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## Antihyperglycemic and Antioxidant Effect of Ginger Extract on Streptozotocin-Diabetic Rats

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**Abstract:** The present study was carried out to investigate the antidiabetic and antioxidant potentials of ginger (*Zingibar Officinale*) on Streptozotocin (STZ)-induced diabetic rats. An aqueous extract of raw ginger was administrated daily (0.5 g/kg, orally) for a period of 60 days to STZ-induced diabetic rats. At the end of the experiment, blood samples, plasma and erythrocytes were separated from part of the blood samples and Fasting plasma blood glucose and serum total cholesterol, Low Density Lipoprotein Cholesterol (LDL-cholesterol), High Density Lipoprotein Cholesterol (HDL-cholesterol), triglyceride were analyzed. Changes in plasma total antioxidant capacity and Malondialdehyde (MDA) were measured. The activities of erythrocytes Super-oxide Dismutase (SOD) and blood Glutathione Peroxidase (GSH-Px) were determined. The STZ-diabetic rats exhibited hyperglycemia accompanied with weight loss. Ginger extract, at a dose of 0.5g/kg, was significantly ( $P<0.05$ ) effective in lowering plasma glucose, total cholesterol, LDL-cholesterol and triglyceride levels in the ginger-treated diabetic rats compared with the control diabetic rats. Furthermore, ginger treatment resulted in a significant ( $P<0.05$ ) reduction in plasma malondialdehyde. On the other hand, ginger extract significantly ( $P<0.05$ ) increased plasma total antioxidant capacity and the activities of SOD and GSH-Px enzymes. This study demonstrates that ginger possesses hypoglycemic, hypocholesterolemic and hypolipidemic potentials in STZ-diabetic rats. Additionally, ginger extract causes a decrease in lipid peroxidation and an increase of plasma antioxidant capacity.

**Key words:** Ginger, blood glucose, lipid peroxidation, antioxidant status, diabetic rats

### INTRODUCTION

The current number of diabetics worldwide is 150 millions which is likely to increase to 300 million people or more by the year 2025 (King *et al.*, 1978). Reasons for this rise include an increase in sedentary lifestyle, the consumption of energy-rich diet, obesity, a higher life span, etc. (Yajmk, 2001). Regions with the greatest potential are Asia and Africa, where Diabetes Mellitus (DM) rates could rise to 2-3 folds than the present rates (ADA, 1997). Previous reports showing that oxidative stress and free radicals play a significant role in diabetic complications. Hyperglycemia is an important factor responsible for the intense oxidative stress in diabetes and toxicity induced by glucose autoxidation is one of the most likely sources of active oxygen form (Ceriello *et al.*, 1993). Furthermore, lipid peroxidation plays a role in the production of free radicals and oxidative stress in diabetes (Bonfont-Rousselot, 2000; Keaney and Loscalzo, 1999). Before the discovery of insulin in the 1920s and the development of oral hypoglycemic agents, diabetes mellitus was treated mainly by a combination of fasting, diet control and plant therapeutics (Bailey and Flatt, 1990). Several studies have shown that the consumption of nutrients rich in polyphenolic antioxidants such as tea, garlic, olive oil, ginger, tomato and others decrease diabetic complications and improve the antioxidant system of the

body (Aviram and Kasem, 1993; Bianca *et al.*, 2000; George *et al.*, 2004; Serafini *et al.*, 1994; Kur *et al.*, 2003; Srinivasan, 2005).

Ginger is a well-known herbaceous species which is consumed in most parts of the world. Antioxidants in ginger include gingerols, shogaols and some related phenolic ketone derivatives. Its dried extract contains monoterpenes and sesquiterpenes. Ginger extract has antioxidative properties and scavenges superoxide anion and hydroxyl radicals (Gao *et al.*, 1993; Krishnakanta and Lokesh, 1993).

The medicinal properties attributed to ginger include anti-arthritis (Srivastava and Mustafa, 1989; Srivastava and Mustafa, 1992; Bliddal *et al.*, 2000), anti-migraine (Cady *et al.*, 2005), anti-thrombotic (Thomson *et al.*, 2002), anti-inflammatory (Thomson *et al.*, 2002; Penna *et al.*, 2003), hypolipidemic (Bhandari *et al.*, 2005; Fuhrman *et al.*, 2002) and anti-nausea properties (Portnoi *et al.*, 2003). Gingerols derived from ginger have been shown to inhibit both prostaglandin and leukotrien biosynthesis (Kiuchi *et al.*, 1992). In addition, several ginger components exhibit serotonin receptor blocking activity (Kim *et al.*, 2005; Abdel-Aziz *et al.*, 2005; Huang *et al.*, 1991). Akhani *et al.* (2004) observed that ginger juice exhibits hypoglycemic activity in both animal and STZ-induced diabetic rats.

Mascolo *et al.* (1989) reported a significant hypoglycemic activity in normal rabbits at different times after a variety of administration schedules and doses. Moreover, ginger acts as a hypolipidemic factor in rabbits fed nutrients containing cholesterol (Bhandari *et al.*, 1998; Ozaki *et al.*, 1991). Feeding rats with ginger significantly elevated the activity of hepatic cholesterol 7  $\alpha$ -hydroxylase which is a rate-limiting enzyme in the biosynthesis of bile acids and stimulates the conversion of cholesterol to bile acids, leading to the excretion of cholesterol from the body (Srinivasan and Sambaiah, 1991).

The present study was conducted to evaluate the effect of ginger extract on blood glucose and blood lipid levels as well as total antioxidant capacity, malondialdehyde and antioxidative enzyme activities Superoxide Dismutase (SOD) and Glutathione Peroxidase (GSH-Px) in STZ- induced diabetic rats.

## MATERIALS AND METHODS

**Plant material and preparation of the extract:** Aqueous ginger extract was prepared from locally available ginger roots. The ginger roots were peeled on crushed ice and 50g ginger were cut into small pieces and homogenized in 75ml cold, sterile 0.9% NaCl in the presence of some crushed ice. The homogenization was carried out in a blender at high speed using 2 min bursts for a total of 12 min. The homogenized mixture was filtered three times through cheese-cloth (very little material was retained on the cheesecloth). The filtrate was centrifuged at 2000 relative centrifugal force for 10 min and the clear supernatant fraction was made up to 100 ml with normal saline. The concentration of this ginger preparation was considered to be 500 mg/ml on the basis of the weight of the starting material (50 g/100 ml). The aqueous extract of ginger root was stored in small samples at 0°C until use.

**Induction of diabetes in rats:** Male albino wistar rats (180-200 g) were housed in clean cages at a 20-24°C temperature, 12-h light/12-h dark cycle and relative humidity 52% in the animal house at the College of Medicine, King Saud University, Riyadh-Saudi Arabia. Rats were given free access to water and standard diets (American Institute of Nutrition). Rats were allowed to acclimatize to the new environmental condition and received a standard diet for one week before the experimental period which extended over 60 days. After fasting for 18 h, rats were injected intravenously through tail vein with a single dose of 40 mg/kg streptozotocin (Sigma Chemical Co., USA), freshly dissolved in citrate buffer (pH 4.5). After injection, they had free access to food and water and were given 5% glucose solution to drink overnight to counter hypoglycaemic shock. Three days later, the fasting blood glucose levels were determined and rats showing fasting plasma glucose

more than 240 mg/100 dL were considered diabetic and selected for experimentation.

**Experimental procedure:** Twenty four rats were randomly divided into 3 groups, each consisting of 8 rats. Group 1, normal healthy control fed with standard diet and orally administered 1 ml distilled water. Group 2, diabetic control (streptozotocin treated only) fed with standard diet and orally administered 1 ml distilled water. Group 3, diabetic fed with standard diet and orally administered ginger extract (0.5 g/kg body wt) for 60 days.

**Analytical methods:** At the end of 60th day, rats were fasted overnight and were anesthetized with light ether. Blood samples were collected in heparin-coated tubes. Part of the blood was used for GPxase determination, using Randox Assay Kits according to the methods of Pogia and Alentine (1970). Briefly, GSH-Px was catalyzed by the oxidation of reduced glutathione in the presence of cumene hydroperoxide. The generation of nicotinamide adenine dinucleotide phosphate then was measured. The remaining blood sample was centrifuged at 2000 g for fifteen minutes at 4°C. Erythrocytes were washed by saline and used for SOD determination using Randox Assay Kits according to the methods of Wolliams *et al.* (1983) which was based on the production of  $O_2^-$  anions by the xanthine/xanthine oxidase system. Plasma was analyzed for total antioxidant capacity, malondialdehyde and lipid profile. Plasma concentrations of total antioxidant capacity were determined using the Total Antioxidant Status Assay Kits according to the method of Miller *et al.* (1993). This assay relies on the ability of antioxidants in the sample to inhibit the oxidation of 2, 2'-Azino-di-[3-ethylbenzthiazoline sulphonate] (ABTS) to  $ABT^+$  by metmyoglobin. The amount of  $ABTS^+$  produced can be monitored by reading absorbance at 600 nm.

Plasma concentrations of malondialdehyde were determined using Kits method according to the method of Ohkawa *et al.* (1979). Plasma concentrations of glucose, total cholesterol, HDL-Cholesterol and triglycerides determinations were performed by standard procedures with the Cobas Integra analyzer (Roche Diagnostic Systems, Switzerland) (Neeley, 1972; Allain *et al.*, 1974; Hino *et al.*, 1996; Fossati and Prencipe, 1982). Plasma concentration of LDL-Cholesterol was calculated with the Friedewald formula (Reidewald *et al.*, 1972).

**Statistical analysis:** Data analysis was performed using Statistical Package for the Social Sciences, version 11.0 (SPSS) computer software. Descriptive statistics were adapted to display data in means $\pm$ SD. The statistical method of one way analysis of variance (ANOVA) was used to compare the mean values obtained among the

different groups. Differences were considered significant whenever the P-value is ( $p < 0.05$ ).

## RESULTS

Table 1 shows the effect of ginger extract on body weight in normal and diabetic rats. A significant body weight loss ( $P < 0.05$ ) was observed in the diabetic rat (group 2) as compared to Group 1 (Normal). Significant improvement ( $P < 0.05$ ) of body weight was observed in the rats treated with ginger extract as compared to Group 2 (diabetic).

Table 2 shows the effect of ginger extract on blood glucose and lipids profile in normal and diabetic rats. There was a significant rise ( $P < 0.05$ ) in blood glucose level in Group 2 (Diabetic) as compared to Group 1 (Normal). Oral administration with ginger extract significantly reduced ( $P < 0.05$ ) plasma glucose in Group 3 (Treatment) when compared to Group 2 rats. Also ginger extract significantly ( $P < 0.05$ ) reduced serum total cholesterol and triglycerides, LDL-cholesterol and increased the HDL-cholesterol levels as compared to diabetic rats i.e., Group 2.

Table 3 shows the effect of ginger extract on serum antioxidant capacity, serum malondialdehyde, superoxide dismutase and glutathione peroxidase activities in diabetic rats. There was a significant decrease ( $P < 0.05$ ) in antioxidant capacity, superoxide dismutase and glutathione peroxidase in diabetic rats (Group 2) as compared to normal rats (Group 1). The extracts of ginger significantly raise ( $P < 0.05$ ) antioxidant

capacity, superoxide dismutase and glutathione peroxidase in Group 3 rats when compared to Group 2 rats. There was a significant increase ( $P < 0.05$ ) in malondialdehyde among diabetic rats (Group 2) as compared to normal rats (Group 1). The extract of ginger significantly lowered ( $P < 0.05$ ) malondialdehyde among Group 3 when compared to Group 2 rats.

## DISCUSSION

The present study was undertaken to evaluate the antidiabetic properties of an aqueous extract of ginger in STZ-induced diabetic rats. STZ-induced diabetic rats showed significant increases in plasma glucose, total cholesterol, LDL-cholesterol triglyceride level which were accompanied by a significant reduction in body weight and HDL-cholesterol. The present results clearly show that an aqueous extract of raw ginger effectively lowers plasma glucose, total cholesterol, LDL-cholesterol and triglyceride. However, it should be noted that all the previous values in ginger-treated diabetic rats did not reach normal levels at the dosage used in the present experiment. A similar results was reported by Akhani *et al.* (2004) who concluded that ginger juice exhibits hypoglycemic activity in both normal and streptozotocin-induced diabetic rats, through its inhibitory effect on serotonin-induced hyperglycemic and hypoinsulinemia.

Several reports have detailed the serotonin receptor-blocking activity of ginger and its component (Abdel-Aziz *et al.*, 2005; Huang *et al.*, 1991; Akhani *et al.*, 2004) since serotonin has been reported to induce hyperglycemic

Table 1: Effect of ginger extract on body weight (g) in diabetic rats

Parameter	Group 1 (Control)	Group 2 (Diabetic)	Group 3 (Diabetic+Treatment)*
Pre-treatment	186.21±2.22	185.41±2.11	184.60±3.22
Post-treatment	250.52±2.32 <sup>a</sup>	180.15±2.31 <sup>b</sup>	190.12±2.32 <sup>c</sup>

Data are expressed as mean±SD (n = 8)

<sup>abc</sup>Different letters in a given row denote a significant difference,  $p < 0.05$

\*Diabetic+ginger extract (0.5 g/kg body weight)

Table 2: Effects of ginger extract on blood glucose and lipids profile in diabetic rats.

Parameter	Group 1 (Control)	Group 2 (Diabetic)	Group 3 (Diabetic+Treatment)*
Blood glucose (mg/dl)	90.21±5.21 <sup>a</sup>	452.72±31.21 <sup>b</sup>	292.92±41.30 <sup>c</sup>
Total cholesterol (mg/dl)	75.22±3.40 <sup>a</sup>	105.1±3.10 <sup>b</sup>	89.5±1.21 <sup>c</sup>
LDL-Cholesterol(mg/dl)	53.60±1.42	77.30±1.92	61.30±1.42
HDL-Cholesterol (mg/dl)	59.71±1.30 <sup>a</sup>	43.32±3.40 <sup>b</sup>	51.31±4.0 <sup>c</sup>
Triglycerides (mg/dl)	61.42±2.90 <sup>a</sup>	118.21±2.51 <sup>b</sup>	77.51±3.0 <sup>c</sup>

Data are expressed as mean±SD (n = 8)

<sup>abc</sup>Different letters in a given row denote a significant difference,  $p < 0.05$

\*Diabetic+ginger extract (0.5 g/kg body weight)

Table 3: Effect of ginger extract on plasma total antioxidant capacity and malondialdehyde, erythrocytes superoxide dismutase and glutathione peroxidase activities in diabetic rats

Parameter	Group 1 (Control)	Group 2 (Diabetic)	Group 3 (Diabetic+Treatment)*
Antioxidant capacity (mM)	1.30±0.25 <sup>a</sup>	0.99±0.17 <sup>b</sup>	1.28±0.29 <sup>a</sup>
Malondialdehyde (nmol/mL)	1.32±0.31 <sup>a</sup>	2.76±0.29 <sup>b</sup>	1.29±0.33 <sup>a</sup>
Superoxide dismutase (U/mL)	110.25±4.21 <sup>a</sup>	90.40±3.10 <sup>b</sup>	109.30±3.70 <sup>a</sup>
Glutathione peroxidase (U/mL)	28.31±1.11 <sup>a</sup>	22.90±0.89 <sup>b</sup>	26.31± 2.10 <sup>a</sup>

Data are expressed as mean±SD (n = 8)

<sup>abc</sup>Different letters in a given row denote a significant difference,  $p < 0.05$

\*Diabetic+ginger extract (0.5 g/kg body weight)

rats (Yamada *et al.*, 1999). On the other hand, Akhani *et al.* (2004) reported that ginger juice partially alleviated hypoinsulinaemia observed in STZ- induced diabetic rats.

Moreover, the hypolipidemic effect of ginger has been shown by other investigators (Sharma *et al.*, 1996). Afshari *et al.* (2007) mentioned that the hypocholesterolemic effects of ginger stem from the inhibition of cellular cholesterol synthesis. The attenuation of cholesterol synthesis results in augmenting the LDL receptor activity, leading to the elimination of LDL from plasma (Ness *et al.*, 1996).

In this experiment, the level of plasma malondialdehyde in streptozotocin-induced diabetic rats showed significant increases while total antioxidant capacity and antioxidant enzymes activities (GSH-Px and SOD) showed significant decreases in comparison with control rats. These results are in conformity with the results of (Sozmen *et al.*, 2001), who mentioned that, in addition to increasing Reactive Oxygen Species (ROS) production and lipid peroxidation, hyperglycemia decreases the antioxidant capacity through glycation of the antioxidant enzyme activities of glutathione peroxidase and superoxide dismutase (Sozmen *et al.*, 2001). On the other hand, the administration of ginger extract to STZ-induced diabetic rats caused significant decreases in plasma malondialdehyde concentration and significant increases in total antioxidant capacity as well as erythrocyte antioxidant enzyme activities (GSH-Px and SOD). The reduction in malondialdehyde level in ginger-treated diabetic rats, is in conformity with previously reported data (Afshari *et al.*, 2007; Wolff *et al.*, 1991; Cho *et al.*, 2002). It was found that administering ginger powder to streptozotocin-induced diabetic rats caused significant decreases in TBARS levels. It was also mentioned that decreases in TBARS levels may increase the activity of glutathione peroxidase in treated rats. Thus, an augmentation of plasma antioxidant capacity decreases plasma-free radical and lipid peroxidation (MAD) (Sozmen *et al.*, 2001; Wolff *et al.*, 1991), when consuming herbal extracts containing antioxidants. Our results confirm this result, when we found that a decrease in the malondialdehyde level was accompanied by significant increases in the activities of GSH-Px and SOD, thus causing inactivation of lipid peroxidation in ginger-treated diabetic rats.

**Conclusion:** Raw ginger extract has significant potential in the treatment of diabetes through decreasing blood glucose, blood lipids, free radicals, malondialdehyde and increasing the total antioxidant capacity and antioxidative enzyme activities (GSH-Px and SOD). Further research should be done to investigate the active components of ginger responsible for beneficial effects in diabetic conditions.

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