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EFFECT OF *CASSIA AURICULATA* FLOWERS, LEVES AND SEEDS DOSE DEPENDENT STUDY IN STREPTOZOTOCIN - INDUCED DIABETIC RATS.

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Abstract
Diabetes is a major health problem affecting major populations worldwide. *Cassia auriculata* L. (Ceasalpiniaceae) has been used traditionally as antidiabetic and has been proven scientifically to possess high antioxidant activity and anticancer properties. *Cassia auriculata* L. is a shrub that has attractive yellow flowers, commonly used for the treatment of skin disorders and body odour. It is a native plant present in different parts of India. Indigenous people use various parts of the plant for diabetes mellitus. Streptozotocin (STZ)-nicotinamide type 2 model shares a number of features with human type 2 diabetes and is characterized by moderate stable hyperglycemia, glucose intolerance, altered but significant glucose-stimulated insulin secretion, *in vivo* and *in vitro.* Oral administration of *Cassia auriculta* flower extract (CFEt), leaf extract (CLEt) and seed extract (CSEt) at 0.45 mg/kg body weight to diabetic rats for 45 days. In the present study, we have investigated of Tanner's cassia CFEt, CLEt and CSEt on glucose levels were assayed. Our results indicate that administration of CFEt, CLEt and CSEt to diabetic animals normalizes blood glucose and causes marked improvement of altered blood glucose and plasma insulin during diabetes. The CFEt administration showed more effective than CLEt, CSEt and glibenclamide.

Key words: blood glucose, plasma insulin, pancreas, *Cassia auriculata*

Introduction
Type 2 diabetes mellitus (DM) is a chronic metabolic disorder in which prevalence has been increasing steadily all over the world. As a result of this trend, it is fast becoming an epidemic in some countries of the world with the number of people affected expected to double in the next decade due to increase in ageing population, thereby adding to the already existing burden for healthcare providers, especially in poorly developed countries. (WHO, 2006).
Pancreatic β-cell dysfunction and insulin resistance are the two hallmarks of type 2 diabetes mellitus. Treatment of diabetes without any side effects is still a challenge to the medical system.

There is an increasing demand by patients to use the natural products with antidiabetic activity, because insulin and oral hypoglycemic drugs are having so many side effects. STZ - nicotinamide model shares a number of features with human type 2 diabetes. Hence, STZ-nicotina mide induced diabetes model was used in the present study (Murugan and Pari, 2006).

Cassia auriculata L. (Ceasalpiniaceae) is a shrub that has attractive yellow flowers, commonly used for the treatment of skin disorders and body odour. It is a native plant present in different parts of India. Indigenous people use various parts of the plant for diabetes mellitus. It is widely used in Ayurvedic medicine as a "Kalpa drug" which contains five parts of the shrub (roots, leaves, flowers, bark and unripe fruits) which are taken in equal quantity, dried and then powdered to give "Avarai Panchaga Choornam", for the control of sugar levels and reduction of symptoms such as polyuria and thirst in diabetes (Shrotri and Aiman, 1960). A literature survey showed that a decoction of leaves, flowers, and seeds of the *Cassia auriculata* mediate an antidiabetic effect (Shrotri and Aiman, 1960). Thus, the available reports show that very little work has been done with respect to *Cassia auriculata* flowers, other than its hypoglycemic effects (Pari and Murugan, 2007; Murugan, 2010; Murugan, 2015a). In our previous study, we have demonstrated the antidiabetic effect of CFEt in STZ induced diabetic rats (Pari and Latha, 2002; Murugan, 2015b; Murugan, 2015c).

Materials and methods

Chemicals

Stereptozotocin was obtained from Himedia Laboratory Limited, Mumbai, India. All other reagents used were of analytical grade.

Plant Material

Cassia auriculata flowers were collected freshly from Neyveli, Cuddalore District, Tamil Nadu, India. The plant was identified and authenticated at the Herbarium of Botany Directorate in Annamalai University. A voucher specimen (No.231) was deposited in the Botany Department of Annamalai University.

Preparation of plant (Flower, leaves and seeds) extract

Five hundred g of *Cassia auriculata* flowers and leaves were extracted with 1,500 ml of water by the method of continuous hot extraction at 60ºC for six hours and evaporated. The residual extract was dissolved in water and used in the study (Jain, 1968).

Ethanolic extract

500 grams of fresh whole *Cassia auriculata* Seeds cleaned off adhering dust and unwanted plant material, shade dried, cut and pulverized (powdered) were chopped into small pieces soaked overnight in 1.5 litre of 95% ethanol. This suspension was filtered and the residue was resuspended in an equal volume of 95% ethanol for 48 h and filtered again. The two filtrates were pooled and the solvents were evaporated in a rotavapor at 40°-50°C under reduced pressure and lyophilized. A greenish-black material was obtained (20-30 g). It was stored at 0-4°C until used. When needed, the residual extract was suspended in water and used in the study (Hossain et al. 1992).

Induction of diabetes

Non-Insulin dependent diabetes mellitus was induced (Masiello et al. 1998) in overnight fasted rats by a single intraperitonial injection (i.p) of 65 mg/kg body weight STZ, 15 min after the i.p administration of 110 mg/kg body weight of nicotinamide. STZ was dissolved in citrate buffer (pH 4.5) and nicotinamide was dissolved in normal saline. Hyperglycemia was confirmed by the elevated glucose levels in plasma, determined at 72 h and then on day 7 after injection. The animals with blood glucose concentration more than 200 mg/dl will be used for the study.

Dose dependent effect of aqueous, ethanolic extracts of *Cassia auriculata* in STZ-induced diabetic rats

Diabetes was induced to rats with 65 mg/kg body weight STZ, 15 min after the i.p administration of 110 mg/kg body weight of nicotinamide. Rats with blood glucose ranging from 200-300 mg/dl were used for the experiment. Preliminary studies using aqueous (Aq), ethanolic (Alc) extracts of CFEt, CLEt and CSEt was done at four doses viz., 0.15, 0.30, 0.45 and 0.60 g/kg body weight.

Experimental procedure

In the experiment, a total of 36 rats (30 diabetic surviving rats, six normal rats) were used. The rats were divided in to six groups of six rats each.

Group 1: Normal untreated rats.

Group 2: Diabetic control rats given 1 ml of aqueous solution daily using an intragastric tube for 45 days.

Group 3: Diabetic rats given CFEt (0.45 g/kg body weight) in 1 ml of aqueous solution daily using an intragastric tube for 45 days.

Group 4: Diabetic rats given CLEt (0.45 g/kg body weight) in 1 ml of aqueous solution daily using an intragastric tube for 45days.

Group 5: Diabetic rats given CSEt (0.45 g/kg body weight) in 1 ml of ethanolic extract daily using an intragastric tube for 45days.

Group 6: Diabetic rats given glibenclamide (600 µg/ kg body weight) in 1 ml of aqueous solution daily using an intragastric tube for 45days.

Analytical procedure

Measurement of blood glucose and plasma insulin

Blood glucose was estimated colorimetrically using commercial diagnostic kits (Sigma Diagnostics (I) Pvt Ltd, Baroda, India) (John and Lott Turner, 1975). Plasma insulin was assayed by ELISA using a Boehringer-Mannheim kit with an ES300 Boehringer analyzer (Mannheim, Germany).

Histopathological study

The pancreas samples fixed for 48h in 10% formal-saline were dehydrated by passing successfully in different mixture of ethyl alcohol – water, cleaned in xylene and embedded in paraffin. Sections of Pancreas (4-5 µm thick) were prepared and then stained with hematoxylin and eosin dye, which mounted in neutral deparaffinated xylene (DPX) medium for microscopic observations.

Statistical analysis

The data for various biochemical parameters were analyzed using analysis of variance (ANOVA), and the group means were compared by Duncan's multiple range test (DMRT). Values were considered statistically significant if $p < 0.05$ (Duncan, 1957).

Results

Blood glucose

In all groups prior to STZ administration, the basal levels of blood glucose of the rats were not significantly different. However, 48 h after STZ administration, blood glucose levels were significantly higher in rats selected for the study. In contrast, non-diabetic controls remained persistently euglycemic throughout the course of the study.

Table 1 shows the effect of treatment with various extracts of *Cassia auriculata* on blood glucose levels. In all the CFEt, CSEt and CLEt treated groups (all doses), although a significant antihyperglycemic ($p<0.01$) effect was evident from first week onwards, decrease in blood sugar was maximum on completion of the third week (66.5%) ($p<0.001$) in the group receiving 0.45 g/kg body weight of aqueous extract of *Cassia auriculata.* On the other hand, ethanolic extracts treated groups showed an antihyperglycemic effect much later in groups receiving 0.45 mg/kg body weight (60.5 and 56.3% respectively). Although 0.60 mg/kg showed blood glucose lowering activity, the

effect was not significant when compared with 0.45 g/kg body weight of CFEt, CSEt and CLEt (aqueous). On the basis of this study, dose of 0.45 g/kg body weight of aqueous and ethanolic extract of CFEt, CLEt and CSEt was selected for further biochemical evaluation.

In all groups prior to STZ administration, the basal levels of blood glucose of the rats were not significantly different. However, 48 h after STZ - nicotinamide administration, blood glucose levels were significantly higher in rats selected for the study (Table 2). In contrast, non-diabetic controls remained persistently euglycaemic throughout the course of the study.

Table 3 shows the level of blood glucose and plasma insulin of different experimental groups. The diabetic control rats showed a significant increase in the level of blood glucose with significant decrease in the activity of plasma insulin. Oral administration of CFBEt, CLEt, CSEt and glibenclamide to diabetic rats significantly reversed the above biochemical changes. The administration of CFBEt, CLEt, CSEt and glibenclamide to normal rats showed a significant effect on blood glucose and plasma insulin levels. The CFBEt administration showed more effective than CLEt, CSEt and glibenclamide.

Histopathological observations

Pathological changes (Fig.1a) of pancreas include shows atrophic acini, no islet cells in diabetic control rats (Fig. 1b,c). The above pathological changes were reduced in rats treated with CFEt, CLEt and CSEt. Diabetic control rat's pancreas showed Preservation of islet cells with few atrophic acini. These changes were reduced in CFEt, CLEt, CSEt and glibenclamie treated rats (Fig.1d,e,f and g).

Discussion

Diabetes Mellitus is a multi-factorial chronic health condition triggered by several genetic and/or environmental factors (WHO, 2010). Indeed, this pathology is characterized by strong familiarity and the frequency of diabetes varies in different ethnicities, such as black and Hispanic people, and some minorities, like American Indians and Natives of Alaska, are more likely to have diabetes for a specific genetic profile.

The World Health Organization (WHO) Global report on diabetes shows that the number of adults living with diabetes has almost quadrupled since 1980 to 422 million adults and is expected to increase to 693 million by 2045 (WHO, 2010). The disease is characterized by high blood sugar levels, due to a deficiency of concentration and/or of activity of insulin, the pancreatic hormone involved in managing glycaemia (Murugan and Pari, 2005)..

Type 2 diabetes mellitus is a heterogeneous disease, characterized by low blood glucose control (intolerance to glucose) and result either from resistance to glucose in peripheral tissues (skeletal muscle and adipocytes) or relative decrease of β-cell activity. Depending on several factors (obesity, age and onset, severity of glucose intolerance and mode of inheritance), clinical features of individual suffering from type 2 diabetes are highly variable ((Murugan and Pari, 2007).

Global estimates suggest that three fourth of the world population cannot afford the products of allopathic medicine and thus, have to rely upon the use of traditional medicines, which are largely derived from plants (Hu et al. 2003). For the study of antidiabetic agents, STZ-induced hyperglycemia in rodents is considered to be a good preliminary screening diabetic model (Ivorra et al. 1989) and is widely used. STZ is a potent methylating agent for DNA and acts as NO donor in pancreatic cells (Spinas, 1999). The present study was undertaken to assess the antihyperglycemic property of *Cassia auriculata*, which has been reported in Ayurveda to be useful in treatment of diabetes mellitus. In the present study, treatment with aqueous, ethanolic and chloroform extracts of *Cassia auriculata*, showed significant antihyperglycemic activity. The maximum reduction in glucose levels was seen in groups receiving 0.45 g/kg of the three extracts respectively. This is probably indicative efficacy of the plant. CFEt, CLEt and CSEt at 0.60 g/kg caused a significant decrease of the glycemia however, in these cases dose-dependence of the extract was not apparent. It is likely that the higher doses could not produce the expected higher antihyperglycemic effect by

the presence of some other substances in the extract, which interfere with the antihyperglycemic activity.

In order to find the efficacy of *Cassia auriculata* on long-term administration, the treatment period was extended upto 6 weeks. The antihyperglycemic action exhibited at 0.45 g/kg body weight might have been in part due to protection of β-cells against the cytotoxic action of STZ and/or more insulin release from the surviving β-cell mass. Since plasma insulin activity also increased in drug treated group, it is suggestive of insulin secretagogue activity of *Cassia auriculata*. The possible mechanism of action of extract could be correlated with the reminiscent effect of the hypoglycemic sulphonylureas that promote insulin secretion by closure of K^+-ATP channels, membrane depolarization and stimulation of Ca^{2+} influx, an initial key step in insulin secretion. In this context, number of other plants have also been reported to have antihyperglycemic and insulin stimulatory effects (Venkateswaran and Pari, 2002a; Latha and Pari, 2003a; Latha and Pari, 2003b). Like the plant extract, glibenclamide also produced significant reduction in blood glucose levels of STZ diabetic rats. Since STZ is known to destroy pancreatic β-cells, the present findings appear to be in consonance with the earlier suggestion of Jackson and Bressler (1981) that sulphonylureas have extra- pancreatic antihyperglycemic mechanism of action secondary to their insulin secreting effect and the attendant glucose uptake into, and utilization by, the tissues.

In the present investigation, treatment with CFEt, CLEt and CSEt showed significant antihyperglycaemic activity. The maximum reduction in glucose levels was seen in groups receiving 0.45 g/kg of the CFEt, CLEt and CSEt. This is probably indicative of efficacy of the plant. Moreover, it indirectly indicates that part of the antihyperglycaemic activity of this plant is due to release of insulin from the existing β–cells of pancreas. The possible mechanism of action of extract could be correlated with the reminiscent effect of the hypoglycaemic sulphonylureas which promote insulin secretion by closure of K+ - ATP channels, membrane depolarization and stimulation of Ca2+ influx, an initial key step in insulin secretion. In this context a number of other plants have also been reported to have antihyperglycaemic and insulin-release stimulatory effects (Murugan and Pari, 2007, Murugan, 2010).

CFEt, CLEt and CSEt might enhance glucose utilization since it significantly reduces blood glucose in diabetic rats. From the data obtained with the oral glucose tolerance test, it is clear that blood glucose levels reached a peak and returned to near normal values after 120 min in both normal and treated rats (0.45g/kg body weight of CFEt, CLEt and CSEt). Elevated blood glucose levels remained high even after 120 min in diabetic control rats. CFEt, CLEt and CSEt administration effectively prevented the increase in blood glucose without causing a hypoglycemic state, and this effect may be due to the restoration of the delayed insulin response (Murugan, 2015a; Murugan, 2015b; Murugan, 2015c).

Rasch (1980) reported that the rise in body weight was far less in the poorly controlled diabetic rats as compared to well-controlled diabetic rats. Similar observation was made in this study. Loss of body weight may be due to excessive breakdown of tissue proteins during diabetes (Chatterjee and Shinde, 2002). The daily administration of CFEt, CLEt and CSEt to STZ diabetic rats for 6 weeks caused a statistically significant increase in the body weight when compared with diabetic control rats.

In our study, histopathological observation in diabetic control rat's causes shows atrophic acini, no islet cells in the pancreas. The reaction is provoked by the increased production of highly reactive intermediates of STZ, which are normally detoxified by endogenous GSH but when present in excess, can deplete GSH stores, allowing the reactive intermediate to react with and destroy hepatic, renal cells (Blum and Fridovich, 1985). The above pathological changes were reduced in diabetic rats treated with CFEt, CLEt and CSEt. The histological evidence of diabetic control rats suggest that structural alterations at the end of 45 days are due to STZ-induced free radical generation quite early in diabetes. Thus in addition to blood glucose lowering effect, histopathological observations also supports the notion that CFEt, CLEt and CSEt at 80 mg/kg produced significant

antihyperglycemic activity by protecting the tissues against STZ action. The protective effect of CFEt was more prominent compared with CLEt, CSEt and CSEt.

Conclusion

Administration of CFEt, CLEt and CSEt has significant antidiabetic effect in STZ-nicotinamide induced diabetes. The CFEt, CLEt and CSEt exhibited its antidiabetic effect by influencing the histopathological changes. The antidiabetic effect of CFEt, CLEt and CSEt provide sufficient documentation to define its role and action for it's potential and promising use in treating diabetes. The CFEt administration showed more effective than CLEt, CSEt and glibenclamie.

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Figure 1

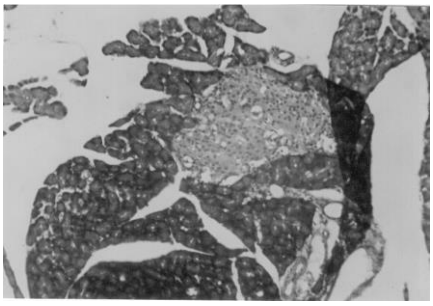

Figure a

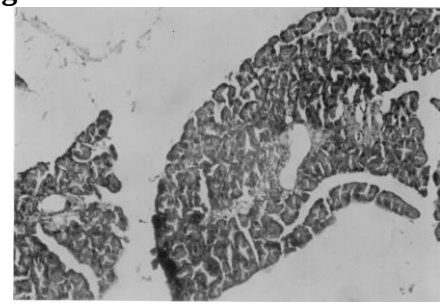

Figure b

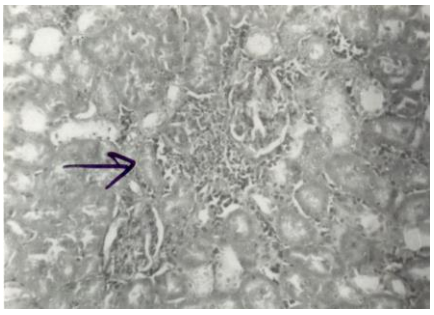

Figure c

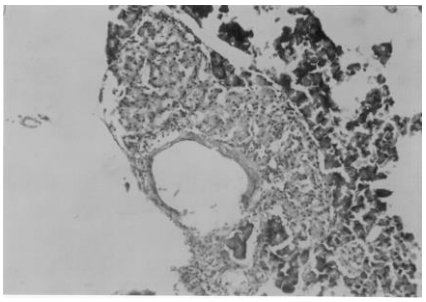

Figure d

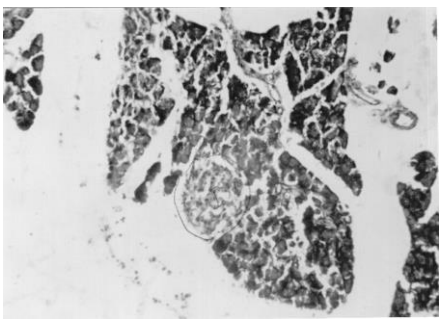

Figure e

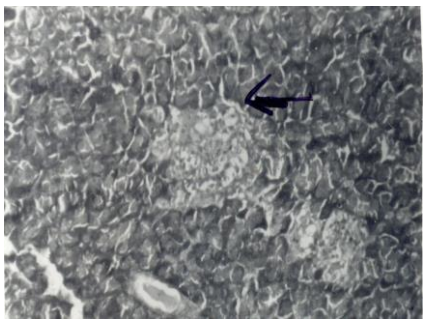

Figure f

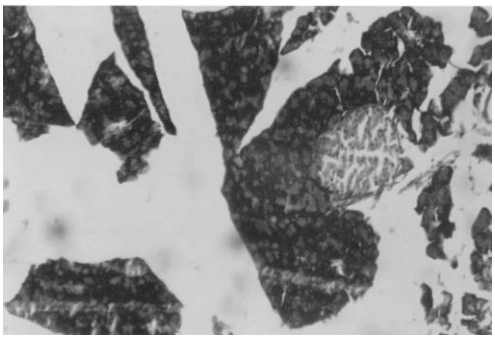

Figure g

LEGENDS

Figure 1

Figure a: Normal rat pancreas: H and E × 100. Pancreas showing □-islets.

Figure b: Diabetic treated rat pancreas: H and E × 100. Shrunken in atrophic islets.

Figure c: Diabetic treated rat pancreas: H and E × 100. Fatty infiltration of islet cells and shrinkage.

Figure d: Diabetic + CFEt treated rat pancreas: H and E × 100. Normal appearance of islets.

Figure e: Diabetic + CLEt treated rat pancreas: H and E × 100. Almost normal appearance of islet cells

Figuref: Diabetic + CSEt treated rat pancreas: Parenchymal inflammation and necrotic areas (→)

Figure g: Diabetic + glibenclamide treated rat pancreas: Preservation of islet cells in the pancreas.

Table 1. Effect of 3-week treatment with various doses of aqueous, ethanolic extracts of *Cassia auriculata* on fasting blood glucose in normal and experimental rats

Groups	'0' day	48 h after STZ injection	I week (after treatment)	II week	III week
	Blood glucose (mg/dl)				
Normal‡	79.6 ± 3.0	84.1 ± 5.1	82.1 ± 5.9	80.6 ± 6.0	81.4 ± 5.9
Diabetic control	81.6 ± 4.4	265.0 ± 19.4**	279.6 ± 12.9**	285.5 ± 12.9**	298.0 ± 15.7**
Diabetic+CFEt-Aq-0.15	78.8 ± 3.3	254.6 ± 16.2	235.0 ± 13.8* (6.3)	209.1 ± 11.4** (16.6)	184.7 ± 9.7** (26.4)
Diabetic+CFEt-Aq-0.30	84.0 ± 6.9	247.1 ± 13.7	211.0 ± 12.1* (14.6)	161.8 ± 13.2** (34.5)	112.8 ± 7.3** (54.3)
Diabetic+CFEt-Aq-0.45	77.2 ± 4.0	256.3 ± 16.6	190.0 ± 12.9** (25.8)	128.7 ± 12.1** (49.7)	85.7 ± 6.5** (66.5)
Diabetic+CFEt-Aq-0.60	80.2 ± 4.1	258.1 ± 18.6	193.2 ± 10.0** (25.1)	135.0 ± 11.0** (47.6)	102.4 ± 5.0** (60.5)
Diabetic+CLEt- Aq-0.15	78.8 ± 4.3	245.5 ± 13.2	236.3 ± 10.2* (3.7)	218.0 ± 9.7* (11.2)	189.9 ± 6.5** (22.6)
Diabetic+CLEt- Aq -0.30	81.9 ± 4.7	253.0 ± 14.1	214.0 ± 11.4* (15.4)	172.9 ± 8.6** (31.6)	131.1 ± 5.1** (48.1)
Diabetic+CLEt-Aq-0.45	77.3 ± 4.2	258.8 ± 18.8	199.1 ± 13.0** (23.0)	137.8 ± 6.1** (46.7)	102.1 ± 6.8**(60.5)
Diabetic+CLEt-Aq-0.60	83.4 ± 3.9	255.0 ± 12.3	204.0 ± 11.0** (20.0)	144.5 ± 9.1** (43.5)	111.2 ± 7.0** (56.0)
Diabetic+CSEt-Alc-0.15	80.0 ± 3.2	248.0 ± 14.0	238.0 ± 11.1* (4.0)	224.1 ± 6.7* (9.6)	205.8 ± 6.5**(17.0)
Diabetic +CSEt- Alc -0.30	79.0 ± 4.5	241.3 ± 14.5	218.0 ± 9.3* (10.8)	180.4 ± 9.8** (25.2)	142.9 ± 9.2** (40.7)
Diabetic + CSEt- Alc	82.2 ±	251.8 ± 13.0	202.8 ± 13.0** (19.4)	151.8 ±	110.0 ± 7.0**

-0.45	6.0			13.3** (39.7)	(56.3)
Diabetic+CSEt- Alc - 0.60	80.0 ± 4.0	250.3 ± 15.2	205.0 ± 13.0** (08.3)	158.2 ± 10.1** (36.8)	114.3 ± 6.2** (54.3)

Values are given as mean ± SD from 6 rats in each group. Values in parentheses indicate the percentage lowering of blood glucose in comparison to basal reading after streptozotocin (STZ) administration at 48 h. ‡ - Normal rats did not receive any STZ. Diabetic control was compared with normal. Experimental groups were compared with corresponding values after streptozotocin injection (48 h). * - p< 0.01, **- p<0.001. Aq - Aqueous extract, Alc - Ethanolic extract,

Table 2. Effect of 6-weeks treatment with various doses of CFEt, CLEt, CSEt on glucose levels in normal and experimental rats

Groups	'0' day	48 h after STZ injection	I week after treatment)	II week	III week	IV week	V week	VI week
	Blood Glucose (mg/dl)							
Normal	83.62 ± 4.53	84.41± 5.37	83.43 ± 5.21	84.57 ± 3.66	84.66 ± 4.63	83.45 ± 4.31	83.28 ± 5.28	83.53 ± 4.84
Diabetic control	79.32± 4.55	257.25 ± 15.21**	259.41 ± 21.75**	280.41 ± 16.52**	301.32 ± 15.47**	320.54 ± 20.25**	325.42± 15.74**	331.57 ± 26.81**
Diabetic+ CFEt (0.45 g)	77.46 ± 3.32	258.41± 15.41**	215.40 ± 10.42** (15.24)	175.25 ± 6.15** (28.41)	115.09 ± 8.48** (50.96)	106.30 ± 6.11** (50.61)	91.53 ± 6.25** (61.52)	85.19 ± 5.20** (65.63)
Diabetic+ CLEt (0.45 g)	76.21 ± 4.38	245.53 ± 13.78**	218.32 ± 7.35* (10.70)	191.66 ± 9.0** (21.98)	118.36 ± 4.0** (51.86)	110.71 ± 5.26** (54.92)	97.50 ± 5.10** (60.18)	88.89 ± 6.52** (63.42)
Diabetic+ CSEt (0.45 g)	75.21 ± 4.38	240.25 ± 11.78**	220.32 ± 7.35* (11.70)	195.77 ± 9.0** (19.53)	121.39 ± 4.0** (50.77)	115.66 ± 5.33** (52.77)	99.43 ± 5.01** (58.18)	90.43 ± 6.52** (60.22)
Diabetic+ Glibencalamide (600 µg/ kg)	73.35 ± 4.39	237.36 ± 10.36**	223.41 ± 7.45* (10.60)	199.51 ± 7.0** (15.42)	123.41 ± 4.0** (48.54)	119.54 ± 6.21** (50.62)	103.15 ± 5.28** (50.35)	95.21 ± 6.54** (58.12)

Values are given as mean ± S.D for 6 rats in each group. Values in parentheses indicated the percentage lowering of blood glucose in comparison to basal reading after streptozotocin (STZ) administration at 48 h. Diabetic control was compared with normal. Experimental groups were compared with corresponding values after streptozotocin injection (48 h). * - p< 0.01, **- p<0.001.

Table 3. Effect of CFEt, CLEt and CSEt on the levels of blood glucose, plasma insulin in normal and experimental rats

Groups	Fasting blood glucose (mg/dl)	Plasma insulin (µU/ml)
Normal	98.51 ± 6.12^{a}	12.32 ± 0.62^{a}
Diabetic control	275.42 ± 9.31^{b}	3.91 ± 0.21^{b}
Diabetic + CFEt (0.45 g/kg)	112.25 ± 7.31^{c}	9.25 ± 0.38^{c}
Diabetic + CLEt (0.45 g/kg)	129.23 ± 8.21^{d}	8.58 ± 0.31^{d}
Diabetic + CSEt (0.45 g/kg)	133.41 ± 8.58^{d}	8.25 ± 0.35^{d}
Diabetic+ Glibencalamide (600 µg/ kg)	141.29 ± 7.21^{d}	8.19 ± 0.45^{d}

Values are given as mean ± S.D for 6 rats in each group.
Values not sharing a common superscript letter differ significantly at p<0.05 (DMRT).