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Hepatoprotective Effect of Alcoholic Extract of *Ficus carica* Leaves Against Cypermethrin-Induced Liver Toxicity in Male Albino Rats

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A B S T R A C T

Cypermethrin (CYP), a synthetic pyrethroid, is recognized for its insecticidal properties but poses potential risks of hepatotoxicity. In traditional medicine, *Ficus* (*F*.) *carica* (common fig) leaves have historically been used for various therapeutic applications. This study aimed to evaluate the hepatoprotective effect of the methanolic extract of *F. carica* leaves against CYP-induced liver damage in adult male albino rats (*Rattus norvegicus*). The animals (n=30), 8-12 weeks old and weighing 200-250 g, were randomly divided into five experimental groups (n=6) and treated as follows: the negative control group received distilled water; the CYP-Only group was exposed to 4.74 mg/kg BW for 45 days; the CYP+post-treatment group received the same CYP dosage followed by *F. carica* methanolic leaf extract at 500 mg/kg BW orally for two weeks; the pre-treatment+CYP group received *F. carica* methanolic leaf extract at 500 mg/kg BW orally for two weeks followed by CYP exposure for 45 days; and the *F. carica* extract-Only group was administered the methanolic leaf extract at 500 mg/kg BW orally for two weeks. At the end of the experiment, serum and liver samples were analyzed for biochemical and histopathological changes. CYP-Only exposed group showed significantly increased serum alanine aminotransferase (ALT) and alkaline phosphatase (ALP) and caspase-3 levels (*P*<0.05). Histopathological examination in group exposed CYP only revealed liver damages as evidenced by central vein congestion, scattered perivascular mononuclear cell infiltration, prominence of Kupffer cells, nuclear pyknosis, and severe hepatocytic necrosis. Treatment with *F. carica* leaf extract, either before or after CYP exposure, as well as solely with *F. carica* leaf extract, ameliorated both the biochemical and histological indices of liver damage. The findings suggest that the methanolic extract of *F. carica* leaves provides promising hepatoprotective effects against CYP-induced liver damage in albino rats, likely via its antioxidative properties.

Keywords: cypermethrin, *Ficus carica*, hepatotoxicity, albino rats, antioxidant

INTRODUCTION

Cypermethrin (CYP) is a Type II class of synthetic pyrethroid pesticide (1), synthesized in 1974 and marketed in 1977 (2). Utilized extensively across diverse fields such as agriculture, forestry, household sanitation, and notably in veterinary medicine for the management of livestock and poultry, the widespread use of CYP is cause for considerable attention (3) Inhalation, ingestion, and skin contact are among the different ways that the chemical can be absorbed (4), showing a broad spectrum of harmful effects on several species, including humans, birds, animals, and aquatic organisms (5-8). A particularly alarming feature of CYP is its long-lasting presence in environmental

matrices, notably in soil and water bodies, thereby escalating ecological risks and emphasizing the imperative for effective countermeasures (9, 10).

The fig tree, scientifically known as *Ficus* (*F.*) *carica* and a member of the Moraceae family (11), is acknowledged for its varied pharmacological potentials (12). Rich in bioactive constituents, including phenolic compounds and flavonoids, the tree manifests strong anti-inflammatory and antioxidant qualities, making it a good choice for reducing oxidative stress-related health problems (13-17).Considerable research efforts, both globally and within the context of Iraq, have focused on understanding the toxic effects of CYP across diverse biological systems. Examples include studies on the histopathological consequences of CYP on reproductive and hepatic tissues in albino rats, alterations in blood parameters in common carp, and histological changes in the skin of indigenous rabbit breeds (18-21). Additionally, scholarly work has been conducted to find environmentally friendly solutions for CYP pollution, such as its biodegradation via Pseudomonas aeruginosa (22), and the potential protective roles of plant extracts such as rosemary against CYP-induced organ damage in rabbits (23). Concurrently, *F. carica* has been examined for its therapeutic (24), antimicrobial (25, 26), and genetic attributes (27). Yet, there exists a notable research void regarding the application of *F. carica* leaf extracts for mitigating the detrimental health outcomes of CYP exposure, especially within the domain of veterinary medicine where such pesticides are commonly used. This absence in the existing literature highlights an essential avenue for subsequent investigations aimed at discovering alternative, potentially safer, and more sustainable modalities for managing the health implications of CYP exposure. Therefore, the present study aims to assess the hepatoprotective efficacy of an alcoholic extract of *F. carica* leaves against liver damage induced by CYP in adult male albino rats.

MATERIALS AND METHODS

Ethical Approval

Ethical approval for the study was obtained from the local Animal Care and Use Committee, College of Veterinary Medicine, University of Baghdad. under approval number 1899/P.G., dated September 14, 2023.

Plant Materials and Extraction

Fresh *F. carica* leaves were collected from local orchards in Baghdad province and a reference sample was authenticated by the Iraqi National Herbarium, Directorate of Seed Testing and Certification belong to the Iraqi Ministry of Agriculture with a certified Number of 3422 on 16th November 2022.

The leaves were first washed with tap water to remove dirt and dust, then rinsed with distilled water. Afterward, the leaves were left to dry at room temperature for two weeks. The dried leaves were then crushed by hand, then further ground using an electric mill, and sifted through a manual sieve. A total of 100 g of fig leaf powder was weighed and added to 1 L of methanol alcohol (Fluka, Switzerland). A Soxhlet extractor (Olympus, Japan) device was used for 72 h, followed using a rotary evaporator (Heidolph, Germany) to eliminate the alcohol (28).

Animals and Experimental Design

A total of 30 healthy adult male albino rats (Rattus norvegicus), aged between 8 and 12 weeks and weighing 200-250 g, were utilized in this experiment. The rats were bred and maintained at the animal house, College of Veterinary Medicine, University of Baghdad. Prior to the initiation of the experiment, the rats were acclimated for 4 weeks in standard cages (20×30 ×50 cm^3) with 6 animals per cage under controlled environmental conditions of 22 (±3) °C, 50(±5)% relative humidity, and a 14/10-hour light/dark cycle (29). Standard feed pellets and water were available ad libitum throughout the experimental period.

The rats were randomly allocated into five treatment groups of six animals. The negative control group was administered distilled water to establish baseline responses. The CYP-Only group (Cypermethrin 10 EC, Bharat Insecticides Limited, India) was exposed orally to a sub-lethal dose of 4.74 mg/kg BW CYP to induce hepatotoxicity. The CYP+post-treatment group was treated with the same dose of CYP for 45 days, followed by a two-week regimen of 500 mg/kg BW of *F. carica* methanolic leaf extract orally to assess potential for hepatic recovery. The pre-treatment+CYP group received the *F. carica* methanolic leaf extract 500 mg/kg BW orally for two weeks prior to the CYP exposure for 45 days to evaluate potential prophylactic benefits. The *F. carica* extract-Only group was administered orally 500 mg/kg BW of the methanolic leaf extract for two weeks to evaluate its intrinsic effects on hepatic function.

Cypermethrin Dose Calculation

The experimental dose of CYP for assessing sub-chronic toxicity in adult male albino rats was derived as 1/50th of the determined median lethal dose (LD$_{50}$). The LD$_{50}$ was calculated using the Up-and-Down method (30, 31). The sequential dosing and response outcomes were recorded, facilitating the calculation of the oral LD$_{50}$ (Table 1). The dose of CYP LD$_{50}$ was determined using the following equation: LD$_{50}$= *xf* + *kd*, where *xf* = last dose administered, *k*= value from the appendix, and *d* = difference between dose levels. In this test, single doses were sequentially administered to each animal at intervals of 24 h. After 24 h of poisoning, the animals were observed. According to a predetermined dose progression factor, the dose was decreased after each death and increased after each survival the increase and decrease was by a constant amount (50 mg/kg BW). The LD$_{50}$ for CYP was determined to be 237 mg/kg BW (Table 1). Subsequently, an

experimental dose equivalent to 1/50th of the LD$_{50}$ (4.74 mg/kg BW) sub-chronically administered to the animals to assess liver injury (32).

Table 1. Result of Up and Down method for calculating LD$_{50}$ of cypermethrin in male rats

Initial dose	Last dose	No. of animals	Outcome	difference between doses	LD$_{50}$
50	200	8	OOOOXOXO	50	237

O=Survival animal, X=Dead animal, *k*=0.741. All doses in mg/kg BW

In the determination of the experimental dose of CYP, a 1/50th LD$_{50}$ dose was chosen to reflect sub-lethal, environmentally relevant exposure levels, and occupational exposures, which are not often in acutely toxic ranges. Importantly, this study utilized a commercial cypermethrin product as opposed to a purified laboratory-grade chemical. This decision was made to better simulate real-world scenarios, as animal owners typically utilize commercially available products for pest control, including tick treatment. Such products often contain a mixture of active ingredients and adjuvants, which can influence the toxicity profile and metabolic fate of the pesticide in vivo. Thus, the selected dosage not only represents a sub-toxic threshold but also aligns with the concentrations that animals might realistically encounter, thereby enhancing the translational value of the research findings.

Blood Sample Collection

At the end of the experiment, blood samples (about 4 mL) from all animals (n=6 group) were collected under chloroform inhalation anesthesia (CDH, Italy) via cardiac puncture using 5 mL disposable syringes. The blood samples were collected in plain gel tubes, left at room temperature for 10-20 min. to be clotted, and centrifuged at 3500 rpm for 5 min. The sera were aliquoted into labeled Eppendorf tubes (Karl, China) and kept frozen at -20 °C until used for biochemical analysis (33).

Biochemical Analysis

Serum alanine aminotransferase (ALT) activity was determined using the Reitman and Frankel method (34). Briefly, the assay involved the conversion of alanine and α-ketoglutarate to pyruvate and glutamate in the presence of ALT. The reaction was conducted in a buffered solution containing necessary cofactors and substrates. Following incubation (37 °C for 30 min) the reaction was stopped using sulfuric acid (H$_2$SO$_4$), and the concentration of pyruvate produced was measured spectrophotometrically using a microplate reader at 340 nm, providing a direct measurement of ALT activity.

The serum activity of alkaline phosphatase (ALP) was measured using the Alkaline Phosphatase (AKP/ALP) Activity Assay Kit (SunLong Biotech Co., LTD, China; CAT No. AK0402), following the manufacturer's protocol. The assay involved the hydrolysis of a para-nitrophenyl phosphate to para-nitrophenol by ALP, which reacts with 4-aminoantipyrine and potassium ferricyanide resulting in the generation of a yellow-colored product which its intensity was measured after 15 min incubation at 37 °C spectrophotometrically using a microplate reader at 405 nm. The procedure was conducted in triplicate using known standards and the obtained data were analyzed according to the kit's instructions to determine ALP serum activity levels.

The level of caspase-3 was determined utilizing the Rat Caspase-3 ELISA Kit (SunLong Biotech Co., LTD, China; CAT No. SL0152Ra), according to the manufacturer's instructions. The assay was based on the Sandwich-ELISA method, in which the monoclonal anti-caspase-3 capture antibody, was immobilized on 96-well ELISA microplate, and incubated with the serum rat sample and the fluorescently conjugated polyclonal anti-caspase-3 detection antibody. After a thorough washing step to remove unbound components, 3,3',5,5'-tetramethylbenzidine (TMB) as a substrate was added for enzymatic reaction initiation. The reaction was stopped using H2SO4. The intensity of the blue color developed was measured spectrophotometrically using a microplate reader at a wavelength of 450 nm. The incubation temperature and duration, as well as the recommended antibody dilutions, were followed as in the kit's protocol.

Histopathological Examination

After blood collection, rats were euthanized using overdose anesthesia and liver tissues were collected and fixed in 10% phosphate-buffered formalin for 48 h. Following fixation, samples were sectioned to 0.5 cm thickness and placed in plastic cassettes. Dehydration and clearing of the tissues were automated using a Histo-Line Laboratories ATP1000 tissue processor (Italy). Subsequently, the dehydrated tissues were embedded in paraffin wax via a Histo-Line Laboratories HESTION TEC2900 embedding system, with temperature regulation managed by a TEC2900 Thermal Console (Histo-Line Laboratories, Italy). Tissue blocks were then sectioned at 4-5 μm thickness using a Histo-Line Laboratories MRS3500 rotary microtome (Italy). The sections were floated in a water bath (37 °C) and temperature-controlled hot plate, both regulated by the TEC2900 Thermal Console, before mounting on glass slides. Staining was performed using Hematoxylin and Eosin (H&E, Dakocytomation, Denmark). The stained tissue sections were examined under a light microscope (Olympus, Japan) at 40× and 10× magnifications for detailed histological assessment (35).

Statistical Analysis

Data were analyzed using the Statistical Analysis System (SAS) 2018 software. The Least Significant Difference (LSD) test was employed for pairwise comparisons of means in

the Analysis of Variance (ANOVA) on probability (*P*≤0.05) (36).

RESULTS

Serum Biochemical Markers

The serum levels of ALT and ALP were indicative of liver function status among the different study groups (Figure 1

A, B). The CYP-Only group exhibited elevated ALT and ALP levels, signifying hepatocellular damage when compared to the negative control group. Contrarily, groups that received methanolic *F. carica* leaf extract post- and pre-CYP exposure, as well as the group solely treated with the extract, showed enzyme levels that were not significantly different from the control group, suggesting a hepatoprotective effect of the extract).
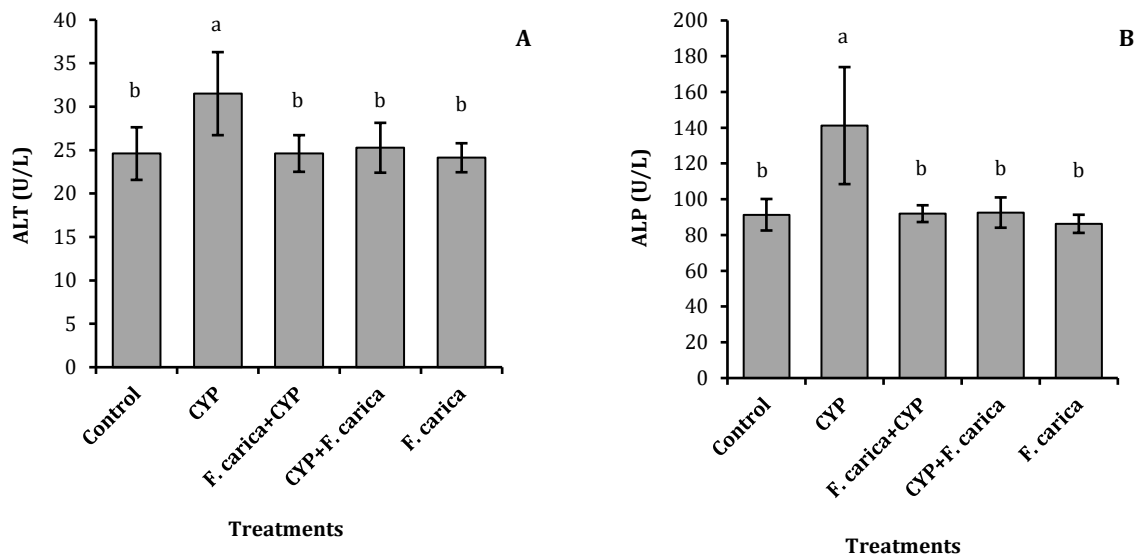
Figure 1. Effect of *F. carica* methanolic leaf extract on **(A)** serum alanine aminotransferase (ALT) and **(B)** alkaline phosphatase (ALP) levels in adult male albino rats pre- and post-cypermethrin exposure Bars and error bars represent the mean and SEM, respectively, n=6. Different letters indicate statistical significance among treatment groups (*P*≤0.05)
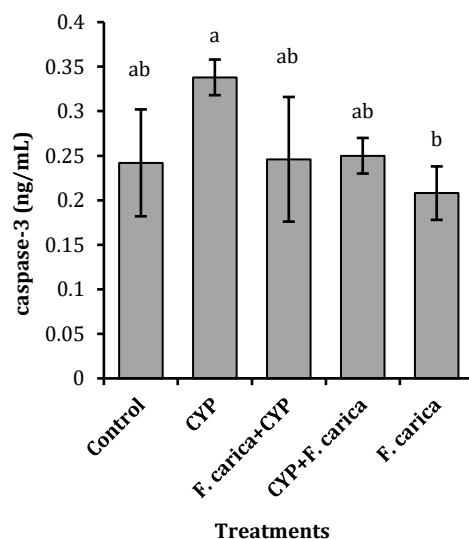
Figure 2. Effect of *F. carica* methanolic leaf extract on serum caspase-3 levels in adult male albino rats pre- and post-cypermethrin exposure Bars and error bars represent the mean and SEM, respectively, n=6. Different letters indicate statistical significance among treatment groups (*P*≤0.05)

As illustrated in Figure 2, caspase-3 showed numerical increased concentrations in the serum of the CYP-Only group. Although non-significant, this increment emphasizes the cytotoxic impact of CYP. The groups treated with *F.*

carica extract, both pre- and post-CYP exposure, along with the group receiving only *F. carica* methanolic leaf extract, had caspase-3 levels comparable to the control group.

Histopathological Findings

The histopathological results from the CYP group revealed that a 45-day treatment with CYP at 4.74 mg/kg BW (1/50th of the LD$_{50}$ calculated in this study as 237 mg/kg BW) induced severe hepatocyte necrosis, congested blood vessels with central vein congestion, scattered perivascular and apoptotic cells, prominence of Kupffer cells, diffuse nuclear pyknosis of hepatocytes, and portal mononuclear cells (MNCs) infiltration accompanied by portal vein congestion and dilation with a few inflammatory cells in the lumen (Figure 3 A, B).

The group treated with *F. carica* methanolic leaf extract post-CYP exposure exhibited pseudolobular formation, degenerative changes in hepatocytes, narrowing of sinusoids with peripheral apoptotic hepatocytes, (Figure 4).

In the pre-treatment+CYP group, photomicroscopy revealed marked cytoplasmic granularity of hepatocytes, a few erythrocytes in some dilated sinusoids, and apoptotic cells, massive hydropic swelling of hepatocytes, mild and few inflammatory cells in some dilated sinusoids with apoptotic cells, multifocal necrosis of hepatic tissue accompanied by cellular swelling of adjacent hepatocytes, and portal vein dilation and congestion (Figure 5 A-C).

Furthermore, liver tissues from the *F. carica* extract group displayed normal radiating hepatocytes and a normal portal area (Figure 6 A, B).
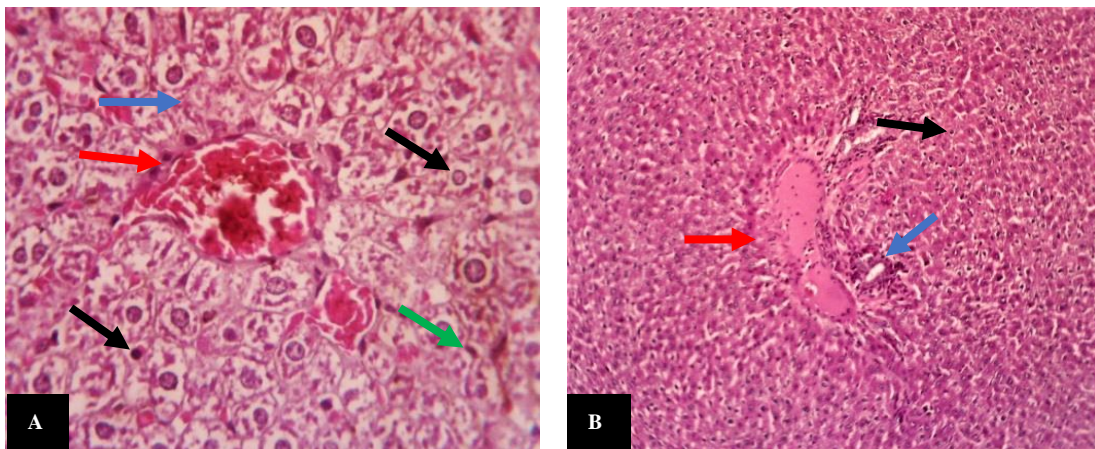

Figure 3. Histopathological sections of adult male rat liver from cypermethrin (CYP) treated group. **(A)** Shows severe necrosis of hepatocytes (blue arrow), congested blood vessel with central vein congestion and scattered perivascular (red arrow) and apoptotic cells (black arrow), and prominence of Kupffer cells (green arrow). H&E stain 400×. **(B)** Shows diffuse nuclear pyknosis of hepatocyte (black arrow), with portal MNCs infiltration (blue arrow) accompanied with portal vein congestion and dilation with few inflammatory cells in lumen (red arrow). H&E, 100×
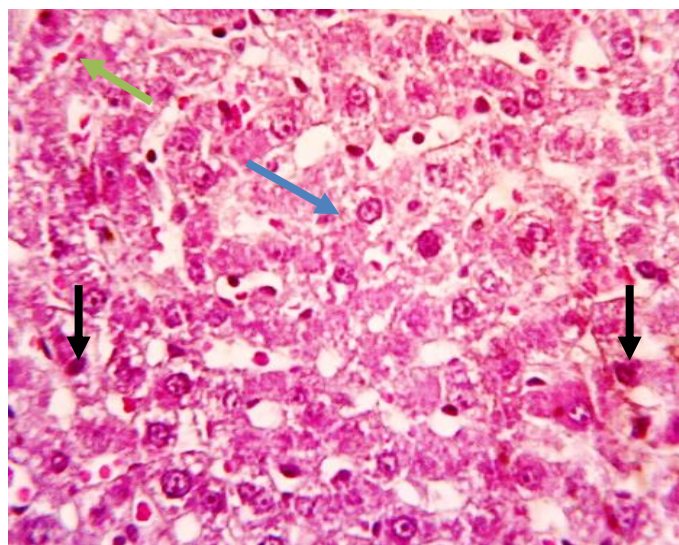

Figure 4. Histopathological sections of adult male rat liver from CYP+post-treatment group. Shows pseudolobular formation, degenerative changes in hepatocytes (blue arrow), and narrowing of sinusoids with peripheral apoptotic hepatocytes (black arrow). H&E, 100×
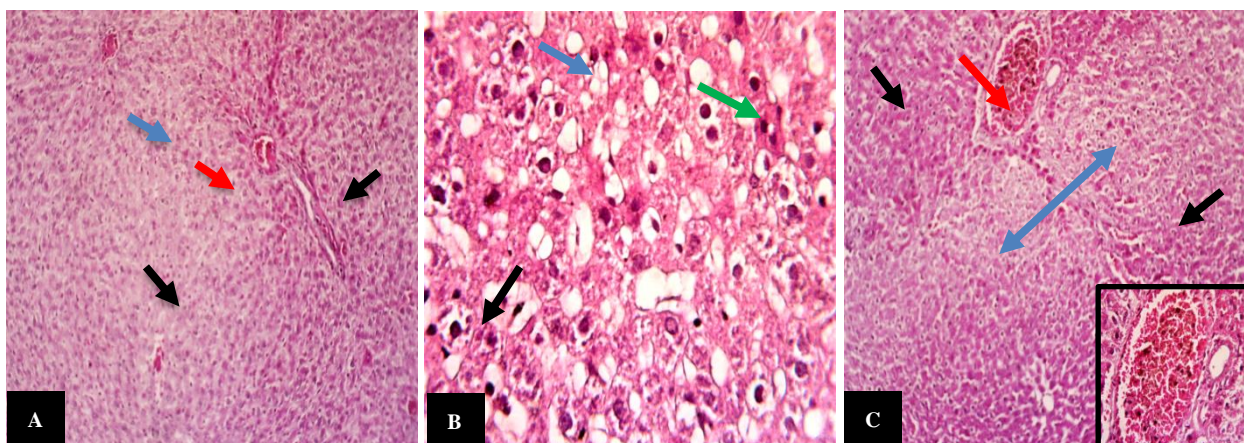
Figure 5. Histopathological sections of adult male rat liver from the pre-treatement+CYP with F. carica group. **(A)** Shows marked cytoplasmic granularity of hepatocytes (blue arrow), with few erythrocytes in some dilated sinusoid (green arrow) apoptotic cells (black arrow). H&E, 100×. **(B)** Shows massive hydropic swelling of hepatocytes (blue arrow), mild and few inflammatory cells in some dilated sinusoids (black arrow), and apoptotic cells (green arrow). H&E, 400×.. **(C)** Shows multifocal necrosis of hepatic tissue (blue arrow), accompanied by cellular swelling of adjacent hepatocytes (black arrow), and portal vein dilation and congestion (red arrow). H&E, 100×, insertion 400×.
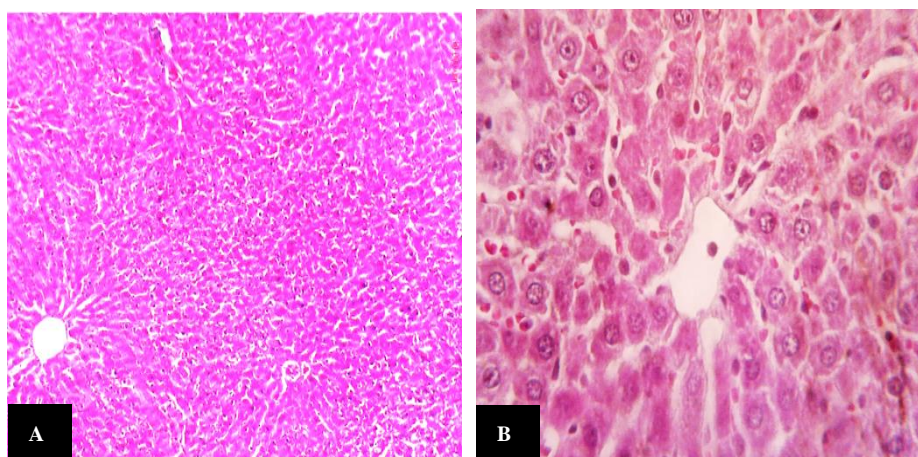

Figure 6. Histopathological sections of adult male rat liver from *F. carica* group. (**A**) Shows normal radiating hepatocytes. H&E, 400×. (**B**) Shows normal portal area. H&E, 400×

DISCUSSION

ALT and ALP are enzymes predominantly found in the cytoplasm and are often employed as biomarkers for liver function due to their increased presence in the bloodstream following hepatic cell damage (37-39). Such damage can be precipitated by the formation of free radicals during CYP metabolism, leading to cellular injury and the subsequent release of these enzymes into the circulation (40-42). This study's findings are in alignment with previous research (41, 43), reinforcing the concept that CYP metabolites may induce hepatic cell injury through oxidative stress. Oxidative stress, in turn, can cause damage to lipids, proteins, and DNA (44), which may lead to the activation of inflammation and apoptosis, evidenced by increased caspase-3 activity, as observed in the liver cells of rats treated with CYP (45). These results corroborate those reported by (44) further emphasizing the consistency of the observed effects.

The liver, a principal organ in detoxification, is susceptible to damage through free radical-induced oxidative stress (46, 47). This can compromise cellular integrity, lead to lipid peroxidation, and cause extensive tissue damage, including DNA base oxidation and the covalent binding of lipid peroxidation byproducts to DNA. Such events are typified by morphological changes in hepatocytes, cellular disruption, necrosis, and inflammatory cell infiltration (48-53).

The metabolism of CYP in the liver involves both hydrolytic ester cleavage and oxidative pathways mediated by the cytochrome P-450 enzyme system. This metabolic process can result in oxidative stress and a decrease in antioxidant capacity (53, 54). Additionally, the biochemical alteration observed in liver profile could be linked to the damage of hepatocyte (54). The consequent reduction in hepatic ATPase activity and mitochondrial respiration inhibition can initiate structural changes in hepatocytes, including DNA fragmentation and denaturation, potentially

leading to apoptosis, hepatic degeneration, and necrosis (56-58).

Moreover, Kupffer cells and mononuclear cells (MNCs) in the liver serve as important immunological barriers against pathological components and tissue damage (59-61). Their prominence, along with portal MNCs infiltration and portal vein congestion, signifies a response to tissue damage (62). These histopathological changes of this study somewhat similar to the findings of (63-66).The reversal of these symptoms through treatment with F. carica leaf extract suggests its potential therapeutic effects, attributed to bioactive compounds like phenols, flavonoids, saponins, and glycosides, known for their antioxidant properties (67-69).

For the group treated solely with *F. carica* leaf extract, no significant effects were observed compared to the control group, indicating the extract's safety and supporting the general belief in the benign nature of herbs used for protection against various toxicities (70-73).

The findings of the current study elucidate the deleterious effects of CYP on rodent hepatic function, primarily through oxidative stress and subsequent cellular damage. Contrastingly, the pre-emptive and remedial administration of *F. carica* methanolic leaf extract demonstrated a mitigatory effect against oxidative injury, likely due to its inherent antioxidant properties.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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التأثير الوقائي الكبدي للمستخلص الكحولي لأوراق نبات التين ضد تسمم الكبد الناتج عن السايبرمثرين في ذكورالجرذان البيضاء

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الخلاصة

السايبرمثرين، وهو بيرثرويد اصطناعي، معروف بخصائصه المبيدة للحشرات ولكنه يشكل مخاطر محتملة للتسمم الكبدي. تم استخدام أوراق التين في الطب التقليدي في العديد من التطبيقات العلاجية. لقد كان الغرض من الدراسة الحالية هو تقييم تأثير المستخلص الكحولي لأوراق نبات التين ضد تلف الكبد الناجم عن السايبرمثرين في ذكور الجرذان البيضاء البالغة. تم تقسيم الحيوانات (عددها=٣٠) بعمر ١٢-٨ أسبوع ووزن ٢٥٠-٢٠٠ غرام عشوائياً إلى خمس مجموعات تجريبية ، المجموعة ١: السيطرة اعطيت الماء المقطر والطعام فقط ، المجموعة ٢: أعطيت سايبرمثرين فقط بجرعة ٤,٧٤ ملغم/كغم من وزن الجسم لمدة ٤٥ يوماً، المجموعة٣: اعطيت سايبرمثرين بجرعة ٤,٧٤ ملغم /كغم من وزن الجسم لمدة ٤٥ يوم وأعطيت المستخلص بجرعة ٥٠٠ ملغم/كغم من وزن الجسم لمدة أسبوعين. المجموعة ٤: أعطيت المستخلص بجرعة ٥٠٠ ملغم/كغم من وزن الجسم لمدة أسبوعين والسايبرمثرين بجرعة ٤,٧٤ ملغم/كغم من وزن الجسم لمدة ٤٥ يوم. المجموعة ٥: اعطيت المستخلص فقط بجرعة ٥٠٠ ملغم/كغم من وزن الجسم لمدة اسبوعين. تم أخذ جزء من الكبد و مصل الدم من هذه المجموعات للتحضيرات النسيجية والكيميائية الحيوية. وفقا للنتائج البيوكيميائية فقد اظهرت المجموعة٢ ان السايبرمثرين يسبب زيادة معنوية (P<0.05) بمستويات (ALT ; ALP) وتركيز Caspase-3. و أظهرت أنسجة كبد الحيوانات المعالجة بالسايبرمثرين أوعية دموية محتقنة مع احتقان الوريد المركزي و ارتشاح للخلايا الالتهابية حول الأوعية الدموية ، مع وجود خلايا كوبفر، وتصلب انوية خلايا الكبد الرئيسية، وموت الخلايا المبرمج، ونخر شديد لخلايا الكبد. أظهرت الحيوانات المعالجة بالسايبرمثرين و مستخلص أوراق التين تحسناً في التغيرات النسيجية والكيميائية، حيث اظهر مستخلص اوراق التين حماية كبيرة ضد التسمم الكبدي الناجم عن السايبرمثرين في ذكور الجرذان البيضاء من خلال تأثيراته المضادة للأكسدة .

الكلمات المفتاحية: سايبرمثرين، التين، الفئران البيضاء، تأثيرات مضادة للأكسدة

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