

*Full Length Research Paper*

# The protective effects of cinnamon and sugar tea extract on diabetic rats with interrelationships between oxidative stress and DNA damage

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Accepted 30 July, 2012

Diabetes mellitus (DM) is diagnosed by the presence of hyperglycemia, which leads to increased oxidative stress. In this study, we aimed to determine whether cinnamon and sugar tea extract have protective effects on streptozotocin (STZ)+nicotinamide-induced diabetic rats. The therapeutic potential of cinnamon and tea extract on DM was assessed through analysis of their effects on both oxidative stress and DNA damage. Seventy-eight Sprague Dawley rats were divided into nine groups, including control groups, untreated diabetic group, and treated diabetic groups. Diabetes was induced by intraperitoneal administration of STZ and nicotinamide. Cinnamon and sugar tea extracts were administered to diabetic treatment groups for 30 days after diabetes was induced. At the end of the experiment, tissue and blood samples were taken from all rats. The levels of glutathione peroxidase, superoxide dismutase, catalase and malondialdehyde were determined in the liver homogenate. Comet assay was used to assess DNA damage in blood cells. DNA damage as assessed by comet length was increased in diabetic groups and decreased in cinnamon and sugar tea treated groups relative to controls. Our study revealed that treatment with either cinnamon or sugar tea extract has protective effects against oxidative stress in type II diabetic rats.

**Key words:** Comet assay, antioxidant enzymes, cinnamon, streptozotocin-nicotinamide (STZ-NA), induced diabetes.

## INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease characterized by an imbalance in carbohydrates and lipids levels and is diagnosed by the presence of hyperglycemia. DM is a pathologic condition resulting in intensive metabolic derangements and non-physiologic changes in many tissues (Anderson et al., 1998; Coşkun et al., 2005; Hannon-Fletcher et al., 2000; Siti Balkis et al., 2008; Song et al., 2007).

It is widely accepted that metabolism abnormality and hyperglycemia resulting in an increase in oxidative stress mark the progression of diabetes and its complications. Hyperglycemia is the cascade of reactions that cause an

overproduction of free radicals. These abnormally high levels of free radicals result in reduced antioxidant defense mechanisms, which can lead to cellular organelle damage (Song et al., 2007). Thus, diabetic patients may have reduced antioxidant defenses, such as diminished activity of glutathione peroxidase (GPx), catalase (CAT) and superoxide dismutase (SOD) (Anderson et al., 1998; Hannon-Fletcher et al., 2000; Siti Balkis et al., 2008; Atalay and Laaksonen, 2002; Bagatini et al., 2008; Ceretta et al., 2012; Matough et al., 2012; Moussa, 2008).

Recently, experimental diabetic models which could be studied with usage of genetic, chemical and surgical methods have been developed. The new experimental type 2 diabetes rat model is characterized with reduction of 40% of pancreatic beta islets. In this model, combination of 290 mg/kg nicotinamide (NA) and 60 mg/kg

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**Table 1.** The substrates given to control and experimental groups.

Group	Receiving substrates
1	Control (Saline i.p.)
2	Cinnamon extract (250 mg/kg i.g.)
3	Cinnamon extract (500 mg/kg i.g.)
4	Sugar tea (8.5 ml/kg i.g.)
5	Diabetic control (60 mg/kg STZ+290 mg/kg NA i.p.)
6	Cinnamon treated (60 mg/kg STZ + 290 mg/kg NA + 250 mg/kg Cinnamon Ext.)
7	Cinnamon treated (60 mg/kg STZ + 290 mg/kg NA + 500 mg/kg Cinnamon Ext.)
8	Sugar tea treated (60 mg/kg STZ+290 mg/kg NA + 8.5 ml/kg Sugar Tea)
9	Sugar tea + Cinnamon treated (60 mg/kg STZ+290 mg/kg NA+ 8.5 ml/kg Sugar tea+250 mg/kg Cinnamon Ext.)

STZ: Streptozotocin; NA: nicotinamide; i.p.: intraperitoneally; i.g.: intragastric; Ext.: extract.

streptozotocin (STZ) were injected intraperitoneally (Novelli et al., 2001; Özbayer et al., 2011). STZ, an antibiotic produced by *Streptomyces achromogenes*, is a commonly used agent to induce experimental type 1 diabetes. STZ can cause permanent damage to pancreatic  $\beta$  cells and STZ treatment triggers destructive cellular pathways, including genotoxic DNA methylation and hydroxyl radical (OH $\cdot$ ) formation (Coşkun et al., 2005; Golubnitschaja et al., 2006).

NA, which is a form of vitamin B3, is involved in a wide range of biological processes with help of its metabolite nicotinamide adenine dinucleotide (NAD $^{+}$ ). The anti-diabetogenic potential of NA is well known, and there are numerous studies involving combined application of STZ and NA in type 2 diabetic rat models (Nakamura et al., 2006; Roche et al., 2006).

The main basis of this model is to maintain nicotinamide source that is consumed during cellular processes within the body and to protect beta cells via nicotinamide. As a result, this model mimics the features of human type 2 diabetes, such as stable mild hyperglycemia and glucose intolerance both histologically and metabolically (Novelli et al., 2001; Özbayer et al., 2011).

Alkaline single cell gel electrophoresis, known as a comet assay, is a sensitive method enabling the detection of single-stranded DNA damage in single cells when performed in alkaline condition (Bagatini et al., 2008; Mozaffarieh et al., 2008; Hartmann et al., 2003; Sliwinska et al., 2008; Kushwaha et al., 2011; Dinçer and Kankaya, 2010).

Due to the side effects associated with the current therapeutic agents used for the treatment of BM, there is a growing interest in the discovery of herbal remedies to treat this disease. Many traditional folk medicinal herb extracts have been used for the treatment of DM. Cinnamon is one of the traditional folk herbs used in Korea, China and Russia used to treat DM. Cinnamon belongs to the Lauraceae family, and its main components are cinnamic aldehyde, cinnamic acid, tannin and methylhydroxychalcone polymer (MHCP). *Cinnamomum cassia* also exhibits insulin-potentiating capabilities and therefore may have beneficial effects on

cellular glucose uptake. Cinnamon bark possesses significant anti-diabetic, anti-allergic, anti-ulcerogenic, antipyretic and antioxidant properties (Kim et al., 2006; Kannappan et al., 2006; Solomon and Blannin, 2007).

Sugar tea extract is widely used in areas such as Kütahya (Turkey), and it contains *Olea europaea* leaves, *Juglans regia* leaves, *Rosmarinus officinalis*, *Viscum album*, *Lavandula stoechas*, *Melissa officinalis*, *Artemisia absinthium* and *Rubus fruticosus* fruit or leaves. Hypoglycemic and antioxidant effect of these herbs have been tested using manifold studies (Lee et al., 2008; Topal et al., 2007; Büyükbacı and El, 2008).

The aim of the present study was to determine the effects of cinnamon and sugar tea extracts on oxidative stress and DNA damage in STZ-nicotinamide-induced diabetic rats.

## MATERIALS AND METHODS

### Test animals

Experiments were performed on Sprague Dawley rats of 2 to 3 months of age (Eskişehir Osmangazi University Animal Laboratory, Eskişehir, Turkey) housed in individual cages at room temperature with 12 h cycles of light and dark and left for 1 week for acclimatization prior to the start of the experiment. The experimental protocols were approved by the institutional animal ethics committee and all rats were fed a commercial standard diet. All rats used in the following experiments were subject to the Guiding Principles for the Care and Use of Laboratory Animals and the Recommendations of the Declaration of Helsinki.

### Diabetes induction, grouping and treatment

At the beginning of the experiment, glucose levels were measured from all rat tail veins by glucometer, and then rats were divided into nine groups (Table 1). Diabetes was induced by intraperitoneal administration of STZ (60 mg/kg) and nicotinamide (290 mg/kg) (Novelli et al., 2001; Özbayer et al., 2011; Şimşek, 2005) and diabetic groups were treated with cinnamon and sugar tea extracts after diabetes was induced. Cinnamon bark were purchased from herbalist (Eskişehir, Türkiye) and 10 g of powdered cinnamon bark was weighed and mixed with 100 ml distilled water, kept in a water

bath (60°C, 2 h) and was filtered. This cinnamon extract was diluted with water (1:10). Sugar tea mixture were purchased from herbalist (Kütahya, Türkiye), and it contains *O. europaea* leaves, *J. regia* leaves, *R. officinalis*, *V. album*, *L. stoechas*, *M. officinalis*, *A. absinthium* and *R. fruticosus* fruit or leaves. One gram of mixture consisting of eight plants (sugar tea mixture) was stored in 200 ml boiling water for 5 min and was filtered. These two extracts were administered at appropriate doses by gavage as an intragastric (i.g.) to cinnamon and sugar tea control groups and diabetic treatment groups for 30 days following the induction of diabetes (from the 9th week) (Kim et al., 2006; Kannappan et al., 2006; Kwon et al., 2006; Safdar et al., 2004).

At the end of the treatment (13th week), liver tissue and blood samples were collected from the rats using appropriate techniques under ether anaesthesia. SOD, CAT, malondialdehyde (MDA) and GPx were measured in liver tissue homogenates and DNA damage were analyzed by comet assay in blood.

### Markers of oxidative stress and antioxidant capacity

SOD activity was measured by FLUKA SOD Determination Kit (Cat. No:19160), CAT activity was measured by ammonium molybdate-hydrogen peroxide reaction (Goth, 1991), MDA as a lipid peroxidation product was measured by TBA reaction (Uchiyama and Mihara, 1978) and GPx activity was measured by Glutathione Peroxidase Assay Kit (CAYMAN) (Cat. No: 703102) in liver homogenate.

### The preparations of liver tissue homogenates

Liver tissue samples (1 g for SOD and GPx, 0.4 g for CAT and MDA) were washed with physiological saline. These samples were homogenized on ice using ultrasonic homogenizer at 8000 cycle and 10 pulse in buffer solutions (Şimşek, 2005). Afterwards samples were centrifuged at +4°C, 4000 rpm and 15 min. Finally, the supernatants were used for measurements.

### Cryopreservation of whole blood for comet assay

Whole blood (100 µl) was added to 100 µl of cold RPMI 1640 medium containing 10% pre-cooled dimethyl sulfoxide (DMSO), as described previously by Chuang and Hu (2004). The mixture was transferred to a cryogenic vial, capped and immediately frozen at -80°C for 60 days.

### The alkaline comet assay procedure

The alkaline comet assay procedure performed in this study was a modification of the method described by Singh et al. (1988). Slides were prepared in triplicate per sample. Fully frosted microscopic slides were covered with 1% normal melting point agarose (NMPA). The addition of 7.5 µl of whole blood to 0.5% of 75 µl of low melting point agarose (LMPA) at 37°C comprised the second layer, and this mixture was pipetted onto the pre-coated slides and allowed to solidify on an ice tray for 10 min. A final, third layer of 1% LMPA was pipetted onto the slides and allowed to gel on ice tray for 10 min.

The slides were immersed in a freshly prepared lysing solution (2.5 M NaCl, 100 mM ethylenediaminetetraacetic acid (EDTA), 10 mM Tris and NaOH with Triton X-100 and DMSO). The Triton X-100 and DMSO were added immediately prior to use and incubated overnight at 4°C.

The slides were then removed from the lysing solution, drained and placed in a horizontal gel electrophoresis tank. The cold

electrophoresis solution with fresh 1 mM EDTA and 300 mM NaOH was filled into the tank. Slides were left in the solution for 20 min to allow unwinding of the DNA and expression of alkali-labile damage prior to electrophoresis. Electrophoresis was conducted at 4°C for 30 min at 25 V and a current of 300 mA.

Following electrophoresis, slides were washed three times in Tris buffer (0.4 M Tris, pH 7.5) to neutralize the excess alkali. Finally, slides were stained with 80 µl ethidium bromide (20 µg/ml). Slides were stored in a light-proof box and viewed within 12 h of staining. Cells were analyzed using a fluorescence microscope (Olympus BX51) and OSIRIS program (Head+Tail=Comet length).

### Statistical analysis

Statistical analyses were done by one-way analysis of variance (ANOVA) and Tukey test (Statistical Package for Social Sciences, SPSS 13.0). Probability value of  $P < 0.05$  was considered statistically significant.

## RESULTS

Homogenate SOD, MDA, CAT and GPx levels are presented in Table 2. Homogenate SOD and GPx activities significantly decreased in the diabetic control groups relative to the control group. There was no significant difference in the CAT activities between the control and diabetic groups.

Comet length measurements collected are shown in Table 3. While there was no significant difference seen between the STZ-nicotinamide-induced diabetic group (Group 5) and diabetic treatment groups (Groups 6, 7, 8, and 9) relative to the control group (Figure 1), however, comet tail length was decreased ( $P < 0.05$ ) in sugar tea and cinnamon-treated diabetic group relative to the diabetic group (Group 5).

## DISCUSSION

Oxidative stress has been proposed to be a potential contributor to the development of complications resulting from DM. Current evidence has shown that oxidative stress is increased in cells of diabetic rats due to the overproduction of reactive oxygen species (ROS) and decreased efficiency of antioxidant defenses due to hyperglycemia. Oxidation of lipids, proteins and other macromolecules such as DNA occurs during the development of diabetes and its complications. Hyperglycemia leads to increased production of free radicals, lipid peroxidation products, DNA damage and mutations that contribute to diabetes (Siti Balkis et al., 2008; Atalay and Laaksonen, 2002).

In this study, we tested the anti-hyperglycemic, anti-diabetic and anti-oxidant effects of cinnamon extract and sugar tea in the STZ-nicotinamide-induced diabetic rat model.

ROS interact with the lipid bilayer of the cell membrane resulting in lipid peroxidation. MDA is the end product of lipid peroxidation. An increased MDA level impairs the

**Table 2.** The levels of homogenate SOD, MDA, CAT and GPx.

Group	n	SOD	MDA	CAT	GPx
		(% inhibition)	(U/g wet tissue)	(KU/ml protein)	(nmol/min/ml)
Control	7	87.14 ± 3.97	61.42 ± 1.51	2.19 ± 0.65	13.71 ± 3.63
Cinnamon extract (250 mg/kg)	7	86.00 ± 2.44	45.71 ± 3.40***	1.61 ± 1.05	14.28 ± 2.75
Cinnamon extract (500 mg/kg)	7	90.85 ± 1.34	45.57 ± 3.30***	1.74 ± 0.77	15.71 ± 3.81
Sugar Tea extract (8.5 ml/kg)	7	90.14 ± 3.38	57.57 ± 2.93	2.37 ± 0.77	16.14 ± 5.20
Diabetic control (60 mg/kg STZ+ 290 mg/kg NA)	7	75.71 ± 2.49***	68.14 ± 4.37*	3.89 ± 2.13	4.14 ± 1.95***
Diabetic + Cinnamon (250 mg/kg)	7	78.14 ± 1.21***	59.71 ± 6.55 <sup>††</sup>	3.38 ± 1.13	10.57 ± 3.90 <sup>†</sup>
Diabetic + Cinnamon (500 mg/kg)	7	82.00 ± 1.91 <sup>†††</sup>	77.42 ± 3.15 <sup>††††</sup>	2.24 ± 1.11	13.00 ± 5.77 <sup>††</sup>
Diabetic + Sugar tea (8.5 ml/kg)	7	86.28 ± 1.60 <sup>†††</sup>	74.57 ± 2.99***	1.48 ± 0.49 <sup>††</sup>	11.85 ± 3.18 <sup>††</sup>
Diabetic + Sugar tea (8.5 ml/kg) + Cinnamon (250 mg/kg)	7	92.14 ± 1.34 <sup>††††</sup>	53.28 ± 3.40 <sup>††††</sup>	1.50 ± 0.50 <sup>††</sup>	20.42 ± 2.69 <sup>††††</sup>

SOD: Superoxide dismutase; MDA: malondialdehyde; CAT: catalase; GPx: glutathione peroxidase; STZ: streptozotocin; NA: nicotinamide. \*P < 0.05, \*\*P < 0.01, \*\*\* P < 0.001, all groups compared with the control group; <sup>†</sup>P < 0.05, <sup>††</sup>P < 0.01, <sup>†††</sup>P < 0.001 treatment groups compared with the diabetic control group.

**Table 3.** Comet length of all groups.

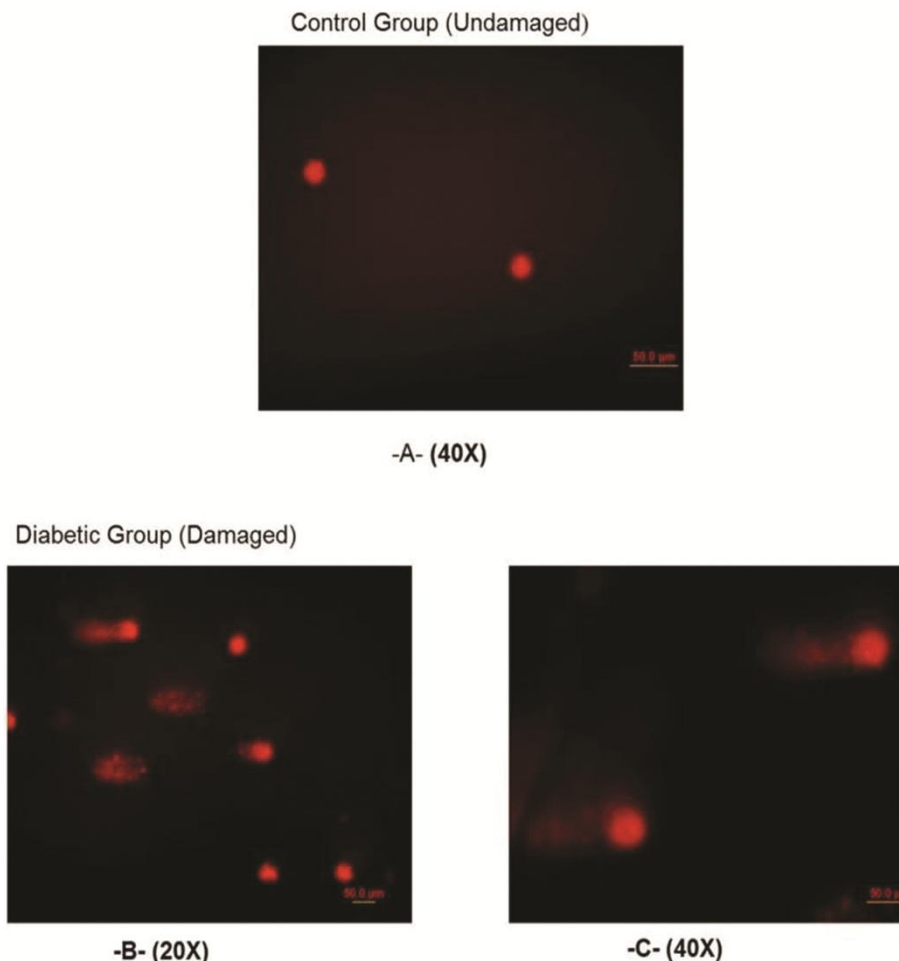
Group	n	Comet length (µm)	Statistical analysis								
			1st group	2nd group	3th group	4th group	5th group	6 <sup>th</sup> group	7th group	8th group	9th group
Control	7	49.68 ± 4.20	-	ns	ns	ns	ns	Ns	ns	ns	ns
Cinnamon extract (250 mg/kg)	7	44.43 ± 2.35	ns	-	ns	ns	*	Ns	ns	ns	ns
Cinnamon extract (500 mg/kg)	7	44.46 ± 6.14	ns	ns	-	ns	*	Ns	ns	ns	ns
Sugar tea extract (8.5 ml/kg)	7	39.76 ± 3.69	ns	ns	ns		***	**	*	*	ns
Diabetic Control (60 mg/kg STZ+ 290 mg/kg NA)	7	56.11 ± 2.69	ns	*	*	***	-	Ns	ns	ns	*
Diabetic + Cinnamon (250 mg/kg)	7	53.98 ± 7.82	ns	ns	ns	**	ns	-	ns	ns	ns
Diabetic + Cinnamon (500 mg/kg)	7	50.73 ± 6.77	ns	ns	ns	*	ns	Ns	-	ns	ns
Diabetic + Sugar tea (8.5 ml/kg)	7	50.92 ± 6.61	ns	ns	ns	*	ns	Ns	ns	-	ns
Diabetic + Sugar tea (8.5 ml/kg) +Cinnamon (250 mg/kg)	7	44.15 ± 6.10	ns	ns	ns	ns	*	Ns	ns	ns	-

STZ: Streptozotocin; NA: nicotinamide; ns: not significant, \* P < 0.05, \*\*P < 0.01, \*\*\*P < 0.001, all groups compared with the control group.

structural integrity of the cell membranes by decreasing membrane fluidity and changing the activity of membrane-bound receptors. The products of lipid peroxidation are associated with a variety of diseases, such as DM. Most published studies

have found increased lipid peroxidation in DM patients (Siti Balkis et al., 2008; Atalay and Laaksonen, 2002; Moussa, 2008; Salem et al., 2011). In this study, MDA levels were increased in the diabetic control group and were decreased in

cinnamon (250 mg/kg) and sugar tea and cinnamon (250 mg/kg)-treated diabetic groups relative to the diabetic control group. Additionally, MDA levels of the cinnamon extract groups (groups 2 and 3) were decreased according to control group (group 1).



**Figure 1.** Images of cells analyzed by comet assay. (A) Control group (Undamaged) magnification x40, (B) Diabetic group (Damaged) magnification x20, and (C) Diabetic group (Damaged) magnification x40.

It is known that free radicals are formed in cells by both cellular metabolism and exogenous agents. These species react with biomolecules in cells, including DNA, causing oxidative stress and DNA damage (Moussa, 2008; Kushwaha et al., 2011; Dizdaroglu et al., 2002). Oxidative stress occurs when ROS are not adequately removed by the cellular antioxidant system. Antioxidant enzymes decrease oxidative stress in diabetic rats. Previous studies have shown that SOD, CAT and GPx are major antioxidant enzymes (Moussa, 2008). Decreased activities of SOD, CAT and GPx were found in diabetic rats through quantitation of  $H_2O_2$  and other species hydrolysis (Coşkun et al., 2005; Atalay and Laaksonen, 2002). We also found that tissue SOD levels were decreased in diabetic control groups, although they were increased in the diabetic groups treated with either sugar tea or sugar tea + cinnamon (250 mg/kg). Similarly, GPx levels were decreased at the diabetic control groups and increased in cinnamon and sugar tea treated diabetic groups relative to the diabetic control group.

The comet assay has been shown to be a very sensitive method for the evaluation of DNA damage in individual cells. Studies using the comet assay have shown increased DNA damage in diabetic patients with hyperglycemia (Anderson et al., 1998; Hannon-Fletcher et al., 2000; Siti Balkıs et al., 2008; Bagatini et al., 2008; Sliwiska et al., 2008; Kushwaha et al., 2011; Dinçer and Kankaya, 2010). This study corroborated these findings, as we utilized the same method to reveal an increase in DNA damage in STZ-nicotinamide-induced diabetic group relative to the control groups. We went on to further to show that DNA damage levels decreased in cinnamon and sugar tea treated diabetic groups relative to STZ-nicotinamide induced diabetic group. Unfortunately, no article could be found about cinnamon and sugar tea effects on oxidative stress from the earlier studies.

Conclusively, our experimental results suggest that cinnamon bark extract and sugar tea may provide beneficial effects on antioxidant enzyme activities and

DNA damage. Further studies are required to understand the mechanism of the effects of cinnamon and sugar tea extracts on oxidative stress in STZ-nicotinamide-induced diabetic rats.

## ACKNOWLEDGEMENT

This study was supported by a grant of the Research Foundation of Eskişehir Osmangazi University, TÜRKİYE (Project No: 200711031).

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