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Abstract

Deltamethrin is globally used in crop protection and control of malaria and other vector-borne diseases. It has a potent insecticidal activity with an appreciable safety margin. However, a number of studies have demonstrated nephrotoxicity of deltamethrin in mammalian and nonmammalian species. Lycopene, a carotenoid occurring naturally in tomatoes, has attracted considerable attention as an antioxidant. This study was focused on investigating the possible protective effect of coadministration of lycopene on deltamethrin toxicity. In this study, male albino rats were divided into four groups of 10 animals each: group I served as control, which received standard diet; group II received oral administration of deltamethrin (1.28 mg/kg per day) for 30 days; group III received both deltamethrin and lycopene (1 mg/kg per day); group IV received lycopene (1 mg/kg per day). After the experiment, the animals were anesthetized and the cytokine, tumor necrosis factor-α (TNF-α), in the serum was measured; the kidney was taken for histological and ultrastructural studies. Deltamethrin significantly increased the TNF-α. The histopathological examination of kidney showed mild necrotic changes. Ultrastructural changes in renal proximal tubules of deltamethrin-treated group included an increased number and irregular shape of mitochondria with sparse fragmented cristae, serious ultrastructural lesions in renal proximal tubular lining cells, vacuolar degeneration in the epithelial cells, increased number of lysosomes and loss of apical microvilli. In addition, focal segmental thickening and the duplication of glomerular basement membrane and podocyte changes were observed. Histopathological and ultrastructural study showed some protective effect of lycopene on kidney tissues.

Keywords

Lycopene, deltamethrin, nephrotoxicity, transmission electron microscopy, histopathology

Introduction

Pesticides play an important role in modern agriculture and their use has increased steadily. Because many of them are suspected to have mutagenic and carcinogenic activities (IARC, 1991), large-scale application of pesticides to crops and forests may contribute to the presence of toxic substances in the environment. These chemical compounds can find their way into the water reservoirs, streams and rivers, thus producing an adverse impact on the aquatic biota, animals and human health (Handy et al., 2002; John and Prakash, 2003). Pyrethroid pesticides have emerged as a major class of highly active insecticides due to their high bioefficacy and relatively low toxicity in comparison with organochlorine and organophosphorous pesticides (Casida et al., 1983). The use of pyrethroids as insecticidal and antiparasitic formulations has markedly increased in the last two decades (IPCS, 1990; Mestres and Mestres, 1992). The main advantages of their use are their photostability, high efficacy at low concentrations, easy disintegration and low toxicity to birds and mammals (Maud et al., 1984).

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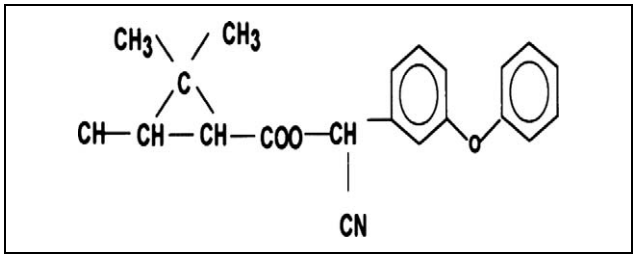

Figure 1. Chemical structure of deltamethrin.

Deltamethrin is an α-cyano type II synthetic type II parathyroid (Figure 1), which has a wide range of application in industrial and agricultural purposes and commonly used pesticides in Vietnamese shrimp farms (Tu et al., 2007). It is also used as an alternative pesticide in animal health, in vector control and in public health. It has been shown to be toxic for fish species (Capkin et al., 2006; Kprücü and Aydin, 2004; Kprücü et al., 2006; Ural and Saglam, 2005), aquatic invertebrates (Ratushnyak et al., 2005) and honeybees (Badiou et al., 2008). Acute poisoning with this insecticide results in symptoms such as contortion, salivation and convulsion (Anadón et al., 2006, 2009; Burr and Ray, 2004).

Deltamethrin is reported to cause various adverse effects in epidemiological and experimental studies. Deltamethrin, when given to pregnant rats from days 6 to 15 of pregnancy, caused retardation of growth, hypoplasia of the lungs, dilation of the renal pelvis and increase in placental weight (Abdel Khalik et al., 1993). It is also known to suppress immune system in BALB/c mice (Lukowicz and Krechniak, 1992). In rats, deltamethrin administration was found to inhibit the mitotic index in a dose-dependent manner and increased the frequency of chromosomal aberrations in the bone marrow at 24 h postexposure (Agarwal et al., 1994). However, a number of studies have demonstrated genotoxic, immunotoxic and tumorogenic effects of deltamethrin in mammalian and nonmammalian species (Shukla et al., 2001). Evidence from both population-based and laboratory studies have shown an inverse relationship between regular consumption of fruits and vegetables and the risk of cancer in general. Recently, attention has shifted to nonnutritive phytochemicals present in plant-based diet as potential chemopreventive agents. It is now estimated that more than 1000 different phytochemicals possess chemopreventive activities (Surh, 2003).

Tomato is a versatile vegetable that is consumed fresh as well as in the form of processed products. Tomatoes and tomato products are rich in health-related food components, as they are good sources of carotenoids in particular, lycopene, ascorbic acid (vitamin C), vitamin E, folate and flavonoids. In addition, tomato contains essential amino acids and, particularly, high amounts of minerals (Fe, Mn, Zn and Cu) and monounsaturated fatty acids (especially, oleic acid) (Odriozola-Serrano et al., 2008). Lycopene is a dietary carotenoid synthesized by plants and microorganisms not synthesized by humans and other animals. It occurs primarily in red fruits, vegetables, tomatoes, watermelon, pink grape fruit, apricots, pink guava and papaya (Giovannucci, 1999). Recent epidemiological studies have shown that the supplementation of diets rich in lycopene is associated with reduced risk of many chronic diseases (WHO, 2003), cancer (Kotake-Nara et al., 2001; Sgherri et al., 2008), heart diseases (Jacob et al., 2008), a reduction in blood pressure (John et al., 2002; Lee et al., 2000), diabetes, ageing and other degenerative diseases in humans (Boumerfeg et al., 2009; Sun et al., 2007). These positive effects are believed to be attributable to tomato antioxidants, particularly carotenoids, flavonoids, lycopene and beta-carotene (Odriozola-Serrano et al., 2008).

The antioxidant activity of lycopene has been extensively evaluated based on its ability to scavenge free radicals in cell culture and in animal models (Di Mascio et al., 1989). Experimental evidence also suggests that lycopene can quench singlet oxygen ($_1O^2$), scavenge free nitrogen dioxide (NO_2U), thiyl radicals (RSU) and sulphonyl (RSO_2U) radicals, contributes to defense against lipid peroxidation (Stahl and Sies, 2003), prevents the oxidative DNA damage (Riso et al., 1999), inhibits interleukin-6 (IL-6) and androgen (Siler et al., 2004), inhibits 5-lipoxygenase (Hazai et al., 2006) and modulates carcinogen metabolizing enzymes (Jewell and O'Brien, 1999) All these lines of evidence substantiate the antioxidant role of lycopene (Yaping, et al., 2002). Therefore, this study is aimed to investigate the possible protective effect of coadministration of lycopene on deltamethrin toxicity.

Materials and methods

Chemicals

Deltamethrin (98% pure) was purchased from Mitchell Cotts Chemicals (West Yorkshire, UK). Lycopene were purchased from Sigma-Aldrich Chemical (St Louis, Missouri, USA). All other chemicals used

in the present study were of analytical grade available commercially.

Animals and treatments

This study was carried out in compliance with the relevant national laws related to the conduct of animal experimentation. In this investigation, 40 healthy adult male rats were used. The average initial body weight of the animals was 150 ± 2 g (±SE). The animals were obtained from the Laboratory Animal Breeding Colony, Faculty of Agriculture, Alexandria University. Animals were allowed to acclimate in an environment of controlled temperature (22–25°C), humidity and light/dark cycle for a minimum of 1 week prior to the study. The rats were fed standard commercial pellet diet. Feed and water were provided *ad libitum*. The animals were divided into four groups of 10 rats in each group and were treated as follows:

- Group I control; these rats received a single dose of 0.5 ml corn oil.
- Group II toxic control, animals received deltamethrin at a dose of 1.28 mg/kg body weight (BW; median lethal dose (LD_{50}) of 1–100). The LD_{50} of deltamethrin when given orally to rats was reported to be 128 mg/kg BW (Worthing, 1983).
- Group III animals were treated with deltamethrin in doses of group II plus lycopene at the doses of 1 mg/kg BW.
- Group IV lycopene was suspended in corn oil and administered by gavage at the doses of 1 mg/kg BW. The dose of lycopene used in this study was selected on the basis of previous studies (Yusuf et al., 2006).

Rats were orally treated with repeated doses of deltamethrin and lycopene daily for 30 days.

Clinical observations

Rats were individually handled and carefully examined for abnormal behaviors and appearance before the treatment. Each rat was observed at least twice a day throughout the study to determine mortality or the onset, duration of any behavioral changes, changes in posture, reactivity to handling or evidence of toxicity and to observed changes in skin, fur, eyes, mucous membranes, occurrences of secretions and excretions. Changes in gait were assessed weekly by allowing the animal to walk freely to allow evaluation of gait. Body weight data were obtained before experimental diet administration, weekly during the treatment periods and fasted weights at necropsy. Food conversion and food efficiency (grams of weight gain per 100 g of food consumed) were also calculated.

Autopsy study

At the end of the experiment, the animals in different groups were killed by cervical decapitation to avoid stress conditions and dissection. During dissection, the color and texture of parenchymatous organs were carefully examined. The color and integrity of the mucosa of the cavity were also examined. In the meantime, the weight of the kidney were measured and recorded. The organ–body index was calculated according to the following formula

$$\text{Organ} - \text{bodyweightindex}(\%) = \text{wetorganweight}/\text{bodyweight} \times 100\%$$

Cytokine assays

Determination of TNF-α assay. The levels of TNF-α in kidney tissue homogenate were determined using specific enzyme-linked immunosorbent assay kits (Biosource, California, USA). The analyses were performed according to instructions of the manufacturer. Standard plots were constructed using standard cytokines, and the concentrations for unknown samples were calculated from the standard plot.

Morphmetric analysis

The cross-sectional areas of the glomeruli and glomerular capillary tufts were measured using SIS automatic image analyzing system (Software Imaging System GmbH, Munster, Germany). Capsular space was calculated as the difference between these two values. The thickness of the basement membranes of the Bowman's capsule and of glomerular capillary endothelium was measured at several randomly chosen points. Features of cell injury and necrotic changes were scored on a semiquantitative scale (0: *absent*; +: *mild* (less than 25% of the tissues were affected); ++: *moderate* (25–50% of the tissues were affected); +++: *severe* (more than 50% of the tissues were affected)), according to Ayyildiz et al. (2004).

Table 1. Effects of deltamethrin and lycopene (deltamethrin + lycopene) on weight gain, food intake and absolute kidney weight[a]

Parameters and treatments	Weight gain (%)	Food intake (g/rat per day)	Absolute kidney weight (g)
Control	37.57 ± 1.16	12.77 ± 0.95	0.657 ± 0.03
Deltamethrin	22.57 ± 3.21[b,c]	9.37 ± 0.33[b,c]	0.797 ± 0.05[b,c]
Deltamethrin lycopene	35.337 ± 1.22	11.57 ± 0.55	0.597 ± 0.02
Lycopene	36.277 ± 1.05	11.97 ± 0.21	0.617 ± 0.04

[a]Significant differences: values are mean ± SEM (n=6).
[b]$p < 0.01$ versus control group.
[c]Deltamethrin group versus deltamethrin + lycopene group, $p < 0.05$.

Histopathological examinations

One kidney block per animal from each group was cut. The tissues were fixed in 10% formalin, processed routinely and embedded in paraffin. Blocks were cut into 4 micron metre thickness using a microtome Leitz 1512 (Leitz, Wetzlar, Germany) and stained with hematoxylin and eosin stain and examined under light microscope (Olympus, Tokyo, Japan) at ×100, ×200 and ×400 magnification. To evaluate kidney fibrosis, sections at 4-mm thickness were stained with Masson's trichrome.

Transmission electron microscopy

After 12 weeks, kidney specimens ($n = 5$) from each group were fixed for 24 h in formalin–glutaraldehyde ($_4F_1G$) and then rinsed in phosphate buffer solution (pH 7.4) at 4°C for 3 h. Specimens were then postfixed for 2 h in 2% osmium tetraoxide and then were washed with phosphate buffer several times for 10 min. Specimens were dehydrated in a graded ethanol series, followed by propylene oxide and embedded in Araldite-Epon mixture and viewed under Jeol transmission electron microscope.

Statistical analysis

All values were presented as means ± SEM. Differences in means between the groups were calculated by a one-way analysis of variance and *post hoc* Duncan's test using the SPSS/PC computer program (version 12.0). Results were considered statistically significant when $p < 0.05$.

Result

Clinical observations and survival

One male rat from the deltamethrin group was found dead during the experiment, few clinical signs such as reduced activity, increasing weakness and slight diarrhea were noted in deltamethrin group, which was considered to be the remaining deltamethrin. All rats of the other groups survived and no obvious abnormal appearance and behavior were observed.

Body weight, feed consumption and feed efficiency

Mean body weight of male rats in deltamethrin group were significantly lower when compared with controls (Table 1). Food intake was obviously lower in the first week in male rats of deltamethrin group compared with the respective controls. Food utilization efficiency is obtained by dividing the increase in body weight by the food consumption. The significant decreases in feed efficiency were observed in 1.28 mg/kg deltamethrin male rats when compared with controls. Occasionally, no significant changes were noted in the feed efficiency of other groups when compared with control values.

Effect of deltamethrin on the release of TNF-α

TNF-α is involved with the late phase reaction of hypersensitivity (Gordon and Galli, 1990). In the deltamethrin-treated group, animals showed greatly elevated serum TNF-α level when compared with that in the control group ($p < 0.05$). Treatment with lycopene significantly decreased the serum TNF-α compared with that in the deltamethrin group (Figure 2).

Light microscopic morphometric results

The mean cross-sectional area of deltamethrin glomeruli is significantly increased by 22% and that of the subcapsular urinary space by more than 60%. Addition of lycopene to deltamethrin rats leads to insignificant increase in these parameters when

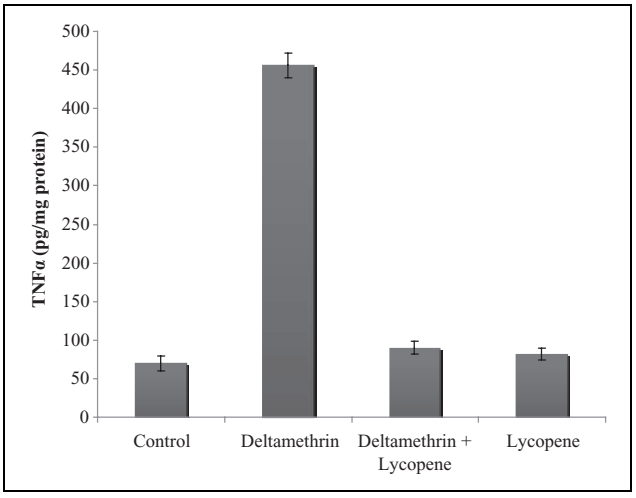

Figure 2. Changes in serum tumor necrosis factor-α (TNF-α) after deltamethrin induced kidney damage in rats.

compared with the animals treated with deltamethrin alone. Lycopene prevents glomerular hypertrophy and diminishes capsular space enlargement (Table 2).

Histological results

Photomicrographs of rat kidney sections of control and experimental groups stained with hematoxylin and eosin are represented in Figure 3(a) to (d). Figure 3(a) illustrates the section of kidney tissue of control group that showed no pathologic changes; rats exhibited normal renal tissue, where normal glomeruli and proximal tubular epithelium were observed. The deltamethrin-exposed animals (Figure 3(b)) showed pathologic alterations such as congestion, hemorrhages and tubular degeneration. Tubular degenerative changes included hyalinic degeneration, necrosis and inflammation. These features included tubular cell swelling, pyknotic nuclei, congestion, tubular dilatation and moderate-to-severe necrosis. Glomerular structures were found to be hypercellular and swollen and were of the subcapsular urinary space. Also, Karyomegaly with eosinophilic intranuclear inclusions was abundant despite the fact that the abovementioned changes were observed in all parts of the nephrons, the proximal tubules showed the most prominent alterations. Infiltrations of inflammatory cells, largely representing mononuclear cells, were observed. Also, in animals exposed to deltamethrin alone vessel wall thickness and interstitial fibrosis also happened. The rate of renal tissue degenerative changes in rats that received deltamethrin along with lycopene was significantly reduced (Figure 3(c)) when compared with the animals treated with deltamethrin alone. Animals given lycopene alone showed normal architecture (Figure 3(d)).

Evaluation of kidney fibrosis

The results of the histopathological analyses with Masson's trichrome (to detect collagen deposition) staining are given in Figure 4(a) to (d) and Table 2. Control rats fed with starch plus casein diet exhibited normal glomeruli and tubules with negligible collagen (Figure 4(a)). The architecture of the kidney tissue is complete and there is neither fibroplasia nor inflammatory cell infiltration. Figure 4(b) represents the kidney section from deltamethrin group, which displays higher degree of fibrosis, an increased amount of collagen deposited in perivascular region and intraglomerular region. The architecture is disturbed. Bluish circular pattern shows that the deposition is well-defined and extensive. Figure 4(c) represents the kidney section from deltamethrin and lycopene-treated group that showed considerable reduction in collagen deposition, while the kidney section from lycopene-treated group showed minimal collagen deposition in tubules and glomeruli; perivascular fibrosis, hyalinization of glomeruli and proximal tubular epithelium tissue were not determined (Figure 4(d)).

Transmission electron microscopic results

The ultrastructural changes occurred in the kidney glomerular tissues of control and experimental groups of rats are exemplified in Figure 5(a) to (d). The electron micrograph of control rats kidney glomeruli shows a normal ultrastructure (Figure 5(a)). In the deltamethrin rats, degeneration in glomerular capillaries was observed. Also, the glomeruli appears larger and dilated; Bowman's capsule is partially thickened; pycnosis in podocyte and podocyte processes appear broadened or show degenerative features such as vacuolization, blebbing and myelin figures (Figure 5(b)). Oral administration of lycopene normalized the abovementioned alterations (Figure 5(c)). Animals given lycopene alone showed normal architecture (Figure 5(d)).

In the proximal tubule epithelium, the electron micrograph of control rats kidney proximal tubule shows a normal ultrastructure (Figure 6(a)). In the deltamethrin rats, pycnosis in proximal tubules, nuclei shrunk with clumping and margination of nuclear chromatin with pale cytoplasm, slightly swollen

Table 2. Effect of lycopene (1 mg/kg) treatment on morphometrical and morphologic parameter changes as assessed by histopathologic examination of renal cortex of the rats exposed to deltamethrin (1.28 mg/kg)[a]

Groups	Control	Deltamethrin	Deltamethrin + lycopene	*Lycopene*
Tubular necrosis	−	+++	−	−
Tubular degeneration	−	++	−	−
Tubular dilation	−	++	−	−
Tubular vacuolization	−	+++	+	−
Thickened basement membrane	1.02 ± 0.34[b]	2.23 ± 0.32[c]	0.91 ± 0.27[b]	0.97 ± 0.15[b]

[a]Values are mean ± standard error for 10 rats in each group.
[b]$p < 0.01$ versus DM-treated group.
[c]$p < 0.01$ when compared with the control group.

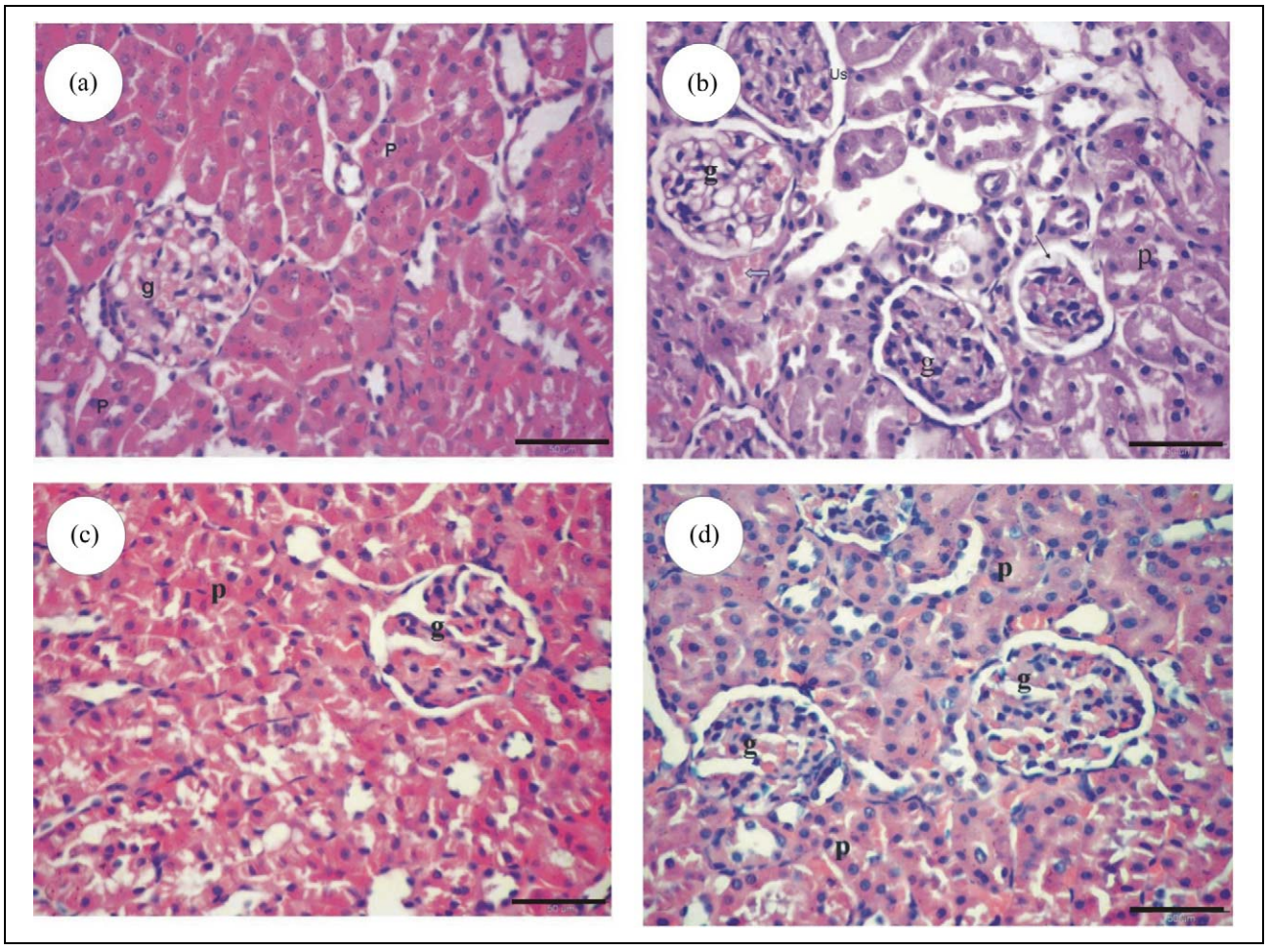

Figure 3. Light micrographs of hematoxylin and eosin staining of kidney tissues of control and experimental groups of rats. (a) Group I shows the histoarchitecture of the renal cortex, which is intact in control rat with normal size of glomeruli and with small subcapsular spaces. (b) Group II deltamethrin rats larger degenerated glomeruli are observed; also, the subcapsular space appears dilated. Karyomegalic cells, swelling of proximal tubules and various degenerative changes with focal tubular necrosis invaded by inflammatory cells (arrow) are seen. (c) Group III that received deltamethrin and lycopene shows apparently normal architecture. (d) Group IV showing kidney section of lycopene rats; it did not show any morphologic changes demonstrating normal renal cortex. g: glomeruli; p: proximal tubules. Scale bar: 50 μm.

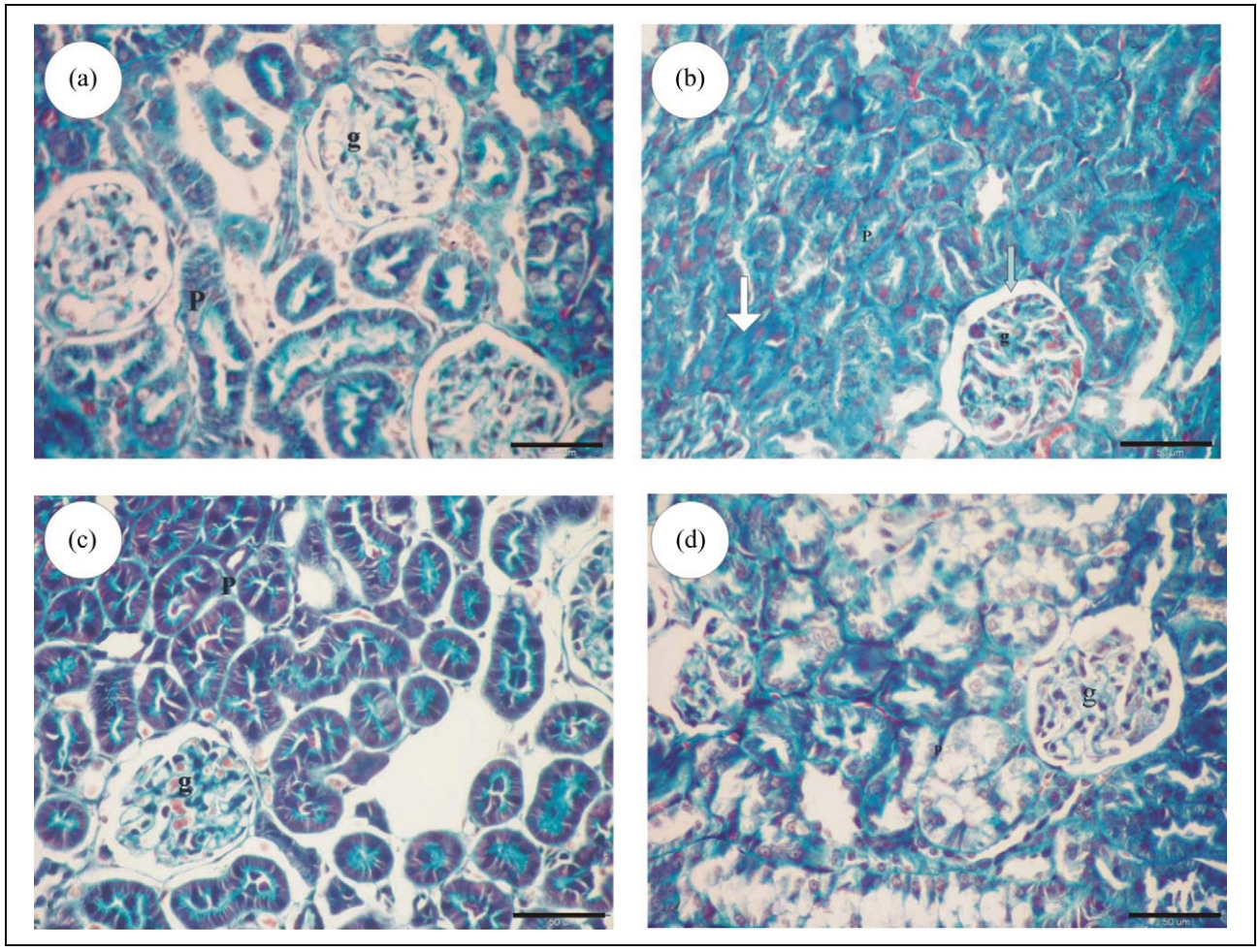

Figure 4. Histology of kidney stained with Masson's trichrome. (a) Control group shows normal quantum of collagen in glomeruli and tubules. (b) Sections of deltamethrin group show collagen deposition (white arrows pointing out blue color) in perivascular and intraglomerular region. (c) Section from lycopene-treated deltamethrin group shows marked reduction in collagen deposition. (d) Lycopene-treated control group shows negligible collagen deposition. g: glomeruli; p: proximal tubules. Scale bar: 50 μm.

mitochondria and irregularly arranged microvilli were seen. There was increased number of lysosomes and numerous vacuoles in the apical cytoplasm (Figure 6(b)). Electron microscopic examination did not show any significant differences in proximal tubule tissue between control and experimental animals (deltamethrin along with lycopene or lycopene alone (Figure 6(c) and (d)).

Discussion

Environmental pollutants such as pesticides are known to induce a broad spectrum of toxicological effects and biochemical dysfunctions constituting serious hazards to health. Several studies have demonstrated that pesticides such as organochlorines, organophosphates and carbamates induced embryo toxicity, genotoxicity, teratogenicity and tissues damages (Cavas and Ergene-Gozukara, 2003; Soni and Bhatnagar, 2005; Tisch et al., 2005). Animal models are useful for testing putative chemopreventive agents before embarking on clinical trials. The kidney is the critical target organ, involving tubular cells and glomerulus, for synthetic pyrethroid pesticide compounds, which produce a variety of renal toxic effects (Mohamed et al., 2003).

In the present study, a reduction in weight gain (%) and a decrease in absolute kidney weight in deltamethrin-treated group were observed. The reduction in body weight is probably attributed to the reduction in food intake and toxic effects of deltamethrin in treated rats. Similar results have been found in animals exposed to different pyrethroid compounds (deltamethrin, fenvalerate and diazinon) (Kalender

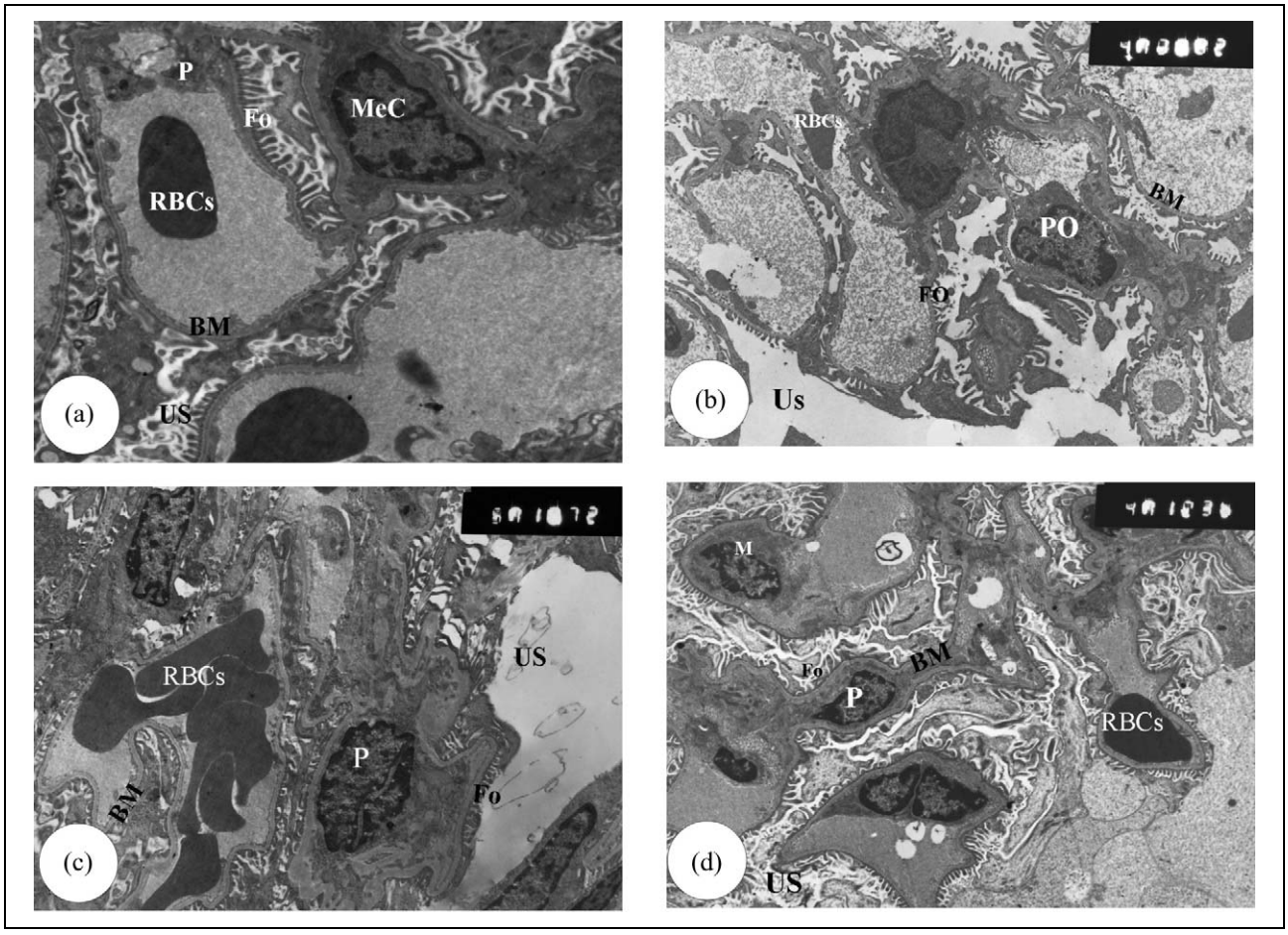

Figure 5. Electronmicroscopic images of glomerular capillaries from rat kidney. (a) Glomerular capillaries of control rat show urinary space and podocytes with regularly arranged foot processes with slit pores that are separated from the endothelium by a basement membrane. The BM is continuous with the mesangial matrix. Capillary lumen lined with endothelial cells and containing red blood cells, mesangial cell. (b) Glomerular capillaries of deltamethrin rat. Note that glomerular endothelium contains gaps instead of regular pores. A podocyte exhibits signs of degeneration: myelin figure. (c) Glomerular capillaries from a rat given deltamethrin and lycopene, (d) glomerular capillaries from a rat given lycopene only show the glomerular and podocyte processes appeared normal. US: urinary space; BM: basement membrane; P: podocyte; E: endothelial cells; RBCs: red blood cells; MeC: mesangial cell; Ma: mesangial matrix; My: myelin figure. Scale bar, 2 μm.

et al., 2006; Kilian et al., 2007). The decrease in weight gain and absolute kidney weight observed here in deltamethrin-treated animals was simply a reflection of decreased food consumption or due to toxicity of deltamethrin, perhaps by malabsorption of nutrients induced by the effects on the gastrointestinal tract or inhibition of protein synthesis. Deltamethrin treatment resulted also in a significant increase in relative kidney weights of rats. Increased weights of soft tissues such as kidney and pancreas were observed in several cases of organophosphorus insecticide (OPI) poisoning in rats such as fenthion (Ikizceli et al., 2005) and deltamethrin (Kamath and Rajini, 2007). This may probably be due to edema and inflammation, according to Kamath and Rajini (2007).

Cell apoptosis or necrosis can inevitably affect glomerular filtration rate and endothelial function, resulting in renal failure (Bonegio and Lieberthal, 2002; De Vries et al., 2003). Several reports suggest that DNA becomes an easy target for both apoptosis and necrosis, and the stability of the cellular genomic apparatus is constantly challenged by a wide-spectrum of environmental toxicants that generate DNA lesions (Hickey et al., 2001). Moreover, high reactive oxygen species (ROS) concentrations contribute to the apoptotic cell death whenever they are generated in the

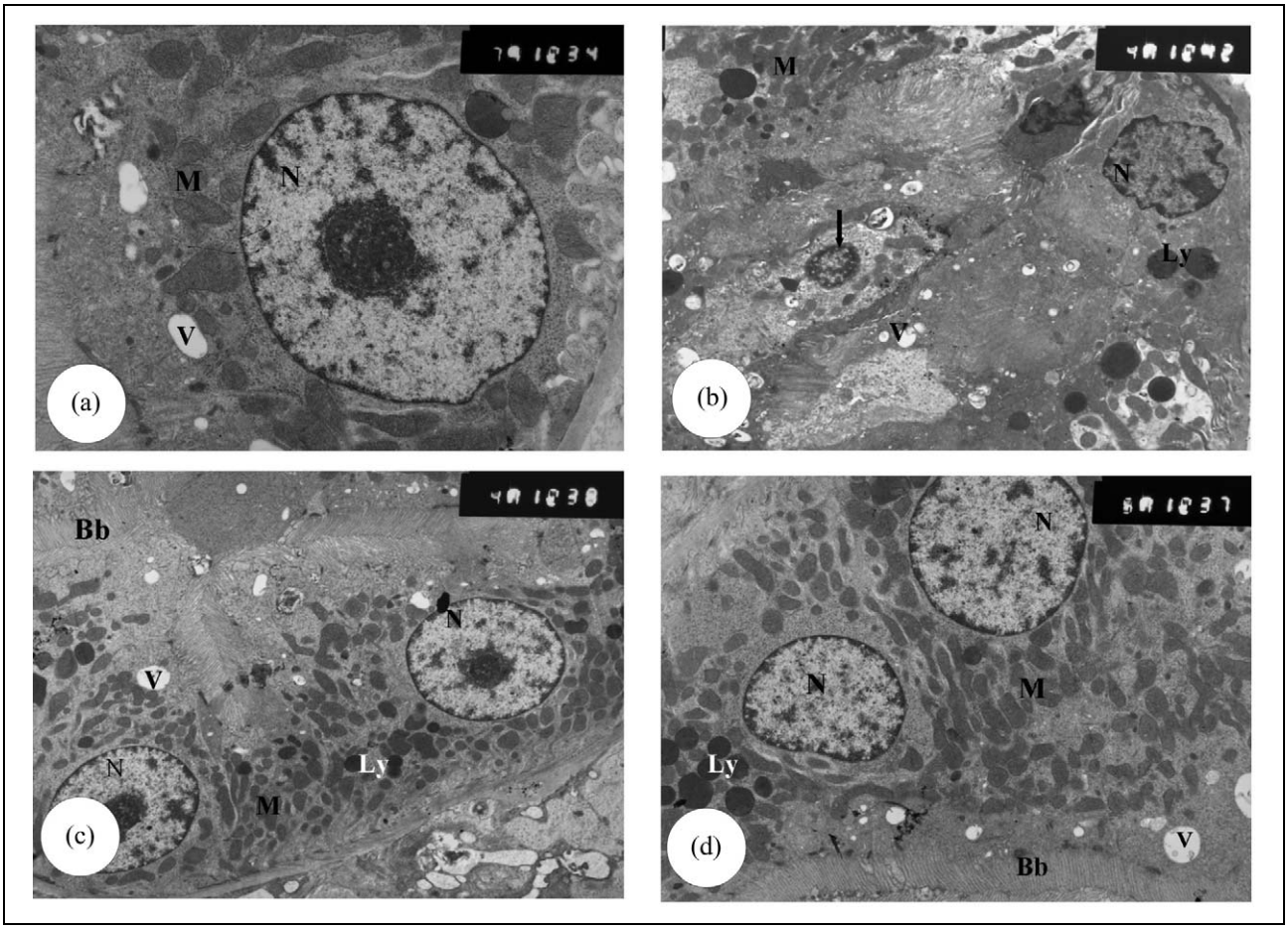

Figure 6. Electron micrographs of proximal tubular epithelial cells from rats. (a) Proximal tubular epithelial cells from control rat show luminal bottler lined with nucleus, apical endocytic vesicles and numerous closely packed mitochondria with thin, transverse and interdigitating cristae. (b) Proximal tubular epithelial cells from a rat given deltamethrin show severe damage. Note the necrotic epithelial cells with loss of cytoplasmic organelle and disappearance of brush border, nuclei with chromatin condensed circumferentially. There is a swelling in the mitochondria with loss of crystae with an increase in the number of secondary lysosomes and numerous vacuoles (arrow), probably representing dilatation of the endoplasmic reticulum, myelin figure are seen. (c) and (d) show normal architecture of proximal tubular epithelial cells from a rat given deltamethrin and lycopene or lycopene only. Ev: endocytic vesicle; N: nucleus; M: mitochondria; ly: lysosomes; Bb: brush border. Scale bar: 2 μm

context of the apoptotic process (Franco et al., 2009; Liu et al., 2010). TNF-α is a pleiotropic proinflammatory cytokine produced by mesangial, glomerular, endothelial, dendritic and renal tubular cells (Dong et al., 2007). TNF-α-induced cytotoxicity occurs through varying mechanisms including the overproduction of ROS, which in turn damages the cellular components such as protein, lipids and DNA.

The histopathological observation in deltamethrin-treated rats showed glomerular congestion, tubular degeneration, necrosis and swelling of tubules and vacuolization at different foci throughout the cortex in renal tissues of rats. The results confirmed previous findings of Sulak et al. (2005) and Kalender et al. (2007), who had found degenerative changes in the kidney of adult rats exposed to methidathion and methyl parathion. Moreover, severe interstitial mononuclear cells' infiltration (Oncu et al., 2002 and Sulak et al., 2005), hyperplasia and hypertrophy of tubular cells (Kalender et al., 2007) had also been observed. Interestingly, in the current study, the deltamethrin rats develop nephropathic changes like thickening of basement membrane, changes in architecture and decrease in podocyte number. In the recent years, there has been a growing interest on the importance of podocyte in maintaining the glomerular size-selective barrier finding. The podocyte is an integral part of glomerular basement membrane, and it has

complex cellular morphology with a cell body bulging in to the urinary space giving rise to numerous foot processes through which they affix to the capillaries. The foot processes of neighboring podocyte interdigitate, leaving between them the filtration slits bridged by an extracellular structure, known as the slit pore diaphragm. Structural abnormalities and loss of podocyte have been implicated in glomerular basement membrane thickening and abnormal glomerular permeability to proteins (Smoyer and Mundel, 1998). Loss of cytoskeletal integrity may destabilize and disrupt the filtration slit membrane structure, leading to broadening of the base of podocyte, disruption of the filtration slit structure and subsequent podocyte foot process effacement and albuminuria (Zhou et al., 1999). All these changes were observed in the deltamethrin rats. Lycopene deltamethrin administration modulated podocyte foot process changes and reduced the thickening of basement membrane, glomerular basement membrane and podocytes with clear linear images and without angles or artifacts. This could be due to the accumulation of free radicals as the consequence of increased lipid peroxidation by deltamethrin in the renal tissues In fact, it has been reported that several OPI compounds produced oxidative stress in different tissues through the formation of ROS (Abdollahi et al., 2004; Akhgari et al., 2003; Ogutcu et al., 2006). ROS were a part of normal oxidative metabolism. When produced in excess, they caused tissue injury including lipid peroxidation, DNA damage and enzyme inactivation (Dal-Pizzol et al., 2003). Oxidative damage has been recognized as one of the primary causes of subcellular toxicity of pesticides (Banerjee et al., 2001). Deltamethrin and environmental pollutants such as pesticides are known to induce a broad spectrum of toxicological effects and biochemical dysfunctions constituting serious hazards to health. Several studies have demonstrated that the pesticides such as organochlorines, organophosphates and carbamates induced embryo toxicity, genotoxicity, teratogenicity and tissues damages (Cavas and Ergene-Gozukara, 2003; Soni and Bhatnagar, 2005; Tisch et al., 2005).

Generally, the use of dietary food additives has gained increasing popularity for the past few years. Tomato, which contains lycopene and other antioxidants, exerts an inhibitory effect against certain diseases that have an oxidative stress component (Roa and Agarwal, 2000; Toniolo et al., 2001). Lycopene treatment, after deltamethrin administration, provided a significant protection against deltamethrin-induced nephrotoxicity. The histological evaluation of the kidney preparations in the group administered with lycopene treatment also revealed a histological amelioration in deltamethrin-induced glomerular congestion, tubular degeneration, necrosis and hyaline cast. Lycopene has been reported as the most efficient biological carotenoid $_1O^2$ quencher (Di Mascio et al., 1989). In organic solution, lycopene was the most rapidly destroyed carotenoid upon reaction with peroxyl radicals, indicating its presence in the first line of defense (Woodall et al., 1997). The results obtained suggest that lycopene could prevent and reduce the ultrastructural changes induced by deltamethrin. This is in agreement with Atessahin et al. (2005), who determined that pre- and posttreatment with lycopene provided protective effects against cisplatin-induced nephrotoxicity. Earlier reports demonstrated the anti-inflammatory and antioxidant effect of lycopene (Giovannucci, 1999; Rao and Agarwal, 1999). Lycopene is an efficient scavenger of free radicals and prevents lipid peroxidation (Rao and Agarwal, 1999). Moreover, the administration of carotenoids with fruits and vegetables instead of carotenoid supplements such as lycopene is rarely associated with protective effects (Stahl and Sies, 2003).

A diet rich in carotenoid-containing food is associated with a number of health benefits. Interest in the effect of tomatoes and tomato-based products has increased as a consequence of many epidemiological studies, which showed the protective action of carotenoids, in particular lycopene, on cancer and cardiovascular diseases (Cohen, 2002; Stahl and Sies, 2003; Visioli et al., 2003). Lycopene is a major carotenoid, available primarily from tomatoes and its products. Of all the carotenoids, lycopene has been shown to exhibit the highest physical quenching rate constant with ROS (Gupta et al., 2003; Heber and Lu, 2002; Michael McClain and Bausch, 2003; Wertz et al., 2004). Carotenoids are well known as highly efficient scavengers of $_1O^2$ and other excited species. During $_1O^2$ quenching, energy is transferred from $_1O^2$ to the lycopene molecule, converting it to the energy-rich triplet state. Trapping of other ROS, like $OH^{\bullet}$, NO^2 or peroxynitrite, in contrast, leads to oxidative breakdown of the lycopene molecules. Thus, lycopene may protect *in vivo* lipids, proteins, and DNA against oxidation (Matos et al., 2000; Reifen et al., 2004; Tapiero et al., 2004).

Many investigators observed that oral administration of carotenoids had a protective potential against several diseases in clinical and *in vivo* or *in vitro*

experimental investigations. Reifen et al. (2004) suggested that lycopene as well as 5-aminosalicyclic acid act simultaneous as both antioxidants in oxidative stress and anti-inflammatory against colitis induced by iron in rats. Gupta et al. (2003) reported that lycopene might be useful as a preventive agent against cataracts. Velmurugan et al. (2002) observed that supplementation of lycopene significantly reduced the extent of lipid peroxidation and enhanced the antioxidant levels such as glutathione peroxidase, glutathione, Vitamins C and E in rats with gastric carcinogenesis induced by *N*-methyl-*N*-nitro-*N*-nitrosoguanidine.

Lycopene may act by various mechanisms such as: (i) inhibiting the growth and induction of differentiation in cancer cells by modulating the expression of cell cycle regulatory proteins (Karas et al., 2000), (ii) modulating the IGF-1/IGFBP-3 system (Giovannucci, 1999; Mantzoros et al., 1997), (iii) upregulating the gap-junctional gene connexin 43 and increasing gap-junctional intercellular communication (Zhang et al., 1992), (iv) modulating the redox signaling (Gius et al., 1999), (v) preventing the oxidative DNA damage (Riso et al., 1999), (vi) inhibiting IL-6 and androgen (Siler et al., 2004), (vii) inhibiting 5-lipoxygenase (Hazai et al., 2006) and (viii) modulating carcinogen metabolizing enzymes (Jewell and O'Brien, 1999). Also, Lycopene has been reported as the most efficient biological carotenoid $_1O^2$ quencher. During $_1O^2$ quenching, energy is transferred from $_1O^2$ to the lycopene molecule, converting it to the energy-rich triplet state. Lycopene in the triplet state can return to the ground state by dissipating the energy as heat or by physical quenching, leaving the lycopene molecule intact and ready for further quenching events. Trapping of other ROS, like $OH^{\bullet}$ $NO^{\bullet}{}_2$ or peroxynitrite, in contrast, leads to oxidative breakdown of the lycopene molecule (Stahl and Sies, 2003; Wertz et al., 2004).

In conclusion, this study demonstrates that the lycopene has a potential protective effect against deltamethrin-induced renal damages. It is important when considering the possibility of using lycopene and/or plants rich in this antioxidant for men in agriculture practice to minimize nephrotoxicity effects and to limit the toxicity against pesticides exposure.

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