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Pathological Aspects of Rabbits Hepatotoxicity and Fibrosis Experimentally Induced by Thioacetamide and The Role of Silymarin as Anti fibrotic Effects

Angham G. F. Al-Hadad and Ahmed M. Al-Saidya*
Department of Pathology and Poultry Diseases, Faculty of Veterinary, Mosul University, Mosul, Iraq.

THIS study was designed to estimate the pathological aspects of hepatotoxicity and fibrosis of the liver using Thioacetamide (TAA) and the hepatoprotective effects of Silymarin in rabbits via biochemical tests and histopathological changes. A total of 24 male rabbits were used, randomly separated into 4 groups: Group I worked as a negative control, group II treatedwith Silymarin only by oral administration, group III was given IP injection TAA only, and finally Group IV was given TAA followed by Silymarin through oral route. Results revealed that rabbits treated with TAA had indicated a significant rise in total serum bilirubin, alkaline phosphatase, aspartate transaminase, and alanine transaminase levels. Histopathologically, liver sections showed severe centrilobular, periportal, hepatocellular vacuolation and necrosis respectively. Cholangitis with severe collagen fibres deposition was detected in the portal area accompanied by biliary duct epithelium hyperplasia and ductal fibrosis. The treatment with Silymarin followed by TAA exposure leads to enhancement of both biological parameters and pathological features of the liver in Group IV. Finally, the present study concludes that Silymarin has a hepatoprotective and anti-fibrotic activity mechanism.

Keywords: Histopathology, Liver, Fibrosis, TAA, Silymarin.

Introduction

Hepatotoxicity is one developing casebecause of the high use of compounds and environmental contact with xenobiotic substances [1,2]. The liver has multifunctions in metabolism, detoxification, secretion, and storage [3]. Liver fibrosis develops as a result of a large aggregate of scar tissues, which occurs when the liver starts to restore and replace damaged cells [4, 5]. It is a changeable reaction to any acute or chronic hepatocellular damage that reflects a balance between hepatic repair and fibrosisdevelopment [6]. Many disorders can lead to fibrosis, especially when the damage continues repeatedly or persistently, sometimes occurring after just one injury. When severe inflammation-induced as a result of acute hepatitis, the liver usually repairs itself by regeneration of new hepatocytes and attaching them to a network of connective tissue [7]. When a repetitive liver injury occurs, necrotic hepatocytes will be substituted by newly regenerated cells. If the liver injury is chronic, a failure of replacement and regeneration of hepatocytes with rich extracellular matrix and collagen fibres will be seen [8, 9].

Thioacetamide (TAA) is well recognized as a hepatotoxic substance(10). It is an organo-sulfur compound, which is frequently doing as a fungicide for controlling the decay of the fruit, also, in the leather industry, it works as an organic solvent [11]. So, exposure to TAA has a toxic effect through skin contact and/or inhalation [12, 13]. TAA is used as a model to induce both hepatotoxicities and to prompt fibrosis in different lab animals. TAA induces hepatotoxicity through oxidative stress as a

Corresponding author: Ahmed M. Al-Saidya, E-mail.: al2011saidya@uomosul.edu.iq
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consequence of inflammatory reactions, though TAA is metabolized by cytochrome P450 to thioacetamide-sulfoxide (TASO) [14]. There are slightly experimental studies of the rabbit as a model for TAA-induced liver injury, acute hepatotoxicity and chronic hepatitis and fibrosis.

Silymarin a milk thistle component (*SilybumMarianum*) has antioxidant (free radicals scavenging), hepato-protective, hepatocyte regeneration, anti-neoplastic, anti-inflammatory, membrane stabilizing, antifibrotic, and immune moderating characteristics [15]. There is a slightly experimental investigation of TAA induce liver injury in the rabbit as a model study of acute hepatotoxicity and fibrosis.

Material and Methods

Chemicals

TAA was purchased from Sigma (AVONCHEM, UK). The dose of TAA was calculated from a pilot study. A Silymarin dose was obtained from previous studies [16, 17].

Animals

Our research was permitted by the Ethical Committee of the Mosul University of the College of Veterinary medicine.

Experimental protocol

A total of 24 male rabbits were separated into main (4) groups (6 each), the groups are: Control group (group I), and Group II, rabbits were given Silymarinorally dissolved in saline200mg/kg B.W. daily for 5 weeks.In group III, rabbits were orally treated with TAA (I/P) at a dose of 150 mg/kg B.W. twice weekly for 8 weeks. Group IV, animals receiving TAA for 8 weeks followed by Silymarinorally dissolved in saline200mg/kg B.W. daily for 5 weeks. Toward the end of this investigation, samples of blood are taken for serum tests and liver samples are stored in a formalin solution of 10% neutral buffer for histopathological examination [18].

Assessment of hepatotoxicity

Hepatotoxicity was measured by calculating the total serum proteins (TSP), total serum bilirubin (TSB), alkaline phosphatase (ALP), and alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels in serum. Blood samples were collected from all groups, and collected serum was evaluated by spectrophotometer via a diagnostic kit (BIOLABO /French). The numbers were investigatedvia the statistical program SPSS, and the mean and standard error were calculated using the ANOVA test (one-way analysis of variance), the significant difference for all tests was at the level of significance of $P \leq 0.05$. Liver samples were kept in a neutral buffered formalin (10%) for the tissue slide preparation and histopathological examination.

Results

The results of the biochemical tests are summarized in (Table 1). Levels of liver enzymes in group III were significantly elevated, and there was an increase in the level of (TSB, ALP, AST, and ALT). In the TAA-treated rabbits, in contrast, to control and other groups ($p<0.05$), while in group IV, which represent the treatment with Silymarin after TAA-intra peritoneal injection in

TABLE 1. Liver function test results in the studied groups

GROUPS	TSP	TSB	ALP/ALK	AST/GOT	ALT/GPT
CONTROL	7.34 ±0.47^{a}	0.69 ± 0.16^{a}	34.48 ± 4.49^{a}	16.58 ± 1.63^{a}	8.88 ± 0.87^{a}
SILYMARIN	7.48 ± 0.53^{a}	0.73 ± 0.29^{a}	30.14 ± 0.57^{a}	18.52 ± 1.47^{a}	6.48 ± 1.63^{ab}
TAA-	6.6 ± 0.27^{a}	2.02 ± 0.35^{b}	49.36 ± 3.17^{b}	25.92 ± 1.21^{b}	11.38 ± 1.07^{ab}
TAA-SILYMARIN	7.02±0.48^{a}	1.2±0.22^{ab}	39.86 ±4.95^{ab}	19.38 ± 0.99^{a}	9.06 ± 0.58^{a}

Data expression as Mean ± Standard error SE
The difference letters mean there are significant differences between groups at $p \leq 0.05$

rabbits revealed significantly ($p<0.05$) decreased these enzymes related to TAA group ($p<0.05$).

The histopathological assessment of liver sections demonstrates many pathological changes as a result of treatment with each TAA and in combination together (groups III and IV) respectively. Data revealed no pathological changes not only in the control group but also in group II (Silymarin). The deviation in the histology of liver sections in the TAA-treated group a severe centrilobular and periportal hepatocellular vacuolation and necrosis were seen, and dilatation and congestion of central veins are noticed as well. Hepatic cells in the affected lobule were less eosinophilia. Cholangit is with severe collagen fibres deposition in the portal area with biliary duct epithelium hyperplasia, in addition to the priductular fibrosis and mononuclear inflammatory cells, infiltrate the portal triad. The portal fibrosis extends towards the Neighboring portal areas and inside the hepatic lobules. Liver sections from group IV displayedminor changes in the histopathological picturein comparison to TAA alone. This group displayed minor portal fibrosis with moderate

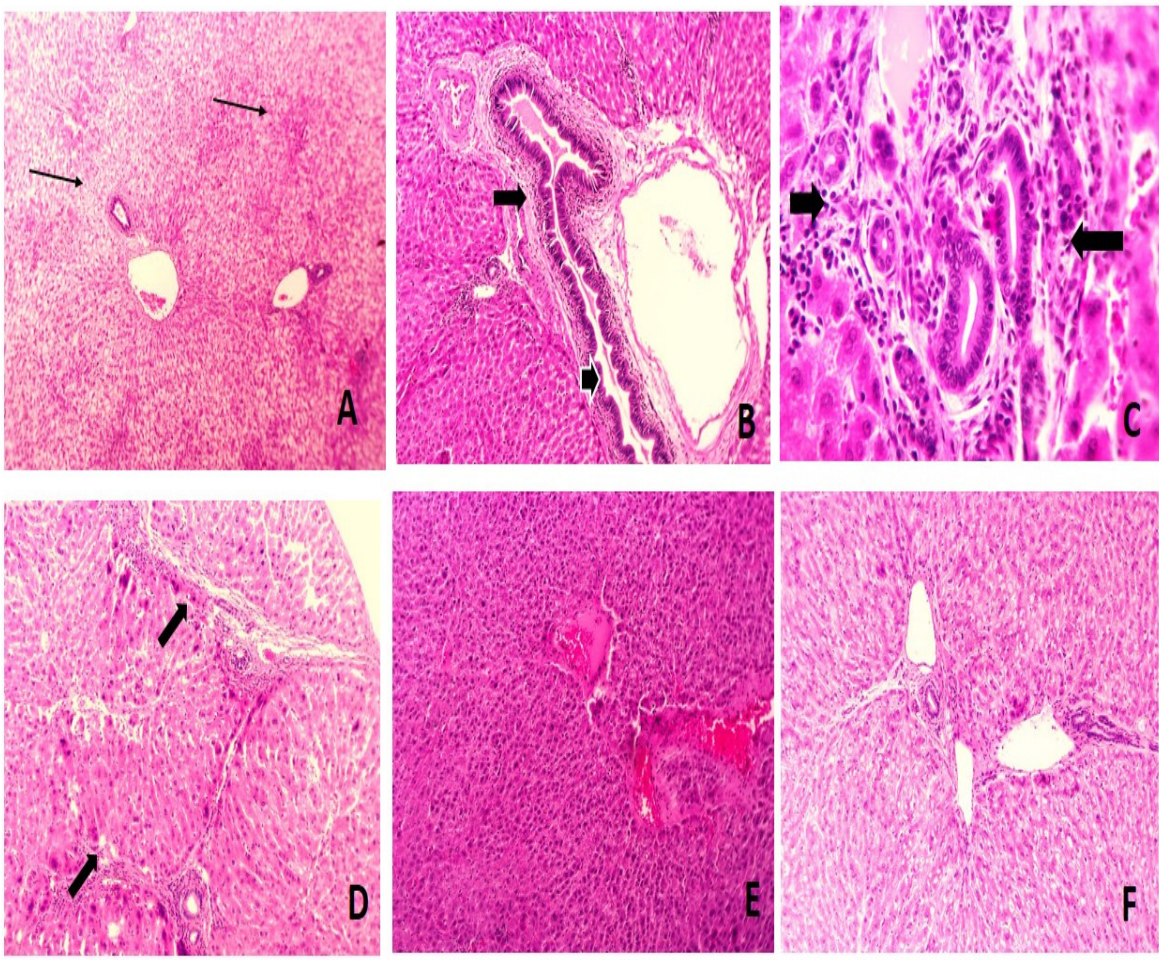

Fig.1. Liver of Male rabbits treated with TAA - silymarin. (A) dilation of central veins with severe centrilobular and periportal hepatocellular vacuolation and necrosis (Arrow) (H & E stain, 10x). (B) Severe collagen fibres deposition in the portal area (Arrow) with biliary duct epithelium hyperplasia with priductular fibrosis (Arrow head) (H & E stain, 10x). (C) mononuclear inflammatory cells infiltration in the portal triad (Arrow) (H & E stain 40x). (D) portal fibrosis extends towards the neighbouring portal areas and inside the hepatic lobules (Arrow) (H & E stain 10 x). (E & F) group of TAA followed by Silymarin displayed mild portal fibrosis with inflammatory cell accumulation in the portal area. Hepatocytes show less vacuolation and necrosis (H & E stain 10 x).

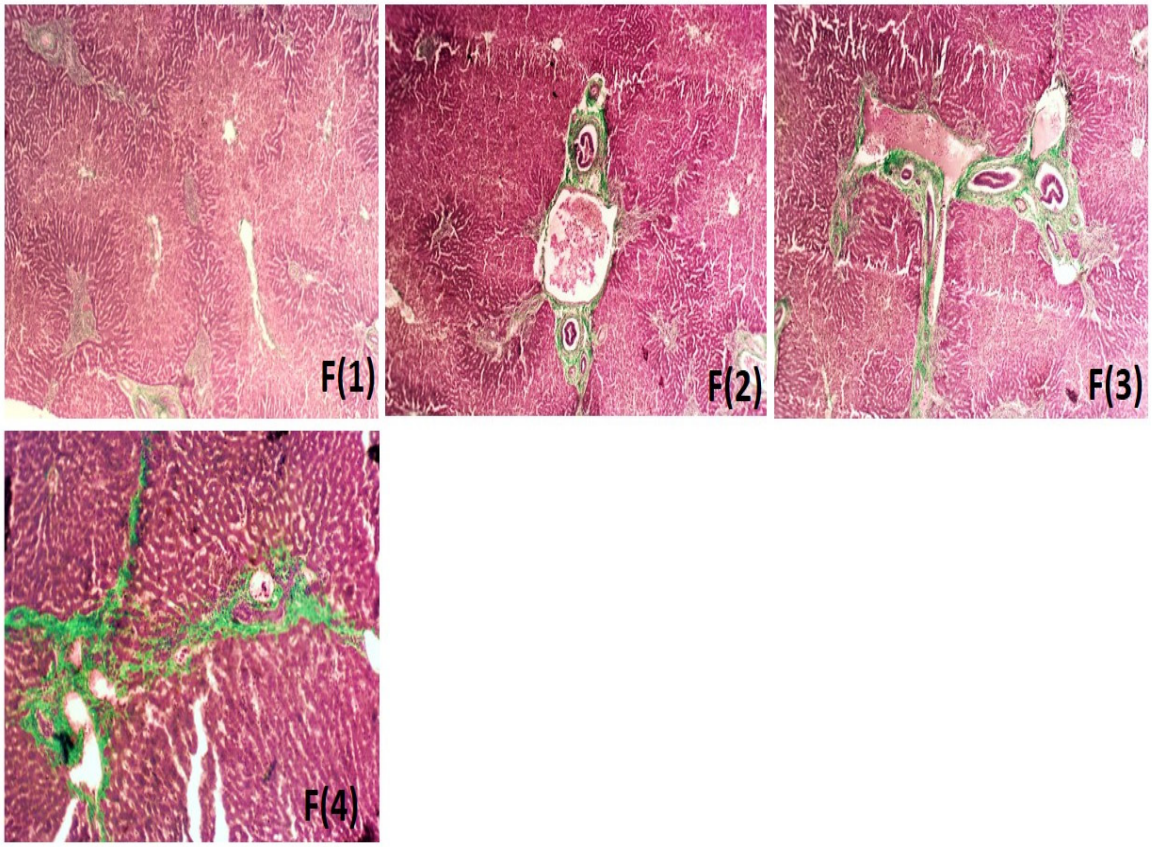

Fig. 2. Liver of Male rabbits (group IV) treated with TAA-silymarin. Histopathological staging of liver fibrosis. F(1) Fibrosis development to some portal triad with small fibrous septa. F(2) Fibrosis spreading out of portal areas with moderate fibrous septa. F (3) Fibrosis enlargement in portal areas with a marked portal to portal connecting as well as a portal to central fibrous septa. F(4) Fibrosis spreading out of portal triad with an obvious portal to portal connecting besides portal to central fibrous septa. Liver of Male rabbits (group III) treated with TAA (Masson's trichrome stain 10 x).

inflammatory cell accumulation in the portal area. Liver cells illustrate less vacuolation and necrosis. (Fig. 1 and 2).

Discussion

The liver is the essential glandular vital organ in the body and has numerous roles in regulating biological processes [19]. This study focused on the follow-up of TAA to induce hepatotoxicity and fibrosis, whereas the pilot study was used to determine the chronic dose in rabbits.TAA is used as a model to cause hepatotoxicity and induced fibrosis [20]. The objective of our experiment was to identify the properties of Silymarin against fibrosis in TAA-model and hepatic damage in rabbits. Results of this study declared that Silymar incaused a significant improvement in the numbers of liver enzymes and histopathological pictures of liver section and fibrosis recovery. Additionally, the results presented a significant increase in the numbers of TSB, ALP, ALT and AST enzymes in the serum of rabbits treated with TAA compared to the control group and this confirm by many types of research [21].

Various researchers indicated that chronic use of TAA causes severe injuries in the liver, ranging from severe necrosis to cirrhosis. TAA is metabolized by cytochrome P450 to thioacetamide-sulfoxide (TASO) [22] which is an effective free radical that binds to macromolecules in hepatocytes and triggers changes in the permeability of cell wall and Ca^{+2} influx. This disturbance of Ca^{+2} levels in the cell leads to inhibits the activity of mitochondria, leading to hepatocytes vacuolation and necrosis [23, 24].

The generation of ROS is well-known to have a significant role in hepatotoxicity [25, 26]. Cytochrome P450 is the most source in the induction of oxidative stress in the liver, as well as the role of TAA metabolites in reactive oxygen species (ROS) formationat a large level, leading to impairment of the antioxidant defence mechanism and cellular components,leading to peroxidation oflipid and DNA damage [27, 28]. Liver fibrosis is highlighted by the increased deposition of both collagen fibres and extracellular matrix.Triggeredhepatic stellate cells (HSCs)cells, fibroblasts from portal triad, and myofibroblasts of bone marrow origin have been recognized as the main collagen-producing cells in the damaged liver[29]. These cells are activated by cytokines and growth factorslike TGF-β1, and angiotensin II [30, 31].

The hepatoprotective characteristics of Silymarin are suggested to its anti-inflammatory, anti-oxidative, anti-fibrotic, cellular regeneration and immunomodulatoryproperties [32]. Several studies tested the role of silymarinagainst liver inflationand fibrosis in many animal models. The anti-inflammatory effects of Silymarin are via inhibition of neutrophils migration to the site of inflammation and thus decreased the inflammatory mediators and cytokines as well as elimination of the radicals' species and preventing lipid peroxidation [33,34]. The anti-fibrotic effects of Silymarin are commonly due to its capability to prevent the activation and transformation of HSCs into myofibroblasts[35,36], which is responsible for collagen deposition by inhibition of fibrogenic pathways of the cytoskeletal formation, pro-fibrogenic collagen, and through depressed-regulates TGF-ß1 mRNA, which stops NF-kB activation and prevents the stimulation of HSCsF[37,38].

Conclusions

This study concludes that Silymarin is a hepatoprotective and antifibrotic medical plant in curing hepatotoxicity and liver fibrosis induced by TAA through the biochemical examination and histopathology of liver sections.

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Conflict of Interest

The investigator announces there is no conflict of interest exists.

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الجوانب المرضية لتسمم وتليف الكبد في الارانب المحدث تجريبياً عن طريق الثايواسيتامايد ودور السليمارين كمضاد للتليف

أنغام غازي فيصل و أحمد محمد علي السيدية
فرع الأمراض وأمراض الدواجن - كلية الطب البيطري - جامعة الموصل - الموصل - العراق .

صممت هذه الدراسة لتقييم الجوانب المرضية للسمية الكبدية والتليف الكبدي باستخدام مادة الثايواستامايد والتأثيرات الوقائية للسيليمارين في الأرانب عن طريق استخدام الاختبارات الكيموحياتية ودراسة التغيرات المرضية النسجية. تم استخدام ٢٤ من ذكور الأرانب قسمت بشكل عشوائي إلى ٤ مجموعات: المجموعة الأولى مجموعة سيطرة ، المجموعة الثانية عوملت بالسيليمارين فقط عن طريق التجريع بالفم ، المجموعة الثالثة عوملت بمادة الثايواستامايد عن طريق الحقن داخل الخلب والمجموعة الرابعة عوملت بمادة الثايواستامايد والسليمارين. أظهرت النتائج أن الأرانب التي عوملت بـالثايواستامايد اظهرت ارتفاعاً معنوياً في مستويات كل من البيليروبين الكلي وخميرة الفوسفاتيز القلوي (ALP) وخميرة ناقلة أمين الأسبارتات (AST) وخميرة اقلة أمين الألانين (ALT) ، أما نتائج الفحص المجهري ، أظهرت مقاطع الكبد وجود تفجي وتنخر الخلايا الكبدية في مركز الفصيص الكبدي والخلايا الكبدية حول البوابة الكبدية ووجود التهاب في القنيوات الصفراوية مع ترسب لألياف الكولاجين في منطقة البوابة الكبدية فضلاً عن فرط تنسج في ظهارة القناة الصفراوية وتليفها. سبب استخدام السيليمارين بعد المعاملة بـالثايواستامايد إلى التحسن في كل من نتائج الاختبارت الكيموحياتية فضلاً عن التغيرات المرضية النسجية للكبد في المجموعة الرابعة. أخيرًا ، خلصت الدراسة الحالية إلى أن السيليمارين لديه خصائص في حماية الكبد ويعد كمضاد للتليف.

الكلمات الدالة: التشريح المرضي ، الكبد ، التليف ، الثايواسيتامايد ، السيليمارين.