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INVESTIGATING THE PROTECTIVE ACTIVITY OF *POLYGONUM AVICULARE* EXTRACTS AGAINST THE METHOTREXATE-INDUCED HEPATIC INJURY IN EXPERIMENTAL ANIMALS

Wiam Hmidan[1*], Adawia Kitaz[1], Mohammad Yaser Abajy[2], Samer Haj Kaddor[3]

[1]*Department of Pharmacognosy and Medicinal Plants, Faculty of Pharmacy, University of Aleppo, Aleppo, Syria*
[2]*Department of Biochemistry and Microbiology, Faculty of Pharmacy, University of Aleppo, Aleppo, Syria*
[3]*Department of Laboratory Diagnostics, Faculty of Medicine, University of Aleppo, Aleppo, Syria*

Synthetic antimetabolite methotrexate (MTX) is widely used therapeutically, but its clinical use is constrained by liver damage, often resulting from oxidative stress. The purpose of this study is to examine the hepatoprotective properties of Polygonum aviculare against MTX-induced liver damage in Wistar rats. Ethanolic and aqueous extracts were prepared from aerial parts of P. aviculare. Adult healthy rats were divided into five groups and given the following treatments over a 10-day period: Group I (Control-Untreated), Group II (Methotrexate at 40 mg/kg Body weight, intraperitoneally), Group III (Methotrexate + Silymarin at 100 mg/kg, orally), Group IV (Methotrexate + ethanolic extract at 100 mg/kg, orally), and Group V (Methotrexate + aqueous extract at 100 mg/kg, orally). Serum levels of aspartate aminotransferase (AST), alkaline phosphatase (ALP), and alanine transaminase (ALT) significantly increased, indicating liver damage from MTX. Pre-treatment with P. aviculare extracts has significantly reduced these elevations, and this result has been additionally confirmed by the histological findings. The serum parameters ALT, AST, and ALP were measured using blood samples.

Keywords: *Methotrexate, ALT, AST, ALP, Hepatoprotective*

INTRODUCTION

Not only does the liver serve as the body's primary site for metabolism, synthesis, and processing (biotransformation), it also serves as the primary entry point for xenobiotics, poisons, and other foreign substances. The liver is able to transform these compounds into various types of inactive and active metabolites because of the abundant blood supply and the existence of numerous redox systems.[1] Hepatitis and alcoholism are the principal causes of liver diseases. Inflammation, scarring, cirrhosis, or other forms of dysfunctional liver may result from the buildup of harmful compounds in hepatocytes caused by xenobiotic exposure, injury, infection, autoimmune, or genetic abnormalities.[2,3] Hepatotoxicity has also been linked to a number of medicinal medications, which have been removed from the market due to their high morbidity and mortality from drug toxicity.[4] Although the precise cause of drug-induced liver injury (DILI) is still not fully understood, it is thought to be caused by direct cell stress, mitochondrial dysfunction, and adverse immune responses.[5] One of them, Methotrexate (MTX), a cytotoxic antifolate drug with many clinical applications, including anti-inflammatory and immunosuppressive at relatively low doses and antineoplastic at higher doses, is one of the most frequently used medications known to cause hepatotoxicity. However, liver toxicity of MTX has attracted a

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*Corresponding author: Wiam Hmidan, E-mail: weamhm@gmail.com

lot of attention. Methotrexate has a number of different mechanisms of action, but the most significant of which is the inhibition of the dihydrofolate reductase enzyme. This reduces the level of tetrahydrofolate, which is a precursor to many essential cellular proteins and nucleic acids. As a result, MTX prevents the synthesis of purines, pyrimidines, DNA, RNA, thymidylate, and other proteins.[6-8] The predominant mechanism for MTX-induced liver damage is believed to be the disruption of oxidative balance within liver tissue, due to excessive production of reactive oxygen species (ROS) from mitochondrial dysfunction, depletion of endogenous antioxidants through NADPH inhibition, and prolonged accumulation of MTX and its polyglutamate metabolite in hepatic cells.[7, 9]

Modern medicine has made many strides, but there are very few medications that can assist regenerate hepatic cells and protect a damaged liver.[10] Herbal medicines have been used traditionally for a very long time, and they are now widely acknowledged as being both safe and effective, gaining acceptance as a complementary form of medicine within the traditional scientific-based healthcare system.[11] Over the last ten years, there has been an increase in the use of medicinal plants in complementary and alternative medicine for the prevention and treatment of diseases. According to current scientific technique, herbal medicines are quickly becoming safer alternatives or adjuncts in many chronic diseases. This has been noticed in many inflammatory diseases.[10,11] The traditional texts on Ayurveda, Unani, and other traditional medical systems can give us useful instructions on how to choose, prepare, and use herbal formulations. Hepatoprotective medications can be produced from a variety of medicinal plants. For the treatment of liver problems, a variety of Indian medicinal herbs are frequently utilized in Indian traditional medicine. Plant-based hepatoprotective medications are increasingly important and marketed internationally due to their affordability, minimal side effects, and widespread trust among the public. There are about 170 phytoconstituents with hepatoprotective activity that have been identified from 110 plants in 55 families.[12] Clinical efficacy of *Silybum marianum* and *Picrorhiza kurroa* in the treatment of toxic hepatitis, fatty liver disease, cirrhosis, radiation toxicity, ischemia injury, and viral hepatitis has been demonstrated. This is due to their impact on liver regeneration, immunomodulation, antifibrotic, anti-inflammatory, antioxidative, and antilipid peroxidative properties.[13] Furthermore, research has shown that specific phytochemicals, including silymarin, glycyrrhizin, and matrine, can treat liver cirrhosis, alcoholic liver disease, and hepatitis.[14] The annual herbaceous plant *Polygonum aviculare* L., often known as common knotgrass, is a member of the Polygonaceae family and is typically found in fields or along the side of roads.[15] The Plant has taproot.[16] It has traditionally been used to treat a number of illnesses, including hemorrhage, diarrhea, hemorrhoids, and gastric and duodenal ulcers.[17] According to scientific research, alcohol extracts of *P. aviculare* exhibit pharmacological benefits, including antioxidant effects, obesity combat, antibacterial, anti-inflammatory, anti-gingivitis, anti-fibrosis, and even anti-cancer properties.[17-23] Using a UHPLC-DAD with two mass detectors, numerous chemicals have been discovered from *P. aviculare* like protocatechoic acid, gallic acid, and chlorogenic acid.[21,24-30]

This study aims to evaluate the hepatoprotective efficacy of *Polygonum aviculare* using methotrexate induced hepatic damage in experimental animals, as well as to conduct a histological study on the livers of these animals after the end of the experiment.

MATERIALS

Chemicals

Double distilled deionized water (dd. H_2O). Ethanol (Scharlab S.L., Spain). Dimethyl Sulfoxide (Hi media labs, India). Chloroform (Merck, Germany). Formalin (Quimica clinical aplicada, S.A., Spain). Methotrexate (Kwality pharmaceuticals LTD., India).

Equipments

Ultrasonic apparatus (POWERSONIC 405, Hwashin Technology Co., Korea), Rotary evaporator apparatus (Heidolph instrument, Germany), Ultrapure TM water purification

system (Lotun Co., Ltd., Taipei, Taiwan), and Sensitive balance (Sartorius TE214, Germany).

Plant material

In August 2021, *Polygonum aviculare* was collected from Aleppo city, Syria (36°12'15.1"N 37°07'58.9"E) and identified by Dr. Abdel Aleem Bello (Department of Plant Biology, Faculty of Science, University of Aleppo, Aleppo, Syria) according to The World Flora Online. The plant was cleaned, air-dried for ten days in the shade, then crushed into a fine powder, and stored in airtight, opaque containers until further use.

METHODS

Preparation of Plant Extracts

Using an ultrasonic bath device, 20 grams of powdered *P. aviculare* aerial parts were extracted three times for 45 minutes at a temperature of 50 - 60 °C for aqueous extracts and 30 - 35 °C for ethanolic extracts. After that, each sample was filtered using filter paper (Whatman No1) and then evaporated at 50 °C in a rotary evaporator until they dried under low pressure.[31]

For further study, the dried extracts were kept in the fridge at 4 °C.

Experimental animals

Twenty Wistar rats (105-170 g; 3 months old) were obtained from the Animal House of the Faculty of Pharmacy at Aleppo University. The rats were kept in aerated plastic cages with a 12/12-hour light/dark cycle at controlled room temperature (25 °C). Each cage contained four rats. Water and food were freely available to the rats. The Ethics Committee of the Faculty of Pharmacy at Aleppo University in Syria gave its approval to the study's protocol (registration number: 15/V, 2022). The Guide for Care and Use of Laboratory Animals (2011), which is an established set of public health standards, has been followed in all experiments and procedures for this study.[32]

Experimental design

The experimental animals have divided into five groups. Each group includes four rats:[32]

- **Group I:** served as a normal control without any treatment.
- **Group II:** served as the negative control; animals were injected intraperitoneally with 40 mg/kg of Methotrexate on the 10th day.
- **Group III:** served as the positive control; animals were treated with 100 mg/kg of silymarin orally for ten consecutive days. On the 10th day, Methotrexate was injected intraperitoneally in a dose of 40 mg/kg.
- **Group IV:** served as the test group; animals were treated with 100 mg/kg of ethanolic extract orally for ten consecutive days. On the 10th day, Methotrexate was injected intraperitoneally in a dose of 40 mg/kg.
- **Group V:** served as the test group; animals were treated with 100 mg/kg of aqueous extract orally for ten consecutive days. On the 10th day, Methotrexate was injected intraperitoneally in a dose of 40 mg/kg.

Serum sample preparation

The blood was collected from the heart using a 5 ml syringe on the 11th day after the rats had amnestied with chloroform. The blood was then placed in a dry tube for 30 minutes and centrifuged at 5000 rpm for 15 minutes at room temperature.[33]

Tissue sample preparation

Rats were sacrificed, and their livers were extracted using fine scissors after collecting blood samples from the heart. The livers were then stored at room temperature in a 10% formalin solution for later histological analysis.[33]

Measurement of liver function test

Alkaline phosphatase (ALP), aspartate aminotransferase (AST), and alanine transaminase (ALT) levels in serum have been measured using an automatic analyzer (Mindray BS-600, Jonuta, Mexico).

Statistical Analysis

All experiments were replicated in triplicate (n=4), and the results were expressed as mean ± standard deviation (mean ± SD) of the four replicates. Differences in mean values were analyzed using one-way variance analysis (one-way ANOVA), and differences were considered to be significant at $p < 0.05$.

RESULTS AND DISCUSSION

Results

The Effect of the plant extracts on the serum hepatic enzymes levels

From the results in Table 1, we note a significant increase in the levels of the enzymes ALT, AST, and ALP in the groups II, III, IV, and V. The normal levels of liver biochemical parameters (ALT, AST, and ALP) were 34.0000 ± 9.12871, 71.5000 ± 33.07063, and 292.5000 ± 23.95134 U/L in the normal group (Group I), which increased to 98.7500 ± 8.01561, 115.2500 ± 11.26573, and 577.2500 ± 19.39716 U/L, respectively, upon MTX intoxication (Group II). On the other hand, there was a decrease in the levels of the enzymes in the groups III, IV, and V, compared to the negative group II, as evidence of hepatic improvement ($p < 0.05$), while there is no significant difference among the groups III, IV, and V. These results indicate the importance of *P. aviculare* in enhanced the liver health.

Effect of MTX and various treatments on histological changes in liver tissue

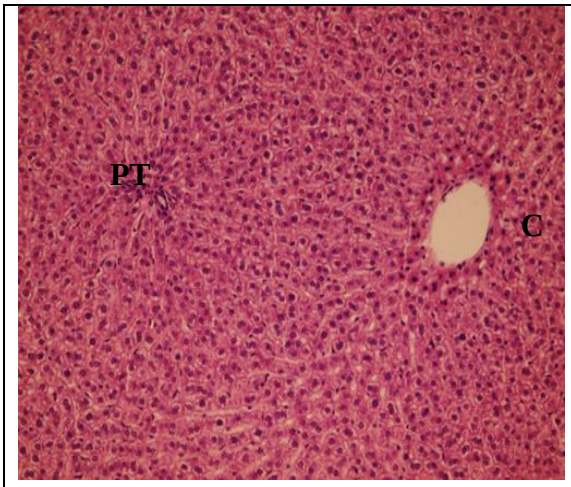
A brief description of the histopathological alterations in each of the study groups is given in **Fig. 1**. The control group **(Fig. 1 A&B)** displays typical liver tissue architecture in general. On the other hand, the Methotrexate group **(Fig. 1 C&D)** shows several histological alterations including sinusoidal dilatation, congested blood vessels, hemorrhage, microvesicular steatosis, pyknotic nucleus and variable-sized areas of necrotic foci, especially around central veins. Pre-treatment with silymarin showed liver lobules with the central vein in the core and the portal tracts (PT) at periphery and normal hepatocytes radially arranged around central veins (Fig. 1 E&F). Groups treated with Ethanolic (Fig. 1 G&H) and Aqueous (Fig. 1 I&J) extracts of *P. aviculare*/MTX showed no evidence of hepatocyte necrosis, presence of fewer dilated sinusoids and congested blood vessels, and fewer hepatocytes with microvesicular steatosis.

Results were relatively better with the ethanolic extract compared to the aqueous extract in reducing the percentage of cells showing microvesicular steatosis.

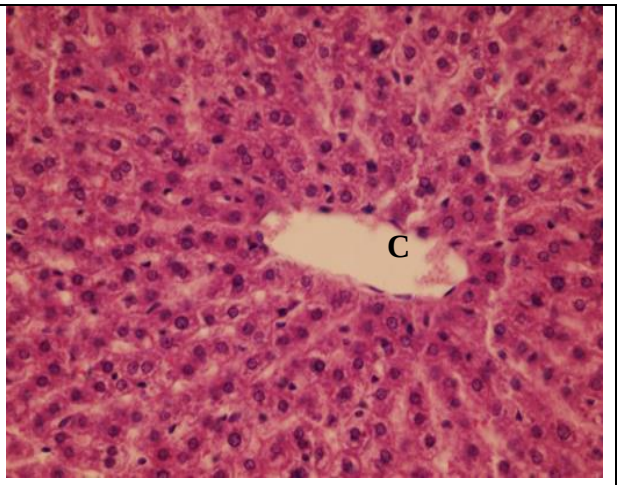
Table 1: The different values of the serum marker enzymes (ALT, ALP, and AST).

Parameters / Groups	Control (Normal)	MTX (Negative control)	MTX + Sylimarine (Positive control)	MTX + POLY. ETH	MTX + POLY. AQUA
ALP (U/L)	292,5000± 23.95134	577,2500 ± 19.39716*	367,0000± 27.58019**	3507500± 38.23066**	385,0000± 16.14517**
ALT (U/L)	34,0000± 9.12871	98.7500 ± 8.01561*	82,2500± 44.37999**	94,5000± 24.82606**	26.0000 ± 4.96655**
AST (U/L)	71,5000 ± 33.07063	115.2500 ± 11.26573*	96,0000± 10.42433**	80.7500 ± 6.02080**	93,0000± 16.75311**

For every treatment group, there are four records, represented as means ± SD. * $P < 0.05$ a significant difference from the control group. ** $P < 0.05$, a significant difference from the MTX group. MTX, Methotrexate; ALT, alanine transaminase; ALP, alkaline phosphatase; AST, aspartate aminotransferase



A.



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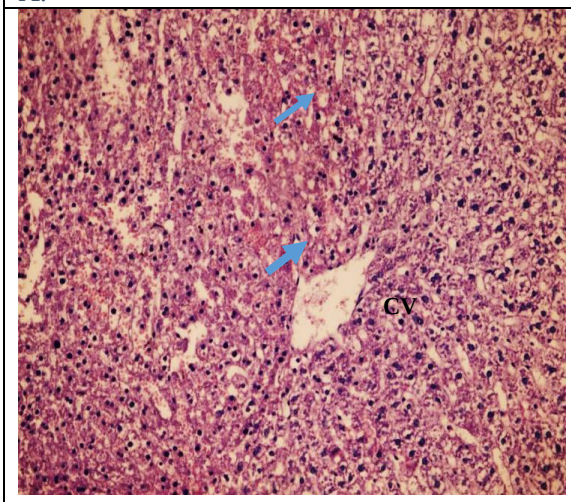
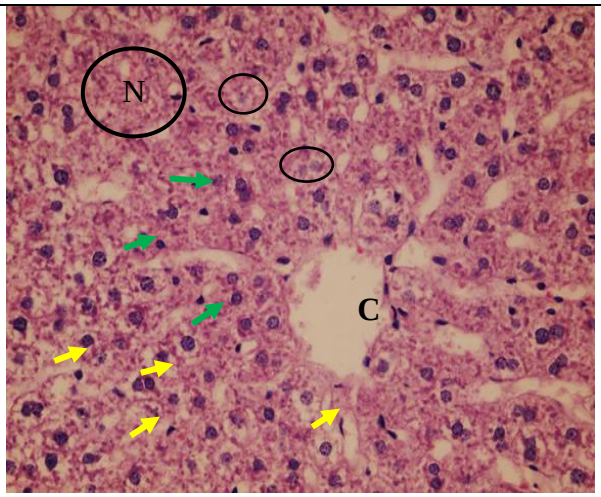


C.



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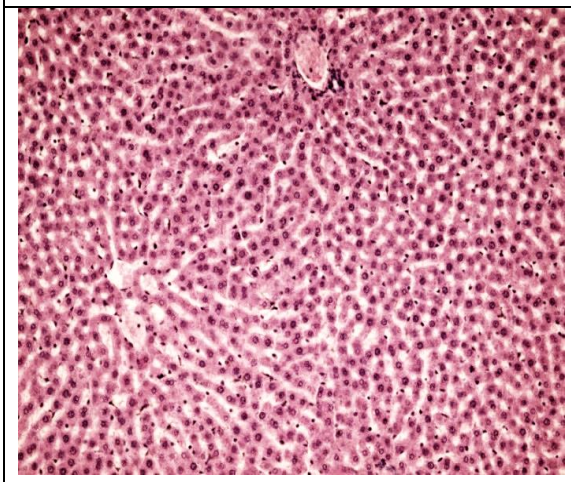

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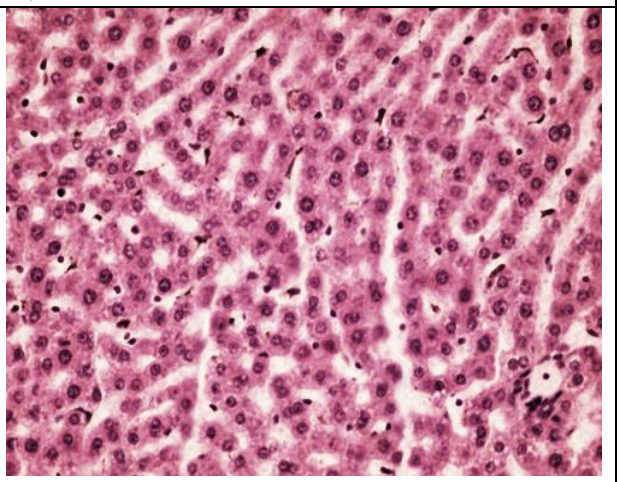

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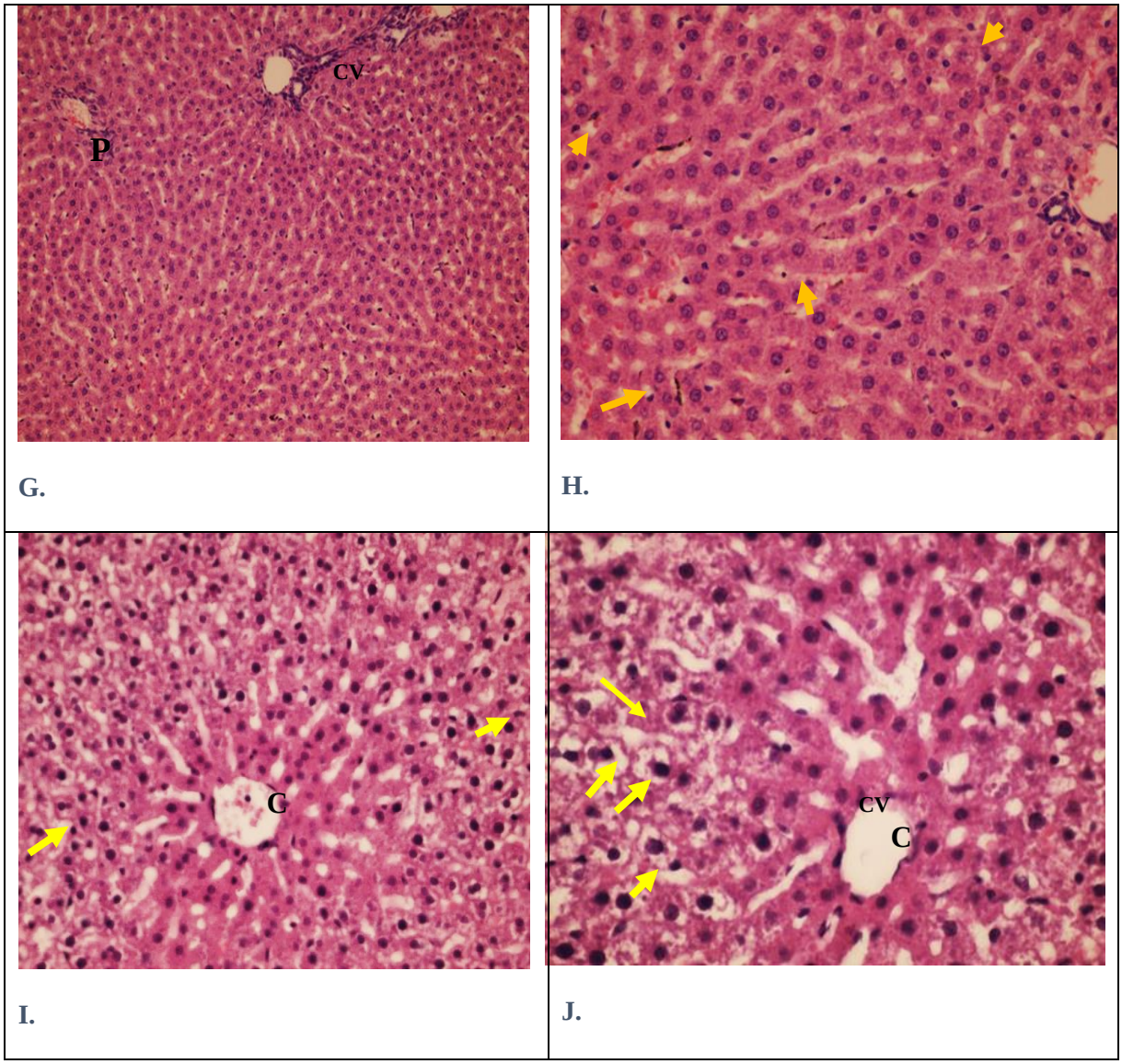

Fig. 1a. normal hepatocytes radially arranged around central veins. **(Cx200- Dx400)** showed several histological alterations including Sinusoidal dilatation, congested blood vessels and hemorrhage (**Blue arrows**), Microvesicular steatosis (**yellow arrows**), Pyknotic nucleus, (**green arrows**) and Variable-sized areas of necrotic foci, especially around central veins (**Circle**). **(Ex200- Fx400)** showed Protective effect of silymarin. **(Gx200- Hx400- Ix200- Jx400)** showed no evidence of hepatocytes necrosis, presence of fewer dilated sinusoids and congested blood vessels, and fewer hepatocytes with microvesicular steatosis (Yellow arrows).

Discussion

The main causes of liver disease, which is considered to play a significant role in the death rates in the world, are hepatitis and alcoholism.[2,3] One of the widely used drugs known to cause hepatotoxicity is methotrexate (MTX), a cytotoxic antifolate medicine with a wide range of clinical applications.[6-8] Due to their widespread acceptance, affordability, and minimal adverse effects, plant-based hepatoprotective drugs are gaining popularity and being sold internationally.[12] This study evaluated the hepatoprotective activity of *P. aviculare* ethanolic and aqueous extracts against methotrexate-induced liver injury. Both *P. aviculare* extracts showed protective activity against the acute methotrexate-induced liver injury.

Superoxide dismutase (SOD), a critical endogenous antioxidant enzyme, converts reactive oxygen species (ROS) produced by mitochondria, primarily superoxide (O_2^-), into

less harmful substances such as hydrogen peroxide (H_2O_2) or molecular oxygen (O_2).[34] In contrast, methotrexate impairs the mitochondrial membrane, leading to an increase in superoxide (O_2^-) production and a subsequent reduction in SOD activity.[35] The oxidative balance will be changed toward oxidative stress due to overproduction of ROS and loss of endogenous antioxidants; ROS will also promote mitochondrial stop functioning and further production of ROS, which will lead to lipid peroxidation of the cell's lipid contents and the release of malondialdehyde (MDA).[36] Furthermore, mitochondrial failure and lipid peroxidation both eventually lead to membrane damage and cell injury. As a result, the cell loses its integrity and release ALT, AST, and ALP into the bloodstream.[37] ROS-induced neutrophil activation further exacerbates cell damage.[37] [38] A study by Shafi Dar in 2021 on the aqueous extract of *Polygonum persicaria* at 200 mg/kg showed AST and ALT levels at 64 and 157, respectively, contrasting with the results of this study, which were 93.0000 ± 16.75311 and 26.0000 ± 4.96655 U/L.[39]

Assays for lipid peroxidation, superoxide radical scavenging, free radical scavenging, and hydroxyl radical-induced DNA strand scission have all been used to examine the antioxidant activity of *P. aviculare* extract. The primary cause of phenolics' antioxidant activity is their redox properties, which allow them to operate as hydrogen donators, reducing agents, and singlet oxygen quenchers.[40] Phenolic compounds, particularly prevalent in plant parts, include flavonoids, phenolic acids, stilbenes, lignans, lignin, and tannins.[41] The *P. aviculare* extract contains a significant amount of flavonoids such as avicularin, quercetin, isorhamnetin, luteolin, kaempferol, myricetin, myrceterin, astragalin, and rutin. This suggests that the extracts of *P. aviculare* have clearly antioxidant properties.[٢٥]

Conclusion

The development of hepatotoxicity is associated with disruption of the oxidative balance in the liver tissue and induction of lipid peroxidation, as evidenced by the elevated level of MDA caused on by MTX. *P. aviculare* exhibits the capacity to restore the oxidative balance and lower MDA levels, thereby reducing the MTX-induced hepatic damage, as evidenced by the considerable decreases in ALT, AST, and ALP. Furthermore, the biochemical results have been confirmed by the histological findings.

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نشرة العلوم الصيدلية
جامعة أسيوط

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تقييم النشاط المضاد للتسمم الكبدي لنبات العقدي الطيري المحدث بالميثوتركسات عند حيوانات التجربة

وئام حميدان[1*] – عدوية كيتاز[1] – محمد ياسر عباجي[2] – سامر حاج قدور[3]

[1] قسم العقاقير والنباتات الطبية، كلية الصيدلة، جامعة حلب، حلب، سوريا

[2] قسم الكيمياء الحيوية والأحياء الدقيقة، كلية الصيدلة، جامعة حلب، حلب، سوريا

[3] قسم التشخيص المخبري، كلية الطب، جامعة حلب، حلب، سوريا

يستخدم الميثوتركسات المضاد للأيض الاصطناعي (MTX) في نطاق واسع من التطبيقات العلاجية، لكن استخدامه السريري مقيد بسبب تأثيره على الكبد سلباً، والذي يحدث في الغالب بسبب الإجهاد التأكسدي. نبات العقدي الطيري هو مضاد للالتهابات ومضاد للأكسدة. تهدف هذه الدراسة إلى تقييم النشاط المضاد للتسمم الكبدي لنبات العقدي الطيري المحدث بالميثوتركسات عند جرذان الويستر. تم تحضير الخلاصات الإيثانولية والمائية من أوراق وسيقان نبات العقدي الطيري. تم تقسيم الجرذان السليمة البالغة إلى خمس مجموعات وتم إعطاؤها العلاجات التالية على مدار فترة ١٠ أيام: المجموعة الأولى (غير المعالجة)، المجموعة الثانية (الميثوتركسات بجرعة ٤٠ مغ / كغ من وزن الجسم، حقناً داخل الصفاق)، المجموعة الثالثة (ميثوتركسات + سيليمارين بجرعة ١٠٠ مع/كغ عن طريق الفم)، المجموعة الرابعة (ميثوتركسات + مستخلص إيثانولي بجرعة ١٠٠ مغ/كغ عن طريق الفم)، والمجموعة الخامسة (ميثوتركسات + مستخلص مائي بجرعة ١٠٠ مغ/كغ عن طريق الفم). لُوحظ الضرر الكبدي الناجم عن الميثوتركسات من خلال زيادة ملحوظة في أنزيمات المصل الآتية: ALT (ناقلة الأمين آلانين)، AST (ناقلة الأمين أسبارتات)، وALP (الفوسفاتاز القلوية). إن المعالجة المسبقة بالخلاصات المائية والإيثانولية لنبات العقدي الطيري سوف تقلل بشكل كبير من ارتفاع هذه الأنزيمات، وتم تأكيد هذه النتيجة أيضاً من خلال الدراسة النسيجية لكبد الجرذان. تم قياس أنزيمات المصل ALT وAST وALP باستخدام عينات الدم.