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Original Article

Aleppo galls alleviate paracetamol-induced hepatotoxicity and tissue damage: an experimental study

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Abstract: Background: Acute paracetamol toxicity is a common and potentially life-threatening emergency causing liver failure that may necessitate liver transplantation. Unfortunately, current therapies are still defective. Objectives: To investigate the protective effects exerted by Aleppo galls (Quercus infectoria Olivier) extract against acute paracetamol toxicity in mice. Methodology: Eighteen mice were divided into three experimental groups, each included six mice in each group. The groups included: negative control group, paracetamol toxicity group that received an acute toxic intraperitoneal dose of paracetamol (250 mg/kg) for four consecutive days, and treatment group (received 250 mg/kg paracetamol followed few hours later by Aleppo galls extract for the same duration). Animals were anaesthetized using ether anaesthesia. Animals were sacrificed by decapitation and blood samples were drawn. Paracetamol toxicity effects versus Aleppo galls protection were evaluated on liver function tests, liver histology, serum cholesterol and serum triglycerides. Results: Acute paracetamol toxicity caused significantly elevated serum transaminases (ALT and AST), decreased serum albumin, and increased serum cholesterol and triglycerides. Aleppo galls extract exerted significant protective effects and restored near normal serum levels of the previously-mentioned parameters. Upon histopathological evaluation, mice in the control group showed normal hepatic architecture with preserved hepatic cords and sinuses. Acute paracetamol toxicity induced peripheral

zonal degeneration with focal necrosis of the hepatic tissue. The hepatocytes showed cytoplasmic vacuolation with indistinct cell borders. Central hepatic venules were congested. Administration of Aleppo galls extract reduced the tissue damaging effects induced by paracetamol toxicity with only minimal residual degenerative changes that were observed with absent necrosis. Conclusion: *Quercus infectoria Olivier* (Aleppo galls) is a promising source of phytochemicals and future therapeutics.

Keywords: Aleppo galls, paracetamol toxicity, hepatotoxicity, phytochemistry, liver enzymes

Introduction

High doses of paracetamol may cause hepatic and renal damages. Paracetamol toxicity is among the most common causes of acute hepatic failure. Lethality was reported when paracetamol was taken in a single dose of 300 mg/kg [1]. Paracetamol toxicity is the most common cause of drug-induced liver injury in the United States causing more than half of all acute liver failure cases. Paracetamol metabolism occurs through the protein cytochrome P450E1 causing the production of reactive oxygen species that are responsible for the liver injury in paracetamol overdose. Mitochondrial malfunction is the main supply of free radicals and oxidative stress in paracetamol-induced hepatotoxicity via forming drug-protein adducts between N-acetyl-p-benzoquinone imine, the reactive paracetamol metabolite, and other mitochondrial proteins responsible for the electron transport chain [2]. Moreover, the activity of mitochondrial complex I increased during paracetamol toxicity that caused increased production of both superoxide and peroxynitrite radicals causing increased both oxidative and nitrosative stress [3].

Current treatments of paracetamol toxicity focus on giving of N-acetylcysteine to improve the outcomes in patients who present with acute liver failure via maintaining the intracellular glutathione stores and via detoxifying the electrophilic N-acetyl-p-benzoquinone imine metabolite. Although intravenous N-acetylcysteine is generally well-tolerated, anaphylactoid reactions may occur particularly at loading doses and necessitate discontinuation of N-acetyl L-Cysteine infusion and the intake of antihistamines [4]. Patients with paracetamol toxicity-induced acute liver failure may need liver transplantation. Other suggested treatments for paracetamol overdosage include ethyl pyruvate. Ethyl pyruvate significantly attenuated liver injury and prevented cellular injury induced by the toxic metabolite, *N*-acetyl-*p*-benzoquinone imine [5]. There is an urgent need to develop new, safe and potent treatments to paracetamol toxicity. In this article, the authors introduce the medicinal plant *Quercus infectoria* for possible treatment of paracetamol toxicity.

The plant *Quercus infectoria Olivier* (Family: Fagaceae) is a small tree reaching around 2.5 m in height and having a lot of spreading branches [6]. This tree grows in many Euroasian countries as Syria, Greece, Persia and Asia Minor [7]. Aleppo galls contain triterpenoids, steroids, phenolic acids, flavonoids, and tannins. Many research studies on Aleppo galls ingredients confirmed their so many therapeutic benefits as antioxidant, anti-inflammatory, antidiabetic, anticancer, anti-hypertensive, antimicrobial, insecticidal, antiparasitic, monoamine oxidase-inhibitory, and anticholinesterase effects. Aleppo galls grown in Asia are of the best quality owing to their rich tannin content. Galls are powerful astringent agents due to their rich tannin content [8]. Interestingly, Aleppo oak galls extract gave the highest yield of phenolics and tannins reaching around 884.79 mg tannic acid equivalents (TAE)/g extract and 672.13 mg gallic acid equivalents (GAE)/g extract, respectively. Aleppo galls favoured the growth of the beneficial prebiotic Lactobacillus acidophilus bacteria and inhibited the growth of the pathogenic bacteria Yersinia enterocolitica [9].

In experimental animals, high doses of Aleppo galls were quite safe. Liver function tests as well as renal function tests (serum urea and creatinine levels) were not affected upon intake of Aleppo galls extract even at high doses (1000 mg/kg body weight). Interestingly, Aleppo galls extract exhibited significant anti-inflammatory effects against carrageenan and formalin, respectively. Pre-treatment of fasted rats with Aleppo galls extract (100 and 500 mg/kg body weight) also demonstrated significant protective effects against ethanol-induced gastric ulcers. Aleppo galls extract also exhibited antibacterial activity against many patho-

genic bacteria e.g. Proteus mirabilis, Citrobacter braaki, Staphylococcus aureus and methicillin-resistant Staphylococcus aureus [10]. In addition, galls were reported to exert potent analgesic effects [11]. For all these medicinal merits, Aleppo galls may be promising for developing potent therapeutic ingredients for treating paracetamol toxicity. In this study, we aimed at investigating the protective effects exerted by Aleppo galls extract against acute paracetamol toxicity in mice.

The aim of this article was also to investigate the possible tissue-protective effects exerted by Aleppo galls extract against paracetamol hepatotoxicity.

Materials and methods

Study design and ethical aspects

An approval of the ethical committee of the College of Medicine, Taibah University, Saudi Arabia was obtained. This study investigated possible tissue-protective effects by Aleppo galls extract against an acute toxic dose of paracetamol (250 mg/kg). White albino mice were maintained in the animal house unit of Taibah University in pathogen-free and sterile conditions. Mice received care, optimal conditions of temperature and lighting and easy access to food and water according to the ethical standards of the medical research ethics committee of The College of Pharmacy, Taibah University, Al-Madinah Al-Munawwarah, Saudi Arabia. Mice were also used in investigating the paracetamol toxicity studies [1]. Eighteen male mice were enrolled in this study. White mice are easy in handling, giving treatments, investigating the effects of given treatments and sacrifice. They were reported in similar studies before [17]. A total of six male mice per group was allocated:

1. Group I: Negative control group where mice received sterile water injection.

2. Group II: Acute paracetamol toxicity that took 250 mg paracetamol injected intraperitoneally. This is a sublethal dose as the lethal dose is 300 mg/kg.

3. Group III: Toxicity treatment group that took 250 mg paracetamol injected intraperitoneally in addition to oral Aleppo galls extract.

After four days, all the animals were sacrificed by decapitation where blood samples were collected via cardiac puncture (The decapitation was performed for obtaining sufficient blood samples to perform the biochemical assays). Then, blood was collected in plain sterile tubes and centrifuged (4000 rpm/minute). All sera samples were preserved in -30°C for future biochemical assays. Histological liver examination was done in the four experimental groups.

Preparation of Aleppo galls extract

Quercus infectoria (Aleppo galls) were bought from a local herb shop in Al-Madinah Al-Munawwarah, Saudi Arabia where the galls were identified by an expert pharmacognosist. Extract of Aleppo galls was prepared at the pharmacognosy department at Taibah College of Pharmacy. Firstly, Aleppo galls were grinded using a grinder followed by lyophilization and were then dried via freezing. That was followed by maceration twice in one litre of hydro-alchohol (ethanol and water in a ratio of 80:20) that was added to the powder. Incubation was done twice at room temperature for 48 hours. That was filtered using Whatman filter paper Grade 4: having circles of 27 mm to 400 mm in a Büchner funnel. Ethanol was eliminated by a rotary vacuum evaporator at 50°C. The plant extracts were dissolved in 50 ml distilled water and kept in a refrigerator at 4°C for future tests. The ethanolic extract of Aleppo galls was concentrated and pressurized at 50°C using a rotary vacuum evaporator to get solvent-free plant extracts. Then storage took place in the refrigerator at 4°C for further tests and applications.

Liver function tests assay

Serum liver enzymes e.g. serum glutamate pyruvate transaminase (SGPT = ALT, alanine transaminase), serum glutamate oxaloacetate transaminase (SGOT = AST, Aspartate transaminase), and serum albumin were estimated using BioSystems kits (Barcelona, Spain) according to manufactures instructions.

ALT assay was done according to manufacturer's instructions. Briefly, working reagent, samples and controls were preincubated to reaction temperature (37°C). Working reagent and

serum samples were mixed gently by inversion. Incubation was done for 1 minute with recording the initial absorbance reading. The absorbance readings were repeated after 1, 2 and 3 minutes. Calculating the differences between absorbance was done. Finally, calculating the mean of the results was done to get the mean absorbance reading per minute (ΔA/min). Using Biotek Synergy multimode microplate reader (VT, USA), readings of the absorbance of ALT samples and standard were done against the blank at 340 nm.

AST assay was also done based on manufacturer's methodology. Briefly, the reagents (a mixture of AST substrate and AST coenzyme to form the working reagent), samples and controls were put outside the refrigerator to get the room temperature. Distilled water was set as the blank to adjust the microplate reader. A gentle mixing was done by inversion followed by incubation for 1 minute and recording the initial absorbance reading. Repeating the absorbance readings was done after 1, 2 and 3 minutes and the different absorbance readings were averaged. Reading the absorbance of AST samples and standards was done using Biotek Synergy multimode microplate reader (VT, USA) (against the blank at 340 nm).

Serum albumin was assayed using Albumin (BCG kit) from BioVision (CA, USA). Assay Kit Reagents (Albumin Assay Buffer, Bromocresol Green and bovine serum albumin) were stored according to manufacturer's instructions and then put at the room temperature. Serum samples preparation was done at first via adding 25 µl of undiluted serum into desired well(s) in a 96-well plate. The volume was adjusted to 50 µl/well with Albumin Assay Buffer. Incubation was done using the incubation plate at room temperature (~25°C) for 20 min, with protection from light. Measurement of the absorbance was done at 620 nm using Biotek Synergy multimode microplate reader (VT, USA). Standard curve was prepared. Serum albumin values were estimated accordingly.

Assay of serum lipids

Serum total cholesterol and triglycerides were assayed in mice's sera using commercially available kits (Biodiagnostics, Egypt). Briefly, for serum total cholesterol assay, blood samples were centrifuged at 4000 RPM and serum was aspirated into eppendorff tubes. About 0.05 ml of serum was added to 0.5 ml of the precipitating reagent (a mixture of heparin and citrate buffer) followed by vortexing, standing for 10 minutes at room temperature and centrifugation at 4000 RPM. Total cholesterol was assayed in the supernatant via the enzymatic methodology for total cholesterol assay via adding sample supernatant to the working reagent and comparing that with the blank (added distilled water) and the standard. This was followed by proper mixing and incubation at 37°C for 10 min. Reading the absorbance of the samples and standard was done against the blank at 500 nm (495-550 nm) using Biotek Synergy multimode microplate reader (VT, USA).

For serum triglycerides assay, the mixtures of the blank, standards and samples were prepared after adding the kits components (buffer, chromogen and the supplied enzymes: Lipase, glycerol-3-phosphate oxidase, glycerokinase, and peroxidase), and ATP according to the manufacturer's instructions. Samples were mixed well, incubated for 10 min at 37°C where the absorbance of samples and standards were assayed using Biotek Synergy multimode microplate reader (VT, USA) versus the blank, at 505 nm (492-550 nm). The colour intensity was stable for 30 min.

Liver histological analysis

Liver tissue samples were fixed in 10% buffered formaldehyde for 2 days at 4°C and then paraffin sections were prepared. Liver tissue sections (5 µm in thickness) were cut using a microtome and then stained with hematoxylin and eosin (H&E) stain. The slides were examined under a high-resolution microscope (Nikon, Tokyo, Japan).

Statistical analysis

Data collection was done followed by data, analysis using SPSS software and presented as (Mean ± standard error of mean). Paired samples t test was used to compare the results between the experimental groups. Significant indicators were used as * that indicated $P<0.05$, ** indicated $P<0.01$ and *** indicated $P<0.001$. For comparing significant differ-

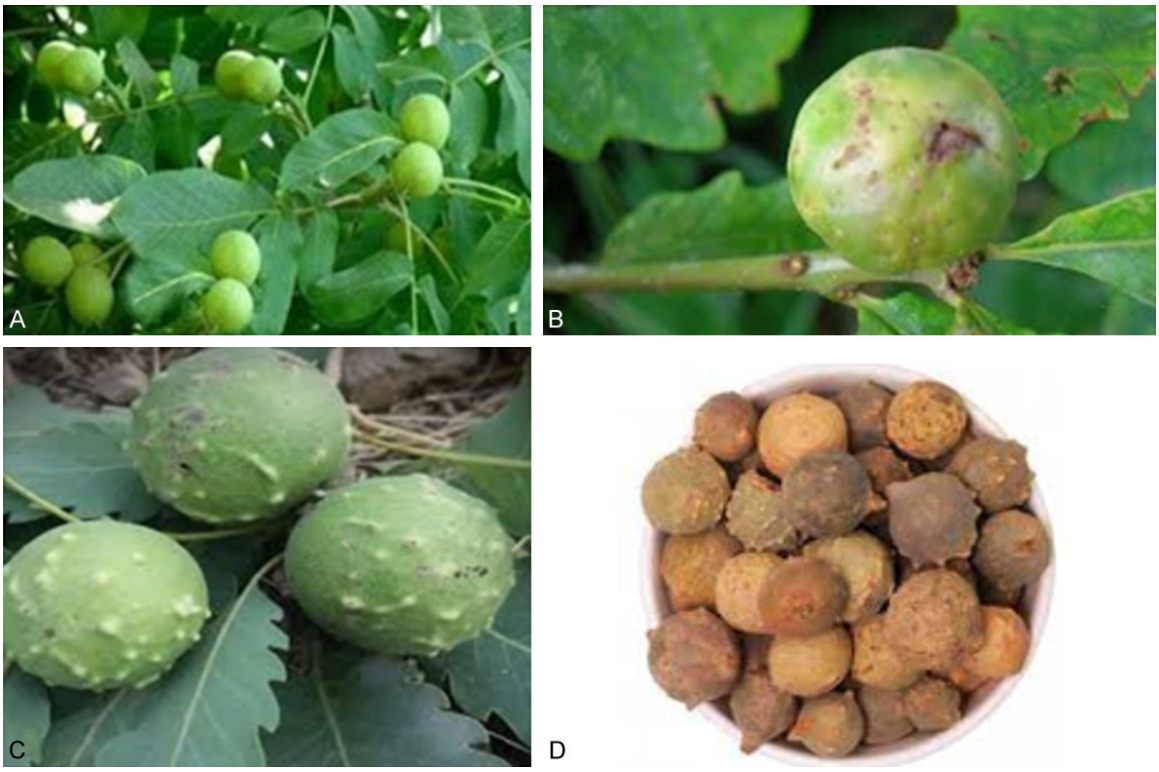

Figure 1. Aleppo galls (*Quercus infectoria*) are natural medicinal pharmacy that may carry a lot of promising therapeutic benefits. A-C. *Quercus infectoria* galls in their green state before ripening. D. Ripenend *Quercus infectoria* galls.

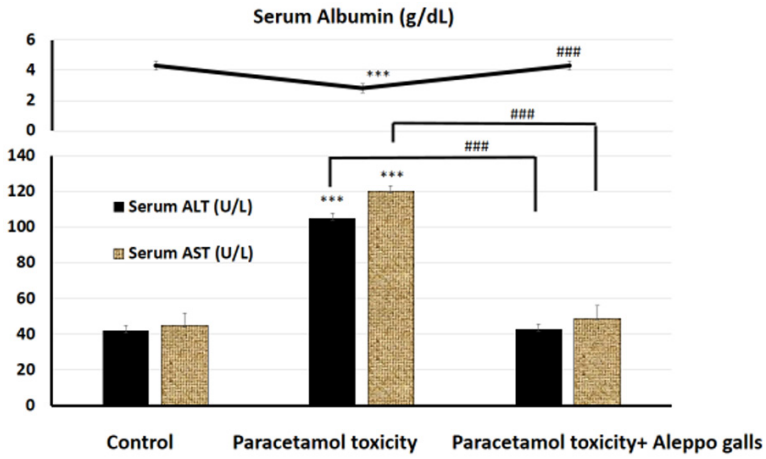

Figure 2. Acute paracetamol toxicity caused disturbed liver function tests. Acute paracetamol toxicity caused significantly raised serum ALT (GPT). That was therapeutically restored to baseline using Aleppo galls treatment. Acute paracetamol toxicity caused significantly raised serum AST (GOT). That was therapeutically corrected to baseline using Aleppo galls treatment. Acute paracetamol toxicity caused significantly decreased serum albumin. That was therapeutically corrected to baseline using Aleppo galls treatment. *** means P<0.001 between control group and paracetamol toxicity group. ### means P<0.001 between paracetamol toxicity group and paracetamol toxicity group after receiving Aleppo galls extract.

ences among different groups, # indicated P<0.05, ## indicated P<0.01 and ### indicated P<0.001.

Results

Acute paracetamol toxicity caused raised serum liver enzymes and decreased serum albumin

Acute toxicity with paracetamol significantly increased serum ALT (P<0.001) and serum AST (P<0.001) and significantly decreased serum albumin (P<0.001).

Aleppo galls extract significantly improved paracetamol toxicity-induced hepatotoxicity

Intake of Aleppo galls extract significantly decreased para-

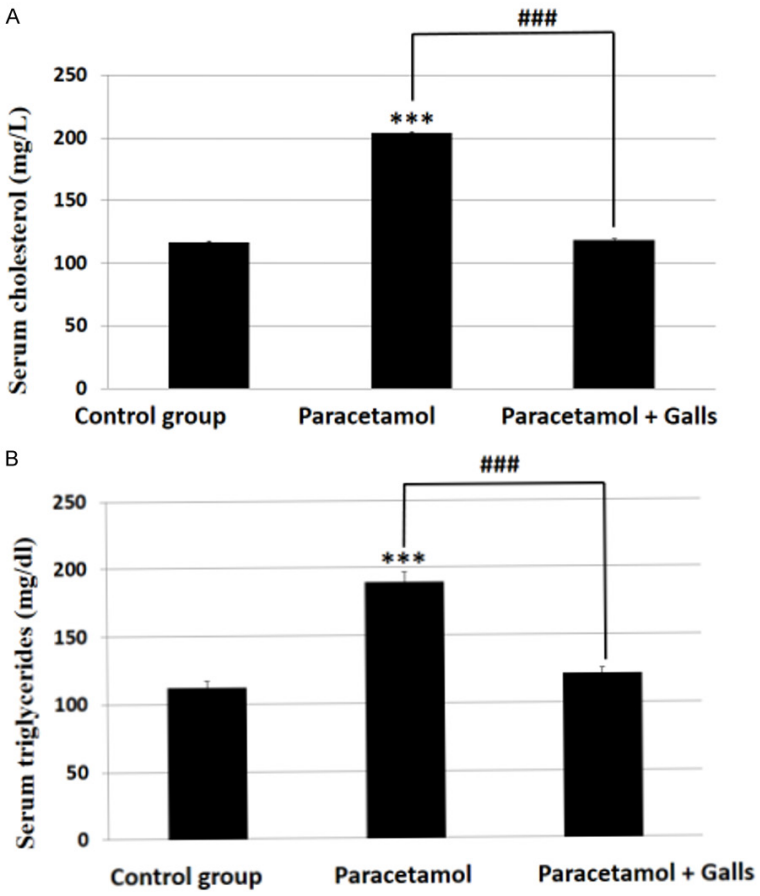

Figure 3. Acute paracetamol toxicity caused disturbed serum lipids. A. Acute paracetamol toxicity caused significantly raised serum cholesterol. That was therapeutically restored to baseline using Aleppo galls treatment. B. Acute paracetamol toxicity caused significantly raised serum triglycerides. That was therapeutically corrected to baseline using Aleppo galls treatment. *** means P<0.001 between control group and paracetamol toxicity group. ### means P<0.001 between paracetamol toxicity group and paracetamol toxicity group after receiving Aleppo galls extract.

cetamol toxicity-induced elevated ALT (P< 0.001) and restored serum AST to normal state. Aleppo galls extract significantly decreased paracetamol toxicity-induced elevated AST (P<0.001) and restored serum AST to normal state. Intake of Aleppo galls extract significantly alleviated paracetamol toxicity-induced decrease in serum albumin (P<0.001) and restored serum albumin to baseline.

Acute paracetamol toxicity-induced disturbances in serum lipids

Acute toxicity with paracetamol significantly increased serum cholesterol (P<0.001) and serum triglycerides (P<0.001).

Aleppo galls extract significantly improved paracetamol toxicity-induced hepatotoxicity

Intake of Aleppo galls extract significantly decreased paracetamol toxicity-induced elevated serum cholesterol (P< 0.001) and restored serum cholesterol to normal state. Aleppo galls extract significantly decreased paracetamol toxicity-induced elevated serum triglycerides (P<0.001) and restored serum triglycerides to normal state.

Histological liver damage caused by acute paracetamol toxicity and protective effects exerted by Aleppo galls extract

Upon histopathological evaluation, mice in the control group showed normal hepatic architecture with preserved hepatic cords and sinuses. Acute paracetamol toxicity induced peripheral zonal degeneration with focal necrosis of the hepatic tissue. The hepatocytes showed cytoplasmic vacuolation with indistinct cell borders. Central hepatic venules were congested. Administration of galls reduced the damaging effects of paracetamol with only minimal residual degenerative changes were observed with absent necrosis (**Figure 4** and **Table 1**).

Discussion

Toxicity with paracetamol (acetaminophen) constitutes a major health concern that necessitates introducing more potent treatments. Acetaminophen, a common analgesic/antipyretic, is a frequent cause of acute liver failure in Western countries [5]. Paracetamol toxicity-induced liver damage may necessitate liver transplantation [18]. Toxicity with paracetamol (acetaminophen) is quite vital as paracetamol is a commonly used drug in so many medical

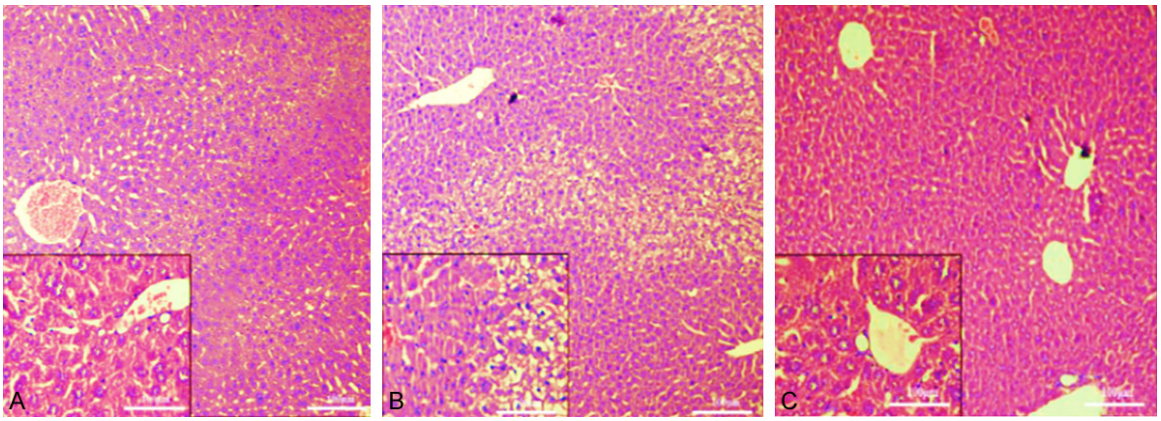

Figure 4. Aleppo galls extract alleviates histological hepatic damage induced by paracetamol toxicity. A. Normal hepatic architecture in negative control group. B. Paracetamol toxicity-induced damage to the liver. Acute toxic doses of paracetamol induced peripheral zonal degeneration and focal necrosis of the hepatic tissues. The hepatocytes showed cytoplasmic vacuolation and indistinct cell borders where the central venules are congested (inset). C. Aleppo galls extract dramatically improved the histological structure of the liver. Administration of galls reduced damaging effects induced by paracetamol toxicity apart from very minimal degeneration and absent cytoplasmic vacuolation (inset). H&E stained sections; ×10 for main images and ×20 for insets.

Table 1. Quantitative results of the histopathological features

Histopathological characters	Group 1 (Negative control)	Group 2 (Paracetamol toxicity)	Group 3 (Paracetamol toxicity + Aleppo galls)
Congested blood sinusoids	-	+++	+
Central venous congestion	-	+++	++
Hydropic degeneration	-	+++	+
Hepatocytes necrosis	-	+++	-
Hepatocyte Fatty changes	-	+++	+
Haemosiderin laden macrophages	-	+++	++

N.B. (-) means no change, (+) means trivial changes, (++) means moderate changes and (+++) means massive changes.

and surgical specialties to treat pyrexia and pain. Paracetamol commonly induces acute hepatic toxicity and chronic hepatic toxicity. In this study, Aleppo galls (**Figure 1A-D**) are introduced as promising natural materials for future therapeutics for treating acetaminophen toxicity.

Galls have a rich phytochemistry that suggests galls to be a promising source for future therapeutics. Purpurogallin is an orange-red active ingredient extracted from nutgalls and oak bark. Purpurogallin exerts anticancer, antioxidant, and anti-inflammatory effects [12]. Other active ingredients in galls include polyphenols (having anti-venom activity), tannins (having anti-tumor activity), and strong antioxidants as methyl gallate, gallic acid, and ellagic acid [13]. Gall's polyphenolic compounds, flavonoids and tannins exert potent anti-inflammatory, antioxidant and anticancer effects [8].

Major ingredient in Aleppo galls tannins is gallotannic acid (50-70%). Other ingredients include triterpenoids, steroids, phenolic acids, and flavonoids that collectively exert antihypertensive, monoamine oxidase-inhibitory, anticancer, antidiabetic, antimicrobial, insecticidal, antiparasitic, antioxidant, anti-inflammatory effects and anticholinesterase activities [14].

Antioxidant effects of galls are promising in treating many disease conditions. Galls were reported to be promising therapeutic agents against the diabetic complications that may affect the thyroid gland and testicular functions [15]. *Quercus infectoria* galls extracts have a confirmed antioxidant potential owing to their large content of polyphenols that possess a potent antioxidant reductive power both in chemical and biological models. Aqueous, ethanolic, and methanolic extracts of *Quercus*

infectoria galls exhibited potent antioxidant activities [16].

Our data revealed that paracetamol toxicity causes impaired liver functions tests e.g. raised serum transaminases (ALT and AST) and decreased serum albumin. Our data (**Figure 2**) are in agreement with the previous report by Mazaraati et al. where acetaminophen toxicity takes place via depletion of reduced glutathione and impairing serum liver enzymes (AST and ALT) [19]. Our data (**Figure 3A**, **3B**) revealed also that acetaminophen toxicity caused suppressed serum albumin while serum lipids (cholesterol and triglycerides) increased. This is in agreement with the study reported by Soliman et al. [20] and other recent reports [21, 22]. Our findings also agreed with the report by Sohail et al. where paracetamol toxicity caused elevated serum levels of cholesterol and triglycerides [23]. Interestingly, all these metabolic derangements were significantly corrected upon using Aleppo galls extract denoting cytoprotective and tissue-protective effects (**Figures 2**, **3**).

In histological studies, normal hepatic architecture was evident in the negative control group. Paracetamol toxicity caused a histological damage to the liver tissue in the form of peripheral zonal degeneration and focal necrosis of the hepatic tissues. The hepatocytes showed cytoplasmic vacuolation and indistinct cell borders where the central venules were congested (inset, arrow). Interestingly, Aleppo galls extract dramatically improved the histological structure of the liver. Administration of galls reduced the damaging effects induced by paracetamol toxicity apart from very minimal degeneration and absent cytoplasmic vacuolation (inset). Shortcomings of this study is the promising introduction of Aleppo galls in the manufacture of future drugs for treating paracetamol toxicity.

Conclusion

Paracetamol toxicity caused evident histological liver damage including zonal degeneration of hepatocytes and cytoplasmic vacuolation. Administration of Aleppo galls caused a significant decrease in paracetamol-induced damaging effects with very minimal degeneration and absent cytoplasmic vacuolation. Aleppo galls are a promising source for future drug industry in synthesizing promising antioxidant, anti-inflammatory and antitoxic compounds. It is strongly recommended to add Aleppo galls as a therapeutic nutrient to foods and drinks given to patients having paracetamol toxicity and other medical purposes.

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Disclosure of conflict of interest

None.

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References

[1] Rostami A, Baluchnejadmojarad T and Roghani M. Sinapic acid ameliorates paracetamol-induced acute liver injury through targeting oxidative stress and inflammation. Mol Biol Rep 2022; 49: 4179-4191.

[2] Rotundo L and Pyrsopoulos N. Liver injury induced by paracetamol and challenges associated with intentional and unintentional use. World J Hepatol 2020; 12: 125-136.

[3] Du K, Ramachandran A and Jaeschke H. Oxidative stress during acetaminophen hepatotoxicity: sources, pathophysiological role and therapeutic potential. Redox Biol 2016; 10: 148-156.

[4] Yarema M, Chopra P, Sivilotti MLA, Johnson D, Nettel-Aguirre A, Bailey B, Victorino C, Gosselin S, Purssell R, Thompson M, Spyker D and Rumack B. Anaphylactoid reactions to intravenous N-acetylcysteine during treatment for acetaminophen poisoning. J Med Toxicol 2018; 14: 120-127.

[5] Nagatome M, Kondo Y, Kadowaki D, Saishyo Y, Irikura M, Irie T and Ishitsuka Y. Ethyl pyruvate attenuates acetaminophen-induced liver injury and prevents cellular injury induced by N-acetyl-p-benzoquinone imine. Heliyon 2018; 4: e00521.

[6] Shakir MA and Mahmood IN. Hyperlipidemia that induced in male rats and role of flavonoids extract of quercus infectoria in treatment. Indian J Forensic Med Toxicol 2020; 14: 1-11.

[7] Melillo ED. The butterfly effect: insects and the making of the modern world. New York: Knopf; 2020.
[8] Alam A, Siddiqui JI, Viquar U, Rasheed Naikodi MA and Ahmad I. The traditional uses, phytochemistry, pharmacological, and botanical description of Quercus infectoria galls (Mazuphal). JDDT 2022; 12: 214-221.
[9] Nanasombat S, Kuncharoen N, Ritcharoon B and Sukcharoen P. Antibacterial activity of Thai medicinal plant extracts against oral and gastrointestinal pathogenic bacteria and prebiotic effect on the growth of lactobacillus acidophilus. Chiang Mai J Sci 2018; 45: 33-44.
[10] Khouzami L, Mroueh M and Daher CF. The role of methanolic extract of Quercus infectoria bark in lipemia, glycemia, gastric ulcer and bacterial growth. J Med Plant Res 2009; 3: 224-230.
[11] Birjandi M, Soltanifard R and Nahidi F. The effect of Quercus infectoria pair cream on the severity of episiotomy pain in nulliparous women. J Herbmed Pharmacol 2021; 401-407.
[12] Kelly-Hunt AE, Mehan A, Brooks S, Leanca MA, McKay JE, Mahamed N, Lambert D, Dempster NM, Allen RJ and Evans AR. Synthesis and analytical characterization of purpurogallin: a pharmacologically active constituent of oak galls. J Chem Educ 2021; 983-993.
[13] Satirapathkul C and Leela T. Growth inhibition of pathogenic bacteria by extract of Quercus infectoria galls. Int J Biosci Biochem Bioinform 2011; 1: 26-31.
[14] Elham A, Arken M, Kalimanjan G, Arkin A and Iminjan M. A review of the phytochemical, pharmacological, pharmacokinetic, and toxicological evaluation of quercus Infectoria galls. J Ethnopharmacol 2021; 273: 113592.
[15] Ibrahim SH. Impact of Quercus infectoria galls extract on thyroid gland and testicular functions in diabetic rats. Iraqi J Vet Sci 2021; 45: 51-59.
[16] Guedes LM, Torres S, Sáez-Carillo K, Becerra J, Pérez CI and Aguilera N. High antioxidant activity of phenolic compounds dampens oxidative stress in Espinosa nothofagi galls induced on Nothofagus obliqua buds. Plant Sci 2022; 314: 14-22.
[17] Erfidan MA, Akkol EK, Sevimli A and Civelek T. Effects of pomegranate (Punica granatum L.) on paracetamol induced acute hepatic damage in mice. Kocatepe Vet J 2016; 9: 273-280.
[18] Rouphael C, D'Amico G, Ricci K, Cywinski J, Miranda C, Koval C, Duggal A, Quintini C, Menon KN and Miller C. Successful orthotopic liver transplantation in a patient with a positive SARS-CoV2 test and acute liver failure secondary to acetaminophen overdose. Am J Transplant 2021; 21: 1312-1316.
[19] Mazraati P and Minaiyan M. Hepatoprotective effect of metadoxine on acetaminophen-induced liver toxicity in mice. Adv Biomed Res 2018; 7: 67.
[20] Soliman A, Rizk H, Shalaby M and Elkomy A. Mechanisms of hepato-renal protective activity of ocimum basilicum leaf extract against paracetamol toxicity in rat model. Adv Anim Vet Sci 2020; 8: 385-391.
[21] Hussain S, Ashafaq M, Alshahrani S, Siddiqui R, Ahmed RA, Khuwaja G and Islam F. Cinnamon oil against acetaminophen-induced acute liver toxicity by attenuating inflammation, oxidative stress and apoptosis. Toxicol Rep 2020; 7: 1296-1304.
[22] El Menyiy N, Al-Waili N, El Ghouizi A, Al-Waili W and Lyoussi B. Evaluation of antiproteinuric and hepato-renal protective activities of propolis in paracetamol toxicity in rats. Nutr Res Pract 2018; 12: 535-540.
[23] Sohail N, Hira K, Tariq A, Sultana V and Ehteshamul-Haque S. Marine macro-algae attenuates nephrotoxicity and hepatotoxicity induced by cisplatin and acetaminophen in rats. Environ Sci Pollut Res 2019; 26: 25301-25311.