

Anti-Obesity and Antidiabetic Activities of Red Ginseng Plant Extract in Obese Diabetic Male Rats

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Abstract: The effects of red ginseng extract (RGE) on adiposity index, serum levels of liver enzymes, lipid profile, blood glucose, leptin and insulin hormones and renal antioxidant capacity in obese diabetic rats were investigated. Forty five adult male Sprague-Dawley rats were randomly divided into 5 equal groups. Group (1) was fed on basal diet (negative control), while 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 (120 mg/kg/day) for 5 days. Thereafter, group (2) obese diabetic was kept as 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 separating the serum which used for biochemical analyses. Kidneys were taken to assay the activity of tissue antioxidant enzymes. The results showed that oral administration of RGE significantly ($P < 0.05$) reduced adiposity index; decreased serum levels of aspartate aminotransferase, alanine aminotransferase, gamma- glutamyl transpeptidase enzymes, total cholesterol, triglycerides and low density lipoproteins and improved atherogenic index in obese diabetic rats. Blood glucose and leptin hormone decreased, but insulin increased by administration of RGE. It also increased activities of superoxide dismutase, glutathione peroxidase and catalase antioxidant enzymes in kidneys of obese diabetic rats. These results point to the potential possibility of use of red ginseng plant for the treatment of obese diabetic patients.

Key words: Red Ginseng • Obesity • Diabetes • Liver Enzymes • Lipid Profile • Insulin • Leptin • Antioxidant • Rats

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 cardiovascular diseases, 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 insulin 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 complementary alternative medicine, particularly from medicinal plants.

Red ginseng is one of medicinal plants with fleshy roots that belong to genus *Panax* of family *Araliaceae*. Roots of red ginseng are rich in glycosylated saponins named 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], anticarcinogenic effect [12], hepatoprotective action [13] and hypocholesterolemic and antihyperlipidemic effects [14] 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 [15].

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

MATERIALS AND METHODS

Materials

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 ground using an electric mixer into a fine powder and thereafter subjected to the alcohol extraction.

Alloxan and Biochemical Kits: It 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. Glucose enzymatic kit for estimating blood glucose and radioimmunoassay kits for leptin and insulin hormones were purchased from Gamma Trade Company, Egypt. The other biochemical kits were obtained from Biodiagnostic Company, Dokki, Egypt.

Rats: 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°C temperature, 50%

relative humidity and 12 hr light/12 hr dark cycle. Basal diet and water was *ad libitum*. Rats were acclimatized to the laboratory environment for 7 days before start of the experiment.

Methods: Preparation of basal diet: Basal diet was prepared using AIN 93 according to Reeves *et al.* [16]. It was formulated of 20 % protein (casein), 10 % carbohydrate (sucrose), 5 % fat (corn oil), 2% choline chloride, 1% vitamin mixture, 3.5 % salt mixture and 5% fibers (cellulose). The remainder was corn starch up to 100 %.

Preparation of Plant Extract: 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 [17].

Induction of Obesity and Diabetes in Rats: Obesity and acute hyperlipidemia was induced by feeding rats on high fat-diet (HFD) which supplies 45 % calories from fat (lard) for 6 weeks [18], while normal 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 then rendered diabetic intraperitoneal injection of alloxan in a dose of 120 mg/kg/day for 5 days [19]. The obese diabetic rats were continuously fed on HFD during the experiment period.

Experiment and Groups of Rats: The experiment was carried out on forty five mature (185 -200 g body weight) 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. Thereafter, group (2) was kept obese diabetic (positive control), while groups (3), (4) and (5) were orally given red ginseng extract at 100, 200 and 400mg/kg, respectively once daily for 4 weeks. At the end of feeding period, final body weight of rats was recorded and the adiposity index 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 x100) [20]. Rats were then euthanized using ether anesthetic 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 activity of tissue antioxidant enzymes.

Serum Analysis: Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) [21]; gamma-glutamyl transpeptidase (GGT) [22]; total cholesterol (TC) [23]; triglycerides (TG) [24] and high density lipoprotein (HDL-c) cholesterol [24] were chemically determined using specific diagnostic kits and measured using a spectrophotometer (model T80, UV/visible, double beam, UK). Low density lipoprotein (LDL-c) cholesterol was calculated according to Friedewald formula: $LDL-c = TC - (TG/5) - HDL-c$. Blood glucose (BG) was determined using glucose enzymatic kit [25]. Insulin was estimated using specific antibody radioimmunoassay (RIA) kit [26]. Leptin hormone was determined using enzyme-linked immunosorbent (ELISA) assay [27].

Renal 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 (SOD), glutathione peroxidase (GPx) and catalase (CAT) [28-30 respectively]. Statistical analysis: Data were presented as mean ± SE. Statistical analysis was carried out using one-way analysis of variance (ANOVA) followed by Duncan's multiple range test [31] with SPSS computer program (version 15). 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 and 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 AST, ALT and 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).

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 TC and 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 levels of serum TC and TG when compared with positive (obese diabetic) control rats.

Serum analysis revealed that male rats fed on high fat-diet (HFD) for 6 weeks showed significant decrease in high HDL-c, increase in LDL-c and high atherogenic index (AI) when compared with the negative control group. Oral administration of red ginseng extract for 4 weeks to obese diabetic rats took the values of cholesterol back towards normal where the serum HDL-c increased, the level of LDL-c decreased and the AI improved when 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 ($P < 0.05$) increase 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 SOD, GPx and 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, as recorded in Table (6).

Table 1: Effect of red ginseng extract on final body weight, fat weight and adiposity index in obese diabetic rats

Parameters Groups	B.wt. (g)	F.wt. (g)	Ad.I (%)
Group (1) Negative control	291 ± 13.0 ^c	7.56 ± 0.12 ^c	2.60 ± 0.15 ^c
Group (2) Obese diabetic control	315 ± 19.0 ^a	16.61 ± 0.22 ^a	5.27 ± 0.17 ^a
Group (3) RGE (100mg/kg)	300 ± 10.0 ^b	14.12 ± 0.25 ^b	4.71 ± 0.24 ^b
Group (4) RGE ((200 mg/kg)	283 ± 13.0 ^b	11.20 ± 0.17 ^b	3.96 ± 0.16 ^b
Group (5) RGE (400mg/kg)	280 ± 12.0 ^b	9.45 ± 0.19 ^b	3.38 ± 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 on serum levels of aspartate aminotransferase, alanine aminotransferase and gamma- glutamyl transpeptidase liver enzymes in obese diabetic rats

Parameters Group	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) RGE (100mg/kg)	74.0 ± 5.14 ^b	55.0 ± 4.25 ^b	38.0 ± 2.24 ^b
Group (4) RGE (200 mg/kg)	60.0 ± 5.34 ^b	47.0 ± 3.17 ^c	36.0 ± 2.16 ^b
Group (5) RGE (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

Table 3: Effect of red ginseng extract on serum total cholesterol and triglycerides in obese diabetic rats

Parameters Group	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) RGE (100mg/kg)	122.65 ± 7.34 ^b	144.12 ± 6.25 ^b
Group (4) RGE (200 mg/kg)	118.50 ± 6.42 ^b	138.20 ± 7.17 ^b
Group (5) RGE (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 on serum levels of HDL-c, LDL-c and atherogenic index (AI) in obese diabetic 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 on blood glucose (BG), leptin and insulin hormones levels in obese diabetic 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 on activities of tissue superoxide dismutase, glutathione peroxidase and catalase antioxidant enzymes in obese diabetic 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. n= 9 rats/group

Unit of GPx= nmol of GSH utilized/min/mg protein

Unit of CAT= nmol of H₂O₂ utilized/min/mg protein

DISCUSSION

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 saponins, anthocyanins, flavonoids, diterpenes, triterpenes and others phytochemicals [32].

In the current study, obesity was experimentally induced by feeding rats on high fat-diet for 6 weeks. This model of obesity in rats closely resembles the reality of obesity in humans. However, 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 [33].

The results of the present study showed that the extract of red ginseng (RGE) when given orally to obese diabetic rats for 6 weeks led to marked decreases in the final body weight, fat weight and adiposity index. The anti-obesity effect of RGE was similar to the previously reported by Inoue *et al.* [34] and Kim *et al.* [15] who found that the crude saponins of Korean red ginseng induced anti-obesity effect in rats fed on high fat- diet. Moreover, Amin and Nagy [35] reported that feeding rats on high fat-diet significantly increased the final body weight, fat weight and concentrations of serum triglycerides (TG), total cholesterol (TC) and low density lipoprotein (LDL-c) cholesterol as compared with the rats fed on normal diet.

The mechanism(s) underlying the anti-obesity effect of red ginseng extract could (RGE) be explained by its hyperinsulinemic effect evident in the present study in obese diabetic rats. It was reported that hyperinsulinemia and insulin resistance are common features of obesity in humans [36] and experimental animals [35]. In addition, the anti-obesity activity of RGE could also be due to the high level of leptin hormone that was reported in the current study. In this concern, Friedman [37] mentioned that

leptin is a peptide hormone secreted by adipose tissue in proportion to its mass. 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. 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 from the significant decreases of the elevated serum levels of liver enzymes (AST, ALT and GGT) in obese diabetic rats. The hepatoprotective effect RGE agreed with that reported by Jeong *et al.* [38] and Lee *et al.* [13]. The previous authors concluded that the isolated saponins of Korean red ginseng showed hepatoprotective effect and induced restoration of hepatic enzymes (AST, ALT and ALP) in CCl₄-intoxicated rats. In addition, Kwon and Jang [39] reported that Korean red ginseng extract inhibited high levels of AST and ALT enzymes and ameliorated liver injury after 70 % hepatectomy in rats. The mechanism of hepatoprotection of red ginseng saponins was assumed to be through inhibition of activity of cytochrome P450 enzymes in the rat liver microsomes [40].

The decreases in serum levels of total cholesterol, triglyceride and LDL-c caused by RGE, in this study, were similar to those recorded by Inoue *et al.* [34], Kwak *et al.* [14] and Shin *et al.* [11]. The authors concluded that RGE and its saponins fraction lowers the elevated levels of total cholesterol, triglycerides and LDLc in man and rats. They attributed the effects of RGE due to its content of saponins which inhibit the intestinal absorption of cholesterol and reduce serum cholesterol levels in experimental animal models. In man and rabbits, Kwak *et al.* [14] concluded that red ginseng extract reduces serum levels of total cholesterol, LDL-c and triacylglycerol and improves serum lipid profile.

Rats fed on high fat-diet for 6 weeks, in this study, had significantly lower serum insulin level than those fed on basal diet. This finding agreed with that reported by Huang *et al.* [41] who found that feeding high-fat diet to normal rats resulted in impaired pancreatic function and decreased insulin secretion (hypoinsulinemia). 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 effect of RGE was similar to that reported by Takaku *et al.* [42] in obese rats. Some previous studies revealed that hyperinsulinemia and insulin resistance are common features of obesity in humans [36] and experimental animals [35]. In addition, Lee *et al.* [43] investigated the mechanism of antidiabetic and anti-obesity effects of Korean red ginseng (KRG) extract (200mg/kg, oral) in obese insulin resistant rat model. A significant weight reduction, especially fat mass reduction, was observed in the KRG-treated group. Increased insulin sensitivity was found in the KRG-treated group. The authors concluded that KRG may have antidiabetic and anti-obesity effects due to partly increased insulin sensitivity by increased adipokines (cytokines secreted by adipose tissue) and partly due to enhanced insulin signaling.

The present results showed that normal 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.* [41] who found that HFD elevated serum leptin level in rats. It is known that 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 of Kim *et al.* [15] who reported that saponins of red ginseng reduced body weight, decreased serum leptin level and depressed appetite in obese rats fed on HFD. The authors concluded that red ginseng may be useful in the treatment of obesity and related disorders as anti-obesity agent.

In obese diabetic rats, the activity of antioxidant enzymes (SOD, GPx and CAT) decreased in renal tissues. 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 evident by the increased activity of tissue SOD, GPx and CAT antioxidant enzymes. The antioxidant effect of RGE

may be attributed to its hypoglycemic activity that reported in this study and previously demonstrated by Takaku *et al.* [43], Kim and Kim [10] and Shin *et al.* [11].

In conclusion, oral administration of red ginseng extract to obese diabetic rats exhibited anti-obesity, 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 anti-obesity and antidiabetic effects.

REFERENCES

1. Archer, Z.A., J. Corneloup, D.V. Rayner, P. Barrett, K.M. Moar and J.G. Mercer, 2007. Solid and liquid obesogenic diets induce obesity and counter-regulatory changes in hypothalamic gene expression in juvenile Sprague Dawley rats. *J. Nutri.*, 137(6): 1483-1490.
2. Power, M.L. and J. Schulkin, 2008. Sex differences in fat storage, fat metabolism and the health risks from obesity: possible evolutionary origins. *Br. J. Nutri.*, 99(5): 931-940.
3. Afolayan, H.J. and B.O. Mbaebie, 2010. Ethnobotanical study of medicinal plants in Nkonkobe Municipality in South Africa. *Pharmacogn. J.*, 2(11): 368- 374.
4. Hotamisligil, G.S. and E. Erbay, 2008. Nutrient sensing and inflammation in metabolic diseases. *Nat. Rev. Immunol.*, 8: 923-934.
5. Balakumar, P., V.A. Chakkarwar and M. Singh, 2009. Ameliorative effect of combination of benfotiamine and fenofibrate in diabetes-induced vascular endothelial dysfunction and nephropathy in the rat. *Mol. Cell. Biochem.*, 320: 149-162.
6. Luis-Rodríguez, D., A. Martínez-Castelao, J.L. Gorris, F. De-Alvaro and J.F. Navarro-Gonzalez, 2012. Pathophysiological role and therapeutic implications of inflammation in diabetic nephropathy. *World J. Diabetes*, 15: 7-18.
7. Hayoz, D., T. Ziegler, H.R. Brunner and J. Ruiz, 1998. Diabetes mellitus and vascular lesions. *Metabolism*, 47: 16-19.
8. Bonnefont, D., J.P. Bastard, M.C. Jaudon and J. Dellattre, 2000. Consequences of diabetes status on the oxidant /antioxidant balance. *Diabetes Metabol.*, 26: 163-76.
9. Goedecke, J.H., J.A. Dave and M.V. Faulenbach, 2009. Insulin response in relation to insulin sensitivity: an appropriate beta-cell response in black South African women. *Diabetes Care*, 32(5): 860-865.

10. Kim, K. and H.Y. Kim, 2008. Korean red ginseng stimulates insulin release from isolated rat pancreatic islets. *J. Ethnopharmacol.*, 120(2): 190-195.
11. Shin, S.K., J.H. Kwon, Y.J. Jeong, S.M. Jeon, J.Y. Choi and M.S. Choi, 2011. Supplementation of Cheonggukjang and red Ginseng Cheonggukjang can improve plasma lipid profile and fasting blood glucose concentration in subjects with impaired fasting glucose. *J. Food Med.*, 14: 108-113.
12. Yun, T.K., Y.S. Lee, Y.H. Lee, S.I. Kim and H.Y. Yun, 2001. Anticarcinogenic effect of Panax ginseng and identification of active compounds. *J. Korean Med. Sci.*, 16: 6-18.
13. Lee, H.U., E.A. Bae, M.J. Han and D.H. Kim, 2005. Hepatoprotective effect of 20(S) ginsenosides Rg3 and its metabolite 20(S)-ginsenoside Rh2 on tert-butyl hydroperoxide- induced liver injury. *Biol. Pharmaceut. Bull.*, 28: 1992-1994.
14. Kwak, Y.S., J.S. Kyung J.S. Kim, J.Y. Cho and M.H. Rhee, 2001. Anti- hyperlipidemic effects of red ginseng acidic polysaccharides from Korean red ginseng. *Biol. Pharmaceut. Bull.*, 33(3): 468-472.
15. Kim, J.H., D.H. Hahm, D.C. Yang, K. Kim, H.J. Lee and I. Shim, 2005. Effect of crude saponins of Korean red ginseng on high-fat diet- induced obesity in the rat. *J. Pharmacol. Sci.*, 97: 124-131.
16. Reeves, P.G., F.H. Nielson and G.C. Fahmy, 1993. Reports of the American Institute of Nutrition, adhoc Willing Committee on Reformulation of the AIN 93, Rodent diet. *J. Nutri.*, 123: 1939-1951.
17. Shalaby, M.A. and A.R. Hamowieh, 2010. Safety and efficacy of Zingiber officinale roots on fertility of male diabetic rats. *Food Chem. Toxicol.*, 48: 2920-2924.
18. Bhatt, B.A., J.J. Dube, N. Dedousis, J.A. Reider and R.M. O'Doherty, 2006. Diet- induced obesity and acute hyperlipidemia reduce I kappa B alpha levels in rat skeletal muscle in a fiber-type dependent manner. *Am. J. Physiol.*, 290: 233-240.
19. Ashok, D.C., N.P. Shrimant, M.G. Panadeep and U.A. Akalpita, 2007. Optimization of alloxan dose is essential to induce stable diabetes mellitus for long period. *Asian J. Biochem.*, 2(6): 402-408.
20. Pichon, L, J.F. Huneau, G. Fromentin and D. Tome, 2006. A high - protein, high fat, carbohydrate - free diet reduces energy intake, hepatic lipogenesis and adiposity. *J. Nutri.*, 136: 1256-1260.
21. Bergmeyer, H.U., P. Schreiber and A.W. Wahlefeld, 1978. Optimization of methods for aspartate and alanine aminotransferase. *Clin. Chem.*, 24: 58-61.
22. Persijn, J.P. and W. Van Der Sliks, 1976. A new method for the determination of gamma- glutamyl transpeptidase in serum. *J. Clin. Chem. Clin. Biochem.*, 14(9): 421-427.
23. Richmond, N., 1973. Colorimetric determination of total cholesterol and high density lipoprotein cholesterol (HDL-c). *Clin. Chem.*, 19: 1350-1356.
24. Friedewald, W.T., R.I. Levy and D.S. Frederickson, 1972. Estimation of plasma or serum low density lipoprotein cholesterol concentration without use of ultracentrifuge. *Clin. Chem.*, 18: 499-502.
25. Siest, G., F. Henny and F. Schiele, 1981. Enzymatic determination of glucose. *Interpret. Exam. Lab.*, 2: 206-213.
26. Yallow, R. and W.A. Bauman, 1983. Plasma insulin in health and disease. In: *Diabetes Mellitus: Theory and Practice*. Editors: M. Ellenberg and H. Rifkin, Excerpta Medica, 15: 119-120.
27. Xiong, Y., L. Shen, K.J. Liu, P. Tso, Y. Xiong, G. Wang, S.C. Woods and K. Liu, 2005. Anti-obesity and antihyperglycemic effects of ginsenoside Rb1 in rats. *Diabetes*, 59: 2505-2512.
28. Kakkar, P., B. Das and P. Viswanathan, 1984. A modified method for assay of superoxide dismutase. *Ind. J. Biochem. Biophys.*, 21: 131-132.
29. Paglia, D.E. and W.N. Valentine, 1967. Studies on the quantitative and qualitative characterization of erythrocyte glutathione peroxidase. *J. Lab. Cm. Med.*, 70: 158-69.
30. Sinha, A.K., 1972. Colorimetric assay of catalase. *Anal. Biochem.*, 47: 389-394.
31. Snedecor, G.W. and W.G. Cochran, 1986. *Statistical Methods*, 7th Edition, Iowa State University Press, Ames, USA, pp: 90-99.
32. Veermuthu, D., A. Muniappan and I. Savarimuthu, 2006. Antimicrobial activity of some ethnomedicinal plants used by Paliyar tribe from Tamilnadu. *Indian Complem. Altern. Med.*, 6(35): 1472-1482.
33. Pierpaoli, W. and V.A. Lesnikov, 2011. Effects of long-term intraperitoneal injection of thyrotropin-releasing hormone (TRH) on aging- and obesity-related changes in body weight, lipid metabolism and thyroid functions. *Curr. Aging Sci.*, 4: 25-32.
34. Inoue, M., C.Z. Wu, D.Q. Dou, Y.J. Chen and Y. Ogihara, 1999. Lipoprotein lipase activation by red ginseng saponins in hyperlipidemia model animals. *Phytomed.*, 6(4): 257-265.
35. Amin, K.A. and M.A. Nagy, 2009. Effect of L- Carnitine and herbal mixture extract on obesity induced by high fat diet in rats. *Diabetes Metab. Syndr.*, 1: 1-17.

36. Kay, J.P., R. Alemzadeh, G. Langley, L. D'Angelo, P. Smith and S. Holshouser, 2001. Beneficial effects of metformin in normoglycemic morbidly obese adolescents. *Metab.*, 50(12): 1457-1461.
37. Friedman, J.M., 2011. Leptin and the regulation of body weight. *The Keio J. Med.*, 60: 1-9.
38. Jeong, T.C., H.J. Kim, J.I. Park, C.S. Han, J.D. Park, S.I. Kim and J.K. Roh, 1997. Protective effects of red ginseng saponins against carbon tetrachloride-induced hepatotoxicity in Sprague Dawley rats. *Planta Medica*, 63(2): 136-140.
39. Kwon, Y.S. and K.H. Jang, 2004. The effect of Korean red ginseng on liver regeneration after 70% hepatectomy in rats. *J. Vet. Med. Sci. (Japanese Soc. Vet. Sci.)*, 66(2): 193-195.
40. Kim, J.H., Y.J. Chun, J.D. Park, S.I. Kim and J.K. Roh, 1997. Protection of rat liver microsomes against carbon tetrachloride-induced lipid peroxidation by red ginseng saponins through cytochrome P450 inhibition. *Planta Medica*, 63(5): 415-418.
41. Huang, B.W., M.T. Chiang, H.T. Yao and W. Chiang, 2004. The effect of high fat and high fructose - diets on glucose tolerance, plasma lipid and leptin levels in rats. *Diabet. Obes. Metab.*, 6(2): 120-126.
42. Takaku, T., K. Kameda, Y. Matsuura, K. Sekiya and H. Okuda, 1990. Studies on insulin like substances in Korean red ginseng. *Planta Medica*, 56: 27-30.
43. Lee, S.H., H.J. Lee, Y.H. Lee, B.W. Lee, B.S. Cha, E.S. Kang, C.W. Ahn, J.S. Park, H.J. Kim, E.Y. Lee and H.C. Lee, 2012. Korean red ginseng (*Panax ginseng*) improves insulin sensitivity in high fat fed Sprague-Dawley rats. *Phytother. Res.*, 26(1): 142-147.