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Hypoglycemic and antioxidative effects of fenugreek and termis seeds powder in streptozotocin-diabetic rats

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Abstract. – BACKGROUND AND OBJECTIVES: Diabetes mellitus is a heterogeneous disease characterized by altered cellular metabolism. So, many traditional herbs are being used by diabetic patients to control this disease. In the present study, an attempt has been made to investigate the anti-diabetic and antioxidative effects of water suspension of Fenugreek (F), and Termis (T) seeds powder and their mixture (M) who were studied in Streptozotocin (STZ)-induced diabetic rats.

MATERIALS AND METHODS: Experimental diabetes was induced by injection a single dose of STZ (50 mg/kg, i.p.). Adult male albino rats were divided into five groups; normal control, diabetic control, diabetic-F supplement (1 g/kg b.wt.), diabetic-T supplement (1 g/kg b.wt.) and diabetic-M supplement 1 g/kg b.wt. of each seed powder concurrently for 30 days. Serum glucose, insulin, lipid profile, activities of serum marker enzymes of liver function as well as liver and muscle glycogen content were measured. The oxidative stress was assessed by blood reduced glutathione (GSH) content and enzyme activities of glutathione-S-transferase (GST) and catalase (CAT) in plasma.

RESULTS: The increase in serum glucose, total lipid, triglycerides, total cholesterol, AST, ALT, ALP and decreased insulin, plasma, GSH, GST, CAT, as well as liver and muscle glycogen content were the salient features recorded in diabetic control rats. The F, T and M supplements significantly reverted the levels of the studied metabolites and enzymes activities to near normal control values. Co-administration of F and T seeds powder was considered as an effective agent in modulating the alterations in total lipid, AST, ALT, GSH and muscle glycogen.

CONCLUSIONS: Our data suggest that F, T and M seeds powder supplementation may be beneficial for preventing diabetic complications in this animal model.

Key Words:

Fenugreek, Termis, Streptozotocin, Diabetic rats, Hypoglycemia, Antioxidant enzymes.

Introduction

Diabetes mellitus is a group of metabolic disorders characterized by hyperglycemia, with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both[1]. There is an increasing evidence that complications related to diabetes are associated with oxidative stress induced by the generation of free radicals[2]. Oxidative stress is a condition of imbalance due to excess formation of free radicals and decreased activity of antioxidant defense systems. The levels of reactive oxygen species (ROS) are regulated by a variety of cellular defense mechanisms consisting of enzymatic and non-enzymatic systems[2].

Dietary antioxidants become very important when oxidative stress in living organisms causes endogenous antioxidant depletion (especially glutathione) and they appreciably contribute to the improvement of antioxidant status in various biological fluids[3,4]. Natural remedies from medicinal plants are considered to be effective and safe alternative treatment for hyperglycemic and liver toxicity[5]. There is a growing interest in herbal remedies because of their effectiveness, minimal side effects in clinical experience, and relatively cost effective. Herbal drugs or their extracts are prescribed widely, even when their biological active compounds are unknown[6]. Fenugreek (*Trigonella foenum graecum*) and termis (*Lupinus albus*) seeds are an old herbal remedies used to treat metabolic and nutritive dysfunctions[7,8]. Accordingly, in the present study streptozotocin induced diabetic rats were used to evaluate the possible hypoglycemic, hypolipidemic and correcting antioxidant status effects of an water suspension of fenugreek and termis seeds powder and their mixture.

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Materials and Methods

Experimental Animals

Adult male albino *Rattus norvegicus* rats weighing 100-120 g, purchased from the National Research Centre, Cairo, Egypt, were used in the study. The rats were kept in a controlled environment and were allowed free access to standard chow diet and water during study.

Plant Material and Preparation

The dry seed of Fenugreek (F), *Trigonella foenum graecum,* and termis (T)*, Lupinus albus,* were obtained from a local herbal market. The seeds were identified and authenticated by the Herbarium of Botany Department, Faculty of Science, Cairo University. The seeds were powdered using a commercial blender. Known weight of their powders was used as suspension in constant distilled water volume.

Experimental Design

Rats were divided into normal control (NC), given distilled water orally, and diabetic groups, made diabetic by intraperitoneal (i.p.) injection of Streptozotocin (STZ) (50 mg/kg) freshly prepared in 0.1M Citrate buffer (pH 4.5)[9]. Forty-eight hours after STZ administration, diabetic rats with fasting blood glucose >200 mg/dl were randomly divided into four groups, diabetic control (DC), diabetic treated with Fenugreek (F), treated with Termis (T) and treated with their mixture (M). Treated rats received, by gastric gavage, separately oral daily dose (1 g/kg body weight) of F and T seeds powder suspended in 1 ml distilled water. The last group (M) received oral daily dose 1 g/kg body weight, from each of F and T concurrently. All groups of rats were experimented for 30 days.

Biochemical Evaluations

At the end of the experimental period overnight fasting animals were sacrificed. Blood was collected in two cleaned vials, one with anticoagulant (EDTA) for blood reduced glutathione (GSH) estimation and separation of plasma for determination of glutathione S - transferase (GST) and catalase (CAT) .The second vial was without anticoagulant and used for serum separation. Both plasma and sera were obtained by centrifugation at 3000 × g for 10 min at 4°C. The appropriate kit (Stanbio reagent kit, Stanbio Laboratory Inc., Boerne, TX, USA) was used for the determination of serum glucose[10], serum total lipids[11], triglycerides[12], total cholesterol[13], activities of serum aspartate transaminase (AST) and alanine transaminase (ALT)[14], serum alkaline phosphatase (ALP)[15], plasma GSH[16], GST[17] and CAT[18]. Serum insulin was estimated using Insulin Mouse ELISA kit (American Diagnostica Inc., South San Francisco, CA, USA). The micro plate reader used was Hy-prep system Plus, Hyperion (Hyperion Inc., Miami, FL, USA)[19].

Liver and right gastrocnemius skeletal muscle were dissected out rapidly and washed. Parts of liver (100 mg) and of muscle (200 mg) were immediately digested in 2 ml of 30% KOH solution and were used for determination of glycogen content by anthrone method[20].

Statistical Analysis

Data were expressed as mean ± SE, and were compared using One-way analysis of variance (ANOVA) and Student's *t* test to detect differences between groups. The significance levels were tested at $p < 0.05$.

Results

Table I shows serum glucose, insulin concentrations and glycogen content of liver and muscle. Serum glucose level was significantly elevated in STZ-diabetic rats and the percentage increase was 195.81%. Fenugreek and Termis seeds and their mixture supplementation significantly decreased STZ-induced hyperglycemia and the percentage reduction was 53.66%, 56.29% and 41.67%, respectively in comparison with the diabetic control. Accordingly, there was a significant decrease in serum insulin concentrations in diabetic rats, compared with normal control (23.13%), and administration of F, T, and M tended to increase the insulin levels, and the percentage elevation was 14.62%, 22.94% and 10.60%, respectively as compared to the diabetic control. As shown in Table I, STZ-induced diabetes in rats caused a reduction in the liver and muscle glycogen content as compared with the normal control group (44.97% and 49.18%, respectively). Oral administration of F, T, and M to diabetic rats for 30 days succeeded to significantly elevate liver and muscle glycogen contents. Concerning liver glycogen, the percentage of increase was 96.95%, 88.10% and 83.02%, respectively, whereas for muscle glycogen it was 67.74%, 52.69% and 75.27%, respectively.

Table I. Effect of 30 days treatment with seeds aqueous suspension of *T. foenum* (F), *L. albus* (T) and their mixture (M) on serum glucose, insulin and glycogen concentration in liver and muscle of rats.

Parameters	NC	DC	F	T	M
Glucose (mg/dl)	71.10 ± 2.32	210.32[a] ± 8.15	97.46[b] ± 6.91	91.93[b] ± 4.16	122.67[b] ± 4.63
% of change from NC		195.81			
% of change from DC			-53.66	-56.29	-41.67
Insulin (mg/ml)	27.50 ± 1.56	21.14[a] ± 0.96	24.23[b] ± 0.18	25.99[b] ± 0.15	23.38[b] ± 0.04
% of change from NC		-23.13			
% of change from DC			14.62	22.94	10.60
Liver glycogen (mg/g tissue)	12.52 ± 0.41	6.89[a] ± 0.21	13.57[b] ± 0.33	12.96[b] ± 0.76	12.61[b] ± 0.65
% of change from NC		-44.97			
% of change from DC			96.95	88.10	83.02
Muscle glycogen (mg/g tissue)	1.83 ± 0.25	0.93[a] ± 0.13	1.56[b] ± 0.12	1.42[b] ± 0.06	1.63[b] ± 0.20
% of change from NC		-49.18			
% of change from DC			67.74	52.69	75.27

Values are given as mean ± SE for 7 rats in each group.[a]Significant ($p < 0.05$) as compared with normal control (NC). [b]Significant ($p < 0.05$) as compared with the diabetic control (DC).

Serum total lipids, triglycerides and total cholesterol levels were increased in STZ-diabetic rats and the percentage of increase was 70.93%, 17.26% and 66.71%, respectively when compared with the normal control rats. Daily administration of F, T and M for 30 days succeeded to reduce their concentrations significantly (Table II). Concerning total lipids, the percentage of reduction was 57.82%, 59.86% and 61.90%, for triglycerides it was 53.68%, 44.24% and 45.90% and for cholesterol it was 48.22%, 66.47% and 48.86%, respectively when compared with diabetic control rats.

As shown in Table III, the activities of liver function markers (AST, ALT, ALP) were significantly elevated in STZ-diabetic rats by 14.33%, 42.73% and 91.96%, respectively when compared with the normal controls rats. Rats administrated F, T and M for 30 days showed significant reduction in these marker enzyme activities to almost normal levels. The percentage of decrease, when compared to diabetic control rats, was 38.30%, 37.81% and 38.94% for AST; 42.12% , 41.74% and 42.78% for ALT and 27.12%, 25.42% and 22.58 for ALP, respectively.

A significant decrease in GSH (16.22%), GST (36.20%) and CAT (45.80%) plasma levels in rats with STZ- induced diabetes was recorded compared to that of normal control rats (Table IV). Administration of F, T and M, for 30 days, caused a significant elevation in the levels of GSH (11.02%, 31.42% and 50.18%), GST (65.12%, 101.86% and 42.29%) and CAT (69.60%, 68.69% and 64.44%), respectively when compared to diabetic control

Table II. Effect of 30 days treatment with seeds aqueous suspension of T. foenum (F), *L. albus* (T) and their mixture (M) on serum total lipids, triglycerides and total cholesterol concentrations of rats.

Parameters	NC	DC	F	T	M
Total lipids (g/dl)	0.86 ± 0.07	1.47[a]± 0.02	0.60[b] ± 0.02	0.59[b] ± 0.02	0.56[b] ± 0.01
% of change from NC		70.93			
% of change from DC			-57.82	-59.86	-61.90
Triglycerides (mg/dl)	173.33 ± 0.72	203.24[a] ± 1.11	94.15[b] ± 4.19	113.32[b] ± 5.02	109.95[b] ± 3.92
% of change from NC		17.26			
% of change from DC			-53.68	-44.24	-45.90
Total cholesterol (mg/dl)	86.51 ± 1.55	144.22[a] ± 4.56	74.67[b] ± 3.14	48.35[b] ± 5.66	73.76[b] ± 4.14
% of change from NC		66.71			
% of change from DC			-48.22	-66.47	-48.86

Values are given as mean ± SE for 7 rats in each group. [a]Significant ($p < 0.05$) as compared with normal control (NC). [b]Significant ($p < 0.05$) as compared with the diabetic control (DC).

Table III. Effect of 30 days treatment with seeds aqueous suspension of *T. foenum* (F), *L. albus* (T) and their mixture (M) on serum AST, ALT and ALP activities of rats.

Parameters	NC	DC	F	T	M
AST(U/L)	47.86 ± 1.35	54.72[a] ± 1.27	33.76[b] ± 1.19	34.03[b] ± 0.74	33.41[b] ± 1.09
% of change from NC		14.33			
% of change from DC			-38.30	-37.81	-38.94
ALT(U/L)	34.38 ± 0.58	49.07[a] ± 1.09	28.40[b] ± 0.64	28.59[b] ± 0.62	28.08[b] ± 0.47
% of change from NC		42.73			
% of change from DC			-42.12	-41.74	-42.78
ALP(U/L)	92.73 ± 1.56	178.00[a] ± 3.95	129.72[b] ± 1.23	132.75[b] ± 1.33	137.80[b] ± 1.38
% of change from NC		91.96			
% of change from DC			-27.12	-25.42	-22.58

Values are given as mean ± SE for 7 rats in each group. [a]Significant ($p < 0.05$) as compared with normal control (NC). [b]Significant ($p < 0.05$) as compared with the diabetic control (DC).

rats (Table IV).

Interestingly, the administration of Termis seeds powder, singly, has shown excellent positive outcomes in respect to diabetic complications caused in glucose, insulin, total cholesterol and GST. Concerning triglycerides, catalase and liver glycogen, administration of Fenugreek seeds powder, singly, was the most effective in normalization of alterations caused by diabetes. Combined administration of both seeds powder caused marked amelioration in total lipids, AST, ALT, GSH and muscle glycogen of the diabetic rats.

Discussion

Fasting blood sugar in diabetic rats represents an important indicator of diabetic status. In the present study, we observed significant decrease in serum glucose and elevated insulin level when STZ-diabetic rats were administered F, T, or M seeds powder. The capacity of such seeds to counteract hyperglycemia is an essential trigger for reverting the liver to revert to its normal homeostasis during experimental diabetes. The hypoglycemic activity, exhibited by Fenugreek and Termis seeds, may be attributed to the presence of a significant quantity of bioactive compounds saponins, alkaloids and polyphenol[21,22].

In order to elucidate the modulatory mechanism of Fenugreek and Termis seed on glucose metabolism in rats, we focused on hepatic glucose metabolism which was reflected by changes in hepatic glycogen. The results obtained showed that F and T seeds powder administration increased hepatic and muscle glycogen of STZ-diabetic rats. This suggests that the preservation of glycogen was maintained and the gluconeogene-

Table IV. Effect of 30 days treatment with seeds aqueous suspension of *T. foenum* (F), *L. albus* (T) and their mixture (M) on glutathione reduced (GSH), glutathione-s-transferase (GST) and catalase (CAT) activities of rats

Parameters	NC	DC	F	T	M
GSH (mg/dl)	29.90 ± 1.19	25.05[a] ± 1.17	27.81[b] ± 1.70	32.92[b] ± 1.02	37.62[b] ± 1.83
% of change from NC		-16.22			
% of change from DC			11.02	31.42	50.18
GST (U/g protein)	3.37 ± 0.19	2.15[a] ± 0.04	3.55[b] ± 0.10	4.34[b] ± 0.44	3.07[b] ± 0.09
% of change from NC		-36.20			
% of change from DC			65.12	101.86	42.29
CAT (U/g protein)	6.07 ± 0.53	3.29[a] ± 0.05	5.58[b] ± 0.59	5.55[b] ± 0.38	5.14[b] ± 0.19
% of change from NC		-45.80			
% of change from DC			69.60	68.69	64.44

Values are given as mean ± SE for 7 rats in each group.[a]Significant ($p < 0.05$) as compared with normal control (NC). [b]Significant ($p < 0.05$) as compared with the diabetic control (DC).

sis rat was depressed. In parallel, serum insulin level significantly decreased in the diabetic rats and significantly increased due to F and T administration as compared with normal control and diabetic control, respectively. Insulin deficiency ultimately results in increased production of glucose by the liver, decreased utilization of glucose in peripheral tissues[23]. This indicated that changes in insulin may bring about changes in hepatic glycogen content and lead to the regulatory effect of Fenugreek and Termis on glucose- metabolism in STZ-diabetic rats. Hannan et al[24] indicated that soluble dietary fiber of *T. foenum graecum* seed exerts antidiabetic effects mediated through inhibition of carbohydrate digestion and absorption, and enhancement of peripheral insulin action. Again, the obtained depletion of liver and muscle glycogen content of diabetic rats in the current study was concomitant with the findings of previous investigators[25,26].

Diabetes is a metabolism-associated disease, particularly closed related to lipid metabolism, affecting the plasma lipid and lipoprotein profile[27]. The current data demonstrated the occurrence of serum hyperlipidemia, hypertriglyceridemia and hypercholesterolemia in STZ-diabetic rats. These findings agree with Veerapur et al[28], who indicated that the levels of serum lipids are usually elevated in diabetes mellitus and such elevation represents a risk factor for coronary heart disease. There is significant decrease in serum lipid profile (total lipids, triglyceride and total cholesterol levels) in Fenugreek and Termis treated diabetic rats. This result suggested that Fenugreek and Termis seed would be helpful in the prevention of diabetic complications through improving dyslipidemia. Lemhadri et al[29] reported that administration of *Momordica charantia* lead to decrease in cholesterol levels probably by two mechanisms, one by decreasing absorption of cholesterol from intestine and the other by decreasing the activity of 3-hydroxyl-3-methylglutaryl Co- enzymes A reductase, an enzyme of cholesterol biosynthesis. The same mechanism may be appropriate to explain the current results concerning lipid profile. Again, the hypolipidemic action of Fenugreek and Termis seeds suspension could be the result of the retardation of fat absorption due to the presence of bioactive soluble dietary fiber in the agent[30].

The elevation of biomarker enzymes, such as serum AST, ALT, and ALP was observed in diabetic control rats indicating the hepatic damage[31]. The present study illustrated a significant increase in serum AST, ALT, and ALP activities in STZ-induced diabetic rats. These results agree with the findings recorded by Maritim et al[32] and Jung et al[33], who reported that the rise in activity of these enzymes is mainly due to their leakage from liver into blood stream. Administrating F and T seeds powder to STZ-diabetic rats restore the activities of the aforementioned enzymes to near their normal level. A possible explanation for the effect of both seeds on such enzymes activity is that these seeds may inhibit the liver damage induced by streptozotocin[34] and/or the improved liver function with return of gluconeogenesis toward its normal level[35].

Earlier reports revealed that STZ-induced diabetic animals may exhibit most of the diabetic complications mediated through oxidative stress[36]. Oxidative stress in diabetes is coupled to a decrease in the antioxidant status, which can increase the deleterious effects of free radicals[37]. Besides the enzymatic antioxidants such as GST and CAT, reduced GSH is also an important antioxidant[38]. The findings of our study shows a significant decrease in the activity of GST and CAT and the level of reduced GSH in STZ-induced diabetic rats. Administrating F, T and M to diabetic rats caused a significant increases in the activities of GST and CAT and the content of reduced GSH. These findings suggested that F and T seeds might be involved in the restoration of the antioxidant defense system by regulating the activities of antioxidant enzymes (GST and CAT) and non-enzymatic one (GSH) in STZ-induced diabetic rats. Reduced GSH could protect the cells from the toxic effects of ROS[39] and GST and CAT play a prominent role in scavenging free radical[40].

Conclusions

Fenugreek and Termis seeds powder suspension exhibited a hypoglycemic function and would be helpful in the prevention of diabetic complications through improving hyperlipidemia and enhancing the antioxidant defense system. However, the precise hypoglycemic mechanisms of these seeds were not investigated in this work and further investigations in purifying the active compounds from the seeds will be necessary to elucidate the precise mechanisms of their hypo-

glycemic, correcting oxidative stress and hypolipidemic actions.

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