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Original Article

Role of Silymarin in ameliorating the harmful effects of Diclofenac sodium on renal cortex of the adult male albino rat: Histological and immunohistochemical study

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ABSTRACT

Introduction: Non-steroidal anti-inflammatory drugs are well known as nephrotoxic drugs. Diclofenac sodium is one of the NSAIDs. Silymarin protective effect on kidney have been proven experimentally against many nephrotoxic drugs.

Aim: This work aimed to study the possible role of Silymarin in ameliorating the harmful effects of Diclofenac sodium on renal cortex of the adult male.

Material and Methods: Forty-five adult male albino rats were used in this study. They were equally divided into three groups: Group I: was further equally subdivided into: Group IA: kept as a negative control, Group IB: received 4 ml of distilled water/Kg BW (body weight) and Group IC: received 100 mg of Silymarin/kg BW. Group II: received 4mg of Diclofenac sodium/kg BW. Group III: received 4mg of Diclofenac sodium /kg BW in addition to 100mg of Silymarin /kg BW. All drugs and vehicles were administered orally by gastric tube once daily for two consecutive weeks.

Results: The present work revealed marked histological changes of the renal cortex of group II that received Diclofenac in the form of tubular cells vacuolations with luminal dilatation, shrinking glomeruli and widening of Bowman's space. Group III that received Diclofenac in addition to Silymarin showed nearly regular structure of the renal cortex.

Conclusion: Silymarin greatly protected the renal cortex from Diclofenac induced histological and immunohistochemical changes.

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Key Words: Diclofenac sodium, renal cortex, silymarin.

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INTRODUCTION

Drug-induced nephrotoxicity is considered a major cause of acute kidney damage and it is responsible for 20% of hospital admissions. Mechanisms for drug-induced nephrotoxicity include tubular cell toxicity, glomerulonephritis, interstitial nephritis and microangiopathy. Non-steroidal anti-inflammatory drugs (NSAIDs) are well known as nephrotoxic drugs. Strategies have been proposed to decrease their nephrotoxicity such as good hydration and avoidance of concurrent use of other nephrotoxic drugs. However, they remain a major cause of morbidity and mortality[1,2].

Diclofenac sodium is one of the NSAIDs that acts as an anti-inflammatory, analgesic and antipyretic under many trade names such as Cataflam, Voltaren and others. It is the most world's used NSAIDs[3]. It acts by preventing prostaglandin synthesis by inhibiting cyclooxygenase enzyme activity in cells. Therefore, it is used for the treatment of many inflammatory diseases as in rheumatoid arthritis and acute muscle pain. The toxic doses of Diclofenac sodium proved to cause nephrotoxicity in humans and in experimental animals[4].

Silymarin is an extract from milk thistle plant (Silybum marianum) that has a good safety profile. Silymarin is a worldwide used natural remedy for many liver diseases as in hepatitis, gall bladder disorders and iron overload[5,6]. It has been proven to be a powerful free radicals' scavenger[7] and it has shown to have anti-inflammatory

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and anti-carcinogenic action in experimental animals[8]. Silymarin protective effect on kidney have been experimentally investigated against many nephrotoxic drugs such as Adriamycin[9], Gentamycin[10] and Cyclosporine[11] and it proved to decrease or prevent their nephrotoxicity. To our Knowledge there has been no study to show the histological and immunohistochemical protective role Silymarin against Diclofenac effects on the renal cortex. Therefore, the present work aimed to study the possible role of Silymarin in ameliorating the histological and immunohistochemical effects of Diclofenac sodium on renal cortex.

MATERIAL AND METHODS

Chemicals:

- Diclofenac sodium was purchased in the form of tablets (Epico pharmaceutical Company, Egypt). Each tablet contained 25mg of Diclofenac sodium which was dissolved in 25ml of distilled water.

- Silymarin was purchased in the form of 120ml suspension (Medical Union Pharmaceuticals, Egypt). Each 1ml contained 10mg of Silymarin.

Animals:

Forty-five adult male albino rats were used in this study, aged from 6-8 months, weighting 180 -200 gm. They were obtained and locally bred at the animal house of the medical research center of Faculty of Medicine, Ain-Shams University. Rats were housed in medium sized metal cages (three rats /cage), at room temperature with good ventilation and regular dark/light cycles. Free access to diet and water were allowed, and all rats were kept under the same circumstances throughout the experiment. The experiment followed the guidelines of Ain Shams University Ethics Committee.

Experimental Protocol: Rats were equally divided into three groups:

Group I (Control group): it was composed of fifteen rats that were further equally subdivided into: Group IA (Negative Control): contained five rats that were kept as a negative control with no treatment, Group IB (Vehicle Control): contained five rats that received 4 ml of distilled water/ Kg BW (body weight) and Group IC (Silymarin Control): contained five rats that received 100mg of Silymarin /kg BW.

Group II (Diclofenac group): it was composed of fifteen rats that received 4mg of Diclofenac sodium /kg BW[12].

Group III (Diclofenac + Silymarin group): it was composed of fifteen rats that received 4mg of Diclofenac sodium /kg BW in addition to 100mg of Silymarin /kg BW[13-14]. All drugs and vehicles were administered orally by gastric tube once daily for two consecutive weeks.

By the end of the experimental periods, rats were anesthetized with diethyl ether, both kidneys were carefully dissected and processed for microscopic examination. The rats were then killed by decapitation after collection of the specimens.

Processing of samples:

Preparation of paraffin blocks and staining methods:

Kidneys were fixed in 10% buffered formalin, processed and embedded in paraffin blocks, sectioned longitudinally at 5µm, cut and stained by Hematoxylin and Eosin (H&E)[15] to study the general histological features and other sections were stained with Mallory trichrome stain to clarify the collagen fibers[16].

Immunohistochemical study for the proliferating cell nuclear antigen (PCNA), 5µm sections were used and incubated in mouse monoclonal anti-PCNA antibody (Dako PC10) at a dilution of 1 in 100 in TRIS-buffered saline (pH 7.6) then washed in TBS. PCNA visualization was done using the standard anti-alkaline-phosphatase labelling method[17]. Immunohistochemical study for Desmin were done using mouse anti-Desmin monoclonal antibody (Lab Vision Corp, Neo-markers, Inc /Lab Vision, Fremont, California, USA)[18]. Immunohistochemical study for Caspase-3, sections were washed in phosphate-buffered saline and then incubated with antibody to cleaved Caspase-3 at a dilution of 1:200 (Invitrogen, Sweden AB Stockholm Sweden) overnight at 4°C. Then incubated with (1:500) secondary anti mouse antibody (Invitrogen, Molecular Probes, Eugene, Oregon, USA) for 1h at room temperature

and then incubated in 3,3-diaminobenzidene for 10 min and counterstained by Mayer's hematoxylin and mounted by dibutyl phthalate in xylene[19]. Immunohistochemical control done by omitting the primary antibody and its replacement by phosphate buffered saline to detect any nonspecific binding of the secondary antibody.

Stained sections were examined and photographed using light microscope (Olympus 268M microscope) equipped with an automatic photomicrographic camera system.

Image analysis:

Morphometric analysis was carried out on H&E stained slides using Image j software on a computer in anatomy Department, Faculty of Medicine, Ain Shams University. The computer was connected to Olympus microscope equipped with a digital camera. Six randomly chosen non overlapping fields in six sections obtained from six different animals from the same group were used for measuring the diameter of the proximal tubules and the width of Bowman's space in microns. Pixels were calibrated for actual measurements using a stage micrometer. The magnification used was 400X with an objective lens 40X for the diameter of the proximal tubules and the magnification used was 1000X with an objective lens 100X for the thickness of Bowman's space.

Statistical analysis:

Data analysis was performed using PSPP freeware with one-way ANOVA and Bonferroni Post Hoc test to detect the significance between every two groups. Results were considered highly significant when $P\ value \leq 0.001$, significant when $P\ value \leq 0.05$ and nonsignificant when $P\ value > 0.05$.

RESULTS

Histological Results:

Group I (Control)

Light microscopic examination of H&E stained sections of the renal cortex of the control subgroups IA, IB and IC showed almost the same regular histological appearance of renal corpuscles and its glomerular capillaries that occupies most of the corpuscle, the renal capsule was formed of two layers, an outer layer of simple squamous epithelium and an inner layer formed of podocytes and the two layers were separated by the Bowman's space. The proximal convoluted tubules (PCT) were numerous, lined by cubical cells with brush border of microvilli and they showed basal nuclei and narrow lumina. While, the distal convoluted tubules (DCT) were less numerous, lined by simple cubical cells with minimal microvilli and showed apical or central nuclei and wide lumina (Figs. 1-3). Small interstitial blood vessels were noted. By Mallory Trichrome stain they showed minimal collagen fibers distribution throughout the renal cortex (Fig. 4).

Immunohistochemical staining for Desmin of the control group revealed weak positive immune reaction of the glomerular podocytes (Fig. 5). Whereas, immunohistochemical staining for PCNA revealed, faint positive immune reaction of the tubular cells (Fig. 6). In addition, immunohistochemical staining for Caspase-3 showed negative immune reaction of the cytoplasm of the tubular cells (Fig. 7).

Group II (Diclofenac group)

Light microscopic examination of H&E stained sections of the renal cortex of group II showed marked histological changes in the form of tubular cells vacuolations with luminal dilatation, shrinking glomeruli of renal corpuscles with widening of Bowman's space and dilated congested interstitial blood vessels (Figs. 8-10). Mallory Trichrome stain showed apparent increase of collagen fibers distribution throughout the renal cortex (Fig. 11).

Immunohistochemical staining for Desmin revealed apparent intense positive immune reaction of glomerular podocytes (Fig. 12). Whereas, immunohistochemical staining for PCNA and Caspase-3 revealed apparent intense positive immune reaction of the tubular cells (Figs. 13,14).

Group III (Diclofenac + Silymarin group)

Light microscopic examination of H&E stained sections of the renal cortex of group III showed that most of the renal glomeruli and tubules were having regular structure with apparent average Bowman's space, minimal tubular cell vacuolations and mild dilated congested interstitial blood vessels. (Figs. 15-17). Mallory Trichrome stain showed

minimal collagen fibers distribution throughout the renal cortex (Fig. 18).

Immunohistochemical staining for Desmin of group III revealed apparent mild positive immune reaction of glomerular podocytes (Fig. 19). Whereas, immunohistochemical staining for PCNA and Caspase-3 revealed apparent mild positive immune reaction of the tubular cells (Figs. 20, 21).

Morphometrical results

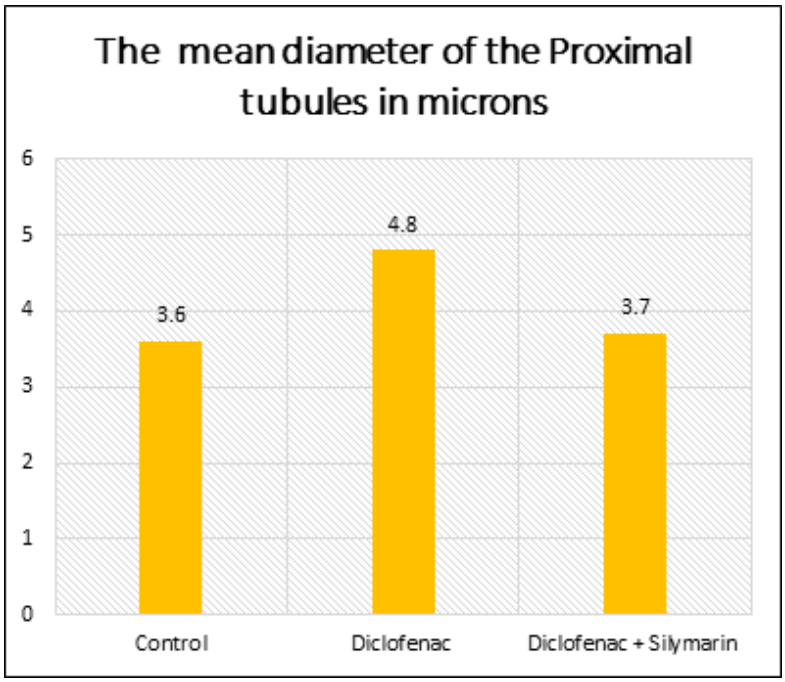
Morphometric studies were used for measuring the mean diameter of the proximal tubules and the mean width of Bowman's space in microns of all groups.

Statistical analysis revealed highly significant difference of the mean diameter of the proximal tubules and the mean width of Bowman's space of group II as compared to the control group (group I) with a *P-value <0.001*. Similarly, a highly significant difference between group II and group III has been found with a *P-value < 0.001*, On the other hand, the difference between group I and group III were statistically non-significant with a *P-value > 0.05* (Tables 1, 2). The comparisons between the morphometric results were further.

Table 1: Comparing the mean diameter of the proximal tubules in microns showing *p-value* either, non-significant (*) or highly significant (**).

		Group I (Control)	Group II (Diclofenac)	Group III (Diclofenac + Silymarin)
The diameter of the proximal tubules in microns (mean ± standard deviation)		3.6± 0.02	4.8± 0.03	3.7± 0.02
T test	Between Group I&II		*P= 0.0002***	
	Between Group II&III		*P = 0.0001***	
	Between Group I&III		*P= 0.06**	

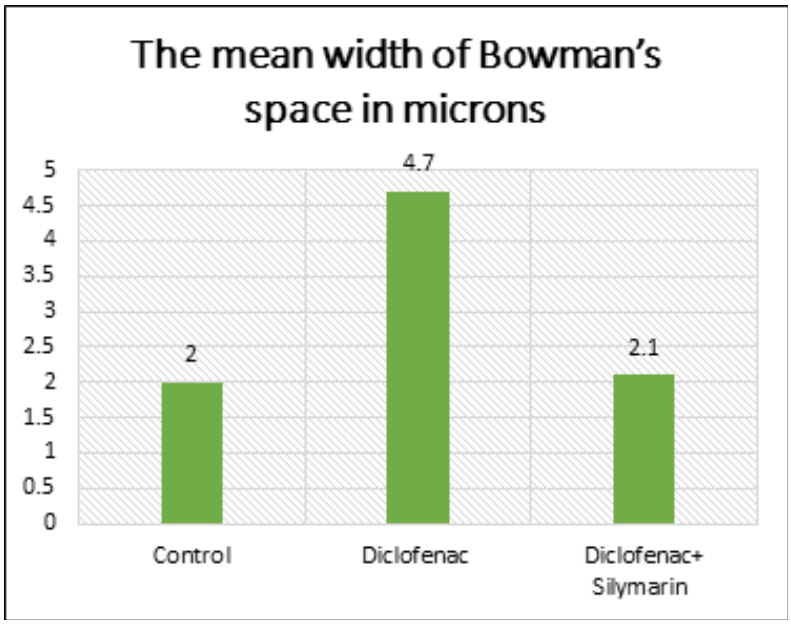
illustrated in column charts 1,2.



Column chart 1: Demonstrating the morphometric comparison as regards; the mean diameter of the proximal tubules in microns.

Table 2: Comparing the mean width of Bowman's space in microns showing *p-value* either, non-significant (*) or highly significant (**).

		Group I (Control)	Group II (Diclofenac)	Group III (Diclofenac +Silymarin)
Width of Bowman's Space in microns (mean ± standard deviation)		2.0± 0.05	4.7± 0.04	2.1± 0.01
T test	Between Group I&II		*P= 0.0005***	
	Between Group II&III		*P = 0.0006***	
	Between Group I&III		*P= 0.1**	



Column chart 2: Demonstrating the morphometric comparison as regards; the mean width of Bowman's space in microns.

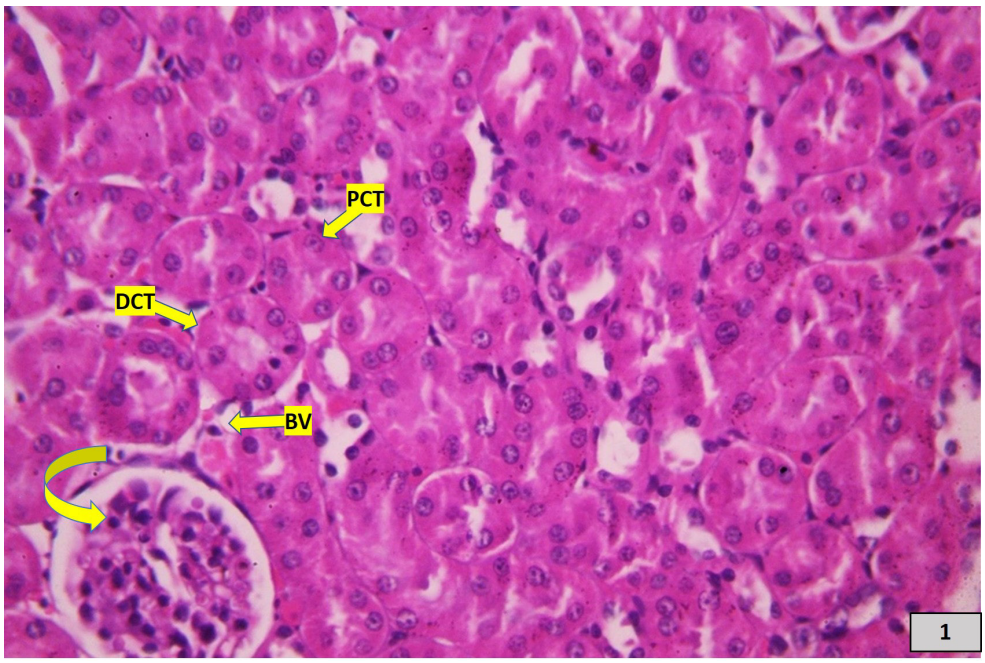


Fig. 1: A photomicrograph of a section of renal cortex of group I (control) showing, renal corpuscle (curved arrow). PCT with narrow lumen. DCT with wide lumen. Notice the small interstitial blood vessels (BV) (H&E X400).

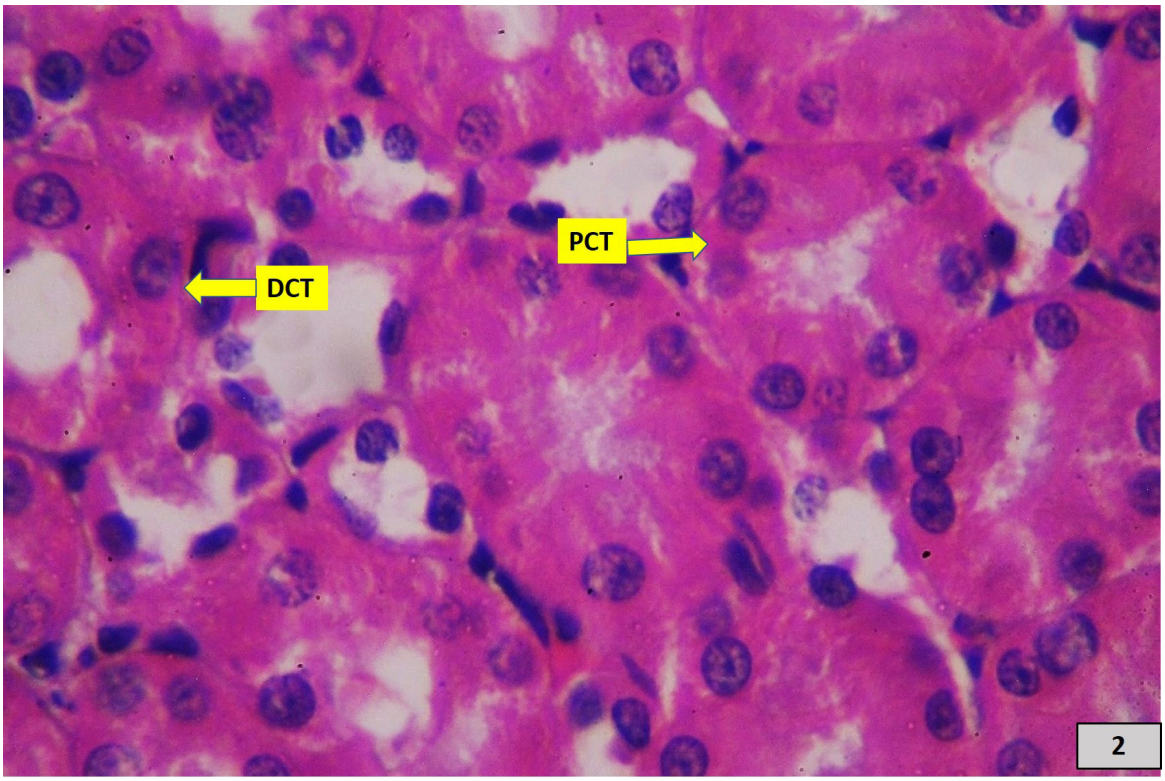


Fig. 2: A photomicrograph of a section of renal cortex of group I (control) showing, PCT lined with cubical cells with brush border and basal nuclei, DCT lined by simple cubical cells with central spherical nuclei and minimal microvilli. (H&E X1000).

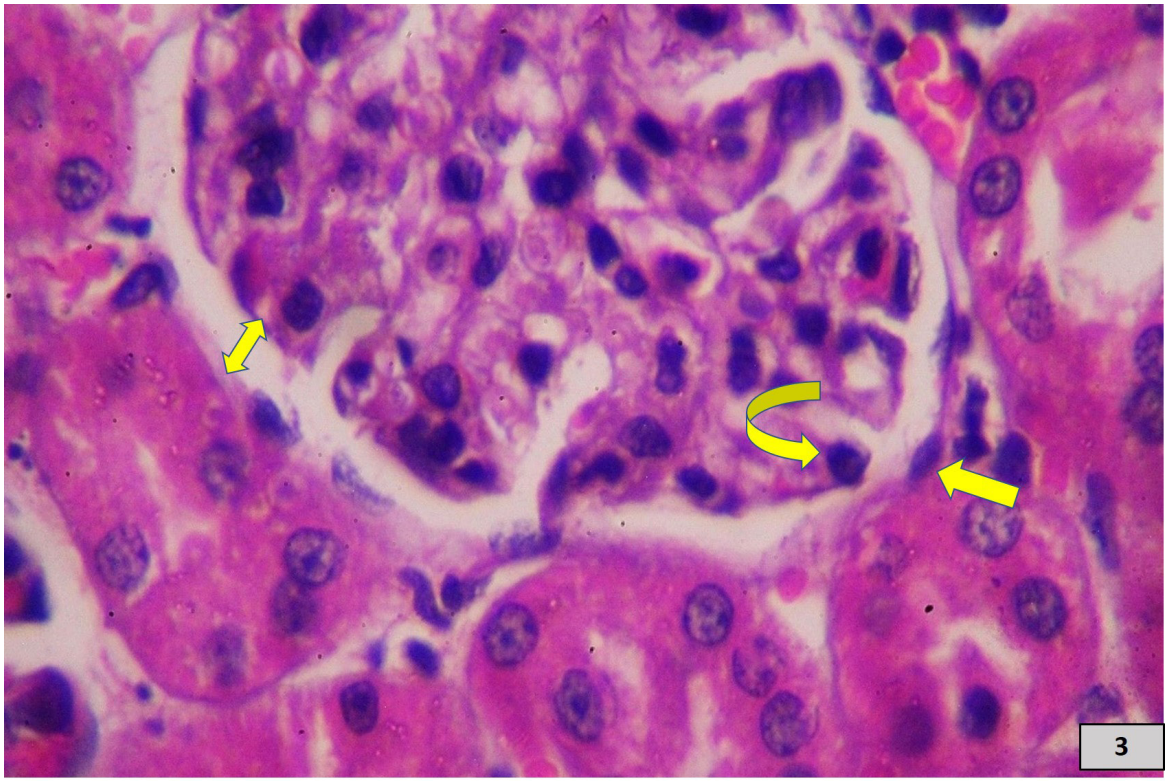


Fig. 3: A photomicrograph of a section of renal cortex of group I (control) showing, renal capsule, outer layer of simple squamous epithelium (arrow), inner layer podocytes (curved arrow) and in-between the Bowman's space (double headed arrow). (H&E X1000).

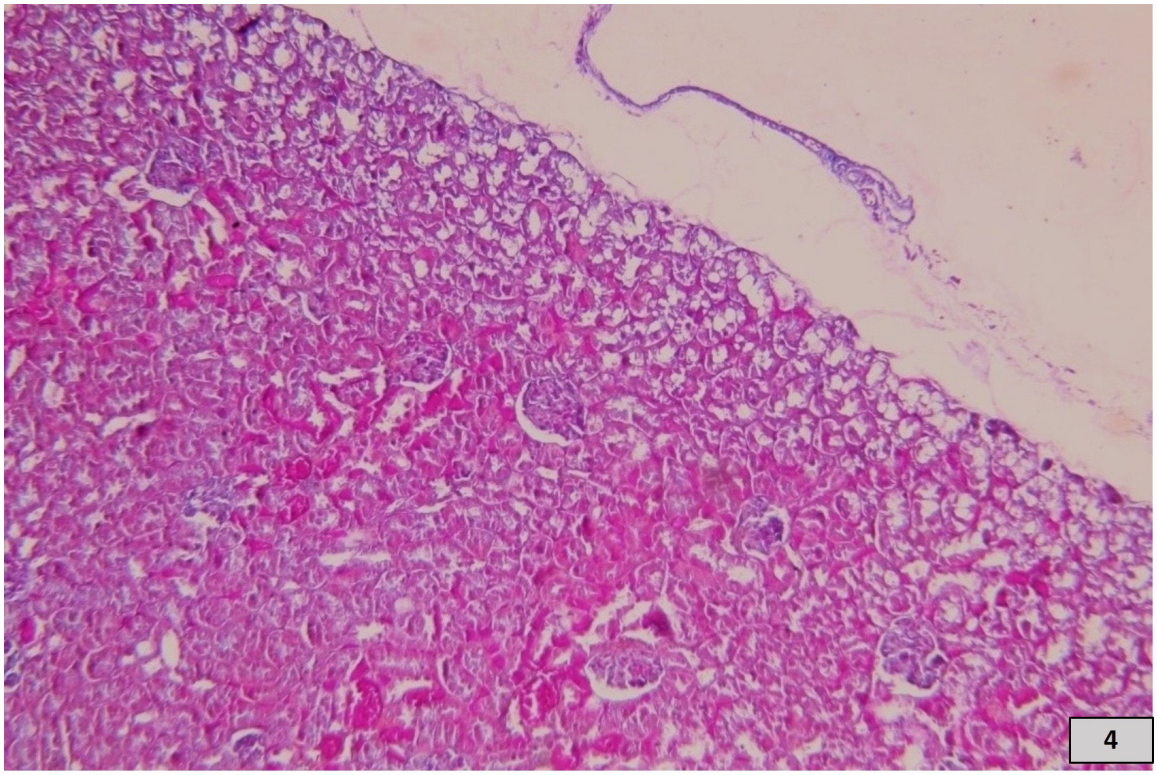


Fig. 4: A photomicrograph of a section of renal cortex of group I (control) showing minimal collagen fibers (blue color) distribution throughout the renal cortex. (Mallory trichrome X100).

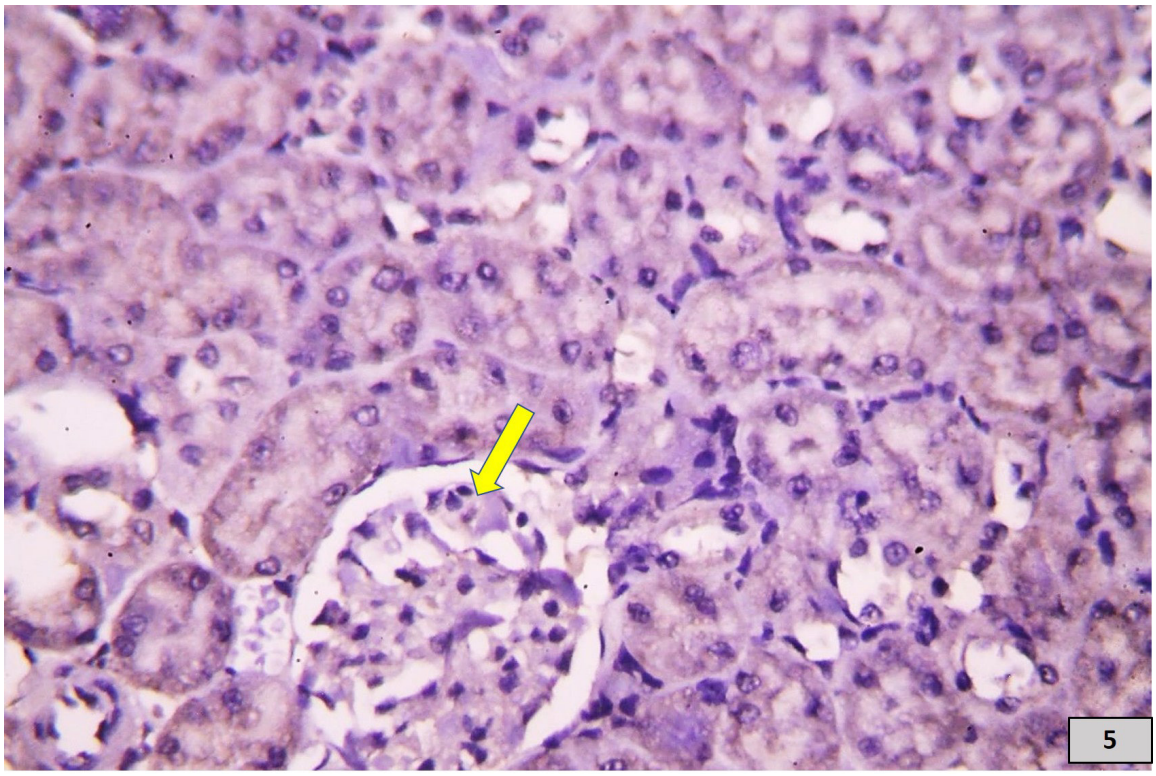


Fig. 5: A photomicrograph of a section of renal cortex of group I (control) showing, weak positive immune reaction (brown color) of glomerular podocytes (arrow). (Desmin X400).

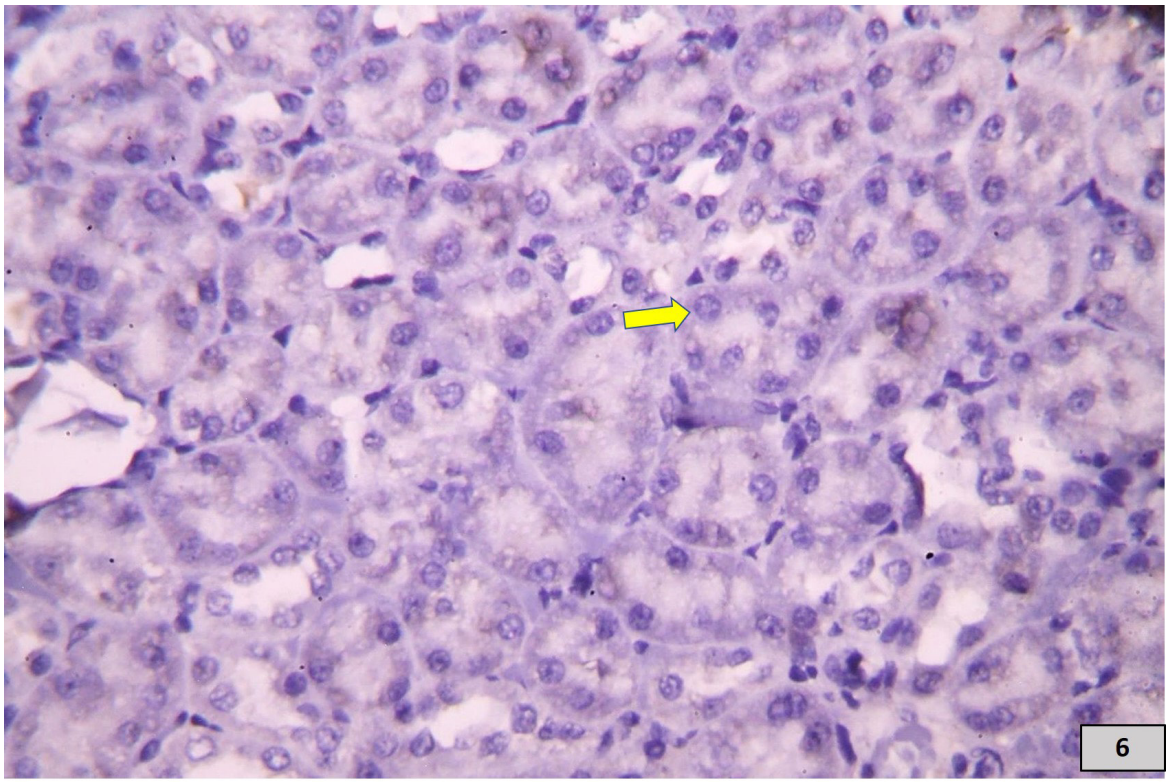


Fig. 6: A photomicrograph of a section of renal cortex of group I (control) showing, faint positive immune reaction (brown color) of the tubular cells (arrow). (PCNA X400).

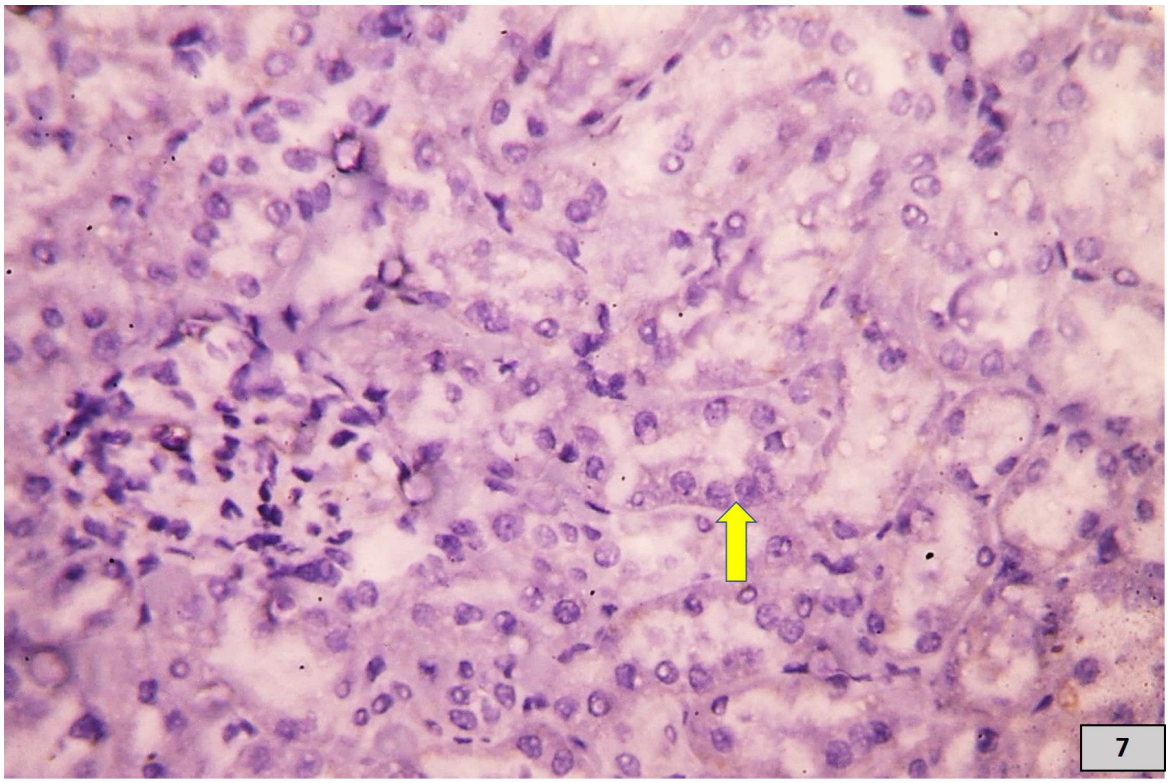


Fig. 7: A photomicrograph of a section of renal cortex of group I (control) showing, negative immune reaction of the tubular cells (arrow). (Caspase-3 X400).

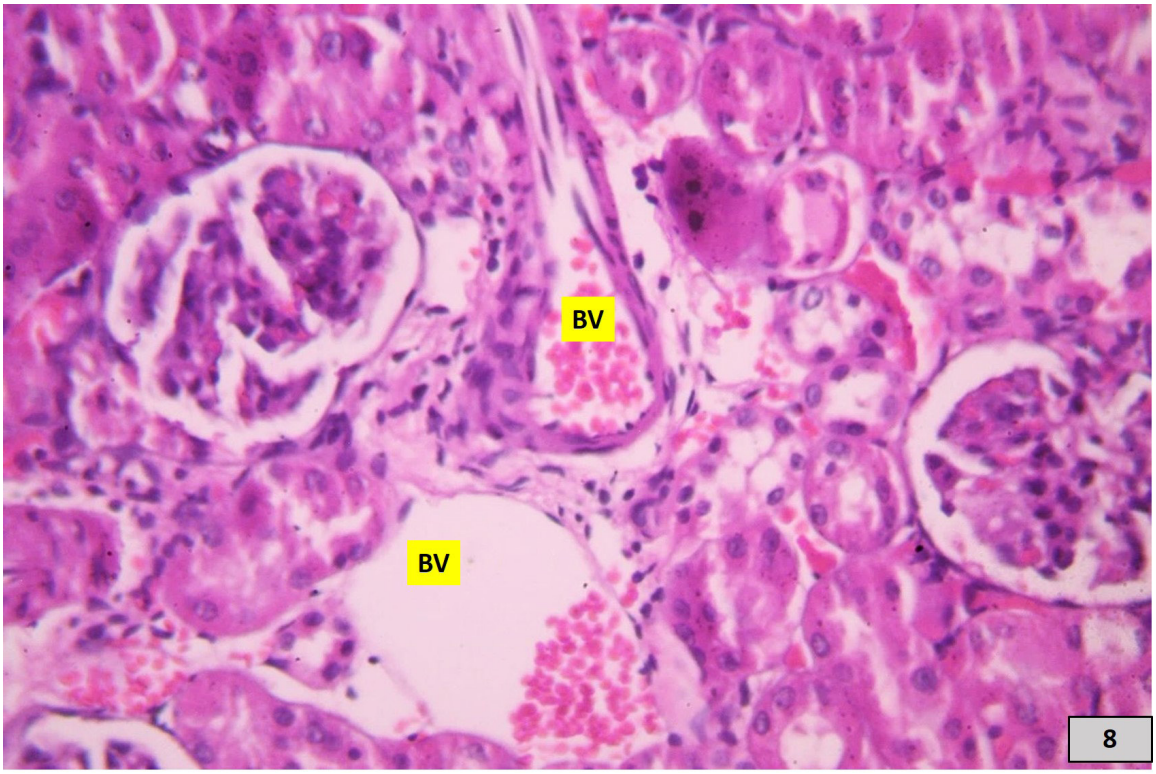


Fig. 8: A photomicrograph of a section of renal cortex of group II showing, dilated congested interstitial blood vessels (BV). (H&E X400)

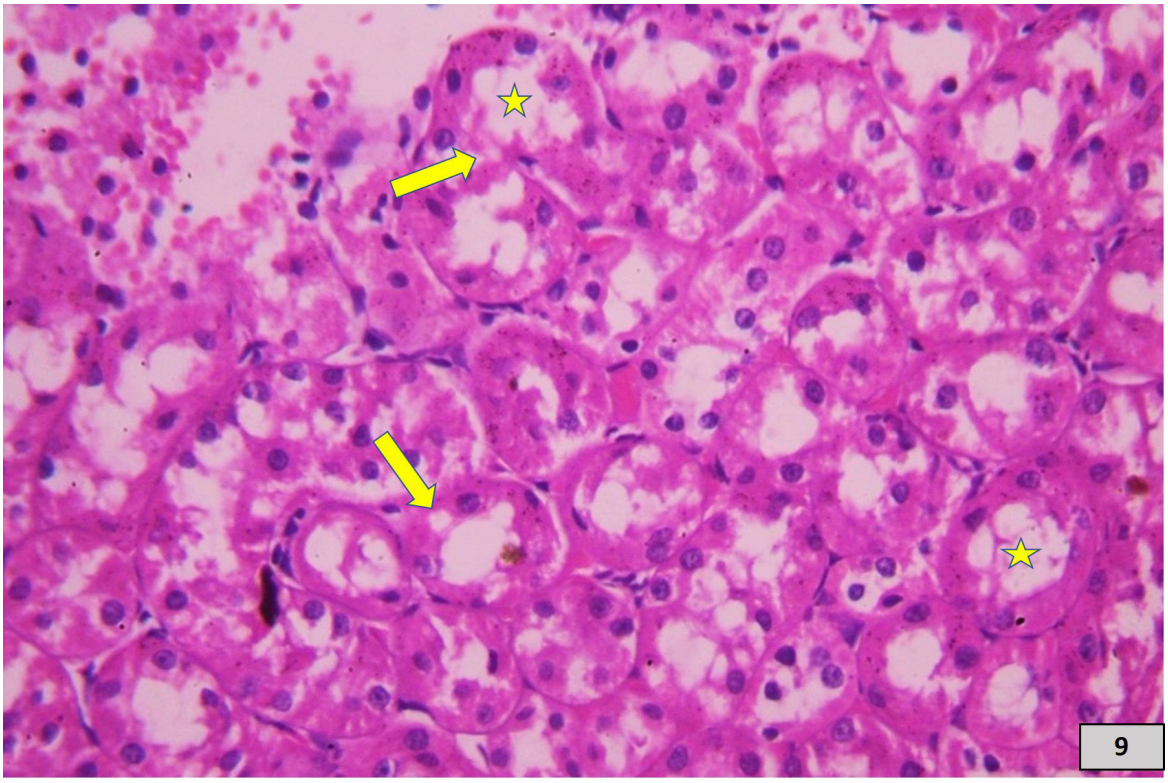


Fig. 9: A photomicrograph of a section of renal cortex of group II showing, tubular cells vacuolations (arrows) with luminal dilatation (stars). (H&E X400).

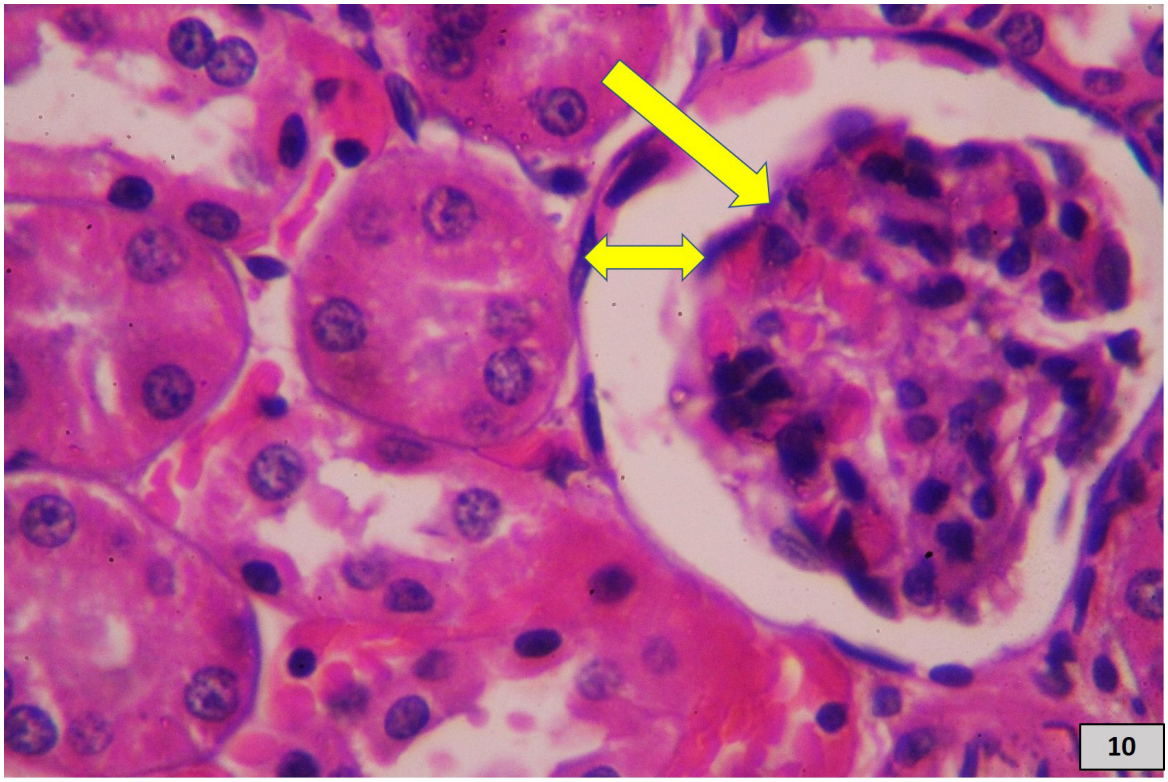


Fig. 10: A photomicrograph of a section of renal cortex of group II showing, renal corpuscle with shrinkage of its renal glomerulus (arrow) and widening of Bowman's space (double headed arrow). (H&E X1000).

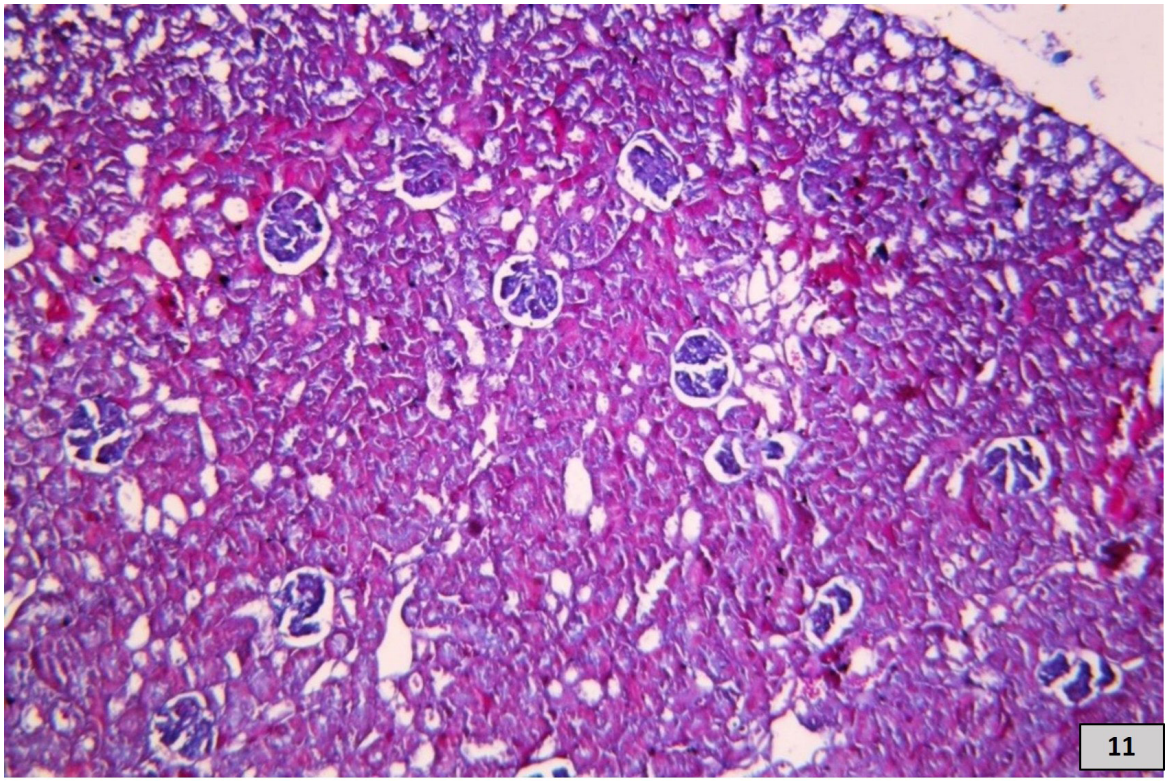


Fig. 11: A photomicrograph of a section of renal cortex of group II showing, apparent increase of collagen fibers distribution (blue color) throughout the renal cortex. (Mallory trichrome X100).

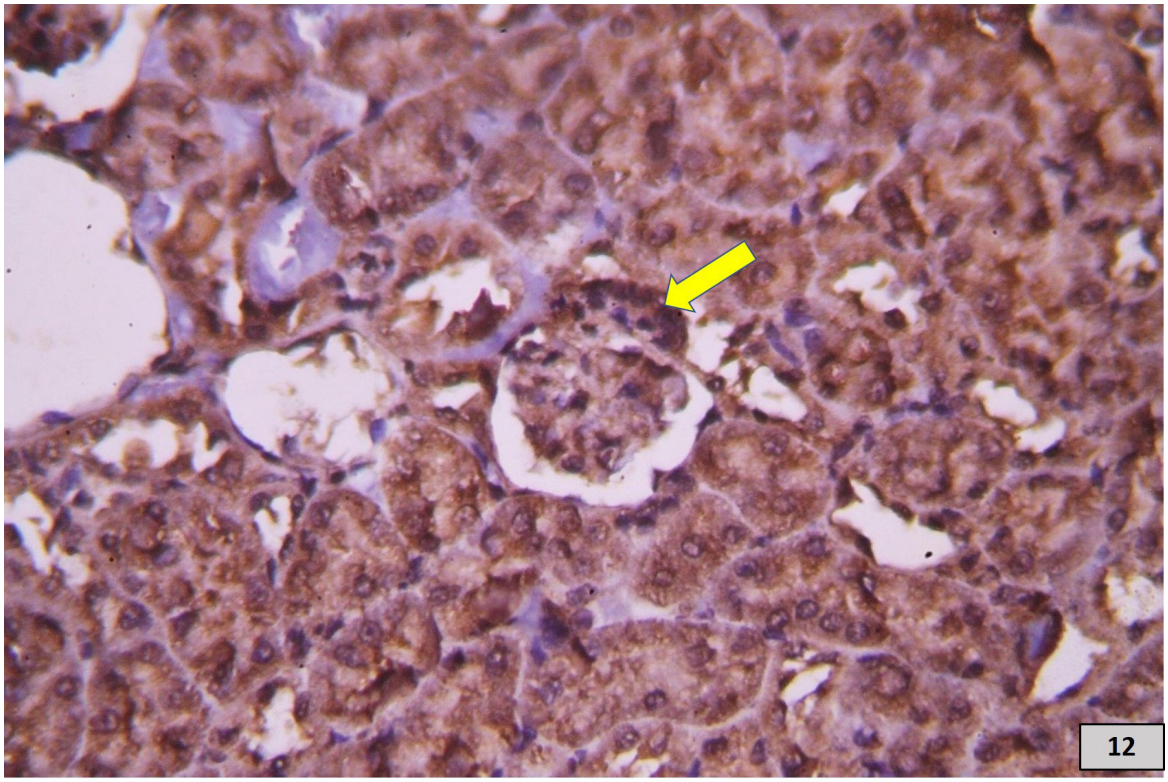


Fig. 12: A photomicrograph of a section of renal cortex of group II showing, apparent intense positive immune reaction (dark brown) of glomerular podocytes (arrow). (Desmin X400).

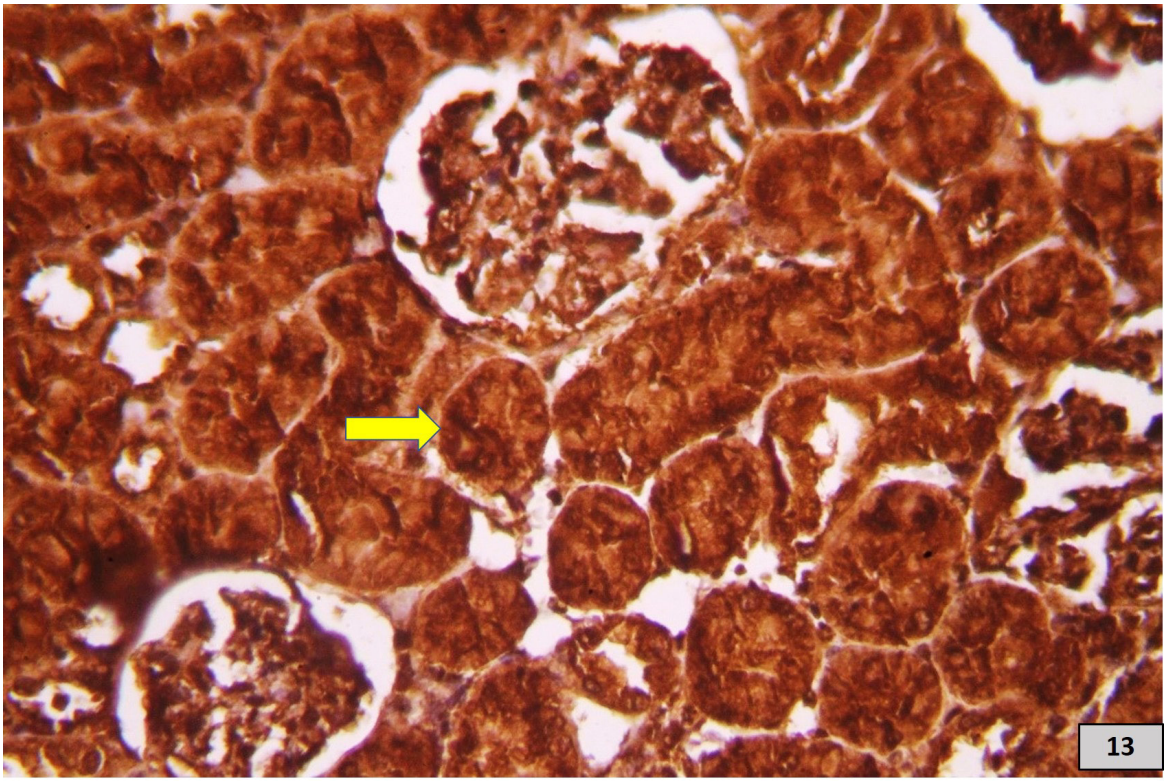


Fig. 13: A photomicrograph of a section of renal cortex of group II showing, apparent intense positive immune reaction (dark brown) of the tubular cells (arrow). (PCNA X400).

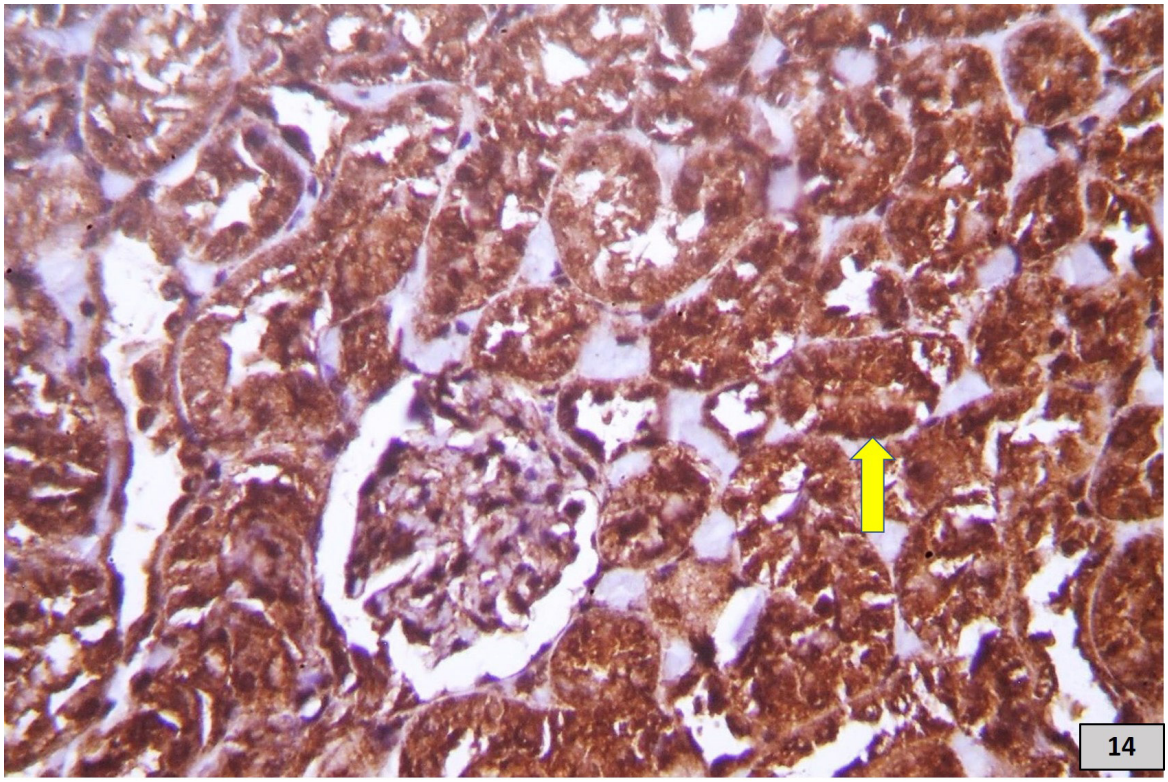


Fig. 14: A photomicrograph of a section of renal cortex of group II showing, apparent intense positive immune reaction (dark brown) in the cytoplasm of the tubular cells (arrow). (Caspase-3 X400).

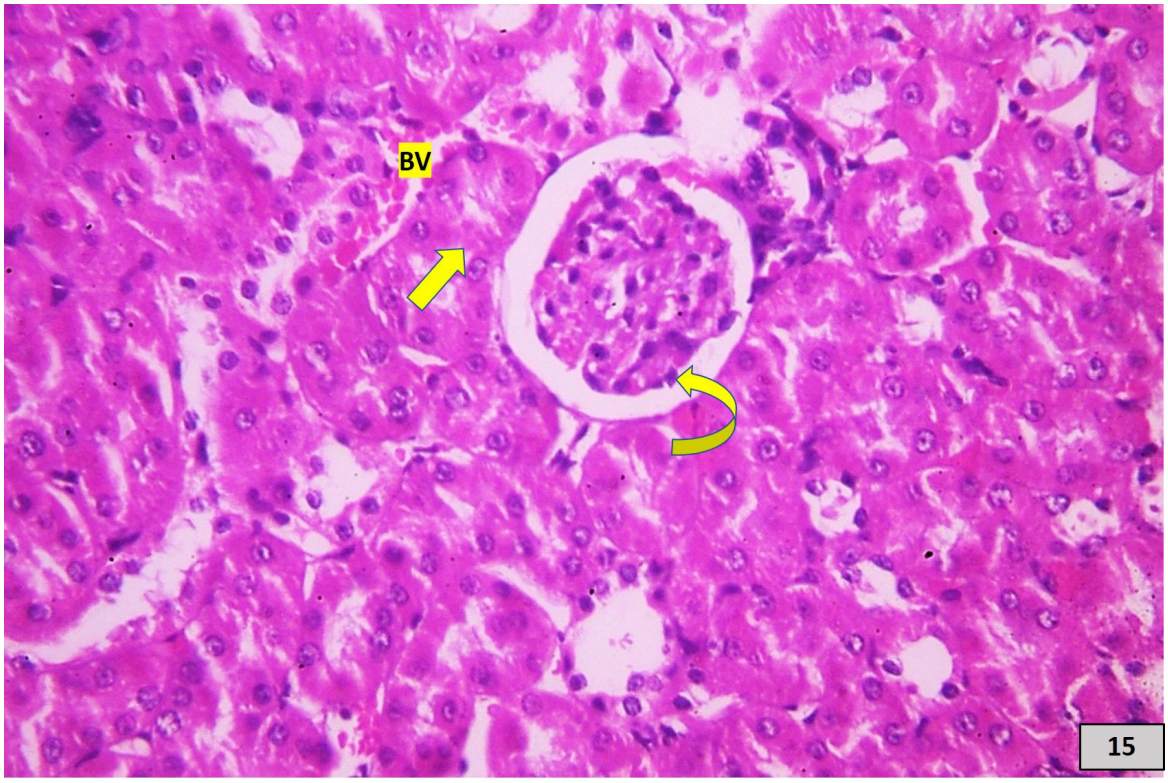


Fig. 15: A photomicrograph of a section of renal cortex of group III showing, regular structure of the renal corpuscle (curved arrow) and tubules (arrow) with mild dilated congested interstitial blood vessels (BV). (H&E X400).

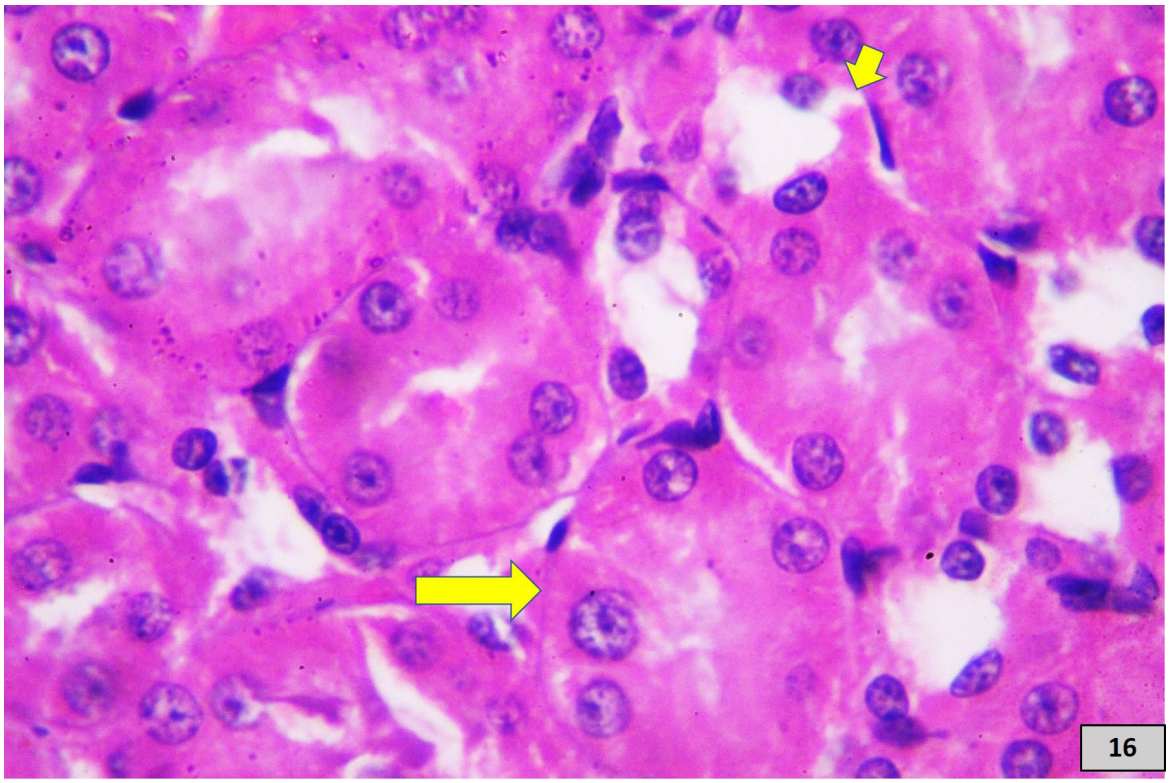


Fig. 16: A photomicrograph of a section of renal cortex of group III showing, regular structure of most tubular lining cells (long arrow) with minimal vacuolations (short arrow). (H&E X1000).

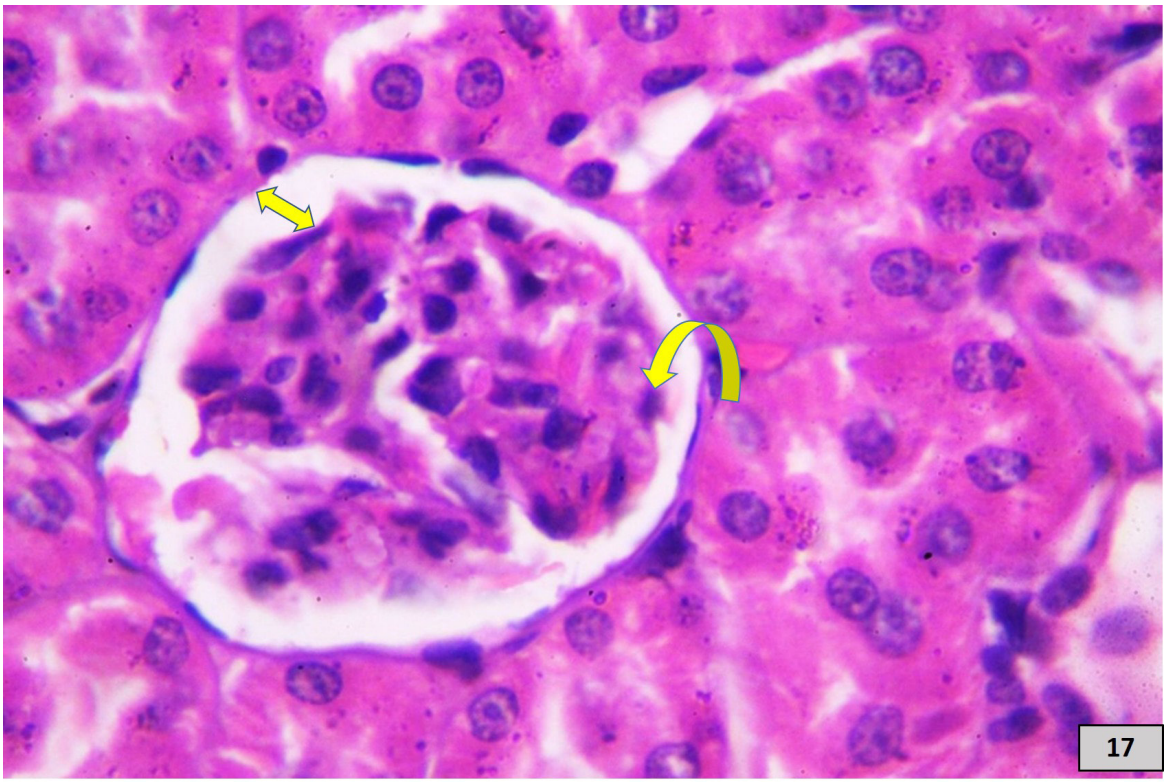


Fig. 17: A photomicrograph of a section of renal cortex of group III showing, regular structure of renal corpuscle (curved arrow) with apparent average Bowman's space (double headed arrow). (H&E X1000).

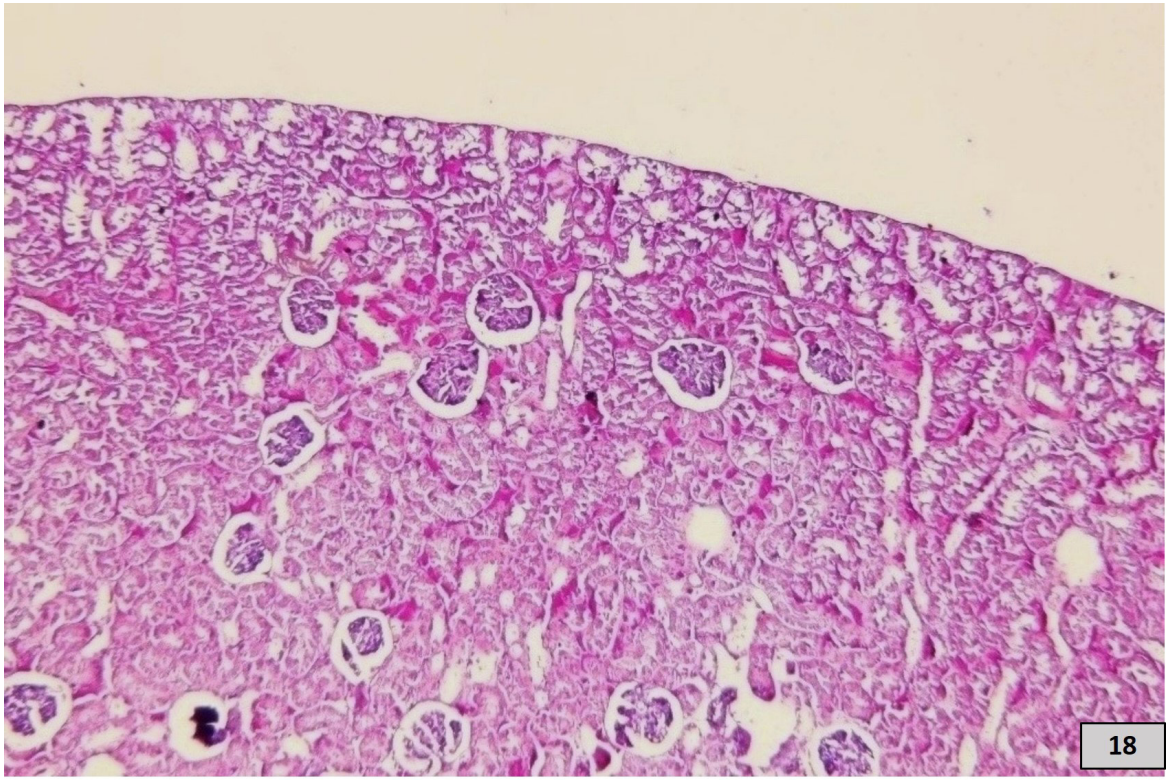


Fig. 18: A photomicrograph of a section of renal cortex of group III showing. minimal interstitial collagen fibers (blue color) distribution throughout the renal cortex. (Mallory trichrome X100).

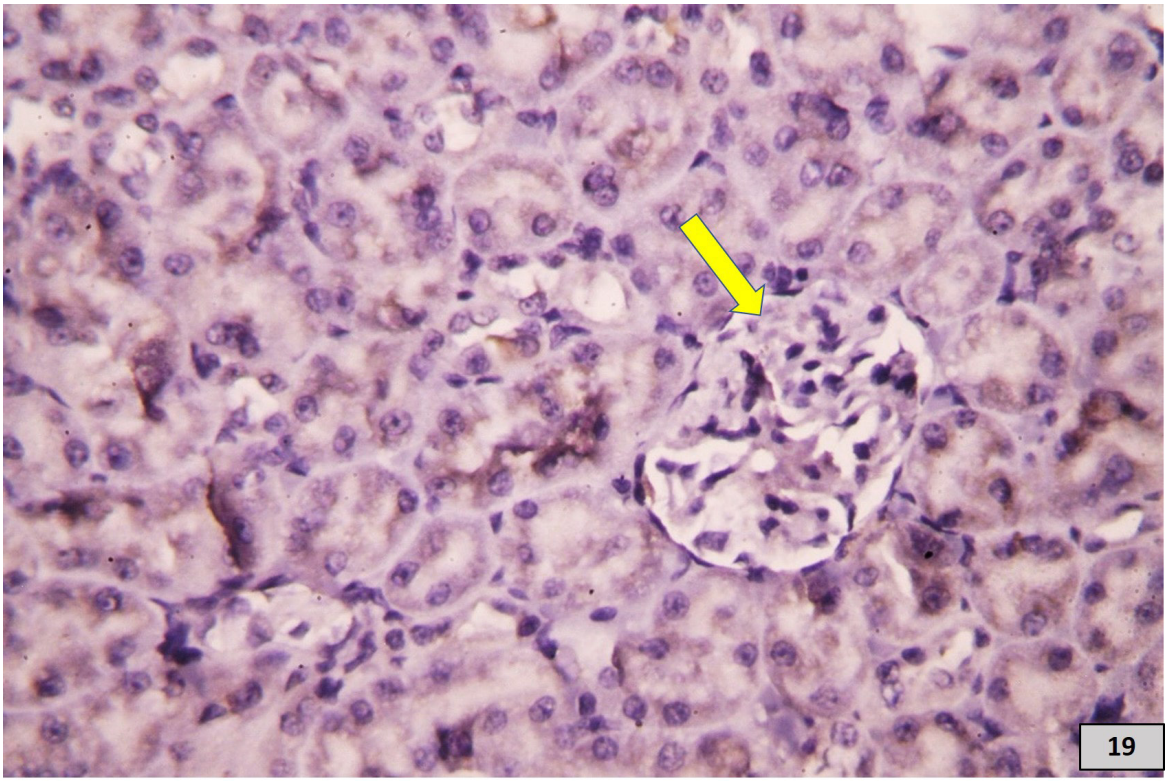


Fig. 19: A photomicrograph of a section of renal cortex of group III showing, apparent mild positive immune reaction (brown color) of glomerular podocytes (arrow). (Desmin X400).

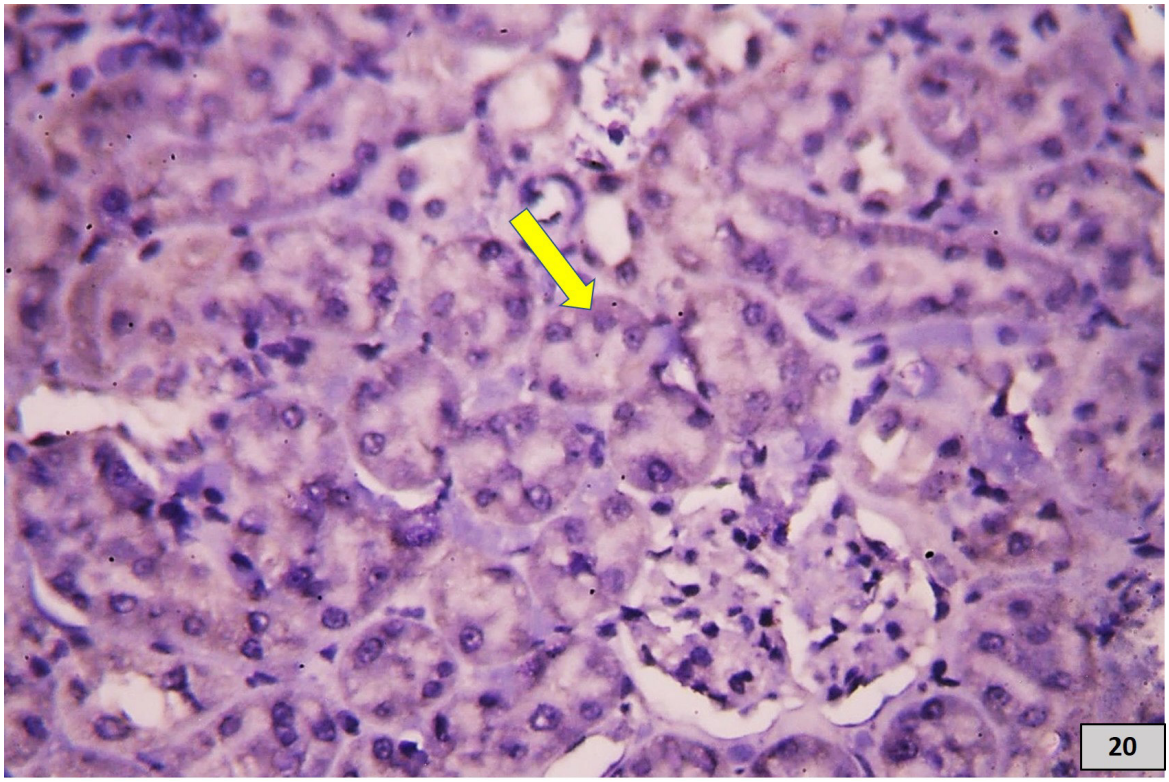


Fig. 20: A photomicrograph of a section of renal cortex of group III showing, apparent mild positive immune reaction (brown color) of tubular cells (arrow). (PCNA X400).

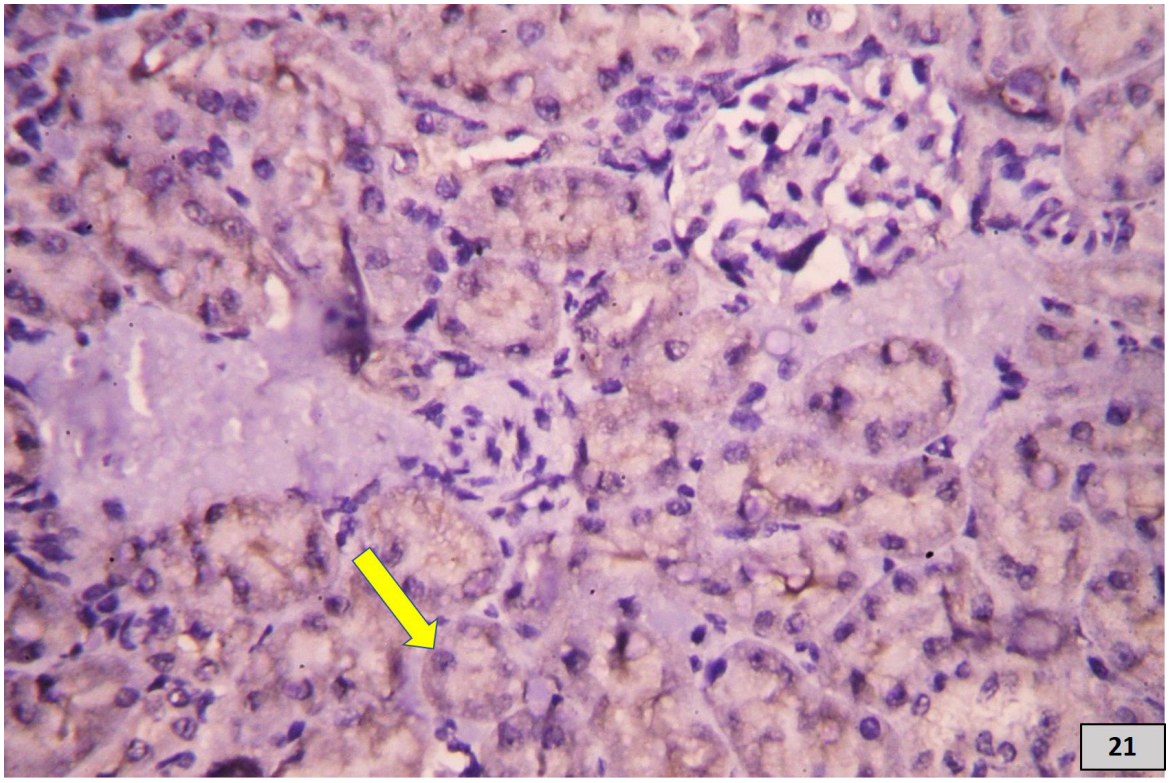


Fig. 21: A photomicrograph of a section of renal cortex of group III showing, apparent mild positive immune reaction (brown color) in the cytoplasm of tubular cells (arrow). (Caspase-3 X400).

DISCUSSION

The kidney is the main primary excretory organ for most drugs and chemicals therefore, it is highly vulnerable to toxic damage by drugs[1]. Diclofenac is a commonly used drug in the control of inflammation and pain due to its effectiveness and its over-the-counter availability, despite its well-known nephrotoxicity[20]. Previous studies supported the biochemical evidences of renal damage by Diclofenac through detection of increased urea and creatinine levels[21,22]. These biochemical evidences were marked in rats that received 4mg/kg BW oral dose of Diclofenac for long duration[12].

The results of the present study revealed marked histopathological changes of the renal cortex of group II that received 4mg Diclofenac sodium /kg BW for two consecutive weeks, by H&E stained sections the renal cortex showed tubular cells vacuolations with luminal dilatation, shrinking glomeruli of renal corpuscles with widening of Bowman's space and dilated congested interstitial blood vessels. Previous studies reported degenerative changes in renal glomeruli and tubular epithelium with cellular vacuolations and interstitial congestion in mice and rats treated with Diclofenac[23-24]. Diclofenac acts by inhibiting prostaglandin production that is important in regulation of renal blood flow, glomerular filtration and tubular ion transport. Diclofenac also acts on the renin–angiotensin–aldosterone system and the renal vascular tone[25]. Renal affection by Diclofenac such as tubular damage and interstitial fibrosis was attributed to decreased prostaglandin synthesis[26-28]. Moreover, inhibition of cyclooxygenase enzyme by Diclofenac may lead to shifting of arachidonic acid to the lipoxygenase pathway instead of cyclooxygenase pathway leading to increased synthesis of leukotrienes that enhance peritubular capillary permeability and precipitate for tubular damage[29]. Statistically there was a highly significant increase in the mean diameter of the proximal tubules and in the mean width of Bowman's space as compared to the control group, both findings were indicators of tubular cells degeneration and early changes of renal failure respectively[28,30]. In addition, increased collagen fibers distribution throughout the renal cortex was revealed by Mallory Trichrome stain. Khoshvakhti *et al*. reported that Diclofenac induced glomerulosclerosis and increased the connective tissue content of the rat kidneys[31]. Renal tubules were proven to contain cells that have a great regenerative power, failed tubular regeneration provoke a signaling activity for interstitial fibroblasts to start proliferation that followed by collagen deposition and eventually tubulointerstitial fibrosis[32].

Immunohistochemical staining for Desmin of Diclofenac group revealed, intense positive immune reaction of glomerular podocytes as compared to the control group. Desmin is an intermediate filament protein that minimally expressed in normal glomerular podocytes. The glomerular podocytes represent the central components of the renal filtration barrier[33]. Desmin function is to raise the mechanical resistance of the cells, when its expression increases in podocytes it represents an indicator of morphological changes of these podocytes in reaction to injury[18]. Moreover, immunohistochemical staining for PCNA revealed intense positive immune reaction of the tubular cells. Diclofenac was shown to induce defect in mouse renal development with increased PCNA expression in tubular cells[34]. PCNA is a marker of cell division and proliferation. Its synthesis begins to increase in the late G1 to S phases of the cell cycle. Increased expression of PCNA in tubular lining cells indicates increased proliferation of these cells in the progression stage of renal injury[35]. In addition, immunohistochemical staining for Caspase-3 revealed intense positive immune reaction in the cytoplasm of the tubular cells. Mustafa *et al*. reported an increase in Caspase immune reaction of tubular cells in postnatal rats treated with Diclofenac[36]. Caspase-3 is a marker for apoptosis that is activated by both extrinsic and intrinsic pathways of apoptosis and finally lead to breakdown of DNA and cell death[37,38].

On the other hand, examination of renal cortex of group III that received Diclofenac and Silymarin revealed nearly regular structure of the renal cortex, almost mimicking that of the control group. Hematoxylin and Eosin stained sections showed that most of the renal glomeruli and tubules were regular with apparent average Bowman's space, minimal tubular cell vacuolations and mild dilated congested interstitial blood vessels. In addition, the statistical results revealed a highly significant difference between group II and group III regarding the mean diameter of proximal tubules and the mean width of Bowman's space and the difference between group I and group

III were statistically non-significant. Mallory Trichrome stain showed minimal collagen fibers distribution throughout the renal cortex. Immunohistochemical staining for Desmin revealed, mild immune reaction of glomerular podocytes. Moreover, immunohistochemical staining for PCNA and Caspase 3 revealed mild positive immune reaction of tubular cells. Previous studies suggested that Silymarin has a strong antioxidant, anti-inflammatory, antifibrotic, immunomodulating and anti-apoptotic properties[39]. Silymarin has been proved to protect the kidney from interstitial fibrosis, tubular dilatation and atrophy induced by many nephrotoxic drugs[9-11], its renoprotective action attributed to its antioxidant and reactive oxygen species scavenging properties[40]. Roozbeh *et al*.[41] reported remarkable improvement in patients on hemodialysis when received Silymarin. They significantly showed decrease in plasma malondialdehyde as a biomarker for oxidative stress and increase in the antioxidant glutathione peroxidase of red blood cells. Recently, in 2019, Nouri and Heidarian[14] reported that Silymarin when added to Diclofenac experimentally in rats led to marked decrease in renal inflammatory cells, lipid peroxidase and TNF-α (tumor necrosis factor α) with increased renal activities of the antioxidants as vitamin C, catalase and superoxide dismutase.

CONCLUSIONS

Diclofenac sodium led to histoarchitectural changes of renal cortex. However, Silymarin greatly protected against such changes. Thus, it could be considered a promising protector for Diclofenac sodium induced renal hazards. Further researches on the renoprotective effect of Silymarin against other NSAIDs are strongly recommended.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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دور السيليمارين في تحسين الآثار الضارة لديكلوفيناك الصوديوم على القشرة الكلوية لذكر الجرذ الابيض البالغ: دراسة هستولوجية وهستوكيميائية مناعية

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ملخص البحث

المقدمة: الأدوية المضادة للالتهابات غير الستيرويدية معروفة جيدًا بتاثيراتها السامة للكلى.يعد ديكلوفيناك الصوديوم واحد من مضادات الالتهاب غير الستيرويدية. اثبت تجريبيا ان للسيليمارين تأثيرا وقائيا ضد العديد من الأدوية السامة للكلى.

الهدف: هدف هذا العمل إلى دراسة الدور المحتمل للسيليمارين في تخفيف التأثيرات السامة لديكلوفيناك الصوديوم على القشرة الكلوية لذكر الجرذ الابيض البالغ.

المواد والطرق: تم استخدام خمسة وأربعين من ذكور الفئران البيضاء البالغة في هذه الدراسة وقد قسمت بالتساوى إلى ثلاث مجموعات: المجموعة الأولى: تم تقسيمها بالتساوي إلى: المجموعة IA: تم الاحتفاظ بها كمجموعة ضابطة سلبية، المجموعة IB: تلقت ٤ مل من الماء المقطر لكل كجم من وزن الجسم والمجموعة IC: تلقت ١٠٠ ملجم سيليمارين لكل كجم من وزن الجسم. المجموعة الثانية: تلقت ٤ ملجم ديكلوفيناك الصوديوم لكل كجم من وزن الجسم . المجموعة الثالثة: تلقت ٤ ملجم ديكلوفيناك الصوديوم لكل كجم من وزن الجسم بالإضافة إلى ١٠٠ ملجم سيليمارين لكل كجم من وزن الجسم. تم تلقى جميع الادوية والمذيبات عن طريق الفم بواسطة أنبوب المعدة مرة واحدة يوميا لمدة أسبوعين متتاليين.

النتائج: كشف العمل الحالي عن تغيرات نسيجية ملحوظة في قشرة الكلى فى المجموعة الثانية التي تلقت ديكلوفيناك الصوديوم ، في شكل فجوات خلايا الانابيب مع توسع التجويف و انكماش الكبيبات الكلوية و اتساع مساحة بومان. أظهرت المجموعة الثالثة التي تلقت ديكلوفيناك بالإضافة إلى سيليمارين هيكلًا منتظمًا تقريبًا للقشرة الكلوية.

الخلاصة: اظهر سيليمارين قدرة كبيرة على الحماية من حدوث التغيرات النسيجية فى القشرة الكلوية الناجمة عن الديكلوفيناك.