

Lycopene Protects the Diabetic Rat Kidney Against Oxidative Stress-mediated Oxidative Damage Induced by Furan

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ABSTRACT

Furan is a food and environmental contaminant and a potent carcinogen in animals. Lycopene is one dietary carotenoid found in fruits such as tomato, watermelon and grapefruit. The present study was designed to explore the protective effect of lycopene against furan-induced oxidative damage in streptozotocin (STZ)-induced diabetic rat kidney. At the end of the experimental period (28 days), we found that lycopene markedly decreased the malondialdehyde (MDA) levels in the kidney, urea, uric acid and creatinine levels in the serum of furan-treated rats. The increase of histopathology in the kidney of furan-treated rats were effectively suppressed by lycopene. Furthermore, lycopene markedly restored superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione-S-transferase (GST) activities in the kidney of furan-treated rats. In conclusion, these results suggested that lycopene could protect the rat kidney against furan-induced injury by improving renal function, attenuating histopathologic changes, reducing MDA production and renewing the activities of antioxidant enzymes.

Key Words: Furan, Lycopene, Kidney, Oxidative stress, Diabetes

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INTRODUCTION

Chemical factors are recognized to play a major role in the etiology of various diseases, including cancer (Koul et al. 2010; Dirican and Kalender 2012). Furan is an important thermal processing contaminant which presents in a number of foods, including canned meats, vegetables, soups and brewed coffee. Furan intake worldwide in which mean intake in European countries was estimated at 0.27-1.17 mg/kg bw/day (Churchwell et al. 2015). In foods, the presence of furan is a toxicological concern because high doses of furan are toxic to organs like liver in animals (Gill et al. 2011). It was reported to mediate its toxicity in animals by inducing oxidative stress (Ajiboye et al. in press). Oxidative stress, defined as a disturbance in the balance between the production of reactive oxygen species (ROS) and antioxidant defenses (Baş et al. 2015). Increased ROS production exerts toxic effects on membrane polyunsaturated phospholipids, resulting in generation of toxic products such as MDA (Arnal et al. 2010).

Diabetes, the most common endocrine disorder, characterized by increased blood glucose levels resulting from defective insulin secretion and its complications are associated with increased oxidative stress (Bhutada et al. 2010; Amin et al. 2015). In the STZ-induced diabetes, MDA levels increase (Baş et al. 2015; Apaydın et al. 2016). Also, antioxidant defence system is significantly altered (Degirmenci et al. 2005). In the long term, diabetes leads to complications in lots of organ systems. There is evidence that, besides the long term diabetes complications, which include accelerated atherosclerosis, renal failure caused by glomerular injury and neuropathy (Arnal et al. 2010).

Supplementation of antioxidants was shown to reduce oxidative damage caused by chemicals and diabetes (Suresh et al. 2013; Uzun and Kalender 2013; Baş et al. 2015). Lycopene is the most extensive carotenoid which found in diet especially in tomato. The consumption of lycopene is associated with reduced oxidative damages of biomolecules such as lipids, proteins and DNA (Palabiyik et al. 2013). It has been indicated to have strong antioxidant potency *in vivo* and *in vitro* (Mordente et al. 2011). It may have important role as a chemopreventive agent against cancers of

prostate, stomach, breast and lung (Palabiyik et al. 2013).

A positive correlation has been confirmed between dietary supplementation with some antioxidants and the reduction of toxic effects of various toxicants, environmental agents (Sharma et al. 2010). In the light of aforesaid medical properties of lycopene, this study was carried out to determine the possible protective effects of lycopene on oxidative stress and toxicity related biochemical and histologic parameters in kidney and serum of furan intoxicated diabetic rats.

MATERIALS AND METHODS

Chemicals and Animals

Furan, lycopene, STZ and all other chemicals were purchased from Sigma. All chemicals and reagents were used of analytical grade. Lycopene and furan were dissolved in corn oil according to studies of Ateşşahin et al. and Hamadeh et al. (Hamadeh et al. 2004; Ateşşahin et al. 2006). Thirty-five adult male Wistar rats (300 - 320 g, 120 days old) were used for this study. The rats were housed in plastic cages and maintained in a controlled environment under conditions of temperature (18-22°C) and light (12-hr light/dark cycle, lights on 07:00-19:00).

The animals were allowed to acclimatize for 10 days before the beginning of the study. They had free access to standard animal diet and water *ad libitum* throughout the experimental period. All the procedures which applied to rats in this work were performed in accordance with ethical guidelines on the care and use of animals. The protocol used in this study was endorsed by the Çukurova University Animal Experiments Local Ethics Committee.

Experimental protocol

For furan, lycopene and STZ, doses used in this study were chosen according to previous studies (Hamadeh et al. 2004; Ateşşahin et al. 2006; Schmatz et al. 2009). Rats were weighed and randomly allocated into five groups of seven individuals: control group (was fed with 1 mL/kg bw corn oil via gavage for 28 days), diabetic control group (was fed with 1 ml/kg bw/day corn oil via gavage for 28 days), diabetic lycopene group (was given lycopene by gavage at dose of 4 mg/kg bw for 28 days), diabetic furan group (was fed with 40 mg/kg

bw by gavage for 28 days), diabetic furan+lycopene group (was fed with 40 mg/kg bw ml/kg bw furan and 4 mg/kg bw lycopene via gavage for 28 days). The rats were sacrificed using combination of ketamin+xylazin and dissected after 28 days. Blood samples were collected in tubes with anticoagulant for urea, uric acid and creatinine assays of serum. The kidney tissues were cleaned and washed with ice cold normal saline for examinations.

Experimental induction of diabetes

Diabetes was induced by intraperitoneal injection of 55 mg/kg STZ. STZ diluted in 0.1 M sodium-citrate buffer at 4.5 pH. Blood samples were taken from the tail after 48 hr STZ injection to evaluate glucose levels. Blood glucose levels were measured with a glucometer. During the experimental period blood glucose levels were determined twice more (14 and 28 days after the beginning of treatment). Animals whose glucose levels were over 300 mg/dl were considered diabetic and used for this study.

Measurement of serum urea, uric acid and creatinine levels

The levels of serum urea, uric acid and creatinine were determined spectrophotometrically using commercial diagnostic kits (Thermo Trace-BECGMAN, Germany) and analyzed by an autoanalyzer (Bayer ope-RA).

Assay of antioxidant enzyme activities

CAT activity was determined by the method of Aebi (Aebi 1984). In brief, to a quartz cuvette, phosphate buffer (pH 7.0) and sample were added and the reaction was started by addition of H₂O₂. The decomposition of H₂O₂ was monitored at 240 nm.

The GPx activity determination was based on the method of Paglia and Valentine (Paglia and Valentine 1967). The assay evaluates the enzymatic reduction of H₂O₂ by GPx by way of depletion of reduced glutathione that is restored from oxidized glutathione in a coupled enzymatic reaction by glutathione reductase. The decrease in absorbance was determined at 340 nm.

SOD activity in kidney homogenate was assessed according to method of Marklund and Marklund (Marklund and Marklund 1974). In quartz cuvette, 1 mL of Tris-HCl buffer,

containing diethylene triaminopentaacetic acid and pyrogallol were mixed with 20 µL of kidney samples. The difference in the absorbance was measured at 440 nm.

GST activity of kidney tissues was investigated by the method of Habig et al (Habig et al. 1974). 1-chloro-2-4-dinitrobenzene is neutralized by the enzyme in the presence of glutathione as a cosubstrate. The change in absorbance was measured at 340 nm.

Assay of MDA level

MDA concentration was determined in kidney homogenate by the method of Ohkawa et al. (Ohkawa et al. 1979). MDA forms a colored complex in the entity of thiobarbituric acid, which is perceptible by measuring the absorbance by spectrophotometer. Briefly, it consisted of the addition of sample to 10% trichloroacetic acid, followed by centrifugation. The supernatant was added to thiobarbituric acid. Then, the samples were placed in a thermoblock warmed at 100°C. Next, the samples were cooled and absorbance was measured at 532 nm.

Histological evaluations

For histological analysis, kidney tissue samples were fixed in 10% formaldehyde and prepared for routine paraffin embedding. Tissue sections (6-7 µm) were prepared by using a microtome (Leica RM2255) and stained with Hematoxylin and Eosin (H&E) dye, which was mounted in a neutral deparaffinated xylene medium for microscopic observations. Slides were examined under a light microscope (Olympus BX-51) and photographed with a camera (Olympus E-330). Ten slides were prepared from each kidney tissue. All sections were evaluated for the degree of renal damage. Each slides were investigated and assigned for severity of changes [none (-), mild (+), moderate (++) and severe (+++) damage].

Statistic analysis

All analyses were carried out using the SPSS software, version 20.0. A one-way analysis of variance (ANOVA; P < 0.05) and Tukey's test were used to determine significant differences between groups. The values were stated as mean ± SD.

RESULTS

MDA Levels and Antioxidant Enzyme Activities

Diabetes increased the level of MDA and decreased enzyme activities compared with control significantly. The MDA levels were decreased and SOD, CAT, GPx and GST activities increased in the diabetic lycopene group compared to diabetic control group.

Animals treated with furan showed a significant ($p < 0.05$) increase in MDA levels, whereas, SOD, CAT, GPx and GST activities were found to decrease significantly. Lycopene supplementation caused increases in all antioxidant enzyme activities and decreases in MDA levels measured compared to diabetic furan group (Fig. 1-5).

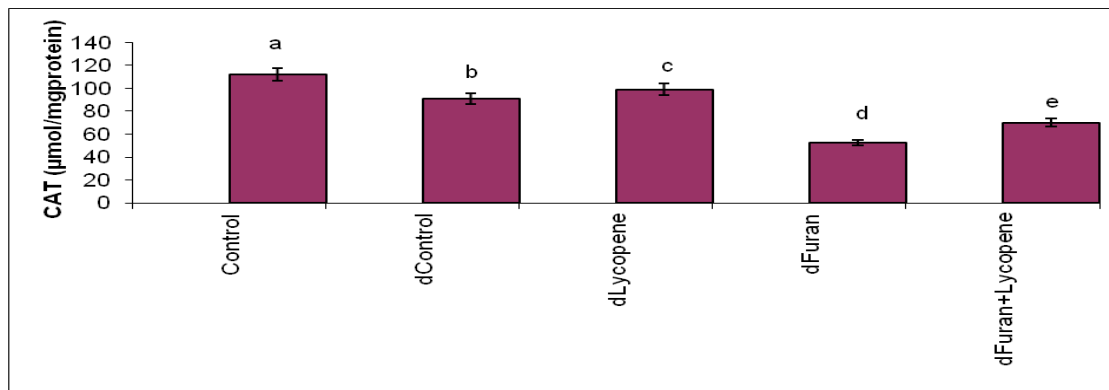


Figure 1- Effects of subacute treatment of furan and lycopene on CAT activities ($\mu\text{mol/mg protein}$) in kidney of rats. Each bar represents mean \pm SD of seven animals in each group. Columns superscripts with different letters are significantly different. Significance at $P < 0.05$.

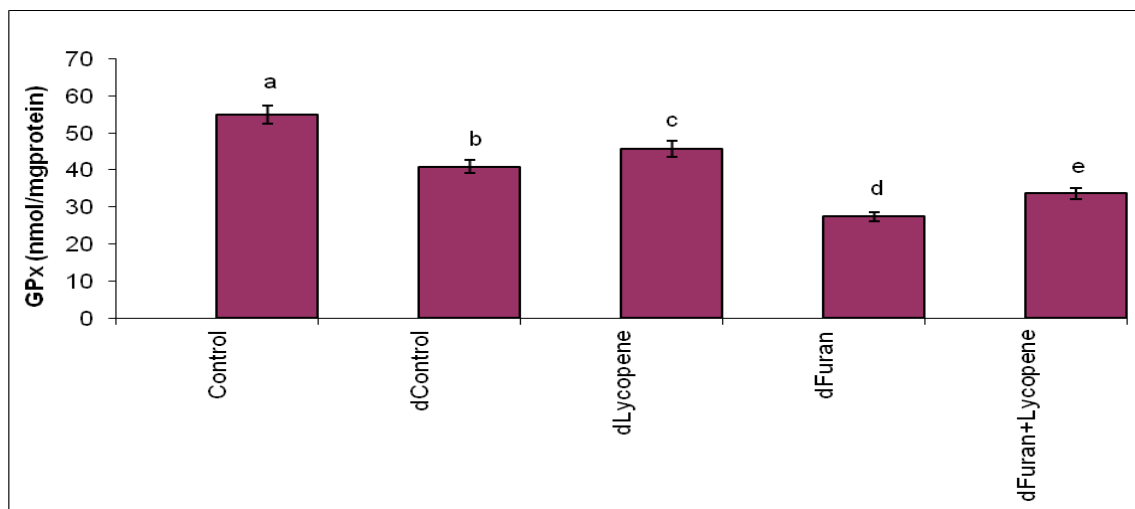


Figure 2- Effects of subacute treatment of furan and lycopene on GPx activities (nmol/mg protein) in kidney of rats. Each bar represents mean \pm SD of seven animals in each group. Columns superscripts with different letters are significantly different. Significance at $P < 0.05$.

Effects of furan and lycopene on nephrotoxicity

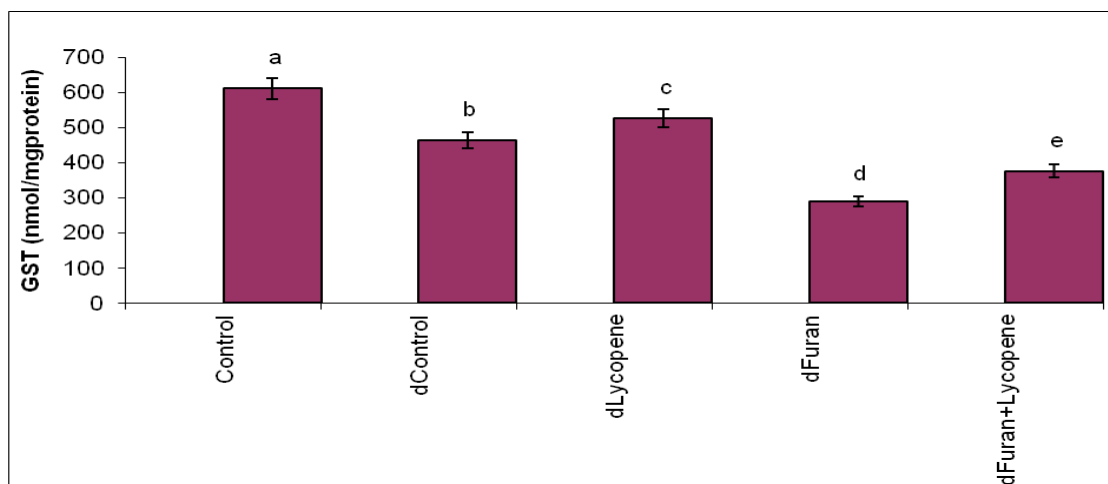


Figure 3- Effects of subacute treatment of furan and lycopene on GST activities (Nmol/mg protein) in kidney of rats. Each bar represents mean \pm SD of seven animals in each group. Columns superscripts with different letters are significantly different. Significance at $P < 0.05$.

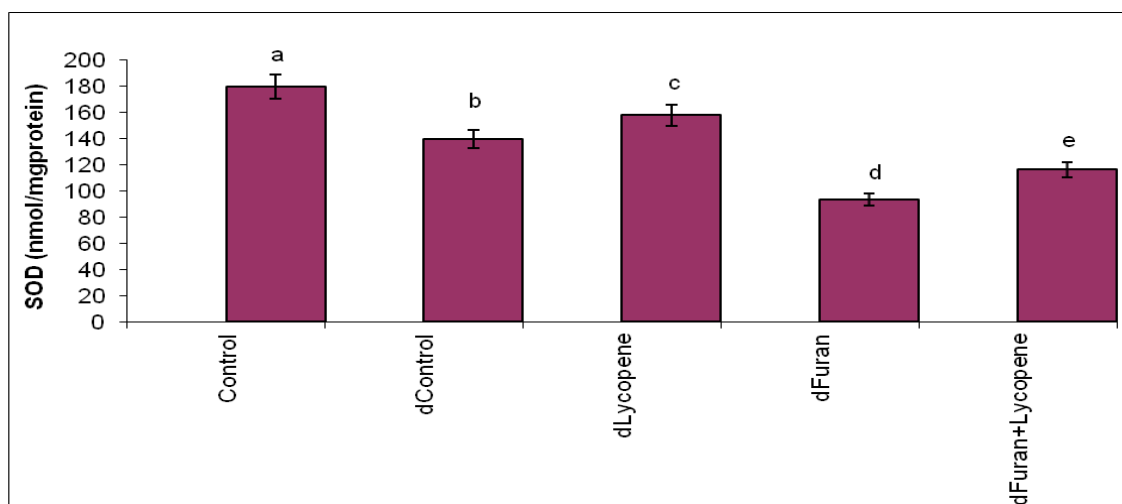


Figure 4- Effects of subacute treatment of furan and lycopene on SOD activities (nmol/mg protein) in kidney of rats. Each bar represents mean \pm SD of seven animals in each group. Columns superscripts with different letters are significantly different. Significance at $P < 0.05$.

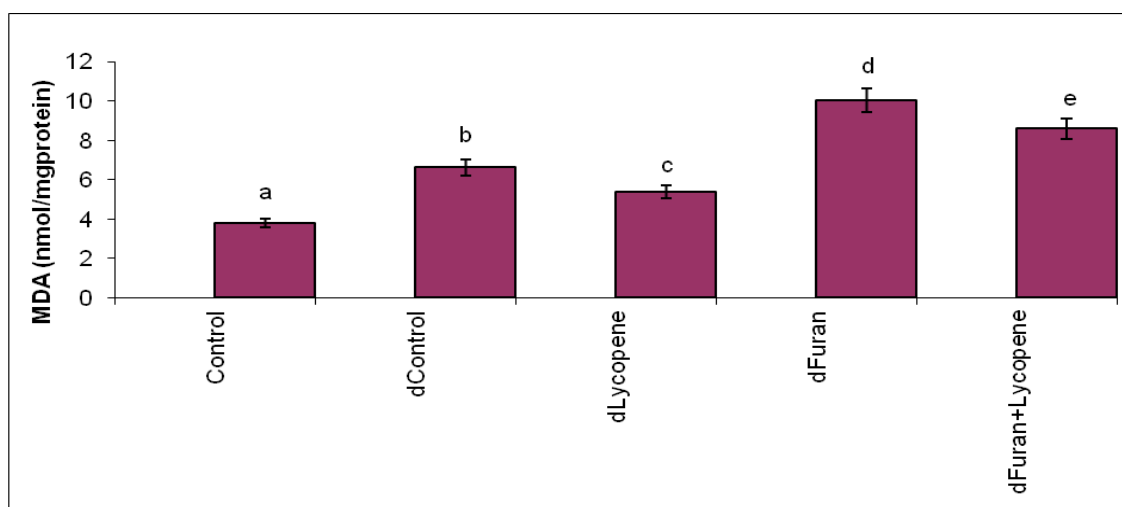


Figure 5- Effects of subacute treatment of furan and lycopene on MDA levels (nmol/mg protein) in kidney of rats. Each bar represents mean \pm SD of seven animals in each group. Columns superscripts with different letters are significantly different. Significance at $P < 0.05$.

Biochemical parameters

Serum biochemical parameters are given in Table 1. When we compared control group with diabetic control group we observed that urea, uric acid and creatinine levels of serum increased. In furan treated diabetic rats, serum urea, uric acid and creatinine levels

increased significantly. Lycopene treatment affect biochemical parameters measured. It cause decrease in urea, uric acid and creatinine levels caused by diabetes and furan.

Table 1- Urea, uric acid and creatinine levels of control and experimental rats

Groups	Urea (mg/dL)	Uric acid (mg/dL)	Creatinine (mg/dL)
Control	26,27±1,1 ^a	1,57±0,08 ^a	0,26±0,01 ^a
Diabetic control	36,9± 1,5 ^b	1,99±0,05 ^b	0,32±0,016 ^b
Diabetic lycopene	33,74±1,3 ^c	1,77±0,06 ^c	0,29±0,013 ^c
Diabetic furan	42,88±1,3 ^d	2,37±0,07 ^d	0,42±0,021 ^d
Diabetic furan+lycopene	39,12±1,2 ^e	2,18±0,06 ^e	0,37±0,018 ^e

Values are mean±SD of seven rats in each group. Significance at $P < 0.05$. Within each column, means superscript with different letters are significantly different.

Histopathological examinations

The light microscopic investigation of kidneys in control group have revealed normal renal structure with well-defined glomeruli and tubules (Fig. 6). As for the pathological studies, they have proven changes caused by diabetes. In fact, diabetic control group showed glomerular lobulation, tubular degeneration, hemorrhage and dilatation of Bowman's space (Fig. 7). Lycopene treatment was partially protective against diabetes induced histopathological changes. Only tubular degeneration and dilatation of Bowman's space were observed in diabetic lycopene group (Fig. 8). Histological damages

were more severe in diabetic furan group, particularly extensive inflammatory cell infiltration, glomerular lobulation, glomerular atrophy, tubular degeneration, hemorrhage and dilatation of Bowman's space (Fig. 9). Lycopene supplementation was protective against furan caused histopathological changes, too. But it not protect completely. In diabetic furan+lycopene group hemorrhage, tubular degeneration and glomerular lobulation were determined (Fig. 10). Grading of the histopathological changes in the kidney sections can be observed in Table 2.

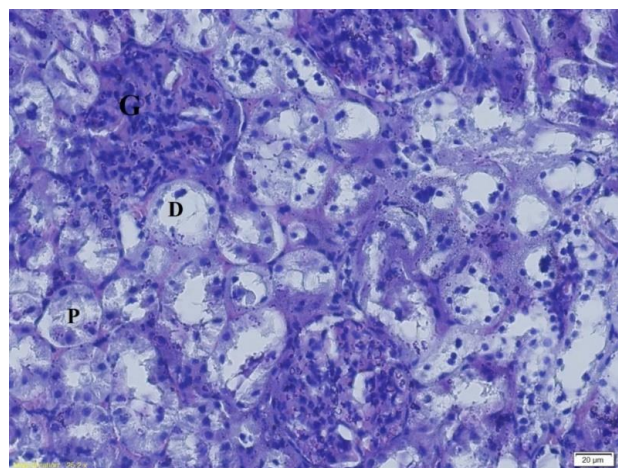


Figure 6- Kidney sections of Control rats X200, H&E. G: Glomerulus, P: Proximal tubule, D: Distal tubule.

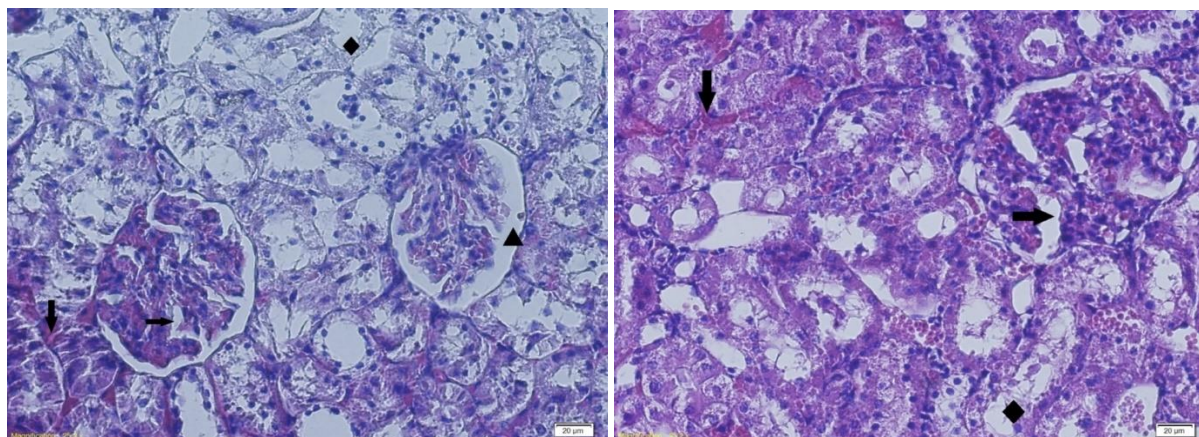


Figure 7- Kidney sections of Diabetic control rats X200, H&E. glomerular lobulation (\rightarrow), hemorrhage (\downarrow), Dilatation of Bowman's space (\blacktriangle), Tubular degeneration (\blacklozenge).

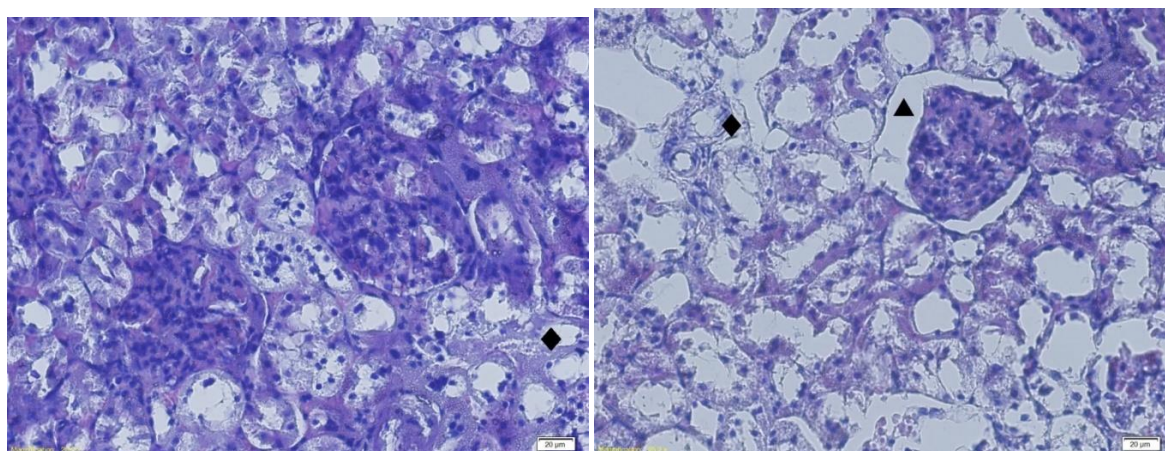


Figure 8- Kidney sections of Diabetic lycopene rats X200, H&E. Tubular degeneration (\blacklozenge). Dilatation of Bowman's space (\blacktriangle)

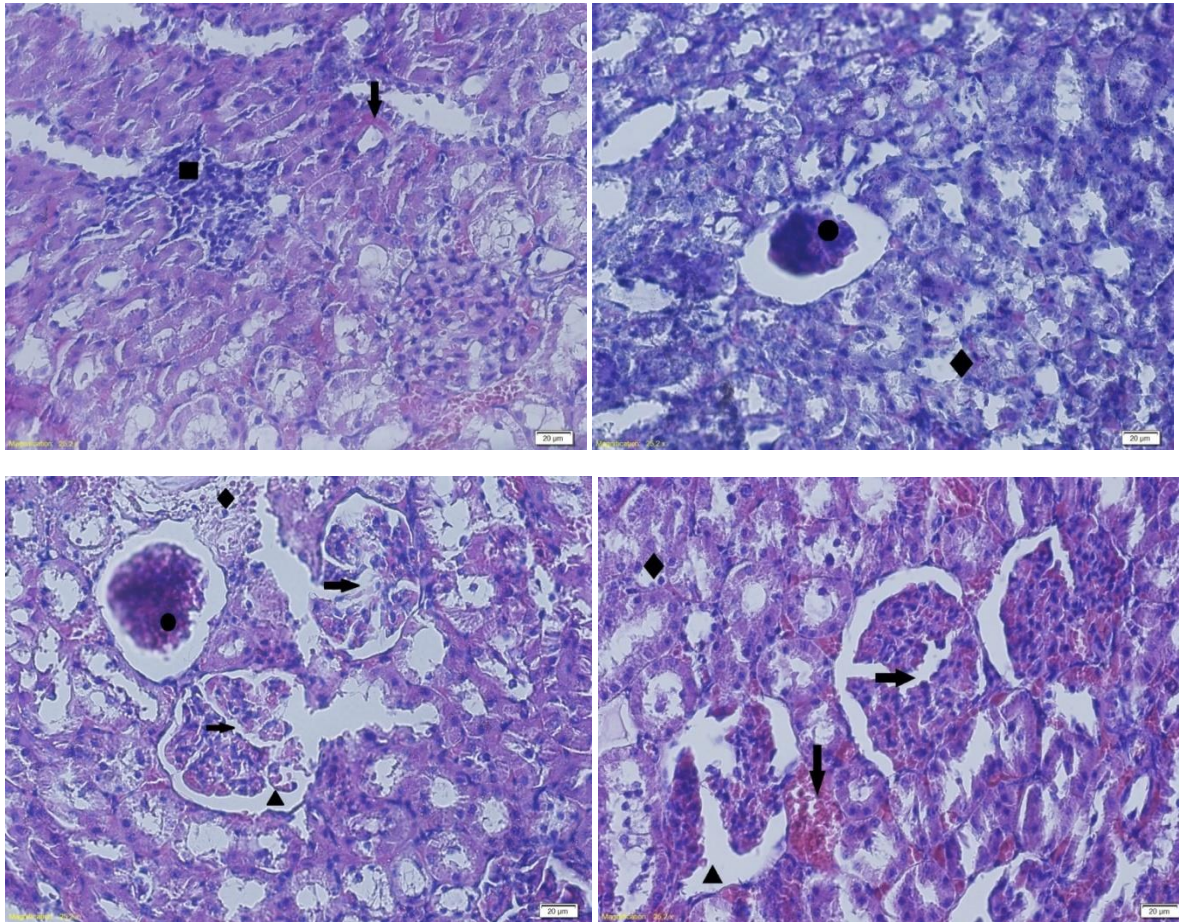


Figure 9- Kidney sections of Diabetic furan rats X200, H&E. hemorrhage (↓), inflammatory cell infiltration (■), Tubular degeneration (◆), glomerular atrophy (●), glomerular lobulation (→), Dilatation of Bowmann's space (▲).

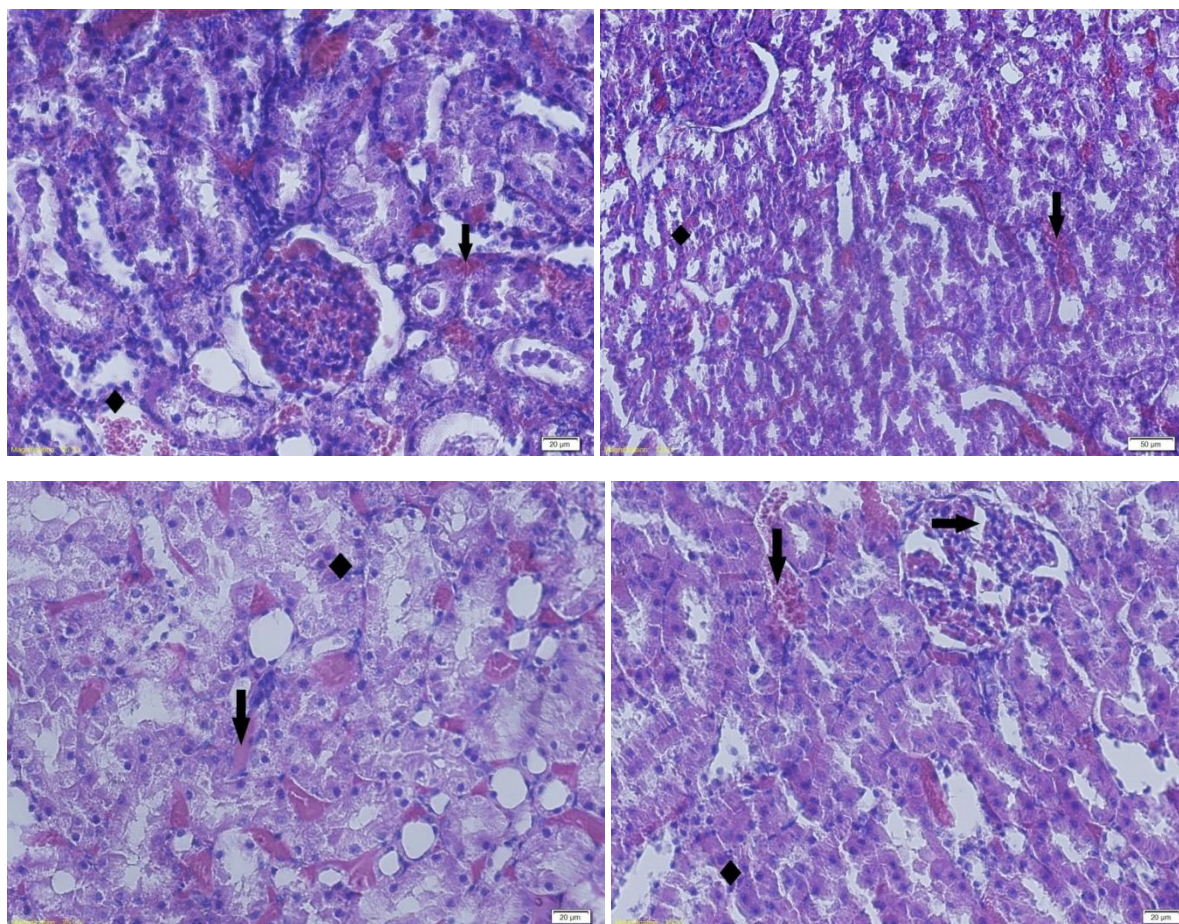


Figure 10 - Kidney sections of Diabetic furan+lycopene rats X200, H&E. hemorrhage (↓), Tubular degeneration (◆), glomerular lobulation (→).

Table 2- Grading of the histopathological changes in the kidney sections

Groups	Control	Diabetic control	Diabetic lycopene	Diabetic furan	Diabetic furan+lycopene
hemorrhage	-	+	-	+++	++
inflammatory cell infiltration	-	-	-	+	-
Tubular degeneration	-	++	+	+++	++
glomerular atrophy	-	-	-	++	-
glomerular lobulation	-	+	-	+++	++
Dilatation of Bowmann's space	-	++	+	+++	+

Scoring was done as follows: (-) none, (+) mild, (++) moderate, (+++) severe

DISCUSSION

There are many studies which have indicated that furan treatment could induce biochemical and physiological dysfunctions in animals and humans (Ajiboye et al. in press; Gill et al. 2011).

Determination of the renal excretion of the waste compounds has supplied useful data on

the health status of the kidneys (Tootian et al. 2012). The values of biochemical parameters, such as urea, uric acid and creatinine, are good indicators of the normal kidney function. For this reason, these parameters have been widely used as indicators (Li et al. 2015). In this study we observed that serum urea, uric acid and creatinine levels increased with diabetes and treatment of furan. These increases are indicators of the biochemical damage to the

kidney induced by furan and diabetes (Tootian et al. 2012). These examinations are agree with our light microscopic investigations. Our data validate the data obtained from previous studies which showed that chemicals and diabetes cause renal functional disorders such as abnormal urea, uric acid and creatinine levels (Ramesh et al. 2007; Palabiyik et al. 2013).

Lipid peroxidation is commonly used as marker for the induction of oxidative stress in cells. The level of MDA, which is generated as an end product during the oxidation of lipids, was used as a marker of lipid peroxidation (Qasim and Mahmood 2015). Treatment of rats with furan increased lipid peroxidation as shown by elevated MDA levels. This situation suggests the induction of oxidative stress in cells. Enhanced MDA levels were reported also in furan toxicity by Selmanoğlu et al. (Selmanoğlu et al. 2012). Recent studies about furan showed the generation of ROS and stimulation of lipid peroxidation supporting the function of oxidative stress in furan toxicity (Huang et al. 2004; Hickling et al. 2010).

The most common antioxidant enzymes that have been determined to investigate chemical-induced oxidative damage are SOD, CAT, GST and GPx (Apaydın et al. 2016). So, in this study, we aimed to determine the possible effects of furan on SOD, GPx, GST and CAT enzyme activities as an indicator of oxidative stress. SOD is an enzyme against the superoxide radical and catalyzes its dismutation into H_2O_2 , which is utilized by CAT or GPx (Kasperczyk et al. 2012). GST catalyzes the conjugation of several substrates to the thiol group of glutathione, transforming toxic materials into less toxic forms (Kalender et al. 2015). In the present study, treatment of rats with 40 mg/kg furan induced significant decreases in the antioxidant enzyme activities as compared to the diabetic control. Antioxidant enzyme activity changes reported in the present study may be due to the generation of ROS. Similarly with our work, in a previous study, changes in antioxidant enzyme activities were observed in furan treated rats, too (Selmanoğlu et al. 2012).

The renal tissue comes over considerable structural and functional alterations in diseases and chemical treatments. There is a damage to the kidneys as the damage progresses, leading to nephropathy (Katyare

and Satav 2005). The tubular system of kidney is sensitive to damage by drugs and environmental agents (Liu et al. 2010). The relationship between chemicals and toxicity of the kidney has been demonstrated in a previous experiment (Renugadevi and Prabu 2009). So, we investigated histopathological alterations in kidney tissues in addition to biochemical assessments. In this study, we determined hemorrhage, inflammatory cell infiltration, tubular degeneration, glomerular atrophy, glomerular lobulation, dilatation of Bowman's space. in furan treated rat kidneys. These pathologic alterations may be due to the generation of ROS and reducing in antioxidant enzyme activities.

Several antioxidants have been applied to provide protection against chemical induced renal toxicity (Ramesh et al. 2007; Kalender et al. 2015). Lycopene is an efficient free radical scavenger (Palabiyik et al. 2013). It has been shown to exhibit physical quenching rate constant with ROS (Koul et al. 2010). Also, it was found to act protector against chemical-induced renal damage in several studies (Aydin et al. 2013; Palabiyik et al. 2013). In the present study, furan exposure and diabetes induced significant decreases in the antioxidant enzyme activities and increases in urea, uric acid, creatinine levels of serum, MDA contents and histopathological changes of kidney, but were protected in the presence of lycopene. According to data which we obtained from this study we can say that treatment of rats with lycopene protected cells from lipid peroxidation induced by furan and diabetes.

Hyperglycemia and the consequent oxidative stress are enhanced in diabetes and can induce defects in cells with an imbalance between cell death and survival, thus favoring the onset of diabetic cell damage and its progression towards organ failure (Amin et al. 2015). Researchers observed in previous studies that diabetes increases lipid peroxidation in several organs and changes the activities of antioxidant enzymes (Shanmugam et al. 2011; Suresh et al. 2013). There are also studies about diabetes causes histological alterations in different tissues (Degirmenci et al. 2005; Arnal et al. 2010; Shanmugam et al. 2011). In STZ-treated control rats the serum urea, uric acid, creatinine levels and kidney MDA contents, histopathological results significantly increased; kidney antioxidant enzyme

activities significantly reduced. While in lycopene-treated diabetic rats, these parameters significantly ameliorated to comparable values with those of the diabetic control rats signifying the efficacy of lycopene. The present results are consistent with the results that lycopene increased antioxidant enzyme activities.

CONCLUSION

Overall, the present data provides evidence that furan exposure to rats and diabetes affect the biochemical parameters, lipid peroxidation and selected antioxidant enzymes in kidney. On the other hand these alterations were found to decrease with lycopene exposure. Lycopene had the potential to reduce the changes of examined parameters.

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