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Research Article

CHEMISTRY

Therapeutic Impact of Telmisartan Against The Thioacetamide Induced Hepatic Fibrosis In Rats

Fatma Amer[1], Mahmoud El-Rehany[2], Entesar Ali[3], Othman Ali[*1]

[1]Biochemistry Division, Chemistry Department, Faculty of Science, Minia University, ElMinia, Egypt.
[2]Biochemistry Department Faculty of Medicine, El-Minia University, Minia, Egypt.
[3]Histology Department Faculty of Medicine, El-Minia University, Minia, Egypt.

***Corresponding Authors:** Othman Ali Othman **e-mail:** *osman.mouftah@mu.edu.eg-*
ORCID: http://orcid.org/0000-0003-4061-6929

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KEY WORDS

Liver Fibrosis, Telmisartan, Thioacetamide, IL-6, TNF-α

ABSTRACT

Background: Hepatic fibrosis is a severe condition related to ongoing liver disorders. Liver fibrosis evolves in response to multiple causes of chronic hepatic disease. At present, the mechanism of its occurrence has yet to be determined, and there are no viable therapeutic medicines. **Goal:** Our aim was to determine the potential of Telmisartan to inhibit the progression of hepatic fibrosis induced in albino rats. **Material and methods:** In a recent study, Thioacetamide was used to induce hepatic fibrosis in a rat model. Randomly, forty albino rats were classified into four identical groups (ten rats per group). These groups were Healthy group, fibrotic group, Prophylactic group with Telmisartan and treated group with Telmisartan. Biochemical and histological analysis were evaluated. By using ELISA, IL-6, IL-1B, and TNF-α were examined. **Results:** The results revealed that there was very highly significant decreased ($P<0.0001$) in ALT, ALP, AST, Total Bilirubin and Direct Bilirubin levels in groups which treated with Telmisartan (G3, G4) compared with fibrotic group (G2), while there was highly significant increase in albumin ($p<0.001$) in Telmisartan treated group. Liver sections from talmisartan groups showed markedly decreased hepatic lesions. We found a very highly significant effect of Telmisartan on IL-6, IL-1B, and TNF-α levels. **Conclusion:** There are a potential therapeutic value and antifibrotic effects of Telmisrtan on hepatic fibrosis in the thioacetamide model.

Introduction

Fibrosis of liver is a chronic condition induced by repeated liver disorder. Excessive accumulation of extracellular matrix replaces destroyed hepatocytes, resulting in fibrous scar formation and induction of fibrosis **(Hernandez-Gea & Friedman, 2011; Pu et al., 2024)**.

Fibrosis can be caused by a variety of chronic hepatic conditions, such as alcoholic steatohepatitis, fatty liver disease, metabolic problems, autoimmune disorders, hepatitis B or C virus infection, and exposure to toxins **(Puche et al., 2013)**. Fibrosis can be reversed by acute or limited liver injuries. On the other hand, sustained liver injuries may result in severe inflammation and chronic accumulation of the ECM, finally leading to permanent cirrhosis or HCC **(Dewidar et al., 2019)**. Telmisartan (TEL) is a recognized angiotensin II receptor blocker used as an antihypertensive therapy. In the experimental models, TEL greatly decreased the amount of inflammation; however, the use of TEL in severe liver disorders has not been completely investigated **(Xu et al., 2011)**. There are no approved drug therapies for fibrosis. As a result, the medical treatment of liver fibrosis requires unique and effective therapeutic targets **(Li et al., 2019)**. Consequently, our goal is to assess the anti-fibrotic efficacy of Telmisartan on TAA-induced hepatic fibrosis.

MATERIALS AND METHODS

Experimental animals:

All techniques in the current investigation have been approved via the ethics council of the Faculty of Pharmacy at Mania University **(MPEC 230203).** The present research included 40 healthy Wistar albino male adult rats weighing 170-210 grams obtained from the National Research Center's animal housing in Giza, Egypt. The National Research Center (Giza, Egypt) approved the rats for liver-free damage. Rats were housed at Deraya University's animal house unit in Mania, Egypt, and fed a conventional laboratory diet with unlimited access to tap water. The rats were housed in an air-conditioned facility with a temperature range of 22–25 degrees Celsius and a 12-hour light/dark cycle. Every animal got human attention, and this research was completed in accordance with the ethical requirements for good care.

Experimental design:

Albino rats were randomly grouped into 4 experimental sets, every one containing 10 rats, as follows:

1) **Group (I): Healthy group.**

This group didn't receive any treatment and hence operated as the control group.

2) **Group (II): liver fibrotic group.**

Rats in this group were injected intraperitoneally with Thioacetamide (Sigma-Aldrich, USA) at a dosage of 20mg/100g. body weight, dissolved into distilled water, twice per week for up to 8 weeks **(Li et al., 2017)**. This group was treated just with TAA and operated as a positive fibrotic group.

3) **Group (III)**: **prophylactic group.**

This group was treated Concomitant administration of Telmisartan (Sigma-Aldrich, USA) (8 mg/kg. body weight) dissolved into 0.9% saline by oral injection (p.o.) by gavage **(Noma et al., 2011)**. Beginning with a TAA injection at a dosage of 20 mg/100 g body weight, dissolved in distilled water, twice weekly for up to 8 weeks.

4) **Group (IV): (Treated group)**

This group was administered Telmisartan (8 mg/kg body weight) diluted in 0.9% saline via oral tradition by gavage. Twice weekly for up to eight weeks following the TAA injection period **(Noma et al., 2011)**.

Serum & Tissue sample collection

After a 12-hour fast, the animals were anesthetized with urethane (1.5 g/kg i.p.) and sacrificed. For collecting serum, a blood specimen was collected and centrifuged at 5000 rpm for 10 min (Jantezki, T30, Germany). After that, Serum preserved at -80°C for biochemical evaluation. Each rat's liver was rabidly separated, cleaned on filter paper, and weighed to calculate the liver weight index. The liver was cleaned with cold saline and preserved in 10% formalin for histological analysis.

Biochemical Analysis

ALT, AST, ALP, Alb, T_Bili, and D_Bili levels were evaluated using conventional methods and readily available colorimetric test kits (Sigma-Aldrich).

Histopathological examination of liver tissues

Liver histopathology was assessed by microscopic analysis and photography. At the end of the experiment, liver specimens were carefully gathered and immersed in a 10% formalin solution. The specimens were then processed to get paraffin sections with 4–5μm thickness. Hematoxylin and eosin were applied for the sections staining, and a light microscope with a digital camera was utilized for photographing them.

A**nalysis of pro inflammatory cytokines**

Proinflammatory cytokines such as IL-6, IL-1β, and TNF-α were detected using ELISA kits (Elabscience, Houston, Texas, USA), based on the manufacturer's guidelines.

Statistical analysis

All statistical analyses were analyzed by the statistical software package "SPSS 22.0 for Microsoft Windows," with a two-sided $P < 0.05$ indicating statistical significance. The numerical data were provided as mean ± SD.

RESULTS

Effect of Telmisartan on liver index

First, we assessed the body weight, liver weight, and liver index of each group of rats. As demonstrated in **Table (1)**, rats in fibrotic group had a higher liver index and weight than the normal group. Fibrotic rats treated with Telmisartan had significantly lower liver index and liver weight, as illustrated in **Fig. (1)**.

Effect of Telmisartan on liver enzymes

TAA induced hepatic fibrosis, leading to a significant differed ($p < 0.0001$) in the levels of ALT, AST, ALP, total bilirubin, direct bilirubin, and albumin in comparison with the control group. Telmisartan significantly restored normal ALT activity ($p < 0.0001$) as compared to the TAA group. Also, AST, ALP, and direct and total bilirubin levels were considerably lower following telmisartan treatment compared to the TAA group, as indicated in **Table (2)** and **Fig. (2)**.

Table (1): The Effect of Telmisartan on the Body Weight, Liver Weight and Liver Index of Rats in Each Group (Mean ± SD).

	Group 1	Group 2	Group 3	Group 4
Body Weight (gm)	203.00 ± 2.73	170± 0.71	194 ± 6.4	241.14 ± 4.67
Liver Weight (gm)	5.60 ± 0.55	8.60 ± 0.55	5.71 ± 0.76	7.43 ± 1.27
Liver Index %	2.76 ± 0.27	5.06 ± 0.34 ^{a***}	2.95 ± 0.45^{b***}	3.08 ± 0 .51^{b***}

*** Very highly significant at $P < 0.0001$ significant between control **(G1)** and fibrotic group **(G2)**, (b) significant between Fibrotic group and treated group **(G3, G4)** in the same parameter.

Table (2): Serum liver function indicators at the end of the eighth week treatment with Telmisartan against TAA-induced hepatic fibrosis in rats (Mean ± SD).

	Group 1	Group 2	Group 3	Group 4
ALT (U/L)	20.68 ± 0.58	88.04 ± 5.52 ^{a***}	29.41 ± 1.12^{b***}	36.57 ± 2.88 ^{b***}
AST (U/L)	41.2 ± 1.6	122.66 ± 3.21^{a***}	61.6 ± 4.08 ^{b***}	67.86 ± 2.54 ^{b***}
ALB (g/dL)	3.88 ± 0.25	2.63 ± 0.1 ^{a***}	3.41 ± 0.17 ^{b***}	3.14 ± 0.15 ^{b***}
Total BILI (mg/dl)	0.91 ± 0.04	1.91 ± 0.06 ^{a***}	1.06 ± 0.08^{b***}	1.09 ± 0.11^{b***}
Direct BILI (mg/dl)	0.16 ± 0.02	0.73 ± 0.04 ^{a***}	0.29 ± 0.08 ^{b***}	0.33± 0.16 ^{b***}
ALP(U/L)	111.00 ± 7.81	404.60 ± 8.85^{a***}	150.43 ± 8.98^{b***}	163.14± 5.21 ^{b***}

*** Very highly significant at $P<0.0001$ significant between control **(G1)** and fibrotic group **(G2)**, (b) significant between Fibrotic group and treated group **(G3, G4)** in the same parameter.

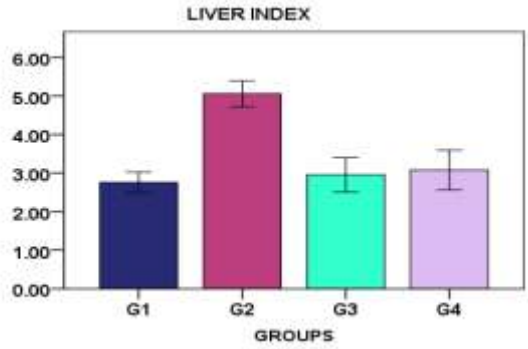

Fig. (1): Liver Index. Liver indices of TAA- rats (G2) was highly significant increased as compared to control rats (G1). Treatment with Telmisartan (G3, G4) attenuated amplification of liver indices

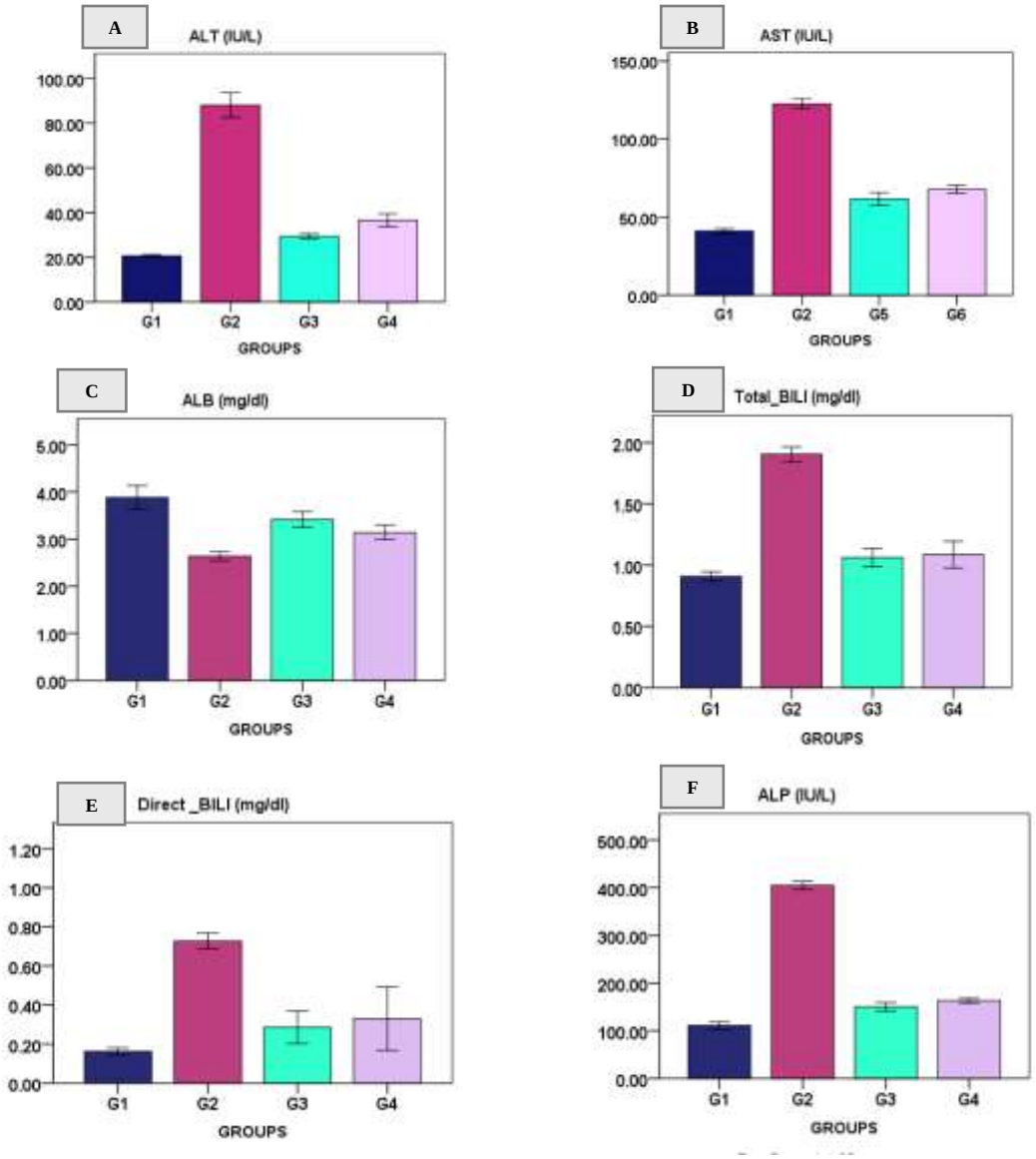

Fig. (2): Serum levels of ALT (A), AST (B), Albumin (c). Total Bilirubin (d), Direct Bilirubin (E) and ALP (F). Bars represent mean ± SD.

Effect of Telmisartan on IL-6, IL-1β, and TNF-α serum levels

The levels of proinflammatory cytokines IL-6, IL-1β, and TNF-α significantly higher ($p < 0.0001$) in the TAA group in comparison with the control group. Telmisartan therapy significantly lowered serum levels ($p < 0.0001$) in rats, whereas IL-6 serum levels reduced significantly ($p < 0.0001$) in treated groups compared to the fibrotic group. Telmisartan therapy significantly lowered the levels TNF-α ($p < 0.0001$) in comparison with the fibrotic group, as seen in **Table (3)** and **Fig.(3).**

Histological Analysis

Histological examination of rat liver tissues from all groups reported in **Fig. (4) (G I, "1", G II "2a &2b" & GIII "5a, b" and GIV "6"). Group I,** the control group, exhibits normal liver tissue architecture, as seen in **Fig. (4), (1). Group II,** the fibrotic group, resulted with TAA, a strong liver-toxic. The liver tissue exhibited major histological alterations, such as severe hepatocyte disarray and hepatic cord breakdown. Occasionally, varying degrees of cytoplasmic vacuolation and nuclear alterations were seen, such as nuclear pyknosis (eccentric, dark stained, and tiny nucleus), fragmentation, or lysis "karyolitic". Previous alterations were associated with considerable congestion and dilatation of the portal veins, central veins, and blood sinusoids as seen in **Fig. (4, 2a).** In the seriously afflicted regions, there is widespread patchy necrosis and inflammatory cellular infiltration, with neutrophils concentrating along the central veins and spreading to the portal area as seen in **Fig. (4, 2b).**

Group III, the prophylaxis group: treated with "Telmisartan" concomitant with TAA: In this group, the hepatic tissue is remarkably identical to that in the normal picture. Delicate interlobular septa and a thin layer of connective tissue surround the liver cells and blood sinuses. Most hepatocytes had typical acidophilic cytoplasm and vesicular nuclei. Nonetheless, several hepatocytes seemed mildly vacuolated. Von kupffer cells were clearly integrated into the endothelial lining of blood sinusoids as shown in **Fig. 4 (5A, B).**

Group IV, Therapy group: triggered with "TAA" and then treated with Telmisartan: This group's liver tissue exhibited hepatocytes organized in radiating and branching cords, with the most evident alteration being portal focal mononuclear cellular infiltration. Some sections showed occasional capsular and lobular foci of inflammation. Increase the quantity of matrix in the interlobular septa, portal regions, and between the malformed hepatocyte cords as shown in **Fig. 4, (6).**

Table (3): Serum cytokines biomarkers at the end of the eighth week treatment Telmisartan with against TAA-induced hepatic fibrosis in rats (Mean ± SD).

	Group 1	Group 2	Group 3	Group 4
IL-6 (pg/ml)	8.2 ± 0.84	37.5 ± 3.5^{a***}	11.34± 0.44^{b***}	12.44 ± 0.89 ^{b***}
TNF-α pg/ml)	40.2 ± 0.84	91.6 ± 3.78 ^{a***}	45 ± 2.57 ^{b***}	48.16 ± 2.70
IL-1B pg/ml)	18.4 ± 3.13	75.6 ± 4.34 ^{a***}	29.67 ± 1.74 ^{b***}	35.66 ± 2.16 ^{b***}

*** very highly significant at P < 0.0001 significant between control **(G1)** and fibrotic group **(G2)**, (b) significant between Fibrotic group and treated group **(G3, G4)** in the same parameter

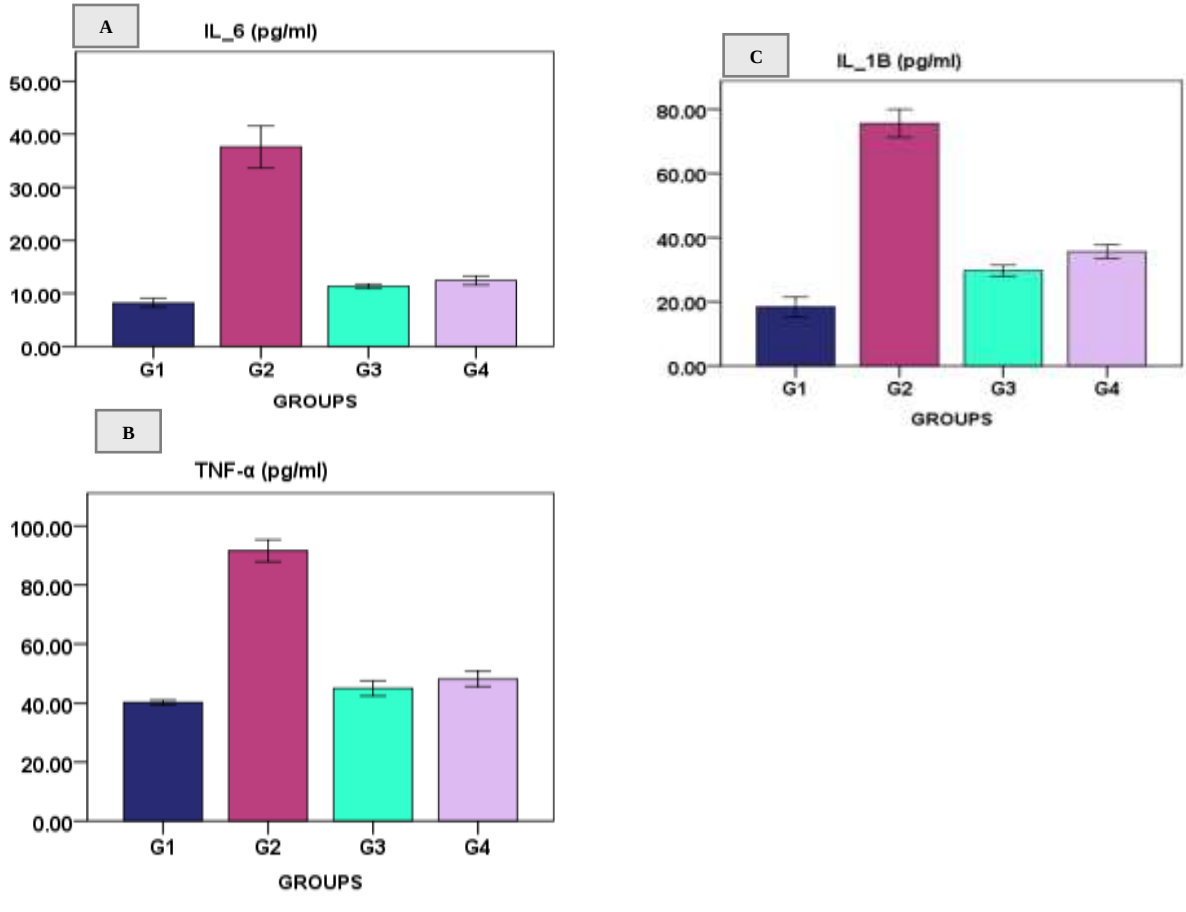

Fig. (3): Serum levels of IL-6 (A), TNFα (B), and IL-1β (C) Bars represent mean ± SD

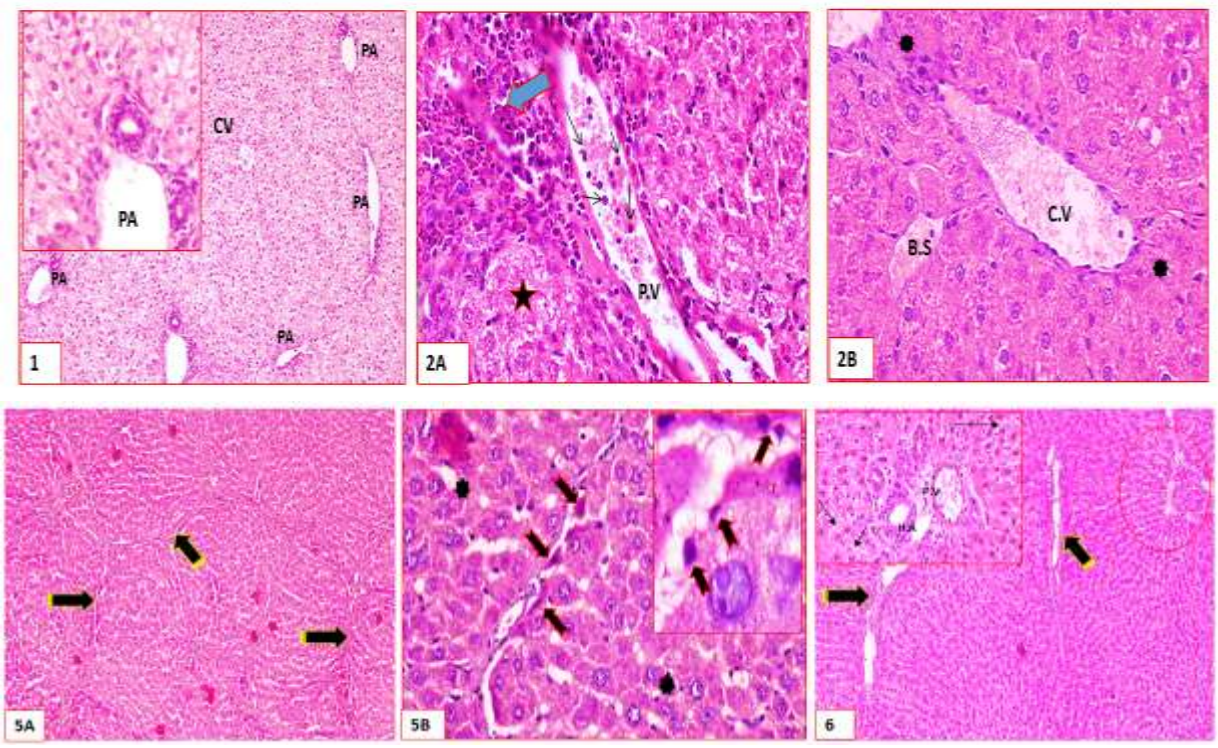

Fig. (4): Photomicrographs of rat liver tissue; **G I, "1", G II "2a &2b" & G III "5 a, b "and G IV "6 " showing**: **1-** Normal liver architecture showing hexagonal classic hepatic lobules with central v (CV) surrounded by portal areas (PA) at each corner. Liver cells arranged in cords and blood sinusoids in-between rows of hepatocytes (arrows). **2A-** Extensive disorganization of hepatocytes, patchy necrosis (star) and inflammation mainly around the portal areas (arrow). Notice dilated portal vein filled with inflammatory mononuclear cells mainly neutrophils (arrows).**2B-** Showing congestion of central vein (CV) and blood sinusoids (BS) and dissolution of hepatic cords (asterisks).**5A, B-** Showing the liver tissue nearly like that of the normal picture. Delicate interlobular septa and connective tissue surrounding the liver cells and the blood sinuses (striped arrows). 5B, showing marked on Kupffer cells incorporated with the endothelial lining of blood sinusoids (tailed arrows). **6-** Dense interlobular septa and connective tissue surrounding the liver cells and blood sinuses (striped arrows). Higher magnification of portal area (inset) showing mononuclear cellular infiltration, portal vein (PV), hepatic artery (HA) and bile canaliculi. Notice that some hepatocytes appear vacuolated (arrows).

DISCUSION

liver is a crucial organ which manages several processes, involving metabolic balance, detoxification, and immunological responses **(Duarte et al., 2015)**. hepatic fibrosis is a complicated process including several signaling methods which occurs in consequence of prolonged damage **(Pellicoro et al., 2014)**. TAA is a routinely used hepatotoxin proven to cause ongoing liver injury **(Ezhilarasan, 2023)**. It is metabolically activated by cytochrome P450 2E1 enzymes, including two oxidative processes. TAA oxidizes to TAA-S-oxide (TASO), then oxidizes to TAA-S, S-dioxide ($TASO_2$). These metabolites covalently bond to amine-lipids and proteins to create hepatotoxic **(Hajovsky et al., 2012)**. As a result, our goal is the determination of the effectiveness of

Telmisartan in both prevention and treatment of hepatic fibrosis. It has been observed that raised. ALT, AST, ALP, Direct bilirubin, and Total bilirubin are related to liver inflammation and injury **(Kalas et al., 2021)**. The present research observed that ALT, AST, ALP levels were considerably higher in the fibrotic group but significantly lower in the Telmisartan-treated groups. On the other hand, ALB showed lower level in fibrotic group compared to telmisartan -treated groups. So, Telmisartan improved liver function and reduced hepatic damage.

IL-1b, TNF-α, and IL-6 are inflammatory biomarkers **(Reyes-Gordillo et al., 2007)**. IL- IL-1b plays an important role in the inflammatory process, which results in tissue damage. It has been previously shown that IL-1 reduces hepatocyte proliferation **(Kimura et al., 2014)**. Research indicates that targeting IL-6 and TNF-α expression can aid in hepatic regeneration. TNF-α promotes liver apoptosis **(Wu et al., 2010)**.

In response to tissue injury, kupffer cells release TNF-α, which leads to the development of IL-6. TNF-α and IL-6 activate neighboring hepatocytes, activating STAT3 (transducer and activator of transcription) and producing various growth factor-mediated proteins. Previous studies demonstrated that the cytokine IL-6 is required for hepatic protection and healing of the liver following liver injury, while excess of IL-6 causes damaging in the liver **(Park et al., 2011; Riehle et al., 2008)**. Telmisartan significantly reduced cytokines like IL-6, TNF-α, and IL-1B.

CONCLUSION

Our research concluded that Telmisartan was anti-fibrotic in the experimental animals. It can be used to treat the liver and has potential therapeutic benefits.

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Conflicts of Interest: The authors declare no conflict of interest.

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التأثير العلاجي للتيلميسارتان ضد التليف الكبدي المحدث بالثيواسيتاميد في الجرذان

فاطمه عامر [١] – محمود الريحانى [٢] – انتصار علي [٣] - عثمان على [١]

[١] قسم الكيمياء (الكيمياء الحيويه) ، كليه العلوم ، جامعه المنيا،المنيا مصر.
[٢] قسم الكيمياء الحيويه ، كليه الطب ، جامعه المنيا، المنيا مصر.
[٣] قسم الهستولوجي، كليه الطب ، جامعه المنيا، المنيا مصر.

التليف الكبدي هو حالة خطيرة تتعلق باضطرابات الكبد المستمرة. يتطور تليف الكبد استجابة لأسباب متعددة لمرض الكبد المزمن. وفي الوقت الحاضر، لم يتم تحديد آلية حدوثه بعد، ولا توجد أدوية علاجية فعالة.
وكان الهدف هو تحديد قدرة تيلميسارتان على تثبيط تطور التليف الكبدي المستحث في الجرذان البيضاء وفي هذه الدراسه تم استخدام ثيواسيتاميد لاحداث التليف الكبدي في نموذج الفئران. تم استخدام أربعين فأراً ألبينو عشوائياً إلى أربع مجموعات متطابقة (عشرة فئران لكل مجموعة). كانت هذه المجموعات هي المجموعة الصحية، المجموعة المتليفة، المجموعة الوقائية بالتيلميسارتان والمجموعة المعالجة بالتيلميسارتان. تم تقييم التحليل البيوكيميائي والنسيجي. باستخدام ELISA، تم فحص IL-6، IL-1B، وTNF-α. واظهرت النتائج وجود انخفاض معنوي جداً ($P<0.0001$) في مستويات ALT، ALP، AST، البيليروبين الكلي والبيليروبين المباشر في المجموعات التي عولجت بالتيلميسارتان مقارنة مع المجموعة المتليفة، في حين كان هناك زيادة معنوية للغاية في الألبومين ($p<0.001$) في المجموعة المعالجة بالتيلميسارتان. أظهرت أقسام الكبد من مجموعات التاليميسارتان انخفاضًا ملحوظًا في الآفات الكبدية. لقد وجدنا تأثيرًا مهمًا للغاية لتيلميسارتان على مستويات IL-6 وIL-1B و TNF-α مما سبق هناك قيمة علاجية محتملة وتأثيرات مضادة للتليف للتيلمسرتان على التليف الكبدي في نموذج الثيوأسيتاميد.