

## HEPATOPROTECTIVE AND NEPHROPROTECTIVE EFFECTS OF THE AQUEOUS EXTRACT OF TURMERIC (*CURCUMA LONGA*) IN RIFAMPICIN AND ISONIAZID-INDUCED HEPATOTOXICITY AND NEPHROTOXICITY IN RATS

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### ABSTRACT

**Objectives:** The present study was designed to estimate the influences of oral administration of aqueous extract of turmeric (*Curcuma longa*) in hepatotoxicity and nephrotoxicity induced in rats by isoniazid and rifampicin (RIF) for 4 weeks. Influences were determined through the estimation of liver and kidney functions and histopathological changes.

**Materials and Methods:** A total of 48 male albino rats were randomly divided into six groups: Normal control, INH+RIF treated rats, Turmeric aqueous extract 100 mg/kg treated rats, Turmeric aqueous extract 100 mg/kg + INH and RIF treated rats, Turmeric aqueous extract 200 mg/kg treated rats, Turmeric aqueous extract 200 mg/kg+ INH and RIF treated rats. Turmeric aqueous extract and INH + RIF (50 mg/kg bwpo, daily) were given for 4 weeks. Liver and kidney function markers (aspartate transaminase [AST], alanine transaminase [ALT], alanine phosphatase [ALP], bilirubin, blood urea, and creatinine) were determined enzymatically. In addition, tissues of liver and kidney were quickly separated and fixed in 10% formalin and subjected to histopathological studies. Statistical analysis was carried out using t-test.

**Results:** The aqueous extract of turmeric (at a dose of 100 and 200 mg/kg bw, p.o. daily) showed hepato- and reno-protective effects in hepato- and reno- toxicity induced by RIF and INH in rats. Significant elevation of serum ALT, AST, ALP, total bilirubin, creatinine, urea, and total protein, due to RIF and INH treatment, were significantly decreased. The histopathological study further confirmed the biochemical results.

**Conclusion:** Results of the present study indicated that turmeric has hepatoprotective and renoprotective action against RIF- and INH-induced hepatic and renal injury in rats.

**Keywords:** Nephroprotective, Hepatoprotective, Turmeric (*Curcuma longa*), Biochemistry, Histopathology, Rifampicin, Isoniazid.

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### INTRODUCTION

The metabolic processes of the human body are controlled and managed by two vital organs, the liver and kidney [1,2]. The liver and kidney actively metabolized numerous of drugs, hormones, and xenobiotics and maintain our systems. The liver is a main organ in the body and is responsible for the metabolism of internal and external agents. It plays a vital role in drug metabolism and detoxification. Liver injury may be caused by xenobiotic, alcohol consumption, malnutrition, infection, anemia, and medications [3]. Moreover, the liver is expected to be susceptible, especially to drugs and chemicals. Renal system is essential to maintain homeostasis, regulating water and electrolyte balance, and acid-base maintenance, among other crucial functions and also possessed an endocrine function [4]. However, the kidney is the well-known target of toxicity of therapeutic and environment xenobiotics, due to its high blood flow, tubular transport processes, and complex metabolic activities [5]. The drug-induced nephrotoxicity is manifested functionally by a decline in urine concentration, tubular proteinuria, lysosomal enzyme-urea, light glycosuria, sluggish ammonium excretion, and declining glomerular infiltration rate [2]; furthermore, drug-induced hepatic and nephritic injury is the most common cause for withdrawal of drugs.

However, antitubercular drugs, especially isoniazid and rifampicin (RIF)-induced hepatotoxicity, range from a non-specific elevation of transaminases to fulminant of liver failure. Furthermore, the incidence of hepatic dysfunction is more, when isoniazid (INH) and RIF are used in combination [9]. They were also induced renal toxicity [6-9].

Many medicinal plants showed hepato- and reno-protective effects [10-12], these included *Agrimonia eupatoria* [13], *Alhagi*

*maurorum* [14], *Allium sativum* [15], *Anchusa strigosa* [16], *Arctium lappa* [17], *Astragalus hamosus* [18], *Bauhinia variegata* [19], *Brassica nigra* [20], *Brassica rapa* [21], *Bryonia dioica* [22], *Bryophyllum calycinum* [23], *Caesalpinia crista* [24], *Calendula officinalis* [25], *Calotropis procera* [26], *Canna indica* [27], *Caparis spinosa* [28], *Capsella bursa-pastoris* [29,30], *Carthamus tinctorius* [31], *Carum carvi* [32], *Cassia occidentalis* [33], *Casuarina equisetifolia* [34], *Celosia cristata* [35], *Chenopodium album* [36], *Cicer arietinum* [37], *Cichorium intybus* [38], *Citrullus colocynthis* [39], *Citrus species* [40], *Clitoria ternata* [41], *Convolvulus arvensis* [42], *Cordia myxa* [43], *Coriandrum sativum* [44], *Crocus sativus* [45], *Crotalaria juncea* [46], *Cuminum cyminum* [47], *Cupressus sempervirens* [48], *Curcuma longa* [49], *Cymbopogon schoenanthus* [50], *Cynodon dactylon* [51], *Cyperus rotundus* [52], *Daucus carota* [53], *Digitalis species* [54], *Dodonaea viscosa* [55], *Ephedra species* [56], *Equisetum arvense* [57], *Eupatorium cannabinum* [58], *Euphorbia hirta* [59], *Fumaria parviflora* [60], *Galium verum* [61], *Helianthus annuus* [62], *Hibiscus cannabinus* [63], *Hypericum triquetrifolium* [64], *Juniperus communis* [65], and *Jussiaea repens* [66]. This study was designed to investigate the hepato- and reno-protective effects of turmeric (*C. longa*) in experimentally rifampin- and isoniazid-induced hepatotoxicity and nephrotoxicity in rats.

### MATERIALS AND METHODS

#### Experimental animals

A total of 80 Wistar albino adult male rats (*Rattus norvegicus*), 150-250 g, were used in this study. They were gained from the laboratory animal house, College of Science, Thi-Qar University. The animals were dwelled individually in well-ventilated polypropylene cage, in conditioned room [at temperature (22±3°C), a 12-h light/dark cycle

and relative humidity were maintained in the room]. Diet and water were allowed *ad libitum*. At temperature (22±3°C), a 12-h light/dark cycle and relative humidity were maintained in the room.

#### Chemicals and plant extract

Kidney and liver function tests were evaluated using an enzymatic kit (Biomedicals Pvt. Ltd.). RIF and INH were purchased from Sigma Chemicals, and all other chemicals used for this study were of analytical grade. Fine crude ground turmeric (*C. longa*) was obtained from the local market of Basrah city, Iraq, and diagnosed by the plant herbarium of the College Of Science, Thi-Qar University.

#### Experimental design

A total of 48 male albino rats were randomly divided into 6 groups: Control, INH + RIF treated turmeric 100 mg/kg without induction of hepato- and reno-toxicity, turmeric 100 mg/kg +RIF and INH, turmeric 100 mg/kg without induction of hepato- and reno-toxicity, and turmeric 200 mg/kg +RIF and INH. The turmeric aqueous extract and INH + RIF (50 mg/kg bw po, daily) were given for 4 weeks [67,68].

#### Blood sampling and estimation of biochemical parameters

About 24 h after the last doses of the treatments, the rats were anesthetized lightly by chloroform inhalation and then killed by neck dislocation, and then blood samples were collected by heart puncture; each sample was kept into non-heparinized tubes. The blood of non-heparinized tubes was abandoned at room temperature for 30 min and then was centrifuged at 3000 rpm for 15 min, and the sera were kept in deep freeze (-20 ° C) until the biochemical examination [aspartate transaminase (AST), alanine transaminase (ALT), alanine phosphatase (ALP), bilirubin, urea in the blood, creatine in the blood, Total protein] were performed.

#### Histopathological assays

Samples of liver and kidney were taken from the treated and control rats and were prepared for light microscopic study according to routine histological techniques.

#### Statistical analysis

Student t-test was used to determine the significance among the treated group in comparison with positive and negative controls [69].

## RESULTS

#### Biochemical investigation

According to biochemical investigation, Group 3 treated by turmeric aqueous extract 100 mg/kg and Group 5 treated by turmeric aqueous extract 200 mg/kg for 28 days showed no significant changes compared with Group 1 (control group) in the serum levels of ALT, AST, ALP, and total bilirubin (Table 1) and serum creatinine, urea, and total protein (Table 2) which clearly indicate that both doses of turmeric aqueous extract are safe. However, in comparison with INH- and RIF-treated group (Group 2), both doses of turmeric aqueous extract significantly decreased the elevated serum levels of ALT, AST, ALP, and total bilirubin (Table 1) and serum creatinine, urea, and total protein (Table 2); however, the level of these biochemical parameters significantly stayed more than normal limits.

#### Histological investigation

The histopathological study revealed that the sections in the liver of rats from control group showed normal cellular architecture with distinguished hepatic cells, sinusoidal spaces, and central vein showing polyhedral hepatocytes and clear-cut hepatic structural architecture regulated in strands around the central vein (Fig. 1).

The livers of rats treated with INH and RIF showed massive, cellular necrosis, vacuolization, and ballooning degeneration displayed hard damage in the hepatic architecture. Most of the hepatocytes fused together forming eosinophilic syncytial masses, part of multiple areas, fine-bluish in color indicated calcifications. Furthermore, histological exam showed dilatation of hepatic sinusoid, severe degeneration of hepatocytes which appeared with huge vacuolated cytoplasm and inconspicuous cell outlines and the infiltration of inflammatory cells mostly around the portal vein (Fig. 2).

On the other hand, sections in livers of rats treated with INH and RIF and turmeric (*C. longa*) aqueous extract (100 and 200 mg/kg) apparently showed regeneration and amelioration of hepatic cells around the central vein. Furthermore, displayed more or less architecture analogous to the control group where the cellular equalization around the central vein was restored. Similarly, it restored the blood vessels to normal condition (angiogenesis) and nearly brought back normal tissue with slight sinusoidal space expansion (Fig. 3).

**Table 1: The effect of oral administration of turmeric aqueous extract 100 and 200 mg/kg on serum liver enzymes (ALT, AST, and ALP) and total bilirubin in IRF- and INH-induced hepatotoxicity in rats**

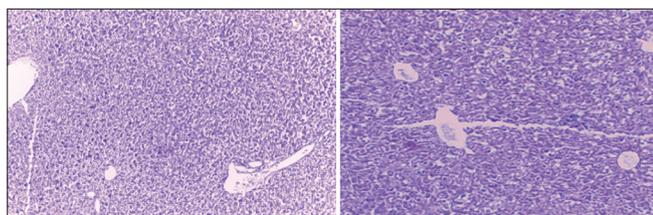
Groups	Groups description	S. ALT IU/L	S. AST IU/L	S. ALP IU/L	Total bilirubin mg/dl
Group 1	Normal control	59.9±2.31 <sup>a</sup>	98.8±4.34 <sup>a</sup>	247.41±11.23 <sup>a</sup>	2.01±0.22 <sup>a</sup>
Group 2	INH+RIF treated rats	158.8±26 <sup>b</sup>	124.44±11.23 <sup>b</sup>	399.30±30.4 <sup>b</sup>	4.06±0.51 <sup>b</sup>
Group 3	Turmeric aqueous extract 100 mg/kg treated rats	62.7±3.34 <sup>NS</sup>	101±3.22 <sup>NS</sup>	234.14±6.34 <sup>NS</sup>	1.97±0.05 <sup>NS</sup>
Group 4	Turmeric aqueous extract 100 mg/kg +  INH and RIF treated rats	138.2±4.98 <sup>c</sup>	115.22±6.61 <sup>c</sup>	356.33±8.33 <sup>c</sup>	2.82±0.04 <sup>c</sup>
Group 5	Turmeric aqueous extract 200 mg/kg treated rats	65.76±2.99 <sup>NS</sup>	109.34±8.44 <sup>NS</sup>	231.33±23.44 <sup>NS</sup>	2.30±0.17 <sup>NS</sup>
Group 6	Turmeric aqueous extract 200 mg/kg+INH and RIF treated rats	131±2.26 <sup>c</sup>	99.21±53 <sup>c</sup>	333.22±16.40 <sup>c</sup>	2.42±0.28 <sup>c</sup>

All values expression by mean±SD, (n=8 in each group). Groups 2, 3, and 5 were compared with Group 1 (normal control) and Groups 4 and 6 were compared with Group 2: Different letters mean significant, NS: Not significant. SD: Standard deviation, AST: Aspartate transaminase, ALT: Alanine transaminase, ALP: Alanine phosphatase, RIF: Rifampicin, INH: Isoniazid

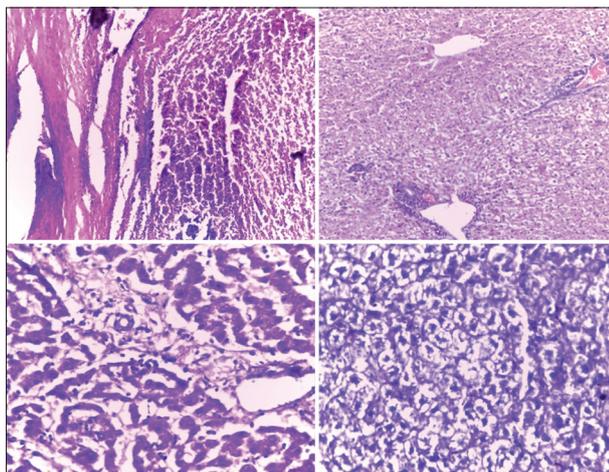
**Table 2: The effect of oral administration of turmeric aqueous extract 100 and 200 mg/kg on serum urea, serum creatinine, and total protein levels in IRF- and INH-induced nephrotoxicity in rats**

Treatment groups	Groups description	Serum creatinine mg/dl	Serum urea g/dl	Total protein g/dl
Group 1	Normal control	1.92±0.06 <sup>a</sup>	3.73±0.36 <sup>a</sup>	7.76±0.18 <sup>a</sup>
Group 2	INH+RIF treated rats	3.19±0.02 <sup>b</sup>	4.68±0.56 <sup>b</sup>	6.08±0.12 <sup>b</sup>
Group 3	Turmeric aqueous extract 100 mg/kg treated rats	2.51±0.01 <sup>NS</sup>	3.98±0.08 <sup>NS</sup>	7.69±0.10 <sup>NS</sup>
Group 4	Turmeric aqueous extract 100 mg/kg +  INH and RIF treated rats	2.22±0.09 <sup>c</sup>	3.09±0.11 <sup>c</sup>	6.56±0.10 <sup>c</sup>
Group 5	Turmeric aqueous extract 200 mg/kg treated rats	2.09±0.3 <sup>NS</sup>	3.49±0.85 <sup>NS</sup>	7.70±0.12 <sup>NS</sup>
Group 6	Turmeric aqueous extract 200 mg/kg+INH and RIF treated rats	2.09±0.14 <sup>c</sup>	3.51±1.28 <sup>c</sup>	6.72±0.43 <sup>c</sup>

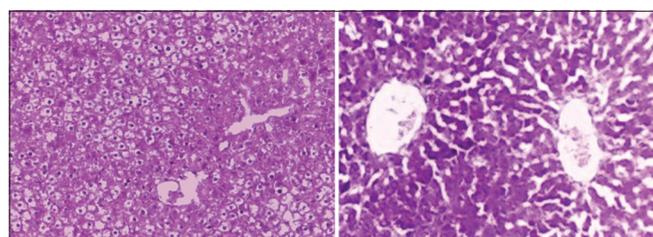
All values expression by mean±SD, (n=8 in each group), Group 2, 3 and 5 were compared with Group 1 (normal control) and Group 4 and 6 were compared with Group 2: Different letters mean significant, NS: Not significant. SD: Standard deviation, RIF: Rifampicin, INH: Isoniazid



**Fig. 1:** Sections in the liver of rats from control group showed normal cellular architecture with distinguished hepatic cells, sinusoidal spaces and central vein, polyhedral hepatocytes, clear-cut hepatic structural architecture regulated in strands around the central vein (Hx and E, ×200)

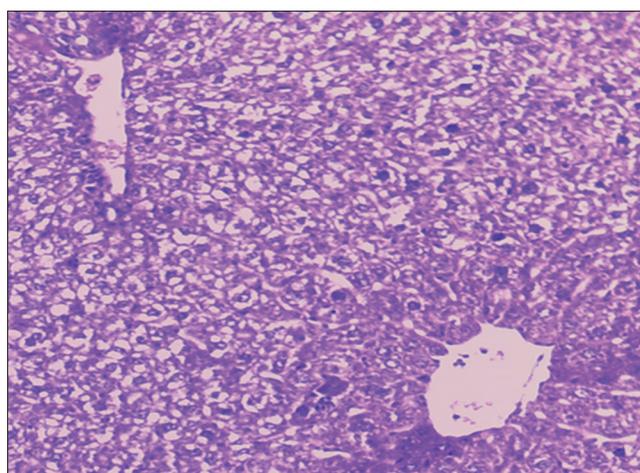


**Fig. 2:** Sections in the livers of rats treated with isoniazid and rifampicin (induction group) showing massive, cellular necrosis, vacuolization, and ballooning degeneration, displayed hard damage in the hepatic architecture. Most of the hepatocytes fused together forming eosinophilic syncytial masses, part of multiple areas, fine bluish in color indicated calcifications. Dilatation of blood sinusoid severe degeneration of hepatocytes, with huge vacuolation of hepatic cytoplasm and inconspicuous cell outlines also with infiltration of inflammatory cells around the portal venule (Hx and E, ×400)

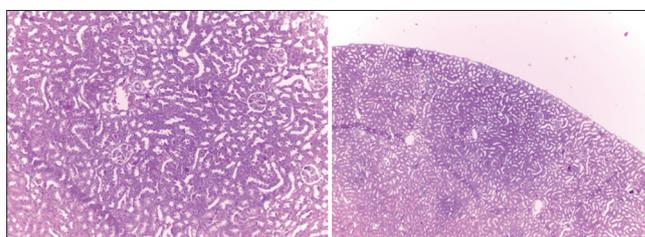


**Fig. 3:** Sections in the livers of rats treated with isoniazid and rifampicin and turmeric (*Curcuma longa*) aqueous extract [100 and 200 mg/kg] showed apparent regeneration and amelioration of hepatic cells around the central vein and noted elaboration around the portal area. Furthermore, it displayed more or less architecture analogous to the control group where the cellular equalization around the central vein was restored. Likewise, it aided to get the blood vessels to normal condition (angiogenesis) noted with the control group and nearly restored normal tissue with slight sinusoidal space expansion [Hx and E, 200X].

Some of the liver sections of rats treated with turmeric aqueous extract (100 and 200 mg/kg) showed normal appearance of hepatocytes and central vein, hepatocytes appeared intact with slight dilatation of central



**Fig. 4:** Sections in livers of rats treated with turmeric (*Curcuma longa*) aqueous extract (100 and 200 mg/kg) showing approximate brought back of normal appearance of hepatocytes and central vein. Hepatocytes appeared intact and slight dilatation of the central vein, the portal area showed a moderate infiltration of mononuclear leukocytes inflammatory cells compared to isoniazid and rifampicin treated rat. Normal condition (angiogenesis) as noted in the control group (Hx and E, ×200)



**Fig. 5:** Sections in the kidney of rats showed normal cellular architecture with distinguished renal cells (Hx and E, ×200)

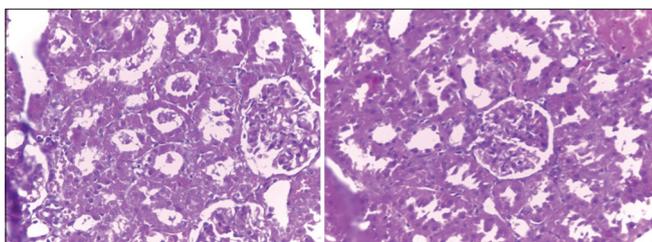
vein, and the portal area showed moderate infiltration of mononuclear leukocytes inflammatory cells with normal angiogenesis (Fig. 4).

Conversely, examination of histopathological sections of kidneys revealed that the control group showed normal renal architecture characterized by normal glomerular and tubular histology, i.e., there were no observable changes in the kidney tissue morphology (Fig. 5).

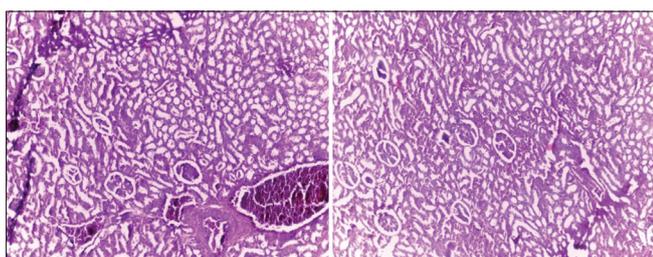
Sections in the kidney of rats treated with INH and RIF showed severe changes evidenced by thickening and vacuolations in the wall of renal blood vessels, perivascular polymorphonuclear cells infiltration simultaneously evident renal casts, conspicuous vacuolations of the glomerular tufts joined and huge cellularity of the glomerulus tufts, areas of necrosis in renal tubular tissue and cell nuclei pyknosis, and focal of interstitial nephritis infiltrated areas with inflammatory cells mostly mononucleosis with dilatation, edema, and inflammation of tubules (Fig. 6).

Sections in the kidney of rats treated with INH and RIF with turmeric (*C. longa*) aqueous extract (100 and 200 mg/kg) significantly showed relieved severity of renal lesions and renal tubular injury, reduced dilation and inflammations of tubules as well as normal renal parenchyma with minimal congestion of blood vessels (Fig. 7).

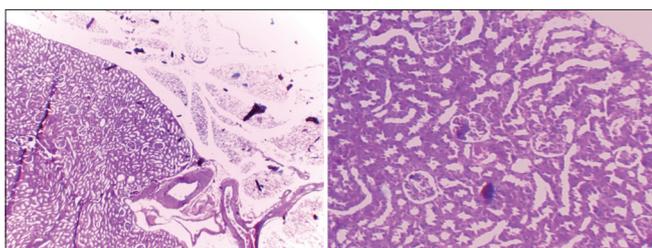
Some sections in the kidney of rats treated with turmeric (*C. longa*) aqueous extract (100 and 200 mg/kg) showed that tubule reveals slight degenerative change, almost normal appearance of glomeruli and tubules as a control group (Fig. 8).



**Fig. 6:** Sections in the kidney of rats treated with isoniazid and rifampicin (induction group) showing histological changes as evidenced by thickening and vacuolations in the wall of renal blood vessels, perivascular polymorphonuclear cells infiltration simultaneously evident renal casts, conspicuous vacuolations of the glomerular tufts joined and huge cellularity of the glomerular tufts, areas of necrotic renal tubular tissue and cell nuclei pyknosis, and focal of areas of interstitial nephritis infiltrated with inflammatory cells infiltration mostly mononucleosis. Dilatation (Hx and E,  $\times 400$ )



**Fig. 7:** Sections in the kidney of rats treated with isoniazid and rifampicin and turmeric (*Curcuma longa*) aqueous extract (100 and 200 mg/kg) showed significantly relieved severity of renal lesions and renal tubular injury in addition to the reduction in dilation and inflammations of tubules (Hx and E,  $\times 200$ )



**Fig. 8:** Sections in the kidney of rats treated with turmeric (*Curcuma longa*) aqueous extract (100 and 200 mg/kg) showing tubule with slight degenerative change, almost normal appearance of glomeruli and tubules

## DISCUSSION

The present study was carried out to evaluate the effect of turmeric (*C. longa*) aqueous extracts on the renal and hepatic functions. INH and RIF which were used as anti-tuberculosis drugs (ATD) were not free from side effects [70]; it was associated with hepato- and reno-toxicity in some individuals [71].

Oxidative stress is the main attribution mechanism beyond ATD-induced hepato- and reno-toxicity [72]. Where, the hepatocytes membrane safety is lost as a result of lipid peroxides generation, due to oxidative stress in the cells [73]. However, the deleterious effect of INH and RIF drugs to the rat tissues was also noticed by elevated activities of enzymes (ALT, AST, and ALP) in the serum. The elevation of these enzymes in our study was matched with previous studies [74]. The elevation in the enzymatic activities of ALT, AST, and ALP can be considered as an important index for the diagnosis of liver diseases

because these increases were attributed to increased lipid peroxidation, in such case, marked alterations in the molecular organization of lipids was occurred in the cellular membranes which increased membrane permeability and facilitated leakage of cytoplasmic markers into circulation [75].

In the previous studies, it was found that serum creatinine and serum urea were dramatically enhanced in INH- and RIF-treated animals [76,77]. Similarly, in the present study, the biochemical evaluation showed increased levels of serum creatinine and serum urea in the INH and RIF group compared with the control group. Elevation of serum creatinine and serum urea could be attributed to retention of ATD in nephrons causing severe injury [78].

Due to the involvement of oxidative stress in the mechanisms of renal and hepatic injury, the antioxidant properties of medicinal plants were involved in the mechanism of their hepatoprotective activity. They inhibited hepatic oxidative stress by many mechanisms. Curcumin, the major phenolic compound in turmeric, which shows preventive effects in various diseases, possessed antioxidant effects and inhibited extracellular matrix formation by enhancing matrix metalloproteinase expression through peroxisome proliferator-activated receptor gamma and by suppressing connective tissue growth factor expression [79,80].

Many medicinal plants produced hepatoprotective effects through their anti-inflammatory activity and attenuation of many inflammatory processes [81].

Curcumin also induced downregulation of cyclooxygenase-2 expression which is involved in acute and chronic inflammation, hemodynamics, tumorigenesis, renal function, and hepatic fibrogenesis [82].

With regard to histopathological alterations in the rats treated with INH and RIF drugs (Group 2) or associated with the use of *C. tinctorius* extract with INH and RIF, were similar to the previous studies [83-86].

We can conclude that the hepatoprotection of the aqueous extract of *C. tinctorius* could be attributed to its antioxidant and anti-inflammatory effects.

## CONCLUSION

The results of the present study indicate that turmeric has hepato- and reno-protective actions against RIF- and INH-induced hepatic and renal injury in rats.

## ETHICS APPROVAL

The experimental work and uses of animals were performed according to Local Regulations of Animal House, Science College, Thi-Qar University.

## AUTHORS' CONTRIBUTIONS

Mahdi M. Thuwaini (single author) drafted and approved the manuscript.

## CONFLICTS OF INTEREST

The authors confirm that this paper's content has no conflict of interests.

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