

Assessment of the possible protective effect of lycopene on monosodium glutamate-induced nephrotoxicity in adult male albino rat

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SUMMARY

Monosodium glutamate (MSG), known as AJI-NO-MOTO, is the sodium salt of glutamic acid. Glutamate is one of the most common amino acids found in nature, and is the main component of many proteins and peptides of most tissues. Glutamate is also produced in the body and plays an essential role in human metabolism. MSG is commonly used as a flavor enhancer. Lycopene (LPN) is a member of carotenoids, and it is an antioxidant substance found in tomato, and in other red fruits, and vegetables. The present study aimed to investigate the potential protective effects of LPN on MSG-induced nephrotoxicity in adult male albino rats. 40 adult male albino rats were divided into 4 groups with 10 rats in each group. Group I (control group). Group II animals received lycopene orally in a dose of 4 mg/kg b.w. per day for 14 days. Group III animals received MSG subcutaneously in a dose of 4 mg/g b.w. per day for 14 days. Group IV animals received MSG Plus LPN. At the end of the experiment, kidney specimens were processed for histopathological, immunohistochemistry and biochemical studies.

Administration of lycopene decreased elevated serum creatinine, blood urea nitrogen and immunopositive expression of the proapoptotic protein (Bax), induced by MSG. It increased the immunopositive expression of the antiapoptotic protein (Bcl2). It also ame-

liorated the morphological changes induced by MSG. MSG has toxic effects on the kidneys as indicated by biochemical, histological and immunohistochemical results. Lycopene has protective effects against MSG-nephrotoxicity by reducing elevated serum creatinine, blood urea nitrogen, kidney damage, and apoptosis.

Keywords: Antioxidants – Lycopene – Monosodium glutamate – Nephrotoxicity

INTRODUCTION

The body susceptibility to oxidative damage can be determined by the balance between production and scavenging of reactive oxygen species (ROS) or free radicals. Possessing antioxidant defense mechanisms enables the organism to diminish the production of free radicals, and protect against oxidative damage, but it may not be sufficient to prevent the damage completely. Many drugs may cause damage to the tissues by generating free radicals. The level of antioxidant mechanisms may not be sufficient for scavenging free radicals after drug intake, and therefore tissue injury occurs (Wang and Jiao, 2000).

The kidneys are vital organs essential for excretion of metabolic waste products, as well as for maintaining chemical homeostasis, among many other functions. The broad use of therapeutic drugs, natural products, environmental pollutants, and industrial chemicals during the last few decades have greatly increased the probability of kidney damage (Gaikwad et al., 2012).

Monosodium glutamate (MSG) known as AJI-NO

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-MOTO is the sodium salt of naturally occurring non-essential amino acid, glutamic acid (Salam and Agha, 2013). It is one of the many food additives being used. MSG contains 78% glutamic acid, 22% sodium and water (Samuels, 1999). Glutamate is one of the most commonly occurring amino acids found in nature, and also produced in the body. It forms the main component of proteins and peptides of various tissues and plays an important role in human metabolism. In general, the natural glutamic acid found in food does not cause problems, but the synthetic free glutamic acid formed during industrial processing is a toxin (Anil et al., 2015).

When added to food, MSG induces a flavoring function by stimulation of sensory receptors in the oral cavity and by producing pleasant taste of meals. It is declared that taste quality obtained by MSG and other related substances was unique (Eweka, 2007). MSG was previously made from wheat gluten, but recently it is made by carbohydrates fermentation using bacterial or yeast species such as *Brevibacterium*, *Arthrobacter*, *Microbacterium*, and *Corynebacterium*. MSG also influences appetite positively and induces weight gain (Rogers and Blundell, 1990).

In spite of taste stimulation and augmentation of appetite produced by MSG, many studies have reported its toxicity to both humans and experimental animals (Belluardo et al., 1990).

Carotenoids are a group of fat-soluble pigments found in tomatoes and their products, as well as in some other fruits and vegetables. Many studies have investigated their benefits in the oxidative stress. Tomato carotenoids include lycopene and other carotenoids (Tapiero et al., 2004). Lycopene had received a particular attention because of its highly efficient antioxidant with free radical scavenging capacity (Wang et al., 2008). Lycopene was shown to be an *in vivo* protective against lipids, proteins, and DNA oxidation. The protective effect of lycopene had been studied with many nephrotoxic agents and its preventive potentials have been demonstrated (Palabiyik et al., 2013).

Hence, this work was performed to evaluate the possible protective effects of lycopene on MSG-induced nephrotoxicity in adult male albino rats.

MATERIALS AND METHODS

Animals

The present study was carried out on 40 healthy adult male albino rats weighing from 200-250 g. They were purchased from the animal house of Assiut Faculty of Medicine, Assiut University, Egypt. The rats were housed in polypropylene cages under standard lightening in a temperature-controlled room (25±2°C) and had free access to laboratory food and water throughout the experiment. They were acclimatized to their environment for at least two weeks before starting the experiment. All animal procedures were approved by the local Institutional Animal Ethical Committee of Faculty of Medicine, NBU, KSA.

Experimental design

After the acclimatization period, rats were randomly divided into four groups (ten rats in each) as follows:

Group I (Control group) received daily injection of normal saline (vehicle) subcutaneously for 14 days.

Group II received lycopene dissolved in corn oil via oral gavage (Sigma-Aldrich Chemical Co. St. Louis, MO, USA) at a dose of 4 mg/kg/day for 14 days (Karahan et al., 2005).

Group III received MSG dissolved in sterile normal saline subcutaneously (Sigma-Aldrich Chemical Co. St. Louis, MO, USA) at a dose of 4 mg/g/day for 14 days (Shilpi et al., 2014).

Group IV received lycopene orally (4 mg/kg/day) and MSG injection (4 mg/g/day) for 14 days.

Twenty-four hours after the last drug regimen, the body weight of each rat was estimated. The rats were anesthetized with intraperitoneal injection of sodium pentobarbital (35 mg/kg body weight). The chest wall was incised to explore the heart. 5 ml of intracardiac blood were drawn, and serum was separated for estimation of blood urea nitrogen (BUN) and serum creatinine.

The rats were then sacrificed by decapitation, and kidneys were removed. The kidneys were perfused with a fixative solution (2% paraformaldehyde and 2% glutaraldehyde solution) in 0.1 M phosphate buffer pH 7.2, and then weighed and sampled for histopathological studies.

Assessment of nephrotoxicity

Levels of BUN and serum creatinine were measured using standard laboratory techniques to assess nephrotoxicity, using commercial kits in an Olympus AU400 Chemistry Analyzer (Olympus Corp., Tokyo, Japan). Results are expressed as mg/dl.

Histological and immunohistochemical examination

The kidney from each animal was sectioned longitudinally into 2 halves and kept in 10% of neutral buffered formalin for 24h. It was then processed, embedded in paraffin wax and sections of 4 µm thickness were taken using a microtome. These sections were stained with hematoxylin and eosin (H&E), and were examined under a light microscope, to detect histological changes (Bancroft and Layton, 2012).

Kidney sections were immunohistochemically stained to assess the immunoexpression of proapoptotic protein (Bax), and antiapoptotic protein (Bcl2). Paraffin sections of kidney were cut at 4 µm thickness on positively charged slides. Sections were incubated with a monoclonal antibody against Bax and Bcl2 (Dako, Carpinteria California, USA); in a dilution of 1:200. Cells displaying brown precipitation were considered positive for Bax, and Bcl2 expressions.

Statistical Analysis

All analyses were performed using the software Statistical Package for Social Sciences version 17

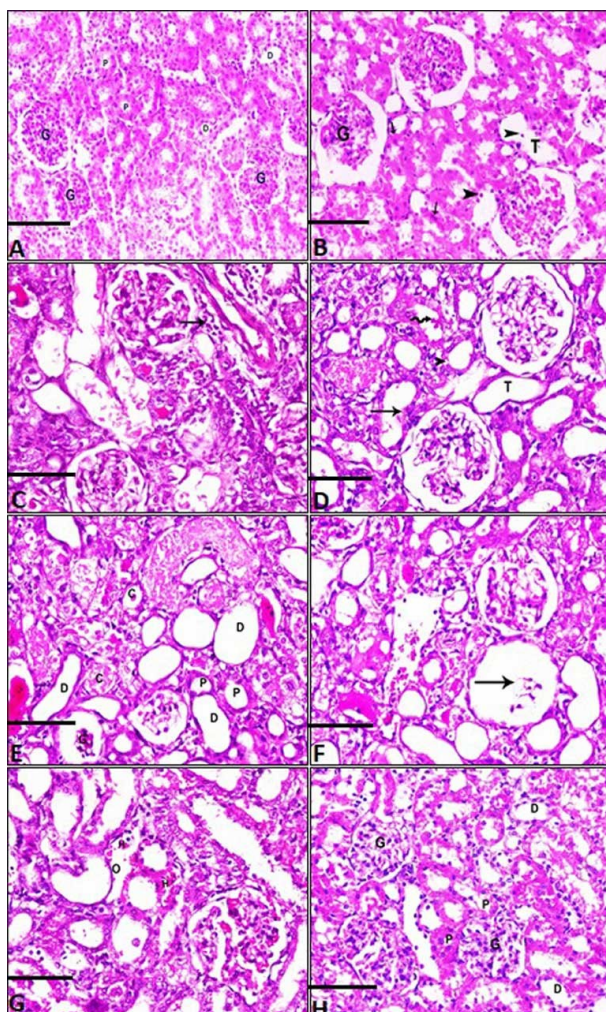


Fig 1. (A) A Photomicrograph of normal architecture of the renal cortex in the control group showing Malpighian corpuscles formed of glomerulus surrounded by a double-walled Bowman's capsule. Proximal convoluted tubules are seen around the Malpighian corpuscles lined by pyramidal cells with narrow lumen. Distal convoluted tubules are lined by cubical cells with wide lumen (H&E, scale bars = 40 μ m). (B-G) Photomicrographs of kidney of MSG treated rats.

(B) Malpighian corpuscles showing shrunken glomeruli with widening of the capsular space. The surrounding tubules are dilated with desquamation of tubular lining cells and also pyknotic nuclei (arrow heads). presence of some apoptotic cells (arrows).

(C) Interstitial cellular infiltration (arrows) is seen within the kidney tissue.

(D) Tubular dilatation (T) with vacuolar degeneration (arrow heads), desquamation of their lining cells (zigzag arrows), and destruction of tubular wall (arrows).

(E) Damaged shrunken glomeruli with widening of the capsular space, and marked degeneration and dilatation of proximal and distal convoluted tubules with intratubular hyaline casts (C).

(F) Hyaline degeneration of renal glomerulus (arrows)

(G) Interstitial hemorrhage and edema (H&E, scale bars = 40 μ m).

(H) A photomicrograph of the renal cortex of MSG + lycopene group with normal looking Malpighian corpuscles proximal, convoluted tubules and distal convoluted tubules. [G: Glomerulus, P: Proximal convoluted tubule, D: Distal convoluted tubule, T: Dilated tubule, H: Interstitial hemorrhage, O: edema (H&E, Scale bars = 40 μ m).

(SPSS Inc, Chicago, IL, USA). Data were presented as the mean \pm standard deviation (SD). Comparisons between two groups were analyzed by unpaired Student "t" test. The probability of chance (P value) < 0.05 was considered statistically significant.

RESULTS

None of the experimental rats died during the experiment period (14 days).

Evaluation of body and kidney weights

At the end of the experimental period, the body weight in the MSG group was significantly higher than the control group, as well as the MSG + lycopene group ($P < 0.05$), while no significant difference in body weight was observed between the control, lycopene and MSG+lycopene groups.

The kidney weights in the MSG-treated group were significantly higher than in the MSG-treated control group, as well as the MSG + lycopene group ($P < 0.05$). Meanwhile, no significant differences were seen between the control, lycopene and MSG+lycopene groups (Table 1).

Biochemical results

There was a significant increase in serum creatinine and BUN in MSG-treated rats compared with normal rats. However, concomitant administration of lycopene along with MSG significantly reduced levels of serum creatinine and BUN, compared to the MSG-treated group. Rats treated with lycopene alone showed normal values (Table 2).

Histological results

The renal cortex of control and lycopene-treated rats of H&E-stained sections were more or less similar, showing multiple glomeruli of normal cellularity surrounded by Bowman's capsule. Proximal convoluted tubules (PCT) were lined by pyramidal cells with deeply acidophilic cytoplasm and rounded nuclei. Distal convoluted tubules (DCT) were lined by cubical cells with acidophilic cytoplasm (Fig. 1A).

In MSG group, the Malpighian corpuscles displayed shrunken glomeruli with widening of the capsular space. The surrounding tubules were dilated with desquamation of tubular lining cells, and also pyknotic nuclei (Fig. 1B). Some tubules displayed damaged shrunken glomeruli with widening of the capsular space (Fig. 1E). Some tubules showed vacuolar degeneration, loss of the lining epithelium, and destruction of the tubular wall (Fig. 1D). Some Malpighian corpuscles displayed hyaline degeneration of glomeruli (Fig. 1F). Besides, there were foci of interstitial hemorrhage and edema in the interstitium (Fig. 1G) with multiple focal collections of mononuclear cells (Fig. 1C).

When lycopene was administered with MSG, the renal cortex appeared with somewhat normal histological architecture with reversal of MSG-induced renal damage. Most of the Malpighian corpuscles and the surrounding tubules (PCT and DCT) appeared normal, having the same features of the

Table 1. Body and kidney weights of rats in the different studied groups.

Parameters	Group I (Control)	Group II (Lycopene)	Group III (MSG)	Group IV (MSG+Lycopene)
Body weight (g)	221.33±10.59	219.54±12.42	254.21± 8.77 ^a	218.72±11.73 ^b
Kidney weight (g)	0.78±0.01	0.80±0.14	1.14± 0.12 ^a	0.77±0.02 ^b

Data is expressed as mean ± standard deviation. Results were statistically analyzed by using Student's t test at P < 0.05.

^ap < 0.0001 compared with the control group (group I).

^bp < 0.0001 compared with the treated group (group III).

Table 2. Serum levels of creatinine and blood urea nitrogen (BUN) in the different studied groups.

Parameters	Group I (Control)	Group II (Lycopene)	Group III (MSG)	Group IV (MSG+Lycopene)
Creatinine (mg/dl)	0.62±1.08	0.61±1.09	3.4±2.29 ^a	0.63±1.19 ^b
BUN (mg/dl)	22.46±0.04	21.65±0.09	74±0.35 ^a	23.9±0.22 ^b

Data is expressed as mean ± standard deviation. Results were statistically analyzed by using Student's t test at P < 0.05.

^ap < 0.0001 compared with the control group (group I).

^bp < 0.0001 compared with the treated group (group III).

control group (Fig. 1H).

Immunohistochemical results

Immunostaining of Bax antigen

In control and lycopene groups, the kidney tissues revealed negative immunostaining reaction for Bax. (Fig. 2A). MSG-treated rats revealed dark brown granules in their cytoplasm throughout most cells of the kidney parenchyma (Fig. 2B). Combined MSG and lycopene group showed Bax activity in the cortical tissues more or less similar to the control group (Fig. 2C).

Immunostaining of Bcl2

In control and lycopene groups, the cortical tissue of the kidneys showed moderate to marked Bcl2 reaction in the cytoplasm of cortical cells (Fig. 3A). Bcl2 immunostaining was markedly less intense in the cytoplasm of cortical cells in MSG-treated rats compared with the control group (Fig. 3B). Combined MSG and lycopene group showed increased Bcl2 expression compared with those of MSG-treated group (Fig. 3C).

DISCUSSION

Drug-induced nephrotoxicity accounts for up to 20% of the hospital admissions by acute kidney injury, and it has been recognized as a major cause of morbidity and mortality. Several therapeutic agents are commonly known as nephrotoxic agents (Himmelfarb, 2011).

Monosodium glutamate (MSG) is frequently used as a flavor enhancer, a fact that makes it one of the most applied food additives in modern nutrition all over the world (Beyreuther et al., 2007). There are many debatable facts about deleterious effects of MSG, so doubts appeared about the safety of its chronic use. Many researchers investigated its toxic effect on different organs, especially on the kidney's metabolism and excreting role (Hosam Eldin et al., 2012).

Many natural agents have been used to improve drugs toxicity. In this research, we were interested in studying the protective effect of lycopene, one of the carotenoids, against MSG-induced nephrotoxicity, as it is well known as a highly efficient scavenger of reactive oxygen species (Wang et al., 2008).

The present study revealed that administration of MSG caused a significant increase in body weight and kidney weight. The increase in body weight was probably because MSG could induce an increase in energy intake, which could lead to obesity (Mozes et al., 2004). Another school of thought suggests that MSG might interfere with signaling systems that regulate appetite centers, also up-scaling food consumption and hence weight gain initially and possibly obesity with chronic consumption (Bergen et al., 1998; Bhattacharya et al., 2011). The increase in kidney weight could be attributed to the increase in inflammatory activity with resultant tissue edema (Onalapo et al., 2013). This result was supported by Anil et al. (2015). Abass and Abd El-Haleem also reported the same results (2011). However, in combined MSG and lycopene group, these values were similar to the control levels.

In the current work, rats injected with MSG showed a significant increase in serum creatinine levels and blood urea nitrogen (BUN), compared to the control group. These results were consistent with Sandharbh et al. (2015), who reported that administration of MSG resulted in impairment of some renal biomarkers in the form of an increase in urea, creatinine and albumin. Our results were in contrast with results of Egbunu et al. (2010), who indicated a significant decrease of serum urea and creatinine in spite of high dose administration of MSG. Significant reduction in serum creatinine and BUN was observed in rats treated with combined lycopene and MSG as compared with MSG group. These data were fairly consistent with previous studies concluding amelioration of creatinine and BUN in gentamicin-induced nephrotoxicity

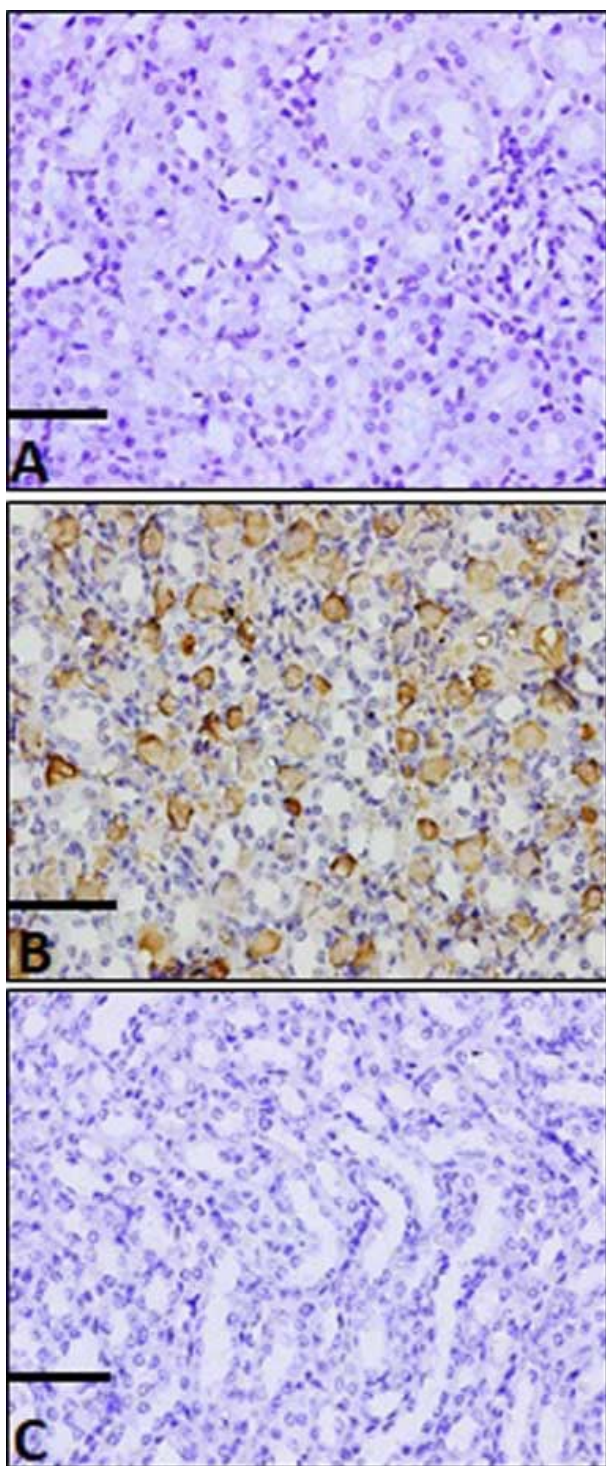


Fig 2. (A) Negative immunostaining reaction of Bax in the convoluted tubules and glomeruli of the renal cortex of the control group. (B) Strong positive immunostaining reaction of Bax in the convoluted tubules and glomeruli of the renal cortex of the MSG-treated group. (C) Negative immunostaining reaction of Bax in the in the convoluted tubules and glomeruli of the renal cortex of group treated with MSG+lycopen (Bax immunostaining, Scale bars = 40 μ m).

treated with lycopene (Wang et al., 2008).

Histological examination of MSG-treated rats revealed that it has many adverse effects on the kidney structure, in which the sections of renal cortex stained with H&E displayed shrunken glomeruli

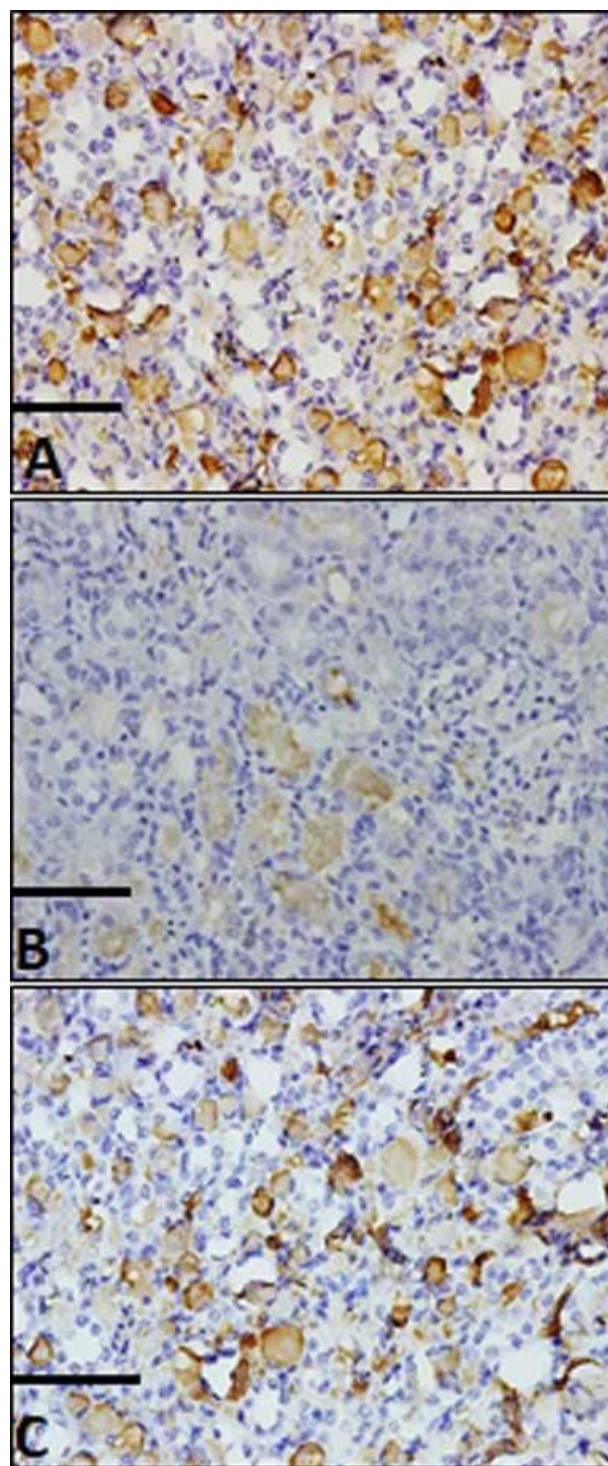


Fig 3. (A) Strong positive immunostaining reaction of Bcl2 in the convoluted tubules and glomeruli of the renal cortex of the control group. (B) Weak positive reaction of Bcl2 in the convoluted tubules and glomeruli of the renal cortex of MSG-treated group. (C) Strong positive immunostaining of Bcl2 in the convoluted tubules and glomeruli of the renal cortex of group treated with MSG+lycopen (Bcl2 immunostaining, Scale bars = 40 μ m).

with the widening of the capsular space. The surrounding tubules showed vacuolar degeneration, extensive necrosis with pyknosis of the nuclei and loss of the lining epithelium, with disruption of the tubular wall. In addition, there were foci of intersti-

tial hemorrhage and edema in the interstitium, with multiple focal collections of mononuclear cells. The findings of the present study were consistent with Onaolapo et al. (2013), who reported dilatation of the Bowman's space and contraction of the renal glomerulus with MSG treatment. Anil et al. (2015) noticed dilatation of PCT and DCT, swelling in Bowman's capsule, injured brush border of PCT and necrotic lesions of the urinary tubules after MSG administration. A third study referred to severe histopathological changes of renal tissue after repeated administration of high dose of MSG (Hosam Eldin et al., 2012). Similar findings were also observed in many studies (Andrew, 2007; Contini et al., 2012).

Results of the present study also showed lymphocytic cellular infiltration in the kidney tissue. Similar findings were reported by Al Agha (2006), who stated inflammatory infiltration and focal hemorrhagic areas in the MSG-treated kidney.

Marked histological amelioration was observed in kidney tissue of rats treated with a combination of MSG and lycopene, compared to MSG group, as most of the Malpighian corpuscles and the surrounding tubules (PCT and DCT) appeared normal having the same features of the control group. The current results are in agreement with Karahan et al. (2005), and Wang et al. (2008), who proved that lycopene had a protective effect against drug-induced nephrotoxicity in rats.

The kidney tissues revealed positive immunostaining reaction for Bax (pro-apoptotic proteins) in MSG-treated rats, while Bcl2 (antiapoptotic proteins) immunostaining was markedly less intense in the cytoplasm of cortical cells in MSG-treated rats compared with the control group. These results agreed with Abass and Abd El-Haleem who observed that MSG can induce a change in the pattern of expression of Bax protein in both glomerular endothelial cells and some tubular epithelial cells (Bhattacharya et al., 2011). Yang et al. also discussed the changes of Bax and Bcl-2 expression in various experimental renal models (Yang et al., 2001). Rats treated with a combination of MSG and lycopene showed a reduction in the Bax activity in the cortical tissues and a significant increase in Bcl2 expression when compared with those of the MSG-treated group, and hence suppress apoptosis. These results were fairly consistent with previously published studies concluding that lycopene reduces programmed cell death in contrast medium-induced renal injury (Buyuklu et al., 2014).

It could be concluded that MSG has deleterious effects on the kidney, as indicated by biochemical, histological and immunohistochemical alterations. Lycopene was found to have protective effects against MSG-induced nephrotoxicity through improvement of kidney function, and reduction of nephrotoxicity and apoptosis.

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