Evaluation of the Possible Protective Effect of Pentoxifylline Against Carbamazepine-Induced Hepatotoxicity in Rat Model

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Article Info:

Received 22 June 2024
Revised 25 Nov 2024
Accepted 26 Dec 2024
Published 30 Oct 2025
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DOI: https://doi.org/10.32947/ajps.v25i4.1216

Abstract:

Hepatotoxicity is considered a primary cause of mortality induced by anticonvulsant medicines such as carbamazepine, which produce inflammation and oxidative stress in the liver; this impact is mitigated by Pentoxifylline, which has an anti-inflammatory and antioxidant action. This study aims to assess Pentoxifylline's protective effect on liver function enzymes and its possible role in minimizing structural changes and cellular death in hepatocytes during Carbamazepine-induced liver injury in a rat model. Forty rats were randomly assigned to five groups. Each group contained eight rats. Group 1 (Control): rats were given 10ml of distilled water per kg body weight. Group 2 (induction): rats administered Carbamazepine 50 mg/kg body weight. In the other groups, rats were given Pentoxifylline 100 mg/kg of body weight, 200 mg/kg of body weight, and 300 mg/kg of body weight one hour before being given Carbamazepine 50 mg/kg of body weight. Orally for 28 days. A serum was obtained to measure alkaline phosphatase and Bilirubin, and small portions of liver tissue were removed and preserved in 10% buffered formalin, which was then used for histological examination. The results demonstrate a significant ($P<0.001$) reduction in alkaline phosphatase and Bilirubin with Pentoxifylline groups. The findings revealed that Pentoxifylline protects hepatocytes from Carbamazepine-induced liver damage by improving liver function enzymes and decreasing histological alterations in hepatocytes.

Keywords: Carbamazepine; Hepatotoxicity; Pentoxifylline; Alkaline phosphatase; Bilirubin.

تقييم التأثير الوقائي المحتمل للبنتوكسيفلين ضد التسمم الكبدي الناتج عن الكاربامازبين في نموذج الفئران

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الخلاصة

تعتبر السمية الكبدية من الأسباب الرئيسية للوفاة الناجمة عن الأدوية المضادة للاختلاج مثل الكاربامازيبين، والتي تسبب الالتهاب والإجهاد التأكسدي في الكبد؛ يتم تخفيف هذا التأثير عن طريق البنتوكسيفيلين، الذي له تأثير مضاد للالتهابات ومضاد للأكسدة. الغرض من هذه الدراسة هو تقييم التأثير الوقائي لبنتوكسيفيلين على وظيفة انزيمات الكبد، بالإضافة إلى دوره المحتمل في تقليل التغيرات البنيوية والموت الخلوي في خلايا الكبد أثناء إصابة الكبد الناجمة عن الكاربامازيبين في نموذج الفئران

تم توزيع أربعين فأرًا بشكل عشوائي على خمس مجموعات. تحتوي كل مجموعة على ثمانية فئران. المجموعة 1 (التحكم): أعطيت الفئران 10 مل من الماء المقطر لكل كيلوغرام من وزن الجسم. المجموعة 2 (التحريض على السمية): أعطيت الفئران كاربامازيبين 50 ملغم / كلغم من وزن الجسم. في المجموعات الأخرى، أعطيت الفئران بنتوكسيفيلين 100 ملغم / كلغم من وزن الجسم، 200 ملغم / كلغم من وزن الجسم، و300 ملغم / كلغم من وزن الجسم قبل ساعة واحدة من إعطائها كاربامازيبين 50 ملغم / كلغم من وزن الجسم. عن طريق الفم لمدة 28 يومًا. تم الحصول على مصل لقياس الفوسفاتيز القلوية والبيليروبين، وتم إزالة أجزاء صغيرة من أنسجة الكبد وحفظها في الفورمالين المخزن بنسبة 10٪، ثم استخدامها للفحص النسيجي.
تظهر النتائج انخفاضًا كبيرًا في قيمة$P<0.001$ الفوسفاتيزالقلوية والبيليروبين مع مجموعات بنتوكسيفيلين. كشفت النتائج أن بنتوكسيفيلين يحمي خلايا الكبد من تلف الكبد الناجم عن الكاربامازيبين من خلال تحسين وظائف انزيمات الكبد وتقليل التغيرات النسيجية في خلايا الكبد

الكلمات المفتاحية: كاربامازيبين؛ سمية الكبد؛ بنتوكسيفيلين؛ الفوسفاتيز القلوية؛ البيليروبين.

Introduction

Several efficacious therapies for neurological diseases exhibit off-target toxicity, posing a significant challenge for certain patients undergoing treatment. Certain medications have adverse effects on vital organs, thereby affecting their metabolizing enzymes and therapeutic advantages.(1). The liver is subject to major toxicity of xenobiotics due to its detoxifying function.(2)

Drug-induced liver damage (DILI) remains the leading cause of acute liver failure (ALF). DILI can be idiosyncratic or unpredictable, depending on the drug's pharmacological activities. Because afflicted people constitute only a tiny fraction of those treated with such medications, nearly many DILI in the clinical context is idiosyncratic (in many situations, the mechanism for idiosyncrasy is immune-mediated). (DILI) is the most prevalent cause of discontinuing medications(3) The pathogenesis of DILI involves genetic, metabolic, and immune factors (4). The prevalence of DILI with antiepileptic drugs (AED) is well reported. The consequences can be quite severe, culminating in death or needing liver transplantation as a result of acute liver failure caused by these drugs(5)

Because most medications undergo metabolism by the liver, starting an antiepileptic drug (AED) might cause significant liver illness, which reduces the drugs' binding ability to serum protein and increases the risk of toxicity. Therefore, selecting the best suitable AED in this susceptible group becomes extremely critical(6)

Carbamazepine (CBZ), one of the AEDs, has a structure similar to tricyclic antidepressants such as imipramine. CBZ includes the treatment of focal-onset and generalized-onset tonic-clonic seizures. CBZ is predominantly converted to CBZ-10,11-epoxide (which is pharmacologically active and possibly hazardous due to its capacity to generate covalent protein adducts). CBZ increases GABA's inhibitory impact while decreasing glutamate's excitatory effect. CBZ-induced liver damage by its metabolites (arene oxide) is subsequent participation of the immune system, which leads to tissue injury, and the consequences can be quite severe, leading to death due to acute liver failure(7) CBZ-induced hepatic toxicity is caused by reactive oxygen species (ROS). This produces hepatitis, which is hepatic tissue inflammation and lymphocytic infiltration, leading to liver apoptosis and necrosis(8)

Pentoxifylline (PTX), a methyl xanthine derivative, is a nonselective phosphodiesterase (PDE) inhibitor, resulting in a large intracellular pool of the second messenger, cyclic adenosine monophosphate (cAMP)(9). By inhibition of the (PDE) has an impact on blood flow. The pharmacological agent PTX improves the elasticity of both red and white blood cells,

reduces the thickness of blood by decreasing the levels of plasma fibrinogen, and prevents the aggregation of platelets and the development of blood clots. PTX acts as an inhibitor of polymorphonuclear leukocyte-mediated processes such as superoxide generation, chemotaxis, phagocytosis, and TNF production (10). Furthermore, PTX inhibits cytokine synthesis, which gives it anti-inflammatory characteristics. It prevents lipopolysaccharide-induced TNF-α generation. Furthermore, the anti-inflammatory actions of Pentoxifylline are most likely connected to its capacity to reduce oxygen radical generation and scavenge reactive oxygen species (ROS)(11) Activation of Kupffer cells, by chemicals, produce massive amounts of ROS (which leads to the production of lipid peroxidation and activation NF-κB) strongly associated with hepatocellular damage (12). PTX can independently inhibit phosphodiesterases and prevent kupffer cell activation in vivo, through its interference with the oxidative stress pathway NF-kappa B and c-myc. (13), so it can protect the liver from injury(14)
Regarding this study, the idea that PTX might be able to protect the liver from CBZ damage is a significant advantage. Therefore, this study aims to evaluate the potential protective effect of PTX in a male rat model of CBZ-induced liver damage.

Materials and methods

Ethical approval

The Scientific Committee of Mustansiriyah University's College of Pharmacy, Pharmacology, and Toxicology Department granted ethical approval for this study (approval number: 24, reference number: 102, date: 28 October 2023)

Animals and Experimental Design

This investigation aimed at studying the effects of specific substances on male rats weighing between 130 and 150 g. The rats were kept in large, comfortable cages, brought from the Iraqi Center for Cancer Research, and placed in the animal house at Mustansiriyah University, College of Pharmacy. They spent seven days in a regulated setting with an average temperature of 25±1℃, Average humidity ranges from 40% to 50%, with a 12-hour light/dark cycle. The rats had unlimited access to both food and water.

Five groups of eight rats per each were formed randomly using a complete block design:
Group 1: (Normal) rats were given orally distilled water 10 mL/kg daily for 28 days.(15)
group 2: (induction) rats were given 50 mg/kg CBZ orally via gastric gavage for 28 days. (16,17)
group 3: (PTX100) rats were given 100 mg/kg PTX orally via gastric gavage one hour before CBZ induction for 28 days.(18)
group 4 (PTX200): rats were given 200 mg/kg PTX orally via gastric gavage one hour before CBZ induction for 28 days.(19)
Group 5: (PTX300): rats were given 300 mg/kg PTX orally via gastric gavage one hour before CBZ induction for 28 days (9) as illustrated in (Figure 1).

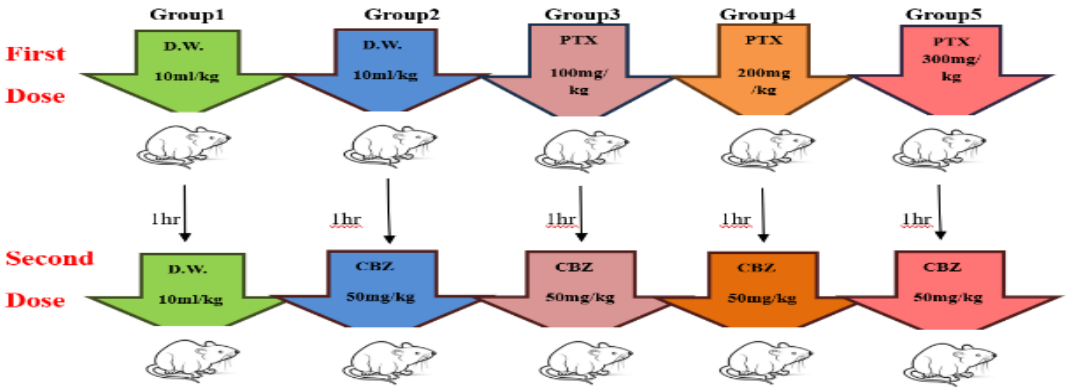


Figure (1): Study design.

collection of blood samples and liver samples

On the 29th day of the experimental study, rats were killed following anesthesia induction with an intraperitoneal injection of ketamine (80 mg/kg) and xylazine (10 mg/kg). Blood samples were taken from the animals by cardiac puncture (20).To separate the serum, blood was collected in a tube containing a chemical that induces clotting and then spun at 5000 revolutions per minute for 10 minutes. Serum was collected in 2ml Eppendorf tubes and stored at -20°C until analysis day.

The rat's abdominal cavity was opened using forceps, and the liver was promptly extracted, rinsed with distilled water, and kept in 10% formalin for histopathological investigation.

Assessment of Biochemical parameters

Analysis of alkaline phosphatase (ALP) and Bilirubin levels in blood samples was conducted using commercially available kits from (Linear Chemical, Spain).

Assessment of Histopathological Changes

"The paraffin-embedded method" was used to prepare the liver tissues for microscopical inspection, and the processes included: **I.** Liver Tissue Fixation: By immersing in 10% neutral buffered formalin. To preserve the liver tissue samples acquired from experimental rats, they were submerged in a solution (37% formaldehyde and 900 mL distilled water) for 72 hours. **II.** Liver Tissue Processing: Take a small specimen and place it in a basket (a procedure known as paraffin embedding). **A.** Tissue dehydration utilizing escalating ethanol concentrations (70%, 80%, 90%, and 100%) for 2 hours each, followed by 1 hour of 100% ethanol (solutions 1 and 2) to eliminate water from tissues and allow alcohol to enter. **B.** Tissue clearing to retract the dehydration alcohol residues by replacing xylene for ethanol (xylene removes alcohol from tissues) for 2 hours, changing tissue color from white to brown-yellowish. In order to facilitate the penetration of paraffin wax into cells, a vacuum oven was employed, with xylene being used owing to its miscibility. **III.** Using xylene to facilitate the embedding of paraffin wax into cells. The processing was carried out in a vacuum oven adjusted to a temperature range of 54-58°C using a paraffin dispenser (LEICA EG115011, Germany). The tissue block implanted in paraffin was stored overnight at 4°C on a frozen plate using the same method. **IV.** Liver Tissue Sectioning: A tissue block

covered in paraffin was excised into 5m slices using a microtome (LEICA RM2245, Germany). The thin slices were subsequently positioned on a slide with a positive charge and allowed to dry naturally for 12-24 hours at ambient temperature. **V.** Slide Preparation and Staining: in order to enhance tissue adhesion and soften the paraffin, tissue slides were placed on a rack and subjected to a minimum of 30 minutes of heating in a dry oven set at 50-60°C. The slides were stained using the hematoxylin and eosin (H&E) technique.

Statistical analysis

Data analysis was conducted using the Statistical Packages for Social Sciences (SPSS) software. The statistical measures were presented as the mean ± standard error of the mean (SEM). An Analysis of Variance (ANOVA) test was employed to confirm the statistical significance of the difference among the five groups under investigation. If a P-value is more than 0.05, it is deemed nonsignificant; otherwise, it is regarded significant.

Results

Effect of PTX on ALP and bilirubin level

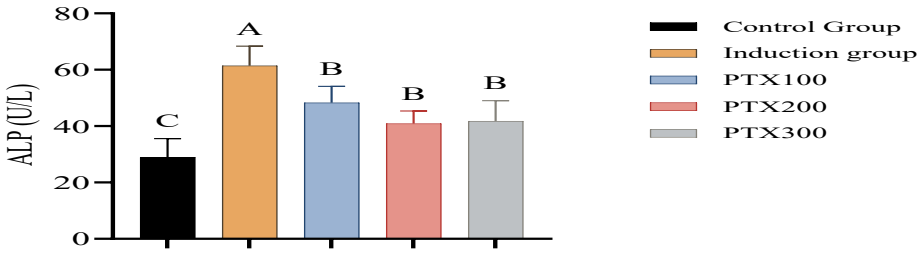
The serum ALP activity was significantly elevated ($p < 0.001$) in the induction group compared to the negative control group. A significant variance in the mean ALP levels was seen among the groups ($p < 0.001$). Categorize the groups based on their mean values, yielding the following classifications: The induction group had the greatest mean value. In contrast, the 100mg, 200mg and 300mg groups of PTX showed no significant difference between them. However, all PTX groups showed an increase in mean value compared to the negative control group, as shown in Table (1) and Figure (2).

The induction group had a significantly greater mean serum Bilirubin concentration than the negative control group with $p < 0.001$. Upon administration of PTX at a dosage of 100 mg/kg, the mean serum concentration of Bilirubin was lower than the induction group, and the same was true for the 200mg and 300mg PTX groups. Groups categories according to mean values: The induction group had the highest mean value, followed by 100 mg, then by (200mg and 300mg) which did not show a significant difference between them, as demonstrated in (table 1) and (figure 3).

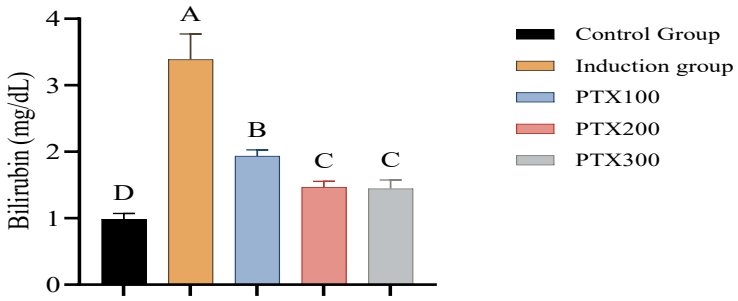
Table (1): levels of ALP and Bilirubin in serum.

	ALP (U/L)	Total bilirubin (mg/dL)
Control group	28.95± 6.608	0.98±0.09
Induction group	61.44± 6.955	3.39±0.39
PTX100	48.29± 5.812	1.94±0.09
PTX200	40.88± 4.494	1.47±0.09
PTX300	41.78± 7.236	1.45±0.13
p-value [#]	<0.001	<0.001

The results were expressed as Mean ±SD. Results show significantly variance (P<0.001).



Figures (2): Levels of ALP after CBZ and PTX treatment groups Displays the mean ALP levels in different groups. Similar letters show no significant variance between them, while dissimilar letters suggest significant variances



Figures (3): Change of bilirubin level in all groups Show the mean Bilirubin levels in different research groups. Similar letters exhibit no significant variance between them, while different letters suggest significant variances.

Histological changes

The control group showed typical hepatic architecture, normal appearance of hepatic lobules, normal central veins, and normally arranged hepatic cords, revealing normal hepatocytes, sinusoids and kupffer cells (Figure 4). The CBZ group showed vascular lymphocytic cuffing, multiple focal necrosis, and aggregation of MNCs (Figure 5). PTX (100mg/kg) showed normally arranged hepatic cords with a normal central vein, and there was mild zonal cellular swelling of hepatocytes without necrosis and no inflammatory infiltration (Figure 6). PTX (200mg/kg) showed portal triad revealed mild proliferation of cholangiocytes (Figure 7). PTX (300 mg/kg) showed mild dilation of the central vein without congestion and mild zonal cellular swelling of hepatocytes without necrosis (Figure 8).

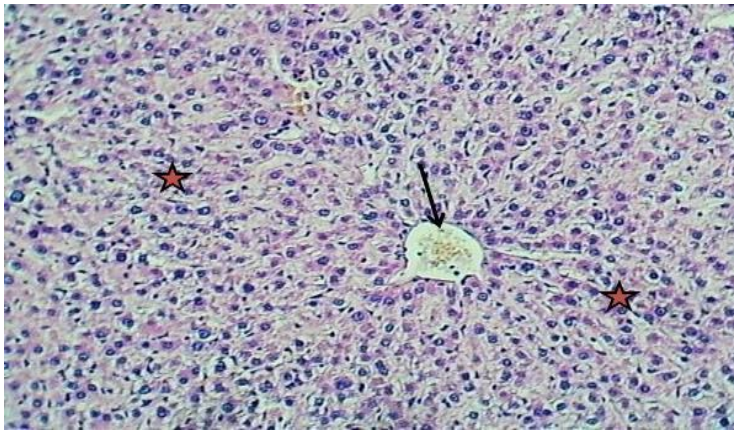


Figure 4: The histological appearance of liver in control group shows the normal appearance of the central vein (Arrow), normally arranged with the appearance of hepatocytes (asterisks). H&E stain.100x

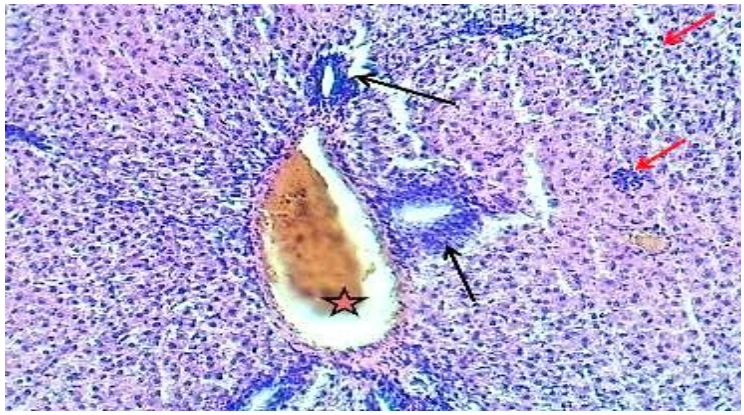


Figure 5: The histological changes in liver in CBZ group shows severe dilation with congestion of portal vein (Asterisk), pre vascular lymphocytic cuffing (Black arrow) with multiple focal necrosis and aggregation of MNCs (Red arrows). H&E stain. 100x.

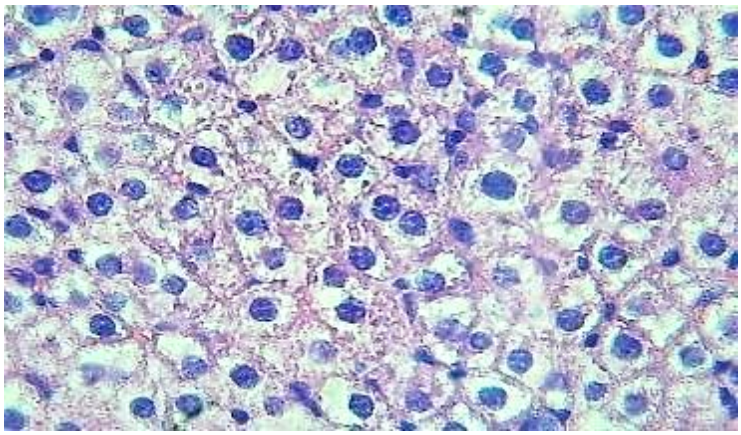


Figure 6: The histological appearance of the liver in (PTX 100 mg) group shows mild zonal cellular swelling of hepatocytes without necrosis (Asterisk). H&E stain.400x.

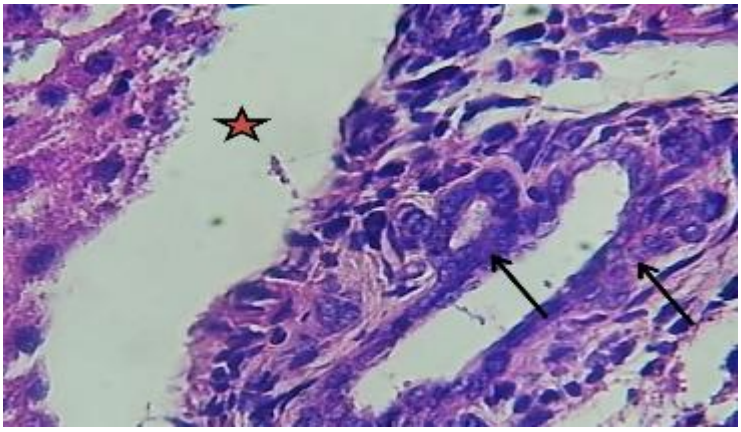


Figure 7: The histological appearance of the liver in (PTX 200 mg) of the portal triad shows the normal appearance of the portal vein (asterisk) bile duct (arrows). H&E stain.400x.

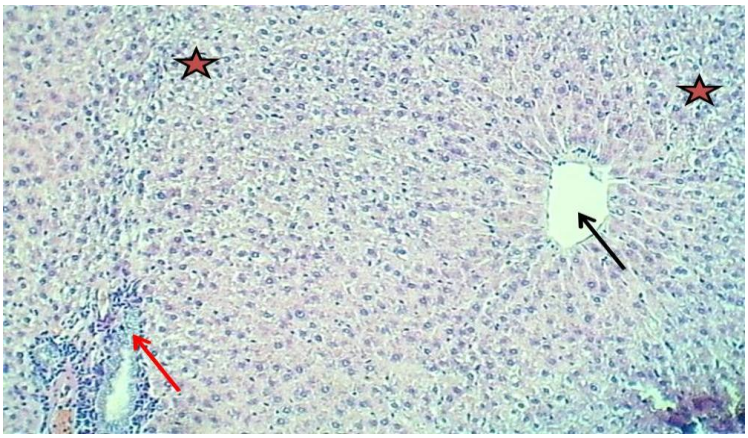


Figure 8: The histological appearance of liver in (PTX300 mg) group shows mild dilation of the central vein without congestion (arrow) & mild zonal cellular swelling of hepatocytes without necrosis (Asterisk) & portal proliferation of cholangiocytes (red arrows) H&E stain.100x.

Discussion

In this study, the CBZ dosage significantly increased ALP serum levels compared to the control and PTX groups. These results may be attributed to cellular necrosis, which in turn enhances the release of enzymes from hepatocytes. The finding agrees with those of Osuntokun OS *et al.* (2021), who found that ALP activity fell significantly after CBZ (21). The results of PTX on serum ALP activities demonstrated that PTX caused a significant drop in serum ALP activities compared to the normal and induction groups. These results consistent with Khairy MH *et al.* (2023) (9).

In regard to Bilirubin is the definitive end product of hemoglobin, which is produced in the reticuloendothelial system. Upon being released in its unconjugated form, it enters the liver where it undergoes a conversion into conjugated forms called bilirubin mono and diglucuronides facilitated by the enzyme UDP-glucuronyltransferase. Elevated blood bilirubin levels indicate liver disorders and imply abnormal laboratory liver functions (24).In this study, the CBZ dosage utilized caused a significant increase in bilirubin

serum levels (an indication of liver function) compared to the control and PTX groups. These findings consistent with Maheswari E *et al.* (2014) (25).

There was a significant improvement in serum bilirubin with PTX groups, these results agree with Khairy MH. *et al* (2023)(9).

In the histological study, the control group was discovered to have normal liver tissue with no signs of liver damage. This group was utilized as a standard for healthy liver tissue.

The study's findings show that CBZ has a long-term influence on hepatocytes, namely pathological alterations. Hematoxylin and eosin -dyed liver sections in the CBZ group exhibited disturbance of hepatic architecture, including significant necrosis, and demonstrated a lower hepatic cell count per unit area, probably due to hepatic cellular necrosis. These alterations include cell death and the creation of fibrous structures, which cause liver cells to retract and become invisible. Significant degradation and necrotic alteration were found in the hepatocytes of rats' livers received with CBZ. This discovery is consistent with the study's outcome Ali A *et al.* (2021)(8).

Animals treated with CBZ showed hepatic parenchyma degeneration characterized by significant dilation of the central vein, generalized cellular swelling of hepatocytes, multiple focal necrosis of cell death, mononuclear leukocytes (MNCs) accumulation, and mild sinusoid congestion. The portal triad showed considerable enlargement accompanied by congestion of the portal vein, notable pre-vascular lymphocytic cuffing, and many localized regions of necrosis and aggregation of mononucleate cells. The number of growing cholangiocytes in the bile duct significantly increased. In this scenario, the observed vacuolated swelling is most likely caused by anoxia and disturbances in membrane metabolism. These disturbances cause a substantial increase in the entry of water and sodium ions into the hepatocyte, resulting in the liberation of lysosomal hydrolytic enzymes and, finally, the deterioration of the hepatocyte membranes (8).

The PTX-treated group exhibited distinctive features; the liver treated with PTX improved its histological appearance, consistent with the findings of Khairy MH *et al.* (2023) (9). Pharmaceutical doses of PTX (100 mg, 200 mg, 300 mg) resulted in the usual organization of hepatic cords with a normal central vein without congestion, necrosis, or inflammatory infiltration. However, there was little zonal cellular enlargement of hepatocytes and slight dilatation of the central vein. The explanation of these results may be linked to PTX therapy, which is demonstrated by decreased levels of cytokine (TNF) (26), which has an anti-inflammatory effect on the cells. Depending on their dosage and the duration of their relevant biological action, cytokines released locally inside the liver and systemically may stimulate or inhibit the liver disease process. The up-regulation of adhesion molecules, induction of cell activation, and recruitment and enhancement of cytotoxicity of lymphocytes, macrophages, and neutrophils, all of which contribute to the pathogenesis of hepatitis, can be facilitated by TNF and other cytokines and chemokines (26).

In the present study, PTX-protected groups showed improvements due to the reactive oxygen species scavenging abilities of PTX and the anti-inflammatory effect. The finding agrees with Du J *et al.* (2014), which demonstrated that PTX therapy led to a considerable improvement in lobular inflammation as observed through histological inspection.(25)

Conclusion

PTX protects the liver by restoring the normal level of liver function enzyme, repairing and preserving its structural integrity and functionality by acting as a nonselective phosphodiesterase inhibitor and an anti-inflammatory against liver toxicity caused by CBZ.

Acknowledgements

The authors express deep appreciation to the College of Pharmacy, Mustansiriyah University, for their support and effort in ensuring the successful completion of this study.

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