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A study of the protective effect of 5 Thiocyanatouracil against paracetamol overdose in rats

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Abstract

A new chemical called 5-Thiocyanauracil (TCU) has been created and is being studied for its potential hepatoprotective, anti-inflammatory, and antioxidant effects. Against paracetamol (PA) overdose oxidative stress in female rats. The study's goal was to investigate data that TCU's protective properties against liver and kidney impairment brought on by PA in rats. Fifty female-rats were employed, classify to five groups; 10 rats each: Control group (C) received 2 ml distal water (DW). Group (PA) take 500 mg/kg/day of PA, TCU group received 50 mg/kg/day, while PA & TCU group, administered TCU 50 mg/kg/day followed by 500 mg PA. Last group is combination of PA &AA (ascorbic acid) at 50 mg /kg /day. The treatments were used orally for 25 days. Blood samples were drowning from the hearts of rats directly. The samples of liver and kidney were collected for histopathological investigation. Liver and kidney function tests were evaluated by an auto-analyzer. TCU treatment reduced total protein (TP) levels in serum, decreased alkaline phosphatase enzyme (ALP), aspartate aminotransferase enzyme (AST), alanine transaminase (ALT), and total bilirubin (TB) levels in liver tissue as compared to rats given PA. TCU treated rats showed normal liver cell structure without damage, and reduced infiltration of neutrophil. Such result proposes the ability to reduce inflammation by PA high dose and reduce tendency of the liver cell to cause necrosis. There is no effect in kidney function and its histology. In conclusion that TCU played a potential hepatoprotective action in liver damage related to PA in rats.

Keyword

5 thiocyanaturacil; Paracetamol, liver function test, renal function test, renal histopathology, liver histopathology.

TCU was synthesized in good yield by KSCN reaction with 5-Iodouracil using an aqueous medium to result white crystalline. To confirm the proposed product structure, a spectroscopic method was used to characterize the synthesized compound. Uracil is one of the important organic molecules that were found in several natural products [(13)]. Uracil and its derivatives have anti-inflammatory, antioxidant, antivirus, antifungal, antibacterial, and cancer protective effect. They are significantly important in the development of drugs [(21)].

Thiols(-SH) are important and hard antiradicals particles in the sulfhydryl containing of +H and -S particle attached to a C particle ([(18)]. These -SH ordered as low molecular weight -SH and great molecular weight protein -SH. It has -SH protein in plasma and -SH protein groups involving of cysteine, cysteinylglycine, homocysteine and reduced glutathione (GSH) [(11)]. Antiradical defense mechanisms such as -SH, which the body uses to protect the organs from the damaging effects of reactive oxygen species, have been examined (ROS) [(4)]. -SH drugs also have broad ant- inflammatory effect associated with their capacity to clean ROS and interfere with inflammatory pathway mediated ROS. They can also prevent the action of myeloperoxidase, inflammation mediator, and oxidative reaction [(10)].

PA stimulate acute liver cell damage as a trial model of drug-prompted acute liver injury is stable and usually used as models for examination of the efficacy of liver protection agents [(19)]. PA is a commonly used anti-pyretic that has been recognized

as a source of hepatotoxicity [16], once used for a long period or high therapeutic dose, it can lead hepatic, renal necrosis, and oxidative stress (OXS) [3]. However, liver toxicity is more suspected than renal toxicity in PA high doses, PA-stimulated nephrotoxicity, such as tubular kidney injury and acute kidney failure [8]. -SH is an essential antiradical that protects cell from damage caused by oxidative stress (OXS). GSH and Taurine are two vital −SH [12]. -SH drugs can break down to cysteine and help GSH production. Assistant GSH production in the hepatic cells stimulates its ability to clean free radical and avoid more association of -SH proteins with NAPQI such as by N-acetylcysteine (NAC) [15]. Therefore, objectives of this study are to control the therapy effects of TCU on PA-induced hepatic and nephrotic toxicity in rats.

Methods and material

Animal preparation

The study was carried out at the college of pharmacy from March 2022 to April 2022. About 50 Female Wister rats at age of 40-60days weighted 149-170g; were brought from the College of Veterinary Medicine at the University of Al-Qadsia. The rats were kept in rat polypropylene cages lined with sawdust. Each cage had a label and was arranged in groups; initially rats provided access lab natural lighting at temperature of 21 ± 4°C. Than rats were

Protective effect of TCU against PA overdose in rats

divided into five groups; Group C received distilled water, as a negative control. A single oral 500mg of paracetamol / Kg / day (provided by: GSK-Co/EGYPT) were administered for PA group as a positive control. TCU

group was given 50 mg/kg orally of TCU once daily dose [13]. The PA & TCU group received daily doses of an oral solution containing 50 mg of TCU after two hours of receiving 500 mg/kg/day of PA orally. The final group (PA & AA) received an oral dose comprising 50 mg per kg of ascorbic acid acquired from TM-Media/India two hours after receiving the dose of PA.

Samples collections and testing

About 25 days were spent on the therapeutic schedule. All rats underwent chloroform anesthesia before being euthanized. The heart's blood was drawn and centrifuged at 3000 r for 10 min. at 4 °C. A collection of serum was made, and then it was divided into vials and kept at -20 °C. The liver and kidney was removed for histopathological studies. The liver tissues were washed thoroughly with normal saline and kept in formalin solution (10%) for 48 hrs. and dehydrated with alcohol in concentration of 70% overnight. Then samples were fixed in paraffin and cutting of the samples into 5 Mm thickness by Rotary microtome, China, and then staining with hematoxylin and eosin (H & E) [14]. Slides examination done via Digital microscope B290 Tb, Italy

Parts of hepatic tissues was weighed and homogenized with buffer and then centrifuged for 15 minutes at 10000r at 4 °C. The supernatant was transported to tubes, storage at -20°C and later examination [1]. Estimation of liver and kidney function tests were measured by Cobas E411analyze, Germany.

Antibacterial Screening

At doses of 100, 150, and 250 g of TCU/ml of DMSO versus ceftriaxone disc, the bactericidal activity of TCU was evaluated against Gram Positive S. aureus and Gram-Negative E. coli pathogens. Than the bacteria were cultured at Muller Hinton agar for bacterial sensitivity using disk diffusion susceptibility test [26] ,used filter paper discs containing 100, 150 ,250µg of TCU/ml of DMSO against ceftriaxone disc.

Statistical Analysis:

Data were analyzed with SPSS program. For the analysis of statistical significance, one-way ANOVA was employed, and then the "Tukey post-hoc "test. The results presented as: mean± SD, and a P value of 0.05 was regarded as statistically significant.

Result

Liver function test

Aspartate aminotransferase (AST) level assessment

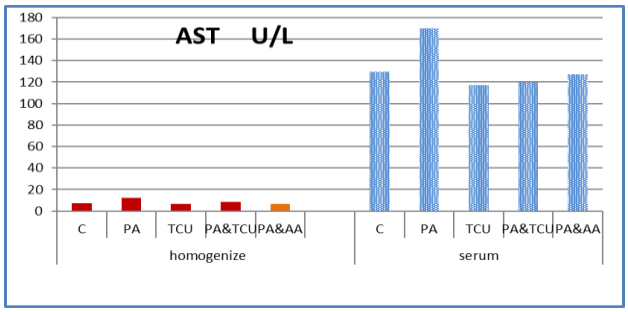

Figure (1): Effect of TCU on AST activity in serum and hepatic tissue.

In serum, AST activity was insignificantly different in all test groups. The AST level was significantly increased in the PA group compared to C group (in liver tissue). PA&TCU group significantly reduced of AST activity compare to

TCU group. TCU alone, PA&TCU and PA & AA group significantly affect the AST level compared to the PA group in liver tissue. (P value < 0.05, (tab.1, fig. 1).

C: Control, PA: paracetamol, TCU: 5-thiolcyanaturaacil, AA: Vitamin C, AST: aspartate aminotransferase.

Table (1): Effect of TCU on liver biomarkers on the serum and hepatic tissue.

Liver function (serum)				
groups	AST U / L	ALP U / L	TB mg / dl	ALT U / L
C(I)	129.875±26.7	160.125± 45.196	0.075±0.09	22±4.656
PA(II)	170.22±39.59	229.285±51.45a	0.198±0.16a	27.5±4.629
TCU(III)	117.5±29.61	184.625± 69.16	0.09±0.03 b	17.857±3.976
PA&TCU (IV)	119.625±27.38	182.375± 46.46	0.0725±0.027 b	20.875±7.809
PA&AA (V)	127.375±50.60	193.57± 56.39	0.0785±0.038 b	22.285±11.47
LSD	NS	69.160	0.108	NS
Liver function (homogenize)				
groups	AST U/L	ALP U/L	TB mg/dl	ALT U/L
C(I)	7.04±1.0	64.85714±9.459	0.257±0.09	17.64±6.59
PA(II)	11.94±2.0 a	125.428±14.4 a	0.61±0.187 a	29.82±4.957 a
TCU(III)	6.57±0.75 b	61.571±8.1415 b	0.307±0.067 b	14.72±3.14 b
PA&TCU (IV)	8.68±2.599 b c	86±20.83 b,c	0.256±0.045 b	25.82±8.36 a c
PA&AA (V)	6.485±1.03 b	61±10.32 b d	0.406±0.137	17.6±4.765 b d
LSD	3.26	24.42	0.207	11.1

(a): significant differences with C group, (b): significant differences with PA group, (c): significant differences with TCU group, (d)significant differences with PA& TCU group
. P <0.05. NS: non- significant.

The effect on alkaline phosphatase (ALP)level

ALP activity was significantly elevated in group of rats treated with PA as compared to group C (serum and tissue), but all test groups showed insignificant alteration in serum. Administration of TCU after PA showed significant reduction in ALP activity compared to TCU group. Treatment with TCU at TCU alone, (PA & TCU) and (PA & AA) group significantly reduced ALP activity compared to PA group in tissue. PA&AA group significantly reduced of ALP activity compared to PA&TCU group. (P < 0.05), (tab. 1, fig. 2).

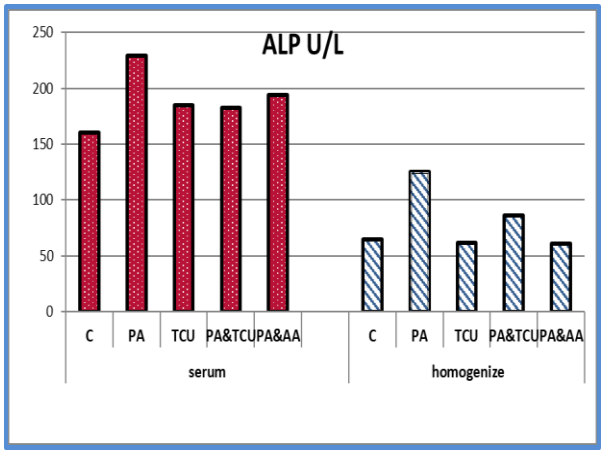

Fig .2: TCU effect on ALP in serum and hepatic tissue.

The effect on total bilirubin

In liver tissue and serum, the TB level was significant elevated in rat group treated with PA as compared to C. Treatment with TCU at TCU and PA&TCU group significantly reduced the levels of TB compared to PA treatment. (P <0.05). (Tab.1, Fig.3).

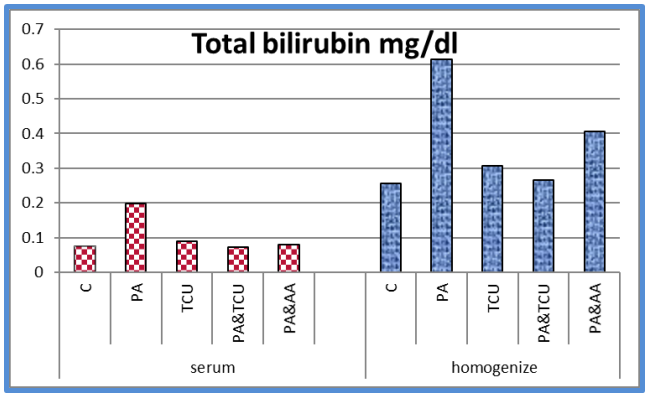

Fig (3): effect of TCU on TB level in serum and hepatic tissue.

The effect on alanine aminotransferase (ALT) level

In serum, ALT activity show insignificant alteration in all test groups. The ALT level was elevated after treatment with PA compared to the C group in tissue, administration of TCU after PA show significant reduction in ALT activity as compared with TCU and C group. The level of ALT was reduced in

TCU alone, and PA&AA group compared to PA group in tissue, PA&AA group significantly reduced of ALP activity compared to PA&TCU group. P < 0.05. (Tab. 1, fig.4)

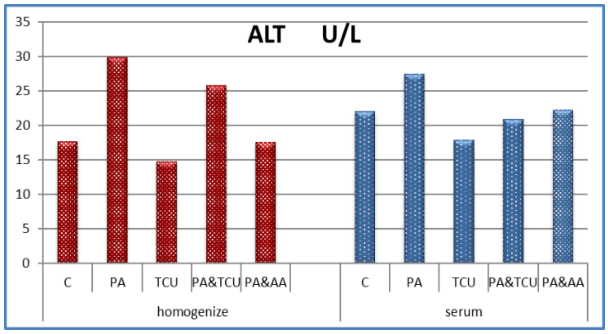

Fig .4: effect of TCU on ALT activity in serum and hepatic tissue.

Total Protein estimation (TP)

TP level was higher in group of rats treated with PA as compared to C. The results obtained from TP levels significantly decreased in treated groups with TCU alone and PA&TCU in comparison with PA group in serum, (P-value <0.05), (Tab.2, Fig.5).

Tab.2: TCU effect on TP level in serum.

Group	Total protein mg/dl
C(I)	73.138±3.838
PA(II)	81.678±5.372 a
TCU(III)	71.235±4.53 b
PA+TCU(IV)	71.148±3.702 b
PA+AA(V)	77.874±4.2
LDS	8.54

(a): significant differences with C group, (b): significant differences with PA group, P <0.05.

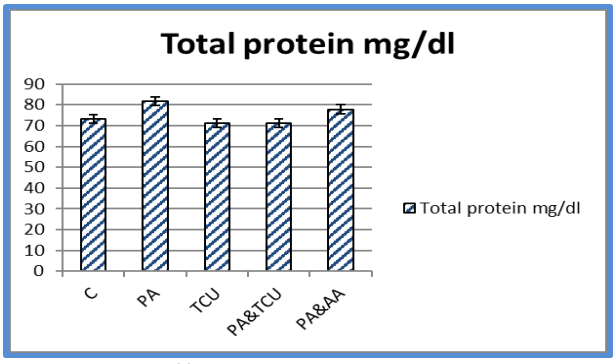

Fig.5: effect TCU on TP level in serum.

Renal Function tests in the Serum

No statistically significant differences in serum Creatinine (Cr) and urea levels were found among all study groups. Comparing rat group C and rats in PA group (P < 0.05), Table 3and Figure 6, 7 shown the data.

Tab.3: effect of TCU on the kidney function test on the serum.

groups	Serum urea mg/dl	Serum Cr mg/dl
C	26.22±4.76	0.377±0.051
PA	28.76±3.96	0.386±0.047
TCU	29.63±6.65	0.37±0.034
PA&TCU	29.72±4.452	0.381±0.046
PA&AA	28.728±4.178	0.375±0.03
LSD	NS	NS

NS: non-significant.

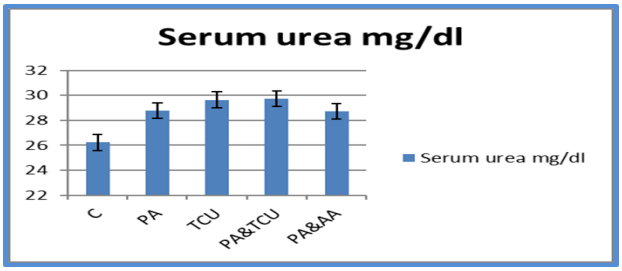

Figure (6): effect TCU on serum urea level.

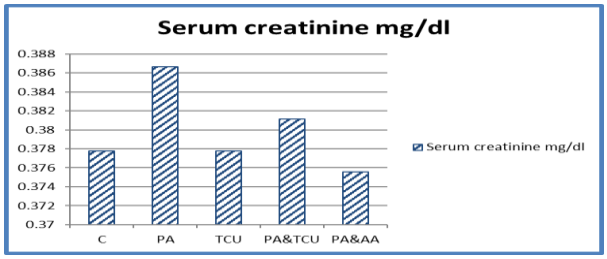

Figure (7): effect of TCU on serum Cr.

Histopathological study of liver

I-Group C

Liver of a control rat, it is composed of triads of peripheral hepatocytes. The normal microscopic organization of the liver is composed of lobules and acini; lobules include the central vein at their center. Hepatocytes are organized as architectures that branch from the central vein, and sinusoids containing Kupffer cells act as a barrier between them. They have a regular form, a substantial spheroidal nucleus, fig.8.

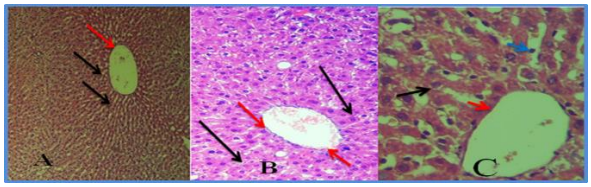

Fig.8: Liver slices from control rats revealing typical hepatic architecture. No congestion is visible, normal hepatocytes (black arrows), Kupffer cells (blue arrows), and intact blood arteries (red arrows).H&E, A: 4x; B: 10x; and C: 40x.

II-PA group

Following PA administration, typical H&E-stained microphotographs of liver tissue sections show liver

swelling, nuclear pyknosis, vascular obstruction, and fatty changes inside the liver parenchyma in addition to zones of centrilobular necrosis and vascular interruption involving the portal triad and distended central veins, which indicate backflow of circulation. According to the research, rats who underwent hepatocyte destruction showed liver damage compared to controls, including centrilobular cell necrosis, neutrophil infiltration, and persistent cell death with necrotic morphology, Fig.9.

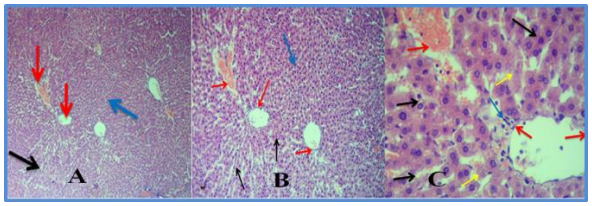

Fig.9: PA group displayed abnormal architecture structure (black arrows), fatty hepatocyte degeneration (yellow arrows), dilated and damaged blood vessels with signs of congestion (red arrows), inflammatory cells, necrotic debris, and a high number of Kupffer cells (blue arrows). A: 4x, B: 10x, and C: 40x H&E staining.

III-TCU group

The liver's normal microscopic architecture was observed in the TCU and TCU&PA groups. Hepatocytes are symmetrical structures with a large, spheroidal nucleus and a distinct nucleolus. A healthy central vein, few Kupffer cells, and no signs of cell congestion or inflammation, no signs of any necrosis were observed, Fig.10.

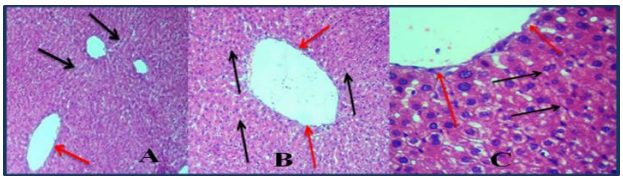

FiG.10: Rats who were given TCU group treatment's liver sections showed normal liver cell, and normal central vein with no signs of congestion. A: 4x, B: 10x, and C: 40x (H and E stain).

IV-PA&TCU group these histopathological alterations were establish to be reduced with the TCU therapy, FiG.11.

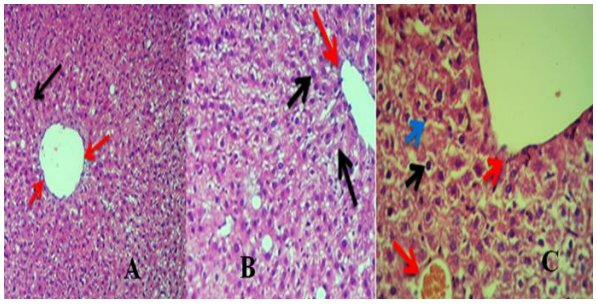

Fig.11: Sections of the liver from the group of rats receiving TCU&PA group treatment showed normal hepatic cell, normal central vein and no congestion. A: 4, B: 10, and C: 40 (H and E stain).

V-PA&AA group these histopathological alterations were found to be reduced with the AA therapy, the liver cross section revealed hepatocytes with a regular shape and a normal nucleus. At a 10x microphotograph, congestion symptoms and an inflammatory patch were visible, Fig.12.

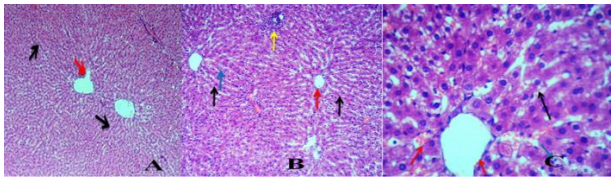

Fig.12: Hepatic cells and central vein were visible in a section of the liver from the PA&AA treated rats group. Mild congestion (red arrow) and moderate of inflammatory cells (yellow arrow). A: 4x, B: 10x, and C: 40x (H and E stain).

Histopathological study of kidney

A control rat's renal cortical region displays normal-looking renal glomeruli, Malpighian renal corpuscle with glomerulus and Bowman's space around it, thin segment, collecting tubules, High cuboidal cells with rounded nuclei line the proximal convoluted tubules, and distal convoluted tubules are bordered by cubical cells with rounded nuclei may be seen in a section of the renal cortex (Fig.12). After paracetamol treatment for more than three weeks, photomicrographs of kidney tissue sections indicate normal glomeruli, extra-vasated red blood cells can be noted (fig.13). The renal sections of TCU, TCU & PA, and PA&AA appear normal structures, with no signs of edema or inflammation (fig.14,15,16).

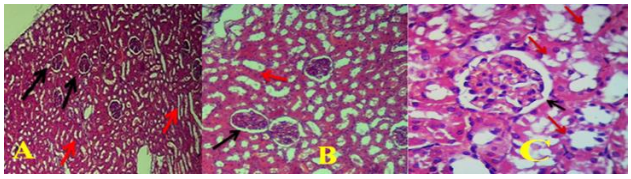

Fig.12: Group C Normal glomerulus tuft, thin segment (upper red Arrow-C), collecting tubules (red arrow -B), proximal convoluted tubules (red arrow bellow the glomerulus-c), and distal convoluted tubules (red arrow laterally to Glomerulus-C) may be seen in a section of the renal cortex (Control) (H&E stain A: at 4x, B: at 10x and C: at 40x magnification)

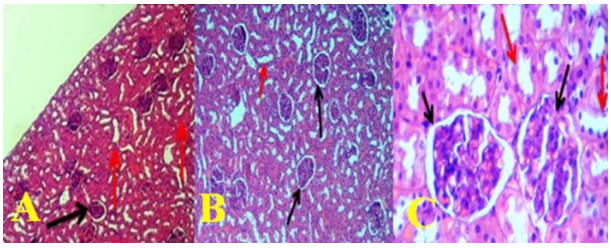

Fig.13: renal section of PA group rats. A: at 4x, B: at 10x and C: at 40x

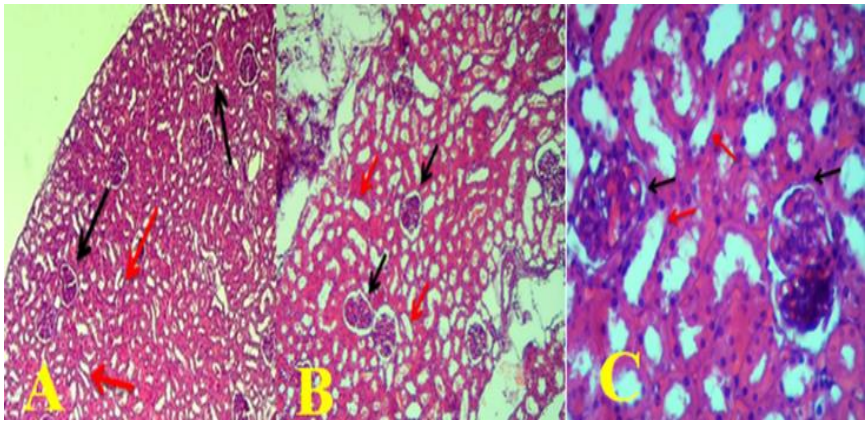

Fig.14: kidney section of TCU group rats. A: at 4x, B: at 10x and C: at 40x

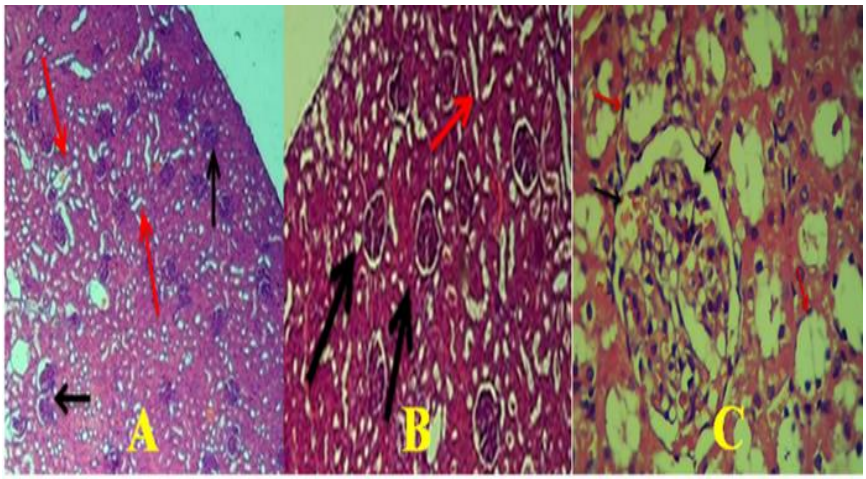

Fig.15: kidney section of PA&TCU group rats. A: at 4x, B: at 10x and C: at 40x

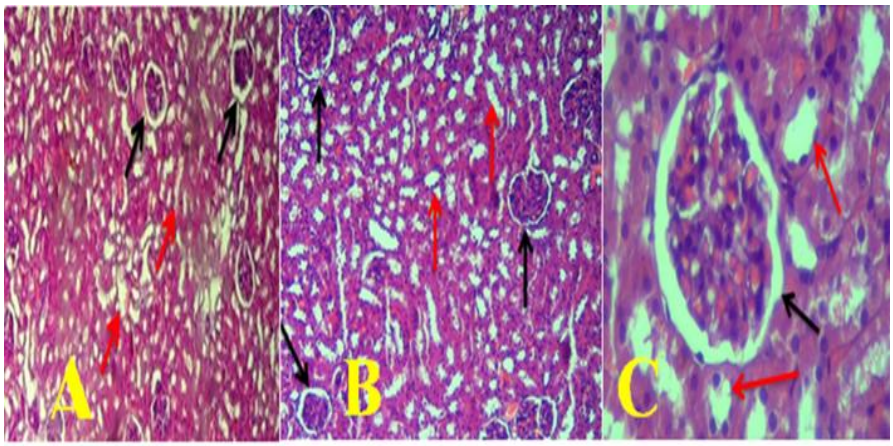

Fig.16: kidney section of PA&AA group rats. A: at 4x, B: at 10x and C: at 40x

Discussion

5-Thiocyanauracil (TCU)therapy has hepatoprotective and antioxidant role in rat by inhibited of Protein Carbonyl and elevated of GPX level in serum and hepatic tissues, and has anti-inflammatory action by inhibit of IL6 level[12].

In our result; only significant increase in serum TP, TB and ALP activity; AST, ALT level increase hepatic tissue.PA established significant hepatic toxicity in rats as existing by a significant rise in AST and ALT activities in liver tissue.

The high dose of PA is prompt liver damage model in experiment and raise liver enzymes, which in turn characterized popular initiation of acute liver damage [1]. PA is mostly breakdown by glucuronidation and sulfation partially by oxidation which catalyze by cytochrome P450 enzyme. However, PA high dose produces formation of high

level of N-acetyl-p-benzoquinone imine (NAPQI) (toxic product), using cytochromes P450 enzyme. NAPQI overpowers the concentration of GSH, which might then decontaminate it. NAPQI links to proteins, resulting in cell death [9].

It is also suggested that the PA poison proliferates through nitric oxide(NO), consequently lead to nitration of protein and tissue necrosis. Nitration of protein is generally reduced by GSH [17]. mainly NAPQI promptly reduce GSH and covalently alteration in proteins of cells courses generation of high quantity of ROS and reduction of the ATP, which produce injuries in liver cell, kidney and mitochondria [6]In the present study, ALP level increased in cholesteric damage, Neamah [14] et al.,(2019) agree with results in the present article. Liver toxicity leads the biliary blocking or congestion causing to the failure of elimination of the ALP from the body that lead to augmentation of the ALP range [22]. The AST, ALT, and ALP generally increased as result to the injury in liver parenchyma [2]. After treatment with TCU, there is reduction in AST, ALT and ALP activity which agreement by Younes [23] et al., 2020, who demonstrated NAC have ability to avoid Hepatotoxicity, inhibit breakdown cellular membranes, leakage of enzymes, keep the integrity of the plasma membranes and reestablishes these enzymes levels via scavenge of free radicals or by GSH replacement to GPX action. That provides safety and hepatoprotective, antioxidant and weakens of obstructive jaundice against liver injury.

Serum and tissue TB level increased after PA administration, conformed by Al-Doaiss [3] ,2020 when hyperbilirubinemia has been detected due to sever heme destruction and biliary tract obstruction. Raised TB levels after cholestasis are one of inflammatory processes. there is an inverse relationship between TB concentration and −SH level [5]. In our study, PA group showed reduction in TB concentration after TCU therapy, Fadime Gьllь Haydar [5] ,2021, revealed that in obstructive jaundice patient, she observed that increased of TB range and decreasing of −SH ranges, the reduction of -SH levels appears OXS. −SH compounds supplement such as NAC may be play role for reduced complication of obstructive jaundice patients and delay stay in hospital. It can serve as antioxidant-SH agent a by free −SH moiety that scavenge of free radicals, or replacement of GSH inside the cells [27]. We think that antioxidant property of TCU, may reduce complication of obstructive jaundice.

Hamid [7] et al., (2018), agree the raised quantity of serum TP after PA therapy at dose 1g/kg might be because of the stimulate production of acute phase protein in the hepatocyte through inflammatory pathway. Then reduced of

TP level after TCU therapy, Pfaff [15] et al., 2019, -SH drugs can break down to cysteine can stimulate to augment GSH synthesis for detoxification of NAPQI. -SH drug such as NAC maintain −SH moiety of enzymes and proteins of membrane in the reduced form [23]. These drugs are act as GSH prodrug, these mechanisms explained inhibition of liver enzyme and repair the damage of liver tissue histology after TCU treatment. Histopathological and Biochemical cleared that treatment TCU, AA after administration of PA revealed the hepatoprotective role of TCU.

In this study, when the liver tissues from all the groups were subjected to histopathological analysis, it was detected that hepatic tissues of group C (I) presented normal cellular structure with discrete hepatocyte, central vein, and sinusoidal spaces. Where PA treatment, hepatic tissues observed signs of hepatotoxicity as necrosis, hemorrhage, inflammation, and liver swelling. In the III, IV, V group these changes were not established. Dose of TCU in IV group inhibit AST, ALT and ALP activity representing its liver protective function, Singh [24] et al., 2022; proposed that the results due to the antioxidant and antiapoptotic activity of NAC. Antiradical protection compound such −SH in the body play a defensive function in organs and cell tissues against the toxic influence of oxidant. −SH display antiradical effect by many mechanisms of action as constituent of −SH/S-S oxidoreduction balance, oxidant reducer and chelater of metal ions [4].

There are discrete mechanisms in control for acute hepatic and renal damage after overdose of PA. Such as, high PA treatment in animal's sources clear depletion of GSH in the hepatic tissue, but not in the renal tissue. Prompting factors are demonstration concomitant of renal harmful agent, staggered ingestion, pre-existing kidney deficiency, dehydration and prolong alcohol drinking. Prominently, the pathophysiological base for PA renal damage performances to be discrete from that of liver injury, and acute kidney failure incidence is detached to hepatotoxicity degree [20] . kidney toxicity is less focused than liver toxicity in PA high doses [8].

These results were in agreement with Hegazy [8] et al., 2019, Administration of PA at dose 2000mg/kg orally to rat considerably raised serum Creatinine and blood urea concentration as compared to their concentration in control group. While in our study use 500mg of PA/kg.

Antibacterial activity showed that 100, 150 ,250mg/mL concentrations of TCU had no role against all test bacteria, H. F. Neamah [13] et al., 2022, exposed TCU has some antibacterial activities, -SH group may linked with sulfonyl moiety in essential proteins or enzyme that leading to oxidation of -SH groups and lacking of microbial cytoplasmic membrane .while our result of resistance may occur

due to Enzyme that alter the antibiotics by the transmitted of functional group, such as acyl, or −SH or another groups , advises many of antibiotics resistance [25] .

Conclusion

TCU was revealed as a protective compound against PA induced hepatotoxicity in rats. This could be illustrated by reduction in Liver function tests. It was also apparent in the normal structure of liver cell where liver damage was not detected. There was also reduction of neutrophil infiltration, suggesting the capability of TCU to inhibit the inflammation responses. But TCU have unknown role for nephrotic protection and antibacterial activity. It did not cause alteration in histology of kidney tissue when TCU given alone to group II. Therefore, this experiment need to make renal injury by increasing of PA doses or by using other renal toxic agent before repeating of this experiment.

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