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Beneficial Effect of UncariaTomentosa against CCl4-Induced Hepatotoxicity: Experimental Study

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Abstract: Background: One of the important an environmental pollutant is the carbon tetrachloride (CCl_4) which induced toxicity in many vital organs. Reactive oxygen species (ROS) can be formed during toxicity with CCl4 pollutant. UncariaTomentosa(UT), cat's claw, is herbal medicine used widely to treat inflammatory disorders, and it is valuable in the curing of several disorders. **Objectives:** The aim of the current work was to explore the defensive role of UncariaTomentosa on CCl_4-induced hepatic injury. **Materials and Methods:** Mice were feed on cat's claw (10 mg kg-1ip1) for 8 days before intraperitoneal injection of 20 ul/kg CCl4for induction of hepatotoxicity. The recorded symptoms of CCl_4toxicity was significant elevations in liver enzymes, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total nitrate/nitrite and lactate dehydrogenase (LDH). Also, a significant reductionin hepatic glutathione (GSH) content and a significant increase in hepatic lipid peroxides. Moreover, the enzyme activities of superoxide dismutase and glutathione peroxidase in the hepatic tissues were decreasedsignificantly. The histopathological examination of hepatic tissues confirmed the results and revealed to obviousnecrosis in the liver with CCl4 treated mice**. Results and Conclusion:** Treatment for 8 days with UT prior to administration ofCCl4 reversed entirely the histopathological and biochemical alterations induced by CCl_4 to the normal condition. In conclusion, UT is efficient in protecting mice from CCl4-induced liver toxicity probablythroughelevated resistance to nitrosative and oxidative stress.

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1. Introduction:

Oxidants are the chemical products generated in the human body as a result of some reaction or metabolism. They can oxidize other substances. This process is dangerous for human bodies. To inhibit this process antioxidants, play a vital role. Antioxidants neutralize the effects of oxidants thus minimizing the harms produce by oxidants. Oxidative stress is a state in the body in which oxidants are present in more quantity than antioxidants. Oxidative stress in the body is the cause of many chronic disorders [1]. It occurs due to an imbalance between the reactive oxygen species (ROS) and antioxidants in the body.

Agents, which are helpful in negating the harmful effect of nitrogen and oxygen free radicals, considered as having therapeutic properties [2].Endogenous anti-oxidants and anti-inflammatory agents are mostly depleted in chronic diseases due to overconsumption [2].So chronic diseases are regarded as conditions in which the body is going through oxidative stress. To cure these chronic disorders anti-oxidants whether from an external source or internally produced are required. These anti-oxidants are also necessary for the body to maintain the regular pH and chemistry of body cells.

Carbon tetrachloride (CCl4) on the other hand is widely used by many researchers to induce hepatotoxicity in mice. It produces hepatotoxic affects in the mice by causing fat deposition and necrosis at the cellular level. Necrosis is considered as a pathological process in which a cell dies due to unfavorable conditions present in the body for its survival. Necrosis also results in the disruption of cell organelles and cell nucleus. A single high dose of CCl4 can cause irreversible damage in the hepatocytes and ultimately the death of the cells [3].

CCl4 is considered as a poison for the body which starts its deteriorating action from cellular level as it has the capacity to generate reactive oxygen species at the cellular level. It along with the reactive

oxygen species has the capacity to damage endoplasmic reticulum of the cells and to release the lipids from the cells. It also decreases the amount of protein synthesis in the hepatic cells [4].CCl4 is metabolized in the hepatic cells through endoplasmic reticulum where cytochrome p450 plays an important role in its metabolism. It is then transformed into a highly reactive radical known as trichloromethyl radical (CCl3). This compound rapidly reacts with lipids to form lipid peroxidation radicals which are hepatotoxic. This is the main mechanism by which carbon tetrachloride rapidly produces hepatotoxicity [5].

UncariaTomentosa (UT) is a plant, which is widely used for many years as herbal medicine to treat certain diseases like arthritis, inflammatory diseases and tumors [6].The common name of UT is cat's claw.It belongs to the family Rubiaceae. It is widely known as the "life giving vine of the Peru" [7].It has been used in the history for healing purpose for above 2000 years. So, it is regarded as a sacred plant in therapeutic herbal drug history [7].

UT have medically important properties to treat different diseases. It is simultaneously an anti-inflammatory agent, an anti-viral agent, anti-tumor agent and has antioxidant properties. It also has the capacity to reduce and downregulate the pro-inflammatory markers production like interleukins and other cytokines [6].

Aim of the work:

The target of the current study is to investigate the probablecy to protective impact of cat's claw against CCL_4 induced liver toxicity.

2. Materials and Methods

Chemicals and Drugs

CCl4 was purchased from Mark chemical company, Germany and Cat's claw was purchased from Sigma- Aldrich, Co. Germany. Through Byoni trading company of Saudi Arabia. All other chemicals were of the highest grade commercially available.

Animals

Male Swiss albino mice weighing 22-25 g were used in all experiments. Animals were maintained under standard conditions of temperature & humidity with regular light/dark cycle and allowed free access to food (Purina Chow) and water.

Induction of liver damage

CCl4 group was treated with a single dose of acetaminophen (500 mg kg-1 i.p.) and killed after 24 hours. The rise in serum ALT was taken as evidence for impaired liver function [8].

Experimental protocol:

Animals were randomly assigned to 4 groups of 10 each:

Group 1 (Control): daily intraperitoneal injections of isotonic saline (10 ml/kg) for eight days.

Group 2 (UT): daily intraperitoneal injections of cat's claw (10 mg kg-1 ip) for 8 days [9]

Group 3 (CCL4): a single dose of CCl4 (20 ul kg-1 i.p.) and killed after 24 hours.

Group 4 (CCL4 + UT): daily intraperitoneal injections of cat's claw (150 mg kg-1 ip) for eight days then given a single dose of CCl4 (20 ul kg-1 i.p.)

At 24 h after last CCL4 injection, blood samples were drawn from the orbital plexus, under light ether anesthesia, into non-heparinized capillary tubes. Serum was separated by centrifugation for 5 min. at 4000 rpm and stored at –20˚C until analysis. The liver was isolated, washed with saline, weighed, and then 10% (w/v) homogenate of the liver was made in ice-cold saline.

Determination of serum enzymes ALT, AST, and LDH

Serum ALT, AST, and LDH were determined calorimetrically and kinetically as described by Bergmeyer et al., 1978 and Buhl & Jackson, 1978 respectively, using commercially available diagnostic kits (bioMērieux-RCS Lyon-France) [10-11].

Determination of total nitrate/nitrite (NO (x)) concentrations in serum

Total nitrate/nitrite (NO (x)) was measured as stable end product, nitrite, according to the method of Miranda et al. [12]. The assay is based on the reduction of nitrate by vanidiumtrichloride combined with detection by the acidic griess reaction. The diazotization of sulfanilic acid with nitrite at acidic pH and subsequent coupling with N-(10 naphthyl)-ethylenediamine produced an intensely colored product that is measured spectrophotometrically at 540 nm. The levels of NOx were expressed as mol g−1 wet tissue.

Determination of lipid peroxides, glutathione content and enzyme activities of Glutathione peroxidaseand superoxidedismutasein liver homogenate:

Glutathione contents and lipid peroxidation (Malondialdhyde (MDA) production) in the hepatic tissues were determined according Ellman,1959 and Ohkawa et al., 1979respectively [13-14].The enzyme activity of Glutathione peroxidase (GSH-Px) and superoxide dismutase were measured in the liver homogenates according Lawrence&Burk,1978 and McCord&Fridovich,1969 respectively [15-16].

Histopathology

Histological examination was performed on about 50% of randomized animals of each group. Liver samples were taken from the distal portion of the left lateral lobe. The tissue was fixed for at least 48 hours in 10% formalin. The samples were then embedded in paraffin, cut into 5 urn sections, and

stained with hematoxylin and eosin for examination by Light micrograph.

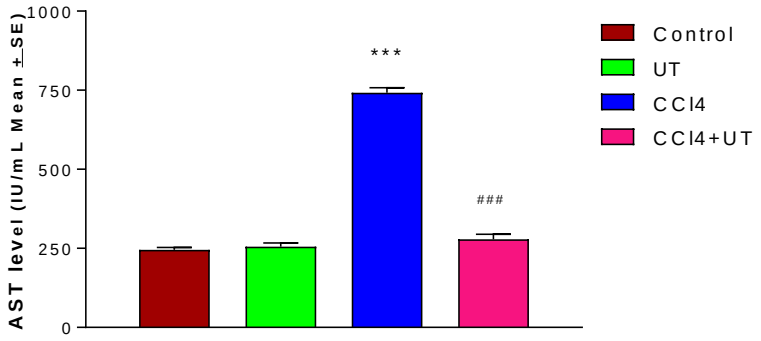
Statistical analysis:

Data are expressed as mean + S.E. for the groups. Comparisons of parameters between different groups were evaluated by One-way analysis of variance (ANOVA) followed by Tukey-Kramer multiple comparisons test. Results considered statistically significant when P< 0.05.

3. Results:

Influence of UT on CCL4-induced biochemical alterations in serum of mice:

Fig (1) Effects of UT on elevated serum enzymes AST activities induced by CCl4

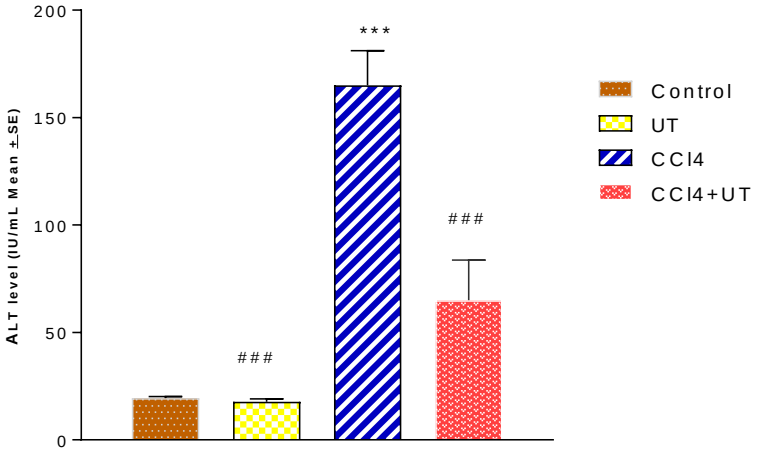


UT (10 mg/kg/day i.p.) was given for 8 day before and during the experimental period, while CCl4 (20 ul/kg i.p.) injected.

· Significantly different from control group # Significantly different from CCl4

#* P<0.05 ##** P<0.01 ###*** P<0.001

Fig (2) Effects of UT on elevated serum enzymes ALT activities induced by ACT

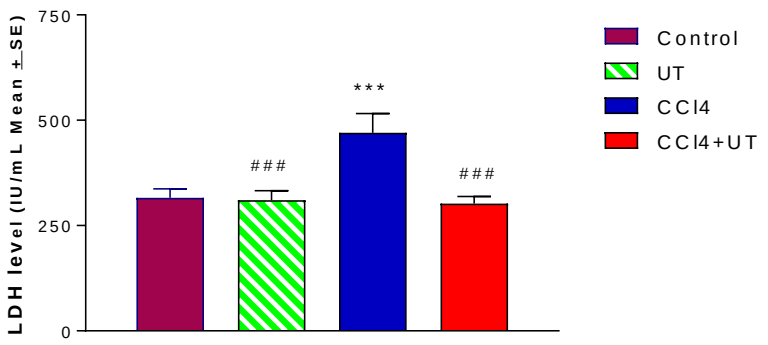


UT (10 mg/kg/day i.p.) was given for 8 day before and during the experimental period, while CCl4 (20 ul/kg i.p.) injected.

· Significantly different from control group # Significantly different from CCl4

#* P<0.05 ##** P<0.01 ###*** P<0.001

Fig (3) Effects of UT on elevated serum enzymes LDH activities induced by CCl4



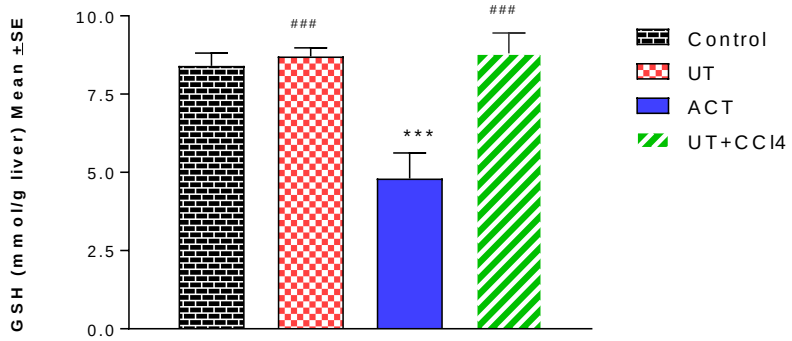
UT (10 mg/kg/day i.p) was given for 8 day before and during the experimental period ,while CCl4 (20 ul/kg i.p.) injected.
· Significantly different from control group # Significantly different from CCl4
#* P<0.05 ##** P<0.01 ###*** P<0.001

The impacts of CCl4, UT and their combination on the function of liver function enzymes (AST, ALT and LDH) are shown in Figs. 1,2,3. CCl4 resulted in significant three folds' increase, four folds increase and one and a half fold'srise in AST, ALT, and LDH in the serum, respectively, in comparison with control mice. Treatment with combinations of UT and CCl4 resulted in a significant decline (*P<0.001*) in the liver function enzyme activity (LDH, ALT and AST) as matched with CCl4 treated group.

Stress Biomarkers: Oxidative and Nitrosative

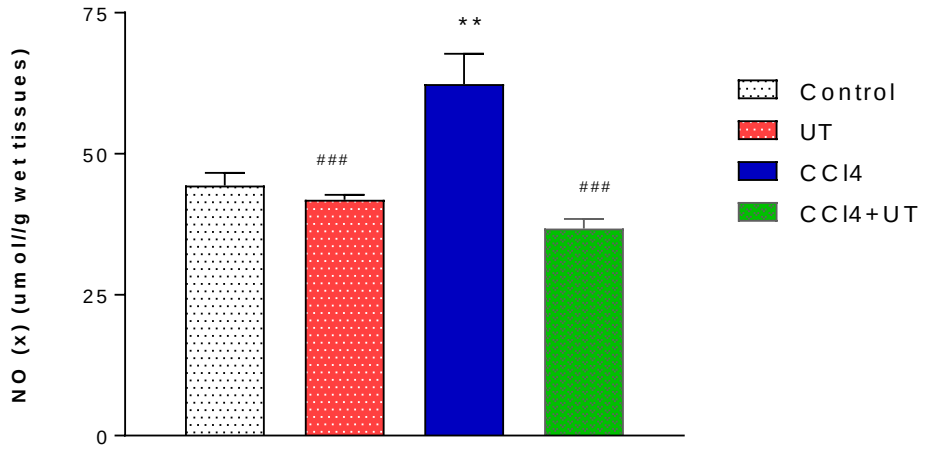
The impacts of CCL4, UT and their combination on some stress biomarkers oxidative (and nitrosative) such as thiobarbituric acid reactive substance (MDA), GSH in liver homogenates and total nitrate/nitrite (NOx) in blood serum are shown in (Figs. 4,5,6). Treatment with CCl4 lead to a significant decline in GSH (50%), a significant rise in MDA (250%) and a significant elevation (149 %) in NOx as matched with the control group. Pretreatment with UT, followed by CCl4 resulted in a significant drop in both MDA and NOx (P<0.01) and nearly restored GSH status in liver tissues as matched with control levels.

Fig (5) Effect of CCl4, UT and their combination on the levels of reduced glutathione in mice hepatic tissues



UT (10 mg/kg/day i.p.) was given for 8 day before and during the experimental period ,while CCl4 (20 ul/kg i.p.) injected.
· Significantly different from control group # Significantly different from CCl4
#* P<0.05 ##** P<0.01 ###*** P<0.001

Fig (6) Effect of CCl4, UT and their combination on the levels of total nitrate/nitrite in serum



UT (10 mg/kg/day i.p.) was given for 8 day before and during the experimental period ,while CC (20 ul/kg i.p.) injected.
· Significantly different from control group # Significantly different from CCl4
#* P<0.05 ##** P<0.01 ###*** P<0.001

Antioxidant Enzyme Activities

The influences of CCl4, UT and UT+ CCl4 on antioxidant enzymes activity (Gpx and SOD) in liver tissues are shown in Figs. 7&8.Administration of CCl4 in mice lead to a significant decline (*P<0.01*) in the levels of Gpx and SOD enzyme activities in comparison with control mice. Whereas, pretreatment with UT, followed by CCL4 resulted in an improvement (*P<0.05*) in the activity of Gpx and SOD enzymes activity in hepatic tissues in comparison with CCL4 treated mice.

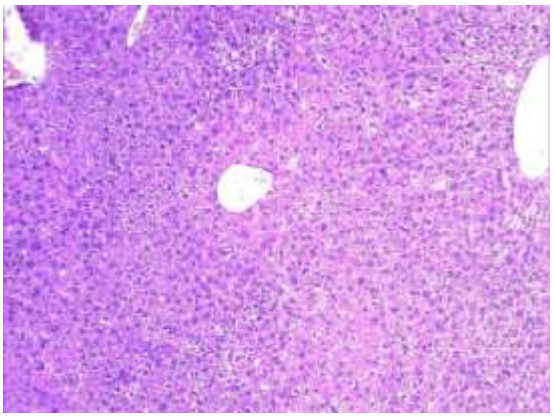


Fig. 7: A photomicrograph of liver of control group showing normal hepatic structure. (H&E...x200)

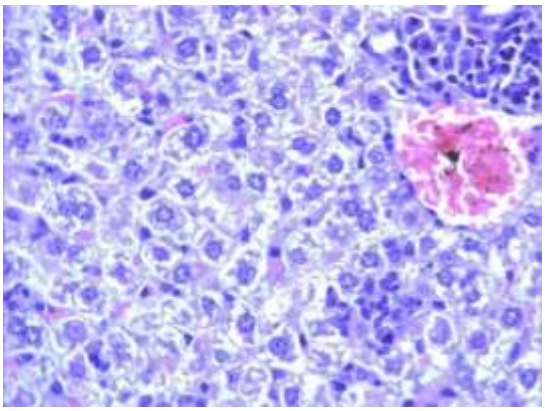


Fig. 8: A photomicrograph of liver of CCl4-treated group showing severe inflammatory infiltrates mainly lymphocytic cells (H&E...x200).

Liver hydropic degeneration + congestion&X400 inflammatory infiltrate.

Histopathological examination:

Pretreatment with UT in mice exposed to CCl4 toxicity resulted in a complete protection againstCCl4 -induced hepatic damage and necrosis (Fig. H-2), without a noticeable signs of liver injury. Sever hepatocellular alteration, vascular degeneration in addition to central zonal necrosis post 24 hrs.from the last injection are shown in CCl4 treated mice (Fig. H-1), whereas normal hepatic architecture were shown in normal control mice.

4. Discussion

The current work demonstrated that pretreatment with UT ameliorated CCl4-induced hepatic toxicity and resulted in restoration of the levels of serum liver enzymes (ALT and AST) and oxidative biomarkers (e.g. MDA and GSH) and confirmed by histopathological results. There are diverse causative components, for instance, tranquilize/substance presentation like acetaminophen [17] or CCl4, metabolic infections [18] and alcohol addiction which add to the liver harm, frequently prompting serious corruption. It is hard to overcome the liver tissue damage with the presentlyexisting medications for severe undesirable side effects and integral toxicities. Accordingly, there is urgent necessity to improve an effective alternatetherapy for controlling liver damage with sufficient safety and efficacy.

There are various causative agents responsible for inducing of hepatic tissue damage like exposure to hepatotoxic drug/chemical e.g. paracetamol [17] or CCl4, metabolic disorders [18] and alcoholism which responsible for induction of hepatic injury, frequently leading to severe alteration and necrosis. The hepatoprotective materials must be characterized by it is ability to repair the normal histologic structure of the hepatic tissues and reservation of the normal physiological pathways affected adversely by the hepatotoxic agents [19]. Hence, we tried to evaluate the efficacy of UT for protection capability in a hepatic injury model in mice.

Using of CCl4-induced liver damage is an excellent model as it causes identical cirrhosis or hepatitis in the hepatic tissues [20-21], mononuclear cell infiltration, and steatotic bubbly deterioration of liver cells [22].Hepatotoxicity induced by CCL4 is described by the release of both reactive intermediate trichloromethyl and trichloromethylperoxy radicals [23] which leads to alkylation of some macromolecules and cellular proteins with a concurrent effect on polyunsaturated fatty acids [24]. It was demonstrated that it produces lipid peroxides as lipid hydro-peroxides, malonaldehyde like materials, conjugated dienes, and other short-chain hydrocarbons which finally causing marked liver cells damage [25].

In the current work, CCl4 treatment is responsible for induction of severe hepatoxicity in mice which was evidenced by a noticeable elevate in the concentration of AST and ALT. These parameters are generally used as biomarkers for liver function impairment. Hepatic cells damage leads to a outflow of liver-specific enzymes, leading to elevation in the concentrations of such enzymes in the blood stream. The elevation in the serum enzyme status such as AST and ALT are used an signs of cellular alteration and functional reliability of hepatic cell membrane [26]. Some authors [27] reported that the elevation in the concentration of ALT and AST after treatment with CCl_4 may be attributed to cell membrane and mitochondrial injury of hepatic cells. Other investigators found a relation between the elevation in the liver enzyme activities and CCl4 treatment [28-31].Administration of UT for experimental animals can protect efficiently the liver from damage (hepatotoxicity) due to CCl4 exposure, as verified by declined in the AST and ALT status in the serum. Earlier researches have documented similar findings on hepatoprotective materials used in the treatment ofCCl4-induced acute liver damage model [14, 29, 30]; though, the current work has demonstrated the impact of UT on CCl4-induced liver injury for the first time.

It has just been appeared past investigations that some of the fundamental factors of CCl4-prompted liver toxicity is the liberation of lipid peroxides via free radical derivatives of CCl4. Accordingly, the inhibition of the release of free radicals or anti-oxidant activity could be considered the most critical tools in the protection protocol against CCl4-induced liver toxicity.

The elevation of hepatic biomarkers levels could be as used as indicators for stresses [31, 32] because of lipid peroxidation produced by free radical derivatives of CCl_4, which subsequently resulted in the liberation of liver function enzymes from liver cells [33, 34].Indeed, CCl4-administration produced a significant elevation in MDA in hepatic tissues in comparison with the control mice group. Administration of UT revealed a significant reverse in CCl4-induced rise in MDA concentration in hepatic tissues. The dropping in MDA levels due to UT treatment documented the property of UT as free radical scavenging. GSH is played an important role in regulating of both intracellular and extracellular contents. Where, GSH could detoxify directly free radicals or ROS by scavenging free radicals or as become a part of the glutathione redox structure which includes glutathione reductase and glutathione peroxidase. A significant decline in GSH concentration in hepatic tissues was initiated in CCl4 treated mice as matched with the control mice which was inverted by UT therapy. The present findingsare in coordination with previous investigations [14, 29, 30].The current results proposed a direct free radical scavenging property, in addition to as becoming a part of flavoproteins e.g. glutathione reductase may be returned to the antioxidant action of UT. Lymphocytes, neutrophils, monocytes and Kupffer cells are documented to be stimulated by different stimulating agents like CCl4 and endotoxins [35].Severe oxidative injury created by CCl4 derivatives similarly stimulate Kupffer cells in the liver which may be result in increased discharge of

TNF-α from inflammatory cells enrolled to the liver [36].The mode of action of UT for protecting from CCl4-induced liver toxicity may be through the suppression of proinflammatory cytokine TNF-α discharge from leukocytic cells. The present findings proposed that the hepatoprotective action of UT in this model may be attributed partially to the suppression of TNF-α.

Histopathological findings paralleled biochemical enhancements post UT treatment. Administration of UT reversed the hepatic lesions produced by CCl4 as it was apparent from the nonexistence of inflammatory infiltrates, cellular degeneration or necrosis, and stabilization of cellular structures in the liver specimen. The present data are in coordination with previous studies, it reported hepatoprotection against chemical-induced liver injury [14,29,30]. Our findings proposed that UT possessing antioxidant and anti-inflammatory activities which are responsible for the normalization of hepatic enzyme function at the structural and biochemical level.

Conclusion

Administration of UT protected mice from hepatotoxic effects of carbon tetrachloride. This beneficial effect is due to the decline in the oxidative and nitrosative stress. These defensive impacts of UT on hepatic tissue damage may have a considerable effect on developing clinically feasible strategies to treat individuals with drug-induced hepatitis.

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