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Original Research

Antiobesity, antioxidant and antidiabetic activities of red Ginseng plant extract in obese diabetic rats

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Abstract

Aim: This study aimed to investigate the effects of red ginseng extract (RGE) on adiposity index, some serum biochemical parameters and tissue antioxidant activity in obese diabetic rats.

Methods: Five groups of male Sprague-Dawley rats were used. Group (1) was negative control and the other 4 groups were fed on high fat-diet for 6 weeks to induce obesity. The obese rats were then rendered diabetic by intraperitoneal injection of alloxan for 5 days. Group (2) was kept obese diabetic (positive control) and the other 3 groups were orally given RGE at 100, 200 and 400 mg /kg /day, respectively, for 4 weeks. Blood samples were collected for biochemical analyses and kidneys were taken to assay of activities of antioxidant enzymes.

Results: oral dosage of RGE to obese diabetic rats significantly ($P < 0.05$) reduced adiposity index; decreased serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma- glutamyl transpeptidase (GGT) enzymes, total cholesterol (TC), triglycerides (TG), and low density lipoproteins (LDL-c) and improved atherogenic index. Blood glucose and leptin hormone decreased, but insulin increased by administration of RGE. it increased activities of superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT) antioxidant enzymes in kidneys tissues.

Conclusion: Red ginseng extract produces antiobesity, antioxidant, and antidiabetic activities in obese diabetic rats. The study suggests that red ginseng plant may be beneficial for the treatment of patients who suffer from obesity associated with diabetes.

INTRODUCTION

Obesity is an excessive fat accumulation in the body that results from an imbalance between energy intake and energy expenditure associated with genetic, metabolic, and behavioral components. Despite of a major contribution of genetic susceptibility, the rapid development of obesity might reflect substantial changes of other factors such as dietary habits [1]. The prevalence of obesity is rising dramatically among all ages with the changes of lifestyles and dietary fat intake [2]. Obesity represents a serious health problem that increased the risk for many diseases such as hypertension and diabetes mellitus [3]. Obesity and insulin resistance are strongly associated with the infiltration of adipose tissue by inflammatory cells [4].

Diabetes mellitus is a chronic and progressive metabolic disease characterized by hyperglycaemia due to insulin deficiency, or resistance, or both. Hyperglycemia occurs when the cells become unable to utilize glucose and/or the liver and skeletal muscles cannot store glycogen [5, 6]. The increased extracellular and intracellular glucose concentrations result in oxidative stress due to increased production of reactive oxygen species (ROS) and sharp decrease in antioxidant body defenses [7]. Oxidative stress plays a key role in the onset and development of diabetes complications, notably diabetic nephropathy [8]. Insulin resistance, a common accompaniment of obesity, is a major risk factor for diabetes mellitus [9]. Because synthetic chemical drugs prescribed for

treating obesity and diabetes had many adverse side effects, therefore there is a great need to search for new and safe alternative drugs from medicinal plants.

Red ginseng (Family *Araliaceae*) is one of medicinal plants with fleshy roots. The Roots of red ginseng are rich in glycosylated saponins (ginsenosides) which have been reported to possess various biological properties. The crude extract of red ginseng roots and the isolated ginsenosides were found to produce hypoglycemic and antidiabetic activities [10, 11, 12, 13]; anticarcinogenic effect [14]; hepatoprotective action [15] and hypocholesterolemic and antihyperlipidemic effects [16] in humans and experimental animals. The crude saponins of Korean red ginseng roots were reported to possess anti-obesity effect in rats fed on high fat-diet [17]. .

MATERIALS AND METHODS

Plant

Dried roots of red ginseng (Family *Araliaceae*) were purchased from a local market of Agricultural Herbs, Spices and Medicinal plants, Cairo, Egypt. The roots were grinded using an electric mixer into a fine powder and thereafter subjected to the alcohol extraction.

Alloxan and biochemical kits

Alloxan was purchased from El-Gomhoryia Company for Chemicals; Cairo, Egypt. It is dispensed in the form of white powder packed in tightly closed brown bottles each containing 25 gram alloxan monohydrate. Kits for biochemical determinations of blood glucose, leptin hormone (radioimmunoassay) and insulin hormone (enzyme-linked immunoassay) were purchased from Gamma Trade Company, Egypt. The other biochemical kits were obtained from Biodiagnostic Company, Dokki, Egypt.

Rats and feeding

Forty five mature male Sprague Dawley rats weighing 185 -200 g body weight and 10-12 weeks old were used in this study. Animals were obtained from the Laboratory Animal Colony, Agricultural Research Center, Egypt. Rats were housed in a well ventilated animal room under standard conditions of 24 ℃ temperature, 50% relative humidity and 12 hr light/12 hr dark cycle. Basal diet was prepared according to report of American Institute of Nutrition (AIN) [18] and water was provided *ad libitum*.

Preparation of plant extract

The crude extract of dry red ginseng roots was prepared according to the method described by Shalaby and Hamowieh [19]. Two hundred grams of powdered red ginseng roots were soaked in 1 liter of 90% ethyl alcohol and kept in a refrigerator with daily shaking for 5 days. Ethanol was thereafter evaporated using a rotatory evaporator connected to vacuum pump. Twenty grams of the obtained semisolid extract were mixed with 2 ml of Tween 80 (suspending agent) and distilled water (98 ml) was gradually added to obtain 20% liquid extract.

Induction of obesity and diabetes

Obesity and acute hyperlipidemia was induced by feeding rats on high fat-diet (HFD) which supplies 45 % calories from fat (lard) for 6 weeks according to Bhatt *et al.* [20], while the basal diet supplies 11% calories from fat (corn oil). This model of obesity closely resembles the reality of obesity in humans. The obese rats were thereafter rendered diabetic by intraperitoneal injection of alloxan in a dose of 120 mg/kg/day for 5 days as described by Ashok *et al.* [21].

Experiment and groups of rats

The experiment was carried out on forty five mature Sprague Dawley male rats randomly distributed into 5 equal groups. Group (1) was fed on basal diet and kept negative control, while the other 4 groups were fed on HFD for 6 weeks to induce obesity. The obese rats were then rendered diabetic by intraperitoneal injection of alloxan (120 mg/kg/day) for 5 days. After induction of diabetes, the group (2) was kept obese diabetic (positive control), while groups (3), (4) and (5) were orally given red ginseng extract in doses 100, 200 and 400 mg/kg, respectively once daily for 4 weeks. At the end of experimental period, final body weights of rats were recorded and the adiposity index (Ad I) was calculated by dividing the total weight of mesenteric, visceral, epididymal and retroperitoneal adipose tissue by the body weight and multiplied by 100 i.e. Ad I = fat weight/body weight x 100 according to Pichon *et al.* [22]. Rats were then euthanized and blood samples were collected from retro-orbital plexuses of veins of eye using capillary tubes. Blood was left to clot and centrifuged at 3000 rpm for 15 min. at 4 °C for separating the serum which was frozen and stored at −18°C until biochemical analyses. Kidneys were taken to assay the activities of tissue antioxidant enzymes.

Biochemical analysis

Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) [23]; gamma- glutamyl transpeptidase (GGT) [24]; total cholesterol (TC) and high density lipoprotein (HDL-c) cholesterol [25] and triglycerides (TG) [26] were chemically determined. Low density lipoprotein (LDL-c) cholesterol was calculated using this formula: LDL-c = TC – (TG/5) – HDL-c). Blood glucose was determined using glucose enzymatic kit according to Siest *et al.* [27]. Insulin was

estimated using antibody radioimmunoassay (RIA) assay [28] and leptin hormone was determined using enzyme-linked immunosorbent (ELISA) assay [29].

Antioxidant activity

One gram of kidney tissue was washed in ice-cooled 0.9% NaCl solution and homogenized in ice-cooled 1.15% solution of potassium chloride and 50 mMol potassium phosphate buffer solution (pH 7.4) to yield 10% (w/v) homogenate. Homogenization was performed using Sonicator, 4710 Ultrasonic Homogenizer. Kidney homogenates were centrifuged at 4000×g for 10 min. at 4°C and the supernatants were used to assay activities of antioxidant enzymes superoxide dismutase, glutathione peroxidase and catalase according to Nishikimi *et al.* [30], Paglia and Valentine [31] and Sinha [32], respectively.

Statistical analysis

Statistical analysis was carried out using one-way analysis of variance (ANOVA) followed by Duncan's multiple range test with SPSS computer program [33]. Differences between the controls and treated groups were considered significant at $P < 0.05$ level.

RESULTS

Feeding of male rats on high fat-diet (HFD) for 6 weeks significantly ($P < 0.05$) increased the final body weight, fat weight and adiposity index as compared to negative control rats fed on basal diet. Oral administration of red ginseng extract at doses 100, 200 , 400 mg/kg to obese diabetic rats for 4 weeks caused significant ($P < 0.05$) decreases in the final body weight, fat weight and adiposity index as compared to positive (obese diabetic) control rats, in a dose dependent manner, as shown in Table (1).

The results showed that male rats fed on high fat-diet (HFD) for 6 weeks had significant ($P < 0.05$) increases in serum levels of liver enzymes aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transpeptidase (GGT) when compared with negative control rats fed on basal diet. Oral administration of red ginseng extract at doses 100, 200 and 400 mg/ kg to obese diabetic rats for 4 weeks induced significant ($P < 0.05$) reductions of the elevated serum levels of AST, ALT and GGT enzymes when compared to the positive control group, in a dose dependent fashion, as recorded in Table (2).

Table 1. Effect of red ginseng extract (RGE) on body weight (B.wt.), fat weight (F.wt.) and adiposity index (Ad I) in rats.

Parameters Groups	B.wt. (g)	F.wt. (g)	Ad I (%)
Group (1) **Negative control**	261 ± 13.0^{c}	7.46 ± 0.12^{c}	2.86 ± 0.15^{a}
Group (2) **Obese diabetic control**	315 ± 19.0^{a}	16.61 ± 0.22^{a}	5.27 ± 0.17^{c}
Group (3) **REG (100mg/kg)**	295 ± 10.0^{b}	14.12 ± 0.25^{b}	4.79 ± 0.24^{b}
Group (4) **REG(200 mg/kg)**	283 ± 13.0^{b}	11.20 ± 0.17^{b}	3.96 ± 0.16^{b}
Group (5) **REG(400mg/kg)**	275 ± 12.0^{b}	9.45 ± 0.19^{b}	3.44 ± 0.19^{b}

Means ± SE with different letters superscripts in the same column are significant at $P < 0.05$ using one way ANOVA test.
n= 9 rats/group.

Table 2. Effect of red ginseng extract (RGE) on levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma- glutamyl transpeptidase (GGT) liver enzymes in rats.

Parameters Groups	AST (U/L)	ALT (U/L)	GGT (U/L)
Group (1) **Negative control**	44.0 ± 2.11^{d}	36.0 ± 2.12^{d}	23.5 ± 1.15^{d}
Group (2) **Obese diabetic control**	82.0 ± 6.12^{a}	64.0 ± 5.41^{a}	44.0 ± 3.17^{a}
Group (3) **REG (100mg/kg)**	74.0 ± 5.14^{b}	55.0 ± 4.25^{b}	38.0 ± 2.24^{b}
Group (4) **REG(200 mg/kg)**	60.0 ± 5.34^{b}	47.0 ± 3.17^{c}	36.0 ± 2.16^{b}
Group (5) **REG(400mg/kg)**	49.0 ± 3.13^{c}	33.0 ± 2.19^{c}	26.0 ± 2.19^{c}

Means ± SE with different letters superscripts in the same column are significant at $P < 0.05$ using one way ANOVA test.
n= 9 rats/group.

As demonstrated in Table (3), feeding of male rats on high fat-diet (HFD) for 6 weeks significantly (P <0.05) increased serum levels of total cholesterol (TC) and triglycerides (TG) when compared to those fed on basal diet. Oral administration of red ginseng extract at doses 100, 200 and 400 mg /kg to obese diabetic rats for 4 weeks significantly (P < 0.05) decreased the elevated serum levels of TC and TG when compared with obese diabetic control rats.

Serum analysis revealed that male rats fed on high fat-diet (HFD) for 6 weeks had a significant decrease in high density lipoprotein (HDL-c), increase in low density lipoprotein (LDL-c), and high atherogenic index (AI) when compared with the negative control group. Oral administration of red ginseng extract to obese diabetic rats for 4 weeks increased serum HDL-c, decreased LDL-c and improved AI as compared with the positive control group (Table 4).

Data in Table (5) showed that male rats when fed on high fat-diet (HFD) for 6 weeks had significant (P < 0.05) increases in serum glucose and leptin hormone and decrease in insulin hormone levels when compared to those fed on basal diet (negative control group). Red ginseng extract when orally given at doses 100, 200 and 400 mg kg to obese diabetic rats for 4 weeks significantly (P < 0.05) decreased serum glucose and leptin hormone, but increased insulin levels when compared with positive control rats, in a dose dependent manner.

Feeding a high fat-diet (HFD) to male rats for 6 weeks caused significant (P < 0.05) decreases in renal tissue levels of superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT) antioxidant enzymes when compared to those fed on basal diet. Oral administration of red ginseng extract at doses 100, 200 and 400 mg/kg to obese diabetic rats for 4 weeks significantly (P < 0.05) increased tissue levels of SOD, GPx and CAT enzymes when compared with the positive control group, in a dose dependent manner(Table 6).

Table 3. Effect of red ginseng extract (RGE) on serum total cholesterol (TC) and triglycerides (TG) in rats.

Parameters Groups	TC (mg/dL)	TG (mg/dL)
Group (1) **Negative control**	95.29 ± 2.03^{d}	63.94 ± 2.19^{d}
Group (2) **Obese diabetic control**	152.70 ± 3.56^{a}	172.60 ± 6.73^{a}
Group (3) **REG (100mg/kg)**	122.65 ± 7.34^{b}	144.12 ± 6.25^{b}
Group (4) **REG(200 mg/kg)**	118.50 ± 6.42^{b}	138.20 ± 7.17^{b}
Group (5) **REG(400mg/kg)**	105.60 ± 4.32^{c}	120.82 ± 6.19^{c}

Means ± SE with different letters superscripts in the same column are significant at P < 0.05 using one way ANOVA test.
n= 9 rats/group.

Table 4. Effect of red ginseng extract (RGE) on levels of high density lipoprotein (HDL-c), low density lipoprotein (LDL-c) cholesterol and atherogenic index (AI) in rats.

Parameters Groups	HDL-c (mg/dL)	LDL-c (mg/dL)	AI LDL-c / HDL-c
Group (1) **Negative control**	70.97 ± 1.89^{a}	12.48 ± 3.11^{d}	0.176
Group (2) **Obese diabetic control**	53.34 ± 2.52^{c}	67.06 ± 5.65^{a}	1.257
Group (3) **REG (100mg/kg)**	59.66 ± 3.22^{b}	44.83 ± 2.25^{b}	0.751
Group (4) **REG(200 mg/kg)**	61.45 ± 4.12^{b}	33.20 ± 2.17^{c}	0.540
Group (5) **REG(400mg/kg)**	65.50 ± 5.16^{b}	31.45 ± 3.19^{c}	0.480

Means ± SE with different letters superscripts in the same column are significant at P < 0.05 using one way ANOVA test.
n= 9 rats/group.

Table 5. Effect of red ginseng extract (RGE) on blood glucose (BG), leptin and insulin hormones levels in rats.

Parameters Groups	BG (mg/dL)	Leptin (ng/ml)	Insulin (ng/ml)
Group (1) **Negative control**	220 ± 12.0[d]	2.50 ± 0.15[d]	2.95 ± 0.15[a]
Group (2) **Obese diabetic control**	285 ± 10.0[a]	4.90 ± 0.11[a]	0.89 ± 0.13[d]
Group (3) **REG (100mg/kg)**	266 ± 13.0[b]	4.10 ± 0.18[b]	1.82 ± 0.24[b]
Group (4) **REG(200 mg/kg)**	245 ± 11.0[b]	3.35 ± 0.17[b]	2.43 ± 0.12[b]
Group (5) **REG(400mg/kg)**	237 ± 10.0[c]	2.75 ± 0.19[c]	2.52 ± 0.14[c]

Means ± SE with different letters superscripts in the same column are significant at
P < 0.05 using one way ANOVA test.
n= 9 rats/group.

Table 6. Effect of red ginseng extract (RGE) on activities of tissue superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT) antioxidant enzymes in rats.

Parameters Groups	SOD (U/mg protein)	GPx (nmol/min/mg protein)	CAT (nmol/min/mg protein)
Group (1) **Negative control**	58.70 ± 2.24[a]	0.69 ± 0.01[a]	0.185 ± 0.001[a]
Group (2) **Obese diabetic control**	38.50 ± 2.88[d]	0.18 ± 0.04[d]	0.138 ± 0.002[d]
Group (3) **REG (100mg/kg)**	44.74 ± 3.46[c]	0.22 ± 0.03[b]	0.145 ± 0.001[b]
Group (4) **REG(200 mg/kg)**	48.95 ± 2.58[c]	0.24 ± 0.01[b]	0.158 ± 0.001[b]
Group (5) **REG(400mg/kg)**	55.25 ± 2.73[b]	0.49 ± 0.01[c]	0.175 ± 0.002[c]

Means ± SE with different letters superscripts in the same column are significant at
P < 0.05 using one way ANOVA test.
Unit of GPx= nmol of GSH utilized/min/mg protein.
Unit of CAT= nmol of H_2O_2 utilized/min/mg protein.
n= 9 rats/group.

DISCUSSION

This study aimed to investigate the effects of red ginseng extract on adiposity index, serum liver enzyme, lipid profile, blood glucose, leptin and insulin hormones levels as well as the activities of renal antioxidant enzymes in obese diabetic rats.

In the present era, medicinal plants and culinary herbs with antihyperlipidemic and antidiabetic activities have gained much attention, especially those with little toxicity properties. It has been widely accepted that the biological value of plants depends on their bioactive constituents such as flavonoids, anthocyanins, saponins, diterpenes and other phytochemicals [34, 35].

In the current study, obesity was experimentally induced by feeding rats on high fat-diet for 6 weeks according to the method described by Bhatt *et al.* [20]. This model of obesity in rats closely resembles the reality of obesity in humans. However, the experimental obesity could be also induced in rats and mice by other methods such as feeding on high carbohydrate diet, damage in anterior hypothalamus and genetically induced obesity [36]. In this study, the rat model used was obese diabetic rats where the obese rats were rendered diabetic by intraperiotoneal injection of alloxan for 5 days.

The results of the present study showed that the extract of red ginseng (RGE) when given orally to obese diabetic rats for 6 weeks caused marked decreases in the body weight, fat weight and adiposity index. The anti-obesity effect of RGE that reported in this study was similar to the previously reported [17, 37, 38]. The previous authors reported that the crude saponins of Korean red ginseng induced an antiobesity effect in rats fed on high fat-diet. Feeding rats on high fat-diet was previously reported to increase the final body weight, fat weight and concentrations of serum triglycerides (TG), total cholesterol (TC), and low density lipoprotein (LDL-c) cholesterol when compared to rats fed on the basal diet [39].

The mechanism(s) underlying the antiobesity effect of red ginseng extract could (RGE) be possibly explained by its hyperinsulinemic effect that was evident in the present study. It is evident that hyperinsulinemia and insulin resistance are common features of obesity in humans [40] and rats [39]. In addition, the antiobesity activity of RGE could also be attributed to the high level of leptin hormone caused by RGE that reported in the current study. It is known that leptin is a peptide hormone secreted by adipose tissue in proportion to its mass and when leptin circulates in blood and acts on the brain to regulate food intake (appetite) and energy expenditure When body fat mass decreases, the plasma leptin levels decreases so stimulating appetite and suppressing energy expenditure till fat mass is restored [29]. On this basis, the reduced adiposity index following administration of RGE to obese diabetic rats could be attributed to the low serum leptin level in the treated rats.

The hepatoprotective effect of red ginseng extract (RGE) reported in this study was evident by the significant decreases of the elevated serum levels of liver enzymes (AST, ALT and GGT) in the treated rats. The reported hepatoprotective effect RGE agreed with that demonstrated by previous authors [41, 42]. The authors concluded that the isolated saponins of Korean red ginseng caused hepatoprotective effect and induced restoration of hepatic enzymes in CCl_4-intoxicated rats. In addition, Korean red ginseng extract inhibited the high levels of AST and ALT enzymes and ameliorated liver injury after 70 % hepatectomy in rats [43]. The mechanism of hepatoprotection of red ginseng saponins was assumed to be through an inhibition of the activity of cytochrome P450 enzymes in the rat liver microsomes [44].

The decrease in serum levels of total cholesterol, triglyceride and LDL-c caused by RGE, in this study, was similar to that previously reported [13, 16, 37]. The authors concluded that RGE and its saponins fraction lowers the levels of total cholesterol, triglycerides and LDLc in man and rats. The hypolipidemic effect of RGE was attributed to its content of saponins which inhibited the intestinal absorption of cholesterol and reduced serum cholesterol levels in rats. In man and rabbits, red ginseng extract reduced serum total cholesterol, LDL-c, and triacylglycerol and so improved serum lipid profile [16]. .

Rats fed on high fat-diet for 6 weeks had significantly lower serum insulin levels than those fed on basal diet. This effect agreed with that the pervious finding that feeding high-fat diet to rats resulted in impaired pancreatic function and decreased insulin secretion [45]. Red ginseng extract when orally given to obese diabetic rats at doses 100, 200, and 400 mg/kg caused hyperinsulinemia, in a dose dependant manner. The hyperinsulinemic and hypoglycemic effects of RGE were similar to that those reported in diabetic mice [10] and in obese rats [11]. Some previous studies revealed that hyperinsulinemia and insulin resistance are common features of obesity in humans [40] and in rats [39]. The mechanism(s) of antidiabetic and antiobesity effects of Korean red ginseng (KRG) extract (200mg/kg, oral) was examined in obese insulin resistant rat model. The results showed that KRG led to a significant reduction in body weight, fat mass reduction associated with increased insulin sensitivity. The authors concluded that KRG may have antidiabetic and antiobesity effects due to partly increased insulin sensitivity by increased adipokines (cytokines secreted by adipose tissue) and partly due to enhanced insulin signaling [12]. .

The present results showed that rats fed on high fat-diet (HFD) had high serum leptin hormone level when compared with those fed on basal diet. This finding agreed with that reported by Huang *et al*. [45] who found that HFD elevated serum leptin level in rats. Leptin plays a key role in regulating energy intake and energy expenditure. Leptin is primarily manufactured in the adipocytes of white adipose tissue, and the level of circulating leptin is proportional to the total amount of fats in the body. RGE significantly decreased serum leptin levels in obese diabetic rats. This result agreed with that previously reported that saponins of red ginseng reduced body weight, decreased serum leptin level and depressed appetite in obese rats [45].

The activity of antioxidant enzymes (SOD, GPx and CAT) decreased in renal tissues in obese diabetic rats fed on HFD, This finding can be explained by hyperglycemia due to alloxan injection that causes renal oxidative stress . It is known that oxidative stress plays a key role in the onset and development of diabetes complications, notably diabetic nephropathy [8]. Red ginseng extract (RGE) when given to obese diabetic rats induced an antioxidant effect that evident by increased activities of renal tissue SOD, GPx and CAT antioxidant enzymes. The antioxidant effect of RGE could be attributed to its hypoglycemic activity that reported in this study. This activity of RGE was similar to that previously reported [11, 12, 13].

In conclusion, oral administration of red ginseng extract to obese diabetic rats exhibited antiobesity, antidiabetic, hepatoprotective, antihyperlipidemic and antioxidant activities. These results suggest the possibility of use of red ginseng plant for treating obese patients who suffer from diabetes mellitus due to its good antiobesity, antioxidant and antidiabetic effects.

CONFLICT OF INTEREST

None.

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