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Nephrotoxicity Evaluation of Captopril and Enalapril in Rats: Comparative Study

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THE objective of this study was to look into the renal toxicity of high-dose captopril and enalapril. The animals in this experiment were separated into five groups of ten animals each, with the first serving as a control group, receiving only distilled water, the second receiving captopril doses 10 and 20% of LD_{50}, and the fourth and fifth receiving enalapril 10 and 20%. For four weeks, the dose is given orally twice weekly. Samples were obtained after one week and again four weeks afterwards. Significant increases in urea and creatinine concentrations were seen after 1 week of therapy with 20% enalapril, as well as urea and creatinine were considerably raised in the 20% captopril and 20% enalapril-treated groups after 4 weeks of treatment. In the one-week 10% therapy groups, kidney tissue showed intact glomeruli and proximal renal tubules comparing with 20% treatment groups revealed glomerular atrophy, dilation of Bowman's space, and vacuolar degeneration of the epithelial cell. After 4-weeks the 10% captopril group revealed glomerular atrophy, and epithelial cell vacuolar degeneration. The 20% captopril group's kidneys revealed atrophy, dilatation of Bowman's space, and necrosis. Enalapril 10% and 20% groups showed glomerular atrophy, dilation of Bowman's space, and vacuolar degeneration. The study examined TNF- expression in immunohistochemistry. The control group had no expression, but the captopril 10% and enalapril 20% groups had minor and moderate expression, respectively. The study concluded that enalapril at a concentration of 20% has more severe toxic effects on the kidneys than captopril at the same dose.

Keyword: Captopril, Enalapril, Nephrotoxicity, Tumor Necrosis Factor, Rats.

Introduction

Nephrotoxicity or Renal toxicity is a result of a variety of factors. A variety of medications is excreted by the kidneys. As drugs are transported and have the potential to accumulate in the proximal tubule intracellular compartment, the renal concentration mechanisms subject the renal tubule cells to extremely high intratubular drug concentrations. Numerous drugs are metabolized and altered by the kidneys, which results in the creation of toxic compounds [1].

Nephrotoxicity is the damage or injury to the kidneys caused by certain drugs or chemicals. The precise processes underlying Captopril and Enalapril-induced nephrotoxicity are unknown and may involve a variety of factors [2]. Captopril and Enalapril can alter renal hemodynamics by suppressing ACE activity and decreasing angiotensin II production. These modifications may cause changes in renal blood flow and glomerular filtration rate, thereby compromising kidney function [3].

ACE drugs can cause electrolyte changes, most notably an increase in serum potassium levels (hyperkalemia). Hyperkalemia can compromise kidney function and cause renal failure [4]. ACE

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inhibitors such as Captopril and Enalapril have been linked to the development of acute renal damage in rare situations. This can be caused by a variety of conditions such as decreased renal blood flow, interstitial nephritis, or renal artery stenosis [5] . Individuals with pre-existing kidney problems, such as chronic kidney disease or renal artery stenosis, are more prone to develop nephrotoxicity. These disorders may make you more susceptible to the nephrotoxic effects of Captopril and Enalapril [6].

Individual patient factors, including genetic predisposition, underlying health conditions, and concomitant medication use, can influence the risk of nephrotoxicity with ACE inhibitors [7]. Monitoring kidney function and adjusting medication dosages based on individual patient characteristics is important to minimize the risk [8]. Individual patient characteristics such as genetic predisposition, underlying health conditions, and concurrent pharmaceutical use can all increase the likelihood of ACE inhibitor nephrotoxicity. To reduce the risk, it is critical to monitor renal function and modify drug dosages based on specific patient characteristics [9].

These findings suggest that the toxic effects on the kidneys can vary depending on the specific medication, dosage, and duration of treatment. It is important to consider these factors when prescribing and administering these medications to ensure the safety and minimize potential harm to the liver and kidneys [10]. The aim of this study was to compare the nephrotoxic effect induced by both captopril and enalapril in rats.

Material and Methods

Female Sprague-Dawley rats, weighing 250 to 300 gm and aged one to two months. When dealing with animals, values and ethics were observed, and they were provided with water and nutrition in cages and raised under laboratory settings. The cycle of light and darkness in keeping animals is 12 /12 light to darkness. Animals were handled in line with the standards, in accordance with the code stated in the Code of Ethics for Handling Laboratory Animals, and approval was obtained from the University of Mosul, College of Medicine, and in accordance with the same coder. Vet 2022.05.2020 Prepare potions

Prepare doses

Captopril and enalapril maleate formulations used pure drug weight on a body weight basis and were dissolved in 2% dilute ethanol before administration to animals.

Experimental Design

In this experiment, the animals were separated into five groups of ten. The first group acted as a control group, containing simply distilled water; groups 2 and 3 received captopril 10 and 20%, respectively, while groups 4 and 5 received enalapril 10 and 20%, respectively. Concentration of Doses (10 and 20%) were derived from LD_{50} mentioned in …..[11] National Centre for Biotechnology Information, 2023) captopril oral LD_{50} is 4245 mg/kg in female rats and enalapril Oral LD_{50} in rats is 2973 mg/kg.

For four weeks, the appropriate dose was administered orally through gavage tube once every three days. Five Animals were slaughtered. After one week, and the remainder after four weeks. Ether was used to kill the animals, and blood was extracted from the eye orbit. For 10 minutes, serum was separated using a spectrophotometer calibrated to 3000 rpm. Collect organs (kidneys) and carefully wash them with tap water before drying them on filter paper and applying diluted formalin till histological examination is complete.

Analysis materials

-Kit for ALT (Alanin aminotrancfereace) from Biolab company, France

-Kit for AST (Aspartate aminotrancferease) from Biolab company, France

-Kit for GSH (Glutathaion) from Biolab company, France

-Kit for MDA (Malondaialdihaid) from Biolab company, France

-Immunohistochemistry Kit for TNF-a from Dacota company, France

Statically analysis

The data were statistically represented using the average and standard error at a level less than 0.05 and the one-way ANOVA test was used using the Sigma Plot program, utilized Duncan›s multiple comparison test.

Results

The urea concentrations showed significant increase in the treated groups (Enalapril 20%) compared with the control group and the rest groups. The Creatinine concentration revealed no significant differences in the treated groups (Captopril 10%, Captopril 20%, Enalapril 10%, while Enalapril 20% revealed significant increase

in compared with the control group and anther groups . All significant differences were at $p \leq 0.05$ (Table 1).

Urea and creatinine increased significantly in the group treated with a dose of 20% Captopril and 20% Enalapril, compared with the control group and the rest of the groups, at a probability level of 0.019 (Table 2).

Histopathological result of the kidney after one-week Captopril and Enalapril treatment

In Figure 1 for kidney section of control group showing normal structure of glomeruli , proximal renal tubules , and distal renal tubules. In Figure 2 for kidney section of Captopril 10% treated dose group (1-week) showing intact glomeruli, and proximal renal tubules with blood vessels congestion and hemorrhage. Figure 3 for kidney section of Captopril 20% treated dose group (1-week) showing intact glomeruli, blood vessels congestion and hemorrhage and mild infiltration of few inflammatory cells, while in figure 4 for kidney of Enalapril 10% treated dose group (1-week) showing mild atrophy of glomeruli, mild dilation of Bowman's space, and blood vessels congestion. Figure 5 for kidney of Enalapril 20% treated dose group (1-week) showing atrophy of glomeruli, dilation of Bowman's space, vacuolar and cloudy degeneration of epithelial cells lining renal tubules, blood vessels congestion and hemorrhage.

Histopathological result of the kidney after four-week Captopril and Enalapril treatment:

Figure 6 for kidney of Captopril 10% treated dose group (4-week) showing atrophy of glomeruli, dilation of Bowman's space, and vacuolar degeneration of epithelial cells lining renal tubules. Figure 7 for Captopril 20% treated dose group (4-week) showing atrophy of glomeruli , dilation of Bowman's space, and vacuolar degeneration and necrosis of the epithelial cells lining renal tubules. Figure 8 for kidney of Enalapril 10% treated dose group (4-week) showing atrophy of glomeruli, dilation of Bowman's space , renal cyst , blood vessels congestion and vacuolar degeneration of the epithelial cells lining renal tubules. Figure 9 for kidney of Enalapril 10% treated dose group (4-week) showing atrophy of glomeruli , dilation of Bowman's space, renal cyst , and vacuolar degeneration and necrosis of the epithelial cells lining renal tubules.

Immunohistochemical expression of TNF-α:

Figure 10 for expression of TNF-α in the rat kidney of the control group (4-week) showing negative expression. Figure 11 for expression of TNF-α in the rat kidney of the Captopril 10% treated dose group (4-week) showing slight positive expression. Figure 12 for expression of TNF-α in the rat kidney of the Captopril 20% treated dose group (4-week) showing moderate positive expression. Figure 13 for expression of TNF-α in the rat kidney of the Enalapril 10% treated dose group (4-week) showing slight positive expression. In Figure 14 recorded expression of TNF-α in the rat kidney of the Enalapril 20% treated dose group (4-week) showing moderate positive expression.

Discussion

Both Captopril and Enalapril contain the same active substance, Enalapril maleate, which has antihypertensive effects. However, high doses of both medications cause different adverse consequences in the liver and kidney. The difference in chemical structure causes the human or animal body to metabolize each drug differently, with Captopril metabolism in the liver being Captopril disulfide, while Enalapril metabolism is Enalaprilat [12].

The chemical structure of Captopril and Enalapril affects their metabolism in the liver. Captopril disulfide is the active metabolite, while Enalaprilat is the active metabolite. These differences cause different adverse consequences in high dosages [13, 14].

The liver and kidney were chosen to compare the effects of the two drugs on them because the liver is responsible for drug metabolism and the kidney is responsible for excreting these metabolites, resulting in different undesirable toxic effects for each of the two drugs.

The result recorded significant increase in urea with animals treated with 20% Captopril after 4 weeks of treatment that may be due to Captopril and its metabolites are mostly removed through the kidneys after metabolism. Unchanged Captopril, Captopril disulfide, and Captopril mercaptopurine are excreted primarily in the urine, with a minor amount excreted in the faeces [15]. Captopril, have negative side effects on kidney when taken in high dosages or for an extended period of time as in our study. The particular hazardous dose of Captopril and its effects on the kidneys, however, might vary depending on a number of factors,

including individual sensitivity, underlying health problems, and concurrent pharmaceutical use [16]. Excessive Captopril use can result in significant blood pressure reductions, electrolyte imbalances, and renal failure [17]. Captopril›s toxic dose, as well as its effects on urea levels when taken at high doses for an extended period of time, can vary depending on individual factors such as overall health, renal function, and other medications being used [18]. Captopril is mostly eliminated by the kidneys and can impair renal function. Prolonged exposure to high dosages of Captopril may have a negative impact on urea levels and renal function [19]. Captopril at high doses can produce an increase in urea levels in the blood, resulting in a rise in blood urea nitrogen (BUN). BUN levels that are elevated may indicate poor renal function [20].

When use Enalapril 10 and 20% for 1 and 4 weeks recorded significant increase in urea and creatinine. Prolonged exposure to high doses of Enalapril may have effect on renal function [21]. Enalapril, like other ACE inhibitors, can impair renal function, especially in people who already have kidney disease or have disorders that limit blood flow to the kidneys [22]. Enalapril can induce acute kidney injury in some people, especially those who are dehydrated, have substantial renal artery stenosis, or have compromised kidney function [23].

Signs of kidney injury may include changes in urine output, swelling in the extremities, and changes in blood urea nitrogen (BUN) and creatinine levels[24]. Creatinine is a waste product created by muscle metabolism and eliminated by the kidneys [25].

Enalapril›s toxic dose, as well as its effects on urea levels when taken in large doses for an extended period of time, can vary depending on several factors such as health, renal function, and other medications being taken [26]. Enalapril, in high toxic doses has potential to impair renal function. Because urea is a waste product excreted by the kidneys, prolonged exposure to high dosages of Enalapril may have a detrimental effect on urea levels. Elevated urea and creatinine levels may suggest bad renal function [27].

Enalapril›s toxic dose, as well as its effects on creatinine levels when taken in large doses for an extended period, might vary depending on individual factors, animal species, age of animal, renal function, and other factor [28].

Histopathological renal changes of toxic long dose cause by Captopril toxic long-term Captopril dosages have been linked to histopathological kidney abnormalities [29]. Depending on the severity and duration of the renal damage, the specific histological findings can vary. Some of the observed alterations could be, toxic dosages of Captopril can cause renal tubular damage. This can show as tubular dilatation, brush border loss, tubular cell necrosis, and tubular epithelial cell sloughing [30]. In reaction to the harm caused by Captopril, inflammatory cells such as lymphocytes and macrophages may infiltrate the interstitial tissue of the kidneys. This inflammation can hasten the progression of kidney damage [31].

Captopril has been related with glomerular alterations such as glomerular capillary dilatation, mesangial proliferation, and endothelial cell edema on rare occasions [32].

Prolonged renal damage caused by toxic Captopril dosages might result in the deposition of excess connective tissue (fibrosis) within the renal interstitium. This fibrotic tissue has the potential to disturb normal kidney architecture and affect renal function [33].

Depending on the severity and duration of the renal damage, the specific histological findings can vary according to several factor as if toxic dosages of Enalapril can cause renal tubular damage. This can cause tubular dilatation, brush border loss, tubular cell necrosis, and tubular epithelial cell sloughing [34].

In reaction to the harm caused by Enalapril, inflammatory cells such as lymphocytes and macrophages may infiltrate the interstitial tissue of the kidneys. This inflammation can hasten the progression of kidney damage [35]. Enalapril has been related with glomerular alterations such as glomerular capillary dilatation, mesangial proliferation, and endothelial cell edoema on rare occasions [36]. Prolonged renal injury from toxic doses of Enalapril can lead to the deposition of excessive connective tissue (fibrosis) within the renal interstitium. This fibrotic tissue can lead to the disruption of normal kidney architecture and impaired kidney function [37].

Prolonged renal damage caused by toxic Enalapril dosages might result in the deposition of extra connective tissue (fibrosis) within the renal interstitium. This fibrotic tissue has the potential to disturb normal kidney architecture and affect renal function [38].

It affects the immunological response in the liver by encouraging the recruitment of immune cells including neutrophils and monocytes/ macrophages. Through the production of extra inflammatory mediators, these immune cells can contribute to liver inflammation and injury [39]. TNF- has a role in the complicated process of liver regeneration. While TNF- can help to hepatocyte proliferation and tissue repair under some conditions, it can also inhibit liver regeneration and cause impaired tissue healing [40]. TNF- interacts with other cytokines and mediators in the liver, including interleukins (IL), TGF-, and chemokines. These interactions have the potential to exacerbate the inflammatory response and accelerate the evolution of liver pathology [41].

Buttar et al. [42] defined Enalapril as an ACE inhibitor that interferes with the RAS, which regulates blood pressure and fluid balance. RAS components such as angiotensin II can impact TNF expression. The suppression of ACE by Enalapril may result in altered RAS activity, potentially affecting TNF- levels [41]. Enalapril has been linked to anti-inflammatory benefits, although it may also produce inflammatory responses in specific situations or contexts. TNF- production can be triggered by inflammatory stimuli as part of the immune response [43]. Enalapril-induced liver damage or inflammation may contribute to elevated TNF-expression. Treatment with Enalapril has been proven to reduce oxidative stress levels [44].

TNF-producing signalling pathways can be activated by oxidative stress. Enalapril medication may contribute to increased TNF- expression if it causes an imbalance between antioxidant defences and reactive oxygen species production [45]. Enalapril therapy may interact with different cellular signalling pathways, including nuclear factor-kappa B (NF-B), which regulates TNF-. TNF-expression in the liver may be affected by Enalapril-induced changes in these pathways [44].

Conclusion

The study found that 20% enalapril treatment significantly increased urea and creatinine concentrations after 1 week and significantly higher levels after 4 weeks. Kidneys showed healthy glomeruli, vascular congestion, and mild inflammation. Enalapril 10% treatment led to kidney atrophy, dilatation, renal cyst, vascular congestion, and vacuolar degeneration. TNF- expression was found to be negative, mild, moderate, and moderate, with the 20% captopril and 20% enalapril groups showing minor and moderate expression, respectively.

Conflict interest: None

Acknowledgment: We thank University of Mosul College of Vet-Med.

TABLE 1. Biochemical changes after acute treatment for 1-week with Enalapril and Captopril with different concentrations of the LD_{50}.

Parameters / Groups	Urea Conc. mg/dl	Creatinine Conc. mg/dl
Control	44.1±2.5	0.44±0.04
Captopril 10%	45.4± 3^{B}	$0.5±0.03^{B}$
Captopril 20%	$56.6±3.2^{B}$	$0.6±0.03^{B}$
Enalapril 10%	$48.6±2.5^{B}$	$0.54±0.02^{B}$
Enalapril 20%	$81.4±7.8^{*A}$	$1.56±0.02^{*A}$
P-value	<0.001	0.105

Data expressed as Mean ± Stander error SE

* Refers to the significant differences between the group with the control group at $p \leq 0.05$

The difference letters refer to the significant differences between groups at $p \leq 0.05$

TABLE 2. Biochemical changes after 4-weeks of treatment with Captopril and Enalapril with different concentrations of the LD_{50}.

Parameters / Groups	Urea Conc.. mg/dl	Creatinine Conc.. mg/dl
Control	44.7±1	0.5±0.04
Captopril 10%	61.3±2.1^{B}	0.5±0.02^{B}
Captopril 20%	75.7±7.4^{*B}	0.55±0.05^{B}
Enalapril 10%	70.2±6^{B}	0.52±0.03^{B}
Enalapril 20%	117.8±29.7^{*A}	1.58±0.04^{*A}
***P*-value**	0.019	0.105

Data expressed as Mean ± Stander error SE
* refers to the significant differences between the group with the control group at $p \leq 0.05$
The difference letters refer to the significant differences between groups at $p \leq 0.05$

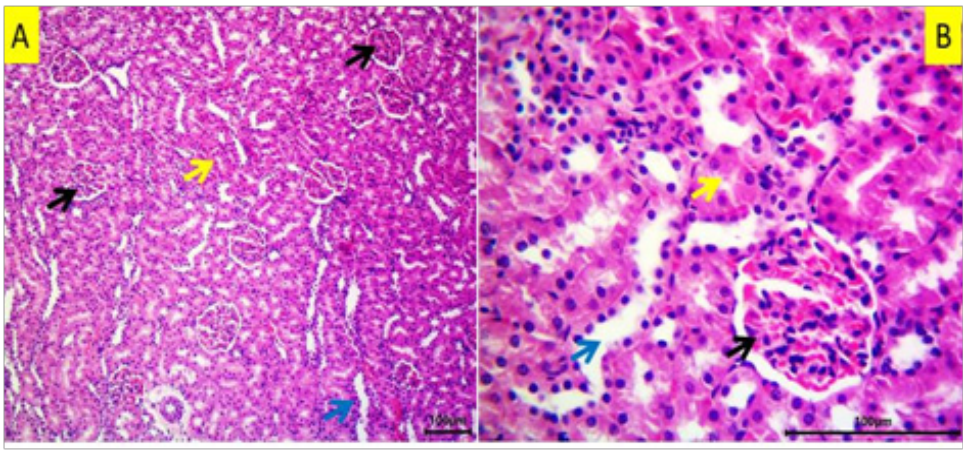

Fig. 1. Photomicrograph of rat kidney of control group showing normal architecture of glomeruli (black arrow), proximal renal tubules (yellow arrow) and distal renal tubules (blue arrow). H&E stain, (A: 100X, B: 400X).

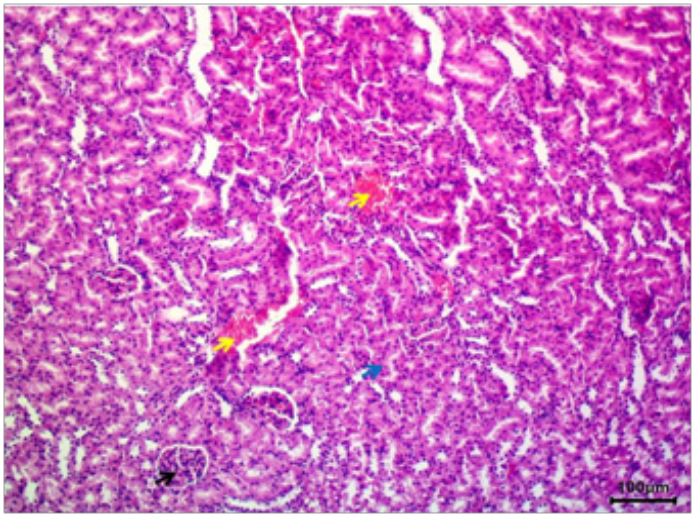

Fig. 2. Photomicrograph of rat kidney of Captopril 10% treated dose group (1-week) showing intact glomeruli (black arrow), and proximal renal tubules (yellow arrow) with blood vessels congestion and hemorrhage (blue arrow). H&E stain, 100X.

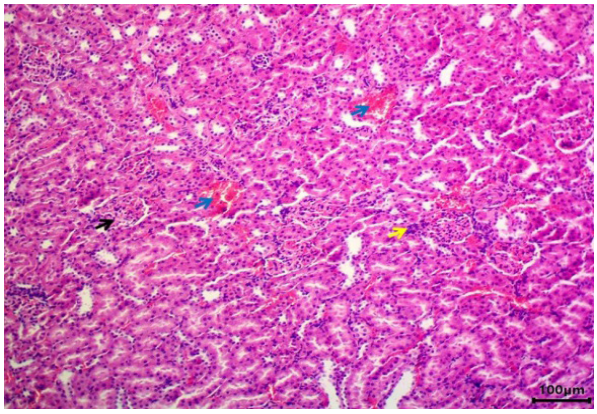

Fig.3. Photomicrograph of rat kidney of Captopril 20% treated dose group (1-week) showing intact glomeruli (black arrow), blood vessels congestion and hemorrhage (yellow arrow) and mild infiltration of few inflammatory cells (blue arrow). H&E stain, 100X.

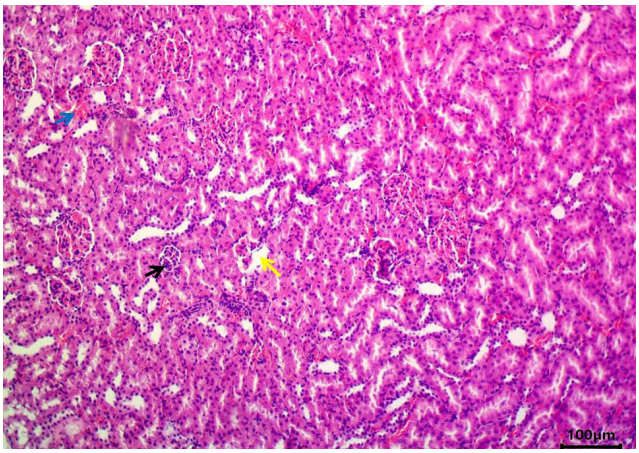

Fig. 4. Photomicrograph of rat kidney of Enapril 10% treated dose group (1-week) showing mild atrophy of glomeruli (black arrow), mild dilation of Bowman's space (yellow arrow), and blood vessels congestion (blue arrow). H&E stain, 100X.

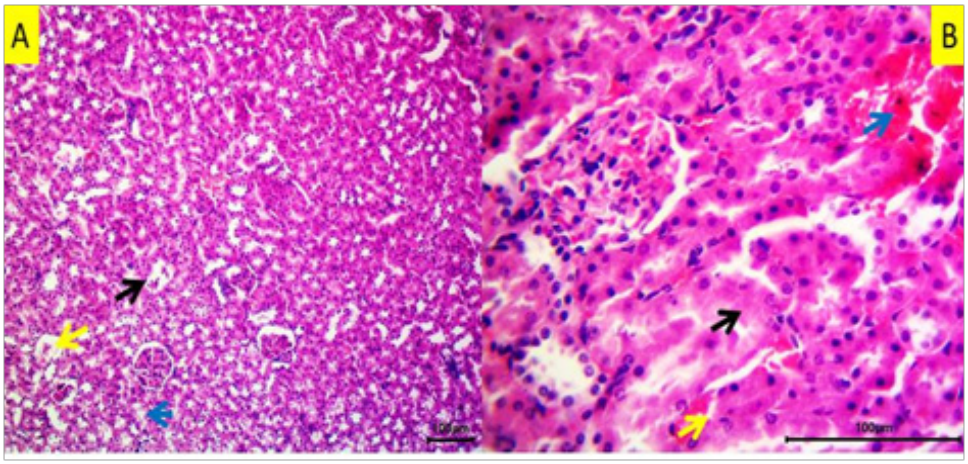

Fig. 5. Photomicrograph of rat kidney of Enapril 20% treated dose group (1-week) showing (A): atrophy of glomeruli (black arrow), dilation of Bowman's space (yellow arrow), and vacuolar degeneration of epithelial cells lining renal tubules (blue arrow). (B): cloudy degeneration of epithelial cells lining renal tubules (black arrow), blood vessels congestion (yellow arrow) and hemorrhage (blue arrow). H&E stain, (A: 100X, B: 400X).

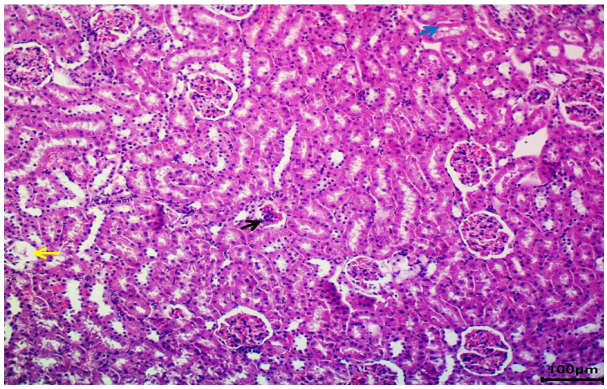

Fig. 6. Photomicrograph of rat kidney of Captopril 10% treated dose group (4-week) showing (A): atrophy of glomeruli (black arrow), dilation of Bowman's space (yellow arrow), and vacuolar degeneration of epithelial cells lining renal tubules (blue arrow). H&E stain, 100X.

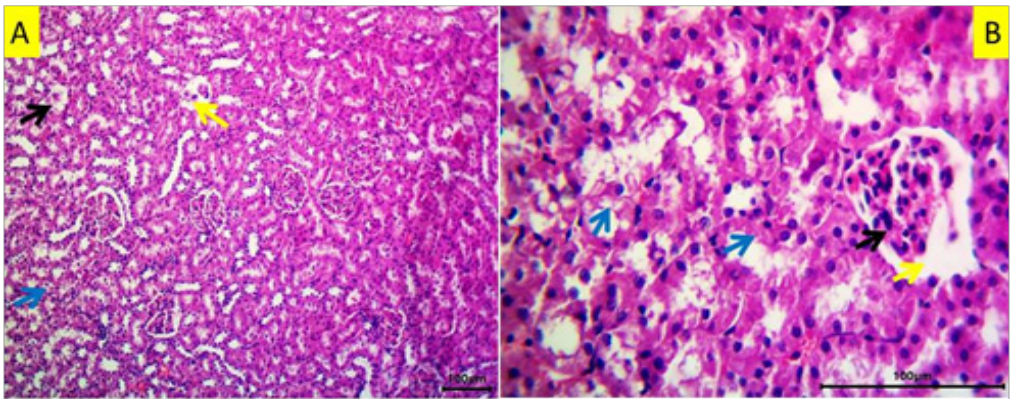

Fig. 7.CF photomicrograph of rat kidney of Captopril 20% treated dose group (4-week) showing (A): atrophy of glomeruli (black arrow), dilation of Bowman's space (yellow arrow), and vacuolar degeneration and necrosis of the epithelial cells lining renal tubules (blue arrow). H&E stain, (A: 100X, B: 400X).

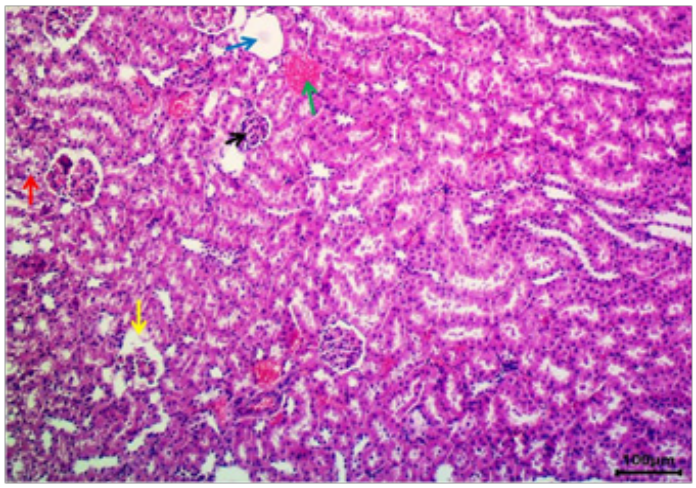

Fig. 8. photomicrograph of rat kidney of Enapril 10% treated dose group (4-week) showing atrophy of glomeruli (black arrow), dilation of Bowman's space (yellow arrow), renal cyst (blue arrow), blood vessels congestion (green arrow) and vacuolar degeneration of the epithelial cells lining renal tubules (red arrow). H&E stain, 100X.

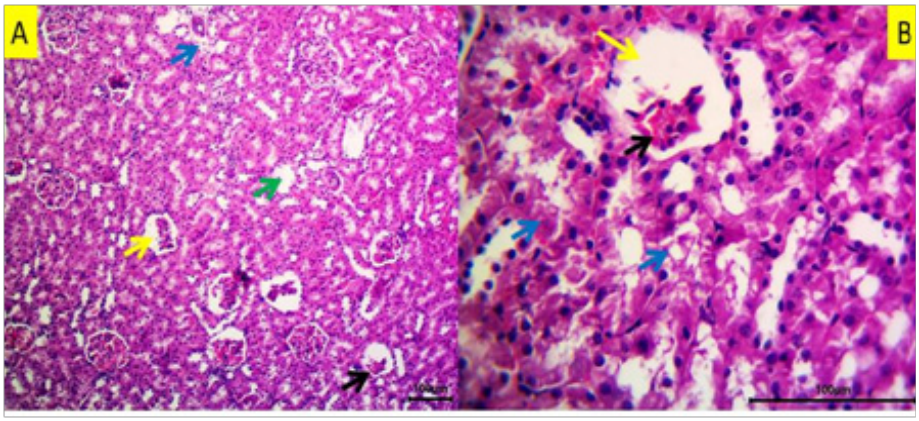

Fig. 9.Photomicrograph of rat kidney of Enapril 10% treated dose group (4-week) showing atrophy of glomeruli (black arrow), dilation of Bowman's space (yellow arrow), (A): renal cyst (green arrow), and vacuolar degeneration and necrosis of the epithelial cells lining renal tubules (red arrow). H&E stain, (A: 100X, B: 400X).

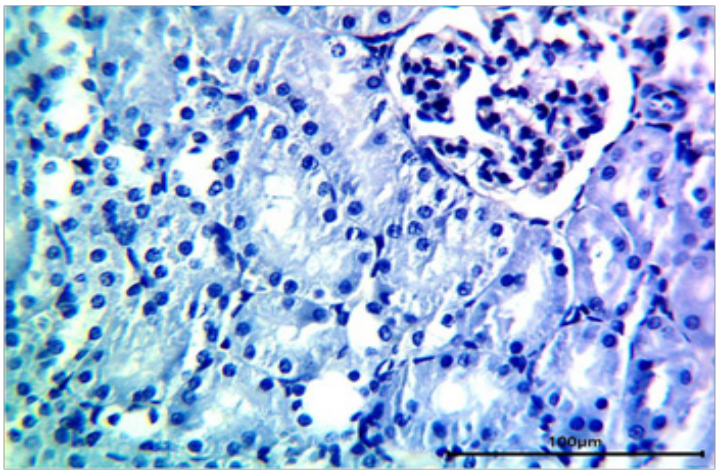

Fig. 10. Immunohistochemical expression of TNF-α in the rat kidney of the control group (4-week) showing negative expression . Hematoxylin stain; 400X.

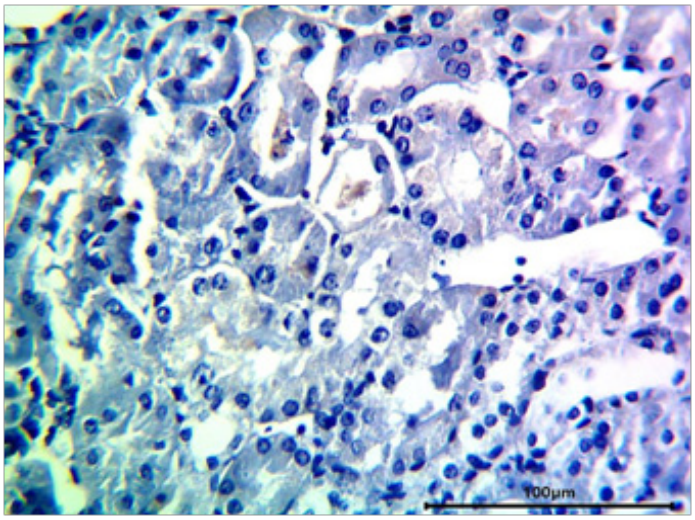

Fig.11.Immunohistochemical expression of TNF-α in the rat kidney of the Captopril 10% treated dose group (4-week) showing slight positive expression (brown color). Hematoxylin stain; 400X.

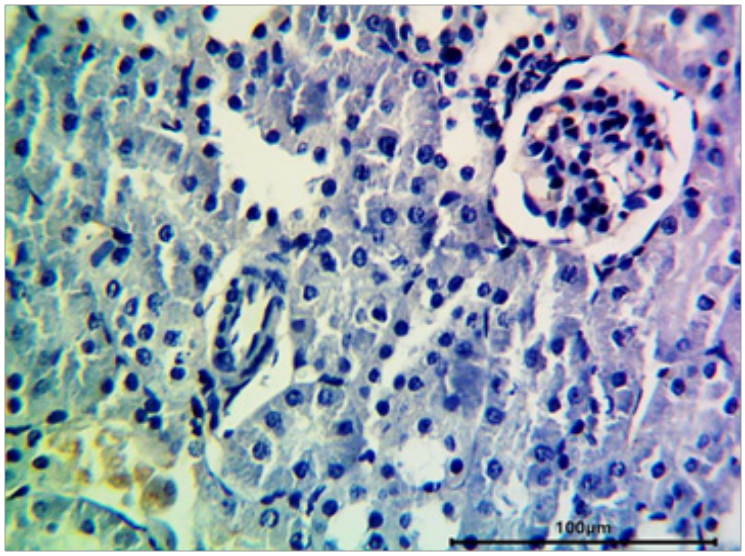

Fig. 12. Immunohistochemical expression of TNF-α in the rat kidney of the Captopril 20% treated dose group (4-week) showing moderate positive expression (brown color). Hematoxylin stain; 400X.

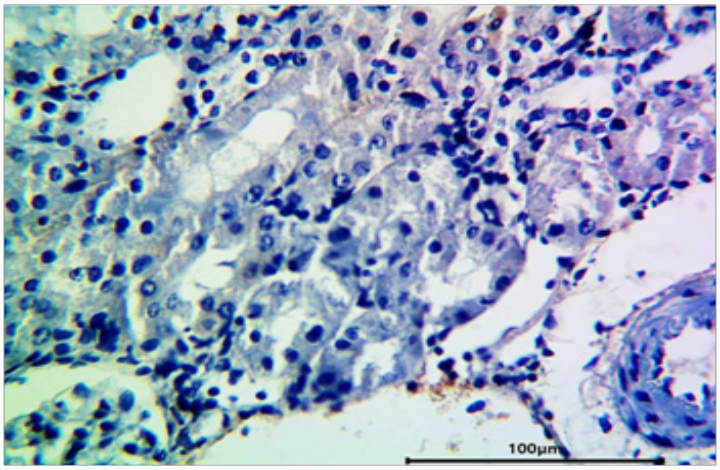

Fig. 13. Immunohistochemical expression of TNF-α in the rat kidney of the Enalapril 10% treated dose group (4-week) showing slight positive expression (brown color). Hematoxylin stain; 400X.

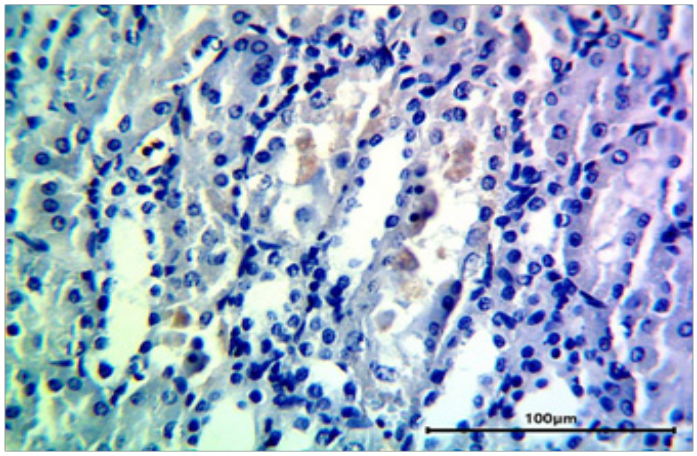

Fig.14. Immunohistochemical expression of TNF-α in the rat kidney of the Enalapril 20% treated dose group (4-week) showing moderate positive expression (brown color). Hematoxylin stain; 400X.

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مقارنة وتقييم السمية الكلوية للكابتوبريل والاينالبرل في الجرذان

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كان الغرض من هذه الدراسة هو مقارنة سمية عقاري كابتوبريل وإنالابريل بجرعات عالية على كلية الجرذان. قسمت الحيوانات في هذه التجربة إلى خمسة مجاميع كل منها عشرة حيوانات، المجموعة الأولى اعتبرت مجموعة سيطرة اعطيت الماء المقطر فقط، المجموعة الثانية والثالثة أعطيت جرعتين من كابتوبريل 10 و 20٪ من الجرعة المميتة الوسطية، المجموعة الرابعة والخامسة تلقت جرعتين من إنالابريل. 10 و 20٪. اعطيت كافة الجرع عن طريق الفم مرتين بالأسبوع ولمدة أربعة أسابيع. تم جمع العينات بعد اسبوع، ثم مرة أخرى بعد أربعة أسابيع. بينت النتائج بعد أسبوع واحد من العلاج باستخدام إنالابريل 20٪ ارتفاع واضح في تركيز كل من اليوريا والكرياتينين وكذلك ازداد اليوريا والكرياتينين بشكل ملحوظ في المجموعتين المعاملتين بكل من 20٪ كابتوبريل و 20٪ إنالابريل بعد 4 أسابيع من العلاج. أظهر نسيج الكلى في المجاميع المعاملة بجرعة 10% لمدة أسبوع واحد الكبيبات الكلوية سليمة مع احتقان الأوعية الدموية وارتشاح طفيف للخلايا الالتهابية. بينما ظهرت الكلية في المجاميع المعاملة بجرعة 20٪ ضمور الكبيبات واتساعًا في محفظة بومان، وتنكس فجوي للخلايا الظهارية. اما بعد 4 اسابيع من المعاملة فأظهرت الكلى في المجاميع المعاملة بالكابتوبريل والانابريل بجرع 10٪ و 20% ضمور في الكبيبات، واتساع في محفظة بومان، وتنكس فجوي في الخلايا الظهارية المبطنة للنبيبات الكلوية. ظهر تعبير TNF-α في الفحص الكيميائي النسيجي المناعي تعبيرًا سلبيًا وخفيفًا ومتوسطًا ومعتدلًا. حيث بينت مجموعة السيطرة تعبيرا سلبيا، بينما أظهرت مجموعتي كابتوبريل 10٪ وإنالابريل 20٪ تعبيرا طفيفا ومعتدلا. خلصت الدراسة الى ان الاينالبرل بتركيز 20% له تاثيرات سمية على الكلية اشد من تأثيرات الكابتوبرل بنفس التركيز.

كلمات المرور: كابتوبرل، اينالبرل، السمية الكلوية، عامل النخر الورمي-الفا ، الجرذان