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Centratherum anthelminticum minimizes the risk of insulin resistance in fructose-induced type 2 diabetes

Hina Akram Mudassir[1], Shamim A. Qureshi[2]

[1]Department of Biochemistry, Federal Urdu University of Arts, Science and Technology, Karachi-75270, Pakistan.
[2]Department of Biochemistry, University of Karachi, Karachi-75270, Pakistan.

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ABSTRACT

The study was focused on investigating the effect of *Centratherum anthelminticum* ethanolic seed extract in fructose-induced type 2 insulin resistance diabetic rabbits after determining its qualitative analysis, acute toxicity, and effect on glucose tolerance. The phytochemical analysis revealed the presence of alkaloids, flavonoids, tanins, gallotannins, phlabotanins, phenols resins, saponins, and steroids. The same extract was found completely harmless up to 3000 mg/kg by showing no sign of acute toxicity in experimental rabbits. In oral glucose tolerance test, all doses (200-600mg/kg) of seed extract effectively produced percent reduction in blood glucose levels at 60 and 120 min. However, its high doses (400 and 600mg/kg) efficiently induced percent reduction (-10 to -11.9%) in post-prandial blood glucose level after 30 min as compared to diabetic control group. Similarly, the oral administration of same three doses (200-600 mg/kg) of extract for 14 days consecutively were found effective in decreasing blood glucose and serum total cholesterol, triglycerides, low- & very low-density lipoproteins while increasing high-density lipoprotein in fructose-induced type 2 diabetic test rabbits. In addition, fasting insulin resistance index (FIRI) was also decreased by normalizing insulin levels in these test groups as compared to fructose-induced type 2 diabetic control group ($P<0.05$). Therefore it is concluded that ESEt of *C. anthelminticum* would be effective in improving hyperglycaemia, hypertriglyceridemia, hypercholesterolemia, hyperinsulinemia in fructose-induced type 2 diabetic rabbits by either decreasing insulin resistance or inhibiting fructose absorption in intestine.

INTRODUCTION

Fructose is an essential sweet component found in honey, fruits and corn syrup (Kumar *et al*., 2014). Over the past 30 years, increase in worldwide consumption of artificial sweeteners like corn syrup also increases the risk of various non-communicable diseases including obesity, diabetes, hypertension and kidney diseases (Johnson *et al*., 2007, Segal *et al*., 2007). Literature described that high consumption of dietary fructose induced insulin resistance, postprandial hyperglycaemia and blood pressure in humans more than glucose (Brown *et al*., 2008, Stanhope *et al*., 2008). Insulin resistance is one of the major characteristics of type 2 diabetes/non-insulin dependent diabetes which usually associated with obesity that affects 90-95% of cases (Tamrakar *et al*., 2011). The impaired carbohydrate utilization in diabetes accelerates lipolysis causing hypertriglyceridemia that further increases the risk of premature arteriosclerosis (Gracheva *et al*., 2014). The estimated rate of deaths in people with diabetes is about 70-80% and is mainly due to vascular diseases (Segal *et al*., 2007). Therefore, for the treatment of diabetes, the potential drug would not only effective in lowering blood glucose but also to prevent other complications (Upendra *et al*., 2010). The available synthetic antidiabetic medicines produce various side effects including hypoglycaemic coma, hepatorenal disturbances and are unsafe during pregnancy (Ouyang *et al*., 2008).

Beside conventional medicines of diabetes, the high percentage of utilization of medicinal plants as hypoglycaemic and antihyperlipidemic agents was reported in rural areas of developing countries just to avoid insulin injections or unavailability of basic medical facilities (Paydar *et al*., 2013). Medicinal plants are famous in the treatment of many ailments including diabetes as these are rich in phytoconstituents *viz*., glycosides, alkaloids, terpenoids, flavonoids, carotenoids, etc, and have few or no side effects (Singh, 2011; Galani and Panchal, 2014).

* *Corresponding Author*
Shamim A. Qureshi, Department of Biochemistry, University of Karachi, Karachi-75270. Email: qureshi29@live.com

Centratherum anthelminticum (L.) Kuntze or *Vernonia anthelminticum* belongs to the family *Asteraceae.* The seeds of this plant called as black cumin/wild cumin and in Urdu it is called as kali zeeri.

The seeds of this plant have been reported for many pharmacological activities like anti-inflammatory, antibacterial, larvicidal, antiviral, antifungal, anticancer, anthelmintic, antioxidant, analgesic, antipyretic, anti-inflammatory, diuretic, wound healing and antidiabetic effects (Pitchai *et al*., 2010). On the basis of its significant antidiabetic effects reported in alloxan- and streptozotocin-induced diabetic rat models (Aguilara *et al.*, 1998; Fatima *et al.*, 2010), this study was aimed to investigate the effect of ethanolic seed extract of *C. anthelminticum* in fructose-induced type 2 insulin resistance diabetic rabbits. In addition, the phytochemical screening, acute toxicity and effect of ESEt of *C. anthelminticum* on oral glucose tolerance were investigated.

MATERIALS AND METHODS

Preparation of ethanolic seed extract

Seeds of *C. anthelminticum* were purchased, authenticated and kept (KU/BCH/SAQ/02) in Department of Biochemistry, University of Karachi, Karachi-75270, Pakistan. The dried seeds were grinded and 40 g of seed powder was soaked in ethanol (1L; 95%) for overnight at room temperature. Then filtered through Whatmann No 42 (125mm) filter paper twice and concentrated at 40^0C till dryness in a rotary vacuum evaporator. Finally obtained brown residue termed as ethanolic seed extract (ESEt) that was stored in refrigerator below 10ºC until used (Qureshi *et al.*, 2009).

Qualitative phytochemical screening

The ESEt was screened for the qualitative determination of major constituents including alkaloids, carbohydrates, tanins, gallotanins, phlabotanin, glycosides, saponins, steroids, etc, by standard methods described earlier (Harborne, 1973; Kondongala *et al*., 2010).

Induction of fructose-induced insulin resistance type 2 diabetes

It was done by giving oral administration of 30 ml of 35% fructose solution once in a day in overnight fasted rabbits for 14 connective days (Neeharika *et al.*, 2012).

Positive control

Commercially available Pioglitazone (Zolid, 15mg/kg) of Getz Pharma, Pakistan Ltd. was used as positive control in the present study.

Acute toxicity study

Acute toxicity was measured by oral administration of ESEt from 100-3000mg/kg. For this, overnight fasting rabbits were randomly divided into different groups (4/group). Doses of ESEt was individually administered orally to the rabbits of their respective test groups, whereas distilled water (1ml/kg) were given orally to rabbits in control group. The rabbits were then allowed free access to food and water. Acute toxicity was observed over a period of 12-24 hours in terms of behavioural change (sedative or not), mortality rate and other side effects such as itching, ruffled hair, clumping together, etc.

Oral glucose tolerance test (OGTT)

The experimental rabbits in overnight fasted state were randomly divided into 5 groups (4 / group), as follows

- Group I: Control group: treated with distilled water 1 ml/kg
- Group II: Negative control treated with 0.05% DMSO 1 ml/kg
- Group III: Test group: treated with ESEt 200mg/kg
- Group IV: Test group: treated with ESEt 400mg/kg
- Group V: Test group: treated with ESEt 600mg/kg

Each group, after receiving its respective treatment orally, immediately administrated with glucose load 2 g/kg from same route. Glucometer (Optimum Xceed, Diabetes Monitoring System by Abbot) was used to monitor blood glucose levels at 0, 30, 60, and 120 minutes in rabbits of each group by pricking the ear vein. Finally, percent glycemic change between control and test groups was calculated by using the following formula

$$\% \text{ Glycemic change} = [(G_x - G_o) / G_o] \times 100$$

Where G_o = mean blood glucose level of control group at different time intervals

G_x= mean blood glucose levels of each test group at different time intervals respective to control

Effect of ESEt in fructose-induced insulin resistance type 2 diabetic rabbits

Albino rabbits weighing from 1-1.2 kg were purchased from the local supplier of Karachi University and kept in animal house of university according to the international guidelines of animal handling. The standard laboratory diet was given to these rabbits along with free access to water *ad libitum* and divided them in control and diabetic groups on the basis of treatments (Fig. 1).

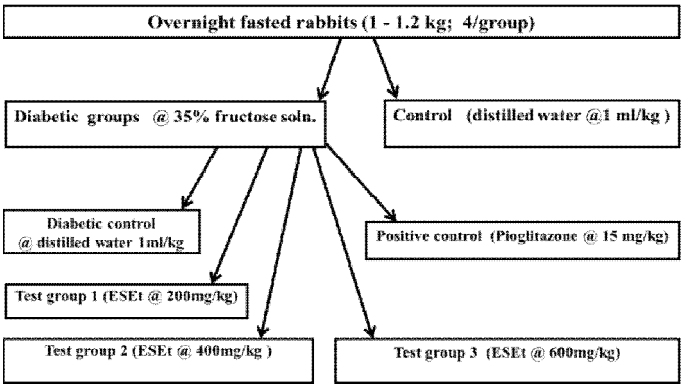

Fig. 1: Animal Grouping.

All treatments were given orally to experimental rabbits in overnight fasted state for consecutive 14 days (once in a day).

Rabbits were sacrificed on 15 day after completing 14 doses to collect blood, serum and liver tissues for analysing the biochemical parameters. Prior to this, fasting blood glucose (FBG) levels were also determined on initial (0) and final (14) day with the help of glucometer from their ear vein.

Determination of biochemical parameters

Commercially available enzymatic kits (Randox, United Kingdom) were used to determine biochemical parameters including serum total cholesterol (TC), triglycerides (TG) and high-density lipoprotein-cholesterol (HDL-c). Whereas low density lipoprotein-cholesterol (LDL-c), and very low density lipoprotein-cholesterol (VLDL-c) were calculated by using following formulae (Azmi and Qureshi, 2012)

$$\text{LDL} - \text{c (mg/dl)} = \text{TC} - \frac{(\text{TG})}{5} - \text{HDL} - \text{c}$$

$$\text{VLDL} - \text{c} = \frac{(\text{TG})}{5}$$

The cobas e411 analyzer, Hitachi (Roche Diagnostics GmbH, Mannheim, Germany) was used to determine serum insulin level whereas fasting insulin resistance index (FIRI) was calculated by formula (Duncan *et al.,* 1995).

$$\text{FIRI} = \frac{\text{Fasting insulin } (\mu\text{U/ml}) \times \text{ Fasting glucose (mg/dl)}}{25}$$

Statistical analysis

The results are expressed as mean ± SEM (Standard Error Mean) and considered significant at $p<0.05$ when data were examined by *one-way* ANOVA followed by LSD (least significant difference) test (SPSS version 18).

RESULTS

Phytochemical analysis of ESEt

Qualitative analysis revealed the presence of alkaloids, flavonoids, tanins, gallotannins, phlabotanins, phenols, resins, saponins, and steroids in ESEt of *C. anthelminticum.*

Acute toxicity and OGTT

No acute toxicity was found by ESEt up to 3000 mg/kg in the form of sedation, itching and mortality in experimental rabbits.

In OGTT, ESEt 200mg/kg after 30 min produced significant (P<0.05) hypoglycaemia as compared to control. A significant reduction in the concentration of blood glucose was found in all doses of ESEt from 200-600 mg/kg (P<0.05) after 120 min. The values of percent glycaemic change after 60 and 120 min of ESEt 200-600 mg/kg administration were -12.35, −24.58, −18.53% and −39.88, −43.25, −30.89% respectively as compared to control group. ESEt 200 and 400mg/kg decreased blood glucose level after 0 min as −2.79 and −1.95% whereas the same extract in doses of 400 and 600 mg/kg showed percent glycemic change about −11.04 and −10.9% respectively after 30 min as compared to control group (Table 1).

Effect of ESEt on FBG and biochemical parameters in fructose-induced insulin resistance diabetic rabbits

ESEt in doses of 200, 400 and 600 mg showed significant decrease up to 115, 103 and 102 mg/dl respectively (P<0.05) in FBG values as compared to diabetic and positive control groups (Fig. 2).

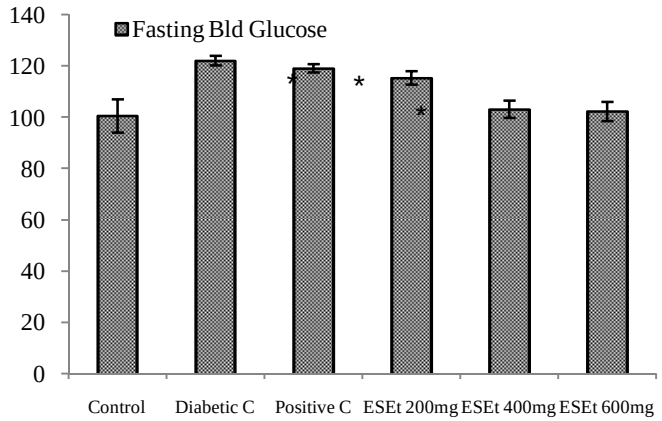

Fig. 2: Effect of ESEt on FBG (mg/dl) levels in fructose induced diabetic rabbits.
Each bar represents the mean ± SEM (n=4). *p <0.05, when compared with Diabetic and Positive control groups.

All doses of ESEt (200-600 mg/kg) showed significant decrease (P<0.05) in the values of serum TC, TG, LDL-c, VLDL-c, and significant increase (P<0.05) in the values of HDL-c in test groups as compared to diabetic and positive control groups (Table 2). A significant decrease (P<0.05) in FIRI was also observed in test groups treated with ESEt (200-600mg/kg) by normalizing the insulin level as compared to diabetic control group that indicated increased insulin resistance (Fig. 3).

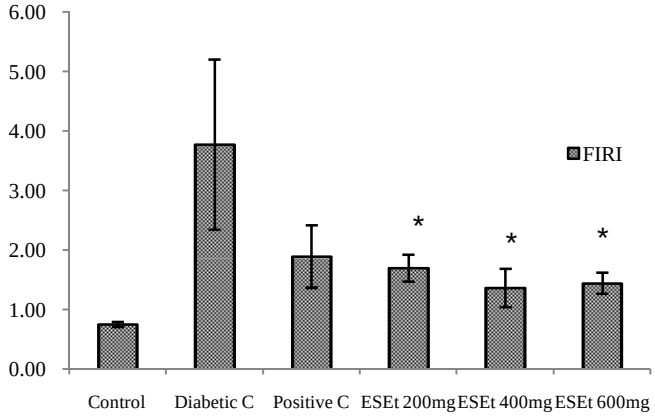

Fig. 3: Effect of ESEt on FIRI in fructose induced type 2 diabetic rabbits.
Each bar represents the mean ± SEM (n=4). *p <0.05, when compared with Diabetic and Positive control groups.

Table 1: Effect of ESEt on Glucose Tolerance in Rabbits.

Groups	Treatments	0 min	30 min	60 min	120 min
Control	d.H_2O (1ml/kg)	89.5±3.40	181±11.88	194.25±5.45	178±4.0
Negative control	0.05% DMSO (1ml/kg)	89.25±7.31	187.5±23.11	185.5±14.33	169.25±8.75
ESEt	200mg	87± 3.87 (-2.79%)	193.25±31.03^{c}(6.76%)	170.25±39.69(-12.35%)	107±8.21^{abc}(-39.88%)
ESEt	400mg	87.75±9.83 (-1.95%)	161.75±9.38(-11.04%)	146.5±11.97(-24.58%)	101.25±4.32^{abc}(-43.25%)
ESEt	600mg	93.75±8.61(4.74%)	161.25±12.16(-10.91%)	158.25±11.14(-18.53%)	123±4.37^{abc}(-30.89%)

All values are expressed as mean ±SEM (n=4).
^{a} p<0.05, when compared with control group, ^{b} p<0.05, when compared with Negative control group
Values in parenthesis show percent blood glucose decrease (-) /increase (+).

Table 2: Effect of ESEt on Biochemical Parameters (mg/dl).

Groups	TC	TGs	HDL-c	LDL-c	VLDL-c
Control	181.09±4.85*	122.34±2.6*	159.50±3.27*	12.0±2.60*	13.26±4.71*
Diabetic control	227.17±4.7	186.03±3.33	81±11.7	90.25±5.61	55.77±10.85
Positive control	174.16±6.7*	155.59±13.8*	118.50±8.25*	31.27±8.49*	20.30±5.19*
ESEt 200mg	141.40±4.81*	107.53±5.6*	152.50±6.27*	26.50±11.98*	13.21±5.2*
ESEt 400mg	160.53±5.0*+	122.24±3.24*+	164.75±4.1*	28.0±1.0*	23.87±0.54*
ESEt 600mg	149.42±3.50*	110.83±1.66*	183.50±14.5*	20.92±18.09*	15.35±4.0*

All values are expressed as mean ±SEM (n=4).
*p<0.05, when compared with Diabetic and Positive control group, $^{+}$$p$<0.05, when compared between test groups.

DISCUSSION

Nature has provided effective balancers in the form of medicinal plants that regulate important functions and provide various nutrients that body fails to receive due to poor diet. The herbal medicines are considered safe than conventional medications and providing a natural alternative treatment for many health problems including type 2 diabetes (Medagama *et al.*, 2014).

ESEt was found non-toxic as there was no sedation, itching and mortality seen in experimental rabbits by using doses of same extract up to 3000 mg/kg. Therefore, according to our pervious study, three doses of ESEt *viz.*, 200, 400 and 600 mg/kg which showed significant antihyperlipidemic activity in high-fat induced hyperlipidemic rabbits (Lateef and Qureshi, 2013) were selected for further study.

Oral glucose tolerance test is used to check whether the individual is diabetic, insulin resistant and suffering from the disorders of carbohydrate metabolism (Li *et al.*, 2014). The current study showed that ESEt of *C. anthelminticum* (200-600mg/kg) was effective in decreasing blood glucose level after 60 and 120 min of glucose load (2g/kg) in their respective test groups. However, the high doses (400 and 600mg/kg) of extract found more efficient in reducing postprandial blood glucose level at 30 min after glucose load. The hypoglycaemic activity of ESEt observed in OGTT might be due to its extra-pancreatic effect by producing delay in glucose absorption at intestinal level or enhancing glucose uptake in muscle and liver tissues in order to increase glucose tolerance and in that way stimulating glycolysis and glycogenesis (Qureshi *et al.*, 2009). Several phytoconstituents including flavonoids, alkaloids, phenols, saponins, steroids which were detected in ESEt could also be responsible for the hypoglycaemic activity of ESEt as it has been reported earlier that phytochemicals have protective or disease preventive properties (Hashim *et al.*, 2013). High intake of fructose induced weight gain that gradually induced insulin resistance and contributed in the progress of type 2 diabetes. Fructose is a lipogenic agent as it is reported to involve in accelerating the synthesis of triglycerides (TGs) in liver after entering in hepatocytes through insulin-independent glucose transporters (GLUT-5) thereby inducing hypertriglyceridemia (Armato *et al.*, 2015). This increased level of TGs could be the reason of insulin resistance by masking the insulin receptors on target cells especially muscles, adipocytes and hepatocytes, thus impaired carbohydrate utilization, induced hyperglycaemia and hyperinsulinemia. This situation is accompanied with high LDL-c, VLDL-c levels and low HDL-c levels (Hsieh*et al.*, 2013). The same was observed in fructose-induced diabetic control group in the present study that showed hyperglycaemia, hypertriglyceridemia, hypercholesterolemia, and hyperinsulinemia. On contrary, three of the doses of ESEt (200, 400, & 600 mg/kg) found effective (P<0.05) in decreasing in serum TC, TG, LDL-c, VLDL-c levels and increasing HDL-c levels in their respective test groups. Interestingly, all doses of extract were also found to normalize insulin levels in their respective test groups thereby showing decrease in insulin resistance which also confirmed by observing low values of FIRI in test groups whereas diabetic control group showed high values of same index. Pioglitazone (15mg/kg) was also found effective in reducing insulin resistance in positive control group (P<0.05). Previously, methanolic seed extract of *C.anthelminticum* has been reported to have insulin secretary effect in type 2 diabetic rats (Arya *et al.*, 2012). Thus, our study would add new concept in the antidiabetic action of *C.anthelminticum* that it could reduce insulin resistance by normalizing the levels of serum insulin and inhibiting triglyceride synthesis thus enhance insulin-receptor sensitivity and improve carbohydrate utilization in body cells.

CONCLUSION

The present findings conclude that hypoglycaemic effect of ESEt of *C.anthelminticum* in fructose-induced type 2 diabetic rabbits may be due to correcting insulin resistance by inhibiting

either fructose absorption in intestine or triglycerides synthesis in liver. Thereby enhancing receptor sensitivity for insulin and correcting carbohydrate utilization in body cells.

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