Original Article

# The Effect of Ciprofloxacin on Renal Cortex of Adult Male Albino Rat and the Possible Protective Role of Olive Oil: Anatomical and Histological Study

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## ABSTRACT

**Introduction:** Ciprofloxacin is an antibiotic administered to treat many bacterial infections but causes kidney damage as one of its side effects.

**Objective:** To investigate the protective role of olive oil against ciprofloxacin-induced renal cortical injury.

Materials and methods: Forty adult albino rats; with average weight of 150-200 gm were randomly divided into five groups. They received medications by orogastric tube for 14 days. Normal control untreated group (Group I). Olive oil group received virgin olive oil (5 ml/Kg body weight) (Group II). Ciprofloxacin group received 20 mg/kg body weight, dissolved in 8 ml of distilled water (Group III). Combined group received the same doses of both ciprofloxacin and olive oil (Group IV). Recovery group received same dose of ciprofloxacin 14 days followed by same dose of olive oil (Group V), rats were scarified after one month from the end of experimental period.

**Results:** The external surface of kidneys showed hemorrhagic spots and white necrotic patches in ciprofloxacin treated group (III). Ciprofloxacin caused mild glomerular atrophy and necrosis of some epithelial cells of proximal and distal tubules. Ultrastructural changes were mitochondrial abnormalities and dilated brush border of proximal tubule cells, necrotic distal tubule cells with increased lysosomal number and increased width of urinary space of glomerulus. Combined group (IV) showed a significant level of protection in the form of restoration of normal glomerular structure with mild dilatation of urinary space and mild tubular structure affection. Recovery group (V) showed a higher significant level of protection, the complete restoration was pointed to be as control one.

**Conclusion:** This study suggests that ciprofloxacin induces marked degenerative changes on the renal tubules with mild effect on the glomeruli, which are regenerated by olive oil and can be recovered.

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**Key Words:** Ciprofloxacin, histopathology, olive oil, renal cortex.

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## INTRODUCTION

Ciprofloxacin (CPX) belongs to the fluoroquinolone (FQ) antibiotic class, and was initially introduced to the market in 1987[1]. It is on the World Health Organization's List of Essential Medicines and is one of the most widely used antibiotics in the world[2].

It is most effective against gram-negative bacteria (Enterobacteriae including E. coli, Salmonella spp., Shigella spp., and Neisseria gonorrhoeae)[3]. Some gram-positive bacteria, such as Pseudomonas aeruginosa, are also susceptible to ciprofloxacin[4].

FQ antibiotics have excellent efficacy in the treatment of bacterial infections such as upper and lower respiratory infections, sexually transmitted diseases, and some skin, bone, and soft tissue infections, as well as community-acquired pneumonia[5].

Ciprofloxacin works by inhibiting bacterial replication, directly threatening their proliferation[6]. It works by inhibiting DNA synthesis in bacteria by prohibiting topoisomerase II from folding DNA strands and forming spatial DNA isomers[7,8]. Also, it prohibits topoisomerase IV enzyme that separates DNA strands after it has been replicated. Inhibiting the action of these enzymes causes DNA damage and blocks a variety of cell activities, resulting in bacterial death[9].

One of the most targeted organs for pharmaceutical and environmental chemical toxicity is the kidney. The high

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blood flow to this organ in relation to its mass, as well as the specific ability of renal tubular epithelium in concentrating urine and its constituents, including medicines and chemicals, make it particularly vulnerable[10].

Despite CPX effects against several bacterial species, it causes a rise in serum lactate dehydrogenase and serum creatinine[11]. It also revealed oxidative damage and inflammation, as well as significant nephrotoxicity and histological abnormalities[12].

Ciprofloxacin has been demonstrated to increase the production of reactive oxygen species (ROS) in different cells. Malondialdehyde (MDA) is one of the most important end products of lipid peroxidation and is known to be an indicator of free radical damage, and indirectly signifies tissue damage[13,14].

As oxidative stress appears to be one of the mechanisms underlying ciprofloxacin-induced organ injury, antioxidant treatment could be a therapeutic option. As a result, antioxidants may have pharmacological benefit in the treatment of ciprofloxacin-induced kidney injury[15].

Olive oil is a fatty acid that is known to have antioxidant properties[16]. It contains monounsaturated fatty acids (MUFAs) and anti-oxidants, which are important for improving cardio-metabolic risk factors[17] and can help to prevent chronic diseases such as cardiovascular disease, atherosclerosis, hypertension, diabetes, and various types of cancer[18,19] as well as reduce DNA oxidation[20].

Vitamin E, oleocanthal, carotenoids, and polyphenols are of the powerful antioxidants found in virgin olive oil (VOO), all of which have been studied and shown to enhance human health[21].

Consumption of polyphenol-rich olive oil has also been linked to improved endothelial function[22] and is known for its anti-inflammatory properties, which are characterized by the down-regulation of inflammatory mediators via transcriptional or post-transcriptional pathways[23].

Olive oil's phenolic components, particularly oleuropeins, protect Low-Density Lipoprotein (LDL) particles from oxidation and scavenge free radicals[24].

Through an increase in olive oil polyphenol metabolites in lipoproteins, olive oil polyphenols have been demonstrated to increase HDL size, promote higher HDL stability, and improve HDL oxidative state[25]. As a result, it is considered as a natural source of protection against degenerative diseases caused by reactive oxygen species (ROS)[26].

Olive oil can lower serum levels of CRP, IL-6, IL-7, and IL-18, and possesses anti-apoptotic effects, which are mediated through the suppression of proapoptotic proteins and the production of anti-apoptotic proteins[27].

The effects of VOO or olive leaf extract on nephrotoxicity generated by various drugs have been proven, with nephrotoxicity in animals being reduced as a result of its administration[28,29].

The aim of our work is to investigate the protective role of olive oil against ciprofloxacin-induced renal cortical injury.

## MATERIAL AND METHODS

### *Materials*

### *Chemicals*

Ciprofloxacin packed tablets purchased from European Egyptian Pharm., virgin olive oil purchased from Olitalia and distilled water solution obtained from a local market.

### *Experimental Animals and treatment*

The study was carried on forty healthy Swiss adult male Albino rats (8 weeks), weighing 150– 200 g, obtained from Animal house of Physiology Department, Faculty of Medicine, Alexandria University. They were housed in an air-conditioned room at 25 ± 1°C and 65-70% relative humidity with a 12 h light-dark cycle following the Egyptian Institute of Nutrition (EIN) recommendations[30]. Diet was administrated following the EIN recommendations. The animals were given food and water without restraint during the experimental period. The forty adult male rats were divided randomly into the following five groups:

- **Group I:** Control group; 8 rats were given food and water ad libitum during the experimental period.
- **Group II:** Olive oil group; 8 rats received virgin olive oil (5 ml/kg body weight) daily by orogastric tube for fourteen days at 10 a.m[31].
- **Group III:** Ciprofloxacin group; 8 rats received ciprofloxacin (20 mg/kg body weight)[32] dissolved in 8 ml of distilled water daily by orogastric tube for fourteen days at 10 a.m[33,34].
- **Group IV:** Combined group; 8 rats received both ciprofloxacin and olive oil concomitantly as the previously described doses.
- **Group V:** Recovery group; 8 rats received first ciprofloxacin for fourteen days then followed by olive oil for fourteen days as the previously described doses. Rats were sacrificed after one month from the end of experimental period.

### *Methods*

At the appropriate date of the experiment, the rats were anaesthetized with ether. The abdominal wall of each animal was incised and the kidneys were exposed and dissected.

#### Gross examination

Kidneys dissected from all groups were rinsed with physiological saline for studying the gross morphological appearance and photographed using Olympus SZ Dissecting Stereo Microscope in Anatomy Department of Faculty of Medicine, Alexandria University.

**Histopathological examination**

The kidney specimens from control and experimental groups were selected and divided into two portions and processed for the following:

**Light microscopic study**

Specimens from right kidneys cortices from different groups were fixed 10% neutral buffered formalin for preparing the paraffin sections to examine the histopathological changes as following:

**Paraffin section preparation**

The kidney samples were Fixed in 10% neutral buffered formalin overnight, dehydrated by series of alcohol, cleared in xylene, and embedded in paraffin wax. Serial sections (5 µm thick) were cut using a rotatory microtome and paraffin sections were mounted on clean slides, placed at 37°C oven.

The kidney Sections were deparaffinized in xylene, rehydrated in descending grades of alcohol to distilled water, stained with Hematoxylin, washed in tape water then stained with Eosin. All stained slides were dehydrated in ascending grades of alcohol and cleared in xylene. Cover slip were applied by Canada balsam and examined under the light microscope then the images were captured at the 20&40X Objective lens magnification[35]. Images were viewed and recorded using Olympus microscope – equipped with Spot digital camera, using MATLAB software programme (image J) for:

Measurement of the number of glomeruli: The number of glomeruli were counted through eight images collected from eight fields for each group stained by H&E stains under image analyzer by 10X magnification.

Measuring width of the urinary space: The width of the urinary space and analysis of data were carried out by eight images collected from eight fields for each group stained by H&E stains under image analyzer by 40X magnification.

The data was based on the mean of number and tabulated.

**Ultrastructural study**

The cortices of left kidneys from each group were cut immediately into small pieces (1x1m) and were subjected to the following procedures, fixation, washing, dehydration and filtration. The specimens were fixed in 3% glutaraldehyde, rinsed in buffer cacodylate buffer (pH 6.5), dehydrated with graded ethanol, rinsed in osmium tetraoxide, infiltrated and embedded in pre-labeled plastic capsules. The tissue was sectioned through diamond knife in ultrathin microtome and picked upon the copper grade, then the grade were stained with lead citrate and uranyl acetate for examining under the transmission electron microscope in Electron Microscope Unit, Faculty of Science, Alexandria University[36,37].

***Statistical analysis***

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level.

The used tests were F-test (ANOVA) for normally distributed quantitative variables, to compare between more than two groups, and Post Hoc test (Tukey) for pairwise comparisons.

Significance of the obtained results was judged at the 5% level, where values ≤ 0.05 are significant[38].

## RESULTS

***Gross anatomy results***

**External features of the kidney**

In the present work, the anatomical external examination of the kidney under the dissecting stereo microscope showed normal smooth glistening surface with no distortion in control group (I) and olive oil group (II). The external surface of the ciprofloxacin group III revealed hemorrhagic spots and white necrotic patches. The combined group (IV) showed dark surface with less hemorrhagic spots than group III with no necrotic white patches. The recovery group (V) showed smooth glistening pink surface with much less hemorrhagic spots and no necrotic white patches. (Figure 1)

***Histopathological results***

**Light microscopic results**

Examination of the renal cortices of control group (I) showed classical architecture of the glomerulus, renal tubules and interstitial tissue. The glomeruli appeared with regular Bowman`s capsule and mesangial cells with dark nuclei, normal glomerular capillaries and normal urinary space. Proximal tubules were lined by pyramidal epithelial cells with basal dark nuclei and homogenous pink cytoplasm and closed lumen by a well organized brush border. Distal tubules were lined by cuboidal epithelial cells that had dark rounded nuclei and pink cytoplasm with narrow lumina and mildly dilated interstitial spaces between renal tubules and glomeruli were also seen. (Figure 2)

Examination of the renal cortices of olive oil group (II) showed the classic structure of the renal cortex. Glomeruli appeared normal with well preserved urinary space and mesangial cells had dark nuclei. The renal tubules appeared mildly disorganized, proximal convoluted tubules with narrow lumina obliterated by a well-organized brush border. Tubules were lined with high cuboidal pyramidal cells with deeply stained eosinophilic cytoplasm and basal vesicular nuclei. Distal tubules had narrow lumina and were lined by cuboidal cells with dark rounded nuclei and dark pink cytoplasm. (Figure 3)

Examination of the renal cortices of ciprofloxacin group (III) showed variable histopathological changes in the glomeruli and renal tubules. Some glomeruli showed atrophy with moderate to marked dilatation of urinary space, others were hyperemic with nearly no urinary space and proliferating mesangial cells and dilated congested blood capillaries, others appeared normal organized. A marked degenerative changes were showed in the renal tubules. They had necrotic epithelial cells with pale cytoplasm and wide lumina. Narrow interstitial tissue spaces due to the crowded necrotic tubules and congested blood vessels were seen. Also, areas of aggregated lymphocytes were detected. (Figure 4)

Examining the renal cortices of combined group (IV) showed amelioration of the histopathological changes. Some glomeruli were disorganized but had narrow urinary space, reorganized mesangial cells with dark nuclei and normal blood capillaries. The renal tubules showed regenerative structure with closed lumen and cells with dark rounded nuclei and homogeneous pink cytoplasm. Others showed moderately dilated lumen. Few congested blood vessels were observed in the interstitial tissue. (Figure 5)

Examining the renal cortices of recovery group (V) showed a higher degree of protection and restoration of normal architecture. Glomeruli had a classical structure with narrow urinary space and mesangial cells with dark nuclei. Tubules showed marked regeneration, they were organized with closed lumen and well defined brush border in proximal tubules. The tubular cells were normal with dark rounded nuclei and homogeneous pink cytoplasm. Other dilated tubules were occasionally detected (Figure 6)

**Electron Microscopic results**

Examination of renal cortical sections of control group (I) revealed the glomerulus fine structure with blood capillaries, thin infiltrating membrane and narrow urinary space. The podocytes had dark nuclei and cytoplasm with long foot processes. The epithelial cells of the proximal tubules were resting on a thin basal membrane with central narrow lumen occluded by a well organized brush border. They had rounded basal nuclei with regular envelope and differentiated chromatin, the cytoplasm showed numerous tubular mitochondria with lamellar cristae, few lysosomes, few granulated vesicles and segmented rough endoplasmic reticulum were also seen. The distal tubular epithelial cells were cuboidal with rounded apical nuclei, normal thickness basal lamina with basal infoldings and narrow lumen. The cytoplasm had many organized normal mitochondria with lamellar cristae, few small vesicles and mildly dilated rough endoplasmic reticulum. (Figures 7,8)

Examination of renal cortical sections of olive oil group (II) revealed the classical structure of the glomerulus with normal capillary lumen,basement membrane,endothelial cell and intact clear urinary space. Podocytes had dark nuclei and foot processes. The cells of the proximal convoluted tubules were resting on a thin regular basal lamina with basal infoldings. They had a rounded nucleus with natural distribution of its chromatin content and prominent nucleols. Tubular mitochondria with lamellar cristae were seen in the infoldings. Few lysosomes and segmented rough endoplasmic reticulum were also seen. Apical surface showed long microvilli forming a brush border towards the lumen.The distal tubule reflected electronlucent cytoplasm with less organized mitochondria, few small vesicles, apical nucleus with prominent nucleolus and short luminal microvilli. (Figure 9)

Examination of renal cortical sections of ciprofloxacin group (III) showed moderate to marked destructive changes of the ultrastructure. The glomerulus appeared with marked dilated blood capillaries with thick infiltrating membrane. Podocytes had dark nuclei and light cytoplasm with wide foot processes and marked width of the urinary space was noticed. The epithelial proximal tubular cells had nuclei with irregular envelope and clumped chromatin, they were resting on a thick basal lamina, had irregular dilated brush border associated with markedly dilated microsomes. The cytoplasm had different sizes of mitochondria; few mitochondria had many dark dots due to the destruction of the mRNA, many large lysosomes and shortening of segmentation of dilated rough endoplasmic reticulum. The distal tubular epithelial cells showed small dark rounded nuclei with irregular envelope and clumped chromatin. The cytoplasm had disorganized bizarre mitochondria, markedly dilated rough endoplasmic reticulum, many small lysosomes and dilated Golgi complex. (Figure 10)

Examination of renal cortical sections of combined group (IV) showed the glomerulus with mildly dilated urinary space and blood capillaries. Podocytes had dark nuclei with mildly dilated and short foot processes. The proximal tubular epithelial cells had eccentric nuclei with regular envelope and prominent nucleolus resting on thin basal lamina. An organized double membrane and short brush border were seen. The cytoplasm had many different sized mitochondria with organized cristae. Few lysosomes and normal rough endoplasmic reticulum were present. The distal tubular epithelial cells showed rounded nuclei with prominent nucleolus, the cytoplasm had different sizes of mitochondria; some were organized with lamellar cristae and others were disorganized. A mildly dilated rough endoplasmic reticulum close to thin basement membrane was shown. There were many granulated vesicles near the Golgi complex, small lysosomes, and many small exosomes at the narrow lumen (Figure 11).

Examination of renal cortical sections of recovery group (V) showed a glomerulus with small blood capillaries, thin infiltrating membrane and mildly wide urinary space were observed. Podocytes had dark nuclei and cytoplasm with organized foot processes. The proximal tubular epithelial cells had rounded eccentric nuclei with prominent nucleolus, regular envelope and organized chromatin. The cytoplasm showed many organized mitochondria, very few lysosomes, rough endoplasmic reticulum with mild dilatation and regular intact double membrane brush border.

The distal tubular epithelial cells had large nuclei with irregular envelope and prominent nucleolus, the cytoplasm had many different sized organized mitochondria, very few small lysosomes and mildly disorganized rough endoplasmic reticulum folded from basement membrane (Figure 12).

### *Statistical results*

Urinary space width was significantly increased in ciprofloxacin group (III) when compared to control group (I) and when compared to the olive oil group (II) was also significantly increased. Also, a statistical significant decrease was noticed in the combined group (IV) and recovery group (V), (Table 1, Figure 13).

There was no statistical significance difference between the control group and the ciprofloxacin group (III) according to ratio of atrophied Bowman's capsules to total number of capsules. But there was a statistical significant increase in ratio in ciprofloxacin group (III) compared to olive oil group (II), (Table 2, Figure 14)

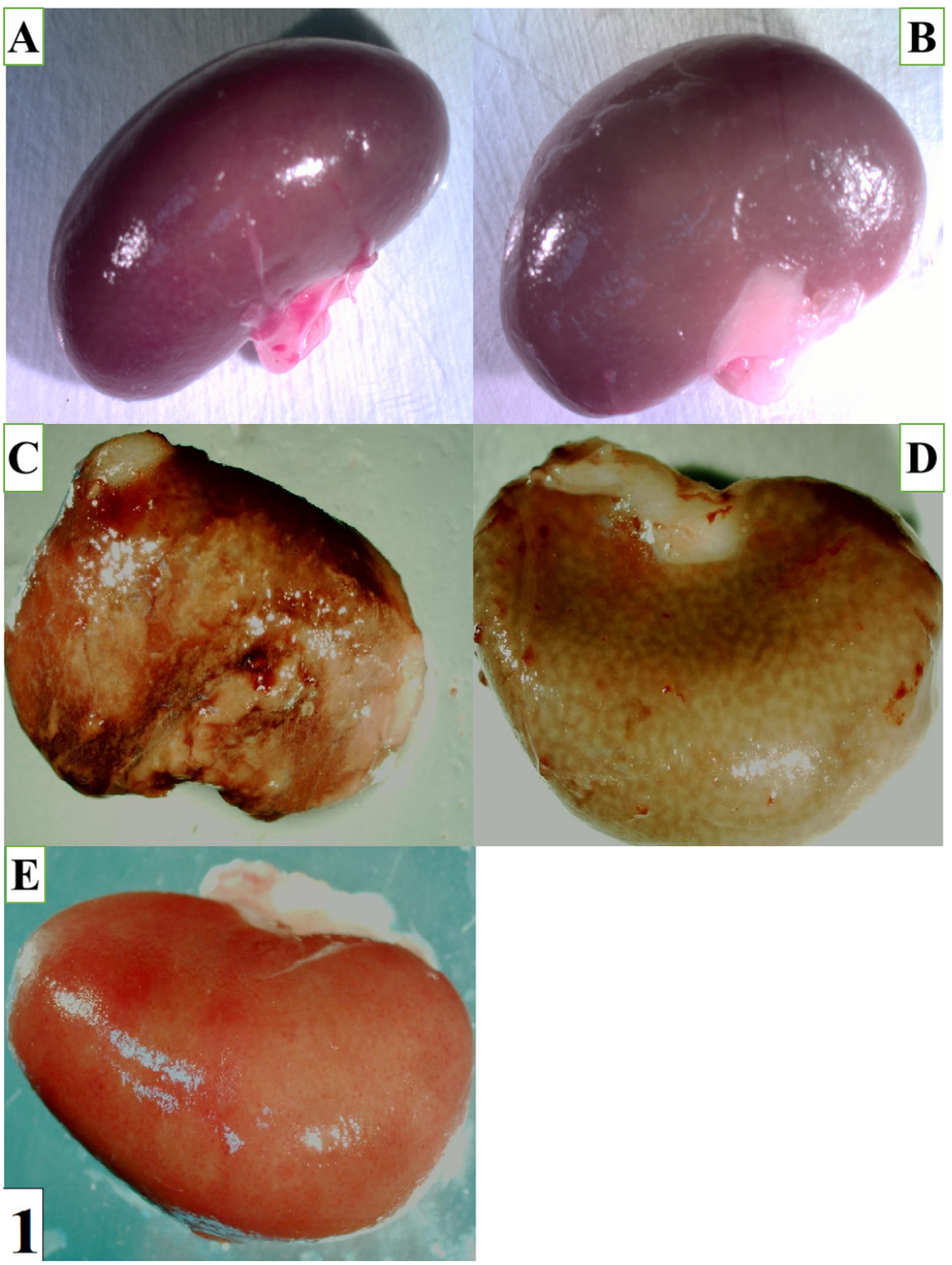


**Fig. 1:** Photographs of kidneys showing A: control group (I) with normal smooth glistening surface. B: olive oil group (II) with normal smooth glistening surface as control group. C: ciprofloxacin group (III) with dark distorted surface with hemorrhagic spots and white necrotic patches. D: combined group (IV) with smooth glistening dark surface with less hemorrhagic spots than group III and no necrotic white patches. E: recovery group (V) showing normal smooth glistening surface with no hemorrhagic spots or necrotic white patches or detached capsule as control group.

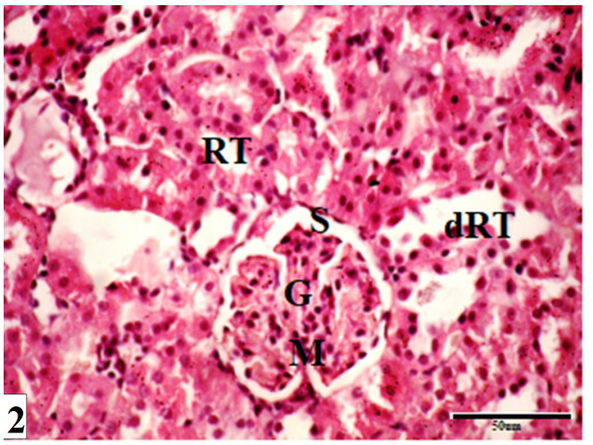


**Fig. 2:** Paraffin section photomicrograph of rat`s renal cortex of control group (I), showing an organized renal cortex, normal organized renal tubules (RT) have closed lumen with well organized brush border in proximal tubules. Other tubules are mildly dilated (dRT), tubular cells have dark rounded nuclei and homogenous dark pink cytoplasm, glomerulus (G) has mesangial cells (M) with dark nuclei and well preserved urinary space (S). (H&E stain Mic Mag X400)

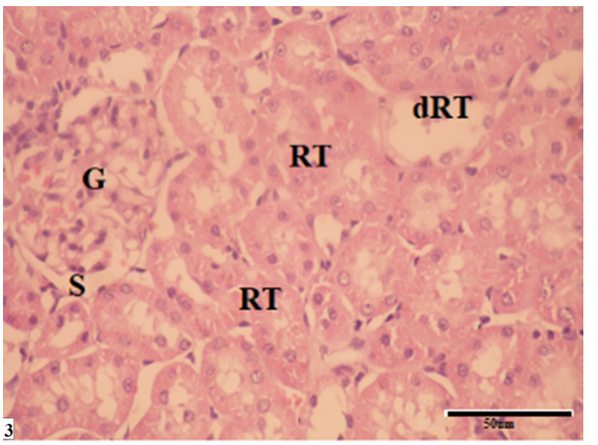


**Fig. 3:** Paraffin section photomicrograph of rat's renal cortex of olive oil group (II), showing the classical appearance of renal cortex. Many normal renal tubules (RT) having narrow lumina, proximal tubules occluded by well-organized brush border. They are lined by pyramidal cells with deeply stained pink cytoplasm and basal nuclei and distal tubular cells have dark rounded nuclei and homogenous dark pink cytoplasm. Normal glomerulus (G) with a well preserved urinary space (S) and mesangial cells were also seen. (H&E stain Mic Mag X400)

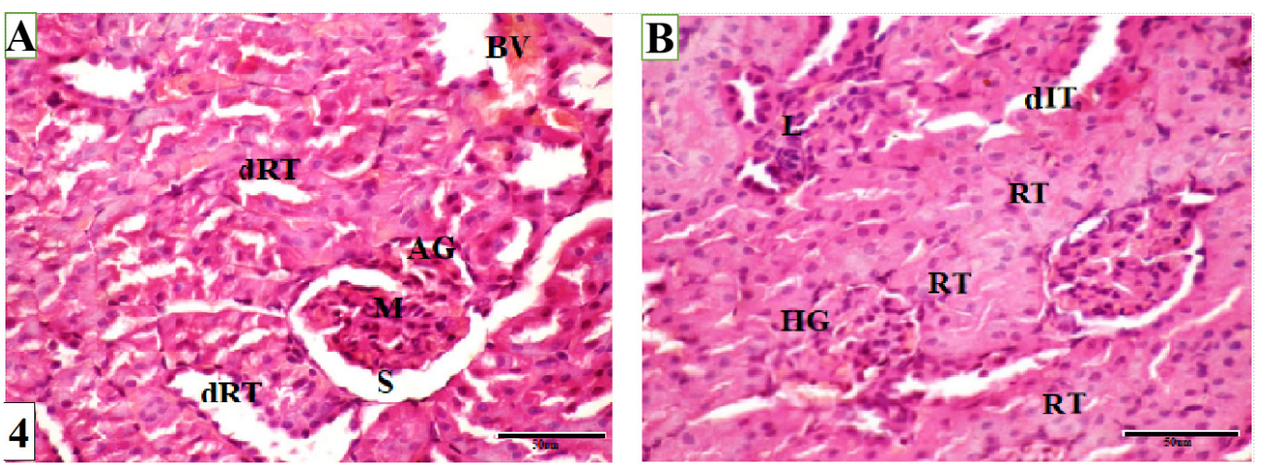


**Fig. 4:** Paraffin section photomicrograph of rat's renal cortex of ciprofloxacin group (III), showing A: crowded necrotic renal tubules with marked dilated lumen (dRT), tubular epithelial cells with dark nuclei. Atrophied glomerulus (AG) with organized basophilic mesangial cells (M) and wide urinary space (S) and congested blood vessel (BV) were seen. B: destructive atrophied structure of the renal cortex was showed. Large number of hyperemic glomeruli (HG) without urinary space and proliferating mesangial cells, an area of aggregated lymphocytes (L) and necrotic and crowded proximal and distal renal tubules (RT) with absent lumen and dilated interstitial tissue spaces (dIT) were seen. (H&E stain Mic Mag A X400, B X400)

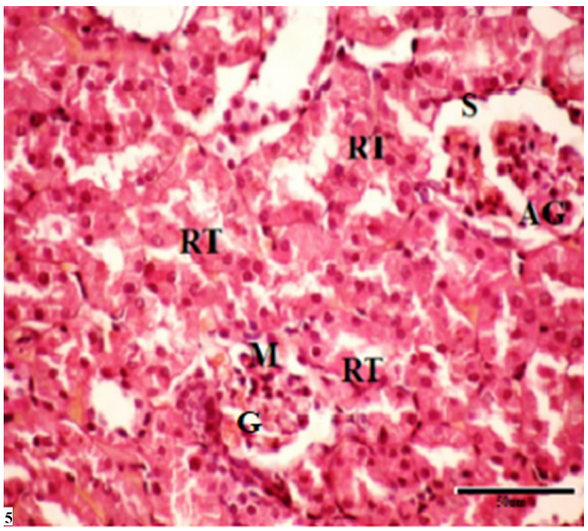


**Fig. 5:** Paraffin section photomicrograph of rat's renal cortex of combined group (IV), showing mild disorganization of the renal cortex, organized renal tubules (RT), tubular cells have dark rounded nuclei and homogenous pink cytoplasm, closed lumen with well organized brush border in proximal tubules, one mildly atrophied glomerulus (AG) with mesangial cells (M) have dark nuclei and dilated urinary space (S). Also, another organized normal glomerulus (G) with organized basophilic mesangial cells (M) was seen. (H&E stain Mic Mag X400)

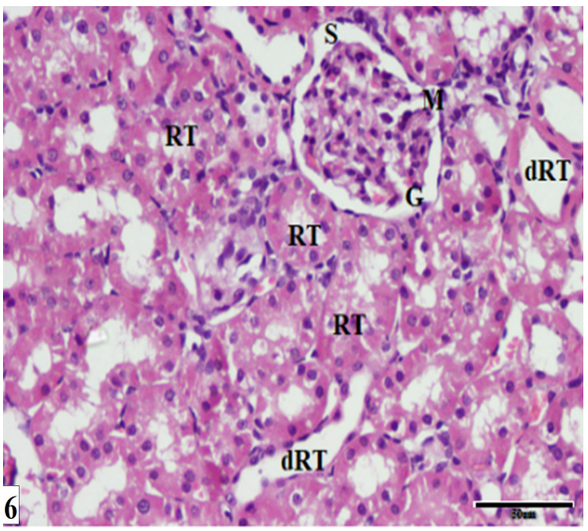


**Fig. 6:** Paraffin section photomicrograph of rat's renal cortex of recovery group (V), showing regenerative structure of renal cortex with mild disorganization, few mildly dilated renal tubules (dRT), others are normal organized tubules (RT) and tubular cells have dark rounded nuclei and basophilic cytoplasm, and an organized normal glomerulus (G) with basophilic mesangial cells (M) and well preserved urinary space (S). (H&E stain Mic Mag X400)

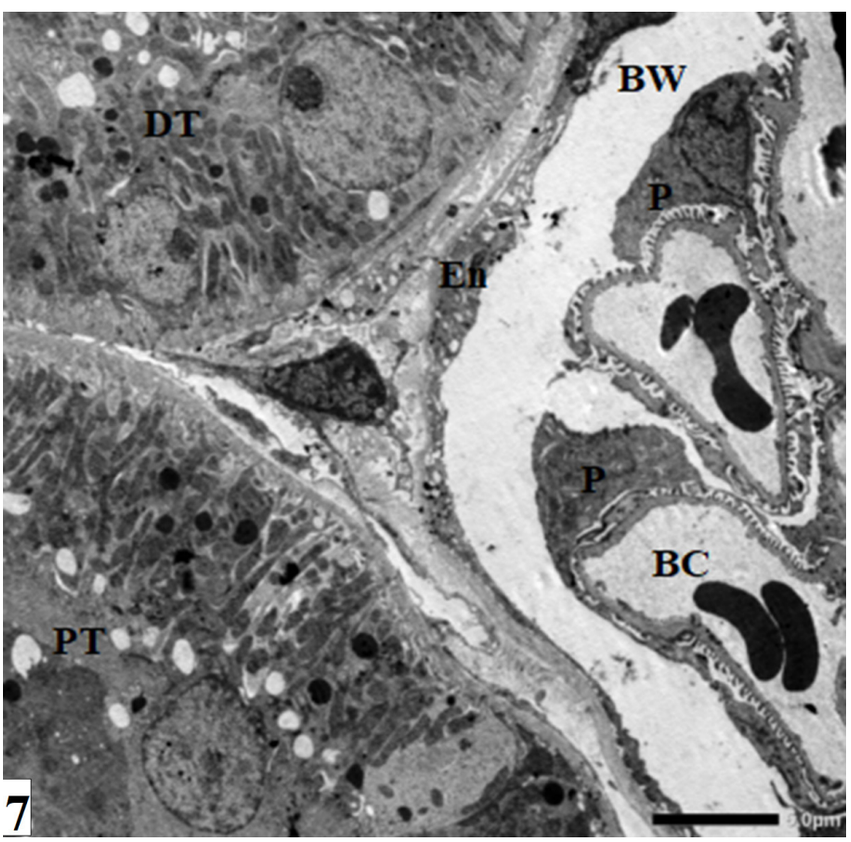


**Fig. 7:** An electron photomicrograph of rat's renal cortex of control group (I) showing proximal tubular (PT) cell, distal tubular cell (DT) associated with Bowman's capsule (BW) (podocytes (P), blood capillaries (BC) and endothelial cells (En)). (Mic Mag 1500)

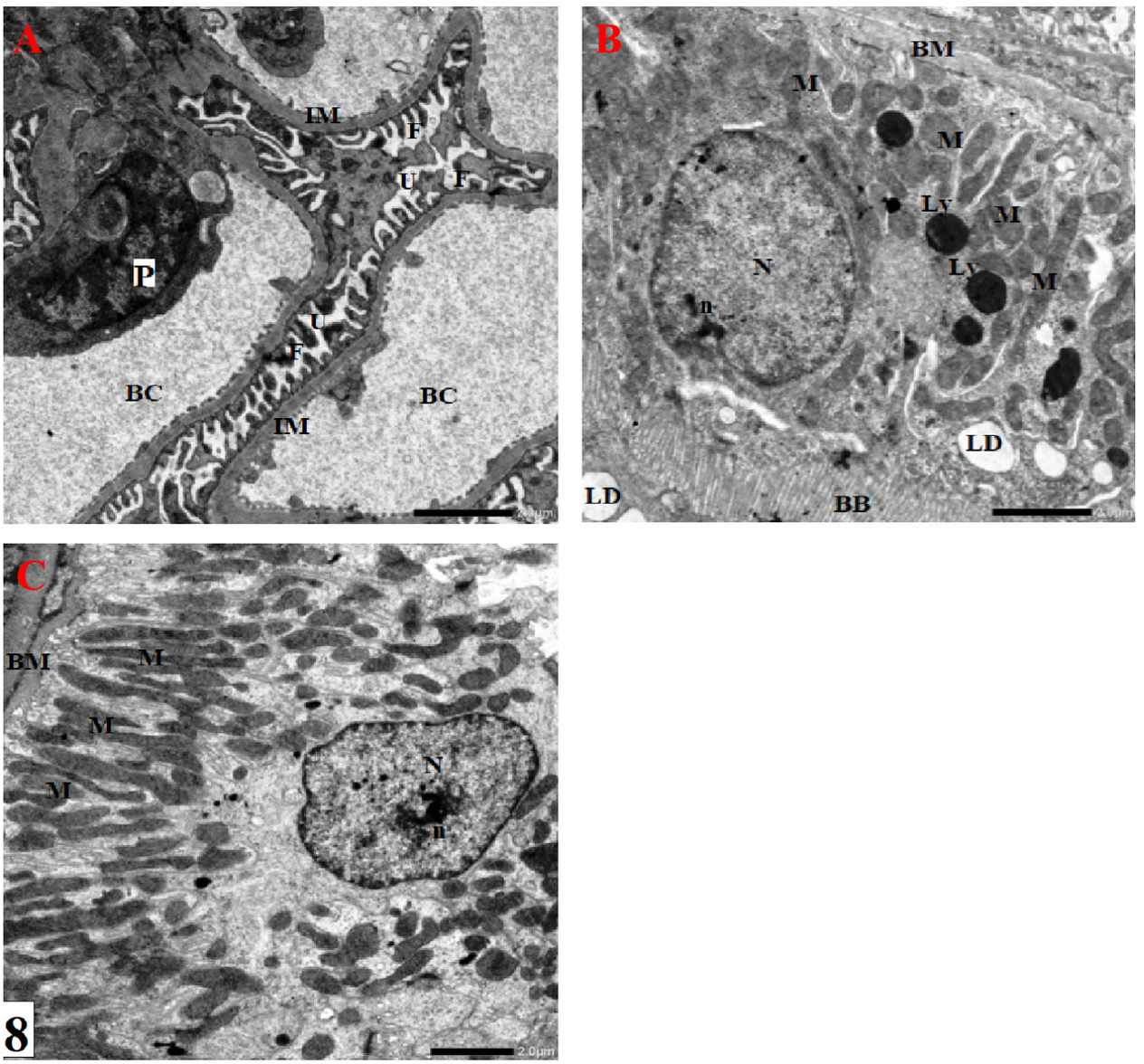


**Fig. 8:** An electron photomicrograph of rat's renal cortex of control group (I) showing A: glomerulus has small blood capillaries (BC), thin infiltrating membrane (IM) and normal foot processes (F). A podocyte (P) with dark nucleus and dark cytoplasm and narrow urinary space (U) was shown. B: proximal tubule cell resting on thin well defined basement membrane (BM) with basal infoldings accommodating many organized mitochondria (M) with prominent lamellar cristae. The apical cytoplasm shows well developed brush border (BB). Lysosomes (Ly) and lipid droplets (LD) were also seen. An euchromatic nucleus (N) with prominent nucleolus (n) and differentiated chromatin was also shown. C: distal tubule cell resting on a well defined basement membrane (BM) with basal infoldings, normal organized parallel mitochondria (M) and central euchromatic nucleus (N) with prominent nucleolus (n). (Mic Mag A*3000, B*3000, C*3000)

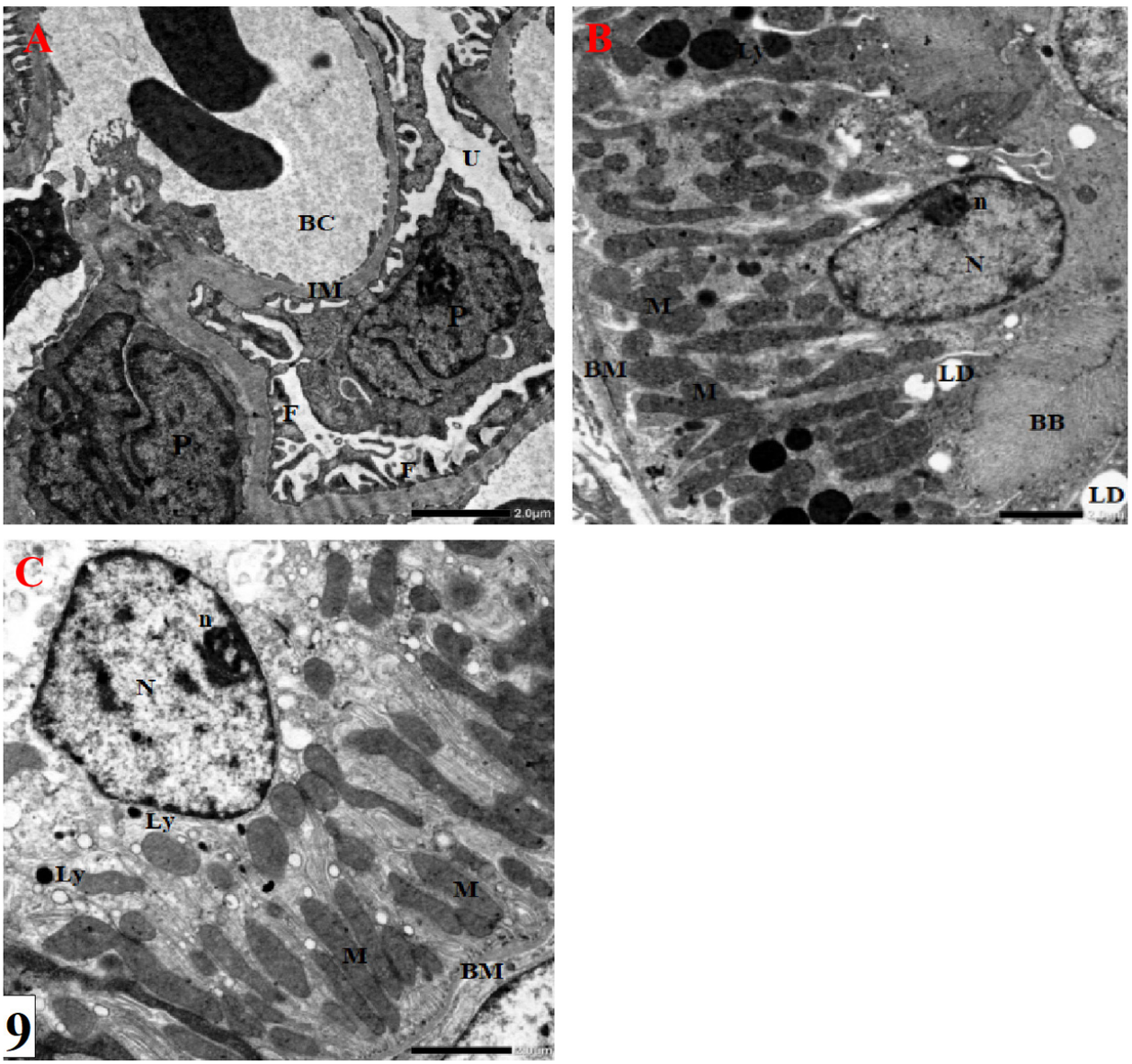


**Fig. 9:** An electron photomicrograph of rat's renal cortex of olive oil group (II) showing glomerulus has small blood capillaries (BC), thin infiltrating membrane (IM) and normal foot processes (F). Podocytes (P) with dark nuclei and dark cytoplasm and narrow urinary space (U). B: proximal tubule cell resting on thin well defined basement membrane (BM) with basal infoldings accommodating many organized parallel mitochondria (M) with prominent lamellar cristae. The apical cytoplasm shows well developed brush border (BB). Lysosomes (Ly) and lipid droplets (LD), an euchromatic nucleus (N) with prominent nucleolus (n) and differentiated chromatin were also seen. C: distal tubule cell resting on a well defined basement membrane (BM) with basal infoldings, normal organized parallel mitochondria (M) and central euchromatic nucleus (N) with prominent nucleolus (n). Lysosomes (Ly) were also seen. (Mic Mag A*3000, B*3000, C*3000)

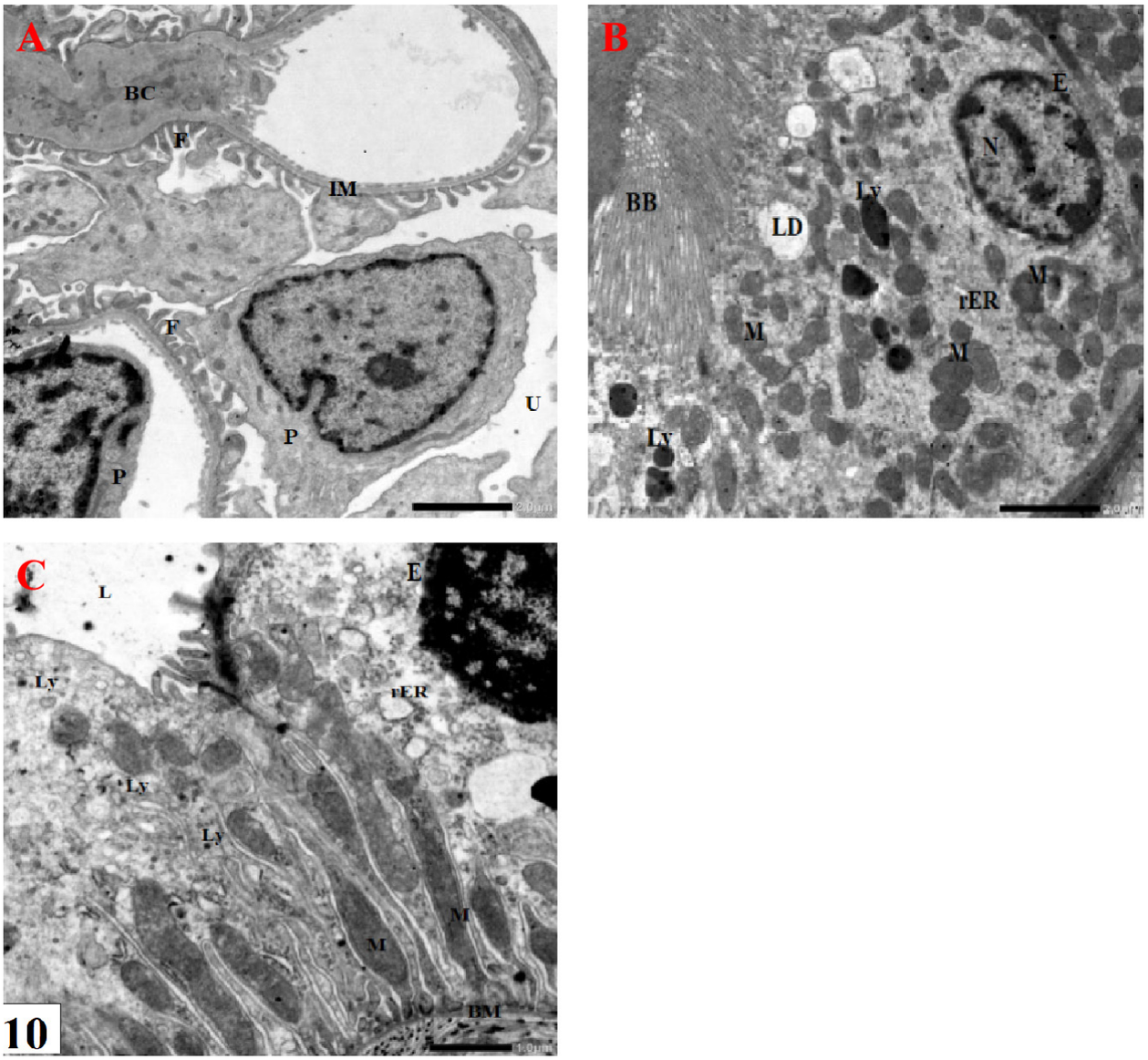


**Fig. 10:** An electron photomicrograph of rat's renal cortex of ciprofloxacin group (III) showing glomerulus has marked dilated blood capillaries (BC) and thick infiltrating membrane (IM) with wide foot processes (F) Podocytes (P) with light nucleus and light cytoplasm. Dilated urinary space (U). B: proximal tubular cell with centric nucleus (N), irregular envelope (E) and clumped chromatin, light cytoplasm has different sized and shaped mitochondria (M) (many small, some large and dark and others with dark dots), many large lysosomes (Ly), large lipid droplets (LD), marked irregular and dilated brush border (BB) associated with residual microsomes, short and dilated rough endoplasmic reticulum (rER) and thick basement membrane (BM). C: distal tubule cell has small dark rounded nucleus (N) with irregular envelop (E) and clumped chromatin as the heterochromatin migrated toward marked dilated lumen (L), with disorganized micro-vacuoles, bizarre disorganized mitochondria (M) and small destructive and atrophied ones and markedly dilated rough endoplasmic reticulum (rER). Many small lysosomes (Ly) and dilated Golgi complex with thin basement membrane (BM) were seen. (Mic Mag A*3000, B*3000, C*5000)

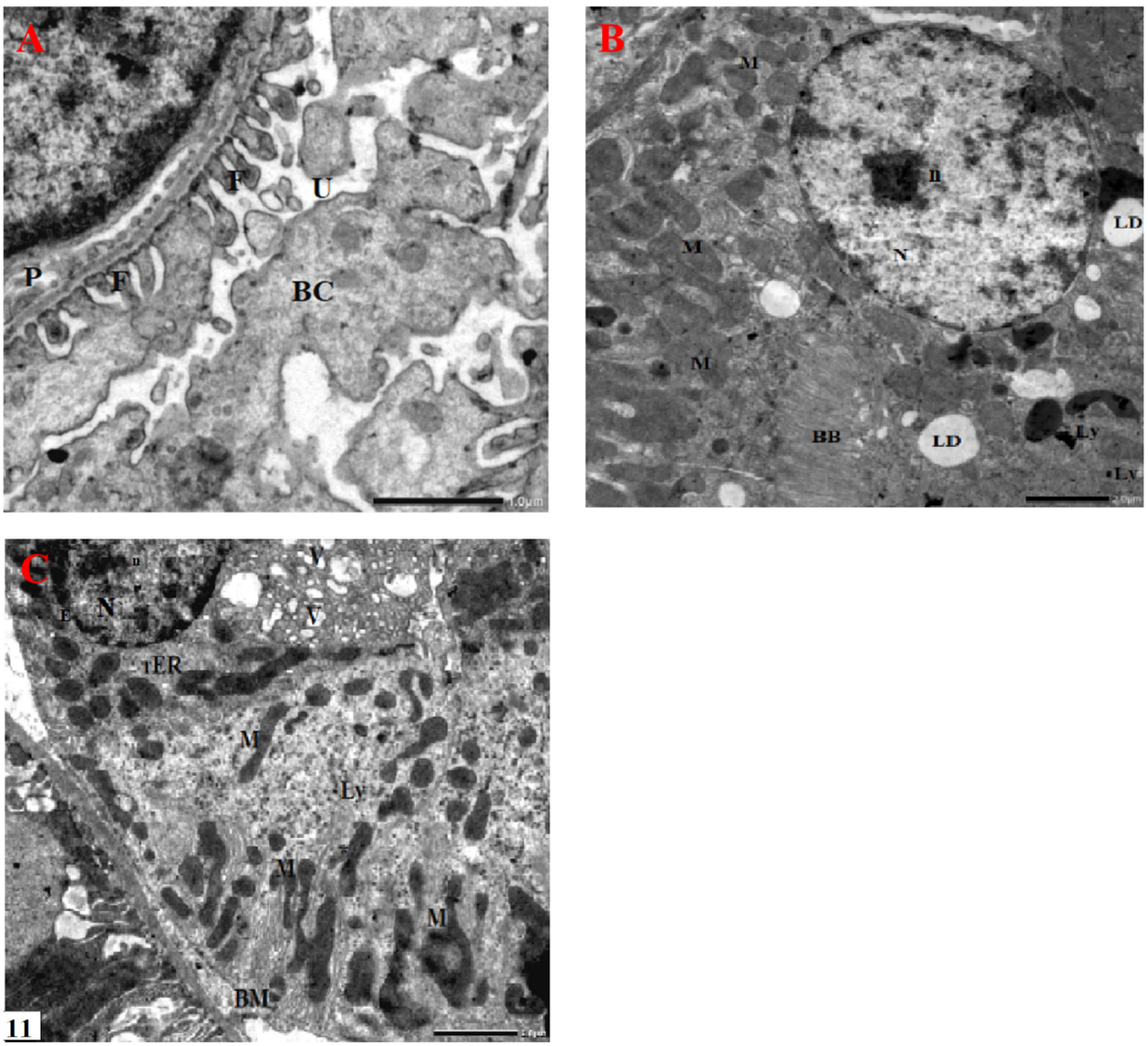


**Fig. 11:** An electron photomicrograph of rat's renal cortex of combined group (IV) showing glomerulus has a podocyte (P) with dark nucleus, short foot processes (F), small blood capillaries (BC) with infiltrating membrane and mildly dilated urinary space (U). B: proximal tubule cell has thin regular defined basement membrane (BM), rounded euchromatic eccentric nucleus (N) with prominent nucleolus, cytoplasm showed many organized mitochondria (M) with lamellar cristae, few lysosomes (Ly) and different sized lipid droplets (LD) and double membrane short organized brush border (BB). C: distal tubule cell resting on normal well defined basement membrane (BM) with basal infoldings, has a rounded nucleus (N) with regular envelope (E) and prominent nucleolus (n), cytoplasm showing different sized mitochondria (M); some long organized and parallel, others are disorganized with dark dots, many vesicles (V), mildly dilated rough endoplasmic reticulum (rER) and few small lysosomes (Ly). (Mic Mag A*5000, B*3000, C*5000)

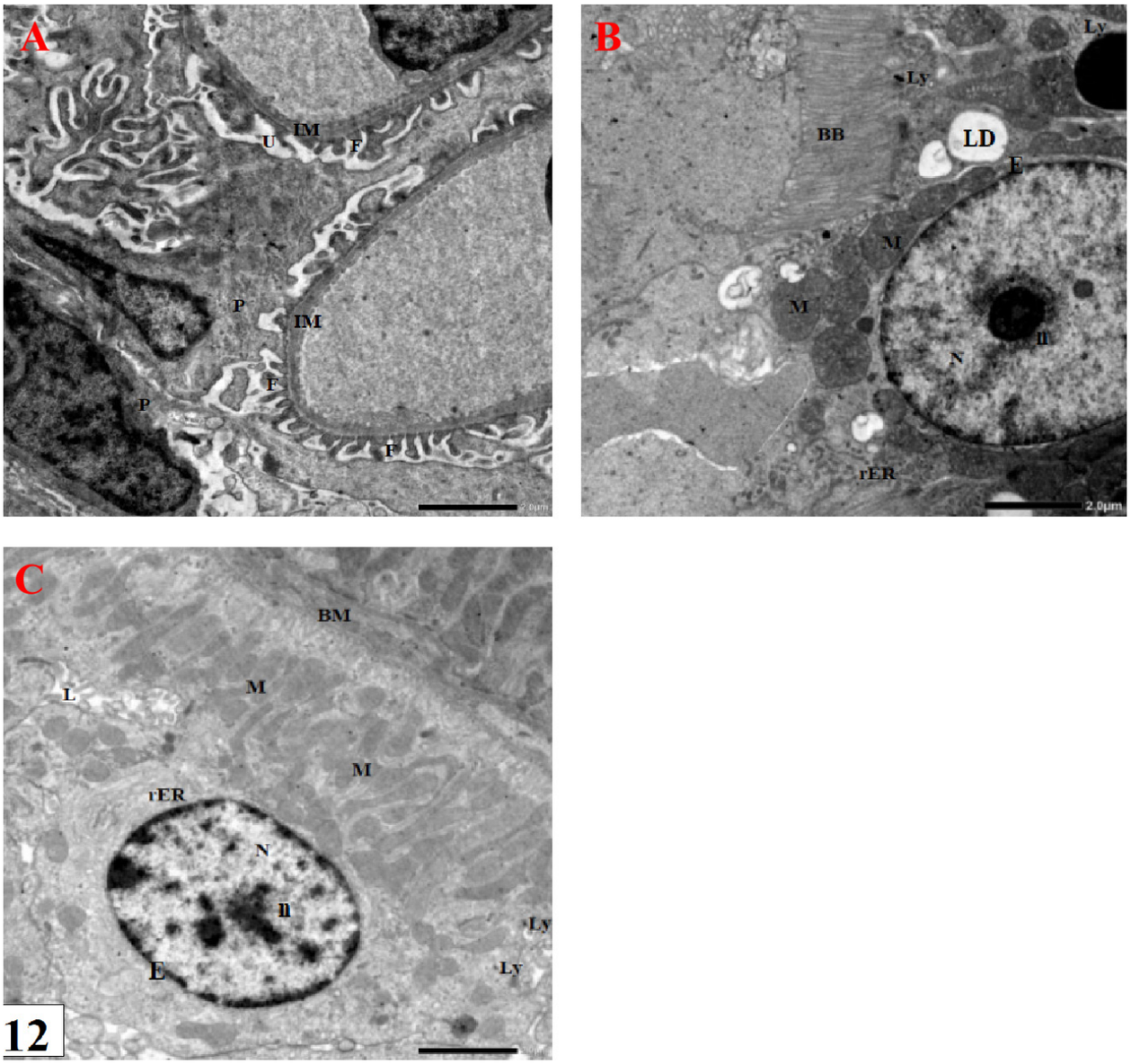


**Fig. 12:** An electron photomicrograph of rat renal cortex of recovery group (V) showing glomerulus has small blood capillaries (BC) and infiltrating membrane (IM). Foot processes (F). Podocytes (P) with dark nuclei and dark cytoplasm. Narrow urinary space (U). B: proximal tubule cell has rounded nucleus (N) with prominent nucleolus (n), regular envelope (E) with differentiated chromatin, cytoplasm showed many organized normal mitochondria (M), very few lysosomes (Ly), few lipid droplets (LD), normal rough endoplasmic reticulum (rER) and regular double membrane brush border (BB). C: distal tubule cell has large nucleus (N) with mildly irregular envelope (E) and prominent nucleolus (n), many different sized organized mitochondria (M), very few small lysosomes (Ly), normal rough endoplasmic reticulum (rER) folded to basement membrane (BM) and narrow lumen (L). (Mic Mag A*3000, B*3000, C*3000)

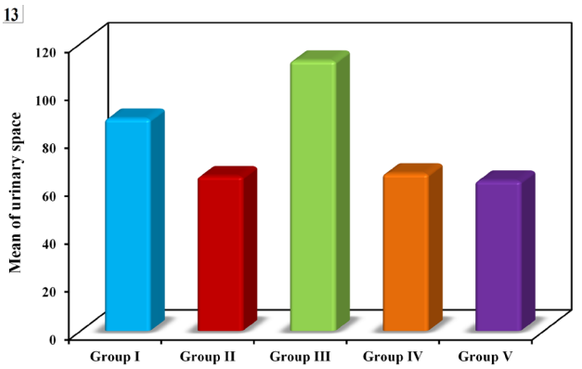


**Fig. 13:** Comparison between the different studied groups according to the width of urinary space.

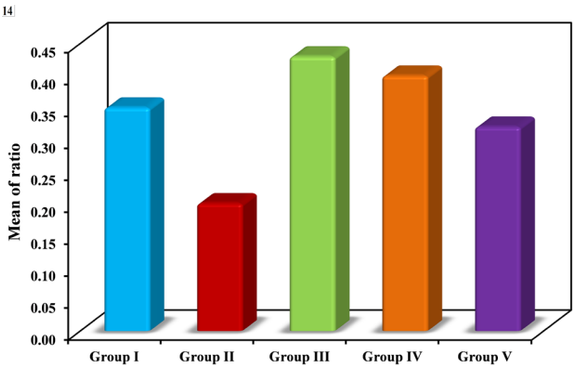


**Fig. 14:** Comparison between the different studied groups according to the ratio between number of atrophied corpuscles to total number of corpuscles.

**Table 1:** Comparison between the different studied groups according to the width of urinary space

| Urinary space | Group I (n = 8) | Group II (n = 8) | Group III (n = 8) | Group IV (n = 8) | Group V (n = 8) | F (*p*) |
|---|---|---|---|---|---|---|
| Min. | 74.13 | 45.36 | 100.96 | 39.30 | 40.45 | |
| Max. | 105.99 | 78.58 | 122.8 | 94.83 | 81.08 | |
| Mean | $88.69^{b}$ | $64.60^{c}$ | $112.9^{a}$ | $65.71^{c}$ | $62.70^{c}$ | F=21.134* (*p*<0.001*) |
| ±SD. | 10.88 | 10.65 | 8.10 | 18.41 | 16.2 | |
| Median | 87.11 | 65.05 | 116.4 | 62.79 | 62.11 | |
| $p_1$ | | 0.006* | 0.005* | 0.009* | 0.002* | |
| $p_2$ | | | <0.001* | 1.000 | 0.999 | |
| Sig. bet. grps. | | | $p_3$<0.001*,$p_4$<0.001*,$p_5$=0.991 | | | |

SD: Standard deviation
F: F for One way ANOVA test, Pairwise comparison bet. each 2 groups was done using Post Hoc Test (Tukey)
*p*: *p value* for comparing between the studied groups
$p_1$: *p value* for comparing between Group I and each other group
$p_2$: *p value* for comparing between Group II and each other group
$p_3$: *p value* for comparing between Group III and Group IV
$p_4$: *p value* for comparing between Group III and Group V
$p_5$: *p value* for comparing between Group IV and Group V
*: Statistically significant at $p \leq 0.05$

**Table 2:** Comparison between the different groups according to the ratio of atrophied glomeruli number to total number of glomeruli

| Ratio | Group I (n = 8) | Group II (n = 8) | Group III (n = 8) | Group IV (n =8) | Group V (n = 8) | F (*p*) |
|---|---|---|---|---|---|---|
| Min. | 0.29 | 0.0 | 0.20 | 0.29 | 0.22 | |
| Max. | 0.45 | 0.29 | 0.78 | 0.45 | 0.40 | |
| Mean | $0.35^{ab}$ | $0.20^{b}$ | $0.43^{a}$ | $0.40^{a}$ | $0.32^{ab}$ | F=3.720* (*p*=0.017*) |
| ±SD. | 0.06 | 0.10 | 0.20 | 0.06 | 0.07 | |
| Median | 0.33 | 0.24 | 0.44 | 0.42 | 0.31 | |
| $p_1$ | | 0.180 | 0.745 | 0.933 | 0.991 | |
| $p_2$ | | | 0.014* | 0.037* | 0.373 | |
| Sig. bet. grps. | | | $p_3$=0.992,$p_4$=0.472,$p_5$=0.731 | | | |

SD: Standard deviation
F: F for One way ANOVA test, Pairwise comparison bet. each 2 groups was done using Post Hoc Test (Tukey)
*p*: *p value* for comparing between the studied groups
$p_1$: *p value* for comparing between Group I and each other group
$p_2$: *p value* for comparing between Group II and each other group
$p_3$: *p value* for comparing between Group III and Group IV
$p_4$: *p value* for comparing between Group III and Group V
$p_5$: *p value* for comparing between Group IV and Group V
*: Statistically significant at $p \leq 0.05$

## DISCUSSION

Ciprofloxacin has an efficacy against different bacterial species but it has nephrotoxic side effects. Its use can cause acute renal failure secondary to interstitial nephritis, which is caused by hypersensitivity reaction type III (immune-mediated interstitial injury) with an infiltrate composed of lymphocytes, plasma cells, neutrophils, and eosinophils[39]. Also, it is associated with the development of a hypersensitivity vasculitis. It is thought that the drug is metabolized to reactive intermediate compounds by MPO (anti-myeloperoxidase). These reactive metabolites may act as a hapten for MPO resulting in the formation of antiMP antibodies[40].

Experimentally, ciprofloxacin nephrotoxicity may also result from the crystallization of ciprofloxacin and its metabolites, with magnesium and proteins leading to intrarenal obstruction and inflammatory changes in the renal tubular walls[41,42].

In this study, the anatomical examination of the kidney of the rats treated by ciprofloxacin revealed hemorrhagic spots and white necrotic patches. The histopathological examination of renal cortices confirmed the anatomical findings as it revealed a variety of degenerative histological changes. At level of glomerulus, some glomeruli were atrophied with marked dilatation of urinary space, some were hyperemic and others were normal. Proximal and distal convoluted tubules showed necrotic changes and wide lumen and others were crowded with occluded lumen, also congested blood vessels and wide interstitial tissue spaces were showed. These findings were in agreement with Elbe. *et al*.[13] who stated that ciprofloxacin caused inflammation, tubular atrophy and lumen dilatation, reduction of Bowman's space, congestion and necrosis in the renal tissue.

Also, ultrastructural histopathological examination revealed marked disorganization of the glomerulus with markedly dilated urinary space and blood capillaries. Proximal and distal tubular cells showed marked organelle affection, different sized disorganized mitochondria, short dilated rough endoplasmic reticulum, many large lysosomes and large lipid droplets. These findings go hand in hand with AL-Rikaby. *et al*.[43] who declared that ciprofloxacin caused vacuolation of tubular cells and dilatation of tubules. Also, Abdullah. *et al*.[44] who stated that ciprofloxacin caused glomerular atrophy and renal cell toxicity that led to necrosis and degeneration of tubular cells. They both attributed all of these to the ROS induced lipid peroxidation in cell membrane and organelles. Malondialdehyde (MDA) is one of the most important end products of lipid peroxidation and is known to be an indicator of free radical damage. The double bonds in membrane polyunsaturated lipids are disrupted by free radicals. Peroxides are produced as a result of unstable and reactive lipid-radical interactions, resulting in an autocatalytic chain reaction.

Free radical reactions can also cause DNA fragmentation and polypeptide fragmentation. Free radical interactions with thymine in nuclear and mitochondrial DNA cause single-strand breaks. Cell death, ageing, and malignant transformation of cells have all been linked to DNA damage. This could account for the current nuclear damage, which included necrosis and apoptosis. Oxidative stress has an impact on a variety of intracellular targets, including proteins, lipids, and nucleotides[45].

Those findings may provide an explanation for the mechanism of ciprofloxacin induced nephrotoxic adverse effects. Ahmed. *et al*.[46] reported similar rates of nephrotoxicity in experimental animals treated with ciprofloxacin in a higher dose (80mg/kg) with marked hemorrhagic renal cast in the lumen of the tubules. Degenerated and desquamated epithelium of some medullary tubules. On high power there was swelling with vascular degeneration of the tubular epithelium and the presence of hemorrhagic cast in the Bowman's space and thickening of Bowman's sac.

Also, Hashim. *et al*.[14] stated that ciprofloxacin use in a higher dose (100mg/kg) caused dilation of Bowman's space with atrophy of some glomeruli, while in other sections there was tubular dilation and sloughing of epithelium of renal tubules.

Approximately, 80% of clinical drugs bio transformation happened by three families of cytochrome P450 oxidase (CYP) CYP1, 2, and 3. CYP 1a2, CYP3a4 and CYP2c9 are among the enzymes responsible for ciprofloxacin metabolism. CYP1a2 and CYP3a4 are inhibited by CIP as stated by Abdelgadir. *et al*.[47] whose study showed that ciprofloxacin dose (40 mg/kg) caused severe damage of renal tissue; mesangium, podocytes and tubulointerstitial cells were affected. Glomerular and tubular hypertrophy in addition to tubular necrosis and dilatation were observed. Also, a higher dose of ciprofloxacin (80 mg/kg) caused sever tubular necrosis, inflammatory cell diffusion and disturbance in distal and proximal convoluted tubules structure and congestion of blood vessels.

Vitamin E, oleocanthal, carotenoids, and polyphenols are of the powerful antioxidants found in VOO, all of which have been studied and shown to enhance human health[21].

In the present study of the groups received olive oil wither with ciprofloxacin or after it, the anatomical examination of kidney organs appeared with smooth glistening pink surface with much less hemorrhagic spots. Histopathological examination showed decrease in number of atrophied glomeruli and of necrotic tubular epithelial cells and narrowing of tubules lumen. The ultra structural examination revealed a recovery in most renal tubular cells as well as the glomerulus ultrastructure, there was reorganization of mitochondria and the brush border of the proximal tubular cell and reduction of the distal tubule lumen and of the basal membrane thickness and rearrangement of basal infoldings, organization of mitochondria and other organelles.

Serreli. *et al*.[48] demonstrated that consumption of a diet rich in VOO polyphenols metabolites was in associated with the ability to prevent the exacerbation of inflammation and oxidative stress at cardiovascular and gastrointestinal levels in particular.

Castaner. *et al*.[49] stated that polyphenols can protect cells not only by scavenging free radicals, but also by modifying signal transduction, cell signaling, gene expression, and cellular communication through various mechanisms.

Mokhtari. *et al*.[50] evaluated the effects of virgin olive oil on ethephon-induced nephrotoxicity in rats and demonstrated that VOO could decline ethephon-induced nephrotoxicity by improving the kidney function and tubular necrosis. In a parallel investigation, Wani. *et al*.[28] stated that administration of extra-VOO reduced cadmium -induced nephrotoxicity in mice. Olive Oil's beneficial effects were due to reduction of ROS which cause direct damage to the podocyte and tubulointerstitial levels. VOO inhibits the lipid and protein peroxidation and improves the antioxidant mechanism because of their high phenolic compounds. Besides phenolic compounds, other compounds have beneficial effects include monounsaturated fatty acids, oleic acid and tocopherols.

In a parallel investigation, Bakeer. et, al.[51] proved that olive oil produced a significant increase of antioxidant parameters, decrease of lipid peroxides and increased tissue alkaline phosphatase which may be due to the fact that antioxidant has an important role in maintaining the physiological integrity of tissue thus protecting it against enzyme leakage. These findings go hand in hand with our results.

In our research we found that olive oil counteracted the side effects of ciprofloxacin on the renal function. Kidney histopathological degenerative effects and ROS formation were decreased by olive oil.

## CONFLICT OF INTERESTS

There are no conflicts of interest.

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**الملخص العربى**

# تأثير مادة السيبروفلوكساسين على القشرة الخارجية لكلية الفأر الأبيض و الدور الوقائى المحتمل لزيت الزيتون : دراسة تشريحية و هستولوجية

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**الخلفية:** السيبروفلوكساسين مضاد حيوى يستخدم فى علاج العديد من الالتهابات البكتيرية و لكنه يسبب ضرر بالكلي كأثر جانبى.

**الهدف:** دراسة الدور الوقائي لزيت الزيتون ضد الضرر المسبب بالسيبروفلوكساسين للقشرة الكلوية فى الجردان.

**المواد و طرق البحث:** أربعون جرذا بالغا من الجرذان البيضاء : بمتوسط وزن ١٥٠ الى ٢٠٠ جرام قسمت عشوائيا الى خمسة مجموعات. تلقوا الأدوية عن طريق أنبوب المعدة لمدة ١٤ يوما.

المجموعة الأولى (مجموعة الضابطة)، مجموعة زيت الزيتون البكر تلقوا زيت الزيتون ٥ مم/كجم (المجموعة الثانية). مجموعة السيبروفلوكساسين تلقوا ٢٠ مجم/ كجم مذابة فى ٨ مم ماء مقطر (المجموعة الثالثة). المجموعة المشتركة تلقوا السيبروفلوكساسين و زيت الزيتون بنفس الجرعات السابقة (المجموعة الرابعة). مجموعة التعافى تلقوا السيبروفلوكساسين بنفس الجرعة لمدة ١٤ يوما ثم بعدها زيت الزيتون بنفس الجرعة السابقة و تم الذبح بعد شهر من إنتهاء التجربة.

**النتائج:** اظهرالسطح الخارجى للكلية بقع دموية و بقع تنخر بيضاء فى المجموعة المعالجة بالسيبروفلوكساسين. كما اظهر الفحص للانسجة ضرر طفيف بالحويصلة وتنخر بخلايا الأنابيب الكلوية. كانت التغيرات على مستوى التركيب الدقيق للخلايا تشوهات الميتوكوندريا واتساع بحدود الفرشاة للأنابيب القريبة, تنخر بخلايا الأنابيب البعيدة وزيادة فى عدد الليسوسومات و اتساع بالزوائد القدمية و اتساع بالفراغ البولى للحويصلة. بينما أظهرت المجموعة المشتركة مستوى كبير من الحماية و استرجاع للهيكل الطبيعى المنتظم للحويصلة مع اتساع طفيف بالفراغ البولى و تأثير طفيف بالأنابيب. كذلك مجموعة التعافى أظهرت استرجاع كامل للهيكل بما يقرب الاشكل الطبيعى.

**الاستنتاج:** النتائج الهستوباثولوجية أظهرت تأثير قوى مدمر للسيروفلوكساسين على الأنابيب الكلوية و لكن تأثير بسيط على الحويصلة و الذى يمكن استرجاعه بتناول زيت الزيتون . كان الدور الوقائى لزيت الزيتون مستمر.