Research Article

BASJVETRES

BASRAH JOURNAL OF VETERINARY RESEARCH, 2023, 22(4):47-65
https://bjvr.uobasrah.edu.iq/

Evaluation of the Hepatotoxicity Induced by Captopril and Enalapril in Rat Liver: A Comparative Study

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DOI: 10.23975/bjvetr.2023.181828

Received: 1 October 2023 Accepted: 12 October 2023.

Abstract

The aim of this study was to look into the toxicity of captopril and enalapril in high doses in the liver. The animals in this experiment were divided into five groups of ten each, with the first group serving as a control group, receiving only distilled water, the second and thrird groups receiving doses of captopril 10 and 20%, and the fourth and fifth groups receiving doses of enalapril 10 and 20%. The dose is taken orally once every three days for four weeks. After one week, samples were collected, and then again four weeks later. After one week of treatment with Enalapril 20%, biochemical testing revealed significant elevations in ALT and AST. After 1 and 4 weeks of treatment with Enalapril 20%, there was a decrease in glutathione and an increase in malondialdehyde, whereas captopril 20% and Enalapril 10 and 20% significantly raised malondialdehyde levels. Rats given captopril 20% revealed diffuse vacuolar degeneration. The 10% Enalapril group experienced similar symptoms, however the 20% Enalapril group experienced vacuolar degeneration, coagulative necrosis, significant inflammatory cell infiltration, portal vein congestion, and sinusoidal dilatation. The researchers looked at the expression of TNF-a in the livers of rats after four weeks of therapy with Captopril 10% and 20% and Enalapril 20% (20%). The results revealed three levels of expression: low, medium, and high. According to the findings of this study, Enalapril has higher adverse impacts on the liver than captopril at the same dose ratio.

Keywords: Captopril, Enalapril, Hepatotoxicity, TNF-a.

Introduction

The liver is the most vital organ in the human body. It is required for the regulation of several physiological functions. It is involved in metabolism, secretion, and storage, among other things. It has a high ability for detoxication and the production of beneficial principles (1). Captopril and enalapril are both angiotensin-converting enzyme (ACE) inhibitors used to treat hypertension and heart failure. Although these medications are generally well tolerated, there have been occasional reports of hepatotoxicity associated with their use. (2). Hepatotoxicity is defined as liver injury or harm induced by specific pharmaceuticals or chemicals (2). medications or other substances. Elevated liver enzymes, liver inflammation, and more severe disorders such as drug-induced liver damage (DILI) can all be symptoms (3).

Hepatotoxicity from therapeutic doses of ACE inhibitors is uncommon and occurs in a tiny percentage of people. Most people tolerate these drugs well and have no adverse effects on their liver. (4). Fatigue, jaundice (yellowing of the skin and eyes), dark urine, abdominal pain, and increased liver enzymes on blood tests are all symptoms of hepatotoxicity (5).Pre-existing liver disorders, the use of other drugs that can harm the liver and alcohol intake can all raise the risk of hepatotoxicity (6). Patients taking ACE inhibitors must have their liver function checked on a regular basis (through blood testing). This helps doctors to detect any early signs of liver damage If hepatotoxicity is suspected, the ACE inhibitor must be stopped promptly and medical treatment sought for further evaluation and therapy. In the event of hepatotoxicity, healthcare practitioners may investigate alternate antihypertensive drugs with a lower risk of liver-related adverse effects (7, 8). The purpose of this study was to look into the toxicity of captopril and enalpril in high doses on the liver.

Materials and Methods

Animals: The animals were female Sprague-Dawley rats with weights ranging from 250 to 300 grammes and ages ranging from one to two months. Throughout the trial, they were given water and food, and all humane and ethical standards for dealing with animals were followed.

Ethical approval: Humane procedures and methods for dealing with animals were used in accordance with the system outlined in the Code of Ethics for Dealing with Laboratory Animals, and approval was received from the University of Mosul, College of Veterinary Medicine, and in accordance with the numbered formUM. Vet.2022.05

Dose preparation: Captopril and enalapril maleate formulations employed pure drug weight based on body weight and were dissolved in 2% diluted ethanol before being administered to animals.

Expediently Design: Divide the animals in this experiment into five groups of ten animals each; the first group served as a control group, containing only distilled water; the second group The third group received Captopril 10 and 20%, whereas the fourth and fifth groups received Enalapril 10

and 20% theses percentage of LD50. doses taken from (Imai et al., 1981, National Center for Biotechnology Information,2023) (9,10). captopril oral LD50 is 4245 mg/kg in female rats and enalapril Oral LD50 in rats is 2973 mg/kg.

The appropriate dose was administered orally through gavage tube once every three days for four weeks. 5 animals were sacrificed. After one week, and the remainder after four weeks. The animals were euthanized using ether, and blood was collected from the orbital of the eye. The serum was separated using a centrifuge set to 3000 cycles per minute for 10 minutes. Organ (liver) collection and thorough washing with tap water, followed by drying on filter paper and placing in diluted formalin until histopathologic examination is completed.

Analysis materials

-Kit for ALT (Alanin Aminotransferase) from Biolab company, France
-Kit for AST (Aspartate aminotrancferease) from Biolab company, France
-Kit for GSH (Glutathione) from Biolab company, France
-Kit for MDA (Malonseladehyde) from Biolab company, France

Statically analysis: The data were statistically represented using the average and standard error at a level less or equal to 0.05 and the one-way ANOVA test was used using the Sigma Plot program, utilized Duncan's multiple comparison test.

Results

After one week of the experiment, the biochemical serological tests obtained by spectrophotometry revealed a significant increase in the Alanine transaminase ALT and Aspartate Aminotransferase AST of the Captopril 20%, Enalapril 10%, and Enalapril 20% treated groups compared with the control group. As well as a significant increase in the ALT of the Enalapril 20% treated group compared with the Captopril 10% All statistically significant differences were at $p \leq 0.05$. The results revealed that after 4th week of the experiment were a significant increase in the Alanine transaminase ALT 20% treated groups compared with the control group (Table 2).

Glutathione GSH and Malondialdehyde MDA parameters:

The group treated with Enalpril 20% recorded a significant decrease in the level of glutathione after a week of treatment compared to the control group and the rest of the groups (Table 3). When measuring the level of malondialdehyde lipid peroxidation, it was found that there was a significant increase in the groups treated with Captopril 20% and Enalapril 10 and 20% compared to the control group and the Captopril 10% group at a probability level less than 0.001 (Table 3). The level of glutathione after four weeks of treatment showed a significant decrease in the groups treated with each of Captopril 20% and Enalapril 10 and 20% compared with the control group and the Captopril group 10% at less than 0.001 (Table 4). While malondialdehyde was recorded after 4 weeks of treatment, there was a significant increase in the groups treated with Captopril 20% and Enalapril 10 and 20%, compared to the control group and the Captopril group 10% at a probability level of 0.003 (Table 4).

Table 1: Biochemical changes after acute treatment for 1-week with Enalapril and Captopril

Parameters Groups	ALT Conc. IU/L	AST Conc. IU/L
Control	18.3±3.2	14.7±0.5
Captopril 10%	21.5±1.9B	18.6±1.4B
Captopril 20%	26±1.1*	20.5±2.5*B
Enalapril 10%	25.1±1.2*	25.3±1.3*A
Enalapril 20%	28.3±0.7*A	28.8±0.9*A
***P*-value**	0.024	0.007

Data expressed as Mean ± Stander error SE for 10 rats' group
*** 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 4th weeks of treatment with Captopril and Enalapril.

Parameters Groups	ALT Conc. IU/L	AST Conc. IU/L
Control	17±1.1	14.4±0.8
Captopril 10%	24.9±4	15.7±0.9B
Captopril 20%	26.1±2.6*	17.9±0.8*B
Enalapril 10%	28.1±3.6*	17.1±0.9B
Enalapril 20%	33.8±2.3*	24±1.2*A
***P*-value**	0.012	<0.001

Data expressed as Mean ± Stander error SE For 10 rats \group
*** 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 3: Glutathione GSH and Malondialdehyde MDA parameters after acute treatment for 1-week with Captopril and Enalapril

Parameters / Groups	GSH Conc. Micromole\ml	MDA Conc. Nanomole\ml
Control	19.2±0.7	2.1±0.1
Captopril 10%	18.5±0.7B	2.2±0.2B
Captopril 20%	18.4±0.9B	3.3±0.2*A
Enalapril 10%	18.7±0.6B	3.4±0.1*A
Enalapril 20%	14.6±0.4*A	3.6±0.1*A
***P*-value**	<0.001	<0.001

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 4: Glutathione GSH and Malondialdehyde MDA parameters after 4th week with Captopril and Enalapril with different concentrations of the LD50.

Parameters / Groups	GSH Conc. Micromole\ml	MDA Conc. Nanomole\ml
Control	15.9±0.6	2.4±0.1
Captopril 10%	14.4±0.5	3±0.2B
Captopril 20%	13.8±0.5*	3.7±0.2*
Enalapril 10%	10±0.7*B	3.4±0.1*
Enalapril 20%	7.3±0.5*C	4.2±0.1*A
***P*-value**	<0.001	0.003

Data expressed as Mean ± Stander error SE

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

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

Histopathological examination of the liver in control animals showed the normal structure of the liver represented by hepatocytes, central vein, portal region, and sinusoids (Figure 1). the histological sections of the liver of animals treated with Captopril 10% (1-week) showed intact hepatocytes, congestion of the central vein , and mild infiltration of few inflammatory cells in the portal area (Figure 2). In Figure 3 for the Captopril 20% treated dose group (1-week) showing mild vacuolar degeneration of the hepatocytes, congestion of central vein, and portal vein. In group of Enalapril 10% treated dose group (1-week) showing vacuolar degeneration of the hepatocytes, with single cell necrosis, and expansion of the sinusoids.

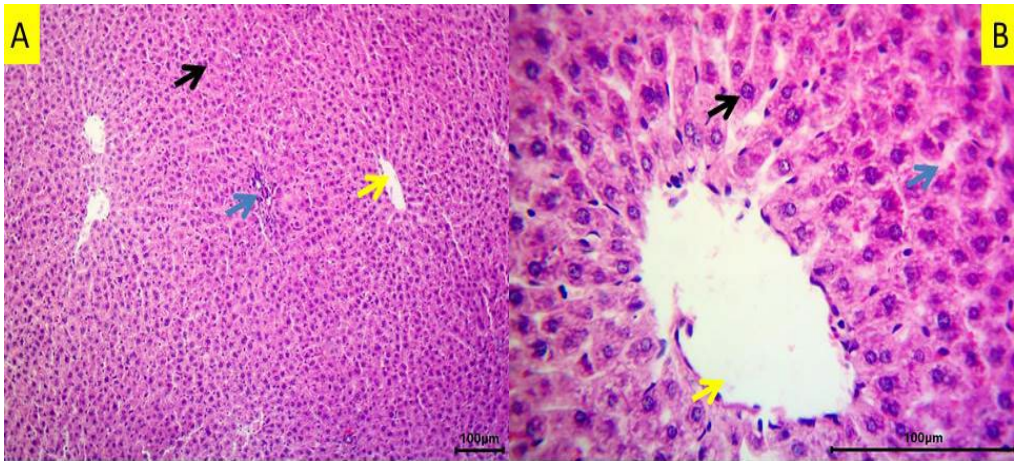

Figure 1: photomicrographs of rat liver of control group showing normal architecture representing by hepatocytes (A&B:black arrow), central vein (A&B: yellow arrow), (A): portal area and (B) sinusoids (blue arrow). H&E stain, (A:100X, B: 400X)

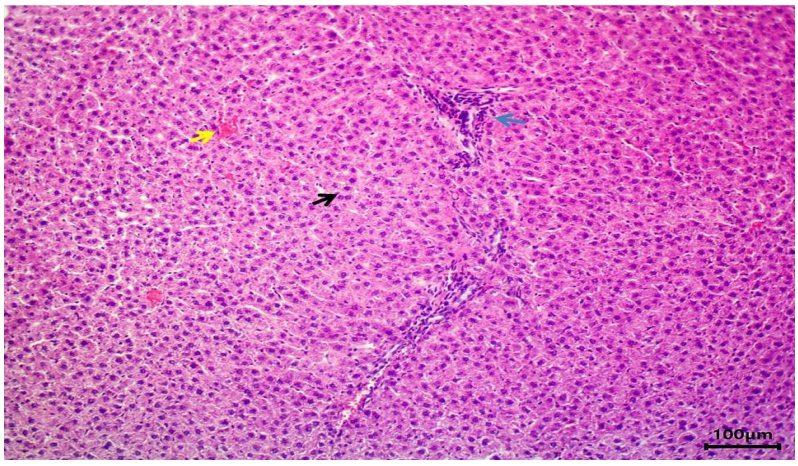

Figure 2: photomicrograph of rat liver of the Captopril 10% treated dose group (1-week) showing intact hepatocytes (black arrow), congestion of central vein (yellow arrow), and mild infiltration of few inflammatory cells in the portal area (blue arrow). H&E stain, 100X.

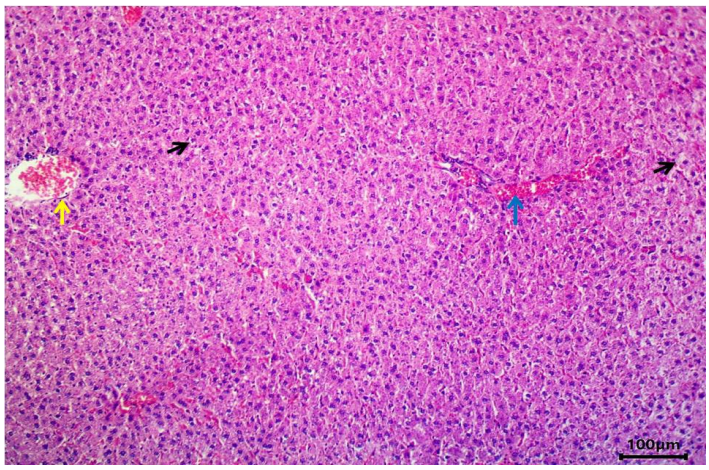

Figure 3: photomicrograph of rat liver of the Captopril 20% treated dose group (1-week) showing mild vacuolar degeneration of the hepatocytes (black arrow), congestion of central vein (yellow arrow), and portal vein (blue arrow). H&E stain, 100X.

Figure 10 of the Captopril 10% treated dose group (4th week) showing diffuse vacuolar degeneration of the hepatocytes , and congestion of central vein. Figure 4 of the Captopril 20% treated dose group (4th week) showing diffuse vacuolar degeneration of the hepatocytes, infiltration of inflammatory cells in portal area and congestion of portal vein. Figure 5 for liver of the Enalapril 10% treated dose group (4th week) showing diffuse vacuolar degeneration of the hepatocytes, infiltration of inflammatory cells in portal area and congestion of central vein. Figure 6 for liver of the Enalapril 20% treated dose group (4th week) showing vacuolar degeneration and coagulative necrosis of the hepatocytes, severe infiltration of inflammatory cells in portal area , congestion of portal vein , and expansion of sinusoids. Figure 7 for liver of the Enalapril 20% treated dose group (4th week) showing vacuolar degeneration and coagulative necrosis of the hepatocytes, severe infiltration of inflammatory cells in portal area , congestion of portal vein , and expansion of sinusoids.

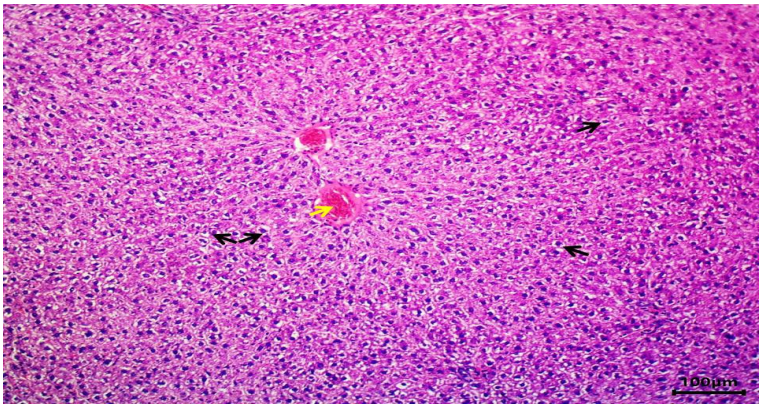

Figure 4: photomicrograph of rat liver of the Captopril 10% treated dose group (4th - week) showing diffuse vacuolar degeneration of the hepatocytes (black arrow), and congestion of central vein (yellow arrow). H&E stain, 100X.

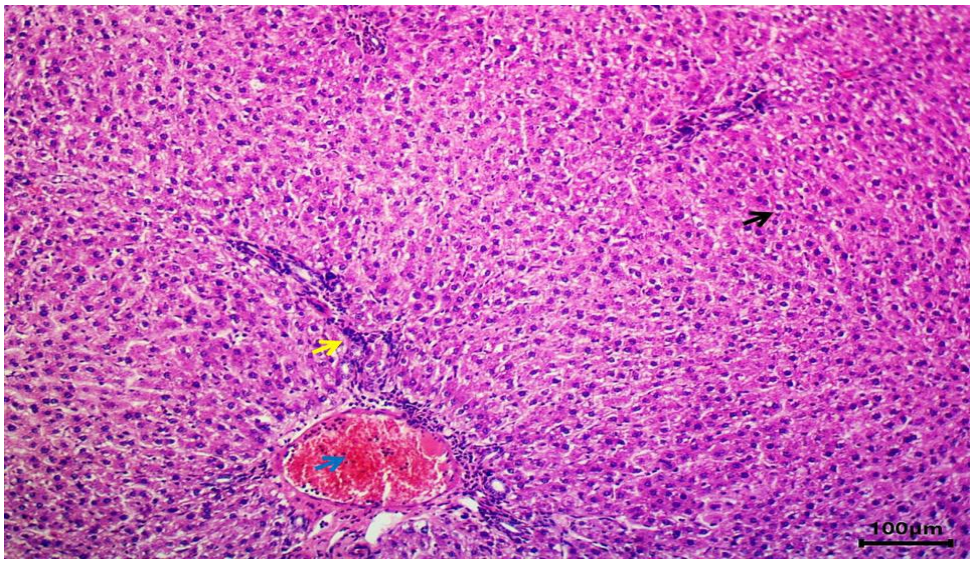

Figure 5: photomicrograph of rat liver of the Captopril 20% treated dose group (4th -week) showing diffuse vacuolar degeneration of the hepatocytes (black arrow), infiltration of inflammatory cells in portal area (yellow arrow) and congestion of portal vein (blue arrow). H&E stain, 100X.

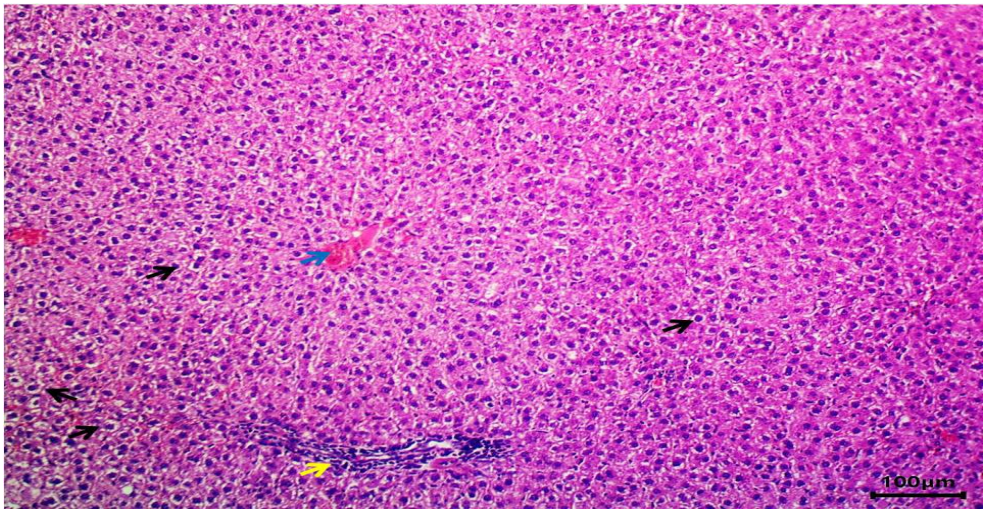

Figure 6: photomicrograph of rat liver of the Enalapril 10% treated dose group (4th -week) showing diffuse vacuolar degeneration of the hepatocytes (black arrow), infiltration of inflammatory cells in portal area (yellow arrow) and congestion of central vein (blue arrow). H&E stain, 100X.

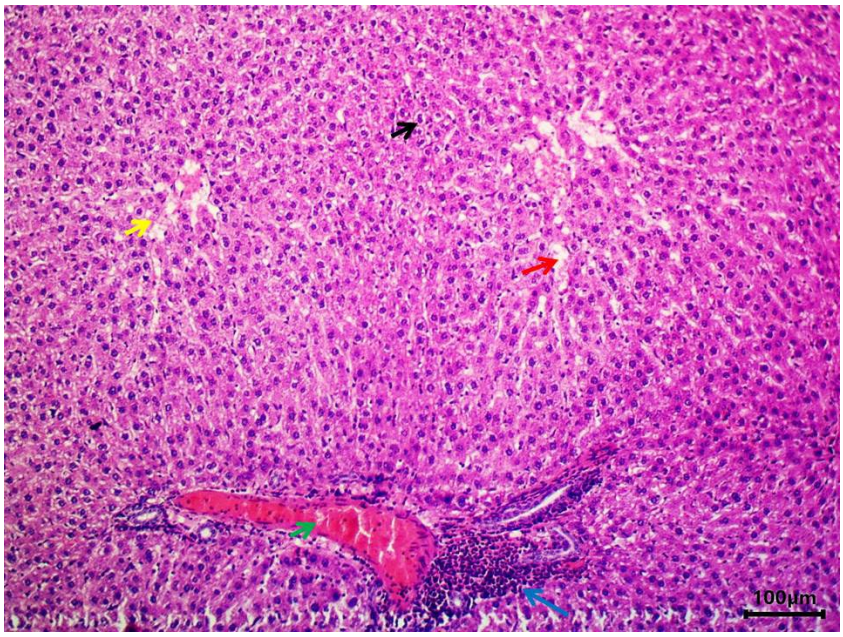

Figure 7: photomicrograph of rat liver of the Enalapril 20% treated dose group (4th -week) showing vacuolar degeneration (black arrow) and coagulative necrosis (yellow arrow) of the hepatocytes, severe infiltration of inflammatory cells in portal area (blue arrow), congestion of portal vein (green arrow) and expansion of sinusoids (red arrow). H&E stain, 100X.

Immunohistochemical expression of TNF-α:

In Figure 8 appeared expression of TNF-α in the rat liver of the control group (4^{th} week) showing negative expression. Figure 9 for expression of TNF-α in the rat liver of the Captopril 10% treated dose group (4^{th} week) showing slight positive expression. Figure 10 for expression of TNF-α in the rat liver of the Captopril 20% treated dose group (4^{th} week) showing high positive expression. Figure 11 for expression of TNF-α in the rat liver of the Enalapril 10% treated dose group 4^{th} week) showing moderate positive expression. Figure 12 for expression of TNF-α in the rat liver of the Enalapril 20% treated dose group (4^{th} week) showing high positive expression.

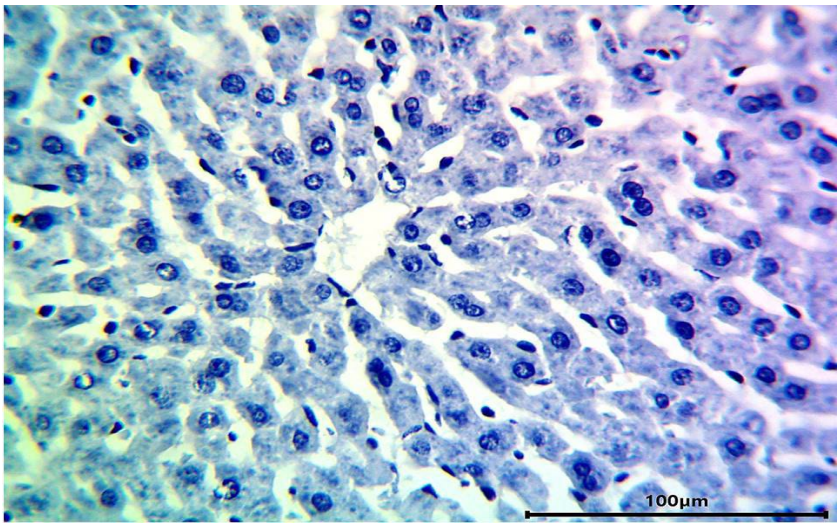

Figure 8: Immunohistochemical expression of TNF-α in the rat liver of the control group (4th -week) shows negative expression. Hematoxylin stain; 400X.

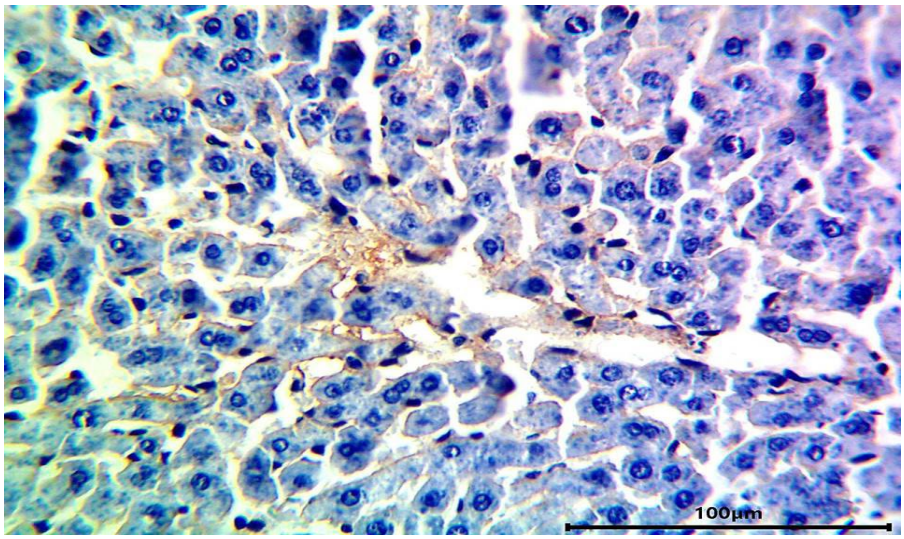

Figure 9: Immunohistochemical expression of TNF--α in the rat liver of the Captopril 10% treated dose group (4th -week) showing slight positive expression (brown color). Hematoxylin stain; 400X.

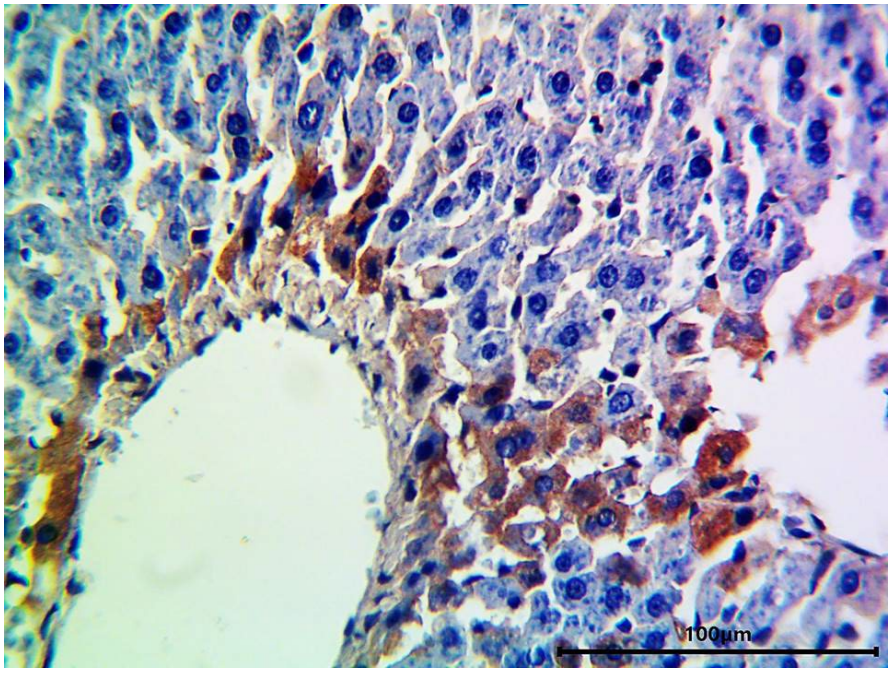

Figure 10: Immunohistochemical expression of TNF-α in the rat liver of the Captopril 20% treated dose group (4th -week) shows high positive expression (brown color). Hematoxylin stain; 400X.

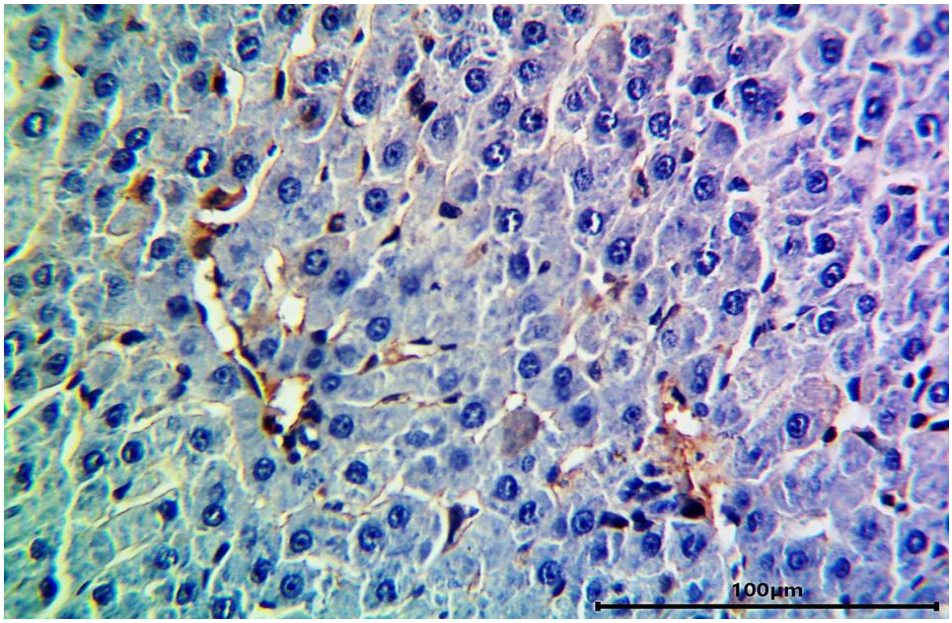

Figure 11: Immunohistochemical expression of TNF-α in the rat liver of the Enalapril 10% treated dose group (4th -week) showing moderate positive expression (brown color). Hematoxylin stain; 400X.

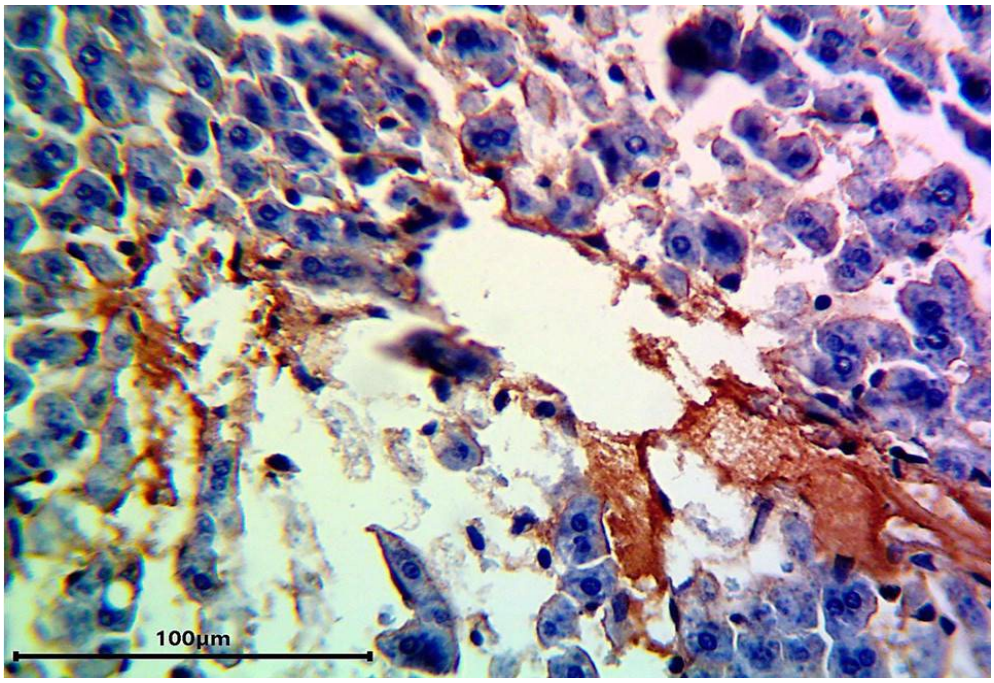

Figure 12: Immunohistochemical expression of TNF-α in the rat liver of the Enalapril 20% treated dose group (4th -week) shows high positive expression (brown color). Hematoxylin stain; 400X.

Discussion

Although both Captopril and Enalapril contain the same active substance that is Enalapril maleate, which has antihypertensive effects, our study utilizing high doses revealed the presence of somewhat diverse adverse consequences in liver and kidney. The primary distinction between the two medications is that Enalapril, does not contain the chemical sulfhydryl group, whereas Captopril contains the chemical sulfhydryl group (11) .

Because of this difference in chemical structure, the human or animal body metabolites each drug differently, with Captopril metabolism in the liver being Captopril disulfide, which is the active metabolite responsible for Captopril's beneficial pharmacological effects, and Enalapril metabolism being Enalaprilat, which is the active metabolite of the drug Enalapril. Despite the fact that both drugs have the same pharmacological action of lowering blood pressure, the presence of two different types of metabolites causes each drug to have different side effects in high doses. (13).

Captopril is an ACE inhibitor that is primarily used to treat hypertension and heart failure (14). Captopril can affect particular liver enzymes; however it has little effect on liver function at therapeutic doses, and the situation is reversed at hazardous concentrations. Enalapril,

commonly known as Enalapril maleate, is an angiotensin-converting enzyme (ACE) inhibitor, similar to Captopril. It is frequently used to treat hypertension, heart failure, and several renal illnesses. (15).

Liver enzymes are proteins that the liver produces to aid in numerous metabolic processes (16). These enzymes may leak into the circulation when liver cells are injured or irritated, resulting in high levels. Alanine aminotransferase (ALT), and aspartate aminotransferase (AST), are the common liver enzymes evaluated in blood testing (17). That may be the causes for the significant increase of ALT and AST in 20% Captopril after 1 and 4 weeks of treatment.

Despite the fact that captopril has been related to a limited number of cases of liver damage, it is generally recognized as a safe drug for liver function in therapeutic levels (18). This result was demonstrated in this study when Captopril 10% was used for one and four weeks. Captopril's effect on liver enzymes has been shown in clinical studies to be limited and transient, with few incidences of clinically significant liver abnormalities. (19).

Captopril 10% for 1 and 4 weeks did not cause a significant difference in glutathione and malondialdehayd, which could be because it is usually well tolerated and does not cause oxidative stress at low or therapeutic doses. However, it is important to remember that in some cases, excessive doses or prolonged use of Captopril, such as 20% Captopril, can cause oxidative stress (20). Another reason for the lack of significant changes in glutathione levels observed in our study of 10% Captopril for 1, 4 weeks Because of its structural resemblance to cysteine (19). Many investigations found no effect of low-dose Captopril use on glutathione depletion (20; 21).

Toxic or excessive amounts can disturb the body's normal balance of oxidants and antioxidants, leading to an increase in reactive oxygen species (ROS) and oxidative stress. When redox equilibrium, or the balance of oxidants and antioxidants, is interrupted, this can occur (22). Long-term Captopril treatment can also affect the oxidative balance of certain animals . Chronic Captopril use may cause long-term ACE suppression by affecting the renin-angiotensin-aldosterone pathway and potentially disrupting the balance of oxidants and antioxidants. (23).

MDA is a lipid peroxidation marker associated with oxidative stress and cellular damage (24). While captopril is generally well tolerated and rarely causes a rise in MDA levels, as demonstrated in 10% Captopril for 1 and 4 weeks. High doses or continuous use of Captopril may produce oxidative stress and subsequent lipid peroxidation in our results for using Captopril 20% for one week and 10% for four weeks. Excessive production of reactive oxygen species (ROS) or a shift in the balance of oxidants and antioxidants can result in lipid peroxidation and increased MDA levels. (24).

Enalapril, like other ACE inhibitors, has not been linked to an increase in oxidative stress when taken at therapeutic levels. However, it is important to note that in circumstances of toxic or excessive doses, or continuous

use of Enalapril 10, 20% for 1, 4 weeks, there is an increased risk of oxidative stress (25). Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to counteract them with antioxidants. In some cases, high doses or long-term use of Enalapril may disrupt the balance of oxidants and antioxidants, resulting in elevated oxidative stress (26).

Captopril may cause liver damage when taken in large doses or for an extended period of time, while this is uncommon. Captopril-induced liver damage is regarded as an unusual and unexpected occurrence (25). Histological alterations associated with hazardous long-term Captopril dosages and liver damage have been identified in a few cases, despite their rarity. The specific histology findings may vary depending on the severity and duration of the liver injury. Some of the observed histopathological abnormalities in the use of Captopril 20% in 1 and 4 weeks include Captopril intoxication, which is distinguished by changes in liver cells. Hepatocyte hypertrophy, vacuolar degeneration, and necrosis are examples (27).

Inflammatory cells such as lymphocytes and macrophages may enter liver tissue in response to Captopril damage. This inflammation has the potential to worsen the progression of liver injury (28). Captopril-induced liver injury can result in cholestasis, a disease characterized by reduced bile flow, in some situations. Cholestasis is indicated by bile duct enlargement and bile pigment accumulation in liver cells (29) .

Prolonged liver injury caused by toxic Captopril dosages may result in the formation of new connective tissue (fibrosis) within the liver. If untreated or severe, fibrosis can proceed to cirrhosis, which is characterized by extensive scarring and liver tissue failure (30). These histological abnormalities are not limited to Captopril-induced liver damage; they can also be found in liver damage produced by other causes. Captopril has a low overall risk of liver damage, with 10% experiencing it between 1 and 4 weeks, and the vast majority of persons who use it do not encounter serious liver-related side effects (31) .

The livers of rats treated with Enalapril 10 and 20% for 1 and 4 weeks showed clear hepatic histological alterations. Our findings strongly suggested that oxidative stress had a role in the etiology of Enalapril-induced liver damage. In accordance of our findings, one study found that mice treated with Enalapril had higher ALT levels, as well as higher HO-1 mRNA expression, serum hydrogen peroxide levels, and hepatic MDA levels. Previous research on mice using Enapril 1800 mg/kg (p.o.) affected the expression of oxidative stress-responsive genes such as glutathione-S-transferase, alpha-2 type, and NAD, H quinone dehydrogenase 1 in the liver (31; 32) Valko et al., 2007).

TNF- is an inflammatory cytokine involved in a range of physiological processes, including inflammation and immune responses. Elevated TNF- levels are typically associated with liver injury and inflammation (33).

TNF- in the rat liver after Captopril and Enalapril administration varies depending on a number of parameters, including dosage, length of treatment, and individual rat physiological differences. After 4 weeks, the liver showed a low positive expression of TNF- in 10% Captopril and a high positive expression in 20% Captopril. This finding could be due to TNF-'s role in the regulation of immune responses and inflammation. TNF- levels that are high can help to initiate and sustain an inflammatory response in the liver (34). TNF- influences liver function by interfering with various metabolic processes. It has the potential to disturb bile acid balance, affect glucose and lipid metabolism, and modulate medication metabolism. (35).

TNF- may activate a number of signaling pathways in the liver, including nuclear factor-kappa B (NF-B) and mitogen-activated protein kinases (MAPKs). These pathways play an important role in the regulation of inflammation, immune responses, and cell survival. TNF-induced pathway deregulation can contribute to liver inflammation and damage. TNF- interacts with a number of different types of liver cells, including hepatocytes, Kupffer cells (resident macrophages), and endothelial cells (36). These interactions can lead to the production of more mediators that are inflammatory, the recruitment of immune cells, and the activation of hepatic stellate cells, all of which promote liver inflammation and fibrosis (34). TNF- stimulates the production of reactive oxygen species (ROS) in the liver. Excessive ROS production might lead to oxidative stress. which can lead to lipid peroxidation, DNA damage, and further hepatocellular injury (35).

Conclusion: The study found that Enalapril 20% treatment significantly increased ALT and AST levels, decreased glutathione, and increased malondialdehyde levels. Rats given captopril 10% or Enalapril 10% showed healthy hepatocytes, central venous congestion, and mild inflammation. The 20% group experienced vacuolar degeneration, central vein congestion, and portal inflammation. The study also examined TNF- expression levels in rats' livers after four weeks of treatment, showing higher adverse impacts than captopril at the same dose ratio.

Conflict interest: All authors declare that there is no conflict of interest.

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

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تقييم السمية الكبدية لكابتوبريل وإنالابريل في كبد الجرذان: دراسة مقارنة

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الخلاصة

الهدف من هذه الدراسة دراسة المرض السام للكابتوبريل وانالبريل بجرعات عالية على الكبد. قسمت الى 5 مجاميع كل مجموعة تتكون من 10 حيوانات، المجموعة الأولى اعتبرت سيطرة، جرعت ماء مقطر فقط ، المجموعة الثانية والثالثة تم تجريعها بكابتوبريل 10 و 20 ٪ ، المجموعة الرابعة والخامسة اعطيت جرع من إنالابريل 10 و 20 ٪. عن طريق الفم مرة واحدة كل 3 أيام لمدة 4 أسابيع.تم جمع العينات بعد اسبوع ثم بعد ٤ اسابيع في الكبد للجرذان ، اظهر إنالابريل 10 ٪ خلايا كبدية سليمة واحتقان الوريد المركزي والتهاب خفيف في منطقة المدخل. أظهر الكابتوبرل 20 ٪ تنكس فجوي واحتقان الوريد المركزي واحتقان الوريد البابي. أظهر الكبد تنكسًا فجويًا منتشرًا لخلايا الكبد واحتقان الوريد المركزي وارتشاح خلايا التهابية في المنطقة البوابية. أظهر كبد مجموعة انالبرل 10 % أعراض مماثلة، بينما أظهر كبد مجموعة انالبرل بجرعة 20 ٪ تنكس فجوي و نخر تجلطي للخلايا الكبدية وارتشاح شديد للخلايا الالتهابية واحتقان الوريد البابي وتوسع الجيبانيات. اظهرت نتائج الفحص الكيميائي النسيجي المناعي للتعبير عن عامل النخر الورمي TNF-α في الكبد بعد ٤ اسابيع من المعاملة بجرع مختلفة من كابتوبريل 10٪ و 20٪ و الاينابرل 10٪ تعبيرا خفيفا الى متوسطا بينما اظهرت جرعة الاينابرل 20% تعبيرا عاليا. نستنتج من هذه الدراسة ان الاينابرل بالجرع المرتفعة له تأثيرات سمية على الكبد اشد من تأثيرات الكابتوبرل وبنفس تركيز الجرعة المعطاة.

الكلمات المفتاحية: كابتوبرل، اينالبرل، السمية الكبدية، عامل النخر الورمي-الفا.