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RESEARCH ARTICLE

Pharmacological Studies on Pentoxifylline and Silymarin in Male Albino rats.

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Abstract

With a purpose to investigate therapeutic efficacy of pentoxifylline (PTX) in Carbone tetrachloride (CCL4) caused hepatotoxicity taking silymarin (SYM) as standard hepatoprotective agent, twenty male adult Albino rats were employed in this study, split into four groups; group 1(control negative), group 2 (control positive) injected intraperitoneallywith 1.5 mg/kg of CCL4 after dilution in olive oil (1:7) three times per a week for 9 weeks, group 3, treated with 280 mg/kg BW of SYM and group 4, treated with 300 mg/kg BW of PTX. After the end of the experiment, serum biochemical analysis of aspartate aminotransferase (AST), alkaline phosphatase (ALP), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), total protein and albumin, globulin, serum bilirubin levels were evaluated in different groups. Hepatic glutathione peroxidase (GPX), catalase (CAT), superoxide dismutase (SOD), and malondialdehyde (MDA) were measured together with histopathological picture of all groups. Group 2revealed significant high levels of hepatic enzymes compared with control; these parameters were significantly decreased in response to treatment with either SYM or PTX. CCL4 administered rats showed marked reduction in albumin and total protein, with significant rise in globulin, serum bilirubin was elevated compared to control. Administration of SYM or PTX resulted in a significant improvement in different serum biochemical parameters where SYM was superior to PTX. Tissue scavenging capacities (GPX, CAT, SOD, and MDA) were evaluated in hepatic tissue, wheresignificant decrease in GPX, CAT, and SODwere observed in rats treated with CCL4, while hepatic MDA was significantly elevated when compared to healthy rats. Treatments with SYM or PTX improved the oxidative stress andSYM showing better outcome.Treatment with SYM or PTX in CCL4 treated male Albino rats defends liver as confirmed by the advancement of various oxidative and biochemical status as well as the recovery of hepatic structural solidity and assignment.

Keywords: Pentoxifylline, Silymarin, Biochemical analysis, Histopathology.

Introduction

Pentoxifylline (PTX) is a methyl-xanthine derivative with variety of anti-inflammatory effects. Although, many studies were conducted on the use and the efficacy of PTX for a variety of dermatological conditions over a long period, United States Food and Drug Administration (FDA) has certified its use for intermittent claudication (IC) only. The primary use of PTX in medicine is to decrease suffering, spasming, anesthesia and failure in the arms and legs, which happens by IC [1].

PTXis an active blood factor for the medication of terminalblood vessels and cerebral ones diseases due to rising red blood cells deformability by decreasing blood viscidity and platelet accumulation as well as thrombus figuration. Moreover, paraesthesia, limb rest pain, cramps, muscles blood outflow and leg sores have been clearly improved; PTX gave a best result compared to placebo. Also, PTX may give favorable results on electroencephalographic in cerebrovascular patients [2]. The drug, a non- specified phosphodiesterase controllerwith anti-inflammatory and antifibrousecharacters,was useful in cases with acute alcoholic hepatitis. It had been mentioned that PTX efficacy was detected in patients when compared with prednisolone in the curative of acute alcoholic hepatitis. PTX significantly decreased deaths, a more useful hazard - support profile, and kidneys protection in comparison with prednisolone in the abovementioned cases may be considered as a great development [3]. Furthermore, PTX is an inhibitor of phosphodiesterase, resulting in a high intracellular pool of the second messenger cyclic adenosine monophosphate (cAMP); also, it has an antioxidant effect [4]. Many studies have shown the curative efficacy of PTX in the patients with peripheral vascular disease. However, using PTX in treatment of IC still remains the main indication. In addition to the previous indication, PTX has found applicable in various disease processes. The drug is used for treatment of neuropathic injuries with a conservatism and prevention of thromboembolic strokes as well as septic shock [5]. The liver does a great role of vital functions in the maintenance and regulating homeostasis of the body. Furthermore, it was used for proteins, lipids and carbohydrates metabolism and excretion of waste products. It cures the growth, metabolism, biochemical pathway, nutrient supply, management against diseases and in reproduction [6].Curative effect of PTX on hepatic infectionshappened by trance has not been investigated but a fewinvestigations have reported that PTX is applied for the curative of liver infections caused via alcohol liver infections after the operationof bacterial-occurred hepatopathy and the other kinds of liver infections [7]. PTX has hepatoprotective potential against chemical induced liver injury; however, mechanism of hepatoprotective effect of PTX remains to be elucidated. PTX may be used for those suffering from chemical induced liver injury [8]. SYM(ripe milk thistle) is used in curing many hepatobiliary defects such as cirrhosis, hepatitis, jaundice and gallstones, as well as kidney ailments [9]. SYM is used in the treatment of hepatitis and biliary diseases, reduce cholesterol, and even improve psoriasis. Also, it can be used to treat deficient lactation. It is recommended by the German Commission for the treatment of toxin-induced liver damage, hepatic cirrhosis and dyspeptic complaints and as a supporter therapy for chronic infections of the liver [10]. It is used as an antitoxin for Amanita mushroom toxicity and to preserve the liver and kidneys from toxic medications [11]. SYM was studied to decrease liver damage, which caused by CCL4, acetaminophen, radiation, and iron over load, phenyl hydrazine, and was effective in alcohol and cold ischemia.Doumas and Biggs [12] reported that SYM have anti-lipid, anti-oxidative, anti-inflammatory, anti-fibrotic, immune modulatory, membrane stabilizing, liver regeneration effects, anti-tumor, anti-atherosclerotic and anti-diabetic activities. SYM has also been indicated in skin,

pancreas, CNS, lungs, kidneys, and prostate illnesses [13]. Intravenous PTX may be of benefit in acute ischemic lesions in systemic sclerosis when used as 1200 mg/day for 21 days [14].So, the objectives of this study is to investigate whether PTXpossess hepatoprotective potentials in hepatic toxicity in maleAlbino rats induced by CCL4 taking SYMas a standardhepatoprotective agent.

Materials and methods

Drugs

Pentoxifylline(PTX) (Trental 400 SR) [R]: it was obtained from SANOFI, Egypt each tablet contains 400mg. Tablets were dissolved in distilled water and given orally via a stomach tube.

Silymarin (SYM): silymarin powder capsules 140 mg were obtained from SEDICO, Egypt. Capsules were dissolved in distilled water and given orally a via stomach tube.

Animals

Twenty adult male Albino rats weighing 150 gm $\pm$ 2.0 were received from animal lab unite, Faculty of Veterinary Medicine, Zagazig University. They housed in metal units with wood shaving bedding, 5 rats in each unit and allowed to become acclimatized to laboratory conditions for one week before the experiment. They were fed on a balanced food and water. The experimental design of the present study was ethically approved by the Ethics Review Committee of the Faculty of Veterinary Medicine, Zagazig University, Egypt (ZU-IACUC/2/F/145/2022).

Experimental layout

Twenty adult male Albino rats were randomly splatted into 4 equal groups (5 rats) in each one as follows:

Group 1 (control group): injected intra-peritoneal (I.P.) 3 times a week for 9 weeks with olive oil (1.5mg \ kgBW.)

Group 2 (Control positive group): injected I.P. 3 times in a week for 9 weeks with 1.5 mg/kg BWof CCL4 after dilution in olive oil (1:7). The dose of control and carbon tetrachloride calculated according to Khan and Alzohairy protocol [15].

Group 3 (Silymarin group): given CCL4 by the same method in group 2 then SYM was orally administered for 30 consecutive days at dose of280 mg/kg BW[16].

Group 4 (Pentoxifylline group):given CCL4 by the same method in group 2 then PTX was orally administered for 30 consecutive daysat dose of 300 mg/kg BW.[17].

Blood sampling and biochemical analysis

At the end of the experiment, the overnight fasted rats were victimized and the following samples were collected:

1) Serum biochemical parameters were determined in separated serum, by centrifugation at 3000rpm/15minutes, from collected blood samples after clot.

2) For determination of tissue free radical scavenging activities, some liver samples were stored at -70ºC, whereas, the others were fixed in formalin (10%) for the histopathological examinations.

Serum biochemical parameters

Serum aspartate aminotransferase (AST), and alanine aminotransferase (ALT) values were quantified calorimetrically. Alkaline phosphatases (ALP), gamma glutamyl transferase (GGT) activity, serum total proteins, serum albumin, serum total and direct bilirubin were estimated. Serum globulin

was estimated as: total proteins - albumin. Serum indirect bilirubin was estimated as: total - direct bilirubin[18, 19].

Antioxidant status and oxidative stress assay

The liver samples stored at 70ºC were used for evaluation of glutathione peroxidase (GPX) level by spectrophotometrically, catalase (CAT) enzyme activities, superoxide dismutase (SOD) levels and malondialdehyde (MDA) contents.

Histopathological examination of liver

Collected samples from the liver of all groups were constant in neutral formalin 10% for 24 h before pattern treatment in paraffin wax. Furthermore, samples were cut into sections (five microns thickness). Samples spotted using Hematoxylin & Eosin (H&E) and checked microscopically [20].

Statistical analysis

Data were analyzed from the result of survival rats using computerized SPSS, version 21. Results of the biochemical variables were registeredas mean ±standard error (SE). The experimental design was completely randomized design (One-way analysis). Significance was determined according to Duncan test. The level of probability less than 0.05 was significant [21].

Results

Regarding Table (1), the serum levels of AST, ALT, ALP, and GGT were significantly elevated in CCL4 treated animals compared with control ones, these parameters were significantly decreased in response to treatment with either SYM or PTX. Moreover,Table (2) showed that serum total protein, albumin and albumin/globulin ratio were significantly decreased in CCL4 in comparison to other groups, with a significant increase in globulin in the same rats. Nerveless, Table (3) revealed significant increase of total and direct serum bilirubin in CCL4 with significant decrease of indirect bilirubin. Treated animals with either SYM or PTX revealed significant improvement in serum levels of AST, ALT, ALP, and GGT, total and direct serum bilirubin values, all outcomes are moved to give SYM the prevalence in its impact looked at over PTX. The results in Table (4) showed that rats in 2nd group had a significant reduction in GPX, CAT and SOD, while MDA was the highest in the same group when compared to other groups. Treatment of CCL4 administered rats significantly improved the antioxidant scavenging capacity of GPx, CAT, and SOD, and MDA level was stunningly reduced in SYM and PTX treated creatures respectively. Silymarin afforded better results than PTX.

Histopathological examination:To verify the biochemical alterations in liver, the histopathological examination of liver was performed. The liver of control group has normal parenchyma, mainly hepatic cells, portal areas and vasculature appeared with the histomorphologic picture. The hepatic parenchyma of CCL4 treated animals suffered from various degenerative changes mainly macrosteatosis and cell death (accidental or programed); the necrotic cells appeared in cluster or focally replaced by fibroses tissue. Some portal areas showed fibroblasts proliferation, mononuclear cell aggregations and newly formed bile ductules. In SYM treated group, a few scattered hepatic cells exhibited microsteatosis or cloudy swelley and the remaining hepatic parenchyma was apparently normal. Concerning PTX treated animals; mild reversible changes

mainly acute cell swelling could be seen below the majority of the hepatic parenchyma, some portal areas showed congested blood vessels and few round cell infiltrations (Figure 1).

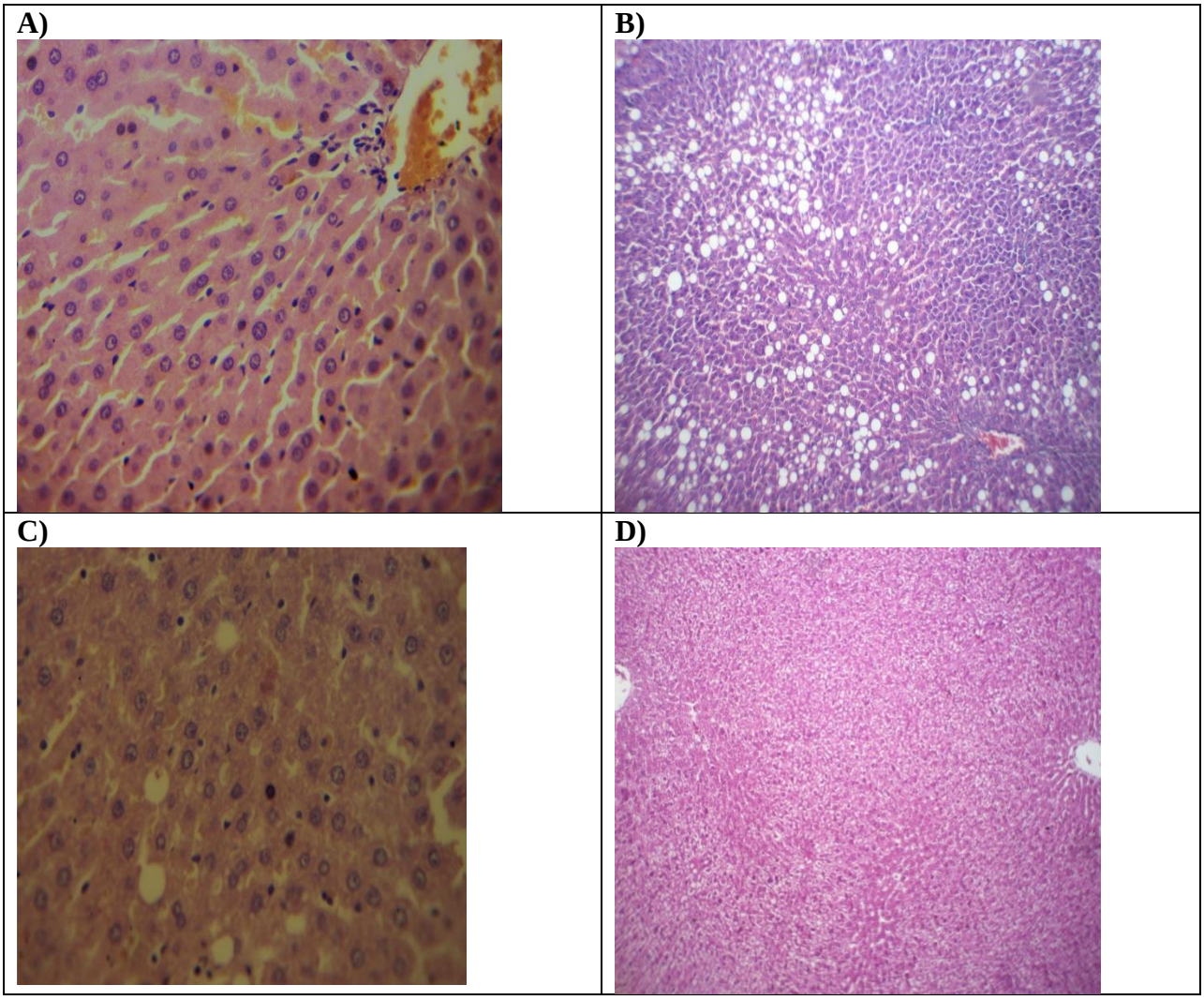

Figure (1): Histopathological analysis to the effects of CCl4 in presence or absence of silymarin or pentoxifylline on liver: A) Liver of the control group illustrates normal parenchymal and sinusoidal structure. B) Liver of CCl4 treated group showing portal areas with thickening and hyalinization of the tunica media of the hepatic arteriole. C) Liver of silymarin treated group showing few scattered hepatic cells exhibited microsteatosis or cloudy swelley and the remaining hepatic parenchyma was apparently normal. D) Liver of pentoxifylline treated group showing mild reversible changes could be seen below the majority of the hepatic parenchyma with few round cell infiltrations.

Table 1: Effect of oral administration of SYMand PTXon liver enzymes of male Albino rats induced hepatotoxicity byCCL4

Group	AST (u/L)	ALT (u/L)	ALP (u/L)	GGT (u/L)
Control	55.5 ± 1.43^{d}	18.52 ± 1.83^{d}	180.66 ± 1.66^{d}	30.52± 1.5^{d}
CCL4	165.33 ± 0.98^{a}	75.22 ± 1.65^{a}	385.36 ± 1.43^{a}	70.63 ±1.22^{a}
SYM	68.88 ± 1.43^{c}	25.42 ± 2.11^{c}	266.28 ± 2.11^{c}	45.43 ±1.53^{c}
PTX	85.23 ± 2.21^{b}	40.52 ± 1.89^{b}	320.22 ± 1.82^{b}	55.25 ±1.88^{b}

The means (± standard error) in the same column bearing different letters are significant at $P<0.01$
SYM= Silmarin (280 mg/kg BW.), PTX= Pentoxifylline (300 mg/kg BW.), CCL4:Carbone tetrachloride (1.5 mg/kg BW diluted in olive oil (1:7) and intra-peritoneal (I/P) injected 3 times a week for 9 weeks).

Table 2: Effect of oral administration of SYM and PTX on protein profile of male Albino rats induced hepatotoxicity byCCL4

Group	Total protein(g/dL)	Albumin (g/dL)	Globulin (g/dL)	A/G ratio(%)
Control	7.52±1.21^{a}	5.22± 1.41^{a}	2.30±1.21^{c}	2.269^{a}
CCl4	5.82±1.33^{c}	3.32± 1.51^{c}	2.50±1.16^{a}	1.328^{c}
SYM	7.02±2.32^{b}	4.72 ±1.22^{b}	2.30±1.22^{c}	2.052^{b}
PTX	6.65± 1.55^{b}	4.21± 1.25^{b}	2.44±1.32^{b}	1.725^{b}

The means (± standard error) in the same column bearing different letters are significant at $P<0.01$
SYM= Silmarin (280 mg/kg BW.), PTX= Pentoxifylline (300 mg/kg BW.), CCL4: Carbone tetrachloride (1.5 mg/kg BW diluted in olive oil (1:7) and intra-peritoneal (I/P) injected 3 times a week for 9 weeks).

Table 3: Effect of oral administration of SYM and PTX on bilirubins of male Albino rats induced hepatotoxicity byCCL4

Group	Total bilirubin(mg/dL)	Direct bilirubin(mg/dL)	Indirect bilirubin(mg/dL)
Control	0.44± 0.12^{c}	0.17 ± 0.03^{c}	0.27 ± 0.02^{a}
CCL4	1.33 ± 0.03^{a}	0.82 ± 0.04^{a}	0.51 ± 0.25^{c}
SYM	0.62 ± 0.15^{b}	0.21 ± 0.02^{c}	0.41 ± 0.22^{b}
PTX	0.76 ± 0.11^{b}	0.33 ± 0.07^{b}	0.43 ± 0.06^{b}

The means (± standard error) in the same column bearing different letters are significant at $P<0.01$
SYM= Silmarin (280 mg/kg BW.), PTX= Pentoxifylline (300 mg/kg BW.), CCL4: Carbone tetrachloride (1.5 mg/kg BW diluted in olive oil (1:7) and intra-peritoneal (I/P) injected 3 times a week for 9 weeks).

Table 4: Effect of oral administration of SYM and PTX on on liver antioxidant enzymes of male Albino rats induced hepatotoxicity by CCL4

Group	GSH-PX (u/mg tissue)	SOD (u/mg tissue)	CAT (u/mg tissue)	MDA (nmol/mg tissue)
Control	8.2 + 0.23a	180.23+ 1.51a	2888.5+ 53.4d	0.08+0.01c
CCL4	4.1 + 0.11d	35.25 + 2.11d	808.16+15.41c	0.21+0.01a
SYM	7.5 + 0.52b	160.42 + 2.55b	2407.5 +51.2b	0.09+0.02c
PTX	6.5 + 0.23c	92.5 + 2.33c	2511.33+48.12b	0.11+0.01b

The means (± standard error) in the same column bearing different letters are significant at $P<0.01$
SYM= Silmarin (280 mg/kg BW.), PTX= Pentoxifylline (300 mg/kg BW.), CCL4: Carbone tetrachloride (1.5 mg/kg BW diluted in olive oil (1:7) and intra-peritoneal (I/P) injected 3 times a week for 9 weeks).

Discussion

Pentoxifylline is non-selective phosphodiesterase (PDE) inhibitor old drug that gave common *in vitro* and *in vivo* anti-fibrotic activities, anti-inflammatory and anti-proliferative. The blood tender specifications of PTX have been correlated to its ability to raise the red blood cells deformability and improve their rheological specifications [22].

Silymarin is standardly extractedfrom the milk thistle (*Silybum marianum*) whose have flavonoids silydianin, silybin and, silychristine. Furthermore, silybin formabout 60% of its composition [23]. Silymarin has hepatoprotective specifications [24].

In this study, serum AST, ALT, and ALP levels, where CCL4 was administrated, were significantly increased when compared to those of healthy animals. Our findings were supported by a previously published work [25], in which significant increase of serum AST, ALT, and ALP levels were reportedin comparing with the control group after carbon tetrachloride was taken. CCL4, which used as a dissolvent in chemical industries, is abasic treatmentto resistand absorbthe volatile chemicals that contaminate the environment, and cause hepatic and renal toxicities. The liver metabolizedCCL4 by cytochrome P450, resulting in free radicals release, like trichloromethyl and its followers,whichcauses fibrosis, steatosis and cirrhosis of liver cells, and cell death [26, 27]. That free radicals formed lipid peroxidation (LPO) through covalent links with lipids [28]. In this study, chronic treatment of CCL4, (1.5 mg / kg b.wt.) was injected I/P three times a week for nine weeks after dilution in olive oil (1:7), increased significant hepatic defect which was indicated from the serum ALT, AST and ALP activities. This is indication of cellular infiltration of hepatocytes membranes [29]. The results were in harmony with Lin and Lin [30] who reported that treated rats with CCL4with 0.1 mL in oil of pea nut (1:1,VV) / 100 g BWtwo times a week for eightweeks revealed a valuable liver defect due to rise serum AST, ALP and ALT levels. Moreover,the results were in the same line with those obtained by Mukherjee[31]; who detected those rats treated with CCL4 in paraffin liquid (1:2, VV, 1 mL/kg. S.C) for eight days registered high AST, ALP and ALT levels. Similarly, Mourelle and coauthors [32] detected significant increase in the serum AST, ALP and ALT activities after CCL4 application. The highest AST, ALP and ALT activities shown in this investigation through the treatment of CCL4, threetimes in a week for seven weeks agreed with the results of a previous research [33] in which hepatitis caused by CCL4 in rats resulted in intoxicating action through the vigorous of the oxidation of free radical with attendant disability of biological membranes, resultingin infiltration of the enzymes viathe loss of functional solidity hepatocytes cell membranes [28].

Concerning the effect of PTX on serum AST, ALT and ALP activities in CCL4, treated rats, the obtained results revealed that PTX afforded a significant decrease in serum activities of ALT and ALP when compared with normal and CCL4 treated groups respectively. These results go hand in hand with Rakhmanin*et al*. [34], which stated that PTX treatment evoked a significant reduction, in serum biochemical parameters (AST, ALT, ALP and GGT). In the same line, Rajesh and Latha[35] observed a distinct decrease in

serum activities of (AST, ALT and ALP) levels following PTX treatment in D-galactosamine induced hepatotoxicity in rats [36].

The liver synthesizes not only the protein it needs but also produces numerous export proteins. Among the later, serum albumin is the most important one. Export proteins are synthesized on polyribosomes bound to the rough endoplasmic reticulum of the hepatocyte; in contrast, proteins destined for intracellular use are synthesized on free rather than bound polyribosomes [37]. Immunoglobulin is synthesized by immunocytes and hyperglobulinemia is found in hepatocellular disorders, appearing as an inflammatory reaction of liver [38].

In this study, application of CCL4, diluted in olive oil, causes marked reduction in serum albumin, globulins and protein. This indicated that the defect in the liver synthetic function returns to fibrosis caused by CCL4. This defect is through the flaw and miscorrelation of polyribosomes from endoplasmic reticulumafterCCL4administration [39].

Our results were confirming by a previous study [29]. The researchers revealed that orally chronic treatment of CCL4 (0.1 mL/100 gm BW.) caused liver damage because of total protein depression. Moreover, Shih *et al.*[40] reported that total proteins and albumin contents decreased after CCL4 administration (0.5 mL /rat orally, two times a week for eight weeks), leading to hepatic fibrosis. The results obtained from this study were harmony with those showed previously [32]. They indicated that the reduction of total protein and A/G ratio was an index of the CCL4-occarred liver flaw. A similar valuable reduction, in total protein was demonstrated by previous works [31, 41]. The researchers attributed these findings to reduce capability of liver to form the protein as a result of hepatic defect due to CCL4 treatment. Similar notes were also registered by Singh *et al.*[42]; they noticed that the treatment of CCL4 (three mL/kg) under the skin of rats for six weeks significantly decreased albumin and increased globulins. Further confirm was the results showed by other researchers [43], who recorded that albumin, and A/G ratio decreased in rats orally treated by CCL4 20% (0.2 mL/100gm of b. wt.) two times a week for eight weeks.

Administration of either PTX or SYM exerted a marked elevation in serum total proteins, and albumin to normal levels [44].

Our results revealed that the PTX administration with 300mg/kg b.wt. for a consecutive 30 days caused a significant increase in serum albumin, globulin and total proteins, comparing with CCL4 treatment [34, 35].

Our results showed that CCL4 increased serum total bilirubin significantly comparing with normal control rat. On the other hand, PTX and SYM decreased serum total bilirubin. Hyperbilirubinemia is very critical conductor to establish the solidity of liver function and the intensity of necrosis, which raises the bound, jointing and secretive ability of liver that is symmetrical to the red blood cells devolution [44]. The liver defect caused by CCL4 in this investigation resulted in a significant increase in serum direct and total bilirubin. During liver infection by hepatotoxin, there is a flaw in secretion of gallvia the liver which is resulted by a rise in gall rate in the blood [45]. The total bilirubin increase in the rat's blood treated

CCL4 for nine weeks may be due to liver absorption of the blood bilirubin or rise in liver B-glucuronidase due to hepatic failure. The other suggestion is that the excess in bilirubin may be correlated to excrescent red blood cells hemolysis. Our results were boost also by Lin and Lin [29], they revealed that treated rats with CCL4, for 2 months gave a valuable rise in bilirubin levels as a result of valuable liver defect. The harmony findings were reported by Shanmugasundaram and Venkataraman [41]; they observed that treated rats with CCL4 had the highest bilirubin as indicator of liver function. Vandenberghe [46] recorded that SYM therapy was effective in prevention of the biochemical changes in CCL4, caused liver cirrhosis. Cirrhosis of the liver was happened by the excess of liver lipoperoxidation, collagen; serum parameterslevels, bilirubin content, glucose and triglycerides. Co-treatment of SYM (50 mg/ kg BW.) totally stopped all the alteration showed in CCL4 cirrhotic rats, excluding collagen, which was decreased by 30%, cirrhotic rats referring these impacts to the antioxidant and membrane- constancy activities of silymarin.

Superoxide dismutase (SOD) catalyzes superoxide anion which is significant reactive oxygen species in cells and engaged with cell membrane harm. The increased activity of glutathione (GSH) and SOD can be a mechanism of compensation for extended over-production of free radicals and oxidative stress [47]. CAT is additionally an antioxidant enzyme situated in peroxisomes and breaks down H2O2 to H_2O and O2 [48].

The MDA is a reactive aldehyde, known for causing concern about the harmful nature of the cells [49]. All these defensive antioxidant enzymes works in an agreeable manner together, and thus, are able to shield from free radicals increase oxidative injury or damage. Treatment of hepatotoxic rats with these medications improves the endogenous antioxidant enzymes (GPX, SOD, and CAT) which may have empowered to avert membrane harm by lessening lipid peroxidation process. This improvement in antioxidant enzyme activity is more than the CCL4 administered group; be that as it may, SYM group was more prevalent in that effect than PTX used on this trail.

Our results consistent with the pathological modifications cleared in this study by inclusive defect caused by steatosis or cell mortality or fibrous tissues, resulting in retraction and invisibility of the plurality of the hepatic cells. These results were confirmed by that recorded by Pradhan and Girish, [50]; they observed intense degradation and necrobiotic variations in the hepatocytes in rats' livers intoxicated by CCL4. These findings were reinforced by that reported by Atta *et al*. [5]; they showed severe degeneration and necrotic changes (Centro lobular) in the hepatocytes in livers of rats intoxicated by CCL4.

Regarding the histopathological findings, the hepatic parenchyma in CCL4 treated animals suffered from various degenerative changes mainly macrosteatosis and cell death (accidental or programed) the necrotic cells appeared in cluster or focally replaced by fibroses tissue. Some portal areas showed fibroblasts proliferation mononuclear cell aggregations and newly formed bile ductules.

A few scattered hepatic cells exhibited microsteatosis or cloudy swilled and the remains of hepatic parenchyma were

apparently normal in PTX treated group. On a similar basis, Taye *et al.* [44] observed a significant improvement in histopathological picture of liver treated with PTX; there were some congested blood vessels in portal areas with leucocytes margination and mild hyperplasia of epithelial lining of the bile ducts.

Conclusion

In conclusion, treatment with silymarin or pentoxifylline defends the liver through their antioxidant activity, as were proven by the improvement of different biochemical markers and oxidative status and the restoration of the hepatic structural integrity and function. However, the non-selective phosphodiesterase inhibitor was less superior to SYM and further studies are recommended on its hepatoprotective activities.

Conflict of Interest

The authors have no conflict of interest to declare.

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الملخص العربى
الدراسات الفارماكولوجية للبنتوكسيفيللين والسيليمارين على الفئران البيضاء

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تهدف هذه الدراسة إلى تقييم التأثير العلاجي للبنتوكسيفيللين على تليف الكبد المستحدث برابع كلوريد الكربون ومقارنة هذا بالسيليمارين ذو التأثير الواقي والمحسن لتليف الكبد والذي يستخدم بكثره كعلاج مساعد مع أدوية الكبد الأخرى.تم استخدام عدد 20 من ذكور الجرذان البالغة تزن 230 جرام تقريبا وقدتم تقسيمهاإلى 4 مجموعات متساوية كل مجموعة مكونة من 5 جرذان. المجموعة الأولى (سالبة) ، المجموعة الثانية (إيجابية التحكم) حيث تم إعطاءهارابع كلوريد الكربون بجرعة قدرها 1.5 ملليلتر / كجم من وزن الحيوان مخففه بزيت الزيتون بنسبة (1:7) ثلاث مرات أسبوعياًلمدة 9 أسابيع متتالية عن طريق الحقن داخل الغشاء البرتوني. المجموعة الثالثة (السيليمارين) وقد تم إعطاءها بجرعه قدرها 280مجم /كجم من وزن الحيوان عن طريق الفم أيضا ولمدة 30 يوما متتالياً وذلك بعد جرعة رابع كلوريد الكربون بنفس الكيفية فى المجموعة الثانية. أما المجموعة الرابعة (البنتوكسيفيللين) وقد تم العلاج بواسطة البنتوكسيفيللين عن طريق الفم بجرعة قدرها 300مجم / كجم من وزن الحيوان لمدة 30 يوما متتالياً وذلك بعد جرعة رابع كلوريد الكربون بنفس الكيفية فى المجموعة الثانية.أظهرت النتائج إرتفاع مستوى إنزيمات الكبد لدرجة معنوية في مصل الجرذان المصابة تجريبياً برابع كلوريد الكربون وذلك عند مقارنتها بالمجموعة الضابطة.إنخفضمستوى هذة الانزيمات بدرجة معنوية نتيجة إعطاء كل من السيليمارين _ البنتوكسيفيللين وذلك مقارنة بمجموعة رابع كلوريد الكربون وكان السيليمارين أفضل في نتائجه من البنتوكسيفيللين. أحدث رابع كلوريد الكربون نقص واضح في مستوي البروتينات والزلال مقارنة بالمجموعة الضابطة وأدى إعطاء السيليمارين و البنتوكسيفيللين إلى إحداث تأثيرات معنوية محسنه لمستوى البروتينات الكلية والزلال عند مقارنتها بمجموعة رابع كلوريد الكربون بينما الجلوبيولين لم يتأثر معنوياً في المجموعة المعالجة بالبنتوكسيفيللين وكان السيليمارين قد أظهر إنخفاض معنوي في نسبة الجلوبيولين مقارنة بالمجموعة المحدث بها التسمم الكبدي. حدث إنخفاض معنوي في صبغة الصفراء الكلية والمباشرة والغير مباشرة نتيجة لرابع كلوريد الكربون عند مقارنتها بالمجموعة الضابطة . حدثت زيادة معنوية في صبغة الصفراء الكلية و المباشرة و الغير مباشرة نتيجة إعطاء البنتوكسيفيللين و السيليمارين عند مقارنتهما بمجموعة رابع كلوريد الكربون.أظهرت النتائج انخفاضاً ملحوظاً في مستويات السوبر أكسيد ديسميوتيز و الكتاليز والجلوتاثيون بير أكسيداز في مجموعة التسمم الكبدي والغير معالجة عند مقارنتها بالمجموعة الضابطة أما التأثير على المالون دايالداهيدفهناك زيادة ملحوظة في مستوياته.كان هناك زيادة معنوية في الجرذان المصابة بالتسمم الكبدي و المعالجة بكلا من السيليمارين والبنتوكسيفيللين في مستويات السوبر أكسيد ديسميوتيز و الكتاليز والجلوتاثيون بير اكسيدازأما المالون دايالدهيد فقد أظهر انخفاضاً معنوياً.كانت نتائج والجلوتاثيون بير أكسيداز, الكتاليز, السوبر أكسيد ديسميوتيز و المالون دايالداهيد فالمجموعة المعالجة بالبنتوكسيفيللين هى 6.5 , 2511 , 92.5 و 0.11 بالترتيب بينما كانت 7.5, 2407.5, 160.42 و 0.09 فى مجموعة الفئران المعالجة بالسيليمارين. تؤكد هذة الدراسة أن البنتوكسيفيللين له تأثير معنوى على التسمم الكبدي المستحدث تجريبيا لرابع كلوريد الكربون. و التى أثبتتها قياس بعض المؤشرات الكيميائية الحيوية في مصل الدم و التأثيرات المضادة للأكسدة.