EXPLORATION THE EFFECT OF HIGHER DOSE OF AQUEOUS AND ALCOHOLIC EXTRACTS OF BAMBER FRUIT (*CORDIA MYXA*) OF SOME HISTOLOGICAL PARAMETER AND SYMPTOM IN MICE

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ABSTRACT

This study was aimed to explore the safe levels of the aqueous and alcoholic extract of the pamper (*Cordia myxa*) fruit in used mice, and its effect on vital organs.Various doses of 1000, 2000, 3000, 4000 and 5000 mg/kg body weight were used in this study for both aqueous and alcoholic extracts for the entire week. The safe doses of aqueous and alcoholic extracts were then used with 1000, 2000 and 3000 mg / kg body weight and continued observation for two weeks. At the end of the experiment, animal weights were taken, mice were then executed and weights of some of important biological organs such as kidney and liver were weighed and examined for histopathological segments. The results of the study did not show any lethal effects due to the use of aqueous and alcohol extracts with low doses concentrations 1000, 2000 and 3000 mg / kg body weight of the animal of the pamber fruit, but some minor side behavior, as well as there is no significant change in the weights of the body of mice. While the histological test of the liver and kidney showed slight discomfort with minor degenerative changes with the depletion of the diabetic protein pellets at the tissue site. After the end of the experiment, animals weights were taken, and mice were then executed and their weights taken from animals and some of its organs were studied with histological changes of important biological organs such as liver and kidneys.

Keywords: *Pamper*, biological organs behavior, kidney

استكشاف تأثير الجرعة العالية للمستخلصات المائية والكحولية لفاكهة البمبر (*Cordia Myxa*) على المعالم النسيجية وأعراضها في الفئران

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المستخلص

تهدف الدراسة إلى استكشاف المستويات الآمنة للمستخلص المائي والكحولي لثمرة البمبر على الفئران المستعملة من خلال فحص القطع النسيجي لبعض الاعضاء. استعملت في الدراسة جرع مختلفة منها 1000 ، 2000 ، 3000 ، 4000 و 5000 ملغ/كغم لكلا من المستخلص المائي والكحولي للبمبر ولمدة اسبوعا كاملا. وبعدها استخدمت الجرع الآمنة من المستخلصات المائية والكحولية وبواقع 1000, 2000 و3000 ملغم/ كغم من وزن جسم الحيوان مع الاستمرار في المراقبة ولمدة اسبوعين مع أخذ الاوزان الكلية للجسم والاعضاء الحيوية, وتم تحليل الفايتوكيميكل للمستخلصات والقطع النسيجي لكل من الكبد والكلى. لم تظهر نتائج الدراسة أي أثار مميتة جراء تناول المستخلصات المائية والكحولية للتراكيز 1000, 2000 و3000ملغ/كغ من وزن جسم الحيوان لفاكهة البمبر الا بعض السلوكيات الجانبية الطفيفة, وكذلك لم يحصل تغير كبير في أوزن الفئران. في حين أظهر اختبار القطع النسيجي للكبد والكلى احتقانًا طفيفًا مع تغييرات تنكسية طفيفة مع نضوب حبيبات البروتين السكري في موقع النسيج.

الكلمات المفتاحية: البمبر, سلوك الاعضاء البايولوجية, الكلية, الكبد

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INTRODUCTION

In the past, different types of herbs and medicinal plants were used as a traditional remedy for different diseases (13) and these herbs are considered of defense in maintaining health and struggling disease and source of new drug due to that therapeutic properties (29). *Cordia myxa* L. (Indian Cherry) belongs to family Boraginaceae, found growing all over different Worldwide, India and Asia .The fruits and other plant parts of Cordia myxa are used in curing various ailments viz. Tracheae hyper-responsiveness and progress of Asthmas, skin diseases, dropsy, dysentery, dyspepsia, cholera and headache etc. The fruits are astringent, anthelmintic, diuretic, demulcent and expectorant (23). The fruit *Cordia myxa* enhanced healing with less scarring of wounds after topical application (18, 26). The fruit *Cordia myxa* contains different active ingredient which played an active role in medicine field. Previous studies have analyzed the chemical analysis of the compounds of these plants and their positive effect and evaluation of their medicinal effectiveness for many different diseases (1). But the potential of these chemical components to heal wounds and burns is still not real well known. The aim of this study was conducted to explore what parameter of safety margin of both aqueous and alcoholic *Cordia myxa* extract which affect mice by changing weights and general contraceptives, as well as changes that appear on the histological sections of both mice's liver and kidney.

MATERIALS AND METHODS

Preparation of *Cordia myxa* aqueous fruit extract

Fresh *Cordia myxa* fruits are used as experimental materials which were collected from farm lands in Agricultural Research Central of Baghdad, Iraq, in April 2007. The collected plant material was placed in a polyethylene bag to prevent loss of moisture during transportation to Market Research & Consumer Protection Center laboratory of Baghdad University. *Cordia myxa* fruits were cleaned good to remove the dirt and extra materials, washed several times with running tap water, its seed removed out by pressing on seed, then dried in cleaned room under fan to prevent any decomposition of chemical compounds present in it. The semi-dried fruit was dried at 40°C/overnight in laboratory oven (JRAD), and then dried samples were powdered by using an electric grinder for further study. Then 30 g of dried powder was extracted with 300ml of distilled water by using water bath for 6 h at 37 °C. The extract was collected and filtered through Whatman No.1 filter paper and the filtrate was evaporated under reduced pressure to get a fine extract, then dried in oven at 45 °C for 6 hours and stored at 4 °C until used as (4, 7).

Preparation of *Cordia myxa* alcoholic fruit extract

It was taken 30 g dried powder of *Cordia myxa* fruit, dip enough with 300ml ethanol 97% solution and set in an orbital shaker rotating 120 rpm for 48 h for regular infusion and good combination of ingredients. The mixture were left for 1-2 hours to settle down, then drained the layer Stir through Whatman filter paper No. 1, diluted into a dry, clean glass container, and then then subjected to evaporation under reduced pressure to get a semisolid extract at a temperature of 40ºC and on 40 rpm. The residue is then placed in a water bath at 45 ° C to remove all the remaining alcohol in the extract. Finally the crude extract was stored in a sterile, labeled container at -20 ° C until used (8). The obtained yield of the extract was 28%.

The initial trial for safe doses

The initial study was carried out to determine what doses levels of safety margin of *Cordia myxa* extract by using 55 adult mice randomly distributed into 3 groups as in table 1: Group (I) as control group with 5 mice were given tap water. Five mice were used for each other sub-groups which treated with different concentrations of both aqueous and alcoholic extraction of *Cordia myxa* fruit. Group (II), that treated with 1000, 2000, 3000, 4000 and 5000 mg/kg body weight of aqueous *Cordia myxa* fruit extract. Group (III), that treated with 1000, 2000, 3000, 4000 and 5000 mg/kg body weight of alcoholic *Cordia myxa* fruit extract as shown in table 1. The extracts were administered in a single dose orally using a stomach tube once time per day. Then it was recorded all the clinical signs such as (skin and fur changing, eye, mucous membrane, respiratory disorder, circulatory, autonomic

and central nervous system, hyperactivity, salivation, diarrhea, lethargy, sleepy and coma), then keeping the mice to 14 days for monitoring (32).This toxicity experiment was done to evaluate the safety and efficacy of different doses of aqueous and alcoholic extract of *Cordial myxa* fruit (32). Then, the experiment was designed later with safe concentration 1000, 2000 and 3000 mg/kg of mice's body weight for each aqueous and alcoholic extract of *the Cordia myxa* fruit. While high doses 4000 and 5000 mg/kg of animal body weight were neglected for both aqueous and alcoholic extracts to show the harmful and deadly effects of the used mice.

Table 1. Experimental design of initial exp. for safely doses, treated with different concentration of both aqueous and alcoholic extract of *Cordia myxa* fruit.

Groups treatments	No. of mice
Control	5
Aqueous extraction	
1000 mg/kg of b.w * 1A	5
2000 mg/ kg of b.w 2A	5
3000 mg/ kg of b.w 3A	5
4000 mg/ kg of b.w 4A	5
5000 mg/ kg of b.w 5 A	5
Alcoholic extraction	
1000 mg/ kg of b.w 6Aq	5
2000 mg/ kg of b.w 7Aq	5
3000 mg/ kg of b.w 8Aq	5
4000 mg/ kg of b.w 9Aq	5
5000 mg/ kg of b.w 10Aq	5
Total	55

***= mice body weight**

Experimental design

Experiment was performed after safety doses determined above on 35 mice using 1000, 2000 and 3000 mg/kg of body weight doses for each aqueous and alcoholic extracts administration. Mice with weight range of 20-25g were bought from the animal house of AL-Razi center/Jadyria/Baghdad and kept in animal house at controlled environmental conditions at room temperature (28±2 ºC) and relative humidity (46±6%) with 12-hrs light-dark cycle and adequate ventilation. They were provided food and water ad libitum during the whole period of the experiment. Then, 35 mice were randomly distributed into three groups with 5 mice for each sub-groups: group (I), as control group were given tap water. Group (II) were treated with aqueous extract of *Cordia myxa* fruit that given at doses 1000, 2000, 3000, mg/kg body weight to 5 mice's for each 3 sub-groups. Group (III) were treated with alcoholic extract of *Cordia myxa* fruit that given at 1000, 2000, and 3000 mg/kg body weight to 5 mice for each sub-groups based on safe doses on the previous experiment (32) as in Table 2.

Table 2. Experimental design, treated with different concentration of both aqueous and alcoholic extract of *Cordia myxa* fruit.

Groups treatments	No. of mice
Control	5
Aqueous extraction	
1000 mg/kg of b.w 1A	5
2000 mg/ kg of b.w 2A	5
3000 mg/ kg of b.w 3A	5
Alcoholic extraction	
1000 mg/ kg of b.w 4Aq	5
2000 mg/ kg of b.w 5Aq	5
3000 mg/ kg of b.w 6Aq	5
Total	35

***= mice body weight**

Phytochemical screening

Phytochemical screening procedures carried out were by the method of (26). The crude C. myxa fruit extract (CME) was analyzed for pH, gum, alkaloids, saponin, steroids, polyphenols, flavonoids, comarines, resins, glycosides, tannin, and oily nitrogenous materials.

Histopathology studies

At the end of the experiment, mice anaesthetized under diethyl ether following collection of liver and kidney of sub group (A, B and C in Figures 2, 3, 5 and 6) for alcoholic and aqueous extract treated groups were immediately removed and preserved in 10% formalin, then sent to the Medicinal City Hospital laboratory for histopathology processing in Baghdad city as (20, 14).

Statistical analysis

For analysis of variance and the means were compared using LSD 0.05 (30).

RESULTS AND DISCUSSION

The initial trial for safe doses

Clinical signs of mice according to treatment and dose: Signs of animals showed differences depending with different doses given as given in table 3. Mice were treated at dose 1000-3000mg/kg, showed no change in their behavior and thus similar to control groups, indicating 1000, 2000 and 3000mg/kg doses are safe from any side effect. While high doses 4000 and 5000mg/kg were showed many signs behavioral included: rapid breathing, accelerated heart beat lasting for few minute then died after given extract orally for both extraction, and from the apparent observations of mice by the competent and experience-based veterinian. In other way, 1000, 2000 and 3000mg/kg doses of both aqueous and alcoholic extract were not recorded and sign of dead or sickness as shown clearly in Table 3. This indicated the possibility of using *Cordia myxa* fruit with low doses safely. This finding was exactly what it was founded by (16). Also it was founded no mortality was observed up to dose as high as 2g/kg body weight dose was considered for further experiment done by (22). The ratio was 350mg/kg of body weight that founded by (19) come close to the safe and good for using in this study.

Table 3. Clinical changes of mice relative to the different concentrations of both aqueous and alcoholic extracts of *Cordia myxa* fruit.

Type of group	Dose mg/kg b.w	Dose Ml/mice	No. of mice ۞	Clinical sign
Group I				
Control	D.W	-	5	No sign
Group II Aqueous extract				
1A	1000	0.2	5	No clinical sign
2A G	2000	0.2	5	No clinical sign
3A	3000	0.2	5	No clinical sign
4A	4000	0.2	5	Hyperventilation still few minute then died.
5 A	5000	0.2	5	Hyperventilation and Tachycardia still few minute then died.
Group III Alcoholic extract				
6A G	1000	0.2	5	No clinical sign
7A	2000	0.2	5	No clinical sign
8A G	3000	0.2	5	No clinical sign
9A	4000	0.2	5	Hyperventilation still few minute then disappeared.
10A	5000	0.2	5	Hyperventilation and Tachycardia still few minute, then disappeared.

Each group has 5 mice before the experiment. ۞ = number of mice still after the end of experiment. *= mice body weight

Changes in the weight of the mice's body and some organs: The results in Table 4 show that the body and its organs, such as the liver and kidney underwent physical changes in the mice treated with the aqueous and alcohol extracts of the fruit. There was no statistically significant differences in the weights of treated mice with high concentrations of aqueous and alcohol extract. However, the total weight of the liver and kidney of the mice treated with the water and alcohol extract was increased ($P < 0.05$) in comparison to the control group as shown in Table 4. In addition, there was an enlarged liver and rat kidneys, which led to a statistically significant increase ($P < 0.05$) in weights as shown in Table 4.

Table 4. Changes in the body and some organs weight of the mice treated with *Cordiamyxa* extracts.

Groups[☼]	We. Of mice (g)		We. Liver		We. Kidney		Duration of Study (days)
	Before exp.	After exp.	Before exp.	After exp.	Beforexp.	After exp.	
				Group I (control)			
C	25.0 ± 1.38 a	25.5 ± 1.41 a	1.84 ± 0.05 a	1.90 ± 0.08 a	0.64 ± 0.04 b	0.75 ± 0.06 a	*14*
				Group II (Aqueous extract)			
1 A	24.5 ± 1.27 a	24.5 ± 1.27 a	1.85 ± 0.06 a	1.92 ± 0.07 a	0.65 ± 0.04 b	0.88 ± 0.09 a	14
2 A	24.5 ± 1.07 a	24.2 ± 0.96 a	1.90 ± 0.06 a	1.95 ± 0.07 a	0.85 ± 0.04 a	0.75 ± 0.03 a	14
3 A	24.3 ± 0.93 a	24.2 ± 1.37 a	2.05 ± 0.06 a	2.20 ± 0.08 a	0.68 ± 0.02 b	0.90 ± 0.06 a	14
				Group III (Alcoholic extract)			
4 AL	24.6 ± 1.18 a	24.8 ± 1.38 a	1.85 ± 0.05 a	1.90 ± 0.08 a	0.77 ± 0.04 a	0.79 ± 0.02 a	14
5 AL	24.7 ± 1.37 a	24.8 ± 1.63 a	1.84 ± 0.09 a	1.92 ± 0.11 a	0.82 ± 0.08 a	0.99 ± 0.08 a	14
6 AL	25.0 ± 1.27 a	25.5 ± 1.33 a	1.89 ± 0.09 a	2.05 ± 0.11 a	0.85 ± 0.08 a	0.85 ± 0.10 a	14
LSD value	2.38 NS	2,09 NS	0.337 NS	0.217 NS	0.118 *	0.126 NS a	---

Means having with the different letters in same column differed significantly * (P<0.05).

☼=five mice for each group

Phytochemical screening

The results of the Phytochemical screening of aqueous and alcoholic extract were presented in Table 5. Results revealed the presence of Alkaloids, Saponin were high contents; then, gum, and coumarins were mild content, then Steroid, polyphenols, flavonoids, resin, glycosides, tannins, and oily nitrogeneous material were low contents in aqueous extract. While, resin was higer content, then alkaloid and flavonoids were mild content, then gum, saponine, steroid, polyphenols, coumarins, glycosides, tannins and nitogeneous material were the lowest content in alcoholic extract as in Table 5. Presences of these phytochemicals have contributed to its medicinal value as well as physiological activity (22). Polyphenols component have been shown to have antibacterial, anti-inflammatory, ant allergic, antiviral and antineoplastic activity (13). Many of these alleged effects, due to their known functions as strong antioxidant and metal chelates (21). Steroidal compounds are of importance in pharmacy because of their relationship with such compounds as sex hormones (10). Saponins have been reported to be linked with tumor inhibiting activity on animals. The positive effects of glycoside and cardiac glycoside are not common but their toxic effects were decreased heart rate, sympathetic activity and systematic vascular resistance (5). While, (6) presented that, the presence of these secondary metabolites has contributed to its medicinal value as well as physiological activity.

Table 5. Phytochemical Screening of *Cordia myxa* fruits

Chem. Tests	Aqueous extract	Alcoholic extract
pH	7.0	6.5
Gum	+	+
Alkaloid	+++	++
Saponine	+++	+
Steroid	+	+
Polyphenols	+	+
Flavonoids	+	++
Comarines	++	+
Resins	+	+++
Glycosides	+	+
Tannins	+	+
Oily nitrogeneous material	+	+

Where '++, +++' means highly available and '+` means low available

Histopathology study of liver

Effect of treating aqueous *Cordia myx*a extract on liver: The liver sections of normal group (control) showed normal cellular architecture with distinct hepatic cells, sinusoidal spaces and central vein as in Fig. 1**.**

While, histopathological section of mice's liver that treated with low concentration of *Cordia myxa* aqueous extract at dose 1000mg/kg body weight showing normal hepatocytes and normal mast cells, The results of the histological segment of the liver were also shown by the hypertrophy of the capillaries located between the plates and the hepatic sinuses as shown in section 1, Fig. 2. Increasing the dose of *Cordia myxa* alcoholic extract to 2000 and 300mg/kg body weight showed a slight depletion of glycoprotein granules with some degenerative changes of the hepatocyte cells as in section 2 and 3, Fig. 2. In addition, it was noted a disorganization of the hepatic parenchyma, hyperemia, and proximity of the central lobular vein as in section 3, Fig. 2.

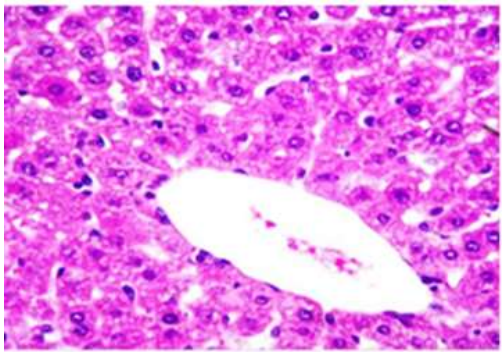

Figure 1. Histological section of control mice's liver stained with hematoxylin and eosin (H & E 40 X).

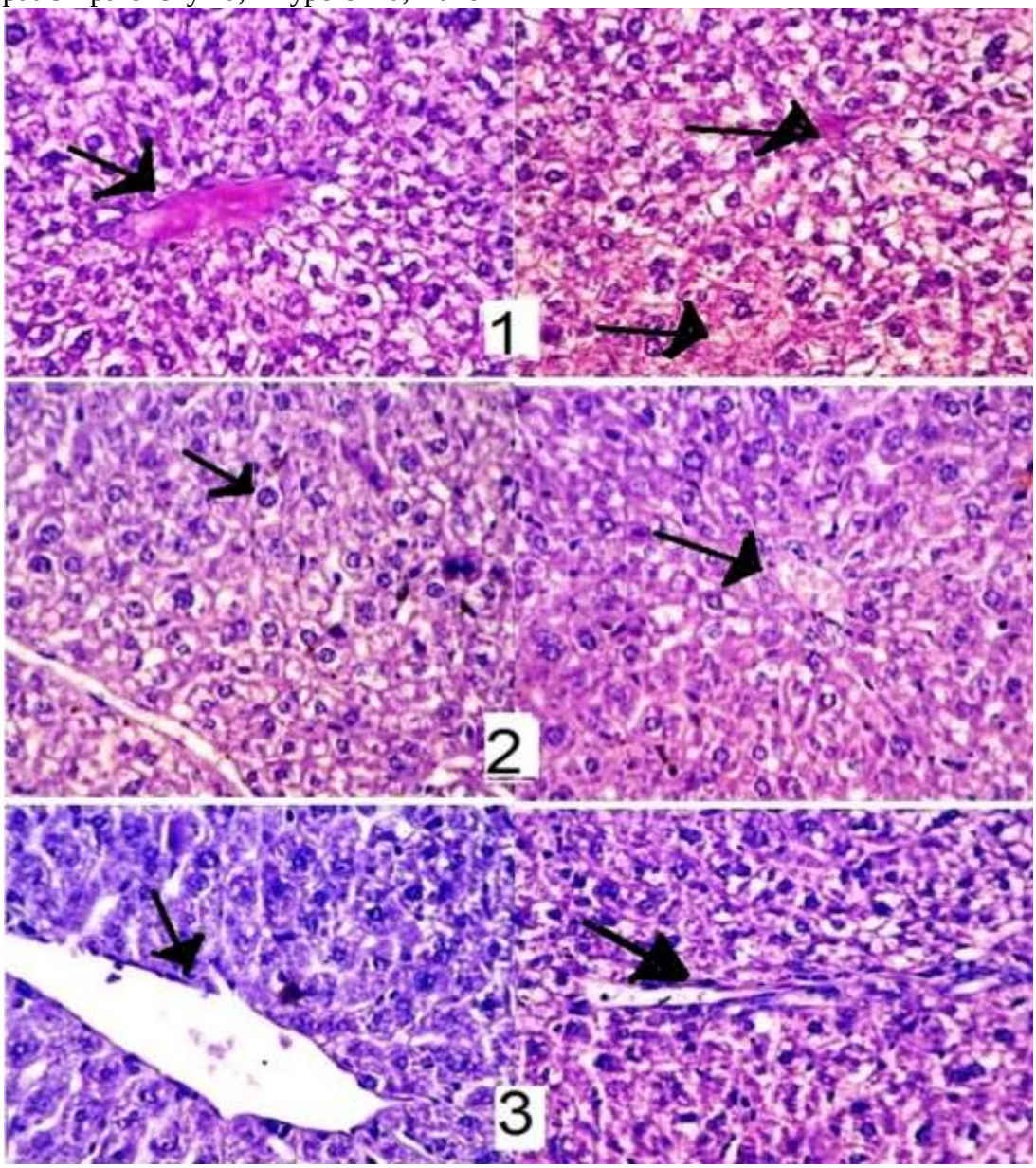

Figure 2. The sections one, tow and three showed the histopathological analysis of mice's liver treated with 1000, 2000 and 3000 mg/kg b.wt. respectively of aqueous *Cordia myx*a extract stained with hematoxylin and eosin (H & E 40 X).

Effect of treating the alcoholic *Cordia myx*a extract on liver

The histopathological sections of mice liver that treated with different concentration of alcoholic *Cordia myxa* extract was showed in Figure 3. At dose 1000mg/kg b.wt. of extract was showed a normal looking appearance of renal tissue which consisted glomeruli and renal tubules (Proximal and distal convoluted tubules) as in Fig. 3 section 1. While at 2000mg/kg body weight of alcoholic extract dose, histopathological section of mice's liver showing a slight depletion of glycoprotein granules with certain degenerative changes of the tissue as in section 2, Fig. 3. On the contrary, at 3000mg/kg body weight of alcoholic extract dose, histopathological section of mice liver showing normal histological structure appearance of hepatic tissue as in section 3, Fig 3.

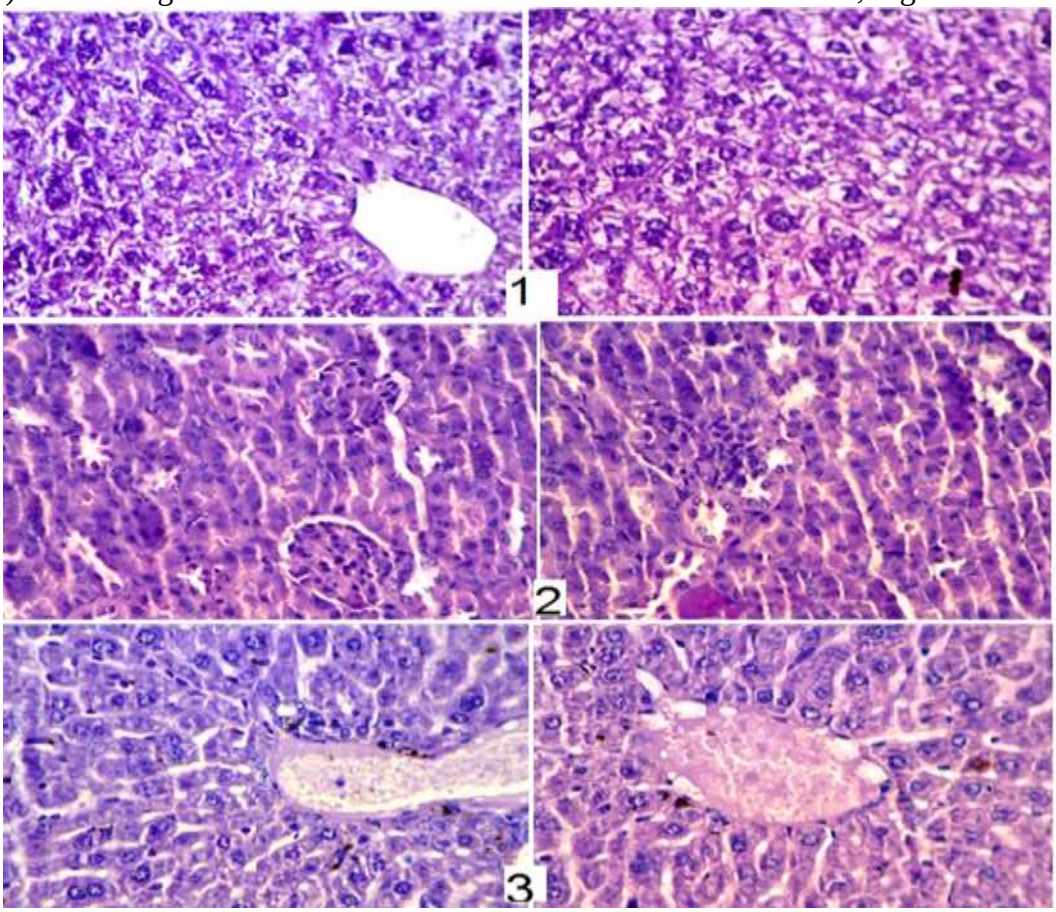

Figure 3. The sections one, two and three showed the histopathological analysis of mice's liver treated with 1000, 2000 and 3000 mg/kg b.wt. respectively of alcoholic *Cordia myx*a extract stained with hematoxylin and eosin (H & E 40 X).

Histopathology study of kidney

Effect of treating the aqueous *Cordia myx*a extract on kidney: The kidney sections of normal group showed normal looking appearance of renal tissue which consisted glomeruli and renal tubules (Proximal and distal convoluted tubules) as shown in Figure 4.

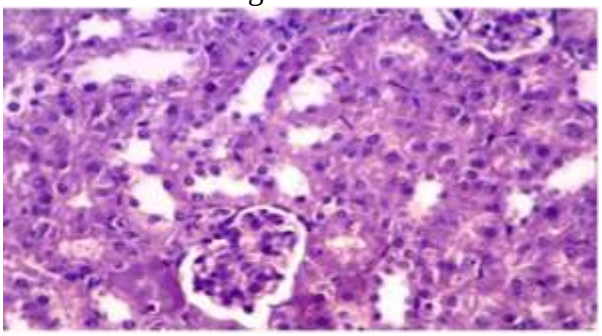

Figure 4. Histological section of control mice's kidney stained with hematoxylin and eosin (H & E 40X).

Histopathological study in mice's kidney that treated with different concentration of aqueous *Cordia myxa* were showed in Figure 5. Mice were administrated with 1000, 2000 and 3000mg/kg b.w dose showed normal looking appearance of renal tissue which consist glomeruli and renal tubules (Proximal and distal convoluted tubules) compared with control as in fig. 4, but it was showed an enlargement and cellular hypertrophy of convoluted tubules as in sec. 1, 2 and 3 respectively compared with control as in Fig. 4.

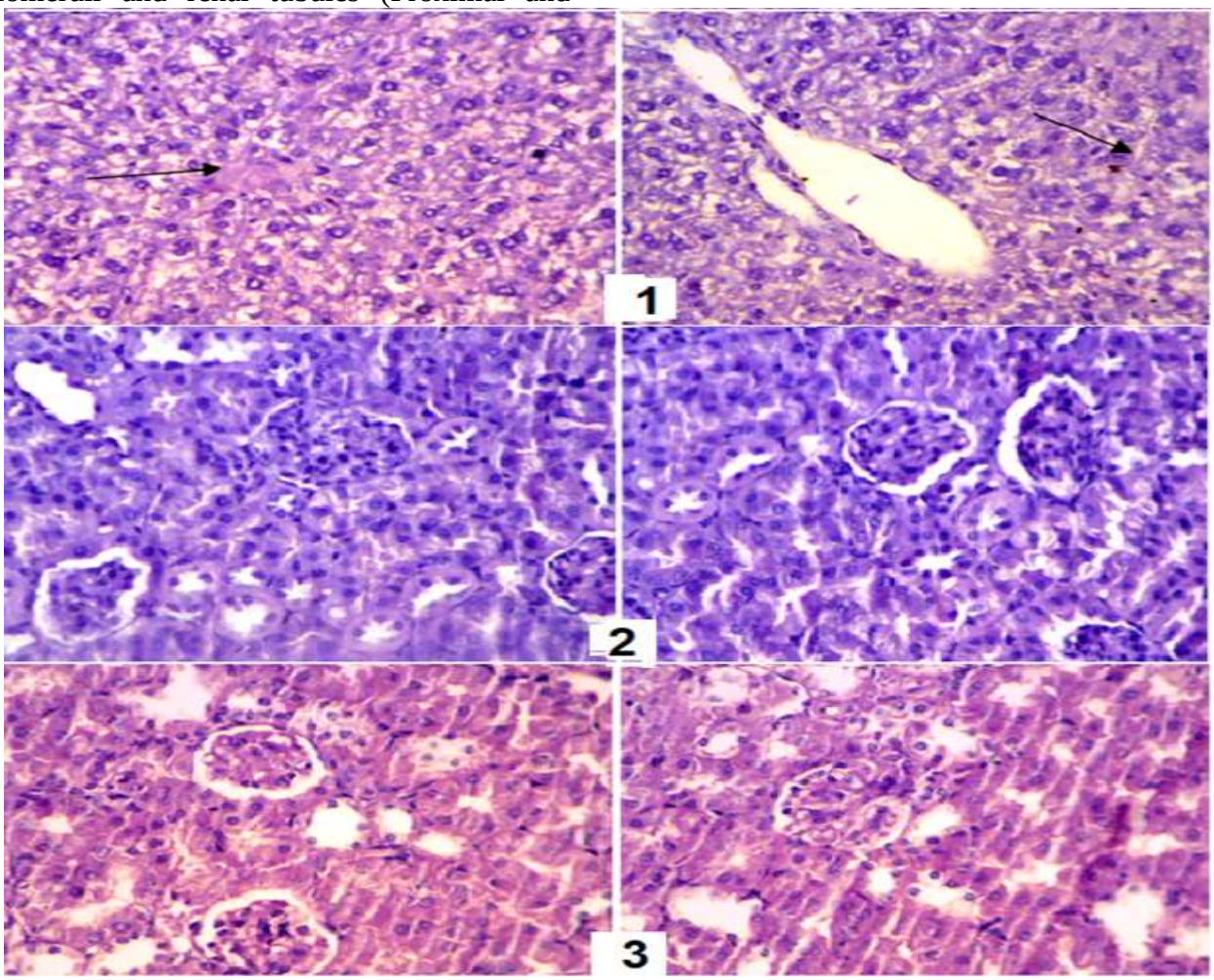

Figure 5:The sections one, two and three showed the histopathological analysis of mice's liver treated with 1000, 2000 and 3000 mg/kg b.wt. respectively of aqueous *Cordia myx*a extract stained with hematoxylin and eosin (H & E 40 X).

Effect of treating the alcoholic *Cordia myx*a extract on kidney

Histopathological study in mice's kidney that treated with different concentration of alcoholic *Cordia myxa* was showed in figure 6. Mice that administration with 1000, 2000 and 3000mg/kg body weight doses showed normal appearance of renal tissue which consisted glomeruli and renal tubules (Proximal and distal convoluted tubules) as in sections 1, 2 and 3 respectively compared with control as in Fig. 4.

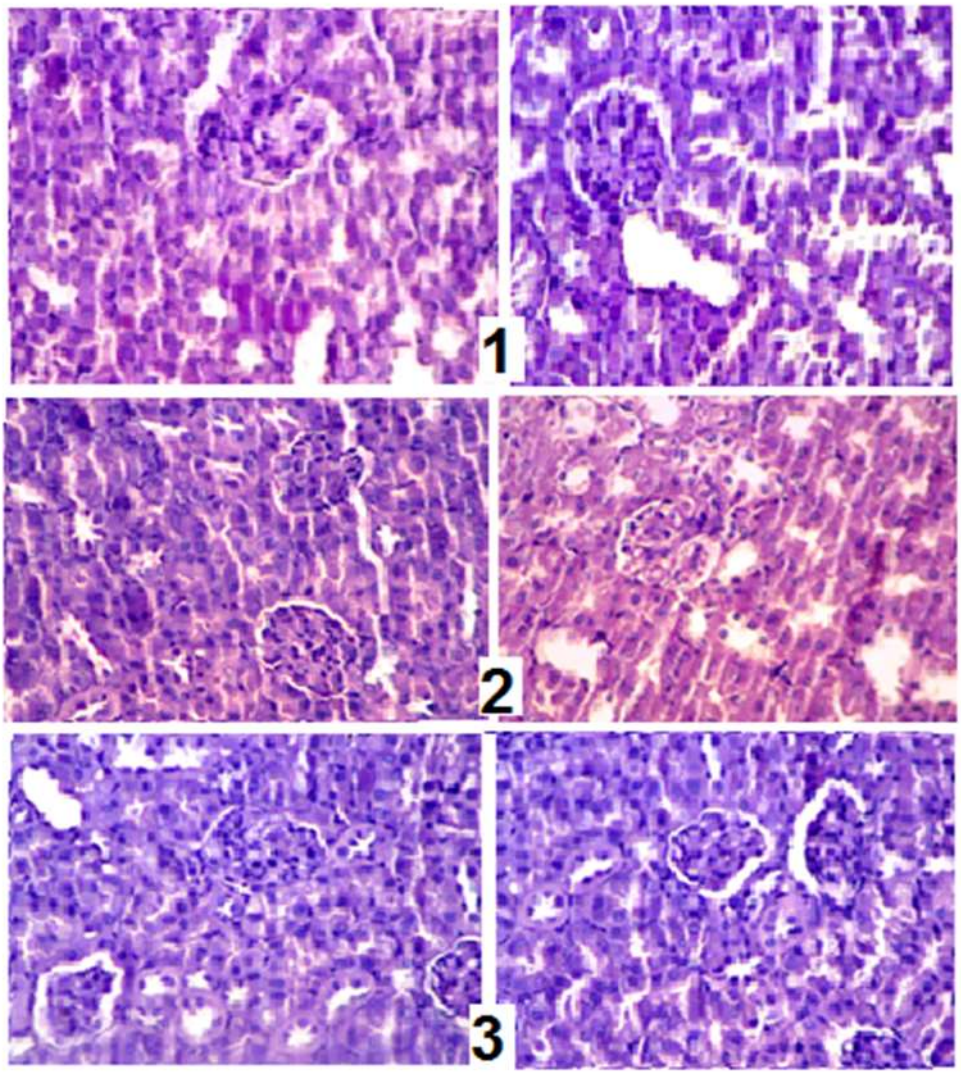

Figure 6. 1, 2 and 3 sections = showed the histopathological analysis of mice's liver treated with 1000, 2000 and 3000 mg/kg b.wt. respectively of alcoholic Cordia myxa extract stained with hematoxylin and eosin (H & E 40 X).

Recently there have been many different and different experiments for many different plants to show its therapeutic importance to many different diseases, where It was found many excellent therapeutic benefits and to prepare a lot of pharmaceutical and cosmetic preparations (28). This study was designed to explore which concentrations of both aqueous and alcohol extracts of *Cordia myxa* were safe for consumption. The results showed no toxicity of the extracts up to 5000 mg / kg body weight concentration. However, there is a slight increase in the weight of both the kidneys and liver, possibly due to many antioxidants in this fruit (11),which play important role in removing toxicity of free radicals from the body (2). The microscopic results of the histological examination of both the liver and the kidneys were shown by the accumulation of fatty or glycogenic drops in cytoplasmic hepatocytes in the group of animals that received low doses of each aqueous extract and this is exactly what that found by (9, 34). Koffler's liver cells are seen as conclusive evidence in the mononuclear phagocytic system and central to both hepatic and systemic response to pathogens as mediator of injury. In other way; those cells may be played important role to promote the resolution of inflammation and enhance maintenance of liver against toxic effect (17) and to control the inflammatory responses due to alcoholic solvent used in extraction (19, 24, 12). In addition of that, the increased population of Koffler's Chuffer cells may be indicated active role of *Cordia myxa* to stimulate the defense mechanism of body against toxic effect as presented by (25). The

results of the microscopic examination of the renal tissue of the kidney showed that there are small fatty vesicles accumulated and some others scattered in the cytoplasm of renal cells, which led to the enlargement of the renal tissue and this finding comparable with (3, 31) who attributed the enlargement of the renal tissue may be due to compress adjacent bile canaliculated, leading to cholestasis. Also, it was presented that these changes could be due to accumulation of one or more of the active pharmacological compounds of the *Cordia myxa* fruit such as flavonoids and alkaloid in the liver tissues of the treated mice (16). While it was observed glycogen depletion could be attributed to the need for production of more energy mainly appeared grossly in hyperventilation of treated mice in high doses and to ability of plant to stimulate endoplasmic reticulum in hepatocyte to synthesis proteins and phospholipids (33; 27). The results of this study showed the importance of pamper fruit, is a natural source of good, cheap, environmentally friendly, easy-to-use with clear biological properties, many medicinal and pharmaceutical uses and also high ethnic properties. Its widely available and can be consumed for the treatment of many diseases of chest and intestines through the use of light doses 1000, 2000 and 3000 mg / kg body weight without any negative effects on health through the diagnosis of tissue for liver and kidneys in animals (mice) used.

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