Journal of Animal and Veterinary Advances 9 (1): 102-107, 2010
ISSN: 1680-5593

Effects of Extract of Green Tea and Ginseng on Pancreatic Beta Cells and Levels of Serum Glucose, Insulin, Cholesterol and Triglycerides in Rats with Experimentally Streptozotocin-Induced Diabetes: A Histochemical and Immunohistochemical Study

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Abstract: This study investigated the effects of oral administration of extract of green tea (*Camellia sinensis*) and ginseng (American ginseng-*Panax quinquefolium L.*), given alone or together, on pancreatic β-cells, blood glucose, insulin, cholesterol and triglyceride levels in rats with experimental diabetes induced by a single injection of Streptozotocin (STZ) (60 mg kg^{-1}, i.p.). Fifty adult Wistar Albino rats were used, 10 in each of these five treatment groups: Group A: healthy controls, Group B: STZ-induced diabetes (untreated), Group C: STZ-induced diabetes plus green tea extract (100 mg/kg/daily), Group D: STZ-induced diabetes plus ginseng root (400 mg/kg/daily) and Group E: STZ-induced diabetes plus ginseng root + green tea extracts as before. At the end of the 6 weeks experiment, blood samples were analysed for blood glucose, insulin, cholesterol and triglyceride levels and samples of pancreatic tissue were examined histochemically and immunohistochemically for endocrine islets and β-cells. Overall, body weight decreased in groups B and C, serum insulin concentrations decreased slightly in groups C-E and total triglyceride levels of blood decreased significantly ($p<0.05$) in groups B and C compared with control, D and E groups. Histopathological examination showed that degenerative changes in pancreatic β-cells in STZ-treated rats were minimised to near normal morphology by administration of ginseng (Group D) and ginseng+green tea (Group E) and there was increased intensity of immunohistochemical staining for insulin in these groups. Degeneration of islets of Langerhans β-cells and weak insulin staining was observed for green tea alone (Group C). These findings demonstrate that ginseng or combined ginseng + green tea decreases blood glucose levels in diabetic rats and increases preservation of β-cells, perhaps by lowering oxidative stress.

Key words: Green tea, ginseng, diabetes mellitus, pancreatic β-cell, hypoglycaemia, streptozotocin

INTRODUCTION

Diabetes mellitus is characterised by hyperglycaemia and long-term complications affecting the eyes, kidneys, nerves and blood vessels. Several earlier investigations have confirmed the role of oxidative stress in developmental diabetic-mediated disorders, possibly via the formation of free radicals (Nogichi, 2007; Manna *et al*., 2009). The pathogenesis of diabetes mellitus is managed by oral administration of hypoglycaemic drugs. However, these agents have a number of side-effects (Olajide *et al*., 1999).

Herbs have been used for medicinal purposes for centuries (Craig, 1999). Flavonoids are an important group of phenolic compounds in plants. Green tea (*Camellia sinensis*) has many advantages over chemical preventive agents and is non-toxic and thus readily available to the general population. Tea is currently the most widely consumed beverage world-wide. Tea is a rich source of flavonoids (Bravo, 1998; Ryu *et al*., 2006) and animal model studies have associated green tea consumption with health benefits, including decreased hyperglycaemia, risk of inflammation, hyperlipidaemia etc. These effects have largely been attributed to the most prevalent polyphenol contained in green tea, the catechin or flavanol (-) epigallocatechin-3-gallate (Katiyar *et al*., 1999; Sato and Miyata, 2000; Dona *et al*., 2003).

Ginseng (*Panax* sp.) is valuable in Chinese medicine and plays an important role in folk medicine in East Asia. Ginseng glycopeptides have pharmacological effects, e.g., immunomodulatory, anti-tumour, anti-ulcer and hypoglycaemic activities. A previous study reported that ginseng contains about 20 ginseng polysaccharides, all of which have anti-hyperglycaemic effects (Miyazaki, 1989).

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Studies have also shown that ginseng can improve the immune response in diabetic patients (Kiefer and Pantuso, 2003; Cho *et al*., 2006). Ginseng has been used to treat a wide variety of diseases including anaemia, insomnia with neurasthenia, gastritis, blood pressure abnormalities, dyspepsia, overstrain and fatigue and to decrease blood coagulation and cholesterol and sugar levels (Cho *et al*., 2006; Wesnes *et al*., 2000). Extensive pharmacological research has revealed that ginseng can decrease blood glucose level by inhibiting intestinal glucose absorption, increasing energy expenditure, improving sensitivity to insulin and stimulating sugar metabolism in normal and experiment-induced hyperglycaemic animals (Yang *et al*., 1990; Wang *et al*., 2003; Xie *et al*., 2005).

STZ, an antibiotic produced by *Streptomyces achromogenes*, is an agent commonly used to induce experimental diabetes (Rakieten *et al*., 1963; Coskun *et al*., 2005). The cytotoxic action of STZ is associated with the generation of reactive oxygen species causing oxidative damage (Szkudelski, 2001).

Considering the potential effects of ginseng root and green tea extract in decreasing hyperglucosaemia, we investigated whether administration of ginseng root and green tea extract had any protective effect against oxidative stress and whether it could ameliorate pancreatic β-cells in the islets of Langerhans and serum glucose, total cholesterol and triglyceride levels in rats with STZ-induced diabetes.

MATERIALS AND METHODS

Animals: Fifty healthy male Wistar albino rats, weighing 220-230 g and averaging 18 weeks old were used. They were housed in macrolon cages under standard laboratory conditions (light period 7.00 am to 7.00 pm, 21±2°C and relative humidity 55%) and fed with standard rat pellets (Van Golu Animal Food Product Co., Van, Turkey) with tap water *ad-libitum*.

Experimental design: Ten rats were randomly allocated into one of the following five experimental groups: Group A (control): Animals received vehicle only and were killed after 6 weeks. Group B (diabetes, untreated): Animals with STZ-induced diabetes were left untreated and were killed after 6 weeks. Group C (STZ-induced diabetes, treated with green tea extract): Animals received green tea extract (Pro Healthy, Green Tea, mega EGCG™, Santa Barbara, CA) suspended in tap water orally at a dose of 100 mg/kg-body weight/daily for 6 weeks and were then killed. Group D (STZ-induced diabetes, treated with ginseng root): Animals received ginseng root suspended in tap water orally at a dose of 400 mg/kg-body weight/daily for 6 weeks and were then killed. Group E (STZ-induced diabetes, treated with ginseng root + green tea extract): Animals received both extracts, with products and rates as described for groups C and D, for 6 weeks and were then killed. Rats in groups B-E received STZ (Sigma, St. Louis MO, USA) in a single intraperitoneal (i.p.) injection (60 mg kg^{-1}, freshly dissolved in 5 mmol L^{-1} citrate buffer, pH 4.5) (Kanter *et al*., 2006). Forty-eight hours after STZ treatment, development of diabetes in rats was confirmed by measuring blood glucose levels in tail vein blood samples. Rats with blood glucose levels of 280 mg dL^{-1} or higher were considered to be diabetic (Kanter *et al*., 2006). Serum glucose levels in control animals remained normal for the duration of the study. Diabetes mellitus was confirmed by eBsensor Glucometer (Visgeneer Inc., Hsinchu City, Taiwan).

The initial and final body weights of rats in the different groups were recorded. At the end of the experiment, all animals were killed under ether anaesthesia, blood samples were taken by cardiac puncture and the pancreas was removed for immunohistochemical analysis. All animals received humane care according to the criteria outlined in the Guide for the Care and Use of Laboratory Animals prepared by the National Academy of Sciences and published by the National Institute of Health.

Biochemical analysis: Serum total cholesterol (Biolabo, 80106) and triglycerides (Ben SRL-TG381 Italy) were determined with commercial kits adapted to a Shimadzu UV-1201, UV-Vis Spectrophotometer (Japan) and insulin concentrations were determined by Radioimmunoassay (RIA) as described previously (Kanter *et al*., 2006). Serum glucose levels were analysed using a kit (Biolabo, 80009) and measured using a Shimadzu UV-1201, UV-VIS Spectrophotometer (Japan).

Histopathological procedures: Pancreatic tissues were fixed in 10% neutral buffered formalin solution, embedded in paraffin and then stained with haematoxylin and eosin (H and E). The preparations were evaluated by means of a bright-field microscope and photographed (Optiphot 2; Nikon, Tokyo, Japan).

Immunohistochemical procedures: Pancreatic tissues were fixed in 10% neutral buffered formalin, embedded in paraffin and sectioned at 5 μm thickness. Immunocytochemical reactions were performed by S-ABC (streptavidin-biotinylated horseradish peroxidase; DakoCytomation Denmark A/S) (Kanter *et al*., 2006). The procedure involved the following steps: endogenous peroxidase activity was inhibited by 3% H_2O_2 in distilled water for 30 min, the sections were washed in tap water for

30 min and in distilled water for 10 min, non-specific binding of antibodies was blocked by incubation with normal goat serum (DAKO X 0907, Denmark) with PBS, diluted 1:4, sections were incubated with monoclonal mouse antisera against human insulin protein (18-0066; Zymed, San Francisco, CA), diluted 1:50 for 3 h and then at room temperature, sections were washed in PBS 3×3 min, sections were incubated with biotinylated anti-mouse IgG (DAKO LSAB 2 Kit, sections were washed in PBS 3×3 min, sections were incubated with ABC complex (DAKO LSAB 2 Kit), sections were washed in PBS 3×3 min, peroxidase was detected with an aminoethylcarbazole substrate kit (AEC kit; Zymed Laboratories), sections were washed in tap water for 10 min, nuclei were stained with haematoxylin and sections were mounted in glycerin-gelatin.

Eight islets of Langerhans from each rat (80 islets for each group) were chosen randomly. All experimental groups were scored for intensity of staining with anti-insulin antibodies of β-cells in pancreatic islets (compared with control) as weak (+), moderate (++), strong (+++), or very strong (++++). The percentage of insulin-immunoreactive β-cell area in the islets of Langerhans (80 islets for each group) was then estimated and the total percentage of insulin immunoreactive β-cells calculated from these results (Cemek *et al*., 2008).

Statistical analysis: All results were expressed as mean±SD. Changes in body weight, blood glucose, insulin, total cholesterol and triglycerides were compared by One-way ANOVA. A $p<0.05$ were considered to be statistically significant.

RESULTS AND DISCUSSION

Blood glucose and body weights of control and experimental rats are shown in Table 1. The initial and final body weights were not different in control rats and in diabetic rats treated with ginseng root and/or green tea extract ($p>0.05$). By the end of the treatment, rats in groups B and C diabetic animals had suffered weight loss ($p<0.05$).

There was a significant increase in blood glucose and the level of serum insulin was significantly reduced in STZ-diabetic rats (groups B-E) compared with control rats ($p<0.01$). Treatment with green tea, ginseng and green tea + ginseng increased blood insulin levels in groups C-E and we observed a significant decrease ($p<0.01$) in serum glucose in groups D and E compared with untreated diabetic rats in group B (Table 1). Effects of green tea, ginseng and green tea + ginseng on serum insulin, cholesterol and triglyceride levels of control, diabetic and treated groups are shown in Table 2. Rats with no treatment (B) and treatment with green tea (Group C) had decreased triglyceride levels compared with groups A, D and E ($p<0.01$).

Immunohistochemical quantification showed that the total number of insulin-positive cells was increased in the pancreas of ginseng-treated rats (D and E) compared with untreated diabetic rats (B). No increase in β-cells was observed in green tea-treated rats (Group C) (Fig. 1, 2 and Table 3).

This study investigated effects of green tea, ginseng root and green tea+ginseng on oxidative stress and β-cell damage in rats with STZ-induced diabetes. Diabetic animal models exhibit high oxidative stress due to persistent and chronic hyperglycaemia, which depletes the activity of the antioxidative defence system and thus promotes free radical generation (Coskun *et al*., 2005; Ihara *et al*., 1999). Because the expression levels of antioxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase are known to be very low in the islets of Langerhans compared with other tissues (Tiedge *et al*., 1997), β-cells may be particularly susceptible to oxidative stress (Kaneto *et al*., 2001).

The hyperglycaemia in STZ-treated rats leads to the formation of hydrogen peroxide, which subsequently generates free radicals such as O^{2-} and OH^{-}. These

Table 1: Body weight and serum glucose levels of control (A), untreated diabetic (B), green tea-treated diabetic (C), ginseng-treated diabetic (D) and ginseng + green tea-treated diabetic (E) groups

Parameters	A	B	C	D	E
Initial body weight (g)	208.1±12.3	195.2±9.5	195.4±7.3	198.8±8.6	210.4±10.3
Final body Weight (g)	205.0±9.4	166.4±14.3[a]	162.3±11.6[a]	196.4±9.8	202.6±12.9
Initial serum glucose (mg dL^{-1})	105.5±7.8	304.6±17.1	379.8±21.1	316.3±11.4	338.6±8.2
Final serum glucose (mg dL^{-1})	106.0±4.2	421.0±15.8[b]	315.5±13.4[*]	209.4±15.5[+]	152.6±9.1[+]

[a]$p<0.05$ compared with groups A, D and E, [b]$p<0.05$ compared with group A, [*]$p<0.05$ compared with group B, [+]$p<0.01$ compared with group C

Table 2: Final serum insulin, total cholesterol and triglycerides levels in control (A), untreated diabetic (B), green tea-treated diabetic (C), ginseng-treated diabetic (D) and ginseng + green tea-treated diabetic (E) groups

Parameters	A	B	C	D	E
Final serum insulin (mU L^{-1})	63.2±13.2	9.3±3.2[*]	14.2±3.8[*]	15.1±6.5[*]	24±3.7[a]
Final total cholesterol (mg dL^{-1})	81.1±7.8[a]	65.8±13.8[b]	63.8±13.2[b]	65.4±8.5[b]	69.9±7.2[b]
Final triglyceride (mg dL^{-1})	223.9±41.4	159.5±11.4[b]	149.6±11.9[b]	197.5±94.9	246.3±24.6

[*]$p<0.01$ compared with group A, [a]$p<0.05$ compared with group A, [b]$p<0.05$ compared with groups A, D and E

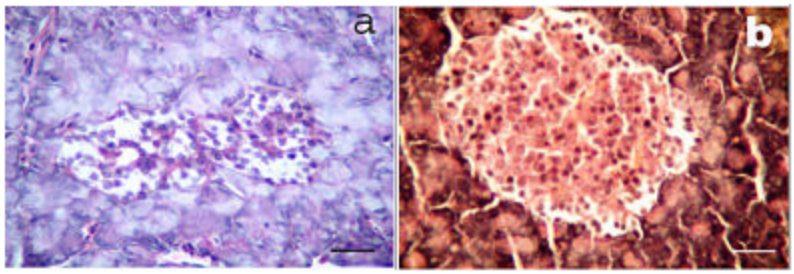

Fig. 1: a) Islets of Langerhans from untreated diabetic group (B), displaying hydopic degenerative and necrotic changes and b) Normal cells in the islets of Langerhans of control group (A). (H and E) (Scale bar 60 μm)

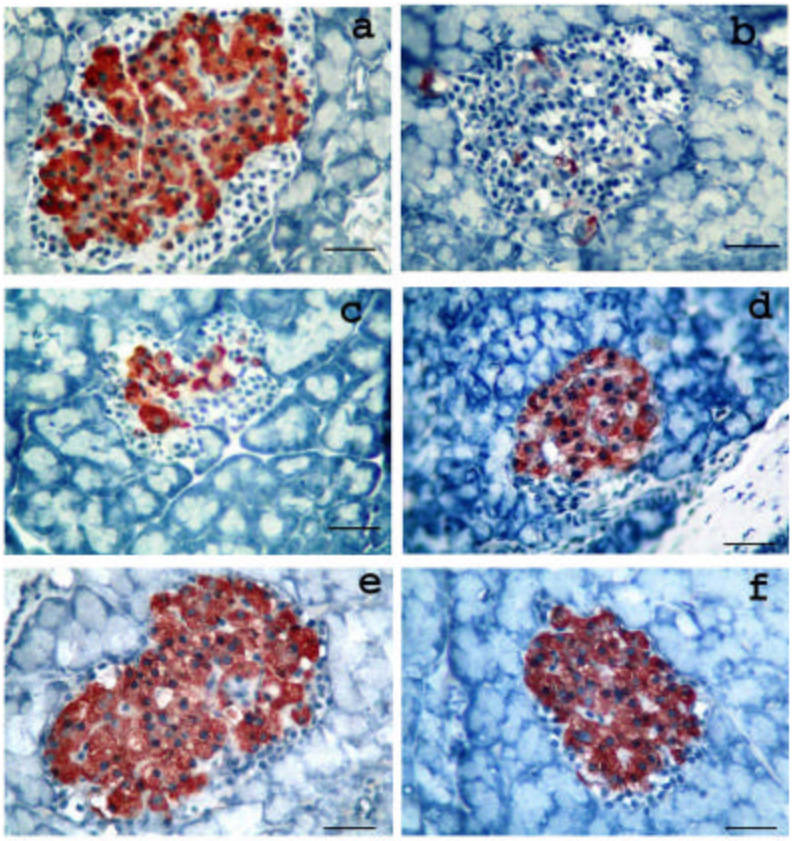

Fig. 2: a) Healthy β-cells in the islet of Langerhans of control group, b) Weak insulin-immunoreactivity can be seen in a few β-cells in the islet of Langerhans in untreated diabetic rats, c) A few β-cells in some islets displaying insulin immunopositivity in very small granules of diabetic rats treated with green tea extract for 6 weeks, d) Increased number of insulin-immunoreactive granules in β-cells of diabetic rats treated with ginseng for 6 weeks and e-f) Ginseng green tea treatment, protected the majority of β-cells in the islets of Langerhans and gave strong staining with the anti-insulin antibody. Immunoperoxidase, haematoxylin counterstain (Scale bar 60 μm)

reactive compounds can cause peroxidation of lipids, resulting in the formation of hydroperoxy fatty acids and endoperoxides (Pushparaj *et al*., 2000). In the present study, green tea, ginseng and green tea + ginseng significantly decreased hyperglycaemia and increased levels of serum insulin in the diabetic rats. However, level of serum triglycerides increased in groups D and E compared with the control group. The possible mechanism by which green tea and ginseng mediate antihyperglycaemic effect may be by potentiating the plasma insulin effect, either the pancreatic secretion of insulin from β-cells or its release from restrict insulin

Table 3: Semi-quantitative analysis of immunohistochemical staining of insulin in β-cells in pancreatic islets of Langerhans in control (A), untreated diabetic (B), green tea-treated diabetic (C), ginseng-treated diabetic (D) and ginseng+green tea-treated diabetic (E) groups

Groups	n	Weak (+)	Moderate (++)	Strong (+++)	Very strong (++++)
A	80	-	-	-	80
B	80	66	14	-	-
C	80	47	23	10	-
D	80	12	20	22	26
E	80	5	28	14	33

Cemek *et al.* (2008) and Kanter *et al.* (2004) reported that the numbers of insulin-immunoreactive β-cells in the islets of Langerhans were increased by treatment with *Matricaria chamomilla* L. and *Nigella sativa*, respectively (Cemek *et al.*, 2008; Evans *et al.*, 1965).

In the study, immunohistochemical staining of the pancreatic tissues of untreated diabetic rats (Group B) showed weak insulin-immunoreactivity in a few β-cells in the islets of Langerhans. Ginseng and green-tea+ginseng treatment protected the cells in the islets of Langerhans. These observations agree with those of Coskun *et al.* (2005) and Cemek *et al.* (2008). Necrotic degeneration was observed in the peripheral part of the islets of Langerhans in diabetic rats, but this necrotic degeneration was lower in groups D and E than in groups B and C. The ginseng also effected insulin release from the pancreas of the diabetic groups.

STZ has a β-cell cytotoxic and slightly carcinogenic effect. Although, the β-cell cytotoxic action of STZ is not fully understood, it is thought to be mediated by the inhibition of free radical scavenger enzymes, thereby enhancing the production of the superoxide radical. Eventually, STZ causes diabetes mellitus, which is associated with the generation of Reactive Oxygen Species (ROS), causing oxidative damage (Coskun *et al.*, 2005; Evans *et al.*, 1965). Chronic hyperglycaemia is accompanied by a decline in glucose-stimulated insulin secretion and insulin biosynthesis, a phenomenon known as glucose toxicity (Kaneto *et al.*, 2001). Decreased glycolysis, impeded glycogenesis and increased gluconeogenesis are some of the changes in glucose metabolism in the diabetic liver (Saravanan *et al.*, 2002).

In the present study, STZ caused a decrease in total cholesterol level in diabetic rats, as compared with healthy control rats. Treatment of rats with STZ-induced diabetes with ginseng or green tea + ginseng for 6 weeks resulted in a marked increase in the total cholesterol and triglyceride levels. In previous researches, consumption of green tea decreased serum concentrations of total cholesterol and low-density lipoprotein (Crespy and Williamson, 2004). Other studies report that ginseng (*Panax* sp.) has consistent antidiabetic (Vuksan *et al.*, 2001) and hypolipidaemic effects (Attele *et al.*, 2002) in diabetic rats.

CONCLUSION

The results demonstrate very good protective effects of ginseng and green tea+ginseng against STZ-induced pancreatic β-cell damage, which is probably due at least partly to antioxidative properties in scavenging STZ-associated free radicals. Further histological and biochemical investigations are now in progress to isolate and identify the active compounds in ginseng and green tea extracts.

ACKNOWLEDGEMENT

This research was support by a grant from the Yuzuncu Yil University Research Fund (2007-VF-B17).

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