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Anti-hyperglycemic and anti-hyperlipidemic effects of *Panax ginseng* root extract in alloxan induced diabetic rats

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Abstract

Diabetes is a third leading life threatening metabolic disorder. Hyperglycemia, dyslipidemia, myocardial infarction and oxidative stress are the major reasons of mortality and morbidity. In the present study we try to evaluate the anti-diabetic and anti-hyperlipidemic properties of *Panax ginseng* root extract (PG). Wistar-male rats were fed on high fat died for 14-days followed by single intraperitoneal dose of alloxan (130mg/kg BW). Hypoglycemia was prevented by giving glucose solution to drink; finally fasting blood glucose was measured after three-days and rats showed blood glucose level higher than 250mg/dl were included in the study. The rats were divided into four groups: Group-1: included non-diabetic rats, Group-II included diabetic rats without any treatment of PG, Group-III: included diabetic rats receiving 150mg/kg BW of PG, Group-IV: included diabetic rats treated with 250mg/kg BW. Rats were treated for 14 weeks. ANOVA followed by PLSD Fisher's test was applied. Body weight and blood glucose was measured on 1st and 14th week. We found a significant reduction in blood glucose and fasting-serum-glucose for group III (306.13±14.14, 273.63±7.90) and for group IV (402.97±12.76; 220.87±9.34) respectively. We found a significant reduction for TC (1.23±0.02), VLDL (0.26±0.01), LDL (0.46±0.01) and significant increased for HDL (0.60±0.01) in Group-IV. Significant increase was found for TG in group III (1.54±0.01) and group IV (1.40±0.01). A significant increased for CAT (19.74±0.58) and significant decrease for MDA (6.56±0.23) was found in group-IV. Furthermore a significant decrease for AST, ALT and creatinine level after treatment. In conclusion PG showed strong anti-hyperglycemic, anti-hypercholesterolemic, anti-hypertriglyceridemic and anti-oxidative properties in dose dependent manner.

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Introduction

Diabetes mellitus have become one of the major health related issues during the last few decades. It is a group of chronic metabolic syndrome, characterized by abnormally high level of blood glucose associated with mortality and morbidity (Nayak and Roberts, 2006; Kumar *et al*., 2012). Diabetes is third major reported disease, after cardiac disorder and cancer and its prevalence has been gradually increasing over the years (Li-Xia *et al*., 2011). Diabetes mellitus is heterogeneous disorder may be associated with impaired insulin secretion by pancreatic-β-cells or may be due to any defect in insulin action or might be due to both factors (Ibrahim *et al*., 2008). Weight loss, muscular weakness, oxidative stress, polyuria, glucosuria, hyper-cholesterolemia, hyper-insulinimia, cardiac diseases and neuronal proplems are the most commonly occurring symptoms in diabetic patients (Krishnamurthy *et al*., 2011). People above 48 years of age, suffering with obesity, poor physical activities, high blood pressure, improper diet and stress full environment are commonly affected with diabetes mellitus (Ripsin *et al*., 2009; Babish *et al*., 2010). Many hypoglycemic drugs i.e. metformin, thiazolidinediones (e.g. TZD or glitazone) and insulin are available in the market to treat diabetes, however due to adverse health side effects of these drugs the interest in natural/ herbal remedies has been increased world-wide (Naseem *et al*., 2016). The World Health Organization (WHO) has listed 21,000 plants, which are used for medicinal purposes all over the world. Among these, 150 species are available and used commercially on large scale (Zohary and Hopf, 2000).

Ginseng is very effective and widely used natural remedy. Various species of ginseng have medical importance; belongs to genus Panax and family *Araliaceae*. Ginseng plants have fleshy root and was first cultivated around 11 BC and has a medical history of more than 5000 years, particularly using as a herbal plants in many Asian countries (Radad *et al*., 2006; Kim *et al*., 2014); to treat sexual disorders, central and peripheral nervous system disorders, cancer, oxidative stress, CVS, anti-tumour, anti-fatigue, hyperglycaemic and to boost immunity etc (Radad *et al*., 2006; Amin *et al*., 2011). The strong anti-oxidant properties of ginseng is attributed to ginsenosides; an active ingredient of ginseng, shows its activity through stimulation of gene expression encoding anti-oxidant enzyme (Murphy and Lee, 2002; Ibrahim *et al*., 2008). There are about fourteen species of ginseng among which most effective anti-diabetic species are: Chinese ginseng (Ohnishi *et al*., 1996), Korean Red ginseng, Sanchi, Siberian (Ohnishi *et al*., 1996; Lee *et al*., 2009), American ginseng (Amin *et al*., 2011) and Asian ginseng (Lim *et al*., 2009). In the present study we try to evaluate the anti-diabetic, anti-hyperlipidemic and anti-oxidative effects of *Panax ginseng* root extract (PG) on biochemical parameters in diabetic rats.

Materials and methods

Experimental Design and animals

A total of thirty two normo-glycemic adult male-Wistar rats (150-200 g body weight), were selected, two rats in each cage were housed at 24± 5°C with 12-h light: 12-h dark cycle and free assess of water and food were given to all rats (El-Mesallamy *et al*., 2011). The experiment was carried out by following the guidelines of ethical committee in animal shed of University of Veterinary and Animal Sciences (UVAS), Lahore, Pakistan.

Rats were feed on high-fat-diet for a period of 14 days and after that single dose of alloxan monohydrate (Sigma, USA) were given intra-peritoneal (130 mg/KG BW) for the induction of diabetes. Hypo-glycemia was prevented by given glucose solution to drink instant of water (Ebuehi *et al*., 2010; Naseem *et al*., 2016). Three days after alloxan, fasting blood glucose were checked by using glucometer (ACCU, Germany) and rats showed blood glucose level above 250 mg/dl were selected for the study (Cheng *et al*., 2013). Rats were divided into following groups (08rats/group).

Group I (G-I): This group served as negative control (non-diabetic), given standard rat (40.7% maize starch, 20% dextrose, 5.8% sunflower oil and 22.5%

casein, 9.7% minerals and 1.3% vitamins) chew without any supplementation of *P. ginseng* root extract (PG).

Group-II (G-II): The rats of this group served as positive control (Diabetic rats); given standard diet only without mixing of any supplementation.

Group-III (G-III): This group included diabetic rats, given standard diet with supplementation of PG at the dose of 150mg/ KG BW.

Group-IV (G-IV): This group has rats surfing with diabetes and given supplementation of PG at the dose of 250mg/KG BW mixed with diet. The therapy of standardized PG (ginsenosides 4%) (Hunan Nutramax Inc, China) was given by mixing it with standard rat diet for the period of 14 weeks.

Blood collection and biochemical parameters:

After 14 weeks the blood was collected in fasting condition directly from heart and serum were collected immediately by centrifugation. The biochemical analysis of fasting serum glucose (FSG), total Cholesterol (TC), Triglyceride (TG), catalase (CAT), malondialdehyde (MDA), creatinine, alanine aminotransferase (ALT) and asparatate aminotransferase (AST) was done by using commercially available kits (Randox, UK). Lipoprotein (VLDL, LDL and HDL) profiles were performed using fast protein liquid chromatography (FPLC) (AKTA FPLC SYSTEM, GE Healthcare, USA).

Statistical analysis

Results were expressed as Mean ± S.E.M. Statistical analyses were performed using Stat view software (SAS Institute Inc., USA). Two-way repeated measure analysis of variance (ANOVA) was performed for body weight and blood glucose. For the rest of the parameters one-way ANOVA followed by PLSD Fisher's test. Differences were considered significant at $P<0.05$.

Results and discussion

Diabetes is a complex metabolic disease characterized by insulin resistance, pancreatic islet β-cell dysfunction, hyperglycemia, hyperinsulinemia dyslipidemia and oxidative stress (Wild *et al.*, 2004). We selected *P. ginseng* root extract (PG) because of its anti-oxidant properties. *P. ginseng* root occupies a well-known position in the herbal drugs and is one of the world's best-selling medicinal plants. A significant reduction in the body weight of diabetic rats was observed at the end of 14th week; however, we found a less suppression in the body weight of both treated groups (Table 1).

Table 1. Effect of *P. ginseng* root extract in Alloxan induced diabetic rats on body weight and blood glucose level at week I and week-14.

Parameters	Group-I		Group-II		Group-III		Group-IV	
	Week1	Week 14	Week 1	Week 14	Week 1	Week 14	Week 1	Week 14
Body weight (g)	171.38±1.67	215.38±2.67	169.81±1.51	141.12±1.62	170.75±1.51	166.80±1.31	171.71±1.62	162.50±1.54
Glucose (mg/dl)	83.43±1.28	83.33±1.28	423.38±17.93	505.58±16.20	495.82±17.18	306.13±14.14	536.13±17.62	402.97±12.76

Data is represented as Mean ± S.E.M.

Group-I (non-diabetic/negative control); Group-II (Diabetic/Positive control); Group-III (*P. ginseng* 150mg/KG/BW); Group-IV (*P. ginseng* 250mg/KG/BW).

Our findings are in agreement with (Lee *et al.*, 2012; Naseem *et al.*, 2016). Since in diabetes the metabolism of glucose, protein and lipids are compromising so the degradation of muscles and adipose tissues occurs for the retain of energy lost due to repaid conversion of glycogen to glucose (Ene *et al.*, 2007; Ramadan *et al.*, 2009). Hyperglycaemia is the characteristic feature of diabetes caused due to improper glucose metabolism and prolonged hyperglycaemia causes pancreatic β-cell necrosis (Naseem *et al.*, 2016). We measured weekly blood glucose level in all the studied groups; but the data of 1st week and last week is given (Table 1). We found a significant blood glucose reduction in both treated

groups. Furthermore, we also measured fasting serum glucose (FSG) at the end of study and found a significant reduction for FSG in both treated groups (Table 2). However, this reduction was more significant in 250mg/kg treated group. Chronic hyper-glycemia decreases blood insulin concentration (Ibrahim *et al.*, 2008); thus elevated blood glucose concentration might be due to dysregulation of pancreatic β-cell or/and dysfunctioning in the action of insulin, leads to insulin resistance (Lim *et al.* 2009; Jung and Kang 2013). Thus sustain decreased in the blood glucose concentration in diabetes helps to reduced certain other complications i.e micro and macro-vascular disorders (Wild *et al.*, 2004).

Table 2. Effect of *P. ginseng* root extract on Biochemical parameters in Alloxan induced diabetic rats.

Parameters	Group-I	Group-II	Group-III	Group-IV
FSG (mg/dl)	83.02±1.24	496.83±20.46	273.63±7.90	220.87±9.34
TC (g/L)	0.83±0.02	1.38±0.02	1.32±0.03	1.23±0.02
VLDL-C (g/L)	0.07±0.005	0.30±0.004	0.29±0.004	0.26±0.01
LDL-C (g/L)	0.06±0.001	0.60±0.013	0.56±0.024	0.46±0.01
HDL-C (g/L)	0.67±0.01	0.44±0.02	0.52±0.02	0.60±0.01
TG (g/L)	1.22±0.009	2.18±0.06	1.54±0.01	1.40±0.01
CAT (KU/L)	20.70±0.36	17.98±0.38	18.06±0.40	19.74±0.58
MDA (mmol/L)	6.67±0.20	7.92±0.30	7.13±0.29	6.56±0.23
AST (µ/L)	76.51±1.38	214.06±3.68	206.93±1.74	199.82±1.54
ALT (µ/L)	36.73±0.99	41.65±1.75	36.85±0.55	36.37±0.37
Creatinine (mg/dl)	1.61±0.12	2.06±0.04	1.96±0.03	1.81±0.03

Data is represented as Mean ± S.E.M. Group-I (non-diabetic/negative control); Group-II (Diabetic/Positive control); Group-III (*P. ginseng* 150mg/KG/BW); Group-IV (*P. ginseng* 250mg/KG/BW). FSG (Fasting Serum Glucose), TC (Total Cholesterol), VLDL-C (Very Low Density Lipoprotein-Cholesterol), LDL-C (Low Density Lipoprotein-Cholesterol), HDL (High Density Lipoprotein-Cholesterol), TG (Total triglyceride), MDA (Malondialdehyde), CAT (Catalase), AST (Asparatate aminotransferase), ALT (Alanine aminotransferase).

We found a significant increase for TC, VLDL, LDL and significant decrease for HDL serum level in diabetic group as compare to non-diabetic group. Whereas; a significant decrease for TC, VLDL and LDL and significant increase for HDL was found in dose dependent manner (Table 2). We found a significant reduction for TG in both treated groups as compared to diabetic rats (Table 2). Many other researchers also reported hyper-triglyceridemia and dyslipidaemia in diabetic condition (Ebuehi *et al.*, 2010; Naseem *et al.*, 2016). In diabetes hyper-triglyceridemia and dyslipidaemia (elevated TC, VLDL and LDL and low HDL) are the primary factors for the development of cardiovascular disorders and may also develop atherosclerosis lesions (Benzi and Morretti, 1995). Improper cholesterol packing is the primary factor in diabetic patients which leads to high blood TG level (Cho *et al.*, 2006). Excess fatty acids are metabolized to acetyl CoA, which is used by liver for the cholesterol synthesis and thus elevated the level of cholesterol in diabetes (Hallliwell and Gutterridge, 1999). Since diabetes is associated with elevated plasma lipid and lipoprotein profile (Zheng *et al.*, 2011). Hypertriglyceridemia leads to insulin resistance (Schwartz, 2006), thus reduction in the TG level is a good sign in diabetes (Liu *et al.*, 2013). The regulation of TC, LDL, HDL and TG in the present study indicates the good anti-hypercholesterolemia and anti-hypertriglyceridemic properties of PG.

We found a significant reduction in CAT and significant increase in MDA in diabetic state, thus the body of diabetic rats suffered with oxidative stress as reported by other (Cheng *et al.*, 2013; Naseem *et al.*, 2016). Although CAT and MDA help to neutralize the toxicity of active oxygen, however, dysregulation in anti-oxidant enzymes is the commonly occurring issue in diabetes (West, 2000). We found significant increase in CAT and a significant reduction in the level of MDA activities in group IV. The anti-oxidant

activities of *P. ginseng* is attributed to ginsenosides, an active ingredient of ginseng (Murphy and Lee, 2002; Amin *et al.*, 2011; Liu *et al.*, 2013). CAT plays significant role to protect body against damage of active oxygen stress by converting the hydrogen peroxide (H_2O_2) into water. CAT is an intracellular portentous enzyme (Kodydkova *et al.*, 2014), commonly found in mammalian erythrocytes and liver (Deisseroh and Dounce, 1970). The MDA is important biomarker of oxidative stress; produced from free radicals induced lipid peroxides during metabolic activities and MDA concentration usually used to measure the index of the lipid peroxides in the body (Ren *et al.*, 2013).

Prolonged hyperglycemia in the body is the primary cause to increased ROS production in the body: an important factor to elevated protein oxidation, lipid peroxidation leads to tissue damage, vascular diseases and neuronal damage (Son, 2012; Cheng *et al.*, 2013). Previously, it was studied in various experimentally induced diabetic animal models that the oxidative stress in diabetes is caused due to chronic hyperglycemia, therefore, depleting activities of anti-oxidative enzymes reduces free oxygen radicals and, if remain untreated, could promote free radicals generation, leading to severe complications (Bohar *et al.*, 2004; Jung *et al.*, 2005).

We found a significant decrease for AST and ALT after treatment indicates the good sing of regulation of these two liver enzymes. The results are in agreement with other workers (Lim *et al.*, 2009; Naseem *et al.*, 2016).Previous data support the fact that dysregulation of AST and ALT (liver enzymes), are associated with diabetes and considered as an important pato-physiological enzymes to identify liver diseases (Kunutsor *et al.*, 2013). We found a significant reduction in serum creatinine level in both treated groups. Creatinine is a waste product and excreted from kidneys. Increased in blood creatinine level indicates impaired renal function. Elevated creatinine level in diabetes is associated with nephropathy (Salih, 2012).

Conclusion

In conclusion we found that *P. ginseng* contain strong anti-hyperglycemic, anti-hypercholesterolemia, anti-hypertriglyceridemic and anti-oxidative properties in does dependent manner.

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