Lind. extract.

Discussions

Diabetes mellitus is a global disease that is a major cause of morbidity in the world [11]. This disorder is basically characterized by high levels of blood glucose caused by defective insulin production and action that are often responsible for severe health problems and early death [12]. Much of the morbidity and mortality associated with diabetes is primarily attributed to micro vascular and macro vascular changes, such as atherosclerosis, retinopathy, nephropathy, coronary artery disease, cerebral vascular disease, and peripheral artery disease [13]. One of the reasons for injury related to hyperglycemia is the formation of glycated proteins, glucose oxidation, and increased free fatty acids [14]. Moreover, some recent studies suggest that reactive oxygen species (including free radicals) may also be involved in the initiation and development of vascular complications in diabetics [15]. Oxidative stress combined with mitochondrial dysfunction leads to the activation of inflammatory signaling pathways, which may damage insulin-producing cells and further aggravate the complications of diabetes [16].

The streptozotocin-induced diabetic rat is one of the animal models of human diabetes mellitus. Diabetes arises from irreversible destruction of pancreatic β cells, causing de-granulation and reduction of insulin secretion [17]. Streptozotocin-induced diabetes is characterized by a severe loss in body weight [18] and may exhibit most of the diabetic complications such as, myocardial, cardiovascular, gastrointestinal, nervous, kidney and urinary bladder dysfunction through oxidative stress [19]. The decrease in body weight in diabetic rats shows that the loss or degradation of structural proteins is due to diabetes, and structural proteins are known to contribute to the body weight [20]. The present study demonstrated that administration of *Elytraria acaulis* Lind. extract for 4 weeks shows antihyperglycemic effect in

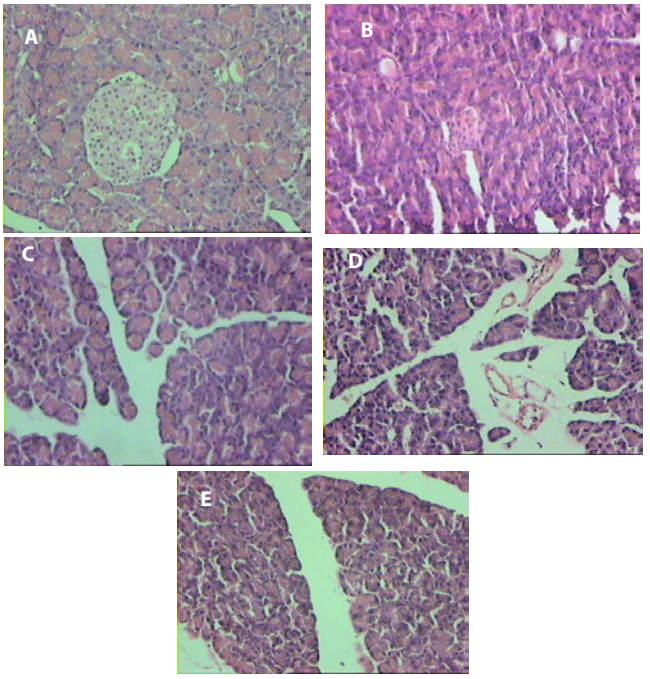

Figure 1: Histopathological study of the pancreas of streptozotocin induced diabetic rats. (A) Normal. Pancreas (GA), showing no pathological changes. The exocrine pancreatic tissue composed of acini with draining ductules, the endocrine component is found as a nodule within the substance. **(B)** Pancreas (Diabetic Control) showing diffused necrotic changes of moderate to marked degree as a result of which they were significantly reduced in size and number. **(C)** Pancreas (*Elytraria acaulis* Lind. extract 200 mg/kg), after 28 days: showing less improvement or restoration of normal cellular population size of islets. **(D)** Pancreas (*Elytraria acaulis* Lind. extract 400 mg/kg), after 28 days: showing marked improvement with nearly normal islets of Langerhans. **(E)** Pancreas (Glibenclamide 500 mcg/kg), after 28 days: showing improvement and minimal degenerative changes.

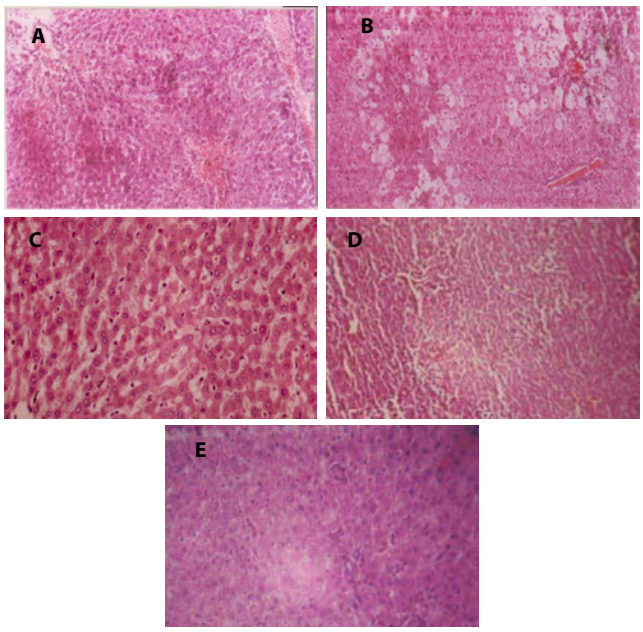

Figure 2: Morphological changes in hepatocytes. (A) Normal. Liver showing no pathological changes. **(B)** Liver (Diabetic Control) after 28 days: showing exhibited severe hepatocyte degeneration, necrosis and higher hepatic lipid droplets. **(C)** Liver (*Elytraria acaulis* Lind. extract 200 mg/kg), after 28 days: showing less improvement or restoration of hepatocyte degeneration. **(D)** Liver (*Elytraria acaulis* Lind. extract 400 mg/kg), after 28 days: showing marked improvement with normal architecture with mild hepatocyte degeneration. **(E)** Livers (Glibenclamide 500 mcg/kg), after 28 days: shows normal architecture with mild hepatocyte degeneration.

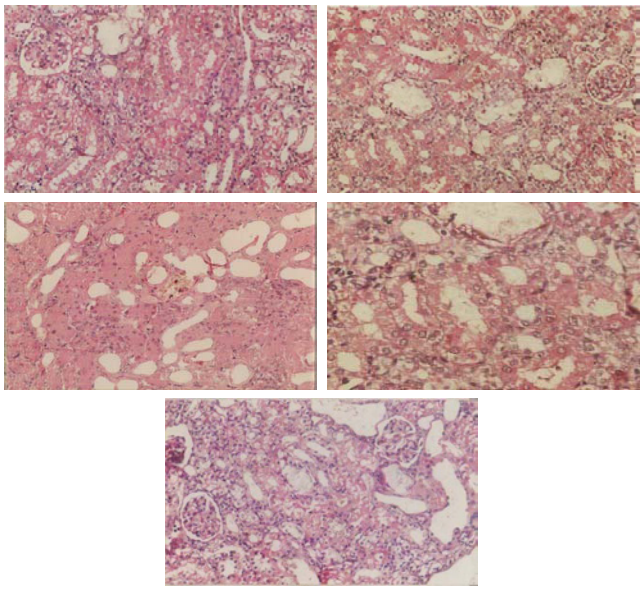

Figure 3: Morphological changes in kidney. (A) Normal. Kidney showing no pathological changes. **(B)** Kidney (Diabetic Control)after 28 days: demonstrated glomerulusclerosis and lymphocyte infiltration. **(C)** Kidney (*Elytraria acaulis* Lind. extract 200 mg/kg), after 28 days: showing less improvement or restoration of normal glomerular hypertrophy, glomerulosclerosis. **(D)** Kidney (*Elytraria acaulis* Lind. extract 400 mg/kg), after 28 days: showing acid significantly inhibited glomerular hypertrophy,glomerulosclerosis. **(E)** Kidney (Glibenclamide 500 mcg/kg), after 28 days significantly inhibited glomerular hypertrophy, glomerulosclerosis and loss of glomerular numbers.

streptozotocin-induced diabetic rats. When diabetic rats were treated with *Elytraria acaulis* Lind. extract the weight loss was recovered, which may be due to its protective effect in controlling muscle wasting i.e. reversal of gluconeogenesis and may also be due to the improvement in insulin secretion and glycemic control.

The capability of *Elytraria acaulis* Lind. extract to protect body weight loss seems to be related to its ability to reduce hyperglycemia. In *Elytraria acaulis* Lind. extract treated diabetic rats, the significant elevation of blood insulin may be due to the stimulation of insulin secretion from the existing β cells of pancreas. According to the present data glibenclamide reduces blood glucose levels in diabetes that is consistent with previous studies [21,22]. Glibenclamide, one of the most widely used oral hypoglycemic agents in the treatment of diabetes mellitus, exerted its beneficial effects on extracellular site by opening Ca^{2+} channels to stimulate insulin secretion and also duodenal insulin-releasing agent [23].

The first idea that comes to mind is that *Elytraria acaulis* Lind. extract acts with the same mechanism of glibenclamide by closure of K^{+}ATP channels, membrane depolarization and stimulation of Ca^{2+} influx, an initial key step in insulin secretion [24]. Some bioactive compounds isolated from plants like terpenoids and flavonoids were reported to affect pancreatic beta-cells and stimulate insulin secretion with numerous mechanisms such as exertion distal to K^{+} ATP channels and L-type Ca^{2+} channels [25], activation of the c-AMP/PKA signaling [26], and antioxidant activities [27]. Since oxidative stress and free radicals injure or destroy pancreatic β cells in diabetes, *Elytraria acaulis* Lind. extracts is able to increase the secretion of insulin via its antioxidant actions [28,29]. Since streptozotocin is known to destroy pancreatic β cells, *Elytraria acaulis* Lind. extract may also act extra-pancreatic and thus influencing glucose uptake and utilization by different tissues [22]. The other possible mechanism of action of *Elytraria acaulis* Lind. extracts might be mediated through liver and affecting gluconeogenesis, glycogenesis or glycogenolysis.

In our study when *Elytraria acaulis* Lind. extract was administered to normal rats fasted for 18 h, the extract at 200 & 400 mg/kg doses did not show any reduction on blood glucose levels in normal rats. Glibenclamide (500 mcg/kg) induced significant reduction in blood glucose level when compared to the control group. Our investigations indicate the efficiency of the *Elytraria acaulis* Lind. extract in the maintenance of blood glucose levels in normal and streptozotocin-induced diabetic rats.

Further, the plant extract was administered to glucose loaded normal rats fasted for 18 h, hypoglycemia was observed after 60 min in glucose loaded rat (OGTT). The decline in blood glucose level reached its maximum at 2h and this fact could be attributed to the potentiating of the insulin effect of plasma by increasing the pancreatic secretion of insulin from existing β-cells or its release from bound insulin. In this context a number of other plants have been observed to have similar patterns of hypoglycemic effects [30,31].

Conclusion

The methanolic extracts of *Elytraria acaulis* Lind. were effective in decreasing blood glucose level in streptozotocin-induced diabetic rats. The high dose of the extract shows more effect of healing than low dose. The methanolic extract of *Elytraria acaulis* Lind. also increases oral glucose tolerance test and moderate alteration in body weight. The anti-hyperglycemic effect of methanolic extracts of *Elytraria acaulis* Lind. may be due to both reductions in glucose level and histopathological study, showing improvement with nearly normal islets of Langerhans,

showing marked improvement with normal architecture with mild hepatocytes degeneration and showing acid significantly inhibited glomerular hypertrophy and glomerulosclerosis. The exact mechanism by which methanolic extract showed anti hyperglycemic effect cannot be explained, it is speculated that this extract may possess anti-oxidant property.

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