SMJ- Sohag Medical Journal, Vol. 29 No(1) 2025

Print ISSN1687-8353 Online ISSN2682-4159

Original Article

The protective effect of the angiotensin converting enzyme inhibitor captopril against ibuprofen-induced hepatotoxicity in the adult male albino rats. Biochemical and Histological study

Mohamed Abdelrahman[1], Hytham Mahmoud Adbel-Latif [2،3], Asmaa Sabry Bassit[1], Bothina Zakria El-Sayed[1], Noha Abd El Magid Ragab Fouda[1]

[1]Department of Human Anatomy and Embryology, Faculty of Medicine, Sohag University, Sohag, Egypt.
[2]Department of Pharmacology, Faculty of Medicine, Sohag University, Sohag, Egypt.
[3]Department of Medical Pharmacology, Al-Rayyan Medical Colleges, AlMadinah Al-Munawwarah, Saudi Arabia.

Abstract

Background: Ibuprofen is one of the non-steroidal anti-inflammatory drugs. It is extensively used to reduce pain and lessen inflammation nevertheless, its extended usage probably leads to hepatotoxic consequences. One of the angiotensin converting enzyme inhibitors, captopril possesses hepatoprotective qualities and is frequently used to lower blood pressure and safeguard the heart.

Aim of the work: To assess captopril's ability to protect the adult male albino rats against ibuprofen-induced hepatotoxicity.

Material and methods: Forty adult male albino rats were used. The rats were divided randomly into four groups with ten animals in each group; group 1 had standard food and distilled water only, group 2 received captopril only, group 3 received ibuprofen only and group 4 received ibuprofen and captopril daily for continuous 6 weeks. All animals were sacrificed at the end of the experiment, then blood samples and livers were harvested for biochemical and histological evaluation.

Results: Ibuprofen administration caused hepatotoxic changes in the form of biochemical and histological findings. The biochemical effects of ibuprofen were in the form of elevated serum levels of liver enzymes with disturbed liver oxidant/antioxidant status that was indicated by elevated malondialdehyde and decreased glutathione levels in the liver tissue. The histological findings were in the form of disturbed liver architecture, degenerative changes affecting the liver cells and excessive fibrosis. The concurrent captopril administration significantly ameliorated all the ibuprofen-induced hepatotoxic effects.

Conclusion: Captopril provided an efficient protective role against the ibuprofen-induced hepatotoxicity hence, it is helpful to be prescribed in the high risk persons.

Keywords: Hepatotoxicity, Captopril, Ibuprofen, Rats.

DOI : 10.21608/SMJ.2024.330372.1502 **Received:** October 22, 2024 **Accepted:** December 15, 2024

Published: January 01, 2025

Corresponding Author: **Mohamed Abdelrahman** **E.mail**: mohamedabdelrahman21031979@gmail.com

Citation: **Mohamed Abdelrahman. et al., The protective effect of the angiotensin converting enzyme inhibitor captopril against ibuprofen-induced hepatotoxicity in the adult male albino rats. Biochemical and Histological study**

SMJ,2025 Vol. 29 No (1) 2025: 30 -40

Introduction

The liver is located just below the diaphragm in the upper belly, the liver is an essential organ. It crosses the epigastrium to reach the left hypochondrium after taking up the majority of the right hypochondrium.[1].. It is the biggest gland in the human body and functions as both an exocrine and an endocrine gland. The exocrine part secretes the bile into the small intestine through the biliary channels while the endocrine part directly secretes vital proteins including prothrombin, albumin and fibrinogen directly into the bloodstream.[2]

Additionally, the liver plays an important role in the synthesis of phospholipids and lipoproteins and fatty acid metabolism. It also contributes to the metabolism of carbohydrates, which includes glycogen production and storage. Additionally, because it receives the toxins and chemical medications ingested from the intestine through the portal circulation, it is crucial for the body's elimination of toxins and chemicals.[2]

Liver dysfunction illness is a public health concern and one of the world's top causes of death. One of the most frequent causes of hepatic disorders is drug-induced hepatotoxicity which is brought on by the adverse effects of several medications on the liver.[3]

Ibuprofen is one of the non-steroidal anti-inflammatory drugs that are commonly prescribed for their ability to alleviate pain, reduce inflammation and lower fevers. However, prolonged use of ibuprofen has been linked to numerous side effects including liver toxicity especially in patients receiving high doses with the long-term treatment.[4]

The liver is particularly vulnerable due to the metabolic products of ibuprofen which can lead to oxidative stress, mitochondrial dysfunction and an excessive inflammatory response. This process can ultimately cause liver cell damage leading to apoptosis, necrosis and in more extreme cases, liver failure.[5]

Ibuprofen is metabolized in the liver primarily by the cytochrome P450 enzyme system resulting in the production of reactive oxygen species (ROS). These ROS disturb the liver's balance between oxidants and antioxidants leading to oxidative stress which in turn

damages cell membranes, proteins and DNA.

This damage promotes an inflammatory response characterized by the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) worsening the liver injury.[6]

Captopril is an angiotensin-converting enzyme (ACE) inhibitor widely used in treating hypertension and heart failure. It produces its antihypertensive and cardio protective effects by decreasing the blood level of angiotensin II that is a strong vasoconstrictor. Captopril prevents the formation of angiotensin II as it competes with angiotensin I for binding with the ACE so, it inhibits the enzymatic proteolysis of angiotensin I to angiotensin II. [7]

Captopril also exhibits potent antioxidant and anti-inflammatory activities. It produces its antioxidant effects through its ability to neutralize the free radicals and inhibit lipid peroxidation. It decreases oxidative stress markers such as malondialdehyde (MDA) and restores the activity of the key antioxidant enzymes like superoxide dismutase (SOD) and glutathione (GSH).

However, it produces its anti-inflammatory properties through modulation of the inflammatory pathways as it significantly reduces the expression of pro-inflammatory cytokine thus, dampening the inflammatory response.[8] Furthermore, captopril increases the bioavailability of nitric oxide (NO) which supports vascular health and improves hepatic blood flow and this potentially reduces the liver damage caused by ischemic injury.[9]

The antioxidant and anti-inflammatory abilities of captopril make it a promising therapeutic strategy for protecting the liver against drug-induced hepatotoxicity. The potential of captopril as an adjunct therapy in patients requiring long-term drug administration warrants further clinical investigation to confirm its efficacy and safety in preventing liver injury.[10]

Aim of the work: The objective of the current study was to evaluate the ability of captopril to counteract the ibuprofen-induced hepatotoxicity in the adult male albino rats.

Material and methods

Location of the study:

1.Animal House, Medical Research Center, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

2.Department of Histology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt.
3.Electron microscopy unit, Al-Azhar University, Cairo, Egypt.

Chemicals: Sigma aldrich Co. (St. Louis, MO, USA)
provided the ibuprofen, captopril, monoclonal antibodies against caspase-3, normal saline and distilled water.

Animals:
Forty adult male albino rats weighing between 180 and 250 grams and six months of age were purchased from the animal health research institute's breeding section in Dokki, Egypt. The rats were housed in a pathogen-free environment for the duration of the experiment. The rats were housed in plastic cages in the animal house of the Center of Researches, Faculty of Human Medicine, Ain Shams University with conventional laboratory lighting, humidity and temperature controls. The rats were given tap water and a balanced food throughout the experiment. The animals were handled in accordance with Ain Shams
University's adopted code of ethics for experimental researches and has the code number of [RE(238)24].

Study design:
The rats were randomly separated into four groups with 10 rats per group and they were given the following treatment daily for continuous four weeks:
1. Group 1 (control group) was given merely the typical food and purified water.
2. Group 2 (captopril group) was given a daily dosage of 10 mg/kg/day of captopril by oral gavage.[(11)]
3. Group 3 (ibuprofen group) was given ibuprofen at a daily dosage of 40 mg/kg/day by oral gavage.[(5)]
4-Group 4 (captopril and ibuprofen group) was given a daily dosage of 10 mg/kg/day of captopril[(11)] and 40 mg/kg/day of ibuprofen by oral gavage.[(5)]
Liver and blood samples were harvested for biochemical and histological analysis at the end of the experiment.

Sample collection:
The animals were anaesthetized by sevoflurane after the end of the experiment by 24 hours [(12)] then, blood samples were gained from the tail vein then, the rats were decapitated and the liver samples were taken from each rat. [(13)]

Biochemical analysis:
i.Evaluation of liver function enzymes: Blood samples were centrifuged at 3000 rpm for 15 minutes in order to separate the serum then,- the serum levels of alanine transaminase (ALT), lactate dehydrogenase (LDH), aspartate transaminase (AST) and alkaline phosphatase (ALP) were measured biochemically.[(14)]
ii. Evaluation of oxidative stress in liver tissue: To assess the oxidant/antioxidant state, portions of the liver tissues from each group were homogenized and kept at -80°C. The levels of glutathione (GSH) and malondialdehyde (MDA)- were then determined in the liver tissue by biochemical measurement.[(15)]

Histological assessment of the liver tissue: The liver specimens were preprocess for histological and immunohistochemical analysis after being fixed in 10% neutral-buffered formalin solution for light microscopy[(16)] and 2% gluteraldehyde for electron microscopy.[(17)]

i) Haematoxylin and eosin: For light microscopic study of the histological structure of liver and any histopathological changes.[(18)]

ii) Masson's trichrome stain: To determine the collagen fibers quantity in the liver, particularly in the portal tract, slides were stained with Masson's trichrome stain. [(19)]

iii) Immunohistochemistry: To identify caspase-3 positive hepatocytes, monoclonal antibodies against caspase-3 were utilized.[(20)]

iv. Electron microscopy: Liver specimens about 1mm³ were obtained from each group.
These pieces were fixed in 2% gluteraldehyde in a pH 7.4 0.1 mol/l phosphate for two hours then, gradually dried with increasing ethyl alcohol concentrations. Following that, the specimens were immersed in a solution containing propylene oxide and resin then, Ballistic Electron Emission Microscopy (BEEM) was used to encapsulate them and an ultramicrotome was used to cut ultrathin slices. The sections were subjected to transmission electron microscopy examination after being treated with lead citrate and uranyl acetate.[(17)]

Analysis of the data using statistics: The results were compiled and shown as means ± SD (standard deviation). In order to determine the signifycance between each group, the data were statist-

ically analyzed using the one-way analysis of variance (ANOVA) using SPSS statistics version 20.0 and the Tukey post hoc test to determine where the differences truly came from. Results and differences were deemed statistically significant when P-values were less than 0.05. [12,21]

Results

A- Results of biochemical analysis:

i- Assessment of liver function enzymes:

The captopril group had non-significant differences in the serum levels of AST, ALT, LDH and ALP when compared to the control group while all of these enzymes had significantly higher levels in the ibuprofen treated one. Group 4 (treated with both ibuprofen and captopril) showed a considerable reduction in these levels compared to the ibuprofen group, approaching the levels of the control one (**Table 1, fig. 1**).

Table 1. The mean values of the serum liver function enzymes.

	Group 1		Group 2		Group 3		Group 4		P value
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	
ALT(U/L)	**11.5**	**2.55**	**12.4**	**2.57**	**89.94**	**4.53** [a]	**17.53**	**3** [b]	**<0.05**
AST (U/L)	**13**	**1**	**16**	**1**	**68**	**3** [a]	**24**	**2** [b]	**<0.05**
LDH(U/L)	**68.8**	**1.14**	**65.76**	**2.34**	**211.63**	**9.44** [a]	**111.4**	**6.77** [b]	**<0.05**
ALP(U/L)	**143.2**	**4.1**	**135.9**	**4.66**	**450.71**	**11.82** [a]	**196.4**	**8.54** [b]	**<0.05**

* One-way ANOVA test was used to compute the P value.
* SD stands for standard deviation.
* a indicates significant relative to group 1 (P < 0.05);
* b indicates significant relative to group 3 (P < 0.05).

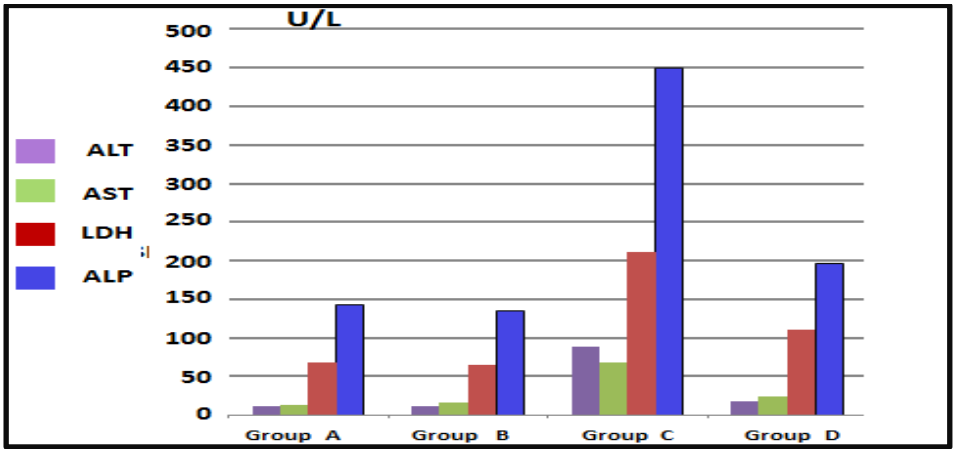

Fig. 1: A chart of the serum level of the liver function enzymes in the four groups. Group B shows no changes in the serum levels of liver enzymes in comparison to group A however in group C there are elevated surum levels of these enzymes. Group D shows decreased serum levels of the measured liver enzymes when compared to group C.

ii- Oxidant/antioxidant status markers:

There were no appreciable variations in the liver tissue's MDA and GSH levels between the control and the captopril groups however, when compared to the control group, the liver tissue in group 3 showed a significantly higher MDA level and a significantly lower GSH level. In group 4, the levels of these 2 indicators were eased greatly to near the control group with significant decrease of MDA and rise of GSH levels in this group in comparison to group 3 (**Table 2, fig. 2**).

Table 2. The mean values of the liver tissue oxidant/antioxidant status markers.

	Group 1		Group 2		Group 3		Group 4		P value
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	
GSH (nmol/mg)	**52.13**	**4.09**	**49.34**	**7.76**	**14.76**	**2.2** [a]	**39.15**	**5.4** [b]	**<0.05**
MDA (nmol/mg)	**6.54**	**1.28**	**6.42**	**1.62**	**65.28**	**6.37** [a]	**9.15**	**1.9** [b]	**<0.05**

* One-way ANOVA test was used to compute the P value.
* SD standard deviation.

* a indicates significant relative to group 1 ($P < 0.05$);
* b indicates significant relative to group 3 ($P < 0.05$).

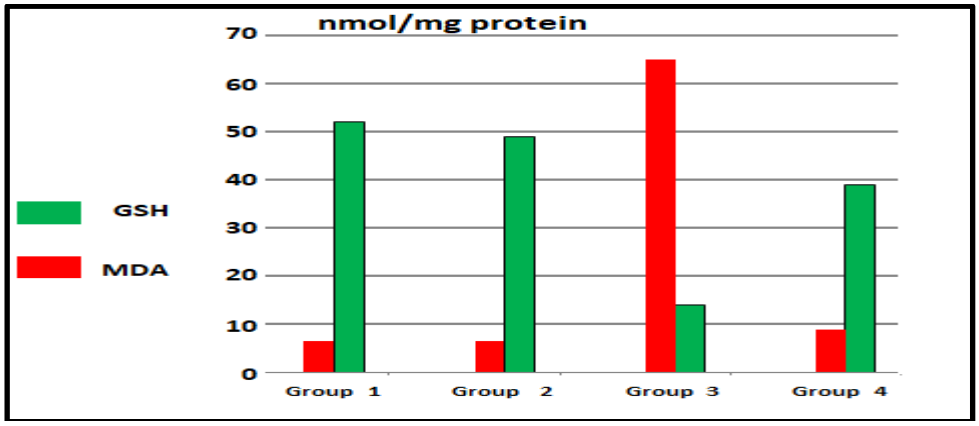

Fig. 2: A chart of the mean values of the levels of GSH and MDA that are oxidant/antioxidant status markers in the liver tissue.

Group B shows no changes in the liver tissue levels of GSH and MDA in comparison to group A however in group C there are decreased GSH and elevated MDA levels. Group D shows elevated GSH and decreased MDA levels in the liver tissue when compared to group C.

B- Results of histological examination:

i- Haematoxyline and eosine sections:

The control and the captopril groups had normal portal tracts, non-dilated central veins, non-dilated blood sinusoids, and well-organized hepatocytes in the hepatic lobule architecture. The group treated with ibuprofen had deformed architecture of the hepatic lobules, many apoptotic aggregates indicating degraded hepatocytes, dilated blood sinusoids, congested dilated central veins and edematous portal tracts however, group 4 shown remission of these histological alterations. In group 4, the sections were close to the control group with average hepatic lobule architecture with well-arranged hepatocytes, average non-dilated blood sinusoids and central veins and average non-edematous portal tracts. (**Fig. 3, 4**).

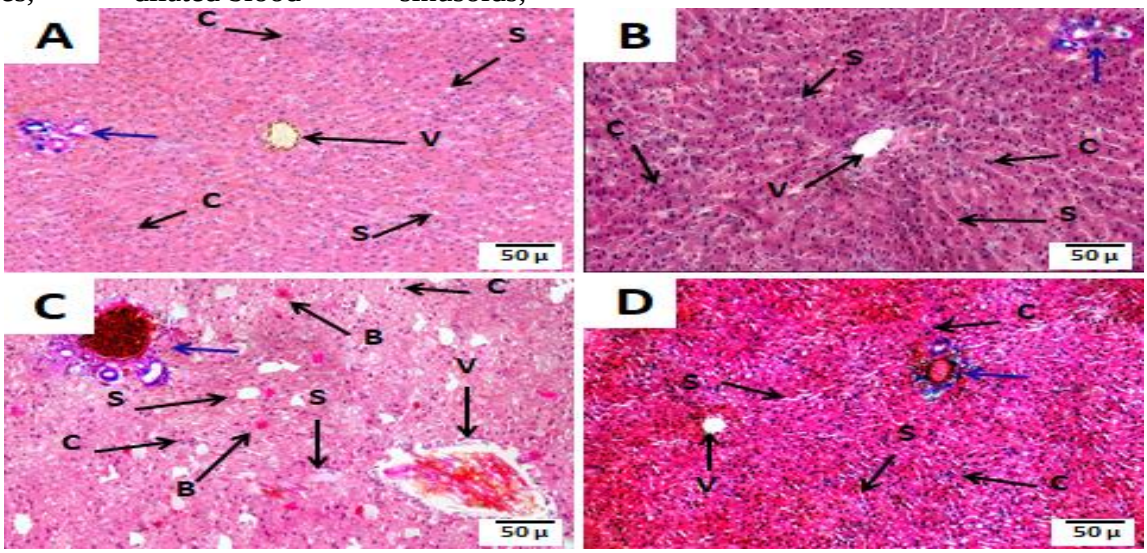

Fig. 3: Photomicrograph A (control group) and photomicrograph B (captopril group) both show typical liver architecture including well-organized hepatocytes (c), average non-edematous portal tract (blue arrow), non-dilated blood sinusoids (s) and a non-dilated central vein (v). The ibuprofen group (photomicrograph C) shows a deformed liver architecture with misaligned liver cells (c), a congested and edematous portal tract (blue arrow), dilated blood sinusoids (s) with scattered degenerative apoptotic bodies (b) and a dilated congested central vein (v). The group treated with captopril and ibuprofen (photomicrograph D) displays typical liver architecture, with well-organized hepatocytes (c), average non-edematous portal tract (blue arrow), non-dilated blood sinusoids (s) and a non-dilated central vein (v).

(H & E, X 200).

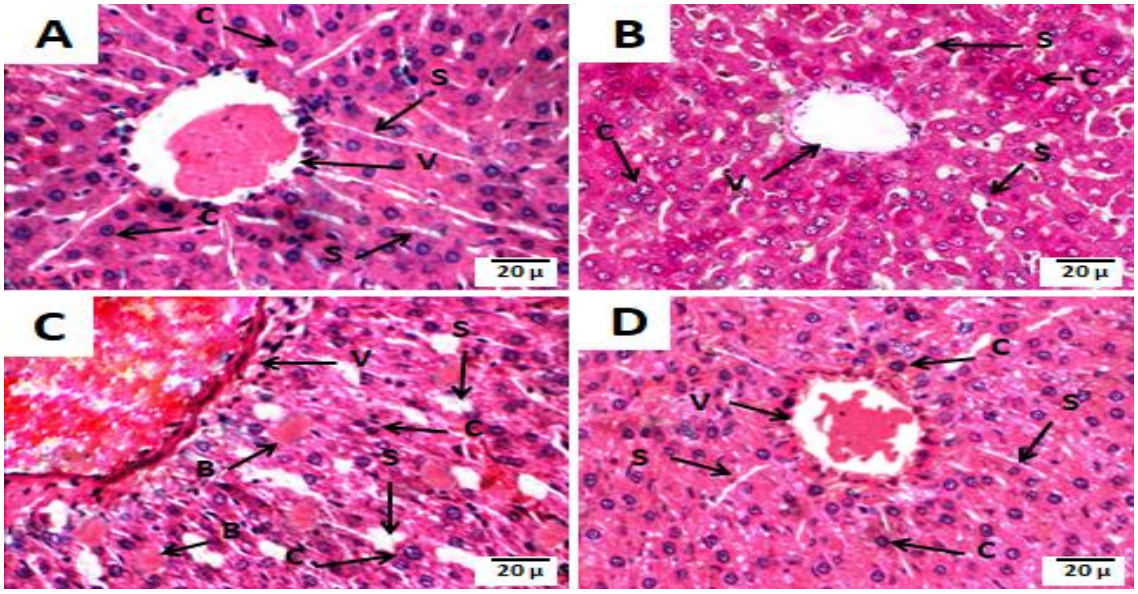

Fig. 4: Photomicrograph A (control group) and photomicrograph B (captopril group) both exhibit typical liver architecture including well-organized hepatocytes (C), non-dilated blood sinusoids (S) and non-dilated central veins (V). The ibuprofen group (photomicrograph C) has a deformed liver architecture with misaligned liver cells (C), dilated blood sinusoids (S) with scattered degenerative apoptotic bodies (B) and a dilated congested central vein (V). Photomicrograph D (the group treated with captopril and ibuprofen) displays typical liver architecture with well-organized hepatocytes (C), non-dilated blood sinusoids (S) and a non-dilated central vein (V) .
(H & E, X 400).

ii- Masson trichrome findings:

Collagen fibers were detected in the portal tracts of the control and captopril groups in the average predicted quantity, but the group treated with ibuprofen had extremely large amount of collagen fibers in the portal tracts. Group 4 displayed a reduction in the amount of collagen fibers compared to the ibuprofen group (**Fig. 5**).

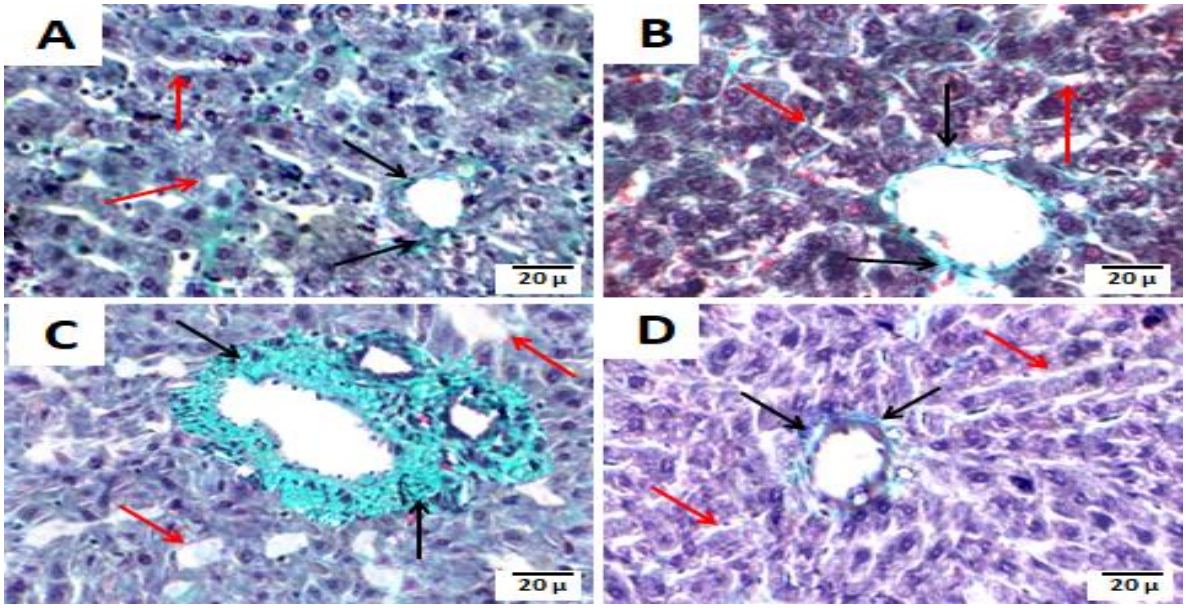

Fig. 5: Average distribution of collagen fibers in the portal tracts (black arrows) and average blood sinusoids (red arrows) are displayed by the control (photomicrograph A) and the captopril (photomicrograph B) groups. The ibuprofen group (photomicrograph C) has dilated blood sinusoids (red arrows) and thick collagen fibers (black arrows) however, group 4 (photomicrograph D) shows a reduction in the effects of ibuprofen due to the concurrent administration of captopril with ibuprofen as shown by the average non-dilated blood sinusoids (red arrows) and average distribution of collagen fibers in the portal tract (black arrows).
(Masson's trichrome, X 400).

iii- Immuno-histochemical results for caspase-3:

Hepatocytes in the control and captopril groups displayed negative cytoplasmic reactivity to caspase-3. Hepatocytes of the ibuprofen group exhibited strong cytoplasmic reactivity against caspase-3, but those of the group treated with captopril and ibuprofen demonstrated modest cytoplasmic reactivity (**Fig. 6**).

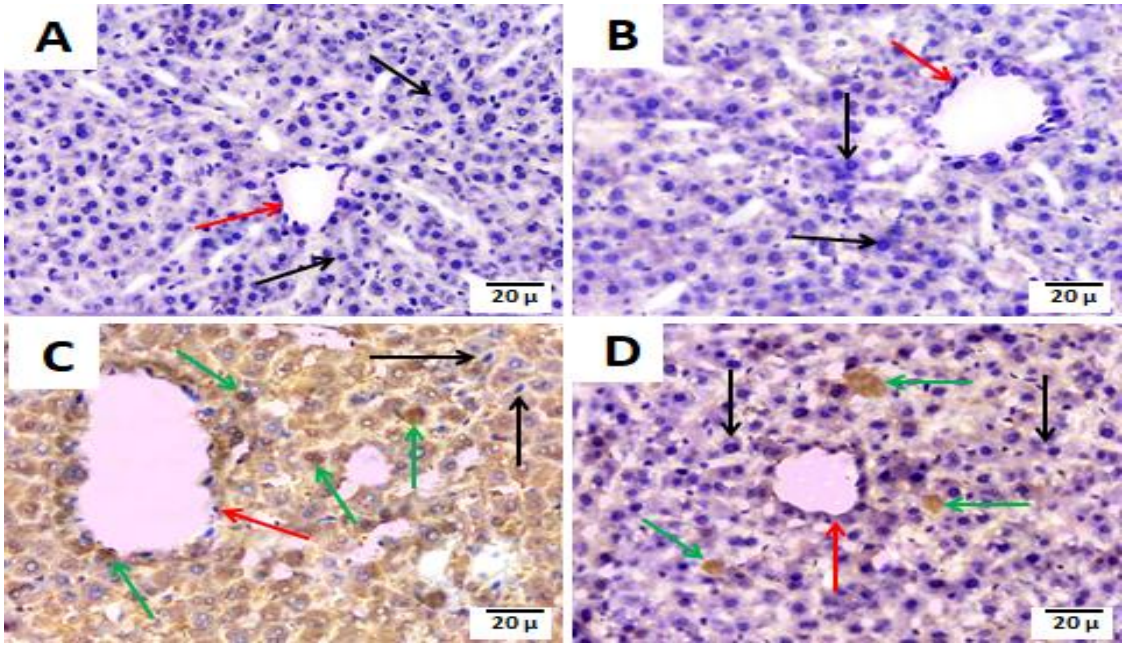

Fig. 6: Both the control (photomicrograph A) and captopril (photomicrograph B) groups exhibit negative caspase-3 cytoplasmic reactivity (black arrows) and average central vein (red arrows). In photomicrograph C, the ibuprofen group has a large number of darkly brown-stained hepatocytes that display positive caspase-3 cytoplasmic reactivity (green arrows), a small number of normal hepatocytes (black arrows) and a dilated central vein (red arrow). The captopril group (photomicrograph D) displays a large number of typical caspase-3 negative hepatocytes (black arrows), a small number of dark brown caspase-3 positive hepatocytes (green arrows) and an average central vein (red arrow).
(Caspas-3 immunostain, X 400).

The mean number of the caspase -3 positive cells in the four groups:

The mean number of the caspase-3 positive liver cells in the control and captopril groups did not differ significantly, according to morphometric analysis while the mean number of these cells was considerably higher in the ibuprofen group than in the control group. The mean number of caspase-3 positive liver cells was significantly lower in the ibuprofen and captopril group than in the ibuprofen only group to be near the mean number of these cells in the control one (**Table 3, fig. 7**).

Table 3. The mean number of the caspase-3 positive liver cells in the four groups at high power field (X 400).

	Group 1	Group 2	group 3	group 4	P value
Mean number of caspase-3 positive liver cells	**0.8**	**1.1**	**39.4** [a]	**3.4** [b]	**<0.05**

* One-way ANOVA test was used to compute the P value.
* a indicates significant relative to group 1 ($P < 0.05$).
* b indicates significant relative to group 3 ($P < 0.05$).

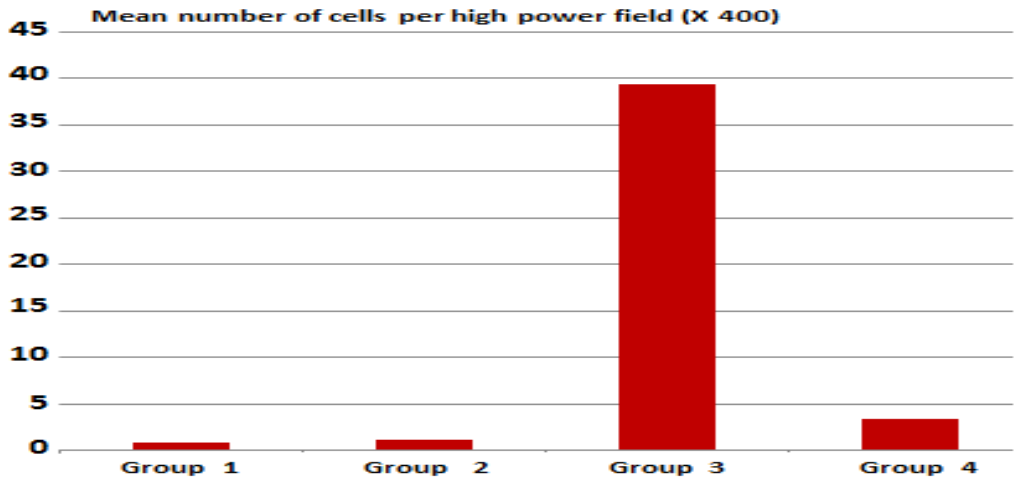

Fig. 7: A chart of the mean number of the caspase-3 positive liver cells in the four groups counted at high power field (X 400). Group B shows no changes in the mean number of the caspase-3 positive liver cells in comparison to group A however in group C there is markedly elevated mean number of these cells. Group D shows decreased mean number of the caspase-3 positive cells when compared to group C.

iv- Electron microscopy findings:

The control and captopril groups' hepatocytes displayed normal organelles and nuclei. The chromatin is uniformly distributed and the nuclei were round or oval in shape. In the cytoplasm, the Golgi apparatus, mitochondria and rough endoplasmic reticula were regular and widely distributed. Hepatocytes in the ibuprofen group (photomicrograph C) displayed signs of cell damage and degeneration including swollen mitochondria with lost cisterns, irregular nuclei with clumping of chromatin content and numerous degenerative vacuoles in the cytoplasm which suggested organelle degeneration. In group 4 (photomicrograph D), the hepatocytes were similar to that of the control group; the RER, mitochondria and Golgi apparatus were regular and widely distributed throughout the cytoplasm and the nuclei were regular and had uniform chromatin dispersion (**Fig. 8**).

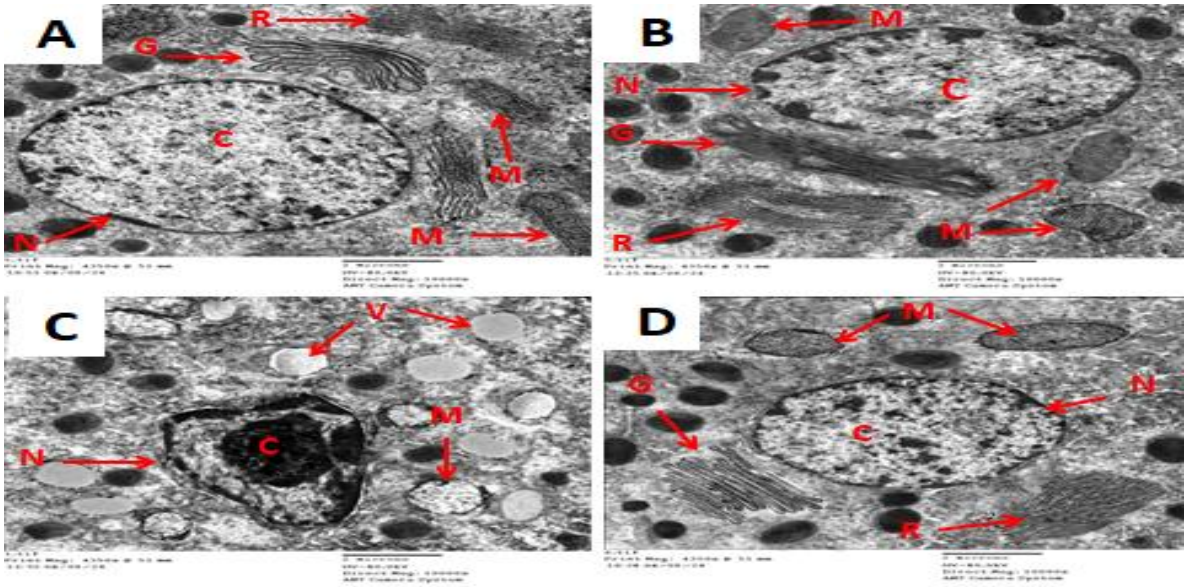

Fig. 8: TEM micrographs of the hepatocytes of the four groups. The control (photomicrograph A) and captopril (photomicrograph B) groups have regular nuclei (N) with uniformly distributed chromatin (C) and the cytoplasm is made up of many regular mitochondria (M), rough endoplasmic reticula (R) and well-developed Golgi apparatuses (G). The hepatocyte of the ibuprofen group (photomicrographs C) has a deformed nucleus (N) with clumped chromatin (C) and the cytoplasm exhibits swollen mitochondria with damaged cristae (M) and degraded organelles indicated by numerous cytoplasmic vesicles (V). The hepatocyte of the captopril and ibuprofen-treated

group (photomicrographs D) has regular nuclei (N) with uniformly distributed chromatin (C) and the cytoplasm has many regular mitochondria (M), rough endoplasmic reticula (R) and a well-developed Golgi apparatus (G). **(X 10000)**.

Discussion

Ibuprofen is a widely used medication that works well as an analgesic anti-inflammatory drug. However, a number of earlier studies demonstrated that, long-term ibuprofen use is likely to result in a number of unwanted side effects, such as stomach inflammation, duodenal and gastric peptic ulcers, headache, dizziness, restless sleep and heart burn.[22] Furthermore, prior research has shown that one of the most dangerous adverse effects is hepatotoxicity that can be brought on by taking high dosages of ibuprofen for an extended length of time.[23]

With the hope of using captopril effectively in high-risk patients to prevent ibuprofen-induced hepatotoxicity, we assessed the efficacy of concurrent administration of captopril in the current study using biochemical and histological methods.

In the current investigation, the ibuprofen-treated rats had significantly higher serum levels of the liver enzymes AST, ALT, ALP and LDH than the control rats. Additionally, elevated MDA and decreased GSH levels in the liver tissue indicated a disrupted hepatic oxidant/antioxidant balance brought on by ibuprofen administration. The histological liver examination showed ibuprofen-induced liver cell damage that further supports the analytical results.

However, concomitant captopril administration greatly reduced the ibuprofen's hepatotoxic effects. Captopril's hepatoprotective benefits were demonstrated by a significant reduction in blood liver enzyme levels, drop in MDAand increase in GSH levels in group 4 compared to group 3. When captopril and ibuprofen were given together, the levels of these indicators in group 4 approached the comparable values in the control group, indicating captopril-mediated restoration of the antioxidant capacity and amelioration of lipid peroxidation. By comparing group 4 to group 3, the histological liver assessment revealed a reduction in the degenerative hepatotoxic alterations, further supporting the hepatoprotective effectiveness of captopril against ibuprofen.

The current study's results were consistent with earlier research that found ibuprofen administeration increased liver enzyme levels and damaged liver cells. Since the liver enzymes were released into the bloodstream from the destroyed hepatocytes, their serum levels provided an indication of the extent of hepatic damage and disruption.[24]

Also, the current findings were supported by earlier results that have proved significant oxidative stress caused by ibuprofen and disruption of the oxidant/antioxidant balance with elevation of MDA and decrease of GSH levels in the liver tissue. Elevation of MDA indicated increased lipid peroxidation (LPO) of the cell membrane since it is a primary result of the oxidation of polyunsaturated fatty acids. Since GSH is a potent antioxidant, a drop in it suggests that the liver tissue's antioxidant capability has been comprromised.[25]

The present investigation found that captopril had hepatoprotective effects against the ibuprofen-mediated hepatotoxicity which was consistent with several other studies.[26,27] The antioxidant efficacy of captopril which prevents liver damage brought on by toxin-mediated oxidative stress is responsible for these hepatoprotective benefits.[28]

The present study findings were in agreement with previous results which have shown that captopril enhances the antioxidant capacity and reduces lipid peroxidation of the cell membrane.[29]

Previously, it was proved that, captopril exhibits potent antioxidant effects both directly as an antioxidant and through its function as a precursor for GSH which increases antioxidant capacity.[8]

In the current study, the presence of disorganized and apoptotic liver cells, dilatation of the blood sinusoids, congestion of the central and portal veins and excessive portal fibrosis in group 3 relative to the control group were indicative of ibuprofen-induced degenerative histological changes of the liver. These results were consistent with earlier research that found ibuprofen to have comparable hepatotoxic effects.[30]

The ability of captopril to counteract the histological hepatotoxic effects of ibuprofen that were observed in this study was consistent with earlier findings that demonstrated the ability of captopril co-administration to preserve the

average histological pattern against toxins-induced hepatotoxicity.[31]

The liver cells in group 3 of the current investigation showed ultrastructural abnormalities indicative of ibuprofeninduced hepatodegenerative changes, including swollen mitochondria, cytoplasmic vacuoles, irregular nuclei with clumped chromatin and missing organelles.

These findings were in agreement with previous results detected that, ibuprofen-induced oxidative stress leads to loss of mitochondria with subsequent cessation of energy synthesis resulting to many detrimental effects that destroy the hepatocytes.[32]

Conversely, the present investigation revealed that captopril effectively mitigates these ibuprofeninduced ultrastructural alterations.

This was consistent with earlier findings that shown captopril has a mitochondrial protective effect that extends hepatocyte cell life and protects its organelles from hepatotoxic chemicals. [10]

Because the mitochondria are the primary source of the energy needed for cell survival, captopril-mediated mitochondrial protection extends the life of the cell.[33]

In conclusion, this study demonstrated that captopril protects against ibuprofeninduced hepatotoxicity, demonstrating the value of prescribing captopril to individuals who use ibuprofen for extended periods of time.

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