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ORIGINAL ARTICLES

Protective Effect of Panax Ginseng Against Streptozotocin Induced Renal Dysfunction in Rats.

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ABSTRACT

As incidence of diabetes is increasing worldwide, besides it is associated with complications, this study aimed to investigate the role of Panax ginseng in protecting renal function in streptozotocin (STZ) induced diabetic rats.Sixty male rats were used in this study and randomly classified into four groups : Control, ginseng, diabetic and treated groups. Fasting blood sugar, kidney functions and kidney oxidant / antioxidants status were estimated.STZ effectively increased fasting blood sugar, kidney functions and malondialdehyde, while Panax ginseng ameliorated their elevation in the treated group.In conclusion, the present study provides scientific evidence of the preventive and therapeutic potential of Panax ginseng against renal failure.

***Key words*:** diabetes, renal dysfunction, ginseng, oxidant/antioxidants.

Introduction

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia (Kang *et al*., 2006). Abnormally elevated blood glucose level causes oxidative stress and the formation of advanced oxidation end products which results in diabetic complications (Ahmed, 2005). In particular, diabetics are at increased risk for several types of kidney disease and disorder diabetic nephropathy (Held *et al*., 1991). However, clinical trials suggested that there is no effective treatment for diabetic nephropathy without undesirable side - effects or contraindications (The Diabetes Control and Complications Trial Research Group, 1993). Therefore, great efforts are focusing on traditional and herbal medicines to find a beneficial agent for diabetic nephropathy without toxic effects (Yamabe *et al*., 2006).

Ginseng has been used as a medicinal plant for more than 2,000 years; it has a wide range of pharmacological and physiological actions, such as anti-aging, anti-stress, anti-fatigue and anti-tumor activities (Kaneko and Nakanishi, 2004). In addition, several studies indicated the properties of ginseng in lowering the blood glucose level (Ohnishi *et al*., 1996) and stimulating sugar metabolism (Xie *et al*., 2005).

Thus this study aimed to investigate the possible beneficial effect of panax ginseng on diabetic renal dysfunction and to clarify its role in ameliorating renal antioxidant status in diabetic rats.

Materials and Methods

Materials:
Chemicals:

-Streptozotocin (STZ) was purchased from sigma chemicals Co. (St. Louis, U.S.A)
- Root powder of Korean ginseng (Panax ginseng C.A. Meyer).

Experimental animals:

Male albino rats weighing 180-200g were obtained from the animal house of National Research Center, Giza, Egypt. The animals were housed in individual suspended stainless steel cages in a controlled environment (22-25°C) and 12 hour light, 12 hour dark with food and water freely available. The guidelines of the ethical care and treatment of the animals followed the regulations of the ethical committee of National Research Center.

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Methods:
Induction of Diabetes:

Streptozotocin was dissolved in 50mM sodium citrate solution (pH 4.5) containing 150mM sodium chloride. The solution (6mg/10.5ml/100g body weight) was subcutaneously administered in rats **(Uchiyama** and Yamaguchi, 2003).

Experimental design:

Sixty male rats were divided into four groups, 15 rats for each group, and classified as follow:
Group I: Control group, normal rats received 0.5 ml distilled water/rat/day orally.
Group II: Panax ginseng group, normal rats received 22.5 mg ginseng dissolved in 0.5 ml distilled water/rat/day orally.
Group III: Diabetic rats received 0.5 ml distilled water/rat/day orally.
Group IV: Diabetic rats received 22.5 mg ginseng dissolved in 0.5 ml distilled water/rat/day orally.

Samples collection:

After sixty days, animals were kept fasting for 12 hours, and anesthetized, the blood was withdrawn from the retro-orbital venous plexus using heparinized capillary tubes. Blood samples were collected and left to clot, then centrifuged for 10 min at 3000 r.p.m. to separate serum. Freshly prepared serum was used for determination of fasting blood glucose according to Trinder (1969), and the rest of serum was divided into aliquots and stored at -20°C until used. Kidney tissues were removed quickly and placed in iced normal saline, the tissues were cut into small pieces and homogenized in phosphate buffer, then centrifuged, the supernatant was used for oxidant/antioxidant parameters estimation (Manna *et al*., 2005).

Biochemical parameters:

Serum creatinine and blood urea were estimated according to Houot, (1985; Fawcett and Scott, 1960.) respectively. Kidney reduced glutathione (GSH) and glutathione S-trnasferase (GST) were measured colorimetrically according to Beautler *et al*., 1963: and Habig *et a*l. (1974). respectively. Also determination of Superoxide dismutase (SOD) and Malondialdehyde (MDA) was passed on the methods of Beuchamp and Fridovich 1971; Uchiyama and Mihara (1978.) respectively.

Statistical analysis:

Data were analyzed by one way analysis of variance (ANOVA). Results were expressed as mean $\pm$ SE, P-values < 0.05 were regarded as statistically significant.

Results:

In this study, the mean values of fasting blood sugar, kidney functions and antioxidant parameters were not changed in ginseng group indicating its safety, while in diabetic group, the mean values of fasting blood sugar and kidney functions were significantly increased. Also, the mean value levels of kidney antioxidants parameters were significantly decreased concomitant with increasing of MDA (table 1, 2).

On the other hand, ginseng significantly improved kidney functions and antioxidants profile in the treated group (table 1, 2).

Table 1: Blood glucose and kidney functions in different studied groups.

Parameter Groups	Fasting blood glucose mg/dl	Serum creatinine mg/dl	Blood urea mg/dl	Blood urea nitrogen mg/dl
Control M $\pm$SE	73^{b} $\pm$0.5	0.6^{b} $\pm$0.02	32^{b} $\pm$ 0.71	13.3^{b} $\pm$0.51
Ginseng M $\pm$ SE	72.1^{b} $\pm$0.64	0.5^{b} $\pm$0.01	31.1^{b} $\pm$0.61	12.95^{b} $\pm$0.6
Diabetic M $\pm$ SE	262^{a} $\pm$ 1.21	1.5^{a} $\pm$0.05	55^{a} $\pm$0.66	22.91^{a} $\pm$0.31
Treated M $\pm$SE	187^{ab} $\pm$ 1.05	1.01^{ab} $\pm$ 0.03	42^{ab} $\pm$0.71	17.5^{ab} $\pm$0.42

Significant P value < 0.05, a = significant difference compared to control group, b = significant difference compared to diabetic group, number of animals in each group = 15.

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Table 2: Kidney oxidant/antioxidants status in different studied groups.

Parameter Groups	MDA nM/mg protein	GSH μM/g tissue	GST μM/min/mg protein	SOD Unit/mg protein
Control M±SE	0.74^{b} ± 0.01	12.21^{b} ±0.11	1.91 ±0.11	23^{b} ±0.71
Ginseng M±SE	0.71^{b} ± 0.02	11.91^{b} ±0.15	1.90 ±0.21	22.6^{b} ±.44
Diabetic M±SE	1.02^{a} ±0.08	7.21^{a} ±0.51	1.44^{a} ±0.25	17.1^{a} ±0.51
Treated M±SE	0.91^{a} ±0.09	9.82^{ab} ±0.31	1.73 ±0.22	20.6^{ab} ±0.61

Significant P value < 0.05, a = significant difference compared to control group, b = significant difference compared to diabetic group, number of animals in each group = 15.

Results And Discussions

Diabetes mellitus is characterized by excessive glucose production; an abnormally elevated blood glucose level caused oxidative stress and the formation of advanced glycation end products, which have been closely linked to diabetic complications such as nephropathy (Ahmed, 2005).

In the current study, blood glucose levels in STZ-diabetic rats were found to be significantly higher than control. This similar to that of earlier reports (Rettig and Teusch, 1992; Sevak and Goyal, 1996). The present investigation showed that ginseng resulted in reduction of the elevated blood glucose concentration in diabetic rats, an effect that was attributed in former studies to ginseng enhancement of glucose uptake through stimulating translocation of glucose transporter GLUT4, inhibition of intracellular inflammatory molecules as Jun N-terminal kinase (JNK) which caused serine phosphorylation to insulin receptor substrate and consequently leads to interruption of signal transduction from insulin receptor to downstream molecules and insulin resistance (Ye, 2007 and Zhang *et al*., 2008). Additionally, other investigators recorded a definite insulinogenic properties of ginseng (Davydov *et al*., 1990) or direct and indirect stimulatory on β cell secretion of insulin (Lee *et al*., 2006).

The current investigation revealed that induction of diabetes resulted in elevation of blood urea, blood urea nitrogen (BUN) and serum creatinine concentrations. These parameters are considered significant markers of renal dysfunction (Feket *et al*., 2008). Ginseng administration resulted in a reduction in these parameters, a finding that was in agreement with that of Kang *et al*., (2008) who indicated that ginseng extract ameliorated renal dysfunction of diabetic rats.

The malondialdehyde (MDA) content, a measure of lipid peroxidation, is parallel with the degree of oxidative stress. Therefore, the assay of MDA could be a maker of cell damage (Zhang *et al*., 2010). In the present study, we observed that MDA level in diabetic rat kidney was significantly increased indicating a generation of free radicals and increase oxidative damage in kidney. We also found a reduction of MDA in ginseng treated group.

Also, we found that kidney reduced glutathione (GSH), glutathione S-transferase (GST), and superoxide dismutase (SOD) in diabetic rats were decreased indicating the role of hyperglycemia in increasing oxidative damage and reducing antioxidant status. In agreement, Godin *et al*., (1988) showed a decrease in Cu-Zn SOD activity in renal tissues during diabetes .Also, Sawiress, (2011) indicated that diabetes induced decrease in glutathione S-tranferase (GST) enzyme activities.

In the current study, it was found that ginseng administration effectively increased antioxidant status in treated group. In agreement, Liu *et al*., (2003) found that ginseng extracts scavenge oxidative species, also Surh *et al*., (2001) indicated that ginseng attenuate lipid peroxidation which may be related to saponins which play a major role in antioxidant activities. The antioxidant activities of ginseng may be attributed to ginsenoids which are important components heavily present in ginseng and have powerful antioxidant activities other than radical scavenging activities by stimulating gene expression of antioxidant enzymes and enhancing their activities (Kim *et al*., 1996).

In addition, ginseng has the ability to bind to glucocorticoid receptor triggering transcriptional activation of glucocorticoid response elements promoting cell proliferation and enhances the survival rate of new-born cells (Shen and Zhang, 2003).

We concluded that hyperglycemia increased oxidative stress in renal tissues and Panax ginseng could effectively prevent renal dysfunction associated with diabetes by attenuating the oxidative stress.

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