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# The effect of ginger on diabetic nephropathy, plasma antioxidant capacity and lipid peroxidation in rats

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**Abstract**

Oxidative stress is a major factor in the pathogenesis of diabetic complications. We studied the effects of ginger powder on nephropathy induced by diabetes, and measured changes in plasma antioxidant capacity and lipid peroxidation.

Wistar rats weighing $250 \pm 20$ g were treated with STZ 60 mg/kg. Rats were divided into 3 groups ($n = 8$) of non-diabetic, diabetic non-treated and diabetic treated with ginger powder. The diabetic treated with ginger group received ginger at 5% of their consumed food daily.

After 8 weeks the rats were anaesthetized with 10% chloral hydrate. Blood samples were collected from the heart of each rat and kidneys were removed and kept in 10% formalin buffer. Plasma and red blood cells were separated. Plasma antioxidant capacity by the FRAP method and red blood cells malondialdehyde (MDA) as an indictor of lipids peroxidation, were measured. After sectioning and staining of renal samples, they were studied for focal cell proliferation and glomerular and tubular structural changes.

The MDA levels in diabetic rats treated with ginger were significantly lower than in the other groups ($P < 0.01$). Plasma antioxidant capacity in ginger treated rats were higher than in the first two groups. Diabetes induced nephropathies were also lower in the ginger treated group.

This study demonstrates that ginger causes a decrease in lipid peroxidation, an increase of plasma antioxidant capacity and a reduction in renal nephropathy.
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*Keywords:* Ginger; Nephropathy; Diabetes; Rat; Lipid peroxidation; Antioxidant

## 1. Introduction

There are numerous reports showing that oxidative stress and free radicals play a significant role in diabetic complications such as nephropathy (Baynes & Thorpe, 1999; Ha & Kim, 1995; Hunt & Wolff, 1991; Wolff, Jiang, & Hunt, 1991). In recent years, it has been shown that lipid peroxidation is augmented during diabetes which can cause tissue damage under this chronic condition (Nourooz-Zadeh et al., 1997). It has also been shown that hyperglycemia is an important factor responsible for the intense oxidative stress in diabetes and toxicity induced by glucose autoxidation is likely one of the important sources of active oxygen forms (Cerriello, Quatraro, & Giugliano, 1993). Furthermore, lipid peroxidation plays a role in the

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production of free radicals and oxidative stress during diabetes (Bonnefont-Rousselot, 2000; Keaney & Loscalzo, 1999).

Free radicals are those molecules and/or atoms possessing one or more uncoupled electrons and are extremely active and unstable. Among the most important free radicals in the reactive oxygen species (ROS) are superoxide anion ($O_2^{\cdot -}$), hydrogen peroxide ($H_2O_2$), alkoxyl radical ($RO^{\cdot}$) and peroxyl radical ($ROO^{\cdot}$).

Moreover, components of reactive nitrogen species (RNS), including nitric oxide (NO) and peroxynitrite, have important biological activities. ROS and RNS are continuously produced under physiological conditions. Uncontrolled production of both ROS and RNS results in the destruction of intracellular macromolecules such as DNA, lipids and proteins (Halliwell & Gutteridge, 1998).

Against these destructive and oxidative materials are several intra- and extracellular antioxidant defensive mechanisms, which counteract the destructive effects of free radicals. A group of enzymatic antioxidant compounds such as CuZnSOD, catalase and glutathione peroxidase function through direct elimination of ROS and causes attenuation or omission of free radicals activities (Halliwell, 1999).

Either non-enzymatic antioxidant systems like ubiquinone and uric acid, which are produced inside the cells, or others which enter the body through the diet like vitamin E, carotenoids, polyphenolic antioxidants, lipoic acids and others, also help to eliminate free radicals (Byun & Pal, 1999).

There is balance between ROS/RNS production and antioxidant defenses in healthy individuals. Oxidative stress is induced when an imbalance occurs between free radical reaction and scavenging capacity of defensive mechanisms (Byun et al., 1999). Increase of free radicals in oxidative stress causes damage in several ways. One way is oxidation of polyunsaturated fatty acids (PUFA), which are embedded in the cell membrane. This oxidation causes vascular damage during diabetes (Pelikanova, Kohout, Valek, Base, & Stefka, 1991; Vessby et al., 1994). Accordingly, it has been proposed that decreases of lipid peroxidation and free radical formation would reduce diabetes disorders. Several studies have shown that consumption of nutrients rich in polyphenolic antioxidants such as tea, garlic, olive oil, ginger, tomato and others decrease diabetic complications and improves the antioxidant system of the body (Aviram & Kasem, 1993; Bianca, Mira, Tony, Raymond, & Michael, 2000; George, Kaur, Khurdiya, & Kapoor, 2004; Serafini, Ghiseli, & Ferro-Luzzi, 1994).

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 monoterpens and sesquiterpens. Ginger extract has antioxidative properties and scavenges superoxide anion and hydroxyl radicals (Cao et al., 1993; Krishnakanta & Lokesh, 1993). Gingerol derived from ginger, at high concentrations, inhibits ascorbate–ferrous complex which in turn induces lipid peroxidation (Reddy & Lokesh, 1992). It has also been suggested that ginger interferes with inflammatory processes.

Moreover, ginger acts as a hypolipidemic factor in rabbits fed nutrients containing cholesterol (Bhandari, Sharma, & Zafar, 1998; Ozaki, Kawahara, & Harada, 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 & Sambaiah, 1991).

In the present study, we investigated the effects of ginger on diabetic nephropathy and measured the antioxidant capacity of plasma and lipid peroxidation in diabetic rats.

## 2. Materials and methods

Twenty-four male Wistar rats with an average body weight of $250 \pm 20$ g were provided by the Animal Care Center in the Faculty of Medicine of Urmia University of Medical Sciences. The animals were divided into 3 groups ($n = 8$) of non-diabetic control (ND), non-treated diabetic (NTD) and treated diabetic (TD) that received ginger powder as 5% of daily food intake (ADAC Company, Samsun, Turkey). Rats were injected streptozotocin (STZ) 60 mg/kg, IP to induce diabetes. Non-diabetic and non-treated diabetic rats received ordinary food and water. After 8 weeks all animals were anaesthetized by administration of 10% chloral hydrate (5 ml/kg, IP). Blood samples, each 3 ml, were directly collected from rat hearts by means of a syringe. Blood samples were mixed with ethylenediamine tetra-acetic acid (EDTA) as anticoagulant and centrifuged at 2000*g* for 10 min. Two samples of plasma (each 0.5 ml) were prepared for the measurement of plasma antioxidant capacity by the ferric reducing-antioxidant power (FRAP) method and a sample of red blood cells was prepared for MDA measurement. Blood samples were stored at −70 °C.

After collecting blood, the abdominal cavities of the animals were opened and the kidneys were removed carefully. Each kidney was slit into small pieces and kept in 10% formalin for pathologic tests.

The total antioxidant activity was measured by the FRAP assay (Benzie & Strain, 1996): 300 mmol/l of acetate buffer (pH 3.6); 10 mmol/l 2,4,6-tri-pyridyl-*s*-triazine (TPTZ) in 40 mmol/l HCl and 20 mmol/l $FeCl_3 \cdot 6H_2O$ in the volume ratio of 10:1:1 give the working FRAP reagent. Seven hundred and fifty microliters of working FRAP reagent is mixed with 25 μl serum or standard in a test tube. After exactly 10 min at room temperature, the absorbance at 593 nm is read against reagent blank. Fe(II) standards are used. Fe(II) (1000 μmol/l) is equivalent to 1000 μmol/l of FRAP. The change in absorbance is directly related to the "total" reducing power of the electron-donating antioxidants present in the reaction mixture.

## 3. Estimation of RBC lipid peroxidation

The extent of lipid peroxidation was estimated through the measurement of thiobarbituric acid reactive substance (TBARS) levels according to the method of Stocks and Dormandy (1971). Briefly, TBARS level was estimated by measuring the characteristic absorbance at 532 nm after reaction with thiobarbituric acid; the results are expressed as nmol/gHb. Trichloroacetic acid extracts of RBC samples were used to avoid interference of proteins with the TBARS determinations.

## 4. Samples pathology

Renal samples were kept for at least 48 h in 10% buffered formalin. After accomplishing tissue processing, samples were stained by the Haematoxylin–Eosin (H&E) method. Prepared slides were studied by light microscopy.

## 5. Results

Plasma antioxidant capacity in the non-diabetic, non-treated diabetic and diabetic treated with ginger groups of rats were $282.7 \pm 23.32$, $586.2 \pm 23.79$ and $763.5 \pm 19.58$ mmol/l, respectively. As presented in Fig. 1, antioxidant capacity in the ginger treated rats was higher when compared to the other two groups ($P < 0.01$). Fig. 2 shows TBARS changes in the different groups. The level of TBARS in healthy rats was $126 \pm 6.6$ nmol/g Hb. The level of TBARS in non-treated diabetic rats showed significant increases and reached to $245.26 \pm 17.2$ nmol/g Hb ($P < 0.001$). The levels of TBARS in the ginger treated group were significantly reduced from levels found in the untreated diabetic rats ($P < 0.001$). Fig. 3 shows the changes in renal histology of the different groups. Part A represents kidneys from healthy rats. As shown in panel B of Fig. 3, mesengial matrix augmentation and glomerular proliferation had occurred in all cases of non-treated diabetic rats. These diffuse changes bring about loading of the Bowman's capsule space and adhesion of capillaries to the wall. Some glomeruli had hyalinized changes. Tubules diffusely showed cellular inflammation whereas vascular degeneration changes were seen mostly in distal areas. Thickening of vessels walls were seen to be associated with hyalinization. Part C of Fig. 3 illustrates the results of the ginger treated rats in which mesengial matrix augmentation, glomerular proliferation and hyalinization were markedly attenuated in all cases.

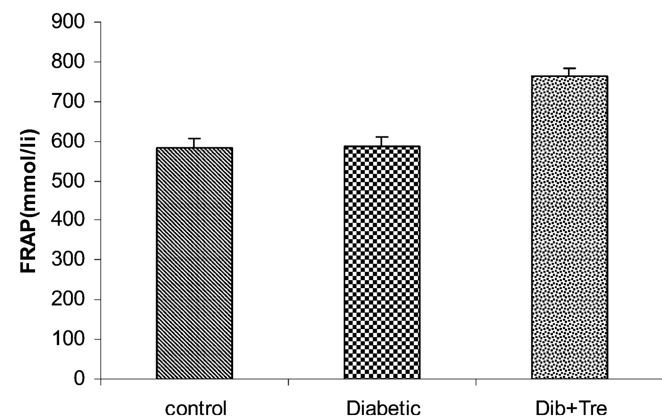


Fig. 1. The changes in plasma antioxidant capacity between different groups of rat ($P < 0.01$, Mean ± SEM).

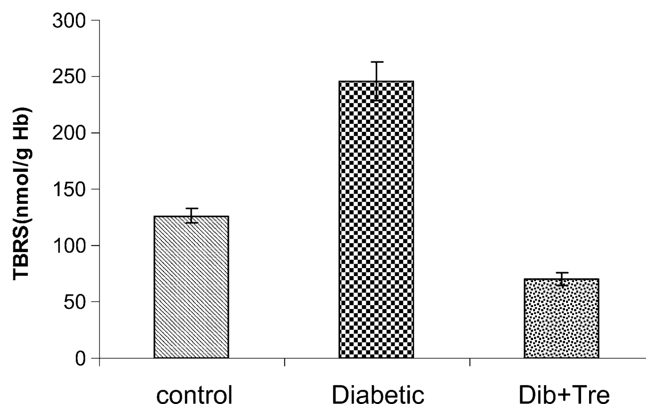


Fig. 2. The changes in TBARS levels of the red blood cell membrane in different groups of rat ($P < 0.001$, Mean ± SEM).

## 6. Discussion

This study has revealed that ginger powder significantly reduces the extent of lipid peroxidation and improves plasma antioxidant capacity. At the same time, ginger treated diabetic rats had significantly reduced nephropathy. The hypolipidemic effect of ginger has been shown by other investigators (Sharma, Gusain, & Dixit, 1996). It is likely that the hypochlosterolemic effects of ginger stems from the inhibition of cellular cholesterol synthesis. Attenuation of cholesterol synthesis results in augmentation of LDL receptor activity that leads to elimination of LDL from plasma (Ness, Zhao, & Lopez, 1996). These results are consistent with previously reported data showing that herbaceous nourishments like β-carotene and lycopene cause attenuation of cholesterol content (Fuhrman, Elis, & Aviran, 1997; O' Brien & Reiser, 1979). It is well established that elevation of LDL oxidation induces oxidative stress and resultant damage. Ginger directly decreases lipid peroxidation and oxidative stress (Fuhrman, Oiknine, & Aviran, 1994). Our results confirm that ginger decreases of lipid peroxidation and increases of plasma antioxidant capacity as shown by measurements of TBARS as a lipid peroxidation indicator. It is known that, impaired glucose metabolism leads to oxidative stress, proteins glycation and formation of free radicals (Ceriello, Quatraro, & Giuglian, 1992). Thus, an augmentation of plasma antioxidant capacity decreases plasma free radicals, as shown by this and other studies (Sozmen, Sozmen, Delen, & Onat, 2001; Wolff et al.,

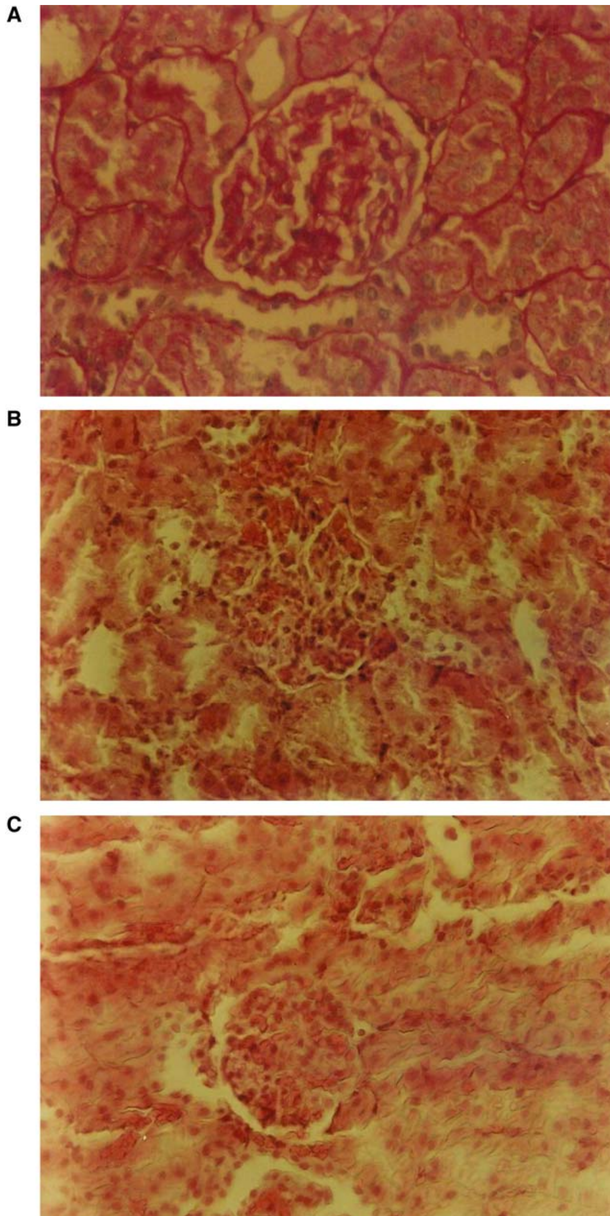


Fig. 3. The light microscopic image from the kidney of a healthy rat (A), a non-treated diabetic rat (B) and a ginger treated diabetic rat (C).

1991) when consuming herbal extracts containing antioxidants. The reduction in TBARS levels in our study is in agreement with previously reported data (Cho et al., 2002; Wolff et al., 1991). Levels of TBARS in non-treated diabetic rats showed significant increases in comparison with control rats and we found that administration of ginger powder caused significant decreases in TBARS levels. This decrease in TBARS levels may increase the activity of glutathione peroxidase (GPX) in treated rats and hence cause inactivation of lipid peroxidation reactions (Aydin et al., 2001; Levy, Zaltzber, Ben-Amotz, Kanter, & Aviran, 1999). It has been proposed that only some lipids produce TBARS by peroxidation (Young, Nielsen, Haraldsdottir, Daneshvar, & Lauridsen, 1999). The large decrease of TBARS levels which reflects decrease of lipid peroxidation suggests that other factors such as reduction of lipids in the liver and plasma by ginger powder may also have a role in decreasing lipid peroxidation and TBARS levels. In our study, TBARS attenuation is accompanied by FRAP augmentation, showing that, plasma antioxidant capacity is increased by consumption of ginger. Elevation of antioxidant capacity raises the antioxidant scavenging capacity of the body and attenuates free radical induced damage. The ROS scavenging capacity by antioxidants is decreased in diabetes such that constant oxidative stress develops and oxidation of lipids, proteins and other macromolecules such as DNA is increased. Augmentation of plasma antioxidative capacity would also attenuate lipid peroxidation through this mechanism (Ohkawa, ohishi, & Yagi, 1979).

In this study, diabetic nephropathy was significantly improved in rats receiving ginger. It is likely that lipid peroxidation and free radicals generation can induce nephropathy by different means. A probable mechanism may result from the increased activity of phospholipase A2 ($PLA_2$) which produces thromboxane $A_2$ ($TXA_2$) and the vasodilator prostacyclin ($PGI_2$). Thus, a balance between $PGI_2$ and $TXA_2$ preserves natural vascular tune. In diabetes, levels of $TXA_2$ are increased while $PGI_2$ levels are decreased and this imbalance leads to a decrease of blood flow which in the kidney will cause nephropathy (Patricia, Nievelstein, Sixma, & Offenhof, 1991; Shohat & Boner, 1993). Another mechanism proposes that hyperglycemia, in addition to increasing ROS production, also decreases antioxidant capacity through glycation of scavenger enzymes. There may also be an important role for protein kinase C in diabetic vascular complications. According to previously reported data (Ha & Kim, 1999), a causal relationship between oxidative stress and diabetic nephropathy exists based on following observation:

1. Lipid peroxides and 8-hydroxy deoxyguanosin with albuminuria are increased in the kidneys of diabetic rats.
2. High glucose concentrations directly raise oxidative stress in glomerular mesengial cells (which are target cells in diabetic nephropathy).
3. Oxidative stress induces expression of $TGFB_2$ and fibronectin mRNA genes which have important roles, in diabetic glomerular damage.
4. Inhibition of oxidative stress improves all disorders related to diabetic nephropathy (Ha & Kim, 1999). Morphometric analysis has shown an advantageous effect of antioxidants on the structure of the basement membrane of glomerular capillaries. Consumption of vitamins E and C decreases the thickness of the basement membrane in rats (Kedziora-Kornatowska et al., 2003). Other studies have also confirmed the useful effects of antioxidants on renal nephropathy (Craven, DeRubertis, Kagan, Melhem, & Studer, 1997; Mdyneux, Glyn, & Ward, 2002). Accordingly, the results of our study could be explained by an elevation of plasma

antioxidant capacity which decreases free radical accumulation and lipid peroxidation induction in diabetic nephropathy (Faure, Corticelli, & Richard, 1993).

It is unlikely that, complete normalization of oxidative stress could be obtained by glucose control so that, damage induced by oxidative stress continues (Sharma, Kharb, Chugh, Kakkar, & Singh, 2000). Consumption of antioxidants such as ginger would be a useful addition to current treatment strategies e.g. with insulin.

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