



Effect of Some Medicinal Plants Extracts and Chemicals on Enzymes and Tissues Liver of Female Rats

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Abstract

The study was carried out on 45 sexually mature female albino rats at the age of 7-8 weeks and weighing 160-180; nine treatments were used in this study, where five rats were isolated for the control treatment (without infection); the remaining rats were injected (Subcutaneous) with Indian-made Alloxan, which was prepared at the time of injection at a dose of 100 mg/kg of body weight. The results showed a significant decrease in liver enzymes AST and the ALP characteristic in T3, T4, T5, T6, T7, T8, and T9, as well as a significant decrease in the ALT characteristic in T3, T5, T6, T7, and T9. Histological effects We notice severe damage to the liver tissue of alloxan-treated rats compared to the proper treatment, represented in the liver tissue by necrosis of liver cells, the presence of a blood clot, the absence of sinusoids, and the thickening of the nuclei. The results have shown that the aqueous extracts positively affect zymes and tissues in female rats.

Keywords: *Curcumin, Origanum majorana, Vitex agnus-castus, metformin, and liver enzymes.*

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Introduction

Diabetes mellitus is a collective term for heterogeneous metabolic disorders [1,2] and is one of the most prevalent diseases worldwide. A global study [3] found that less than half a billion people have diabetes worldwide. The number is expected to increase due to the global prevalence of diabetes in 2019 by about 9.3% (463 million people). It will rise to 10.2% (578 million) by 2030 and 10.9% (700 million)

by 2045. There is an Iraqi study by a group of scholars [4] in which they mentioned that about 1.4 million Iraqis have diabetes; the prevalence rate of the disease according to age ranges from 8.5% to 13.9%; and a local study that included more than 5400 people in the city of Basra, southern Iraq, reported a prevalence of diabetes of 19.7% in people between the ages of 19 and 80. It is expected to infect 693 million adults by 2045 [5], so medical herbs have spread

widely as it treats many diseases and has almost no side effects [6]. *Curcumin* is found in different types of zingiberalezingiber, alessidered as the best natural source[7]. *Curcumin* contains many effective compounds, the most important of which are phenols, considered excellent antioxidants [8]. Studies have shown that dietary *curcumin* inhibits blood glucose levels in diabetic patients and their animal models [9]. An experimental study also showed the effectiveness of turmeric in reducing blood glucose levels in white rats, and this was through its activation of pancreatic cells in stimulating insulin production [10]. In his study, he found that *curcumin* reduces complications of diabetes [11]. *Origanum majorana* is a perennial herbaceous plant, 30-60 cm high. Its stem is rigid, ribbed, and covered with fine hairs. Its color is brown at the top, mixed with red. The leaf is tongue-shaped. Its flowers are white, tending to pink. It is native to Turkey and Cyprus and has spread from there to countries in the Mediterranean basin, such as Lebanon, Hauran, southern Syria, Iran, North America, the Arabian Peninsula, and India [12]. *Origanum majorana* contains phenolic acid, which is the main chemical constituent in *origanum majorana* [13]. It contains flavonoids, tannins, sterols, and triterpenes [14]. The effect of this plant is attributed to its ability to restore the function of pancreatic tissue by causing an increase in insulin production, inhibiting intestinal absorption of glucose, or facilitating the metabolism of insulin-dependent processes [15]. In their study, [16] indicated the possibility of treating diabetes by reducing blood sugar using marjoram leaf extract because it contains flavonoids and phenolic compounds, improving metabolism and reducing oxidative damage. *Vitex aguns-castus* herb, has its originates in the Middle East and Central Asia. The digestive system, as well as the treatment of mood swings and depression symptoms associated with the menstrual cycle, aids in treating infertility in women caused by hormonal and ovulation disorders [17]. The palm of the *vitex aguns-castus* contains one flavonoid compound, isovitexin, and four flavonolic compounds: campferol,

ramnoglucoiside, quercetin, and rutin. Amino acid includes alanine, arginine, proline, phenylalanine, methionine, choline, alkaloids, coumarins, and silicalite [18]. This study investigated the effect of aqueous extracts of (*Curcumin*, *Origanum majorana*, and *Vitex agnuscastus*) at 50-100 mg/kg body weight and chemotherapy (metformin at 50 mg/kg body weight) leaves on the liver enzymes and tissues of female rats.

Materials and methods:

The study was conducted in the animal house in the College of Veterinary Medicine, University of Tikrit, for the period from 19/4/2022 to 18/5/2022 and was done through the following:

Sample collection and preparation:

Metformin originated in a French province and was purchased from a pharmacy in Salah al-Din-Tikrit. Extracts (*curcumin*, *origanum majorana*, and *vitex aguns-castus*) were also purchased locally, with the Al-Emad Company in Iraq, and from abroad, with the Al-Emad Company in the United States.

Animals used in the study:

The white laboratory rat, the Albino, was used at 7-8 weeks with a weight of 160–180 g \pm 10 g. In this study, 45 sexually mature females were used, obtained from the animal house of the College of Veterinary Medicine at the University of Tikrit, and they were monitored for two weeks before the start of the experiment to acclimatize and ensure good health, her health condition, and the fact that she is not pregnant. They were also examined by a veterinarian specialized in the center to ensure that she was safe, healthy, and free from diseases before using her in the experiment.

Experiment design

Induce Diabetes mellitus

Five rats were isolated for the control treatment (without infection). The remaining rats were injected subcutaneously with Alloxan of Indian origin, which was prepared at the time of injection at a dose of 100 mg/kg of body weight. as it was dissolved by 1 gram of alloxan in 10 ml of physiological solution

(normal saline) after starving the animals for 12 hours [19] and [20], decline after decline injection they were directly provided with food and the drinking water was replaced with a 5% glucose solution for a period of 24 hours to reduce the shock of the treatment decline [1]. After 72 hours, their blood sugar was checked using an Accu-Chek blood sugar test device of German origin to confirm that they had developed diabetes mellitus.

Division and distribution of laboratory animals

It was confirmed that the animals had diabetes after examining the fasting blood glucose, which was 150–200 mg/dl for all the injected rats. The rats were kept in nine plastic cages with metal mesh covers and dimensions of 60, 30, and 30 cm; the cages were cleaned and sterilized with a 70% ethanol solution, and the floor was covered with sawdust that was changed every two days. It contains five infected rats in addition to the first cage in which the five healthy rats were placed as the control group. Which was fed on the standard diet according to what was mentioned in [21], consisting of 35% wheat, 34% yellow corn, 20% soybeans, 10% animal protein, and 1% powdered milk, and a period of lighting of 12 hours and darkness of 12 hours. And the temperature was set at 24 ± 2 degrees Celsius, the treatments were numbered in each cage, water was provided continuously, and they were fed the diet assigned to each treatment for the duration of the experiment, which lasted 28 days after the infection was confirmed. And they were followed up continuously under my supervision and that of the specialized people in the center until the end of the experiment.

For each group that was dosed orally, it differed from the other in proportions, in addition to filtered water for a period of 28 days, as the totals and ratios were as follows:

- (T1): included five healthy rats.
- (T2): five animals were infected with induced diabetes with alloxan at a concentration of 100 mg/kg of body weight without any treatment [19].
- (T3): contained five animals were infected with induced diabetes with alloxan at a

concentration of 100 mg/kg of body weight and orally dosed with chemotherapy (metformin) at a concentration of 50 mg/kg of body weight [22].

- (T4): contained five animals infected with alloxan at 100 mg/kg body weight and given curcumin extract at a concentration of 50 mg/kg body weight orally [23].

- (T5): contained five animals were infected with diabetes mellitus caused by alloxan at a concentration of 100 mg/kg of body weight and dosed orally with an extract (curcumin) at a concentration of 100 mg/kg of body weight [24].

- (T6): contained five animals infected with induced diabetes with alloxan at 100 mg/kg of body weight and dosed orally with (*Origanum majorana*) extract at a concentration of 50 mg/kg of body weight. [25].

- (T7): contained five animals were infected with diabetes mellitus caused by alloxan at a concentration of 100 mg/kg of body weight and dosed orally with (*Origanum majorana*) extract at a concentration of 100 mg/kg of body weight [26].

- (T8): contained five animals were infected with diabetes mellitus caused by alloxan at a concentration of 100 mg/kg of body weight and dosed orally with an extract (*vitex aguncastus*) at a concentration of 50 mg/kg of body weight [27].

- (T9): contained five animals were infected with diabetes mellitus induced by alloxan at a concentration of 100 mg/kg of body weight and dosed orally with an extract (*vitex aguncastus*) at a concentration of 100 mg/kg of body weight [28].

Collect blood samples:

After the end of the 28-day experiment period, the animals fasted for 10 hours. Then blood samples were drawn from them by cardiac puncture in an amount of (0.5–5) ml using insulin syringes with a capacity of 1 ml and placed in two sets of test tubes, one with (EDTA) ethyl diamine tetraacetic acid to prevent blood clotting and the other without, and centrifuged at a decline (at 3000 rpm) for 15 minutes to isolate blood serum. After that, it was placed in special binders and preserved by

freezing at a decline of -20°C until it was used in conducting the necessary blood tests [29].

Evaluation of the activity of Alanine Transaminase (ALT) and Aspartate Transaminase (AST) in Serum

The concentration of ALT and AST enzyme activity in blood serum was measured using a ready-made assessment kit from the German company Roche. Two test tubes were taken for each sample. The first tube contained a blank reagent, while the other tube contained the sample in which the activity of the two enzymes was to be measured.

Evaluation of the activity of Alkaline phosphatase (ALP) in serum

The concentration of ALP enzyme activity in blood serum was measured using a ready-made assay kit from the German company Roche based on the colorimetric method, as alkaline phosphatase analyzes phenol phosphate and other phosphates present in the basal periphery [30].

Histopathological study

The anatomized pancreas samples from each group of diabetic animals were collected in 10% formalin-saline solution and stained with fluorescence dye (hemotoxylin and eosin) for section preparation using a microtome, and histopathological studies were carried out (pictures).

Statistical Analysis

The results were analyzed statistically and using **SAS, 2010**, according to a one-way analysis of variance. In addition, the mean of the coefficients was tested using the Duncan '1955 multi rang test at a significant level (0.05) to determine the significant differences between the totals.

Results and Discussion

3.1 The effect on liver enzymes

Aminotransferase (AST), alanine phosphatase (ALT), and alkaline phosphatase (ALP) are among the essential enzymes in biological processes in the body of an organism if they are present in a high percentage in the liver, and the increase in their level outside this

organ, especially in the blood serum, indicates tissue damage. This results in the leakage of these enzymes into circulation [30]. The statistical analysis results shown in Table 1 showed significant differences in AST, ALT, and ALP enzymes. The T2 recorded the highest level compared to the rest of the treatments, and its values were 47,400, 24,540, and 81,980 international units/liter, respectively. While T1 and T3 recorded the lowest level compared to the rest of the treatments, their values were 24,440 and 28,505; 14,120 and 17,190; and 41,455 and 54,235 international units per liter, respectively. The cause of elevated AST, ALT, and ALP enzymes may be attributed to the breakdown of hepatocytes [32]. It is an indication of the damage occurring in the liver cells, leading to the destruction of the cardiac tissue, as well as leading to an imbalance in the metabolism that occurs due to diabetes caused by the use of alloxan, which leads to an increase in the metabolism of liver cells and thus an increase in AST, ALT, and ALP enzymes [33]. This finding was confirmed by [34], who speculated that chronic hyperglycemia in diabetic patients increased the formation of glycation end products that are an inflammatory factor causing cardiovascular disorders, hyperlipidemia, and diabetic nephropathy. These results agreed with the study of [35], who observed increased AST, ALT, and ALP enzyme levels in female diabetic rats. And that the enzymes that indicate hepatic activity represented in AST, ALT, and ALP are responsible for the production of ketone bodies from amino acids and lead to the production of high concentrations of glucose in the blood, and other anti-diabetic groups reduce these liver enzymes (AST, ALT, and ALP). And this lead to a decrease in the level of glucose concentrations in the blood [36]. These results agreed with the study by [37] that there were histological changes in the liver due to insulin deficiency in diabetes mellitus and that after treatment with metformin, there was a partial decrease in liver enzymes. It also agreed with the results of [38]. As it showed a significant increase in the level of ALT (the enzyme alanine phosphatase in the blood) by 93% in

diabetic patients, and it was noted that treatment with metformin led to a significant decrease in the level of the enzyme alanine phosphatase in the blood (ALT) (46%). It was also found that the process of dosing with *curcumin* extract was effective in causing a decrease in the concentration of liver enzymes (AST, ALT, and ALP), compared to the infected treatment and without treatment in female rats for the same period. This decrease may be attributed to the extract's effectiveness as an antioxidant, which reduces oxidative stress from forming free radicals in liver cells, thus protecting hepatocytes from oxidative damage and improving liver function [39]. In their study, [40] concluded that blood ALT and AST levels increased in the diabetic group. At the same time, a significant decrease in these levels was observed in the treatment with marjoram extract due to its antioxidant effect. The results of dosing with the aqueous extract of *vitex agnus-castus* leaves in two doses (50 and 100 mg/kg of body weight) showed a significant decrease in the concentration of liver enzymes compared to infected female rats without treatment. This decrease is attributed to the primary compounds present in the aqueous extract of Maryam leaves, such as flavones, flavonoids, and carotenoids, which act as antioxidants that combat free radicals and inhibit their negative impact [41].

Table 1 shows the effect of medicinal plants and chemicals on AST enzyme (IU/L), ALT enzyme (IU/L), and ALP alkaline phosphatase (IU/L) (means \pm standard error)

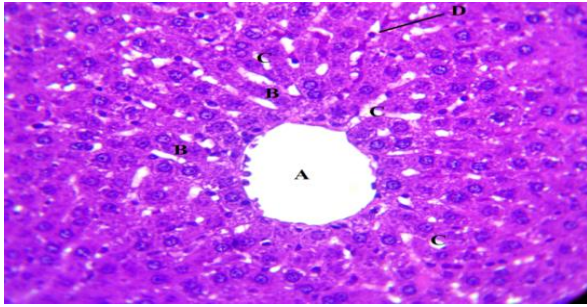
Treatment	AST	ALT	ALP
T1	24.440 $\pm 1.880D$	14.120 $\pm 1.580D$	41.455 $\pm 1.345F$
T2	47.400 $\pm 1.620A$	24.540 $\pm 0.890A$	81.980 $\pm 1.790A$
T3	28.505 $\pm 1.159D$	17.190 $\pm 0.790C$	54.235 $\pm 1.795E$
T4	39.070 $\pm 1.470B$	21.535 $\pm 0.775A$	61.945 $\pm 1.825BC$
T5	36.650 $\pm 0.670C$	19.910 $\pm 0.590BC$	57.395 $\pm 0.965CDE$
T6	41.500 $\pm 1.280B$	20.460 $\pm 1.200BC$	65.860 $\pm 1.540B$
T7	39.605 $\pm 0.995B$	18.880 $\pm 1.560BC$	61.125 $\pm 2.075BC$
T8	42.105 $\pm 1.545B$	22.180 $\pm 0.200A$	60.365 $\pm 0.915CD$
T9	41.720 $\pm 1.170B$	20.400 $\pm 1.170BC$	56.380 $\pm 0.820DE$

* The different capital letters within one column indicate significant differences ($p \leq 0.05$) between the treatments.

* Similar capital letters within one column indicate no significant differences ($p \geq 0.05$) between treatments.

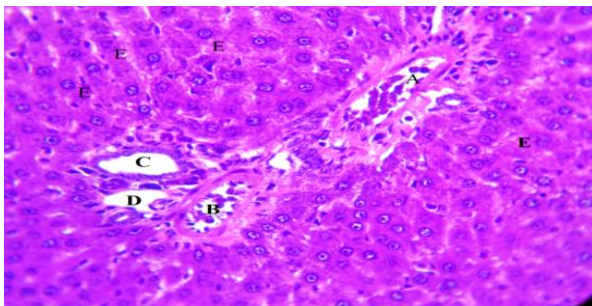
3.2 The effect Histological on the liver:

The cross-section of the liver tissue in T1 showed that it is composed of several lobules, each containing a central vein (A) in the middle of the hepatic lobules. Where a wide cavity appeared, it was surrounded from the outside by rows of polygonal hepatocytes (B) with large spherical nuclei prominent with dark pigment, and between the rows of cells were found blood sinusoids (C) containing some Kupffer cells (D). as shown in the picture (1).



Picture (1) Control.

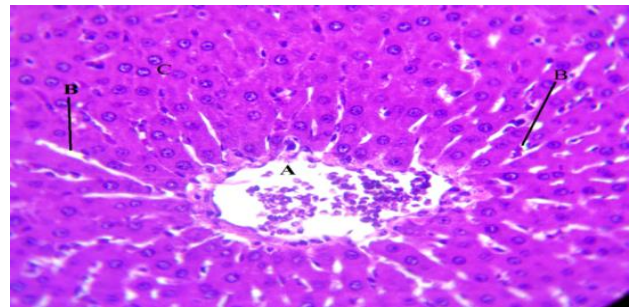
The portal region of the liver was also shown by treatment (T2), in which the hepatic portal vein branch has a blood clot (A), the branch of the hepatic artery (B), the bile duct (C), and the lymphatic vessel (D). The cavity of the vein and artery contained red blood cells, and the ducts and blood vessels were surrounded by white blood cells, and around them appeared hepatic cell necrosis (E), as shown in the **picture (2)**. The study results showed that the creation of diabetes mellitus in female rats led to changes in the liver compared with the livers of females in the control treatment (T1). It agrees with the study of [42], which showed necrosis in the hepatic cells, the absence of sinusoids, and the thickening of the nuclei. As the liver is the most sensitive organ and responds to the high glucose levels in mothers, the other reason for these changes is the lack of insulin.



Picture (2) infected without treatment.

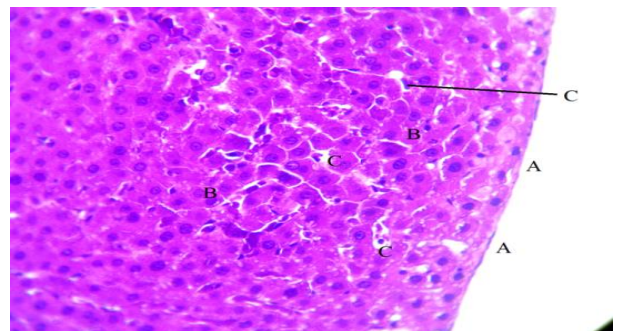
Also, the hepatic lobule contained the central vein in the treatment (T3) for diabetes with metformin treatment at a concentration of 50 mg/kg body weight in several red blood cells (A), and the edges of the vein were continuous with blood sinusoids (B) containing kupffer cells. Where these sinusoids appeared radially around the central vein, rows of hepatocytes were found around the central vein

(C) in a normal. Manner, with cells closely packed together forming a mass with unclear boundaries and nuclei containing more than one nucleus, as shown in the **picture (3)**. In general, the positive effect of metformin treatment was more evident in the liver of young female rats and the improvement of its functions in the case of diabetes [43].



Picture (3) infected with induced diabetes and orally dosed with chemotherapy (metformin) at a concentration of 50 mg/kg of body weight.

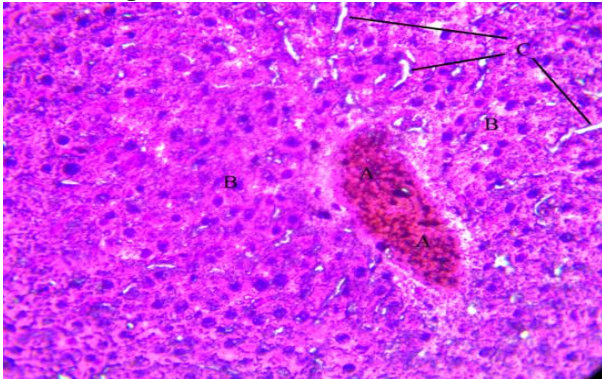
While the periphery of the liver in the treatment T4 with no diabetes mellitus with an aqueous extract of *curcumin* at a concentration of 50 mg/kg body weight contained on aggregates of hepatocytes compact with each other (A) and with regular polygonal shapes (B) and prominent nuclei, and between the cells appeared radial blood sinusoids containing kupffer cells (C), the surface of the liver being covered by an area composed of connective tissue composed of colloidal fibers and fibroblasts. As shown in picture (4).



Picture (4) infected with induced diabetes and orally dosed with chemotherapy (*curcumin*) at a concentration of 50 mg/kg of body weight.

Also, the central vein of the treatment (T5) infected with no diabetes with the aqueous extract of *curcumin* at a concentration of 100

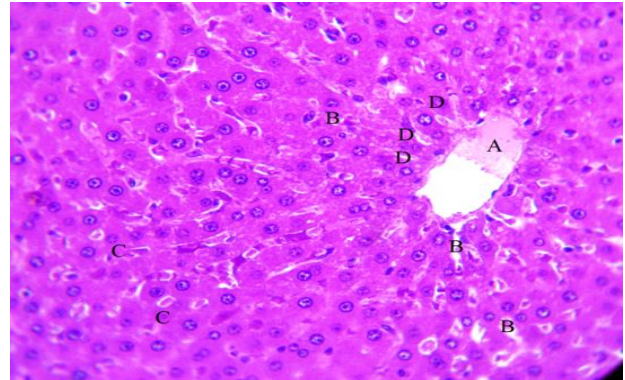
mg/kg body weight contained coagulated blood (A) with abundant hemoglobin in it, and the vein was surrounded by clusters of degenerating cells that had lost their borders (B) and their shape, as several nuclei are irregular in shape, with the presence of clotting in some nuclei and the disappearance of other nuclei (C). In addition, the blood sinusoids appeared in small divergent pockets (C), as shown in picture (5).



Picture (5) infected with induced diabetes and orally dosed with chemotherapy (*curcumin*) at a concentration of 100 mg/kg of body weight.

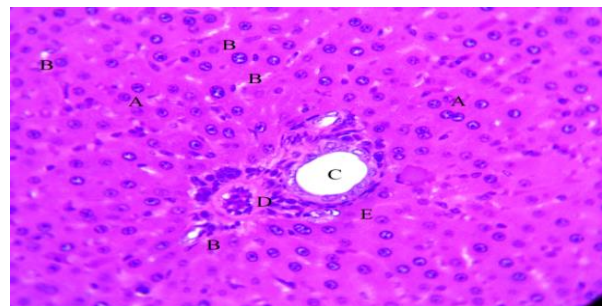
Daily doses of 50-100 mg/kg of body weight significantly improved liver tissue. This result was identical to the study by [44], which showed that the aqueous extract of *curcumin* showed normal liver tissue and a significant improvement by reducing liver enzymes because of flavonoids acting as antioxidants.

While the central vein (T6) was treated for diabetes mellitus with an aqueous extract of *Origanum majorana* at a concentration of 50 mg/kg body weight, it has a bit of decomposing blood (A) and is continuous on its edges with blood sinusoids containing kupffer cells (B) and the presence of some enlarged kupffer cells, The bloody sinusoids are surrounded by hepatocytes that have hyperplasia (C), except that these cells contain cytoplasm and nuclei sphenuclei that are shaped, each with one or more protruding nuclei. And those cells, despite some of their enlargement, are standard in shape (C), as shown in the picture (6).



Picture (6) infected with induced diabetes and orally dosed with chemotherapy (*Origanum majorana*) at a concentration of 50 mg/kg of body weight.

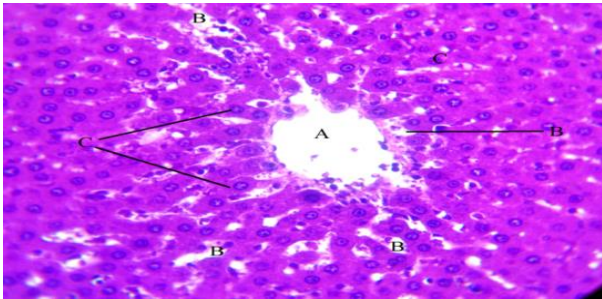
While T7 was treated for diabetes mellitus with an aqueous extract of *Origanum majorana* at a concentration of 100 mg/kg body weight treatment, hyperplasia of hepatocytes (A) was also found, with prominent spherical nuclei, most of which contained more than one nucleus, very narrow blood sinusoids (B), which were not significantly observed, a bile duct branch (C), and a hepatic artery Has a blood clot (D) from some white blood cells (E) As shown in picture (7).



Picture (7) infected with induced diabetes and orally dosed with chemotherapy (*Origanum majorana*) at a concentration of 100 mg/kg of body weight.

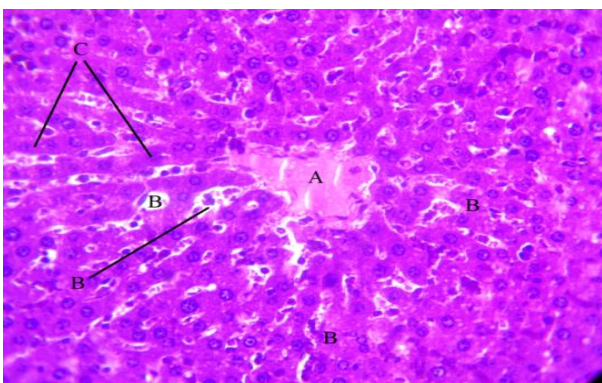
According to the results obtained, we conclude that *Origanum majorana* can protect the liver from alloxan-induced damage [45]. Furthermore, this protective effect is associated with antioxidant compounds such as flavonoids, anthocyanins, tannin derivatives, and rosmarinic acid [46]. As for the central vein (A) in the treatment of T8 infected with newly developed diabetes mellitus with an aqueous extract of *vitex aguns-castus* at a concentration of 50 mg/kg body weight, it has a wide cavity

and is continuous at its edges with blood sinusoids (B) that are regular in the form of a network of blood channels. In addition, and containing large numbers of kupffer cells and red blood cells, and among those sinusoids, rows of normal hepatocytes were found (C). Moreover, the container contains spherical nuclei of a dark color, as shown in the picture (8).



Picture (8) infected with induced diabetes and orally dosed with chemotherapy (*Vitex agnus-castus*) at a concentration of 50 mg/kg of body weight.

While the central vein in the treatment (T9) for newly developed diabetes mellitus with an aqueous extract of *vitex agnus-castus* at a concentration of 100 mg/kg body weight contained dissolved blood (A), The vein opens into the branches of blood sinusoids filled with enlarged Coffe cells (B), red blood cells, and rows of hepatocytes that extend towards the central vein in a radial arrangement (C), as shown in the picture (9).



Picture (9) infected with induced diabetes and orally dosed with chemotherapy (*Vitex agnus-castus*) at a concentration of 100 mg/kg of body weight.

The results also showed some repair that occurred in the liver tissue cells of female rats affected by the action of alloxan and its gradual return to the normal state using the aqueous extract of *Vitex agnus-castus* leaves in two doses of 50 and 100 mg/kg body weight. Because of the active compounds in the aqueous extract have many capabilities, especially as an antioxidant, as it works on cellular repair and stimulates cells to divide to compensate for those affected [47].

Conclusion

The results showed that *Curcumin*, *Origanum majorana*, and *Vitex agnus-castus* aqueous extracts positively affected liver enzymes and tissues in female rats.

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تأثير بعض المستخلصات النباتية والكيميائية الطبية على أنزيمات وأنسجة كبد إناث الجردان

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• تاريخ استلام البحث 11/04/2023 وتاريخ قبوله 07/05/2023.

• البحث مستل من اطروحة الدكتوراه للباحث الاول.

المستخلص

أجريت الدراسة على 45 جرد من الإناث الناضجة جنسيا عمرها يتراوح بين 7-8 أسابيع ووزنها بين 160-180 غم. استخدمت تسعة معاملات في هذه الدراسة تضمنت عزل خمسة من الجردان كمعاملة سيطرة (سليمة)، حقنت الجردان المتبقية (تحت الجلد) بمادة الألوكسان هندي الصنع بجرعة 100 ملغم/كجم من وزن الجسم. أظهرت النتائج انخفاضاً معنوياً في إنزيمات الكبد المتمثلة AST وALP في T3 و T4 و T5 و T6 و T7 و T8 و T9، بالإضافة إلى انخفاض كبير في انزيم ALT في T3 و T5 و T6 و T7 و T9. كذلك اختبرت فعالية تأثير المستخلصات النباتية الطبية (الكرمين، اوراق البردقوش، اوراق كف مريم) بتركيز 50-100 ملغم/كجم من وزن الجسم والعلاج الكيميائي (الميتفورمين بتركيز 50 مجم/كجم من وزن الجسم) على انزيمات وأنسجة الكبد. أظهرت نتائج التأثيرات النسيجية تلعفاً شديداً في أنسجة الكبد لدى الفئران المعاملة بمادة الالوكسان مقارنة بمعاملة السيطرة وذلك بنخر خلايا الكبد ووجود جلطة دموية وغياب أشباه الجيوب بالإضافة إلى تضخم النوى.

الكلمات المفتاحية: الكركمين ، اوراق البردقوش ، اوراق كف مريم ، ميتفورمين ، وإنزيمات الكبد.