



Lycopene and its Potential Role in Diabetic Nephropathy Induced in Rats

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ABSTRACT

Diabetic nephropathy (DN) is an important microvascular complication of diabetes and one of the main causes of end stage renal disease. The protective effect of lycopene against streptozotocin (STZ) induced diabetic nephropathy and oxidative stress in rats was evaluated. Seventy two male albino rats were divided into four groups. Group I (normal group): rats administered buffer citrate. Group II (DN group): rats received a single intraperitoneal (i.p) injected dose of STZ (50 mg/kg b.wt). Group III (DN + insulin treated group): diabetic nephropathy rats treated with insulin (2U/rat/day/i.p). Group IV (DN + lycopene treated group): diabetic nephropathy rats treated with lycopene (20 mg/kg b.wt/day/orally). The obtained results showed a significant increase in serum glucose, urea, creatinine and kidney tissue L-MDA concentrations with upregulation of NF-kB gene expression in diabetic nephropathy induced rats. However, SOD activity and GSH level of kidney tissues were markedly decreased. Administration of lycopene to DN induced rats caused a significant improvement of all previous parameters towards their normal range. These results suggested that, lycopene treatment may have a protective effect against STZ-induced diabetic nephropathy and oxidative stress in rats through free radical scavenging and anti-inflammatory activity as well as regenerating endogenous antioxidant defense system mechanisms.

Key words: Streptozotocin, lycopene, oxidative stress, diabetic nephropathy.

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1. INTRODUCTION

Diabetes mellitus is a group of metabolic alterations characterized by hyperglycemia resulting from defects in insulin secretion, action or both. Chronic

hyperglycemia of diabetes is associated with long-term damage, dysfunction and eventually the failure of organs especially the

eyes, nerves, heart, blood vessels and kidneys (Huang et al., 2005). Type II diabetes mellitus developed by metabolic abnormalities such as impaired insulin secretion, increased hepatic glucose production and decreased insulin-stimulate of glucose uptake in peripheral tissues (Kakadiya et al., 2010).

Diabetes is usually accompanied by an increased production of reactive oxygen species (ROS) and free radicals or by impaired antioxidant defenses which are widely accepted as important in the development and progression of diabetic complications (Kumar et al., 2006). The increased risk of complications occurred particularly in subjects with poor glycaemic control (Gavin et al., 1997). In addition, diabetes causes increased oxidative stress in various tissues as evidenced by increased levels of oxidized DNA, proteins and lipids which are thought to play an important role in the pathogenesis of various diabetic complications (Chung et al., 2003). In diabetic patients with vascular complications, there are significant changes such as increased lipid peroxidation, dyslipidemia and irregularities in the metabolism of proteins, carbohydrates and lipids. Increased lipid peroxidation is accepted to be one of the main causes of diabetic complications (Gallou et al., 1994).

Diabetic nephropathy (DN) is a leading cause of end-stage renal failure worldwide. Its morphological characteristics include glomerular hypertrophy, basement membrane thickening, mesangial expansion, tubular atrophy, interstitial fibrosis and arteriolar thickening. All of these are part and parcel of microvascular complications of diabetes. A large body of evidence indicates that oxidative stress is the common valuable link for the major pathways involved in the development and progression of diabetic microvascular as well as macrovascular

complications of diabetes. Several lines of evidence suggest the central role of oxidative stress in the development of DN and the beneficial effects of antioxidants in renal injury owing to diabetes (Bagchi and Puri, 1998). Traditionally, DN has been described as a glomerular disease with five different stages are glomerular hyperfiltration, incipient nephropathy, microalbuminuria, overt proteinuria and end-stage renal disease (Mogensen et al., 1983).

STZ is a glucosamine-nitrosouria compound that causes damage and destruction of β -cells primarily through nitric oxide mediated DNA damage. It enters β -cells via the reduced glucose transporter type 2 (GLUT-2 transporter) to which it binds readily due to its similarity in structure to glucose (Kaneto et al., 1995). STZ is toxic to the insulin producing beta cells of the Islets of Langerhans in the pancreas so it is widely employed to induce experimental diabetes in animals. It damages the DNA of pancreatic- β cells and triggers multiple pathways including activation of protein kinase-C, poly (ADP-ribose) polymerase and NAD(P) H oxidase with consequent generation of ROS and advanced glycation end products resulting in renal damage and nephropathy (Haidara et al., 2008).

Antioxidants form a diverse group of compounds with different properties which operate by inhibiting oxidant formation, intercepting oxidants and repairing oxidant induced injuries (Ergüder et al., 2007). Tomato products contains lycopene which is believed to be associated with decreased risk of chronic diseases and its effects are suggested to be due to antioxidant effect of lycopene (Jamshidzadeh et al., 2008). The antioxidant properties of lycopene have been demonstrated both in vivo and in vitro (Wertz et al., 2004). There is also recent evidence suggests that lycopene acts as an anti-

inflammatory agent (Kim *et al.*, 2004). Lycopene can inhibit the expression of inflammatory cytokines and reverse the loss of antioxidant enzymes induced by inflammation caused by either injecting lipopolysaccharide or exposure to iron (Riso *et al.*, 2006). This study was to investigate the possible beneficial effect of lycopene against deleterious effect of diabetic nephropathy induced in male rats through investigation of blood glucose, kidney functions, inflammatory and oxidative stress biomarkers.

2. MATERIALS AND METHODS

2.1. Experimental animals:

Seventy two white male albino rats of 5-6 weeks old and weighing 180 – 200 g were used in this study. Rats were housed in separated metal cages and kept at constant environmental and nutritional conditions throughout the period of experiment. The rats were fed on constant ration and fresh, clean drinking water was supplied *ad-libitum*. All rats were acclimatized for minimum period of 15 days prior to the beginning of study.

2.2. Chemicals and antioxidant:

All chemicals were of analytical grade and obtained from standard commercial suppliers. The antioxidant and chemicals used in the present study were:

a- Streptozotocin: STZ [2-deoxy-2-(3-methyl-3-nitrosoureido)-D-glucopyranose], was purchased from (Sigma Chemical Co. P.O. Box. 14508, St. Lowis, U.S.A.). Freshly dissolved in citrate buffer, PH 4.5 and administered intraperitoneally as a single injected dose of (50 mg /kg body wt.) (Ramanathan *et al.*, 1999).

b- Lycopene: lycopene was purchased from Aktin Chemicals, Inc. company (Nature connecting health), Chengdu, China, it was mixed in Tween-80 and saline is added till reach the final required concentration and administered orally to rats at a dose level of

(20 mg/kg b.wt) once daily for 6 weeks (Abdel-Azeem *et al.*, 2013).

c- Other chemicals used in this study were of the highest purified grades available purchased from El Gomhouria Company for Trading Chemicals and Medical Appliances, Egypt.

2.3. Experimental design:

After acclimatization to the laboratory conditions, the animals were randomly divided into four groups placed in individual cages and classified as following:

Group I (normal control group): Consists of 12 rats, received no drugs, served as control non-treated for all experimental groups.

Group II (DN induced group): Consists of 24 rats, received STZ as a single intraperitoneally injected dose of (50 mg/kg b.wt).

Group III (DN + insulin treated group): Consists of 18 rats, received STZ and after 8 weeks treated daily with insulin (2U/rat per day/i.p) for 6 weeks.

Group IV (DN + lycopene treated group): Consists of 18 rats, received STZ and after 8 weeks treated daily with lycopene (20 mg/kg b.wt/ orally) for 6 weeks.

2.4. Sampling:

2.4.1. Blood samples:

Blood samples were collected by ocular vein puncture from all animal groups, at the end of experiment, after 14 weeks in dry clean tubes and allowed to clot for 30 minutes and serum was separated by centrifugation at 3000 r.p.m for 15 minute. The serum was taken by automatic pipette and received in dry sterile tubes and used directly for determination of blood glucose, urea and creatinine concentrations according to the method described by Tietz, (1995), Tietz, (1990) and Tietz, (1986).

2.4.2. *Tissue samples:*

About 0.5 g of kidney tissue specimen was taken from all animal groups (control and experimental groups) once after the end of 14 weeks.

2.5. *Biochemical analysis*

2.5.1. *Kidney tissue for biochemical analysis*

Briefly, kidney tissues were cut, weighed and minced into small pieces, homogenized with a glass homogenizer in 9 volume of ice-cold 0.05 mM potassium phosphate buffer (pH 7.4) to make 10 % homogenates. The homogenates were centrifuged at 6000 r.p.m for 15 minutes at 4°C then the resultant supernatant was used

for the determination of the following parameters: SOD, GSH and L-MDA according to the method described by Kakkar et al., (1984), Paglia and Valentine, (1967) and (Mesbah et al., 2004) respectively.

2.5.2. *Kidney tissue for molecular analysis*

About 0.5 of kidney tissue put in eppendorf tubes and were immediately kept in liquid nitrogen and stored at -80°C till RNA extraction for determination of NF-kB gene expression by real-time quantitative polymerase chain reaction (real- time qPCR) analysis in kidney of rats. Target gene was normalized with β –actin by used the 2^{-ΔΔCt} method (Livak and Schmittgen, 2001).

Forward and reverse primers sequence for real time PCR.

Gene	Forward primer (5' ----- 3')	Reverse primer (5' ----- 3')
<i>NK-kB</i>	CCTAGCTTTCTCTGAACTGCAA	GGGTCAGAGGCCAATAGAGA
<i>β-actin</i>	ACCCACACTGTGCCCATCTA	CGTCACACTTCATGATG

2.6. *Statistical analysis:*

The results were expressed as mean ± SE using SPSS (13.0 software, 2009) program. The data were analyzed using one-way ANOVA to determine the statistical significance of differences among groups. Duncan's test was used for making a multiple comparisons among the groups for testing the inter-grouping homogeneity. Values were considered statistically significant when p<0.05.

3. RESULTS:

The obtained data presented in table (1) revealed that, STZ-induced diabetic nephropathy rats showed a significant increase in serum glucose, urea and creatinine concentrations compared to normal control group.

Lycopene treatment to STZ-induced diabetic nephropathy rats caused a significant decrease in elevated serum glucose, urea and creatinine concentrations when compared with STZ-induced diabetic nephropathy group.

The obtained data presented in table (2) revealed that, STZ-induced diabetic nephropathy rats showed a significant increase in kidney tissue L-MDA with significant upregulation of NF-kB and significant decrease in SOD activity and GSH level compared to normal control group.

Lycopene treatment to STZ-induced diabetic nephropathy rats caused a significant decrease in kidney tissue L-MDA with a significant downregulation of NF-kB and a significant increase in SOD activity and GSH

level compared to STZ-induced diabetic nephropathy group.

Table (1): Effect of lycopene administration on serum glucose, urea and creatinine concentrations in streptozotocin induced diabetic nephropathy rats (mg/dl).

Parameters	Glucose (mg/dl)	Urea (mg/dl)	Creatinine (mg/dl)
Exp. Groups			
Group I: Normal control	93.33 ± 4.03 ^e	26.15 ± 0.86 ^d	0.91 ± 0.01 ^d
Group II : Control DN group	317.33± 9.19 ^a	46.18± 1.49 ^a	1.6 ± 0.03 ^a
Group III: DN + Insulin	159.33±5.19 ^d	29.47±0.94 ^c	0.98±0.03 ^c
Group IV: DN+ Lycopene	243.4± 7.32 ^b	37.12± 1.08 ^b	1.33± 0.03 ^b

Data are presented as (Mean ± S.E). S.E = Standard error.
Mean values with different superscript letters in the same column are significantly different at (P≤0.05).

Table (2): Effect of lycopene administration on kidney tissue SOD, GSH, L-MDA and NF-kB levels in streptozotocin induced diabetic nephropathy rats.

Parameters	SOD (IU/g tissue)	GSH (IU/g tissue)	L-MDA nmol/g tissue	Fold change in NF-kB gene expression
Exp. Groups				
Group I: Normal control	0.96 ± 0.04 ^a	20.00 ± 0.95 ^a	38.67 ± 1.28 ^e	1.00 ± 0.01 ^e
Group II : Control DN group	0.18 ± 0.01 ^e	5.40 ± 0.78 ^d	95.80 ± 3.42 ^a	10.06 ± 0.35 ^a
Group III: DN+ Insulin	0.78 ± 0.03 ^b	15.20 ± 0.70 ^b	51.50 ± 1.10 ^d	2.55 ± 0.14 ^d
Group IV: DN+ Lycopene	0.38 ± 0.02 ^d	9.40 ± 0.32 ^c	74.70 ± 1.59 ^b	6.23 ± 0.19 ^b

Data are presented as (Mean ± S.E). S.E = Standard error.
Mean values with different superscript letters in the same column are significantly different at (P≤0.05)

4. DISCUSSION:**.DI**

Chronic hyperglycemia in the renal milieu stimulates the production of AGEs, the polyol pathway and activation of protein kinase C (PKC) which lead to increased ROS formation and oxidative stress (Pacher et al., 2005). Renal cells (glomerulus, tubules and fibroblasts) express NADPH oxidase and contribute to ROS formation in small amounts in the healthy state. In chronic hyperglycemia the dysfunctional renal cells can increase ROS generation which may enhance renal tissue injury (Shiose et al., 2001). In addition to structural and functional derangements the presence of excessive ROS in the renal milieu can promote dysregulation of renal medullary blood flow leading to renovascular hypertension that help in progression of diabetic nephropathy (Chabrashvili et al., 2002).

Presented findings showed that, a significant increase in serum glucose concentration was observed in STZ-induced diabetic nephropathy rats. These results are nearly similar to those reported by Akbarzadeh et al., (2007) who reported that, serum glucose levels was elevated three-fold in the diabetic animals group compared to normal who added that, Hyperglycemia, hypoinsulinemia, polyphagia, polyuria and polydipsia accompanied by weight loss were seen in adult rats within three days of STZ-treatment which indicates irreversible destruction of Langerhans islets cells. Moreover, glucose metabolism through harmful alternate pathways such as via protein kinase C activation and advanced glycation end products formation contribute to development of DN (Ha, et al., 2008), and increased oxidative stress with subsequent alterations in cellular redox balance (Williamson et al., 1993).

Administration of lycopene to DN rats significantly reduced elevated serum glucose level in STZ-induced diabetic nephropathy rats after 6 weeks from the onset of treatment with lycopene. These results are nearly similar to those recorded by Kuhad et al., (2008), Ali and Agha, (2009) as well as Aydin and Celik, (2012) who reported that, after treatment of diabetic nephropathy rats with lycopene serum glucose levels significantly decreased after week 3 and week 4 respectively when compared with control diabetic nephropathy group. This effect can be explained by the ability of lycopene to promote glycemic bioavailability in organs for body growth and reduction of the pathological symptoms (Ying et al., 2015).

The obtained results showed that, a significant increase in serum urea and creatinine concentrations were observed in STZ-induced diabetic nephropathy rats. These results are nearly similar to those reported by (Sayed, 2012) and (Akram Ahangarpour et al., 2016) who reported that, DN significantly increased serum urea and creatinine in the untreated diabetic nephropathy group in comparison with the non-diabetic nephropathy control group. Also, Lal et al., (2009) reported that, all diabetics have higher blood urea level, and has significantly higher uric acid level as compared to non-diabetic subjects due to continuous catabolism of amino acids high urea will be formed from urea cycle.

Urea is the one of the waste product excreted by the kidney and main end product of protein metabolism. An elevation of blood urea usually signifies decreased renal function (Sakami and Harrington, 1963). Moreover, (Ismail and Abd El-Gawad, 2010) demonstrated that, increase levels of serum

uric acid, urea nitrogen and creatinine concentrations were observed in diabetic rats. Also, Bhatti *et al.*, (2005) reported that, Urine albumin excretion increased by three fold with no change in plasma creatinine levels in the diabetic rats non-treated group.

Administration of lycopene to STZ - induced diabetic nephropathy rats significantly decreased serum urea and creatinine concentrations. These results are nearly similar to those reported by (Wei *et al.*, 2014) and (Dilek *et al.*, 2016) who reported that, lycopene treatment prevented the development of diabetic nephropathy by remarkably decreasing creatinine and BUN in diabetic rats with less renal injury due to the increased elimination of blood creatinine and urea by the kidneys and reduced protein degradation. Also, Shams *et al.*, (2015) reported that, treatment with lycopene for five weeks normalized the creatinine and BUN levels leading to improved GFR in diabetic rats.

The obtained results showed that, a significant decrease in kidney SOD activity was observed in STZ-induced diabetic nephropathy rats. These results are nearly similar to those reported by Daniel *et al.*, (2015) and Kedziora-Kornatowska *et al.*, (2000) who recorded that, reduced kidney activity of SOD three to six weeks after STZ administration compared to control group. Also, Mohora *et al.*, (2006) reported that, increased level of MDA and low SOD activity are found in diabetes which confirmed the involvement of oxidative stress in renal injury induced in diabetic rats.

Treatment with lycopene to STZ-induced diabetic nephropathy rats significantly increased kidney SOD activity. These results are nearly similar to those reported by Bukan *et al.*, (2003) and Daniel *et al.*, (2015) who reported that, lycopene treatment exerts antioxidant activity and

protects the tissue from lipid peroxidation as well as kidney antioxidant enzymes (SOD, CAT and GPx) of diabetic animals were significantly decreased compared to normal control group. Also, Porrini *et al.*, (2005) demonstrated that, consumption of tomato products which contain lycopene may decrease biomarkers level of oxidative stress in healthy subjects, smokers and type 2 diabetic patients.

DN is a serious and important microvascular complication that occurs frequently in patients with diabetes. The pathogenetic mechanisms for the microvascular complications may be associated with oxidative stress which is regarded as the major factor that couples hyperglycemia with vascular complications. Oxidative stress causes an increase of ROS which can attack at various target organ systems (Papaharalambus and Griendling, 2007). Lycopene possess antioxidant activity because of its open β cycle structure. Moreover, lycopene can function as an antioxidant by several mechanisms, and one of the best documented mechanisms is through strong singlet oxygen quencher (Ojha *et al.*, 2013). Another mechanism for the antioxidant activity of lycopene is reaction with free radicals (Krinsky, 1998). In addition to direct quenching of ROS and free radicals, lycopene can up-regulate the antioxidant response element and thereby stimulate the production of cellular enzymes such as SOD, CAT, GPx and quinone reductase that protect cells from ROS and other electrophilic molecules. For example, Ben-Dor *et al.*, (2005) recorded that, lycopene up-regulates the antioxidant response element (ARE) in human liver cancer (HepG2) and breast cancer (MCF-7) cell line through the nuclear factor erythroid 2-related factor 2 (Nrf2) nuclear transcription pathway. Nrf2 is a critical transcription factor regulating the anti-oxidant genes such as GSH, SOD and CAT by binding to

antioxidant response elements (Barcelos et al., 2016).

The obtained results showed that, a significant decrease in kidney reduced glutathione concentration was observed in STZ-induced diabetic nephropathy rats compared to control rats, similar results were recorded by Jagdish and Nehal, (2011) and Jagdish et al., (2010) who demonstrated that, renal ischemia/reperfusion I/R group of diabetic rats showed significantly decreased enzymatic activity of SOD, CAT and GSH when compared with the sham control rats. Glutathione provide a first line of defense against ROS, as it can scavenge free radicals and reduce H_2O_2 . The decreased concentration of GSH in kidney might be due to NADPH depletion or GSH consumption in the removal of peroxide (Gumieniczek, 2005). The ratio of reduced glutathione/oxidized glutathione is one of many cellular redox couples that directly contribute to redox status. Depletion of reduced GSH either by conjugation and removal from the cell or oxidation to GSSG could significantly affect the overall redox potential of the cell (Yadav et al., 1997). GSH-dependent enzymes provide a second line of defense as they primarily detoxify noxious by products generated by ROS and also help to prevent propagation free radicals (Gumieniczek, 2005). Alsaif, (2009) reported that, GSH/GSSG (Reduced glutathione and Oxidized glutathione) ratio were found to be lowest in the kidney of diabetic rats group. Some workers (Obrosova et al., 2003) reported that, the concentrations in the diabetic kidney were found to be significantly reduced, suggesting that the reduced GSH concentrations may play a role in the development of diabetic complications.

Treatment with lycopene to STZ-induced diabetic nephropathy rats showed a significant increase in kidney reduced

glutathione when compared with diabetic nephropathy non treated group. These results agree with the previous results obtained by Subhash and Agrawal, (2007) who reported the beneficial effect of tomato lycopene intake in decreasing oxidative stress in diabetes whose singlet oxygen quenching ability is twice as higher than that of β -carotene and ten times higher than that of alpha tocopherol (Di Mascio and Sies, 1989). Lycopene having a good free radical scavenging capacity because of its unique structure (high number of conjugated double bonds) might have quenched the superoxide and other free radical anions which are highly released in diabetes due to the abnormal metabolism. Lycopene thereby increasing the concentration of SOD, GSH-Px and GR which are the most important cytosolic enzymes involved in antioxidant activities also lycopene thereby reversing the disturbed balance to the antioxidant enzyme side thus it is responsible for decreased oxidative stress. In this study lycopene supplementation also increased the levels of reduced glutathione, the most important antioxidant metabolite that plays an important role in maintaining good levels of glutathione peroxidase activity which is the main enzyme involved in removing the H_2O_2 generated from dismutation of superoxide anions by superoxide dismutase. Moreover, GSH is the co-factor of several reducing enzymes such as dehydroascorbate reductase and endoperoxide isomerase (Lenzi et al., 1994).

Presented findings showed that, a significant increase in kidney L-MDA concentration, a marker of lipid peroxidation in STZ-induced diabetic nephropathy rats in comparison with the control normal group. Lipid peroxidation is a marker of cellular oxidative damage initiated by ROS (Farber et al., 1990). These results are nearly similar to those reported by Bukan et al., (2003), Siddiqui et al., (2011) and Erejuwa, (2012)

who recorded that, a significantly increased kidney L-MDA in experimentally induced diabetes in animals. This increase in the kidney L-MDA indicated enhanced lipid peroxidation which could cause injury to the cells. Increased levels of lipid peroxides in the plasma are usually considered to be the consequence of high production and liberation of tissue lipid peroxides into circulation due to pathological changes (Al-Faris *et al.*, 2010). Hyperglycaemia leads to generation of free radicals due to auto-oxidation of glucose and glycosylation of proteins (Tirgar *et al.*, 2010). And induces oxidative stress which becomes the chief factor that leads to diabetic complications (Shuklak *et al.*, 2012). Abnormal elevated levels of free radicals and the simultaneous reduction of antioxidant defense can result in damage of cellular organelles and enzymes, increased lipid peroxidation and development of insulin resistance (Kumar *et al.*, 2012). The elevated level of lipid peroxidation causes oxidative damage by increasing peroxy radicals and hydroxyl radicals (Singh *et al.*, 2012), and is usually measured through the catabolite, malonaldehyde (MDA) in terms of TBARS as a marker of lipid peroxidation (Kedziora-Kornatowska *et al.*, 2000). Also, increased lipid peroxide may be due to the increased glycation of protein in diabetes mellitus. The glycated protein might themselves act as a source of free radicals. There is a clear association between lipid peroxide and glucose concentration which may be also thought to play a role in increased lipid peroxidation in diabetes mellitus (Suryawanshi *et al.*, 2006).

Oxidative stress is considered as an imbalance between oxidants and antioxidants. The accumulated ROS could interact with polyunsaturated fatty acids leading to the formation of lipid peroxidation in kidney tissues and consequently result in damage or toxicity (Alarcon-Aguilar *et al.*, 2010). It is

widely acknowledged that oxidative stress is the major factor of diabetic complications including diabetic nephropathy (Rolo and Palmeira, 2006). ROS degrades membrane polyunsaturated fatty acids and produces 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA) (Zhu *et al.*, 2015). MDA is a highly unstable aldehyde which could induce oxidative stress by forming a covalent protein adduct which serves as a hallmark of oxidative stress in tissue injury (Chang *et al.*, 2015).

In the present study, the decrease in kidney tissue L-MDA upon administration of lycopene to diabetic nephropathy rats is clearly demonstrated the antioxidant property of lycopene and its role is an efficient free radical scavenger (Palabiyik *et al.*, 2013), because of its unique structure (high number of conjugated double bonds). It has the ability to quench the superoxide and other free radical anions (Bose and Agrawal, 2006). Also, from the above results it is proved that lycopene reduces the lipid peroxidation rate by acting as a good chain breaking antioxidant which reacts with peroxy radicals formed in propagation phase of lipid peroxidation to form carbon centered radical that reacts readily and reversibly with oxygen to form a new chain-carrying peroxy radicals which are highly stable forms than ROS (Aggarwal *et al.*, 2009).

Presented findings showed that, NF- κ B gene expression level in kidney of STZ-induced diabetic nephropathy rats is significantly up-regulated compared to normal control group. Similarly, Iwamoto *et al.*, (2001) who reported that, in STZ-induced diabetes, NF- κ B was up-regulated in renal cortical tissue. Also, Lal *et al.*, (2001) observed that, advanced glycation end-products induced oxidative stress and up-regulated NF κ B in mesangial cells.

Treatment with lycopene to STZ-induced diabetic nephropathy rats caused a significant downregulation in kidney tissue NF- κ B gene expression when compared with diabetic nephropathy non-treated group. These results are nearly similar to those reported by Shams et al., (2015) who showed that, lycopene significantly down regulated gene expressions of NF- κ B and MMP-2 in diabetic nephropathy rats and lowered the inflammatory response markers such as TNF- α , IL-1, IL-6 and IFN- γ by inhibiting the activation of AGE-RAGE signaling when compared with non-treated rats. Possible mechanisms for lycopene anti-inflammatory response may include the inhibition of synthesis and release of pro-inflammatory cytokines, synthesis and modulation of signal transduction pathways including that of the iNOS via its inhibitory effects on NF- κ B (Palozza et al., 2010). Moreover, Feng et al., (2010) indicated that, the anti-inflammatory effects of lycopene depend on inhibition of NO and IL-6 production as well as suppression of NF- κ B transcriptional activity and associated downstream pathways. The activation of NF- κ B, monocyte chemoattractant protein-1 (MCP-1) and macrophage infiltration in the diabetic kidney were explored in a temporal manner. The active subunit of NF- κ B p65 was elevated in the diabetic animals in association with increased MCP-1 gene expression and macrophage infiltration (Cha et al., 2005). The present study is consistent with these results, confirming that the anti-inflammatory activities of lycopene are mediated by down regulation of NF- κ B gene expression resulting in reduced kidney tissue inflammation and tubulointerstitial nephritis.

5. CONCLUSION:

From the obtained results it could be concluded that, the experimental induction of diabetic nephropathy in male rats caused a

significant increase in serum glucose, urea and creatinine concentrations as well as a significant increase in L-MDA level with a significant upregulation of NF- κ B gene expression in kidney tissues. Also, there was a significant decrease in kidney tissue SOD activity and GSH level. However, lycopene treatment in STZ-induced diabetic nephropathy rats relieved all previous parameters towards its normal range so, these results confirm the strong antioxidant and anti-inflammatory effects of lycopene in STZ-induced diabetic nephropathy.

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