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Hypoglycemic and Hypolipidemic Activities of Hydro-Alcoholic Extract of *Echinochloa Frumentacea* Link Grains in Alloxan Induced Diabetic Rats.

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ABSTRACT

To investigate the hypoglycemic and hypolipidemic activities of hydro-alcoholic extract of *Echinochloa frumentacea* Link grains in alloxan induced diabetic rat. A single dose study was studied in the normal rats for 12hrs. Oral glucose tolerance test (OGTT) was performed in normal rats after receiving glucose orally (2g/kg) and in diabetes induced rats after receiving glucose orally (3g/kg). Diabetes was induced by ALX (120mg/kg, i.p.) three different doses of HAEF (200, 400 and 600mg/kg, p.o.) of HAEF were administered orally to experimental diabetic induced rats treatment for 21 days. Glibenclamide (5mg/kg p.o.) was used as reference standard. Fasting blood glucose levels, changes in body weight and organ weight, serum albumin, urea, total protein, creatinine, total lipid profile, haemoglobin, GSH, SOD and TBARS were evaluated. Finally histopathological examination of pancreas was performed. Single dose study of HAEF on normal rats showed a significant decrease in the fasting blood glucose levels when compared with the normal control rats. Oral glucose tolerance test clearly indicate that 400mg/kg and 600mg/kg p.o. of HAEF shown a significant decrease in the blood glucose levels. Whereas, 200mg/kg p.o showed little effect. Oral glucose tolerance test in ALX induced diabetic rats 400mg/kg and 600mg/kg p.o. of HAEF shown a significant decrease in the blood glucose levels.. In diabetic rats, treatment with the 400, and 600mg/kg, p.o. showing significant reduction in the fasting blood glucose levels, serum cholesterol, serum triglycerides, LDL-C and VLDL-C levels. A significant escalation was seen in the levels of HDL-C, haemoglobin, body weight and organ weights. Whereas, the anti-oxidant levels TBARS, GSH and SOD levels were improved than the untreated diabetic rats. HAEF have shown significant *In-vivo* antioxidant property and hypoglycemic and hypolipidemic activity.

INTRODUCTION

Diabetes mellitus is characterized by chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action. The effects of diabetes mellitus include long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, heart, and blood vessels [1]. Most individuals with type 2 diabetes exhibit abdominal obesity which itself causes insulin resistance. In addition, hypertension, dyslipidemia (high triglyceride levels and low HDL-cholesterol levels), and elevated inhibitor plasminogen activator-1 (PAI-1) levels are often present in these individuals [2]. This number is expected to increase to 420 million by 2025. Population-based surveys of 75 communities in 32 countries show that diabetes is rare in communities in developing countries where a traditional lifestyle has been preserved. By contrast, some Arab, migrant Asian Indian, Chinese, and U.S. Hispanic communities that have undergone westernization and urbanization are at higher risk; in these populations, the prevalence of diabetes ranges from 14 to 20%. In addition, most of the population growth in the developing world is taking place in urban areas [3]. This increase will be most noticeable in developing countries, where the number of people with diabetes is expected to increase from 84 million to 228 million [4].

Echinochloa frumentacea Link (Fam. Poaceae) commonly known as indian barnyard millet, siberian millet, white millet a crop plant of India, Pakistan, Nepal, Africa [5]. Robust annual; culms 30-150 cm high, erect. Leaf-blades often broad, 5-30 cm long, 3-20 mm wide; ligule absent; sheaths glabrous [6]. The crop is valued for its drought tolerance, good yield and superior nutritional value. It is the fastest growing crop among all millets and can be harvested in a short period of nine weeks. Barnyard millet is an important dual-purpose crop. Its grains contain 6.2 % protein, 9.8 % crude fibre, 65.5 % carbohydrates and are consumed just like rice. Also it is a nutritive fodder for animals. These aspects make barnyard millet a valuable crop [7].

MATERIALS AND METHODS

Plant material

The grains of *Echinochloa frumentacea* most widely found in the India. The grains were collected from the Bangalore, Karnataka, identified and authenticated by Dr.M.V.C Gowda Project Co-ordinator, AICRP on Small Millets, ICAR, UAS, GKVK, Bangalore, Karnataka, India.

Preparation of plant extract

The fresh grains were collected, cleaned and shade dried at room temperature. The dried grains were coarse powdered by using grinder. The coarse powder was packed in Soxhlet column and then extracted with 70% hydro-alcohol (75-80°C). Thereafter, the extract was concentrated using rotary flash evaporator (50° C) [8, 9].

Determination of Acute Toxicity (LD₅₀)

The procedure was divided into two phases. Phase I (observation made on day one) and Phase II (observed the animals for next 14 days of drug administration). Two sets of healthy female rats (each set of 3 rats) were used for this experiment. First set of animals were divided into three groups, each of one in a group. Animals were fasted overnight with water *ad libitum*. Animals received a single dose of 2000 mg/kg, p.o. was selected for the test, as the test item was a source from herb. After administration of extract, food was withheld for 3-4 hrs [10].

Phytochemical screening

The preliminary phytochemical analysis was carried out by using the standard procedures. Alkaloids, carbohydrates, flavonoids, glycosides, phytosterols/terpenes, proteins and saponins were qualitatively analysed [11].

Experimental animals

Albino wistar rats weighing 150-220g were procured from Biogen, Bangalore. They were maintained in the animal house of Gautham College of Pharmacy, for experimental purpose. Animals were maintained under controlled condition of temperature at 27° ± 2° C and 12 hr light-dark cycles for one week. They were housed in polypropylene cages and containing paddy husk as bedding. They had a free access to standard pellets and water *ad libitum*. All the studies conducted were approved by the Institutional Animal Ethical Committee (IAEC) of Gautham College of Pharmacy, Bangalore (REF-IAEC/04/05/2011) according to prescribed guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Govt. of India.

Preparation of test sample

The grains extract (200,400 and 600mg/kg, b.w. [bodyweight]) were suspended in tween 80 prior to oral administration to animals. The standard hypoglycemic drugs glibenclamide (5mg/kg, Darwin Formulations®) and alloxan monohydrate (120mg/kg, Loba Chemie ®) dissolved on 0.9% sodium chloride solution (normal saline) is used in this study.

Experimental design

Effect of HAEF on blood glucose level of normal rats.

Albino wistar rats weighing 150-200 mg/kg were divided into five groups of six in each group. Animals were fasted overnight for 16 hrs prior to the experiment. The blood glucose levels were measured just prior to and 1, 2, 4, 8 and 12 hrs after drug administration. The blood glucose levels were measured from the tail vein by using Sugarcheck glucometer manufactured by Wockhardt [12].

- Group-I: Distilled water will be supplied and served as control.
Group-II: Animals received a dose of 5 mg/kg of Glibenclamide p.o. and served as standard
Group-III: Animals received a dose of 200 mg/kg of HAEF p.o.

Group-IV: Animals received a dose of 400 mg/kg of HAEF p.o.

Group-V: Animals received a dose of 600 mg/kg of HAEF p.o.

Effect of HAEF on Oral glucose tolerance test normal rats

The oral glucose tolerance test was performed in rats weighing 150-200g. The animals were fasted for 16 hr before the experiment but allowed free access to water. These Rats were divided into five groups, six in each group. Rats of all groups were loaded with glucose 2g/kg p.o 30 min after drug administration. Blood samples were collected from the tail vein prior to drug administration and at 30, 60, 90 and 120 min of glucose administration [13].

Group-I: Animals received distilled water and after 30min a glucose load of 2g/kg is administered p.o. which was served as control.

Group-II: Animals received a dose of 5 mg/kg of Glibenclamide p.o. and after 30 min a glucose load of 2g/kg is administered p.o which was served as standard.

Group-III: Animals received a dose of 200 mg/kg of HAEF p.o. and after 30 min a glucose load of 2g/kg is administered p.o.

Group-IV: Animals received a dose of 400 mg/kg of HAEF p.o. and after 30 min a glucose load of 2g/kg is administered p.o.

Group-V: Animals received a dose of 600 mg/kg of HAEF p.o. and after 30 min a glucose load of 2g/kg is administered p.o.

Effect of HAEF on Oral glucose tolerance test in ALX induced diabetic rats

All the diabetic rats were fasted overnight (at least 16h) prior to the test. Thirty minutes following the various treatment schedules, each rat was given an oral glucose load 3gm/kg. Blood samples were collected from the tail vein at 30 minutes (just before the administration of extract), time 0 (prior to the glucose load), 30, 60, 90 and 120 minutes after the glucose load [14].

Following groups were made for the oral glucose tolerance test in diabetic rats. In each group six rats were used.

Group I: 5% tween 80 + Glucose 3gm/kg p.o.

Group II: Animals received distilled water only and served as diabetic control + Glucose 3gm/kg p.o.

Group III: Standard drug glibenclamide 5mg/kg + Glucose 3gm/kg p.o.

Group IV: Animals received a dose of 200 mg/kg of HAEF p.o + Glucose 3gm/kg p.o.

Group V: Animals received a dose of 400 mg/kg of HAEF p.o + Glucose 3gm/kg p.o.

Group VI: Animals received a dose of 600 mg/kg of HAEF p.o + Glucose 3gm/kg p.o.

Effect of HAEF extract on ALX induced diabetic rats.

Experimentally Induced Diabetes Mellitus

Female Wistar rats weighing 150-220g were used for this study. The animals were overnight fasted for 16h before the induction of diabetes. Diabetes was induced by a single dose of 120 mg/kg body weight of alloxan by intraperitoneal route. After a period of 2 days blood glucose levels were checked by snipping the tail of alloxan treated fasted rats. Rats showing the blood glucose levels more than 300 mg/dl is taken into the study.

Diabetes was induced in fasted female Albino wistar rats (150-220g) by intraperitoneal injection of 120mg/kg body weight of alloxan except Group I. After 72hr, animals with fasting blood glucose levels higher than 300 mg/dl were selected and used.

Group-I: Animals received distilled water only and served as normal control.

Group-II: Animals received distilled water only and served as diabetic control

Group-III: Animals received a dose of 5 mg/kg of Glibenclamide p.o. and served as standard

Group-IV: Animals received a dose of 200 mg/kg of HAEF p.o.

Group-V: Animals received a dose of 400 mg/kg of HAEF p.o.

Group-VI: Animals received a dose of 600 mg/kg of HAEF p.o.

The study was carried out for 21 days. Fasting blood glucose levels were measured before the administration of HAEF. It was recorded as 0 day. The doses of the HAEF (200, 400 and 600mg/kg p.o.) along with the standard (Glibenclamide) were given daily to the animals for 21 days. The blood glucose levels were checked on 0, 7, 14, and 21 day of the treatment period. Blood was collected from snipping of the rat tail. Blood glucose levels were measured by using the glucometer Sugarcheck [13].

Determination of Body Weight

Body weight of the entire animal in each group was noted on the 0, 7, 14 and 21 day of the experiment period. The weight difference was calculated.

Determination of Weights of Pancreas, Liver, Heart, Kidneys, Spleen.

Animals were sacrificed and Pancreas, liver, heart, kidneys and spleen were isolated, washed with saline and weighed by using an electronic balance [15].

Estimation of Biochemical Parameters

The following parameters are estimated by using standard procedures of Excel, Beacon, Erba diagnostics estimating kits. Total Protein, Serum Albumin, Serum Urea, Serum Creatinine, Hemoglobin (Hb) and Lipid Profile (HDL, LDL, VLDL, TG and Total Cholesterol) [16].

Estimation of Antioxidant Activity [17, 18, 19].

Livers of the animals were homogenized with ice-chilled 10% Phosphate buffer and centrifuge at 2000 rpm to 10 minutes. The supernatant liquid is used for the estimation of following parameters. Superoxide Dismutase, Thiobarbituric Acid Reactive Substances (TBARS) and Glutathione.

Statistical analysis

The values are expressed as Mean \pm SEM. The data was analysed by using one way ANOVA followed by Dunnett's test using Graph pad prism software. Statistical significance was set at $P \leq 0.05$.

RESULTS

Extraction

Extraction of grains of *Echinochloa frumentacea* Link was carried out by using the Soxhlet apparatus with 70% of hydro-alcoholic solvent. The percentage yield of HAEF is 3%.

Preliminary Qualitative Phytochemical Analysis

Preliminary qualitative phytochemical studies of 70% (v/v) hydro-alcoholic extract of *Echinochloa frumentacea* grains revealed that the presence of alkaloids, glycosides, carbohydrates, flavonoids, phytosterols/terpenes, proteins, tannins and saponins.

Effect of HAEF on Blood Glucose Levels on Single Dose Study in Normal Rats

Hypoglycaemic activity of HAEF was studied on normal rats and the results were tabulated in Table No. 1.

Low dose (200 mg/kg, p.o.) of HAEF did not show significant reduction in blood glucose levels at 1,8,12 hours, but very less significant reduction in blood glucose levels was shown at 2,4 hour ($P < 0.05$). Medium dose of HAEF (400 mg/kg, p.o.) shows a significant action in reducing the blood glucose levels at 1,2,4,8 hours ($P < 0.01$) onset of action is starts from 1 hour after the treatment. But very less significant reduction in blood glucose levels was shown at 12 hour ($P < 0.05$) compared to the normal untreated group. High dose of HAEF (600mg/kg, p.o) shows a significant action in reducing the blood glucose levels starts from the 1st hour ($P < 0.001$) after administration of the extract and it is almost similar reduction in the blood glucose levels compared with a normal untreated group. It reduces maximum blood glucose levels at 12th hour ($P < 0.001$). Glibenclamide showed its effect from 1 hour after treatment. the onset of Glibenclamide starts from 1 hour after the treatment. It reduces maximum blood glucose levels at 12 hours ($P < 0.001$). Glibenclamide significantly reduced the blood glucose levels after treatment in normal rats.

All the blood glucose levels of treated group were compared with the normal control group animals.

Table No.1: Effect of HAEF on Blood Glucose Levels on Single Dose Study in Normal Rats.

Groups	Treatment	Blood Glucose Levels (mg/dl)					
		0	1	2	4	8	12
Group-I	Saline	90.33 ± 3.343	86.67 ± 5.655	92.50 ± 11.19	84.17 ± 5.443	81.83 ± 4.996	95.67 ± 4.499
Group-II	Glibenclamide (5mg/kg)	78.00 ± 1.238	58.50 ± 3.686***	43.83 ± 4.615***	49.33 ± 2.871***	47.50 ± 1.607***	53.33 ± 3.685***
Group-III	HAEF (200mg/kg)	86.67 ± 3.293	74.00 ± 2.955 ^{ns}	67.83 ± 2.574*	69.33 ± 4.185*	72.83 ± 3.506 ^{ns}	78.50 ± 7.818 ^{ns}
Group-IV	HAEF (400mg/kg)	94.00 ± 5.871	68.83± 1.327**	64.83 ± 2.266**	66.17 ± 3.198**	64.17 ± 1.922**	74.33 ± 6.786*
Group-V	HAEF (600mg/kg)	86.33 ± 1.476	63.00 ± 1.770***	58.33 ± 1.726***	59.67 ± 1.745***	58.33 ± 4.047***	60.83 ± 3.429***

Values are Mean ± SEM (n=6) one way ANOVA followed by Dunnett's test. Where, *** P<0.001, ** P<0.01, * P<0.05 and ns represents Not significant. HAEF- Hydro-alcoholic (70%v/v) grains extract of *Echinochloa frumentacea*.

Effect of HAEF on Oral glucose tolerance test normal rats

The effect of HAEF on oral glucose tolerance test was tabulated in the Table. No. 2.

Low dose (200 mg/kg, p.o.) of HAEF did not show significant reduction in blood glucose levels at 30, min and it shows very less significant reduction effect at 60, 90 min (P<0.05) and significant reduction was observed at 120 min (P<0.01). In Medium dose of HAEF (400 mg/kg, p.o.) very significant reduction was observed at 120 min (P<0.001) and significant reduction was observed at 30, 60, 90 min (P<0.01). Significant reduction was more at 120 min when compared with the 30, 60, 90, min. Whereas, high dose of HAEF (600 mg/kg) p.o also show a significant decrease in blood glucose levels, when administered 30 min before glucose loading. It showed a significant activity at the time intervals of 60, 90 and 120 min (P< 0.001) and less significant reduction was observed at 30 min (P< 0.01). High dose of HAEF showed a significant effect (P<0.001) when compared with the other doses of HAEF but medium dose of this extract also showed significant effect at 120 min (P< 0.001) compared with the low dose of HAEF. Glibenclamide showed its potent antidiabetic activity in normal rats it bring backs the elevated blood glucose levels to normal levels compared to normal control group at 120 min (P<0.001). Overall the grains extracts of *Echinochloa frumentacea* have showed a significant decrease in the blood glucose levels when compared with the normal control group rats at time intervals 30, 60, 90 and 120 min.

Table No.2: Effect of HAEF on Blood Glucose Levels on Oral Glucose Tolerance Test in Normal Rats

Groups	Treatment	Blood Glucose Levels (mg/dl) and Time in min				
		0	30	60	90	120
Group-I	Saline + Glucose 2g/kg	94.50 ± 3.658	124.8 ± 6.036	105.7± 2.376	97.50 ± 3.964	91.33 ± 3.383
Group-II	Glibenclamide (5mg/kg) + Glucose 2g/kg	92.67 ± 6.146 ^{ns}	83.83± 4.743***	70.67± 4.356***	60.33 ± 3.018***	54.67±3.509***
Group-III	HAEF (200mg/kg) + Glucose 2g/kg	81.33 ± 2.459 ^{ns}	106.8± 4.020 ^{ns}	87.33± 3.499*	77.17± 6.002*	71.83± 2.676**
Group-IV	HAEF (400mg/kg) + Glucose 2g/kg	86.33 ± 4.137 ^{ns}	93.33± 5.931**	81.67± 5.690**	70.67± 6.500**	64.67± 5.560***
Group-V	HAEF (600mg/kg) + Glucose 2g/kg	90.50 ± 8.605 ^{ns}	92.50± 6.490**	75.00± 6.583***	66.67± 5.038***	60.17± 4.983***

Values are Mean ± SEM (n=6) one way ANOVA followed by Dunnett's test. Where, *** P<0.001, ** P<0.01, * P<0.05 and ns represents Not significant. HAEF- Hydro-alcoholic (70%v/v) grains extract of *Echinochloa frumentacea*.

Effect of HAEF on Blood Glucose Levels on Oral Glucose Tolerance Test in ALX Induced Diabetic Rats

Oral glucose tolerance test in alloxan induced diabetic rats was carried out and its results shown in the Table No.3.

Hydro-alcoholic (70%v/v) grains extract of *Echinochloa frumentacea* significantly decreased the level of serum glucose from 30 minute to 120 minute. Low dose (200 mg/kg, p.o.) of HAEF significantly reduced blood glucose level ***P <0.001 from 30 minute to 120 minute compared with the diabetic control group. Medium dose of HAEF (400 mg/kg, p.o.) significantly reduced blood glucose level significantly at 30, 60, 90, 120 minute ***P <0.001. High dose of HAEF (600 mg/kg) p.o. very significantly reduced blood glucose level at 30 to 120 minute ***P <0.001. Glibenclamide showed its antidiabetic property and increased glucose tolerance in diabetic rats. In reduced the blood glucose level significantly after 30 minute of glucose load ***P<0.001 compared to the diabetic control.

Table No.3: Effect of HAEF on Blood Glucose Levels on Oral Glucose Tolerance Test in ALX Induced Diabetic Rats

Groups	Treatment	Blood Glucose Levels (mg/dl)				
		0 min	30 min	60 min	90 min	120 min
Group-I	Saline + Glucose 3g/kg	77.33 ± 2.90	139.80 ± 9.99***	148.20 ± 10.38 ***	101.20 ± 4.00 ***	87.17 ± 3.21***
Group-II	ALX (120mg/kg) + Saline + Glucose 3g/kg	319.00 ± 10.34	393.00 ± 23.43	368.70 ± 15.53	346.50 ± 14.06	334.00 ± 11.41
Group-III	ALX (120mg/kg) + Glibenclamide (5mg/kg) + Glucose 3g/kg	174.70 ± 15.26	239.80 ± 9.14***	167.50 ± 9.70***	134.80 ± 5.69***	115.70 ± 3.28***
Group-IV	ALX(120mg/kg) + HAEF(200mg/kg) + Glucose 3g/kg	239.30 ± 22.11	314.70 ± 15.25***	262.30 ± 8.09***	233.80 ± 10.04***	184.80 ± 11.69***
Group-V	ALX(120mg/kg) + HAEF(400mg/kg) + Glucose 3g/kg	185.30 ± 11.66	262.00 ± 11.66***	238.50 ± 13.23***	203.70 ± 8.17***	162.70 ± 10.92***
Group-VI	ALX(120mg/kg) + HAEF(600mg/kg) + Glucose 3g/kg	182.50 ± 9.34	254.70 ± 7.50***	200.20 ± 6.03***	160.00 ± 7.35***	120.80 ± 6.02***

Values are Mean ± SEM (n=6) one way ANOVA followed by Dunnett's test. Where, *** P<0.001, ** P<0.01, * P<0.05 and ns represents Not significant. All the values are compared with the diabetic control group. HAEF-Hydro-alcoholic (70%v/v) grains extract of *Echinochloa frumentacea*.

Effect of HAEF on Blood Glucose Levels in ALX Induced Diabetic Rats

A chronic study of 21days was done in ALX induced diabetic rats with grains extract of *Echinochloa frumentacea* and the results of blood glucose levels are tabulated in the Table No. 4.

Blood glucose levels on day zero showed no significant intra group variation. Administration of ALX (120mg/kg, i.p.) showed a significant increase in fasting blood glucose levels (415.0 ± 20.16mg/dl). After 21 days, diabetic control rats exhibited significantly higher blood glucose levels (324.20 ± 19.170mg/dl) as compared to the normal control rats (83.83 ± 8.526). A daily treatment of HAEF (200mg/kg, p.o.) for a period of 21 days lowered the blood glucose levels in diabetic treated rats. Blood glucose levels on 21 days lowered the blood glucose levels from 398.0 ± 29.19 to 174.50 ± 15.840(P<0.001). Which is less significant reduce in blood glucose levels when compared with the medium, high dose of HAEF groups. Similarly diabetic rats treated with the medium dose of HAEF (400mg/kg, p.o.) also showed a significant activity when compared with the high dose 600mg/kg p.o treated group at 7th day to 21st day, (309.2 ± 527 to 121.80 ± 8.635 mg/dl) (P<0.001). Overall the HAEF 600mg/kg p.o showed a significant decrease in the blood glucose levels when compared with the normal control and 200 and 400 mg/kg groups at day intervals day 7, 14, 21 (P<0.001). Glibenclamide showed its potent antidiabetic activity and reduced the blood glucose levels of diabetic rats to the level significantly (383.5 ± 20.04 to 104.70 ± 4.917mg/dl).

Table No.4: Effect of HAEF on Blood Glucose Levels in ALX Induced Diabetic Rats

Groups	Treatment	Blood Glucose Levels (mg/dl)			
		0 day	7 day	14 day	21 day
Group-I	Saline	90.50 ± 3.294	78.00 ± 3.152***	77.170± 4.118**	83.83 ± 8.526***
Group-II	ALX (120mg/kg) + Saline	415.0 ± 20.16	411.00 ± 16.780	362.80 ± 17.020	324.200 ± 19.170
Group-III	ALX (120mg/kg) + Glibenclamide (5mg/kg)	383.5 ± 20.04	290.30 ± 15.600***	199.20 ± 11.650***	104.70 ± 4.917***
Group-IV	ALX (120mg/kg) + HAEF (200mg/kg)	398.0 ± 29.19	350.30 ± 20.510 ^{ns}	265.20 ± 27.680**	174.50 ± 15.840***
Group-V	ALX (120mg/kg) + HAEF (400mg/kg)	400.2± 16.41	327.80 ± 23.680**	257.30 ± 18.450***	146.20 ± 14.620***
Group-VI	ALX (120mg/kg) + HAEF(600mg/kg)	407.0± 22.55	309.2 ± 527***	210.50 ± 13.000***	121.80 ± 8.635***

Values are Mean ± SEM (n=6) one way ANOVA followed by Dunnett's test. Where, *** P<0.001, ** P<0.01, * P<0.05 and ns represents Not significant. All the values are compared with the diabetic control group. HAEF-Hydro-alcoholic (70%v/v) grains extract of *Echinochloa frumentacea*.

Effect of HAEF on body weight in ALX induced diabetic rats

There is a significant change seen in the body weight of animals after the treatment inducing diabetes with ALX. The decreased body weight of the animals were significantly regains when compare with the diabetic control animals after treatment for 21 days with the extract. And also the body weight of normal control group was significantly increased compared to initial body weight. The changes in body weight of the animals during 0, 7, 14 and 21 days was tabulated in the Table No. 5.

Table No. 5: Effect of HAEF on Body Weight in ALX Induced Diabetic Rats

Groups	Treatment	Body Weight (gms)			
		0 Day	7 Day	14 Day	21 Day
Group-I	Saline	203.8 ± 5.108	210.2 ± 4.498***	213.0 ±5.398***	217.8 ± 4.826***
Group-II	ALX (120mg/kg) + Saline	189.2 ± 5.455	152.5 ± 4.241	151.5 ± 3.253	146.7 ± 1.282
Group-III	ALX (120mg/kg) + Glibenclamide (5mg/kg)	184.0 ± 4.091	182.0 ± 4.131***	187.7 ± 4.93***	191.7 ± 4.937***
Group-IV	ALX (120mg/kg) + HAEF (200mg/kg)	182.0 ± 5.854	170.5 ± 4.794 ^{ns}	178.2 ± 4.037**	179.5 ± 4.006***
Group-V	ALX (120mg/kg) + HAEF (400mg/kg)	184.5 ± 5.50	173.3 ± 1.667*	184.7 ± 5.51***	189.5 ± 5.971***
Group-VI	ALX (120mg/kg) + HAEF(600mg/kg)	189.2 ± 8.455	179.5 ± 8.032**	188.2 ± 7.93***	194.0 ± 8.779***

Values are Mean ± SEM (n=6) one way ANOVA followed by Dunnett's test. Where, *** P<0.001, ** P<0.01, * P<0.05 and ns represents Not significant. All values are compared with diabetic control. All the values are compared with the diabetic control group. HAEF- Hydro-alcoholic (70%v/v) grains extract of *Echinochloa frumentacea*.

Effect of HAEF on Pancreas, Liver, Heart, Kidney and Spleen Weights in ALX Induced Diabetic Rats

Weights of different organs like Pancreas, Liver, Heart, Kidneys and Spleen were observed in ALX induced diabetic rats. The weights of these organs were increased slightly in ALX control group compared to normal control group, and group of 200mg/kg, p.o HAEF did not show any effect where as groups of 400mg/kg and 600mg/kg, p.o HAEF showed slight increased in organ weights were significantly compared to ALX control group. The values of these weights were tabulated in Table No.6.

Table No. 6: Effect of HAEF on Pancreas, Liver, Heart, Kidney and Spleen Weights in ALX Induced Diabetic Rats

Groups	Treatment	Organ Weights (gms)				
		Pancreas	Liver	Heart	Kidney	Spleen
Group-I	Saline	0.863 ±	6.373 ±	0.741 ±	1.618 ±	0.870 ±
		0.079***	0.19***	0.028***	0.067***	0.04***
Group-II	ALX (120mg/kg) + Saline	0.425 ± 0.024	4.298 ± 0.163	0.491 ± 0.023	1.092 ± 0.046	0.366 ± 0.036
Group-III	ALX (120mg/kg) + Glibenclamide (5mg/kg)	0.838 ±	6.157 ±	0.706 ±	1.525 ±	0.850 ±
		0.063***	0.22***	0.033***	0.046***	0.03***
Group-IV	ALX (120mg/kg) + HAEF (200mg/kg)	0.635 ±	5.233 ±	0.628 ±	1.433 ±	0.715 ±
		0.060 ^{ns}	0.331 ^{ns}	0.023*	0.05**	0.079*
Group-V	ALX (120mg/kg) + HAEF (400mg/kg)	0.756 ±	5.585 ±	0.661 ±	1.443 ±	0.726 ±
		0.05**	0.313**	0.043**	0.07**	0.123**
Group-VI	ALX (120mg/kg) + HAEF(600mg/kg)	0.798 ±	6.025 ±	0.703 ±	1.512 ±	0.833 ±
		0.078**	0.251***	0.023***	0.104***	0.086***

Values are Mean ± SEM (n=6) one way ANOVA followed by Dunnett's test. Where, *** P<0.001, ** P<0.01, * P<0.05 and ns represents Not significant. All the values are compared with the diabetic control group.

Effect of HAEF on Serum Albumin, Serum Urea, Serum Creatinine, Serum Total Protein, and Haemoglobin Levels in ALX Induced Diabetic Rats

Serum albumin levels were decreased in the diabetic animals, as compared with the normal control animals. Whereas albumin levels in the diabetic control group is 2.970 ± 0.1042 mg/dl. But albumin levels after treatment with the *Echinochloa frumentacea* Grains extract shows an increased the serum albumin levels. The values of the albumin levels are mentioned in the Table No.7.

Diabetic rats showed an increased in the levels of serum urea. Treatment of these rats with the extract and glibenclamide showed a decrease in the urea levels when compared with the normal animals. The urea levels in the diabetic rats are 110.8 ± 14.99 mg/dl, where it is decrease to 56.94 ± 5.048 mg/dl in treated group and 53.89 ± 3.368 mg/dl in glibenclamide treated rats. Serum Urea levels of treated and Normal rats are expressed in the Table No.7.

Diabetic rats showed an increased in the levels of serum creatinine. Treatment of these rats with the extract and glibenclamide showed a decrease in the creatinine levels when compared with the normal animals. The creatinine levels in the diabetic rats are 1.062 ± 0.0705 mg/dl, where it is decrease 0.6590 ± 0.04749 mg/dl in treated group and 0.6517 ± 0.03454 mg/dl in glibenclamide treated rats. Serum creatinine levels of treated and Normal rats are expressed in the Table No.7.

Serum protein levels are decreased (4.745 ± 0.227 mg/dl) in the untreated diabetic rats compares to the normal control rats (9.163 ± 0.4522 mg/dl). After treatment with the Glibenclamide, 400mg/kg, 600mg/kg p.o dose of HAEF shown a significant increase in the serum protein levels compared with the diabetic control animals. Low dose of HAEF showed a less significant activity in increasing the protein levels. The values of serum total protein levels are shown in the Table No.7.

A daily dose of the HAEF for a period of 21 days showed an increased in the haemoglobin level of diabetic rats. But the low dose of HAEF showed a less significant activity when compared with the diabetic control rats. Glibenclamide restores the haemoglobin levels to normal levels after treatment. The values were tabulated in the Table No.7.

Table No. 7: Effect of HAEF on Serum Albumin, Serum Urea, Serum Creatinine, Serum Total Protein, and Haemoglobin Levels in ALX Induced Diabetic Rats

Groups	Treatment	Serum Albumin Levels (g/dl)	Serum Urea Levels (mg/dl)	Serum Creatinine Levels (mg/dl)	Serum Total Protein Levels (mg/dl)	Haemoglobin (mg/dl)
Group-I	Saline	5.145 ± 0.2042***	45.18 ± 1.738***	0.6493 ± 0.01949***	9.163 ± 0.4522***	12.48 ± 0.240***
Group-II	ALX (120mg/kg) + Saline	2.970 ± 0.1042	110.8 ± 14.99	1.062 ± 0.0705	4.745 ± 0.227	7.783 ± 0.8735
Group-III	ALX (120mg/kg) + Glibenclamide (5mg/kg)	5.043 ± 0.1944***	53.89 ± 3.368***	0.6517 ± 0.03454***	8.997 ± 0.3723***	12.13 ± 0.460***
Group-IV	ALX (120mg/kg) + HAEF (200mg/kg)	3.970 ± 0.2849**	68.61 ± 8.831**	0.8003 ± 0.04784**	7.568 ± 0.7016*	10.82 ± 0.444**
Group-V	ALX (120mg/kg) + HAEF (400mg/kg)	4.658 ± 0.2034***	60.16 ± 8.819***	0.6687 ± 0.03426***	8.263 ± 1.243**	11.25 ± 0.444***
Group- VI	ALX (120mg/kg) + HAEF(600mg/kg)	5.027 ± 0.2384***	56.94 ± 5.048***	0.6590 ± 0.04749***	8.918 ± 0.4612***	12.08 ± 0.583***

Values are Mean ± SEM (n=6) one way ANOVA followed by Dunnett's test. Where, *** P<0.001, ** P<0.01, * P<0.05 and ns represents Not significant. All the values are compared with the diabetic control group

Effect of HAEF on Serum Lipid Profile of ALX Induced Diabetic Rats

The lipid profile was evaluated by estimating triglycerides (TG), total cholesterol (TC), HDL-Cholesterol (HDL-C), LDL-Cholesterol (LDL-C), VLDL-Cholesterol (VLDL-C) in normal and diabetic animals. The ALX diabetic animals showed a significant increased in the TG, TC, LDL-C and VLDL-C levels and suppression of HDL-C levels compared to control group (Table No.8). But after treatment with the grains extracts and glibenclamide diabetic animals Showed decrease in the TG, TC, LDL-C and VLDL-C levels and increase in the HDL-C levels compared to untreated diabetic rat.

Table No. 8: Effect of HAEF on Serum Lipid Profile of ALX Induced Diabetic Rats

Groups	Treatment	Serum Lipid Profile mg/dl				
		TC	TG	HDL-C	LDL-C	VLDL-C
Group-I	Saline	86.03 ± 4.17***	71.33 ± 3.64***	26.53 ± 0.76***	45.21 ± 5.00***	14.25 ± 0.72***
Group-II	ALX (120mg/kg) + Saline	125.8 ± 3.567	127.9 ± 3.691	14.25 ± 0.9412	85.96 ± 4.026	25.58 ± 0.7379
Group-III	ALX (120mg/kg) + Glibenclamide (5mg/kg)	94.53 ± 2.53***	80.57 ± 6.56***	24.74 ± 1.05***	53.69 ± 4.08***	16.11 ± 1.31***
Group-IV	ALX (120mg/kg) + HAEF (200mg/kg)	100.4 ± 3.029**	95.21 ± 5.17***	19.69 ± 1.646*	61.72 ± 4.644*	19.04 ± 1.03***
Group-V	ALX (120mg/kg) + HAEF (400mg/kg)	98.51 ± 8.19***	87.74 ± 5.70***	21.62 ± 1.516**	59.35 ± 8.833**	17.54 ± 1.14***
Group- VI	ALX (120mg/kg) + HAEF(600mg/kg)	95.33 ± 1.49***	82.79 ± 7.02***	23.32 ± 1.97***	54.90 ± 2.14***	16.55 ± 1.40***

Values are Mean ± SEM (n=6) one way ANOVA followed by Dunnett's test. Where, *** P<0.001, ** P<0.01, * P<0.05 and ns represents Not significant. All the values are compared with the diabetic control group

Effect of HAEF on SOD, TBARS, GSH in ALX Induced Diabetic Rats

Diabetic rats exhibited significant lower SOD (7.020 ± 0.491) as compared to those of control rats (15.07 ± 0.631) treatment with the plant extracts significantly elevated the reduced SOD levels. HAEF and Glibenclamide showed a marked increase in the SOD levels ($P < 0.001$) compared to the diabetic control. These values are tabulated in the Table No.9.

Rats treated with ALX had a TBARS level of 3.640 ± 0.145 nmoles of MDA/ 100 mg of tissue when measured on day 21. This was significantly higher when compared to levels in normal control rats of 1.079 ± 0.094 nmoles of MDA/ 100 mg of tissue.

Diabetic rats treated with 200mg/kg, p.o. had a lipid peroxidation levels of 2.146 ± 0.937 nmoles of MDA/ 100 mg of tissue and also rats treated with the 400mg/kg, o.p. and 600mg/kg, p.o. treated rats having a TBARS levels of 1.52 ± 0.17 and 1.390 ± 0.064 nmoles of MDA/ 100 mg of tissue respectively. Whereas in glibenclamide treated rats the levels are restored to normal levels of 1.278 ± 0.051 nmoles of MDA/ 100 mg of tissue. These values are expressed in Table No.9.

Rats treated with ALX had a tissue GSH level of 26.38 ± 1.288 mM/ 100 mg of tissue when measured on day 21. Treatment with HAEF shows increase GSH levels in ALX treated rats. These values are having a significant higher ($P < 0.001$) when compared to GSH levels in diabetic control rats. The values are tabulated in the Table No. 9.

Table No 9: Effect of HAEF on SOD, TBARS, GSH in ALX Induced Diabetic Rats

Groups	Treatment	SOD U/mg Protein	TBARS (nmoles of MDA/ 100 mg of tissue)	GSH (mM/ 100 mg of tissue)
Group-I	Saline	$15.07 \pm 0.631^{***}$	$1.079 \pm 0.094^{***}$	$42.63 \pm 1.915^{***}$
Group-II	ALX (120mg/kg) + Saline	7.020 ± 0.491	3.640 ± 0.145	26.38 ± 1.288
Group-III	ALX (120mg/kg) + Glibenclamide (5mg/kg)	$14.32 \pm 0.755^{***}$	$1.278 \pm 0.051^{***}$	$40.85 \pm 1.153^{***}$
Group-IV	ALX (120mg/kg) + HAEF (200mg/kg)	$11.86 \pm 0.697^{***}$	$2.146 \pm 0.937^{***}$	$36.47 \pm 1.321^{****}$
Group-V	ALX (120mg/kg) + HAEF (400mg/kg)	$13.62 \pm 0.574^{***}$	$1.806 \pm 0.565^{***}$	$38.99 \pm 1.162^{***}$
Group- VI	ALX (120mg/kg) + HAEF(600mg/kg)	$14.14 \pm 0.694^{***}$	$1.390 \pm 0.064^{***}$	$39.99 \pm 0.739^{***}$

Values are Mean \pm SEM (n=6) one way ANOVA followed by Dunnett's test. Where, *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$ and ns represents Not significant. All the values are compared with the diabetic control group.

Histopathological Study of Pancreas**Group –I (Normal Control + Saline)**

Section studied shows pancreatic lobules separated by connective tissue septa. The pancreatic lobules consist largely of the exocrine acini and their intralobular ducts. Most of the lobules show small, round, light-staining islets of langerhans. The center of islet cells consist of aggregates of small Beta-cells (70%, Short-arrow), while the periphery comprises of large Alpha-cells (25%, Long-arrow). Intervening these cells are seen thin walled capillaries.

Group –II (Diabetic Control + Alloxan [120mg/kg])

Section studied shows pancreatic lobules separated by connective tissue septa. The number of islets appears reduced in number. The center of islet cells consist of quantitative decrease in Beta-cells (30%, Long-arrow) having basophilic granules, while the periphery comprises of large Alpha-cells (65%, Short-arrow) having eosinophilic granules. Also seen are some degenerated beta cells and lymphocytic infiltration amidst these islet cells.

Group –III (Alloxan [120mg/kg] + Glibenclamide [5mg/kg])

Section studied shows pancreatic lobules separated by connective tissue septa. Most of the lobules show areas of light-staining islets of langerhans. The center of islet cells consist of quantitative increase in Beta-cells

[compared to Diabetes control] (65%, Long-arrow), while the periphery comprises of Alpha-cells (30%, Short-arrow). Also seen are few congested vascular spaces amidst these cells.

Group – IV (Alloxan [120mg/kg] + HAEF [200mg/kg])

Section studied shows pancreatic lobules separated by thin fibrovascular septa. The center of islet cells consist of quantitative decrease in Beta-cells [compared to positive control] (30%, Short-arrow), while the periphery comprises of Alpha-cells (65%, Long-arrow). Also seen are few degenerated beta cells.

Group – V (Alloxan [120mg/kg] + HAEF [400mg/kg])

Section studied shows pancreatic lobules separated by thin connective tissue septa. The center of islet cells consists of quantitative increase in Beta-cells [compared to positive control] (60%, Long-arrow), while the periphery comprises of Alpha-cells (35%, Short-arrow). There are seen few vascular spaces amidst these islet cells.

Group – VI (Alloxan [120mg/kg] + HAEF [600mg/kg])

Section studied shows pancreatic lobules separated by thin connective tissue septa. The center of islet cells consists of quantitative increase in Beta-cells [compared to positive control] (70%, Long-arrow), while the periphery comprises of Alpha-cells (25%, Short-arrow).

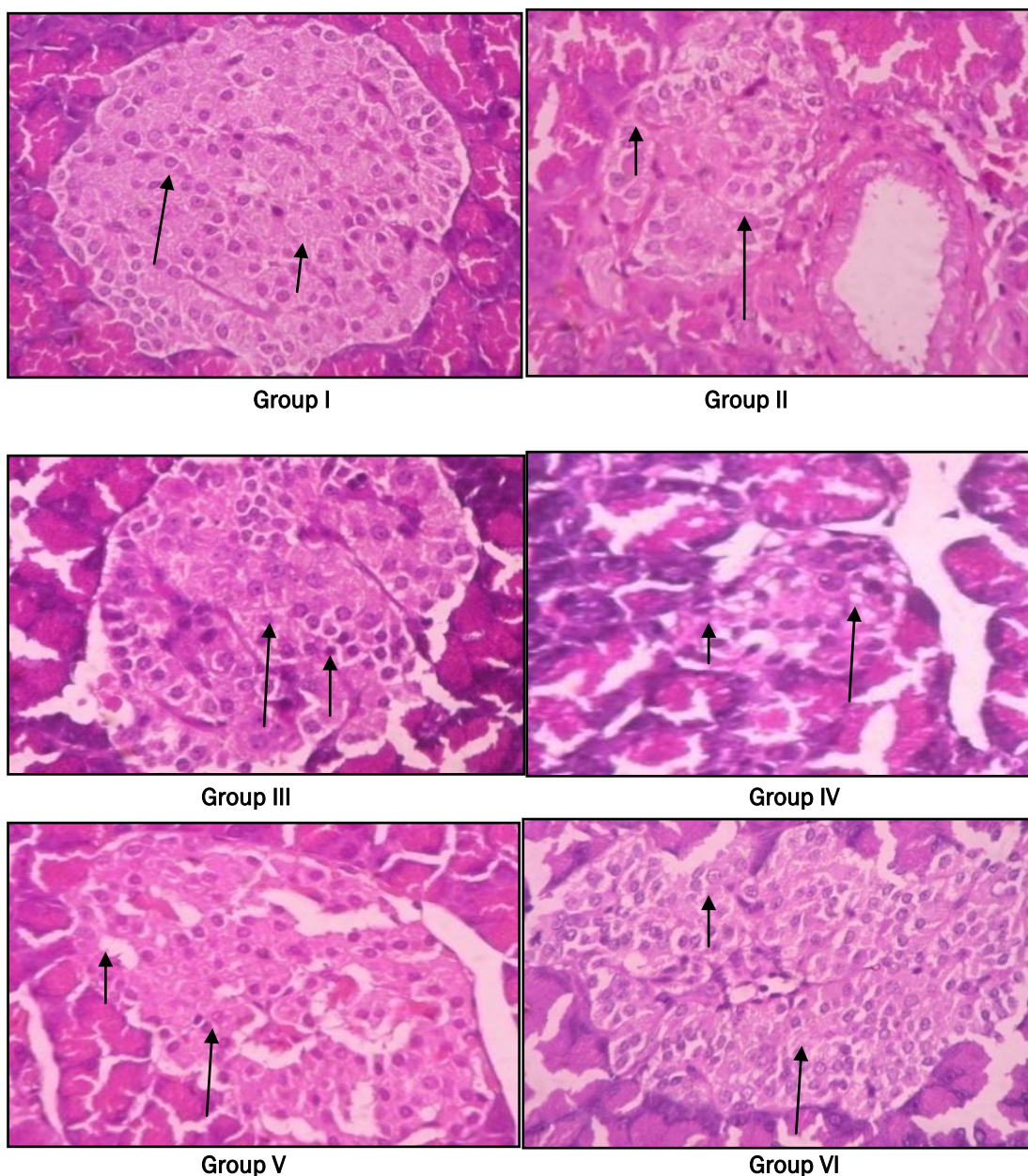


Figure No 1: Histopathology of Pancreas

DISCUSSION

Single dose study for 12 hours was carried out in normoglycemic rats. High dose of HAEF (600 mg/kg, p.o.) showed maximum decrease in blood glucose levels at 12th hour compared to normal group. High dose of HAEF also showed a significant decrease from the 1st hour of the drug administration. Medium dose of HAEF showed a significant decrease in blood glucose level at 2nd hour compared to normal levels. It also showed its activity at 12th hour after the drug administration when compared with the normal control. Low dose shown less significant compared with medium and high dose of HAEF. Glibenclamide (5mg/kg, p.o.) showed a maximum decrease of blood glucose levels in normoglycemic rats at 12th hr of our study. It may produce hypoglycemia in normal animals by stimulating the pancreatic beta-cells to produce more insulin and by increasing the glycogen deposition in the liver [12].

Oral glucose tolerance test was studied on the normal rats. The lowering of glucose can be seen well in assay of glucose tolerance [20]. The fasting blood glucose levels decreases in glibenclamide, along with HAEF high dose and medium dose treated rats. Low dose shows reduced activity at 150 min. Such a phenomenon was already seen in the indigenous plants and reported. The lowering of glucose levels is may be due to the inhibition of intestinal absorption, or it may act by potentiating the secretion of insulin and by increase in the utilization of glucose levels in muscles [21].

Oral glucose tolerance test was performed on normal rats and ALX induced diabetic rats. High dose (600 mg/kg, p.o.) and medium dose of HAEF (400 mg/kg, p.o.) showed maximum tolerance of glucose at 120 minute significantly as compared to the diabetic control. Low dose shown less significant compared with medium and high dose of HAEF. The results showed that the extract increased the glucose tolerance in normal rats, ALX induced diabetic rats.

A dose of 200, 400 and 600 mg/kg, p.o. body weight of HAEF is administered for a period of 21 days in ALX treated rats. HAEF showed a significant reduction in the blood glucose levels than the control group rats. This hypoglycemic activity may be due to the stimulation of surviving β -cells to release more insulin. *Echinochloa frumentacea* may act by inhibiting hepatic gluconeogenesis or inhibiting α -glucosidase enzyme in the intestine, which is the enzyme helpful for breakdown of disaccharides to form glucose [22].

Induction of diabetes with ALX is associated with a characteristic decrease in body weight than the normal rats, this may be due to the wasting and loss of tissue protein. Whereas, diabetic rats treated with 200, 400 and 600mg/kg, p.o. of HAEF showed an improved result when compared with normal diabetic control. Which may be due to the protective effect in controlling muscle wasting i.e., reversal of gluconeogenesis and may also be due to the improvement of glycemic control [23].

A decrease in the pancreas, liver, heart, kidneys and spleen weight was observed in diabetic animals. After 21 days of *Echinochloa frumentacea* in diabetic animals, an increased in the pancreas, liver, heart, kidneys, spleen weight is observed than the untreated rats. Whereas, low dose of HAEF did not show significant activity in organs weight.

A marked reduction in the levels of total protein and albumin levels was observed in the diabetic rats. The decrease in the albumin levels may be due to the increased protein catabolism. Present study showed that the treatment of diabetic rats with the 400mg/kg and 600mg/kg p.o dose of HAEF and glibenclamide showed increased albumin levels and protein levels significantly.

An enhanced increase in plasma serum creatinine, serum urea levels were found in the diabetic rats when compared with the respective control group rats. While after the treatment with HAEF levels were significantly decreased.

In the present study, the groups of normal rats have shown gain in the body weight while fasting serum glucose was maintained in the normal range throughout the study period. The serum cholesterol and serum triglyceride levels of the normal rats were found to be increasing within the normal range during the four weeks of study period and the haemoglobin levels was also found to be maintained within the normal range throughout the study period.

The haemoglobin levels of the diabetic group of rats were found to be reduced significantly as against the normal haemoglobin levels of the normal group of rats, this is due to an increased formation of its glycosylated form. During hyperglycaemic condition protein synthesis is attenuated or reduced in all the tissues and thus the synthesis of haemoglobin also reduced [24].

Under normal condition, insulin activates enzyme lipoprotein lipase and hydrolyses triglycerides. Insulin deficiency results in failure to activate the enzymes there by causing hypertriglyceridemia [25]. This altered lipid

metabolism leads to diabetic complications. Practically it has been observed that there is an altered in levels of serum cholesterol and triglycerides levels in ALX treated rats, causes hypercholesterolemia and hypertriglyceridemia [22]. Diabetic rats treated with the medium, high dose of (400 and 600mg/kg, p.o.) HAEF and glibenclamide has shown a significant decrease in the levels of TG, TC, LDL-C and VLDL-C, where as it increases the levels of HDL-C when compared to the normal diabetic control rats. In low dose of HAEF treated rats HDL-C levels is less significant.

Diabetic rats treated with glibenclamide (5 mg/kg, p.o.) showed significant protection from the body weight loss and progressive reduction of 67.8% in fasting serum glucose levels after a daily dose for 21 days. The glibenclamide treatment also showed the reduced elevated serum cholesterol, albumin, creatinine, total protein and urea levels produced significant reduction in elevated serum triglyceride and allowed significant recovery of reduced haemoglobin content during the period of study when compared with the diabetic group of rats. In agreement with the present results, several studies have shown protection in body weight loss [26], anti-diabetic activity, reduction in serum cholesterol and serum triglyceride [24], and recovery in haemoglobin content [27].

Superoxide dismutase is an enzymatic antioxidant which reduces superoxide radical to hydrogen peroxide and oxygen. A decrease in the antioxidant activity in liver results in the accumulation of free radicals (hydroxyl radical) in diabetic rats. Administration of the high dose, medium dose, low dose of HAEF (200, 400 and 600 mg/kg, p.o.) and glibenclamide increased the activity of SOD levels to a significant level of $P < 0.001$. While the SOD levels of untreated diabetic control rats having lowered levels. The *Echinochloa frumentacea* may act by either directly scavenging the reactive oxygen metabolites or by increasing the anti-oxidant molecules.

In diabetes, lipid peroxidation is one of the characteristic features of chronic diabetes. The increased free radicals react with the polyunsaturated fatty acids in cell membrane leading to lipid peroxidation. This in turn results in the development of free radicals. Low levels of lipoygenase peroxides stimulate the release of insulin. But, if the concentration of this peroxidase increases it results in uncontrolled release of lipid peroxidation. The most commonly used indicator of lipid peroxidation is TBARS. There was a significant elevation of TBARS in liver tissue in diabetic control animals when compared to the normal rats. Administration of high dose, medium dose, low dose of HAEF (200, 400 and 600 mg/kg, p.o.) and glibenclamide significantly reduce the TBARS levels. The effect shown is may be due to prevention of potential glycation of anti-oxidant enzymes.

Glutathione which is a tripeptide normally present at high concentrations intracellularly. Glutathione is helpful for reducing the toxic effects of lipid peroxidation. Decreased level of GSH in liver during diabetes represents its increased utilization due to oxidative stress. Significant increased levels of GSH were shown in the diabetic rats treated with the high dose, medium dose, low dose of HAEF (200, 400 and 600 mg/kg, p.o.) and glibenclamide.

The histological evidence showed in the authenticated injury caused by ALX and the protection offered by HAEF and glibenclamide in pancreatic cells were shown. Microscopically examination revealed loss of architecture and cell necrosis with inflammatory collections in the central zone in ALX induced rats (Figure No. 1) Histopathological study showed that *Echinochloa frumentacea* has the capacity to increase islet cell mass. However, the expansion was better with medium, high dose of HAEF dose.

CONCLUSION

In the present study indicate that hydro-alcoholic grains extract of *Echinochloa frumentacea* link. at the doses 200, 400 and 600mg/kg, p.o. posses significant hypoglycemic activity against ALX induced diabetic rats. 200mg/kg, p.o. of HAEF showed very less effect than the 400 and 600mg/kg, p.o. both reduced the blood glucose levels in diabetic induced rats. The acute toxicity study indicated that the HAEF was devoid of major toxic effects. The effect of HAEF in normal rats and glucose loaded rats also indicated that the HAEF exhibited better glycemic control compared with the normal control animals, besides the drug treated (ALX induced, i.p.) diabetic rats showed a significant reduction in blood glucose levels and the other serum biomarker levels and also increases the haemoglobin levels. HAEF also exhibited antioxidant activity in diabetic rats.

The reports of histopathology study concluded there is an increased mass of β -cells in the pancreatic islets. The results showed in HAEF 600mg/kg, p.o having a more similar to glibenclamide treated group which was used as reference standard. Overall observed significant activity may be due to presence of active constituents present in extract of *Echinochloa frumentacea* grains.

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