

GINSENG EITHER CURATIVE OR PROPHYLACTIC INHIBITS HYPERGLYCEMIA AND OXIDATIVE STRESS IN DIABETIC RATS

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ABSTRACT

In the present work 40 female albino rats were divided into two main groups Prophylactic and Curative. Prophylactic was treated with ginseng for four weeks before and after the induction of diabetes, while curative was treated with ginseng only after the induction of diabetes, besides, non treated control, Ginseng control and Diabetic control (each group 8 rats). Two main experiments were carried out. The first experiment represented the effect of ginseng as prophylactic agent against hyperglycemia induced by streptozotocin (STZ). The second depended on the curative effect of these treatments on hyperglycemic rats. Antioxidant parameters that protect the cell against reactive oxygen species (ROS) were carried out. Activities of antioxidant enzymes catalase (CAT) were measured. In addition, levels of antioxidant biomolecules involving glutathione (GSH), L-Ascorbic acid (vitamin C). Also, lipid profile and lipid peroxidation malondialdehyde (MDA) were measured. Data revealed that Ginseng roots supplementation improved blood sugar levels in diabetic rats and protected rats from diabetic factors like streptozotocin in prophylactic female albino rats.

Keywords: Ginseng, Antioxidant biomolecules, Diabetes, Prophylactic, Curative Blood & Plasma parameters.

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INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia associated with absolute or relative deficiencies in insulin secretion or function. Diabetes mellitus is usually irreversible and its late complications resulted in reduced life expectancy (Paul 1997).

Reactive oxygen species (ROS) are various forms of activated oxygen, which include free radicals such as superoxide anion (O_2^-), hydroxyl radical (HO^\cdot) and peroxy radical (ROO^\cdot), as well as reactive non-radical compounds such as singlet oxygen, peroxy nitrite and hydrogen peroxide (Stahl and Sies, 1997). ROS arise as by products of normal metabolism and as a result of exposure to sunlight, ozone, radiation and other environmental pollutants.

A cellular depletion of the antioxidants and higher levels of free radicals were found in diabetes (Obrosova *et al.*, 2003). Diabetes mellitus and hyperglycemia are a widely known cause of enhanced plasma free radicals concentrations, which is believed to associated with increased oxidative stress (Wolff and Dean, 1987; Baynes, 1992 and Pieper *et al.*, 1995). Clinical and experimental evidence has suggested the involvement of free radicals-

mediated oxidative damage to be a contributor factor in development and complications of diabetes (Damasceno *et al.*, 2002 and Dincer *et al.*, 2002). Cho *et al.* (2004), reported that abnormal glucose metabolism leads to oxidative stress and diabetic rats had higher serum levels of superoxide and nitrite/nitrate. This over-production of radicals associated with diabetes. Glucose autoxidation is believed to represent the main source of free radicals under conditions of hyperglycemia (Wolff and Dean 1987).

Oxidative stress plays a dominant role in the pathogenesis of diabetes mellitus (Huang, *et al.*, 2006). Oxidative stress has been associated with the pathogenesis of chronic diabetic complications, (Cai and Kang, 2003). Recently, the ability of antioxidants to inhibit these injuries has raised the possibility of newer therapeutic treatment for preventing oxidant-induced cell death and in decreasing radical oxygen production (Jang and Surh, 2003). Generally, if diabetes mellitus left untreated, it may be initiate degenerative process and other central nerves system (CNS) complications due to accumulation of oxidative free radicals. (Ramanathan,1999). On the other hand, glycemic control was found to reduce the oxidative damage in diabetes (Renu, 2003).

Antioxidants have important therapeutic potential in conditions where oxidative stress is involved (Dincer *et al.*, 2002). In addition, Kedziora-Komatowska *et al.* (2000) confirmed the presence of oxidative stress in streptozotocin induced experimental diabetes and pointed to the beneficial antioxidants effect. Ginseng roots have been found recently to help and protect against cancer (Helms, 2004), cardiovascular disease (Zhou *et al.*, 2004), and stress (Kaneko and Nakanishi, 2004). Also, antioxidants improve memory (Lian *et al.*, 2005 & Nishijo *et al.*, 2004), and reduced colds (Predy, 2005). These health-promoting effects are thought to be due to the high levels of antioxidants in ginseng (ginsenosides) (Attele, 1999). The herb "ginseng" is actually several different types of plants, mainly Korean or Asian ginseng (*Panax ginseng*), Siberian ginseng (*Eleutherococcus senticosus*), and American ginseng (*Panax quinquefolius*). Panax ginseng has been an important herbal remedy in traditional Chinese medicine for thousands years, where it has been used primarily as a treatment for weakness and fatigue (Mahady *et al.*, 2000). Recently, Wang *et al.* (2006) found that ginseng extract inhibits lipolysis in rat adipocytes in vitro by activating phosphodiesterase 4 (PDE4) enzyme. In addition, Jung (2005) confirmed the effectiveness of wild Panax ginseng leaf extract (WGLE) supplementation in detoxifying free radicals that are produced excessively in diabetic-induced complications.

The present study was established on two ways, curative and protective levels to investigate the effect of ginseng on hyperglycemia by streptozotocin-induced diabetes (STZ) and assay the activities of oxidant and antioxidant enzymes in the diabetic rats. Also, to evaluate through biochemical assays if ginseng could prevent the depletion of endogenous anti-oxidants, lipid peroxidation, inhibits the formation of reactive oxygen and scavenge oxygen free radicals, which mean that ginseng may provide greater benefit for hyperglycemia and diabetes mellitus that synergize with its antioxidant actions.

MATERIALS AND METHODS

Materials:

Animals

Forty female albino Sprague-Dawley rats weight 130 g \pm 10 were purchased from the National Organization for Drug Control and Research (NODCAR), Giza, Egypt. The animals were housed in stainless steel experimental animal's cages in air condition room at a constant temperature of (21 \pm 2) °C, with a 12 h light/dark cycle. Rats were kept for one week to adapt the laboratory conditions before starting the experiment, and maintain on the free access of water and a balanced diet.

Diets:

Balanced diet was prepared daily according to (Ali, 1991). The composition of rat's diet is shown in Table (1).

Table 1. Composition of the Balanced Diet in Gram.

Source	Final Weight	Total Calories	Crude Protein	Crude Fiber	Crude Fat	Carbo-hydrates
Balady Bread *	100	260	8.2	0.5	3.3	58.3
Milk powder ** (Whole Fat)	30	125	6.37	----	6.87	9.37
Carrot ***	15	6.3	0.15	0.12	0.04	1.2
Cucumber ***	15	2.55	0.10	0.06	0.01	0.45

* Balady Bread was purchased from bakeries of North Giza.

** Whole fat milk powder was purchased from (NODCAR).

*** Carrot and Cucumber were purchased from local market.

Preparation of ginseng root for rat's diet:

Daily 500 mg of ginseng root/Kg rat's body weight according to Nariman, (1997) and Vuksan *et al.* (2000) were taken and pulverized using the grinder. Then they were mixed well manually by a spoon in 20 g of the balanced diet and introduced to the rats to make sure that rats ate the complete dose from ginseng root then complete the balanced diet. Ginseng Root (Korean ginseng root) (translucent, yellowish-brown), was purchased from Agricultural Seeds, Spices and Medicinal Plants Co. (Abd-El-Rahman M. Harras), Bab El-khalk, Cairo, Egypt.

Induction of diabetes:

Diabetes was induced by a multi dose of Streptozotocin (STZ) (27.5 mg/kg b.w) as previously described (Said *et al.*, 2000). The survived pre-diabetic rats were subjected to booster injection with five successive doses (11.25 mg/kg b.w.) each week intervals. STZ used was purchased from Sigma Chemical Co., St Louis, Mo, USA. About 72 hours after STZ injection, blood samples were taken from the retro-orbital plexus veins, and glucose levels were measured to make sure of the induction of diabetes and those rats became hyperglycemic.

Experimental Design and Groups:

Age-matched 40 female albino rats were randomly divided into the following five groups 1) Control group (untreated rats were kept on basal diet only for 8 weeks); 2) Ginseng group (rats were treated with certain dose of ginseng 500 mg/Kg b.w.); 3) Diabetic group (rats were made diabetic after 4 weeks of experiment and kept only on basal diet); 4) Prophylactic group (rats were treated with certain dose of ginseng 500 mg/Kg b.w. for 4 weeks after that made diabetic and then, continued supplemented with the same dose of ginseng); 5) Curative group (rats were kept on basal diet for 4 weeks then made diabetic, after that treated with ginseng 500 mg/Kg b.w. for 4 weeks.

Table 2. Groups of Treated Rats and Level of Nutrient Supplements.

No.	Treatments	Supplementation level	Experimental Time
1	(N) Normal Control	Balanced Diet (2) month	2 Months
2	(G) Positive Ginseng	Balanced Diet + Ginseng roots 500 mg/kg b.w (2) month	2 Months
3	(D) Positive Diabetic	Balanced Diet (1) month, STZ and Balanced Diet (1) month	2 Months
4	(GDG) Prophylactic	Balanced Diet + Ginseng roots 500 mg/kg b.w (1) month, STZ and Balanced Diet + Ginseng roots 500 mg (1) month	2 Months
5	(NDG) Curative	Balanced Diet (1) month, STZ and Balanced Diet + Ginseng root 500 mg/ Kg b.w (1) month	2 Months

Methods:

Collection of blood samples:

Blood samples were collected from retro-orbital plexus veins from the individual rat according to Schermer, (1967) using fine capillary heparinized tubes. Blood was centrifuged at 3500 rpm for 15 min, and then plasma samples were carefully separated and stored frozen for different biochemical analysis.

Body and relative organs weight:

During the experiments, body weight was recorded every two weeks up to the end of the experimental period (8 weeks). At the end of the experimental period (8 weeks), the rats were anesthetized with light ether and the heart, liver; kidney and spleen of each rat were removed and weighted compared relatively to the body weight (g of organ/100 g live body weight).

Biochemical analysis:

Determination of Blood Parameters:

Blood hemoglobin was determined according to Van Kampen and Zijlstra (1961). Total protein was determined according to Bradford method (1976), Plasma glucose was determined according to Trinder method (1969), plasma lipids profile were determined as follow: 1) Plasma total lipids were determined according to the method of knight *et al.* (1972). 2) Plasma total cholesterol was measured as mentioned by Flegg (1973), 3) Plasma high density lipoprotein-cholesterol (HDL-C) was determined using the method of Fruchart (1982); LDL-C & VLDL-C were determined as described by Friedewald *et al.* (1972). 4) Plasma triglycerides were done enzymatically according to the method of Fossati and Prencipe (1982).

Determination of Antioxidants markers:

a) Malondialdehyde (MDA) was done according to method of Uchiyama and Mihara (1978). MDA value was estimated according to Strove and Makarova (1989). b) Blood Glutathione (GSH) was determined according to the method of Beutler, *et al.* (1963). c) Catalase (CAT) was done according to the method of Sinha (1972). d) Vitamin C was measured as the method of Jagota and Dani (1982).

Statistical analysis

Data were presented as means \pm standard error (SE). Student's t-test was used for evaluating the statistical significance of differences in means according to the method described by (Chase, 1967).

RESULTS AND DISCUSSION

Body and Organs Weight

Table (3) revealed to the prophylactic and the curative effect of ginseng on body weight and body weight gain compared to the normal and diabetic groups. Data obtained showed insignificant difference between all groups on initial body weight. However, final body weight in diabetic group significantly decreased in comparison to control body weight. Similar finding were obtained by Obrosova *et al.* (2003) who reported that final body weight in rats treated with STZ-induced diabetes was lower than in non-diabetic rats, while the initial body weight was the same.

Decreasing on body weight and body weight gain also was observed in diabetic group treated with ginseng in prophylactic and curative experiments. These results are in agreement with those of Dey *et al.* (2003) who found that body weight in obese-diabetic mice was not changed significantly after the treatment with ginseng root. On the other hand, body weight and body weight gain of normal rats treated with ginseng were not affected significantly compared to normal control group. Similar findings were obtained by Yu *et al.* (2005) who found that body weight gain in normal rats was not changed significantly after treated with panax ginseng. While, different results were obtained by Osfor *et al.* (2002) who indicated that treatment with ginseng increased body weight in normal albino rats.

Table 3. Effect of Ginseng Supplemented Diets on Body Weight in Normal & Diabetic Female Albino Rats.

No.of Group	Animal groups	Initial (g)	Final (g)	Gain (g)	Changing (%)
1	Normal Control	139.6 \pm 4.04	184.4 \pm 3.68	44.8	32.1
2	Ginseng	136.7 \pm 5.43	178.8 \pm 6.06	42.1	30.8
3	Diabetic	137.3 \pm 3.80	155.2 \pm 6.05*	17.9*	15.4
4	Ginseng-Diabetic	136.0 \pm 2.82	157.6 \pm 4.60*	21.6	15.9
5	Diabetic-Ginseng	130.4 \pm 4.13	153.0 \pm 5.87*	22.6*	17.3

Each value represents the mean of 8 rats \pm S.E

* Significant difference from the corresponding control at P< 0.05

Relative organs weight:

Table (4) indicated to the prophylactic and curative effect of ginseng on relative organs weight in normal and diabetic rats. The data showed that the relative percentage of heart weight in all groups values statistically were insignificant. In addition, data revealed non-significant effect on relative liver weight. Also, relative kidney weight was insignificantly affected in normal and diabetic rats. Meanwhile, relative spleen weight decreased but not significantly in diabetic compared to normal group. Moreover, results of curative study showed insignificant decrease in relative spleen weight in diabetic group which treated with ginseng in comparison to diabetic group in prophylactic study that treated with ginseng.

These data are coincided with that of Yu *et al.* (2005) who reported that treatment with panax ginseng had no effect on relative liver weight in adult rats. While, Aphala *et al.* (1998) found that liver weight was significantly increased in rats treated with panax ginseng. Also, Ali (1991) found that liver weight increased significantly in diabetic rats. Meanwhile, Gallaher *et al.* (1992) noticed that, relative kidney weights were significantly greater in diabetic groups than in the normal groups. Also Nandini *et al.* (2003) found that, relative weight of kidney increased during diabetes in rats. However, the present data were in agreement with those obtained by Ali, (1991) who reported that diabetes caused highly significant decrease on weight of spleen, while diabetes was not affected on heart weight.

Table 4. Effect of Ginseng Supplemented Diets on Relative Organs Weight in Normal and Diabetic Female Albino Rats.

Group No.	Animal groups	Heart	Liver	Kidney	Spleen
1	Normal Control	0.33 ± 0.01	3.13 ± 0.16	0.53 ± 0.02	0.37 ± 0.02
2	Ginseng	0.33 ± 0.02	3.08 ± 0.23	0.58 ± 0.02	0.40 ± 0.02
3	Diabetic	0.34 ± 0.01	3.02 ± 0.13	0.54 ± 0.01	0.33 ± 0.03
4	Ginseng-Diabetic	0.33 ± 0.01	3.11 ± 0.27	0.55 ± 0.03	0.41 ± 0.03
5	Diabetic-Ginseng	0.35 ± 0.01	3.24 ± 0.14	0.56 ± 0.04	0.33 ± 0.01

Each value represent the mean of 8 rats ± S.E

* Significant difference from the corresponding control at P < 0.05

Blood hemoglobin (Hb)

Data in Table (5) presented the curative results of blood Hb. The levels of Hb statistically were not affected despite the slight increase which observed after 8 weeks in curative group corresponding to diabetic control group and normal control group. The elevation of Hb associated with ginseng treatment was not high, but the slight elevation proved that ginseng may be having some effects on Hb level on diabetic rats. This effect may be due to the antioxidant properties of ginseng against free radicals, which affected on Hb concentration.

Blood Glucose:

Data in Table (5) represented that, plasma glucose in normal group was not affected during the 8 weeks of experiment. The induction of diabetes with STZ led to elevation of plasma glucose in diabetic control group. While, the values significantly was lower after 4 and 8 weeks in prophylactic group treated with ginseng. However, the values were not changed significantly in normal groups, which treated with ginseng.

Data of prophylactic study revealed that STZ which induces hyperglycemic effect in treated rats led to increase plasma glucose level after 8 weeks by 90.27 % in diabetic group compared to control (non diabetic). However, the hyperglycemia was decreased significantly after ginseng treatment by 58.48% and 48.32 % respectively compared to diabetic control group after 4 and 8 weeks respectively. Also, data of curative study showed that treatment with ginseng decreased blood glucose levels by 3.67% and 24.1 % after four and eight weeks respectively compared to diabetic control group.

It is pointed out that the lowering effect of ginseng on blood glucose levels was a remarkable effect in prophylactic experiment, which markedly showed the ginseng role in curative experiment. The lowering effect of blood glucose in ginseng groups may be attributed to ginsenosides (the effective components in ginseng) which decreased blood glucose as mentioned by Dey *et al.* (2003).

Total protein:

Plasma levels of total protein (Table, 5) were not statistically changed after induction of diabetes with STZ, in diabetic groups compared to normal control group in both prophylactic and curative studies. However, different results were obtained by Nariman (1997) and Akula *et al.* (2003) who found that induction of diabetes with STZ decreased total protein level. Also, Wasif (1997) and Mansour *et al.* (2002) showed that, the level of total protein was significantly decreased in alloxan diabetic rats.

However, treatment with ginseng resulted in slight increase in total protein levels of normal rats after 8 weeks. However, treatment with ginseng led to significant increase of total protein in diabetic rats, only in prophylactic study where the values were (8.71 ± 0.15 g/dl) compared to (6.23 ± 0.09 g/dl) in diabetic control group after 8 weeks. Similar findings were obtained by Nariman (1997) who reported that, when ginseng was supplemented to normal rats, slightly increase in serum total protein was found in comparison to control rats, while when ginseng was administrated to STZ-diabetic rats, total protein levels were greatly elevated compared with the untreated control rats. Also, it is noteworthy that insulin stimulates the incorporation of amino acids into protein (Ganong, 1983). Therefore, the stimulatory effects of panax ginseng on protein synthesis may be attributed to the presence of insulin like substances in its components as reported by (Takaku *et al.*, 1988; Murase *et al.*, 1994). Also, in support, other studies have concluded that ginseng components stimulate insulin production by the pancreas (Kimura *et al.*, 1981).

Table 5. Prophylactic and Curative Effects of Ginseng on Blood Hemoglobin, Plasma Glucose and Plasma Total Protein in Normal and Diabetic Female Albino Rats.

Parameter	Weeks	Control	Ginseng	Diabetic	Prophylactic	Curative
Haemoglobin g/dl	Zero	12.90 ±0.45	13.20 ±0.65	13.10 ±0.20	12.50 ±0.24	12.90 ±0.27
	4	13.00 ±0.34	13.20 ±0.30	12.70 ±0.28	13.20 ±0.22	13.20 ±0.34
	8	13.50 ±0.46	12.00 ±0.34	14.80 ±0.70	12.30 ±0.19	15.50 ±0.74
	Mean ± SE	13.30 ±0.25	12.60 ±0.60	13.80 ±1.05	12.80 ±0.45	14.30 ±11.5
Glucose mg/dl	Zero	59.90 ±4.79	58.00 ±2.88	55.70 ±5.00	58.40 ±3.89	56.30 ±3.65
	4	67.70 ±0.83	60.50 ±3.01	139.0 ±2.39**	57.70 ±2.63	133.9 ±5.60**
	8	72.00 ±4.59	60.2 ±5.01	137.0 ±7.82**	70.80 ±2.72**	104.0 ±10.3
	Mean ± SE	69.85 ±2.15	60.35 ±0.15	138.0 ±1.0	64.25 ±6.55	118.95 ±14.95
Total Protein g/dl	Zero	6.23 ±0.23	6.940 ±0.23	6.500 ±0.15	7.80 ±0.36	6.270 ±0.08
	4	6.41 ±0.19	6.630 ±0.15	6.750 ±0.11	6.90 ±0.24	6.65 ±0.16
	8	6.36 ±0.15	7.260 ±0.18	6.230 ±0.09	8.71 ±0.15**	6.00 ±0.14
	Mean ± SE	6.38 ±0.02	6.94 ±0.31	6.49 ±0.26	7.81 ±0.91	6.33 ±0.32

Each value represents the mean of 8 rats ± S.E ; Mean ± SE = represents the mean after induction of diabetes. * & ** mean Significant & Highly significant difference at $P < 0.05$ & $P < 0.01$ respectively.

Lipid Profile:

Total Lipids (TL)

The prophylactic effect of ginseng on plasma total lipids was presented in Table (6). Data showed that plasma total lipids values in all groups at zero time were statistically insignificant. However, after 4 weeks the values of plasma total lipids were decreased in group treated with ginseng compared to control group. On the other hand, the induction of diabetes by STZ led to increase plasma total lipids in diabetic control group. While, in treated group with ginseng showed insignificant decrease of total lipids in prophylactic group.

Table (6) presented the curative effect of ginseng on plasma total lipids. Data obtained revealed that, after, induction of diabetes the plasma total lipids were increased significantly in diabetic groups, these change was highly significant compared to normal control and at zero time. However, after 8 weeks, plasma total lipids were significantly decreased to 256.2 ± 8.45 mg/dl in curative diabetic group treated with ginseng.

Results of prophylactic study revealed that, ginseng had insignificant effect on plasma total lipids during the experimental period. The curative effect of ginseng on plasma total lipids showed that this supplementation significantly decreased total lipids by 37.3 % compared to diabetic group.

Triglycerides (TG)

Prophylactic data in Table (6) revealed that plasma TG were statistically insignificant in group at zero time. Also, after four weeks, plasma TG was not changed in control groups, while significant decrease was observed in all treated groups with ginseng. However, the induction of diabetes led to a significant increase of plasma TG in diabetic control group compared to normal control group. While, the prophylactic values in diabetic groups treated with ginseng were significantly decreased. Also, TG levels in normal groups which treated with ginseng significantly decreased.

The curative effect of ginseng on plasma TG was shown in Table (6). At zero time, TG was not statistically affected. However, after the induction of diabetes, TG significantly increased in diabetic groups compared to normal control group. At the end of experimental period, after 8 weeks, administration of ginseng significantly decreased plasma TG from $(140.5 \pm 17.5$ to 55.4 ± 5.50 mg/dl).

The present data showed that plasma TG levels decreased due to ginseng treatment in normal or diabetic rats. In prophylactic study the lowering effect of ginseng on TG levels were 62.48% and 45.97% compared to diabetic control group after four and eight weeks respectively. On the other hand, in curative study treatment with ginseng led to decrease of plasma TG levels to 60.6 % after eight weeks in diabetic group treated with ginseng compared to non treated diabetic group.

It is shown that the lowering effect of ginseng on plasma TG levels was markedly noticed more in curative than prophylactic experiment where the lowering after 8 weeks was 60.6 % compared to 45.97% in prophylactic and curative ginseng respectively. This lowering of plasma TG due to ginseng treatment may be attributed to ginsenosides which considers the main effective substance in this supplementation. These results are coincided with Smith (1997) who mentioned that plasma TG concentration was elevated by STZ induced diabetes in the non-diabetic rats. Meanwhile, Morgan and Cupp, (2000) reported that ginseng reduced TG in rats.

Total Cholesterol (TC)

The prophylactic data of ginseng on plasma T. cholesterol was tabulated in Table (6). Data obtained revealed that plasma T. cholesterol at zero time and after 4 weeks were not significantly affected. Meanwhile, plasma TC slightly decreased due to ginseng treatment in prophylactic group comparison to diabetic group. In addition, little lowering was shown in TC in ginseng group.

On the other hand, curative results of plasma total cholesterol are shown in Table (6). Data obtained revealed that plasma T. cholesterol were not affected significantly after 4 weeks in curative group. This indicates that, after the induction of diabetes, the mean values of plasma T. cholesterol were not changed significantly due to ginseng treatment. On the other hand, after 8 weeks plasma T. cholesterol decreased significantly in curative group and reached 67.4 ± 0.56 mg/dl.

Generally, plasma T. cholesterol levels, at the beginning of two experiments (prophylactic and curative), were not significantly changed between all groups. Then, after the induction of diabetes with STZ, plasma T. cholesterol levels were slightly changed in diabetic rats compared to normal group. This may be attributed to growth retardation because the lowering of serum cholesterol levels has previously been documented with the restriction of calorie intake in humans (McDermott *et al.* 1995). However, this reduction in plasma T. cholesterol level was insignificant in prophylactic study.

On the other hand, data of curative study showed that treatment with ginseng significantly reduced plasma T. cholesterol levels in diabetic rats. This result coincided with Attele *et al.* (2002) who reported that panax ginseng reduced plasma T. cholesterol in obese diabetic mice.

Table 6. Prophylactic and Curative Effect of Ginseng on Plasma Lipid Profile in Normal and Diabetic Female Albino Rats.

Parameter	Weeks	Control	Ginseng	Diabetic	Prophylactic	Curative
Total Lipids mg/dl	Zero	320.6 ±17.8	308.0 ±18.0	321.7 ±11.4	312.5 ±11.0	308.8 ±12.3
	4	301.5 ±16.0	275.6 ±15.3	423.2 ±10.3**	292.9 ±9.12	424.4 ±14.6**
	8	310.0 ±11.9	312.1 ±12.6	408.7 ±21.5**	371.2 ±20.9	256.2 ±8.45**
	Mean	340.3	332.05	415.95	293.85	305.75
	± SE	± 84.1	±39.15	±7.25	±18.25	±4.25
Triglycerides mg/dl	Zero	74.7 ±6.50	70.5 ±3.96	75.4 ±2.70	74.6 ±6.74	76.8 ±5.05
	4	84.5 ±3.22	48.9 ±4.90**	133.0 ±8.0**	49.9 ±3.09	135.2 ±10.5**
	8	95.0 ±4.78	52.5 ±3.80*	140.5 ±17.5*	75.9 ±7.50**	55.4 ±5.50**
	Mean	89.8	50.7	136.8	62.9	95.3
	± SE	±5.25	±1.8	±3.75	±13.0	±39.9
Total Cholesterol mg/dl	Zero	77.4 ±4.39	76.0 ±4.13	75.0 ±3.85	72.3 ± 3.71	73.0 ±3.15
	4	77.2 ±2.14	68.7 ±4.71	76.6 ±4.21	71.5 ±6.02	79.1 ±3.02
	8	79.2 ±3.28	69.5 ±3.31	83.5 ±3.58	75.4 ±1.51	67.4 ±0.56**
	Mean	78.2	69.1	80.05	73.45	73.25
	± SE	±1.0	±0.4	±3.45	±1.95	±5.85

Each value represents the mean of 8 rats ± S.E ; Mean ± SE after induction of diabetes.

* & ** mean Significant & Highly significant difference at P < 0.05 & P < 0.01 respectively.

LIPOPROTEINS (HDL, LDL and VLDL)

High Density Lipoprotein-Cholesterol (HDL-C):

Table (7) showed the prophylactic effect of ginseng on plasma HDL-C. Data obtained showed that at zero time, there were not significantly variations observed between all groups. Meanwhile, plasma HDL-C was significantly increased in ginseng group after 4 weeks compared to control group. However, after the induction of diabetes with STZ, plasma HDL-C revealed some decrease in diabetic control group compared to normal control group. In contrary, prophylactic group revealed significant increase in plasma HDL-C compared to diabetic control group.

Table 7. Prophylactic and Curative Effect of Ginseng on Plasma Lipoproteins in Normal and Diabetic Female Albino Rats.

Parameter	Weeks	Control	Ginseng	Diabetic	Prophy-lactic	Curative
HDL-cholesterol mg/dl	Zero	38.9 ±1.75	35.8 ±3.35	41.0 ±1.15	36.60 ± 4.35	37.9 ±2.23
	4	38.3 ±2.12	46.4 ± 2.8*	32.2 ±2.14	47.20 ±2.88*	32.0 ±2.64
	8	39.0 ±2.17	40.6 ±1.59	35.1 ±1.91	43.30 ±2.44*	34.0 ±2.17
	Mean	38.65	43.5	33.65	45.25	33.0
	± SE	±0.35	±2.9	±1.45	±1.95	±1.0
LDL-cholesterol mg/dl	Zero	21.56 ±1.34	26.10 ±0.65	18.92 ±2.16	22.78 ±1.99	19.74 ±0.62
	4	22.00 ±0.62	12.52 ±0.93*	17.80 ±0.47	14.32 ±2.5*	20.06 ±1.72
	8	21.20 ±0.61	18.40 ±0.96	20.30 ±1.83	16.92 ±1.43*	22.32 ±2.17
	Mean	21.6	15.46	19.05	15.62	21.19
	± SE	± 0.4	±2.94	±1.25	±1.3	±1.13
VLDL-cholesterol mg/dl	Zero	16.90 ±1.3	9.78 ±0.79	26.60 ±0.59	9.98 ±1.35	27.04 ±1.01
	4	19.00 ±0.64	10.50 ±0.98**	28.10 ±1.6**	15.18 ±0.62	11.08 ±2.1**
	8	17.95 ±0.95	10.14 ±0.76*	27.35 ±3.5*	12.58 ±0.5**	19.06 ±1.1**
	Mean	17.95	10.14	27.35	12.58	19.06
	± SE	±1.05	±0.36	±0.75	±2.60	±7.98

Each value represents the mean of 8 rats ± S.E; Mean ± SE after induction of diabetes.

* & ** mean Significant & Highly significant difference at P < 0.05 & P < 0.01 respectively.

On the other hand, the curative effect of ginseng on plasma HDL-C in diabetic rats was shown in Table (7). Data obtained of plasma HDL-C at 4 weeks after the induction of diabetes revealed non significant variation between diabetic and curative groups. On the other hand, at the end of the experimental period after eight weeks, plasma HDL-C was lowered to 34.0 ± 2.17 mg/dl in curative group. This result means that ginseng was not effective in remediate HDL lowering in curative study.

Also, data in Table (7) showed that ginseng treatment resulted in significant reduction in LDL-C in ginseng group compared with all treated groups. This reduction may be attributed to the significant increase in HDL-C in this group. However, prophylactic treatment revealed significant reduction in LDL-C compared to both control and diabetic groups. In addition, VLDL-C was also decreased in ginseng group, while diabetic group showed significant increase in VLDL-C. Meanwhile both prophylactic and curative groups revealed significant lowering in LDL-C due to ginseng treatments.

Generally, data obtained showed that plasma HDL-C in prophylactic study was increased due to ginseng treatment after four weeks in normal rats. These findings are consistent with Yamamoto *et al.* (1983) who found that treatment with ginseng led to increase HDL-C in a pilot study. Also, the data

was in agreement with Kim and Park (2003) who found that administration of panax ginseng led to increase HDL-C in humans. On the other hand, after 8 weeks ginseng effect was markedly observed only in prophylactic diabetic group, where HDL-C levels increased by 23.36 % compared to diabetic control group. Moreover, curative study showed that ginseng supplementation had no significant effect on plasma HDL-C.

Antioxidants Markers:

Lipid Peroxidation Malondialdehyde (MDA):

Table (8) reveals the prophylactic effect of ginseng on plasma MDA. The differences between plasma MDA values were not significant at zero time. However, induction of diabetes with STZ led to increase plasma MDA significantly in diabetic control group to 11.6 ± 1.92 nmol/ml compared to 7.53 ± 1.82 in normal control group. Meanwhile, ginseng treatment led to significant decrease on plasma MDA in prophylactic group comparison to diabetic control group.

Curative data in Table (8) showed that plasma MDA in rat group was not significant at zero time. However, induction of diabetes led to increase plasma MDA in diabetic group. Meanwhile, after 8 weeks, plasma MDA increased significantly 12.3 ± 3.0 nmol/ml in diabetic group compared to normal group. On the other hand, significant decrease was observed in curative group due to ginseng treatment.

The present data showed that after 4 and 8 weeks, plasma MDA levels decreased in ginseng group, but that reduction was not significant compared to normal. Meanwhile, MDA after 8 weeks significantly decreased to 56.58% in prophylactic group treated with ginseng compared to diabetic group. On the other hand, results of curative study showed that after 4 weeks of treatment with ginseng plasma MDA levels decreased in curative group 35% compared to diabetic group.

In the present study, it was observed that plasma MDA levels increased significantly after the induction of diabetes in diabetic group compared to normal group. These data are consistent with Slatter *et al.* (2000) who reported that MDA concentration is increased considerably in diabetes mellitus. The lowering effect of ginseng on MDA level is not clearly known, but the study of Hammouda *et al.* (1994) mentioned that whether this is an effect of some residual ginseng components or due to alteration of plasma antioxidant mechanism by ginseng cannot be decided.

Glutathione (GSH):

The prophylactic effect of ginseng on blood GSH in diabetic rats was presented in Table (8) Data revealed that blood GSH at zero time and after 4 weeks was not significantly affected in all groups. However, after 8 weeks the induction of diabetes decreased blood GSH to 51.8 ± 2.28 mg/dl in diabetic group compared to 62.7 ± 3.21 in normal group. On the other hand, ginseng was significantly led to increase GSH level in normal rats to 74.9 ± 3.69 mg/dl.

Moreover, results of curative study obtained in Table (8) revealed that, blood GSH levels after 4 weeks were not changed significantly in diabetic ginseng group after the induction, compared to diabetic control group. However, at the end of experimental period-after 8 weeks, blood GSH was significantly increased to 67.6 ± 4.43 mg/dl in curative group compared to 51.8 ± 2.28 in diabetic control group.

Table 8. Prophylactic and Curative Effect of Ginseng on Plasma Antioxidants Biomarkers in Normal and Diabetic Female Albino Rats.

Parameter	Weeks	Control	Ginseng	Diabetic	Prophylactic	Curative
MDA nmol/ml	Zero	7.42 ± 1.50	7.42 ± 1.10	7.01 ± 0.12	7.23 ± 0.50	7.01 ± 1.32
	4	7.53 ± 1.82	5.63 ± 0.71	11.6 ± 1.92	5.24** ± 1.83	10.2 ± 1.53
	8	7.70 ± 1.10	5.23 ± 1.25	12.0 $\pm 1.52^*$	5.21 $\pm 1.30^{**}$	7.82 $\pm 0.91^*$
	Mean	7.55	6.09	10.2	5.89	8.34
	\pm SE	± 0.1	± 0.88	± 2.12	± 0.89	± 1.23
Reduced Glutathione GSH mg/dl	Zero	59.2 ± 2.12	58.7 ± 3.24	61.4 ± 1.75	57.4 ± 3.60	60.3 ± 2.11
	4	66.9 ± 4.27	70.4 ± 4.31	65.2 ± 5.49	60.7 ± 2.21	68.6 ± 3.09
	8	62.7 ± 3.21	74.9 $\pm 3.69^*$	51.8 $\pm 2.28^*$	60.5 $\pm 1.10^*$	67.6 $\pm 4.43^*$
	Mean	62.9	68.0	59.4	59.5	65.5
	\pm SE	± 3.85	± 5.85	± 1.90	± 1.65	± 4.15
L-Ascorbic acid (mg/dl)	Zero	1.27 ± 0.07	1.19 ± 0.08	1.16 ± 0.01	1.20 ± 0.06	1.21 ± 0.08
	4	1.22 ± 0.06	1.23 ± 0.04	0.77 $\pm 0.13^{**}$	1.19 ± 0.07	0.68 $\pm 0.05^{**}$
	8	1.07 ± 0.09	1.36 $\pm 0.05^*$	0.58 $\pm 0.04^{**}$	1.07 $\pm 0.09^{**}$	1.20 $\pm 0.03^{**}$
	Mean	1.18	1.26	0.68	1.15	0.94
	\pm SE	± 0.07	± 0.06	± 0.21	± 0.05	± 0.23
Catalase umol H ₂ O ₂ / min/mg protein8	Zero	22.8 ± 0.22	21.5 ± 0.65	20.6 ± 1.25	21.2 ± 0.65	23.7 ± 0.89
	4	22.3 ± 0.58	23.1 ± 1.08	23.6 ± 0.63	22.0 ± 1.19	23.9 ± 0.62
	8	21.4 ± 1.63	19.5 ± 0.28	23.6 ± 1.04	20.4 ± 0.69	20.7 ± 2.35
	Mean	22.2	21.3	23.6	21.2	22.7
	\pm SE	± 0.51	± 1.24	± 1.33	± 0.53	± 1.37

Each value represents the mean of 8 rats \pm S.E; Mean \pm SE after induction of diabetes.

* & ** mean Significant & Highly significant difference at $P < 0.05$ & $P < 0.01$ respectively.

In the present study, the induction of diabetes by STZ caused significant decrease in the blood GSH levels. Meanwhile, treatment with ginseng in prophylactic and curative study restores this reduction. These findings are in agreement with several workers, who reported decreasing level of GSH in experimental diabetic rats (Selvam and Anuradha, 1990 & Stanly and Menon, 1998). The decreasing levels of GSH in diabetes may be due to increase utilization of GSH in trapping the oxy radicals (Venkateswaran and Pari, 2003).

L-Ascorbic Acid (L-AsA):

Table (8) showed the prophylactic effect of ginseng on blood L-AsA levels. Data obtained revealed that blood L-AsA at zero time and after 4 weeks, were not significantly affected in all groups. However, the induction of diabetes with STZ, significantly decreased blood L-AsA to 0.77 ± 0.13 mg/dl in diabetic control group compared to 1.22 ± 0.06 mg/dl in normal control group. Moreover, treatment with ginseng significantly increased blood L-AsA to 1.07 ± 0.09 mg/dl in ginseng diabetic group compared to diabetic control group. While, in ginseng group, blood L-AsA levels increased to 1.36 ± 0.05 mg/dl. However, these values are significant compared to normal control group (1.07 ± 0.09 mg/dl).

On the other hand, Table (8) showed the curative effect of ginseng on blood L-AsA level. Results obtained reveal that, at zero time, there was not significant variation between all groups. However, after 8 weeks of treatments, blood L-AsA significantly increased to 1.20 ± 0.03 mg/dl in curative group compared to diabetic group (0.58 ± 0.04 mg/dl). The present results agreed with Selvam and Anuradha, (1990); Stanly and Menon, (1998); Venkateswaran and Pari (2003) who found lowering in levels of vitamin C in experimental diabetic rats.

Building upon previous research showing 3 grams of ginseng led to decrease and help stabilize blood sugar levels (Vuksan *et al.*, 2000a & 2000b), researchers isolated the fat cells of rats to see if Ginseng Extract (GE) could inhibit lipolysis (fat breakdown). Surprisingly, they found that GE inhibited lipolysis by 49 percent from baseline, thereby improving blood sugar levels and increasing insulin sensitivity. When trying to determine how ginseng was able to exert these effects, the researchers speculated that GE increased the activation of an enzyme called PDE4, an enzyme that has gained attention for its ability to possibly help the treatment of a wide range of inflammatory diseases from asthma to lung disease (Houslay, 2005).

Catalase (CAT):

Table (8) revealed the prophylactic effect of ginseng on CAT activity in normal and diabetic rats. Data revealed that CAT activity at zero time and after 4 weeks was not significantly affected in all groups. However, after 8 weeks, the induction of diabetes by STZ slightly increased CAT activity to (23.6 ± 0.63 $\mu\text{mol H}_2\text{O}_2/\text{min}/\text{mg}$ protein) in diabetic control group compared to normal control group (21.4 ± 1.63 $\mu\text{mol H}_2\text{O}_2/\text{min}/\text{mg}$ protein).

Curative effect of ginseng on CAT activity in diabetic rats was tabulated in Table (8). Data obtained revealed insignificant variation between all groups at zero time before the induction of diabetes. However, after the induction of diabetes CAT activity was slightly increased in diabetic groups compared to normal control group. On the other hand, after 8 weeks of treatment with ginseng CAT activity showed insignificant decrease to 20.7 ± 2.35 $\mu\text{mol H}_2\text{O}_2/\text{min}/\text{mg}$ protein compared to diabetic group.

The present results showed that, the induction of diabetes with STZ showed insignificantly increase in CAT activity after 4 weeks in diabetic group. These findings are in agreement with those obtained by Torres *et al.* (1999) who found that, the levels of erythrocyte CAT activity in diabetic rats were

greater than in the normal rats. Also, results agreed with Cekic *et al.* (1999) who measured the activity of CAT in the lenses of diabetic and normal rats, and found that, CAT activity increased in diabetic rats compared with normal rats. However, Kedziora-Kornatowska *et al.*(2000) reported that, the induction of diabetes resulted in a decrease of CAT activity after 6 and 12 weeks.

On the other hand, results of prophylactic and curative studies showed that, treatment with ginseng root insignificantly decrease CAT activity in diabetic rats and normal treated with ginseng after 8 weeks of induction of diabetes compared to diabetic group. In contrary, the results obtained by Deng and Zhang (1991) showed that catalase activity was reported to be increased under the effect of ginsenoside Rb1 and RG1.

CONCLUSION

Oxidative stress was involved in the early diabetic cases that not only led to reduce the activities of antioxidant enzymes, but also they reduce antioxidant capacity and plasma membrane dysfunction due to lipid peroxidation. However, ginseng supplementation increased activities of antioxidant enzymes and improved plasma membrane function. The study indicated that ginseng was beneficial to the treatment of diabetic rats due partly at least to its antioxidant property.

Physicochemical, biochemical, and cellular assays confirmed that ginseng inhibits the formation of reactive oxygen radicals and lipid peroxidation, scavenged oxygen free radicals, and prevented the depletion of endogenous anti-oxidants which that ginseng may provide greater benefit for hyperglycemia and diabetes mellitus for its antioxidant actions that synergize with it. Finally the current work indicated that more attention should be accomplished to natural plants to protect and cure human bodies from oxidative damage and maintain healthy body, also, makes strong defense system for the cells from environmental abiotic and biotic stress.

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الجنسج وقائيا أو علاجيا يثبط ارتفاع سكر الدم والإجهاد التأكسدي فى الفئران البيضاء المصابة بالسكري

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يعتبر مرض البول السكرى واحداً من أهم الأمراض انتشاراً فى جمهورية مصر العربية وهو من الأمراض المزمنة التى تلازم المريض طوال حياته و يعتبر من الأمراض المعقدة نظراً لمضاعفاته الخطيرة و المتعددة على جميع أجهزة الجسم . و الرعاية الغذائية لمرضى البول السكرى من الأمور شديدة الأهمية وذلك للتقليل من مضاعفاته . ويتجه العالم الآن للعودة إلى الطبيعة و استخدام النباتات والأعشاب الطبية التى ثبت علمياً دورها فى علاج العديد من الأمراض و من بينها مرض البول السكرى.

وتهدف الدراسة الحالية إلى معرفة التأثير الوقائى و العلاجى لجذور الجنسج على مستوى سكر الدم وتقدير التغير فى نشاط بعض مضادات الأكسدة وبعض المؤشرات البيوكيميائية مثل سدلولات حدوث عملية الأكسدة كمركب المالمونالدهيد وتغير مستوى بعض مضادات الأكسدة الإنزيمية مثل إنزيم الكاتاليز وبعض الجزيئات الحيوية المضادة للأكسدة مثل الجلوتاثيون المختزل وفيتامين C فى الدم لدى فئران التجارب السليمة و المصابة بالسكري .

تضمنت هذه الدراسة ٤٠ فأراً من الفئران البيضاء الإناث، وزن (١٣٠ ± ١٠ جم) تم شرائها من الهيئة القومية للرقابة والبحوث الدوائية بحالة صحية جيدة وتم وضعهم فى أقفاص من الأستانلس أستيل ثمانية فئران/مجموعة ، وضعت فى جو هوائى مناسب وغذيت على وجبة متزنة فى العناصر الغذائية . وقد اشتملت الدراسة على تجربتين : الأولى تهدف إلى دراسة التأثير الوقائى لجذور الجنسج ، والثانية تهدف إلى دراسة التأثير العلاجى لجذور الجنسج على إناث الفئران التى تم إصابتها بالسكري نتيجة الحقن بمادة الأستربتوزوتوسين. وقسمت الفئران لخمسة مجموعات ، المجموعة ١ كـنترول "سليم" وتم تغذيتها على الوجبة المتزنة لمدة شهرين ، أما المجموعة ٢ "سليم معاملة بالجنسج" تم تغذيتها لمدة شهرين على التوالى بنفس الوجبة المتزنة مضافاً إليها الجنسج لدراسة تأثير التغذية بالجنسج على الفئران السليمة وغير المستحدث بها مرض السكرى . أما المجموعة ٣ "مصائب بالسكري" فقد استحدثت بها مرض السكر بمقار الأستربتوزوتوسين وتم تغذيتها على الوجبة المتزنة كمجموعة مقارنة ، أما المجموعة ٤ فقد جعلت لدراسة التأثير الوقائى حيث غذيت على الوجبة المتزنة مضافاً إليها جذور الجنسج (٥٠٠ مجم/كجم من وزن الجسم) لمدة شهر بنفس الوجبة ونفس الجرعات ثم تم إصابتها بالسكري وبعد ذلك تم استكمال التغذية بنفس الوجبة ونفس الجرعات السابقة لمدة شهر آخر ، بينما اعتبرت المجموعة ٥ لدراسة التأثير العلاجى لجذور الجنسج حيث غذيت على الوجبة المتزنة أولاً لمدة شهر ثم تم إصابتها بالسكري وبعد ذلك غذيت على الوجبة المتزنة مضافاً إليها جذور الجنسج (٥٠٠ مجم/كجم من وزن الجسم) لمدة شهر آخر على التوالى.

أظهرت النتائج فى التجربة الوقائية أن المعاملة بالجنسج أدت إلى انخفاض معنى فى مستوى كل من سكر الدم ٤٨,٣% ، الجلوسيريدات الثلاثية ٤٥,٩% ، المالمونالدهيد ٥٦,٦% و حدثت زيادة معنوية فى مستوى كل من الجلوتاثيون المختزل ١٦,٨% ، وحمض الأسكوربيك ٨٤,٥% فى الفئران المصابة بالسكري . كما أوضحت النتائج فى التجربة العلاجية أن المعاملة بالجنسج أدت إلى انخفاض معنى فى مستوى كل من سكر الدم ٢٤% والدهون الكلية ٣٧,٣% و الجلوسيريدات الثلاثية ٦٠,٦% ، والمالمونالدهيد ٣٤,٨% و حدثت زيادة معنوية فى مستوى الجلوتاثيون المختزل ٣٠,٥% ، وحمض الأسكوربيك ١٠٦,٩% .

توصى الدراسة بالانتباه جيداً لأهمية جذور الجنسج لتأثيرها الوقائى والعلاجى فى خفض مستوى سكر الدم لدى الفئران المصابة بالسكري كما أظهرت الدراسة الدور الوقائى لجذور الجنسج فى خفض مستوى الجلوسيريدات الثلاثية فى الفئران السليمة والمصابة بالسكري علاوة على قدرة الجنسج فى زيادة مستوى كل من الجلوتاثيون المختزل وحمض الأسكوربيك كمضادات أكسدة فعالة فى حماية الجسم من الشقوق الحرة مما يعمل على الحفاظ على حيوية خلايا الجسم سليمة من مهاجمة الشقوق الحرة.