Antioxidant effects of ginger, cinnamon and combination on Streptozotocin-induced hyperglycemia associated oxidative stress in rats

Mohamed Farouk ElSadek[1, 2], Ali Madi Almajwal[1], Mahmoud Mustafa Ali Abulmeaty[1,3]

[1]Department of Community Health Sciences, College of Applied Medical Sciences, King Saud University, Saudi Arabia - E-mail: mfelsadek@gmail.com; [2]Nutrition and Food Science Department, Faculty of Home Economics, Helwan University, Egypt; [3]Obesity Research and Management Unit, Medical Physiology Department, Faculty of Medicine, Zagazig University, Egypt.

Summary. *Background and Aim:* The aim of the present study was to investigate the antioxidant effects of ginger (*Zingiber officinale*), cinnamon (*Cinnamomum cassia*) and combined formula of both powders on the oxidative status on Streptozotocin (STZ)-induced diabetic rats. *Methodology:* Fifty male wistar Albino rats were randomly divided into five groups (n=10). Group (1) Normal control rats received basal diet. Group (2) Diabetic control, which injected intraperitoneally with a single dose of 50 mg/kg STZ and received basal diet. Group (3) received basal diet with 15% of ginger. Group (4) received basal diet with 15% of cinnamon. Group (5) received basal diet with 15% of combined formula (50/50). Herbal powders and combination were placed in rats' diet by 15% of dried materials for 30 days for STZ rats. Oxidative status was investigated by measuring the total antioxidant capacity and the level of antioxidant biomarkers such as malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione peroxidase (GPx) in the serum, in addition to, catalase (CAT), MDA, GPx and SOD in the liver tissue. *Results:* Changes in body weight, food intake and food efficiency ratio were significantly observed between STZ and control groups. Administration of 15% combined formula was the most significantly ($P<0.05$) effective in reduction of plasma glucose, triglyceride, total cholesterol, LDL-C, VLDL-C, and liver enzymes, in addition to an elevation in FER, insulin, and HDL-C compared to diabetic control group. Furthermore, CAT, GPx, and SOD were significantly ($P<0.05$) elevated in liver tissue in combined formula-treated group. *Conclusion*: Administration of ginger and cinnamon powder with 15% showed amelioration of all investigated parameters with synergistic effects than each single herb on hypoglycemic, hypolipidemic effects with a remarkable decrease in both serum and tissue lipid peroxidation with enhancing antioxidant status for diabetic rats.

Key words: ginger, cinnamon, combined formula, Streptozotocin, antioxidant biomarkers.

Introduction

Diabetes mellitus is a complex, chronic disorder of carbohydrate, fat and protein metabolism that is primarily a result of partial, complete or relative lack of insulin secretion by pancreatic β-cells and/or impairment of insulin action (1). Conditions in which the normal balance between the amount of generated free radicals and levels of the endogenous antioxidants is disturbed is called oxidative stress (OS). Exposure or production of excessive quantities of reactive oxidative species (ROS) leads to oxidative degradation of many cellular proteins and molecules that may lead to cell damage. This set a base of many diseases such as aging, cancer, atherosclerosis, cirrhosis and cataract (3). Folk medicine included many plant-based remedies that may ameliorate manifestation of diabetes mellitus. These remedies might be a promising alternative for the diabetes management. Spices such as bay leaves, cloves, ginger, turmeric, cinnamon, garlic have beneficial effects in the treatment of diabetes (4-6).

Roots of ginger (*Zingiber officinale* L., Family Zingiberaceae), the culinary spice, were used in medicine inform of its active ingredients (Zingerone, Gingerdiol, Zingibrene, Gingerols, and Shogaols) due to its hypoglycemic, antioxidant, and androgenic and hypoglycemic activities (7, 10). Cellular organelles especially DNA molecules can be protected by natural antioxidants (11). It was reported that ginger juice exhibits a hypoglycaemic activity in both normal and streptozotocin (STZ)-induced diabetic rats (12). Ginger extracts can protect against superoxide anion and hydroxyl radicals induced deleterious effects (13). It was also reported that ginger treatment significantly decreased both serum cholesterol and triglycerides (12). In addition, animal studies using apolipoprotein-E deficient mice reported a reduction of LDL-cholesterol, VLDL-cholesterol and triglycerides levels (14).

Cinnamon-contained active compounds have insulin-like properties. They enhance glucose uptake by activation of insulin receptor kinase activity, and autophosphorylation of the insulin receptor, in addition to stimulation of glycogen synthase activity (15-17). Many patients with diabetics are already taking cinnamon products even though our knowledge remains limited. Cinnamon serves as an important antioxidant and is beneficial in the prevention and control of glucose intolerance and diabetes. Additionally, cinnamon extracts demonstrated antioxidant and hepatoprotective effects in CCL4 - intoxicated rats (18).

Previously have not yet reported the antioxidant properties of ginger, cinnamon and combination on STZ-induced hyperglycemia associated oxidative stress in rats. Hence, the present study was planned to evaluate the antioxidant properties of ginger, cinnamon, and combination on STZ-induced hyperglycemia associated oxidative stress in rats.

Materials and Methods

Herbals

Ginger and cinnamon were obtained from local market of Herbs, Riyadh, KSA. Fine powders were mixed with a basal diet with 15 % ginger and same ratio for cinnamon and combined formula.

Animals

Fifty male Wistar strain albino rats weighing 180±20 g were obtained from the college of Pharmacy, King Saud University. The rats were housed in clean cages, in groups of six. Rats were maintained in 12 h light and a 12 h dark cycle and a controlled temperature room (27±2°C). Rats fed on based diet for one week for adaptation and water *ad libitum* throughout the experimental period (4 weeks). The research ethics committee of the Collage of Applied Medical Sciences, King Saud University, approved the study protocol under reference number CAMS 52-35/36.

Induction of diabetic condition by streptozotocin

After overnight fasting, rats were intraperitoneally injected with a single dose (50 mg/kg body weight), of a fresh solution of Streptozotocin (STZ). To avoid STZ-induced hypoglycemia, rats ingested by 15% glucose solution. The animals were considered as diabetic, if their blood glucose levels > 250 mg/dl on the third day after STZ injection (19).

Chemicals

In the present study, all the chemicals used were of Analar Grade (AR) and purchased from Sigma (St. Louis, MO, USA) and Fisher (Pittsburg, PA, USA).

Experimental design

Fifty Albino rats were randomly divided into five groups, each consisting of 10 rats. Group 1, normal control (NC) which fed on basal diet. Group 2, Induced control (IC group) which treated with Streptozotocin and fed on basal diet. Group 3, (DG group) diabetic fed on a diet containing 15% ginger powder. Group 4 (DC group), diabetic fed on a diet containing 15% cinnamon powder. Lastly, group 5 (DCF group), diabetic fed on a diet containing 15% combined formula with (50/50) of both powders. After completion of 30 days of treatment, rats sacrificed after an overnight fasting, and the blood samples were collected into clean, dry centrifuge cuvette, left to clot at room temperature, then centrifuged at 300 p.p.m. Sera were

kept frozen at -80°C until the time of analysis. Liver was carefully removed cleaned and homogenized for further determinations.

Assays and biochemical analysis

Food intake (FI), body weight gain (BWG) and food efficiency ratio (FER) were determined (20). At the end of the experiment, blood samples were collected in heparin-coated tubes. Part of the blood was used for GPx determination, using Randox Assay Kits (21). The remaining blood sample was centrifuged at 2000 rpm for 15 min. Erythrocytes were washed with saline and used for SOD determination (22). Total antioxidant capacity was determined using Total Antioxidant Status Assay Kits (23). Catalase (CAT) activity was measured at 240 nm for 1 min in a UV spectrophotometer (24).

Total cholesterol (TC) was estimated (25), in addition to triglycerides (TG) (26) and high-density lipoprotein cholesterol (HDL-C) (27). Equations (28) were used to calculate low-density lipoprotein cholesterol (LDL-C) and very low- density lipoprotein cholesterol (VLDL-C). The activity of Alkaline Phosphatase (ALP) enzyme (30), serum blood glucose (31), and the plasma insulin (32) were measured accordingly. Furthermore, serum levels of liver enzymes (alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities) were analyzed (29).

Liver tissue enzymatic antioxidant biomarkers determinations

Tissue lipid peroxide (MDA), Lipid peroxidation (LPO) was determined by measuring malondialdehyde (MDA) that formed regarding thiobarbituric acid reactive substances (TBARS) in liver homogenates (33). The activities of liver tissues superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) were determined calorimetrically respectively (34-36).

Statistical analysis

SPSS software package 19 was used for statistical analysis. One-way analysis of variance (ANOVA) followed by Duncan's multiple range test was used. Results were expressed as mean ± S.D. from six rats in each group. P values < 0.05 were considered as significant.

Results

Effect of ginger and cinnamon treatments on food consumption, body weight Gain ratio, and FER.

Table 1 shows the effect of Ginger, Cinnamon and combined formula on food consumption in control and STZ-induced diabetic rats. In STZ-induced control rats showed a significant ($p < 0.05$) increase in food consumption compared with rats fed the basal diet (NC), vice versa for food efficiency ratio (FER) and body weight gain ratio. In addition, all STZ groups administered different ratios of Ginger, Cinnamon and combined formula (15%) showed a significant ($p < 0.05$) decrease in feed intake, vice versa for weight gain and FER. No significant ($p < 0.05$) differences in feed intake and FER were observed between all herbs treatments groups.

Effect of ginger and cinnamon treatments on blood glucose and insulin levels

Table 2 shows the effect of Ginger, Cinnamon and combined formula on blood glucose and insulin in STZ-induced diabetic rats. The results were ob-

Table 1. Effect of ginger, cinnamon and combined formula on BWG, FI, and FER in STZ-induced diabetic rats.

Groups Parameters	Normal Control	Induced Control	15% Ginger powder	15% Cinnamon powder	15% combined formula
Weight gain %	63±1.8 b	39±2.0 a	82±2.23 d	61.1±1.7 b	76.4±3.1 c
Feed intake (g/day)	18.36±1.4 a	25.58±1.72 b	18.01±1.1 a	18.32±2.1 a	18.21±1.1 a
FER %	0.143±0.014 b	0.061±0.012 a	0.203±0.027 d	0.178±0.18 c	0.191±0.12 d

Values are means ± S.D n= 10 rats/group.
Values not sharing a common superscript differ significantly at p< 0.05 (DMRT).

Table 2. Effect of ginger, cinnamon and combined formula on serum glucose and insulin in STZ-induced diabetic rats.

Groups Parameters	Normal Control	Induced Control	15% Ginger powder	15% Cinnamon powder	15%combined formula
Glucose (mg/dl)	96±2.37 a	281±4.25 d	158±2.6 c	136±2.50 c	128±2.31b
Insulin (μU/ mL)	16.28±1.22 d	5.63±1.31 a	9.91±0.83b	10.91±0.92bc	11.26±0.74 c

Values are means ± S.D n= 10 rats/group.
Values not sharing a common superscript differ significantly at p< 0.05 (DMRT).

tained in a significant increase in blood glucose levels and a decrease in insulin levels on (IC) diabetic rats. However, with the administration of ginger and cinnamon and combined formula resulted in significantly ($p < 0.05$) attenuates in blood glucose and insulin in IC rats.

Effect of ginger and cinnamon treatments on serum lipid profile

Table 3 shows the effect of Ginger, Cinnamon and combined formula on serum lipid profiles in STZ-induced diabetic rats. IC rats resulted in significant ($p<0.05$) increase in total cholesterol, triglycerides, low-density lipoprotein (LDL-c), and very low-density lipoprotein (VLDL-c) while the level of high-density lipoprotein (HDL-c) showed a significant ($p<0.05$) decrease compared to normal control. Treatment with ginger, cinnamon and combined formula with ratios 15% each, resulted in significant ($p<0.05$) attenuates the levels of those lipid parameters towards normal control levels.

Effect of ginger and cinnamon treatments on hepatic biomarkers

Table 4 shows the effect of Ginger, Cinnamon and combined formula on serum hepatic biomarkers AST, ALT, and ALP in STZ-induced diabetic rats. In diabetic rats the activities of hepatic biomarkers AST, ALT, and ALP significant ($p<0.05$) increased in STZ-induced diabetic rats. On administration of diet containing ginger and cinnamon and combined formula (50/50) with ratio 15% each showed significantly decreased the activities of hepatic function markers ($p<0.05$ in STZ-induced diabetic rats.

Table 3. Effect of ginger, cinnamon and combined formula on serum lipid profiles in STZ-induced diabetic rats.

Groups Parameters	Normal Control	Induced Control	15% Ginger powder	15% Cinnamon powder	15% combined formula
TC (mg/dl)	89.62±2.4 a	113.7±4.2 d	103.5±4.13 c	107.2±5.22 c	99.1±1.32 b
TG (mg/dl)	63.5±4.3 a	127.1±4.7 d	91.42±2.5 c	90.21±1.91 c	78.59±3.4 b
HDL (mg/dl)	51.6±3.5 cd	43.3±2.2 a	47±2.4 b	48.9±4.7 b	53.2±5.6 cd
LDL (mg/dl)	25.32±1.76 a	44.98±1.67 d	38.23±1.84 c	40.25±1.80 d	30.18±1.79 ab
VLDL (mg/dl)	12.7±0.96 a	25.42±0.87 d	18.28±0.68 c	18.04±0.75 c	15.71±0.71 b

Values are means ± S.D n= 10 rats/group.
Values not sharing a common superscript differ significantly at p< 0.05 (DMRT).

Table 4. Effect of ginger, cinnamon and combined formula on serum AST, ALT, and ALP in STZ-induced diabetic rats.

Groups Parameters	Normal Control	Induced Control	15% Ginger powder	15% Cinnamon powder	15% combined formula
AST (U/dl)	29±2.53 a	79±1.37 d	37±4.66 b	53±1.73 c	31±2.61 a
ALT (U/dl)	17±1.72 a	62±3.63 d	23±2.56 b	38±4.52 c	20±3.61ab
ALP (U/dl)	61±2.35 a	159±3.11 e	138.1±2.41 d	111.4±2.31 c	97.3±3.04 b

Values are means ± S.D n= 10 rats/group.
Values not sharing a common superscript differ significantly at p< 0.05 (DMRT).

Effect of ginger and cinnamon treatments on serum antioxidant status

Table 5 shows the effect of ginger, cinnamon and combined formula on serum antioxidant status in STZ-induced diabetic rats. In diabetic rats was observed significant ($p<0.05$) decreases in antioxidant capacity in STZ-induced diabetic rats. On administration of a diet containing ginger and cinnamon and combined formula (50/50) with ratio 15% each showed significantly decreased the antioxidant capacity in diabetic rats. Furthermore, the activities of CAT, GPx and SOD were decreased significantly in STZ-induced diabetic rats compared to normal control rats. Administration of ginger, cinnamon, and combined formula treatments, significantly ($p<0.05$) increases the CAT, GPx and SOD activities, which reflects the restoration of the antioxidant enzyme systems to near-normal values compared to normal control rats.

Effect of ginger and cinnamon treatments on liver tissue antioxidants content

Table 6 illustrates the effect of ginger, cinnamon and combined formula on liver tissue antioxidants contents in rats with oxidative stress. The levels of lipid peroxidation were significantly ($p<0.05$) increased in STZ rats as compared to the normal control A significant ($p<0.05$) decrease in activities of CAT, GPx, and SOD in liver tissue were noted after 30 days from incidence of OS by STZ injection. When rats were fed the basal diet containing our treatments with 15% ratio for four weeks especially for combined formula, the activities of enzymatic antioxidants in liver tissue were significantly ($p<0.05$) restored to near normal.

Discussion

STZ injection was previously reported to induce oxidative damage in several tissues. Oxidative stress is one of the reported mechanisms of development of both experimental and human diabetes mellitus. The current study investigated the effect of ginger, cinnamon and its combined formula against oxidative stress induced by STZ injection to rats. The results showed that STZ induced oxidative stress was characterized by a reduction in body weight and feed efficiency. Thus, weight reduction may be due to the destruction

Table 5: Effect of ginger, cinnamon and combined formula on serum antioxidant biomarkers in STZ-induced diabetic rats

Groups Parameters	Normal Control	Induced Control	15% Ginger powder	15% Cinnamon powder	15% combined formula
Antioxidant capacity (mμ)	1.52±0.3 d	0.92±1.1 a	1.24±0.2 b	1.29±2.9 b	1.12±1.3c
Catalase (nmol/min/mg protein)	21.1±2.1 d	11.3±2.6 a	15.4±1.69bc	16.9±2.02 bc	13.9±2.25 ab
GPx (nmol/min/mg protein)	32.81±1.1 d	23.9±0.97 a	25.33±1.56 b	27.89±1.89 c	24.94±0.97 b
SOD (U/mg protein)	121.33±4.2 c	90.81±2.1 a	117.31±3.2 b	119.24±0.31 b	114.1±4.12 b

Values are means ± S.D n= 10 rats/group.
Values not sharing a common superscript differ significantly at p< 0.05 (DMRT).

Table 6: Effect of ginger, cinnamon and combined formula on liver tissues antioxidant biomarkers in STZ-induced diabetic rats.

Groups Parameters	Normal Control	Induced Control	15% Ginger powder	15% Cinnamon powder	15% combined formula
Lipid Peroxidation (μmol / MDA/mg protein)	3.16±0.03 a	6.25±0.04 d	4.71±0.02 c	4.19±0.03 b	3.89±0.02 ab
Catalase (nmol/min/mg protein)	0.189±0.004 d	0.132±0.003 a	0.152±0.002 b	0.146±0.002 b	0.175±0.001 c
GPx (nmol/min/mg protein)	0.60±0.03 d	0.17±0.02 a	0.289±0.02 c	0.268±0.01 b	0.272±0.01 bc
SOD (U/mg protein)	56.36±1.22 d	31.72±1.24 a	37.32±1.24 b	40.46±1.28 bc	41.46±1.25 bc

Values are means ± S.D n= 10 rats/group.
Values not sharing a common superscript differ significantly at p< 0.05 (DMRT).

of muscle tissue of STZ-treated rats (37). After STZ induced rats had fed with ginger, cinnamon and combined formula with 15% ratio, the body weight was increased significantly (38).

In the present study, we observed a significant increase in blood glucose level and a decrease in insulin level of STZ induced diabetic rats; those may be due to damage of pancreatic beta cells by STZ a combined with generated free radicals due to oxidative stress production (39). Consuming diet containing 15% ginger cinnamon and combined formula from both (50/50) attributed to anti-hyperglycemic compounds of both herbs (38).

In this study, the STZ-injected rats exhibited hyperlipidemia in all lipid fractions, consuming a diet containing 15% of ginger, cinnamon and combined formula caused remarked reduction in the levels of triglycerides, total cholesterol, LDL-cholesterol, and VLDL-cholesterol but the plasma HDL-cholesterol level statistically increased. These findings are on the line with other findings (12,37,40) that expressed the lipid lowering effects of those herbs may be due to phytochemicals components in cinnamon and ginger that interfere with cholesterol biosynthesis in the liver causing its reduction or may be due to antagonistic action on STZ receptors, thereby increasing insulin levels.

The activities of serum hepatic markers such as AST, ALT and ALP were elevated. Results of STZ injected rats were significantly restored to near normal by consuming the diet containing 15 % ginger, cinnamon and combined formula for 30 days, as compared to normal control rats. Our findings in agreement with those of Sakr (41), who reported that these enzymes are increased in serum of rats suffering from liver injury, also the oral administration of ginger induced remarkable changes in the activities of ALT, AST, and ALP. Reactive oxygen species-induced cells oxidative damage related to lowering both enzymatic and non-enzymatic antioxidant activities in STZ diabetic rats (42). The essential oils from spices and medicinal plants exhibited remarkable antioxidant activity increasing the ability to scavenge free radicals (43-45).

Our results showed that serum antioxidant defense enzymes, SOD, CAT, and GPx were decreased significantly in STZ-induced diabetic rats that may be a response to increasing the auto-oxidation of the extra glucose contributed to the formation of H_2O_2 molecules (42). Herbs such as ginger and cinnamon have therapeutic effects in the treatment of different disease conditions such as STZ-induced hyperglycemia due to their antioxidant properties of its polyphenols content (37, 38). Antioxidant capacity is clearly increased by cinnamon, ginger, and combined formula consumption. Ginger, cinnamon and combined formula enhanced the activity of serum SOD, CAT and GPx enzymes which may be due to plenty of many antioxidant ingredients such as polyphenols, volatile oils, and gingerols that may modulate these enzymes activities in diabetic rats (46).

Injection of STZ resulted in significant elevation of the hepatic tissue malondialdehyde (MDA) (a biochemical marker of lipid peroxidation) concentrations to approximately 2-fold of the results of induced control than observed in normal control. On another hand, when STZ rats consumed diet containing ginger, cinnamon and combined formula, the level of MDA showed a significant ($p<0.05$) reduction to near normal. Furthermore, the non-enzymatic antioxidants showed a significant ($p<0.05$) reduction of activities of CAT, GPx, and SOD in hepatic tissue were noted after 30 days from the incidence of OS by STZ injection (47). The rise of antioxidant enzymes such as catalase in the erythrocyte is related to the oxidative degradation of membrane protein and lipid by increased oxygen free radicals in the body (48), which could be due to decrease protein expression levels associated with a diabetic in liver tissues. A consuming diet containing ginger, cinnamon and combined formula with 15% ratio resulted in ameliorates those changes toward the normal levels.

Conclusion

It is concluded that administration of 15 % ginger and same ratio for cinnamon and combined formula may be proven beneficial in attenuation of hyperglycemia, hyperlipidemia, also, the combined formulation found to be beneficial than the separated herb for enhancing the antioxidant status of STZ- induced diabetic rats resulted in reducing oxidative stress. However, the molecular mechanisms should be studied in future researches.

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Correspondence:
Mohamed Farouk ElSadek, PhD
Address: King Saud University (KSU), Riyadh, KSA, PO Box 10219, Riyadh 11433
Tel: +966 59 671 9800
E-mail: mfelsadek@gmail.com