Journal of Scientific & Innovative Research 2013; 2 (3): 585-597
**Available online at: www.jsirjournal.com**


**Research Article**

ISSN 2320-4818
JSIR 2013; 2(3): 509-597

Received: 30-07-2013
Accepted: 10-08-2013

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# Effect of repeated administration of *Peganum harmala* alcoholic extract on the liver and kidney in Albino mice: A histo-pathological study

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## Abstract

Four groups of male albino mice (Mus musculus) were subcutaneously injected with normal saline (0.9 % NaCl2) or peganum harmala alcoholic seed extract (75, 100, 150 mg/ kg) at twice/ weekly interval for one month period. Thereafter, animals were scarified and specimens from the kidneys and liver were examined under light microscope for structural changes. Repeated treatment with peganum harmala seeds alcoholic extract caused dose- related structural changes in the kindney and liver of treated groups. In the kidney, severe changes were observed following 150 mg/ kg dose that were manifested by hemorrhage in interstitial connective tissue and blood vessels of the medulla and cortex as well as degeneration and necrosis in the epithelial lining of kidney tubules., and shrinkage in the glomeruli with widening in Bowman's capsule. *Peganum harmala* seeds alcoholic extract at 75 and 100 mg/ kg caused slight to moderate histological changes in the cortex and medulla manifested as degeneration and hypertrophy of tubular epithelial lining with widening of loop of Henle with signs of glomerulonephritis. In the liver, repeated treatment of peganum harmala seeds alcoholic extract at 150 mg/ kg dose caused severe destruction of hepatic cells, pyknotic of hepatic cell nuclei and vesiculation in the cytoplasm due to fatty degeneration. In addition, widening in hepatic sinusoids and destruction in the walls of central veins were observed. Nuclear polymorph cellular infiltration and cirrhosis as well as widening in hepatic sinusoids and pyknotic in hepatic cell nuclei were noticed in the 100 mg/ kg dose group.

**Keywords:** Emetic toxin, Enterotoxin, Fermented rice noodle.

## Introduction

The peganum harmala L. (Syrian rue) is a wild-growing flowering plant that belongs to the zygophylaceae family[1] commonly known as "Harmal" grows spontaneously in semi-arid rangeland, steppe areas and sandy soils.[2, 3] The plant is widely distributed in predesertic regions of south-east Morocco, North Africa and the Middle East.[4] Peganum harmala is the only species found growing wild in the middle and northen parts of Iraq.[5] Since ancient times, it has been claimed that this plant has medical compounds harmalol and Harman[6], its seed extracts also contain anthroquinons and a small quantity of flavonoid glycosides[7, 8] which are found especially in the seeds and the roots[3], include β-carbolines alkaloids (harmine, harmaline). The alkaloids in the seeds have pharmacological activities which including: antibacterial effects, vasorelaxant, antihemosporidian, anticancer, antinociceptive, antitumor and finally antiprotozoal effects. [9-15]

The using of peganum harmala seeds causes hallucination due to interact with α2- Adrenoceptor subtypes.[1] Other reports indicate that all domesticated animals are susceptible to poisoning from this plant[16] and the animals which are affected mostly with severe intoxication, cattle, donkeys, sheeps and horses.[16-19] The harmine and harmaline of peganum harmala have toxic effects, the toxic power of harmaline is twice as that of harmine[3], these toxic symptoms which are recorded in the animals that consume a sub- lethal amount of peganum harmala[20] include digestive disturbances such as hyper-salivation, vomiting and diarrhea, while the nervous syndromes are excitability, trembling, accelerated breathing, loss of coordination agitation and in some cases paralysis.[3, 21]

On the other hand, the quinazoline derivatives such as vasicine and vasicin-one[22] of peganum harmala seeds have a bortifacient activity, because their stimulatory effects on the uterine tissues[23] and this effect is mediated by the releases of prostaglandins[24].

In other study[5], the aqueous extract of Iraqi peganum harmala seeds had been given intramuscularly at 420 mg/kg to the rats for six weeks and the histological examination of organs and tissues of treated rats were showed a swelling to shrinkage in the skeletal muscle fibers and there is increased eosinophilia of the sarcoplasma with loss of boundaries of muscular cells and loss of their nuclei. The investigation of other histological section was appeared an infiltration by mixed inflammatory cell types like polymorphonuclears. Also there was oedematous and hemorrhagic separation in the bundles of skeletal muscles. While the examination of histological sections have been taken from the animals that treated for five and six weeks were showed a fibroplasias, proliferation of capillaries with formation of a foreign body- type multinucleated giant cells.

Recent study in chicks[1], given diet containing 10 % of peganum harmala L. or (10 %) of Ballota undulate leaves or their 1: 1 mixture, has shown hexpatotoxicity, congestion and hemorrhage in the liver tissues of chicks were fed peganum harmala L. leaves alone, individual-cell necrosis of the centrilobular hepatocytes. In the kidney tissues, there was a mild degeneration in the epithelial cells of the proximal convoluted tubules. Also these chicks were affected with anemia and disturbances in the concentrations of serum proteins such as total protein, albumin, globulin, cholesterol and others.

The present study has been designed to investigate the histological changes following repeated administration of alcoholic extract of peganum harmala seeds in the tissues of mice, in view of scarce studies on the toxic effect of harmaline on kidney and liver.

## Material and Methods

### Laboratory animals:

The present study was carried out in the laboratory animal house of the department of biology, Faculty for Girls Education. Twenty four albino mice (Mus musculus) from strain Balb/c bred in the above mentioned animal house.

Mice were housed in plastic cages (20 × 21 × 45 cm) with wooden waste bedding. The cages were subjected to cleaning and disinfectant three times weekly.

Animals were kept at constant conditions in regards to ventilation, light/ dark cycle (14/ 10 hour) and temperature (22- 28) C°. The animals had free access to water and standard laboratory food (Najaf poultry supplement, Najaf, Iraq). All experiments were carried out between 8: 30 am to 2: 30 pm.

### Alcoholic extract preparation of harmala plant seeds:

The alcoholic extract of harmala plant seeds was prepared according to earlier reported procedures provided.[25] Briefly, the active ingredients were extracted from 20 g dry seeds using soxholate apparatus. Thereafter the extract materials were concentrated by rotatory evaporator at 40- 45 C°. There after the extract materials was weighted in order to prepare the stock solution, then from this solution three doses (75, 100, 150) mg/ kg were made up for the present study.

### Animal's treatment

Experimental sessions were carried out in three months old male mice were divided into four treatment groups (n= 6/ group), one control group and three treated groups. The control group was s/c injected with normal saline (0.9 % NaCl2) and the treated groups were injected s/c with the alcoholic extract of harmala plant seeds at 75, 100 and 150 mg/ kg twice/ weekly for one month period. The body weight was recorded throughout the experiment prior to dosing. Doses were adjusted to body weight prior to each subcutaneously injection. Mice were

observed for 1 hour post dose for any treatment- related clinical symptoms.

Animals scarified and specimen's evaluation

After the injection period was complete, the animals were anaesthetized by diethylether [(C2H4)2O]. The abdominal cavities of animals were opened; kidneys and livers were removed and put into formalin (10 %) for tissue fixation for 48 hours. Thereafter routine histological preparations were carried out according to reported procedures.[26] Briefly, organs were washing by tap water, dehydration by series of ascending concentrations of ethyl alcohol (70 %, 80 %, 90 %, and 100 %) and clearing by xylole and infiltration and embedding by paraffin wax and made up blocks, then mounting by Canada- blasm and cover slides. The histological slides were examined by light microscope (type Olympus, Japan).

## Results

The present study was designed to evaluate the toxic effects of alcoholic extract of peganum harmala seeds at different concentrations (75,100,150) mg/ kg on the histological structures of kidney and liver of the mice.

Figure (1) shows the effect of alcoholic extract of peganum harmala at 150 mg/kg dose on the medulla of kidney, there were severe changes such as hemorrhage in the interstitial connective tissue and blood vessels as well as necrosis in connective tissues and degeneration of epithelial lining of kidney tubules. Also the 150 mg / kg dose of peganum harmala has been caused a clear damage in the cortex of mice kidney.

Figure (2) reveals shrinkage in the glomerulus and widening in the Bowman's space. 150 mg/kg dose also caused severe damage in the proximal and distal convoluted tubules manifested in necrosis and hemorrhage.

The concentration of 100 mg/ kg had moderate effects on the medulla of kidney, figure (3). There was degeneration in the epithelial lining of collecting tubules, necrosis in some of epithelial cells lining of the ascending loops of Henle. Also there were hypertrophy and widening in the loops of Henle.

100 mg/kg dose caused a moderate changes in the cortex of kidney, figure (4) there were alterations such as glomerulonephritis and widening in Bowman's space, hemorrhage , degeneration and necrosis in proximal and distal convoluted tubules .

The peganum harmala seeds at 75 mg / kg caused mild effects on medulla of kidney, figure (5) showed hypertrophy and widening in the loops of Henle , degeneration in epithelial lining of collecting tubules and necrosis in some of epithelial cells in ascending loops of Henle. In mice treated with peganum harmala seeds extract at 75 mg / kg, there were mild effects on the cortex of kidney. Figure (6) shows signs such as glomerulonephritis and hemorrhage in interstitial connective tissues and blood vessels, in addition to necrosis in some of epithelial cells lining the proximal and distal convoluted tubules.

In liver, alcoholic extract of peganum harmala seeds induced severe toxic effects, 150 mg / kg dose led to a severe pyknotic of hepatic cells nuclei and vesiculation in the cytoplasm of hepatic cells and fatty degeneration. Figure (7) , shows widening in same of the hepatic sinusoids , while the others histological sections from this dose group showed a congestion of central vein and hypertrophy of hepatic cells figure (8).

In figures (9) and (10) the histological changes observed at 150 mg / kg of peganum harmala seeds extract were damage in the wall of central veins , hemorrhage, necrotic foci , degeneration and hypertrophy in some of hepatic cells .

In figure (11), 100 mg / kg of peganum harmala showed different changes in liver tissues like fibrosis (cirrhosis) and mononuclear polymorph infiltration besides widening in some of hepatic sinusoids, pyknotic and vesiculation of hepatic cells. On the examination of the other histological section, like in figure (12) showed a vesiculation in cytoplasm of hepatic cells, fibrosis (proliferation) of reticular fibers and pyknotic in the nuclei of hepatic cells.

Eventually there was another toxic effect occurred on some central hepatic veins like congestion and hemorrhage in the branch of portal vein figure (13).

Our investigation shows mild toxic effects at 75 mg/kg of peganum harmala seeds extract as shown in figures (14) and (15) like destruction in central vein, vasiculation in

the cytoplasm of some hepatic cells and pyknotic of cytoplasmic nuclei of hepatic cells.

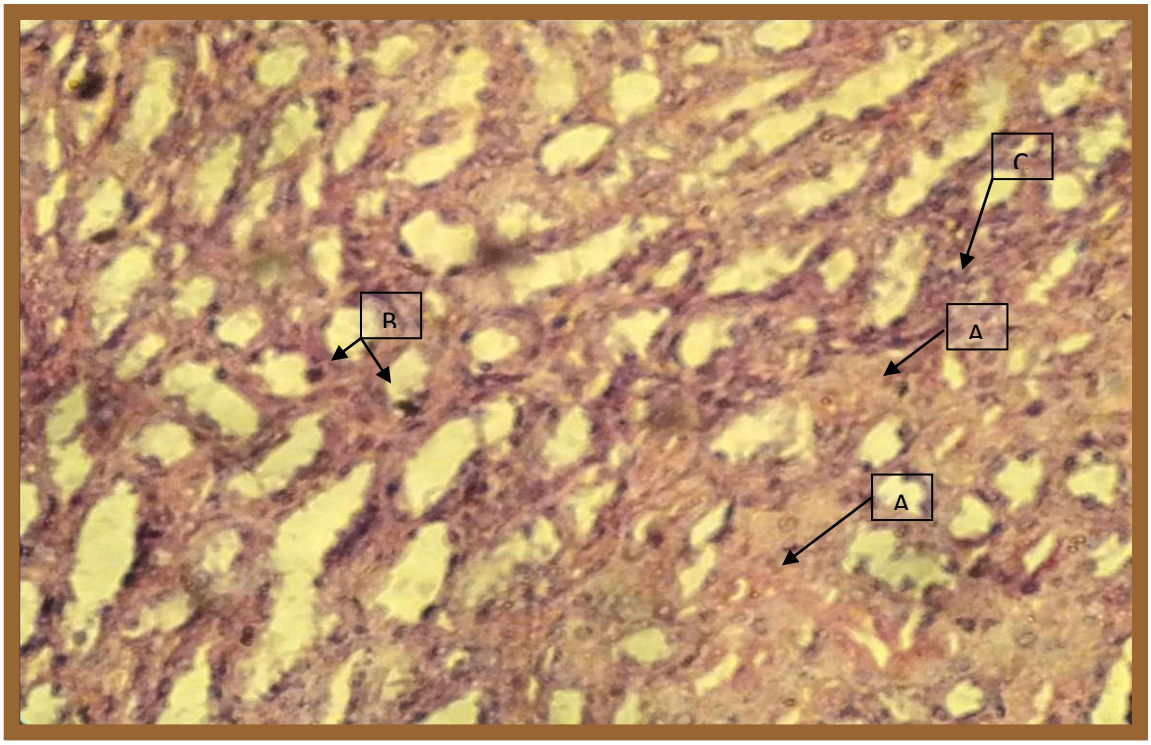


**Figure 1:** the effect of peganum harmala extract on the medulla of kidney at the concentration 150 mg/ kg shows A- hemorrhage in interstitial tissues and blood vessels. B- necrosis in connective tissues. C- degeneration in epithelial lining of kidney tubules H & E 40 X.

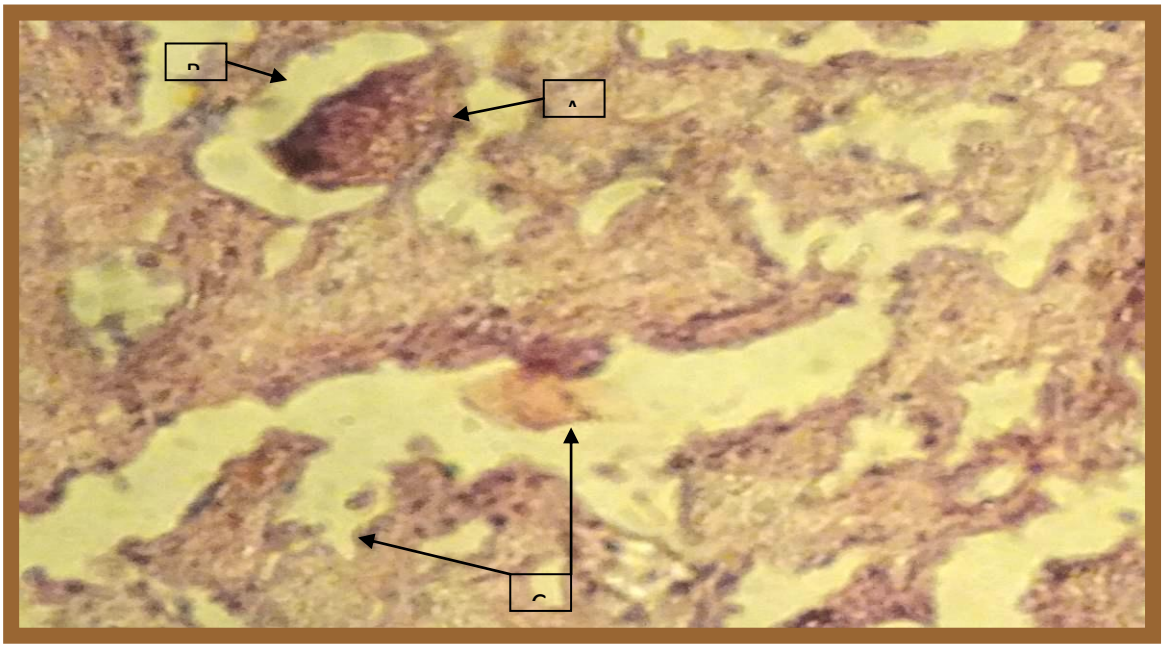

**Figure 2:** the effect of peganum harmala extract on the cortex of kidney at the concentration 150 mg/ kg shows A- shrinkage in glomerulus. B- Widening in Bowman's space. C- Severe damage and hemorrhage in proximal and distal convoluted tubules H & E 40 X.

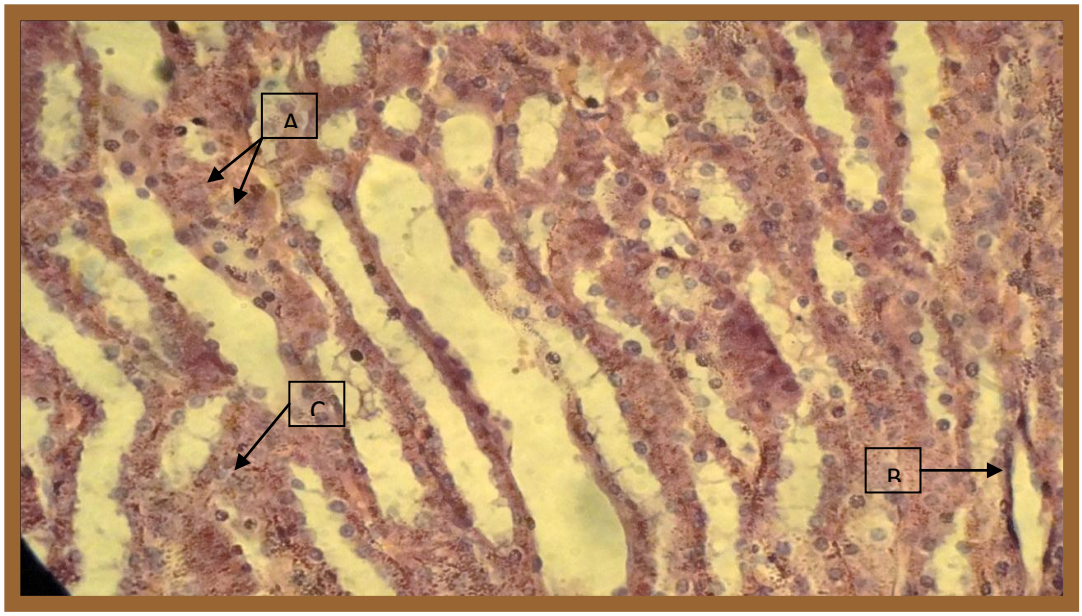


**Figure 3:** the effect of peganum harmala extract on the medulla of kidney at the concentration 100 mg/ kg shows. A- necrosis in some of epithelial cells in ascending loop of henle. B- hypertrophy and widening in loops of henle. C- degeneration in epithelial lining of collecting tubules H & E 40 X.

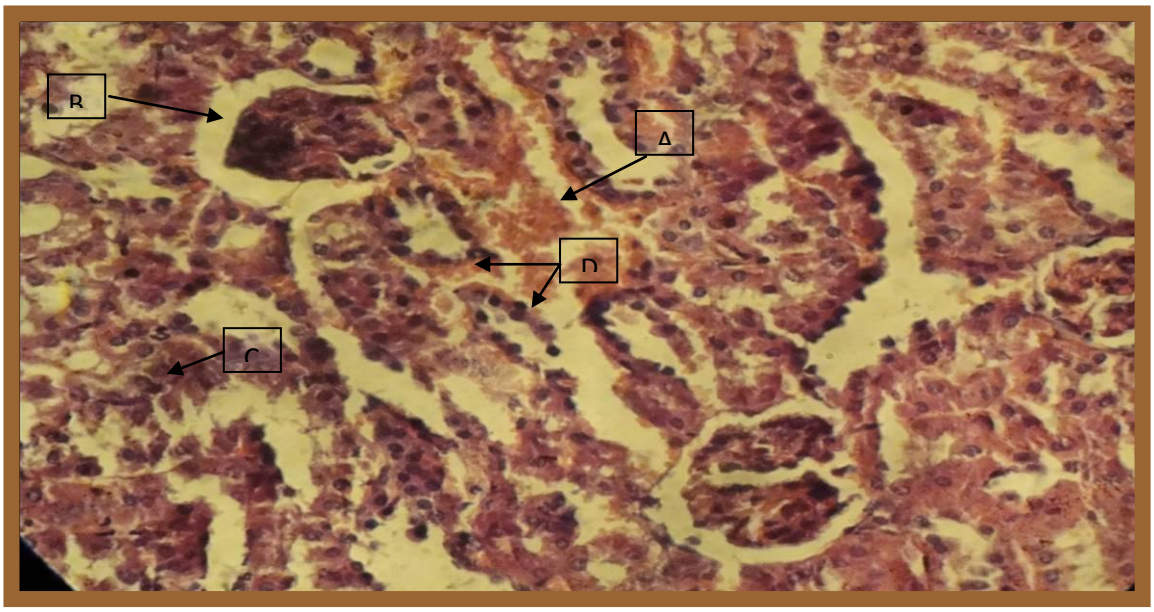


**Figure 4:** the effect of peganum harmala extract on the cortex of kidney at the concentration 100 mg/ kg shows A- hemorrhage in epithelial cells. B-Glomerulonephritis. C- degeneration in epithelial cells. D- necrosis in epithelial cells. H & E 40 X.

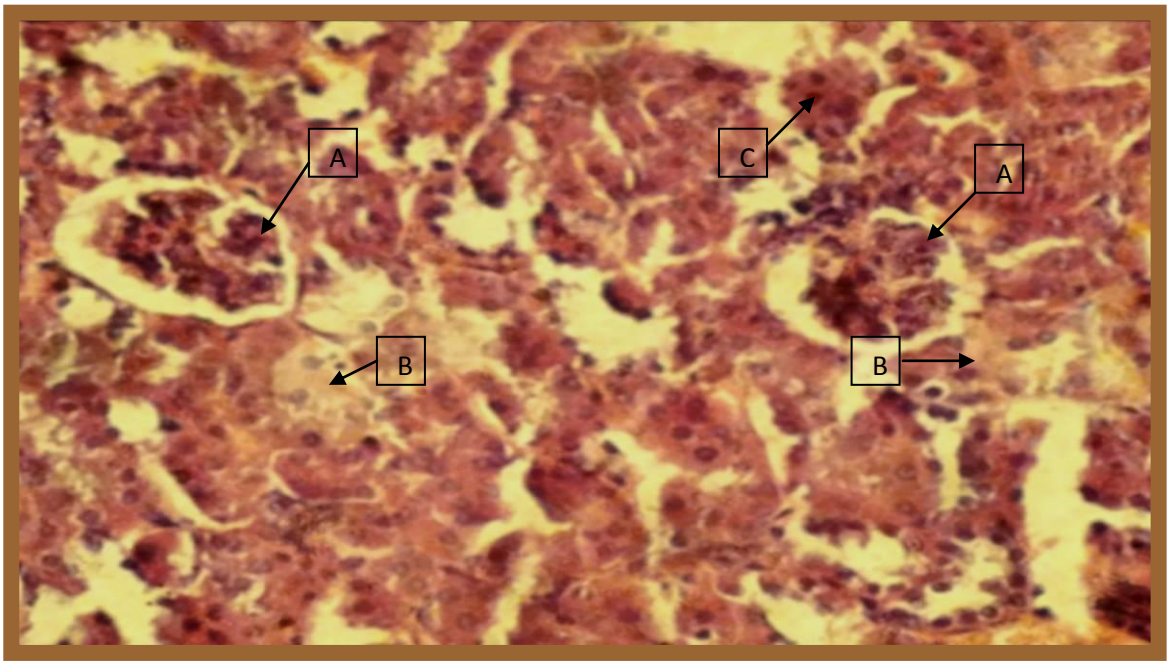


**Figure 5:** The effect of peganum harmala extract on the cortex of kidney at the concentration 75 mg/ kg shows A-Glomerulonephritis B-hemorrhage in the interstitial connective tissue and blood vessels C-necrosis in epithelial cells which lining of proximal and distal convoluted tubules H&E 40x.

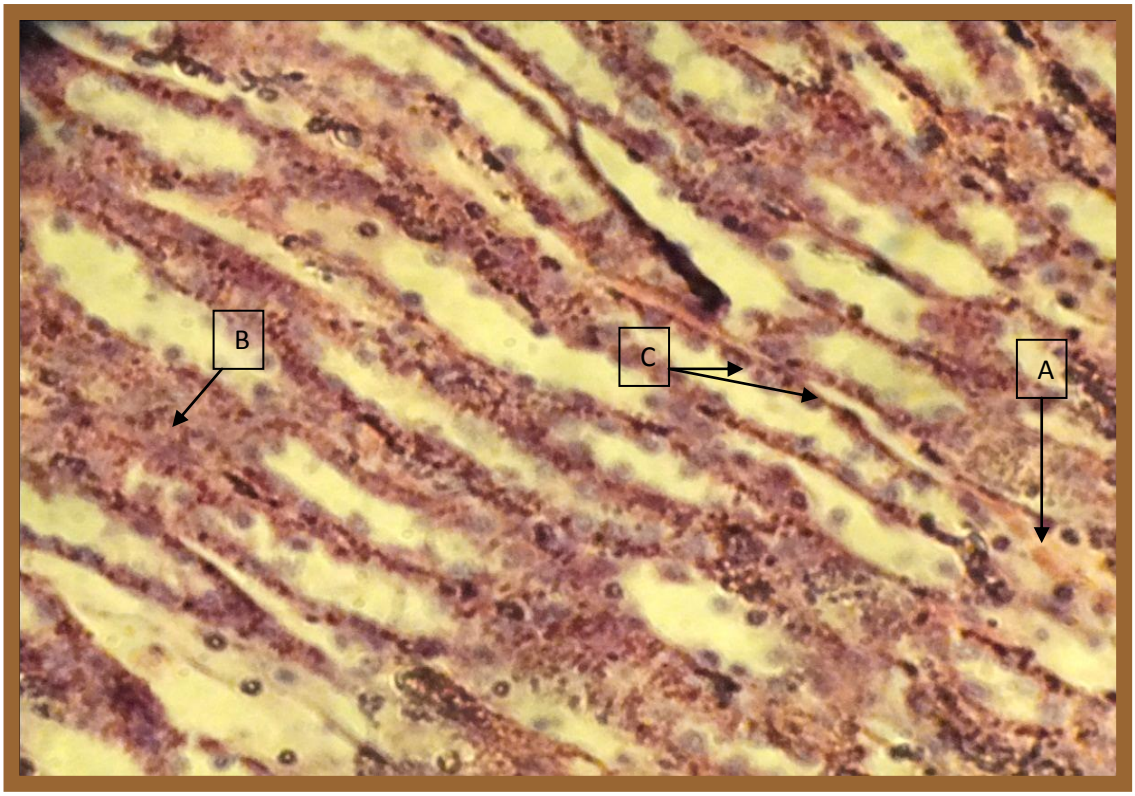


**Figure 6:** the effect of peganum harmala extract on the medulla of kidney at the concentration 75 mg/ kg shows a moderate effect A- hemorrhage in some of epithelial cells B- degeneration C- necrosis H & E 40 X.

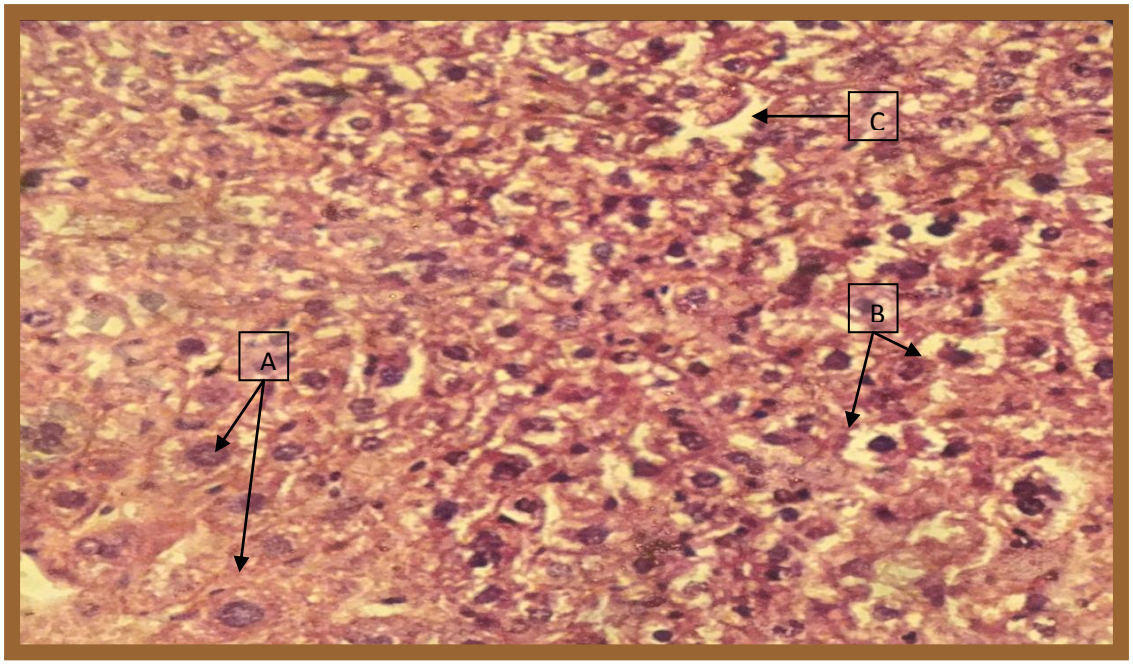


**Figure 7:** the effect of *peganum harmala* extract on the liver tissue at the concentration 150 mg/ kg shows A- pyknotic of hepatic cells nuclei B- vesiculation in the cytoplasm of hepatic cells C- widening in some of hepatic sinusoids H & E 40 X.

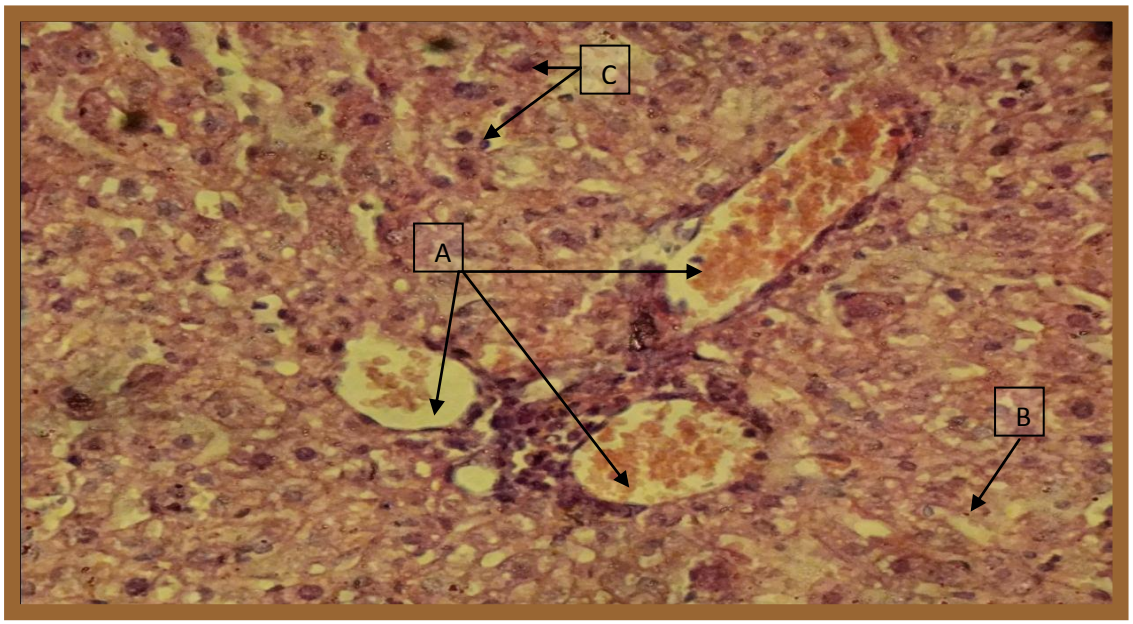


**Figure 8:** The effect of *peganum harmala* extract on the liver tissue at the concentration 150 mg/ kg shows A- congestion of central vein B- hypertrophy of hepatic cells. C. pyknotic of hepatic cells nuclei H & E 40 X.

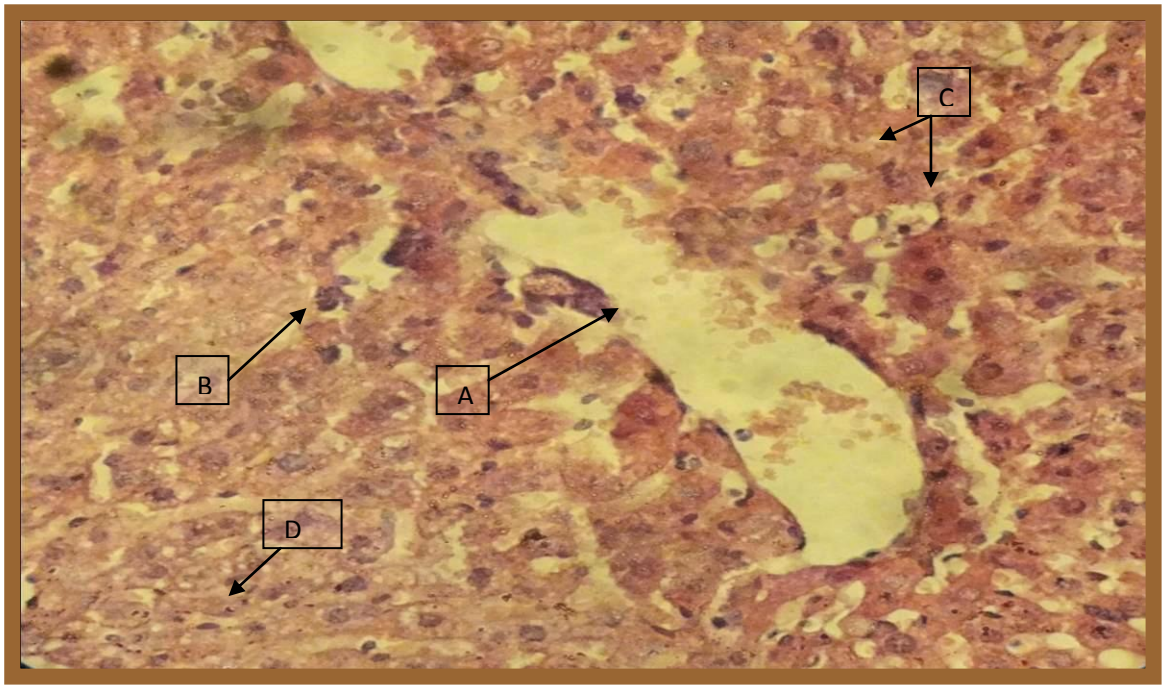


**Figure 9:** The effect of *peganum harmala* extract on the liver tissue at the concentration 150 mg/ kg shows A- destruction in the wall of central vein and hemorrhage B-foci of necrosis in the hepatic cells C- degeneration of hepatic cells D- hypertrophy in some of hepatic cells H & E 40 X.

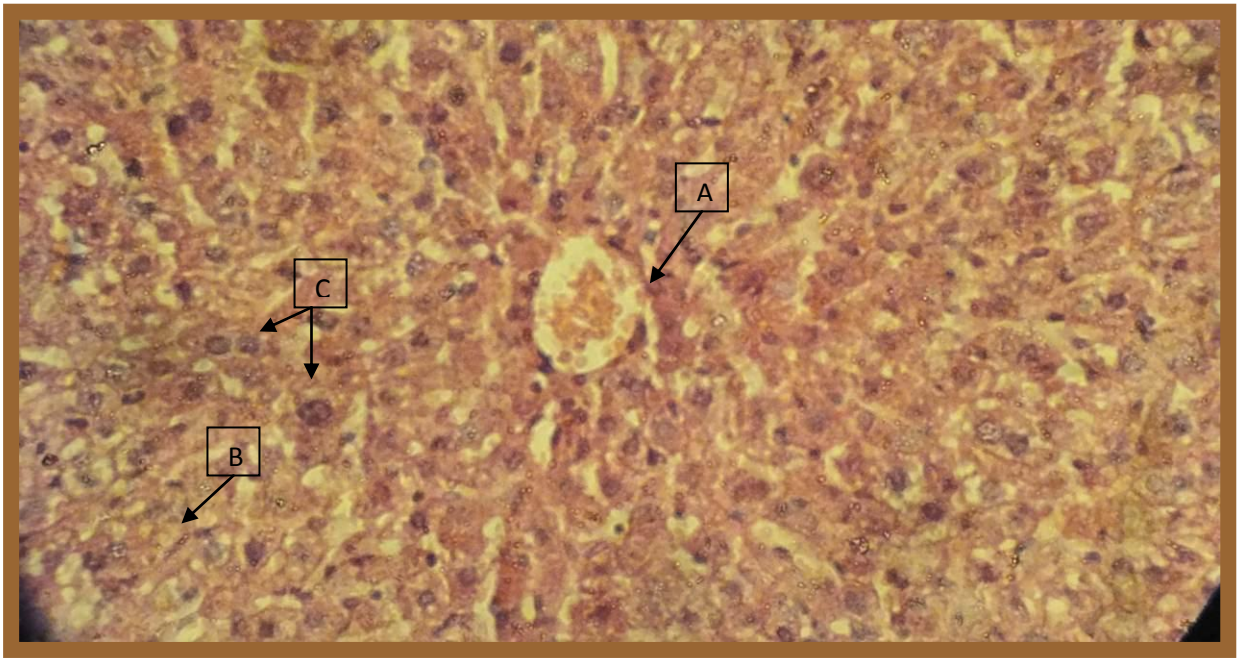


**Figure 10:** The effect of *peganum harmala* extract on the liver tissue at the concentration 150 mg/ kg shows A- congestion in the central vein and hemorrhage B- hypertrophy in some of hepatic cells C- foci of necrosis in the hepatic cells.

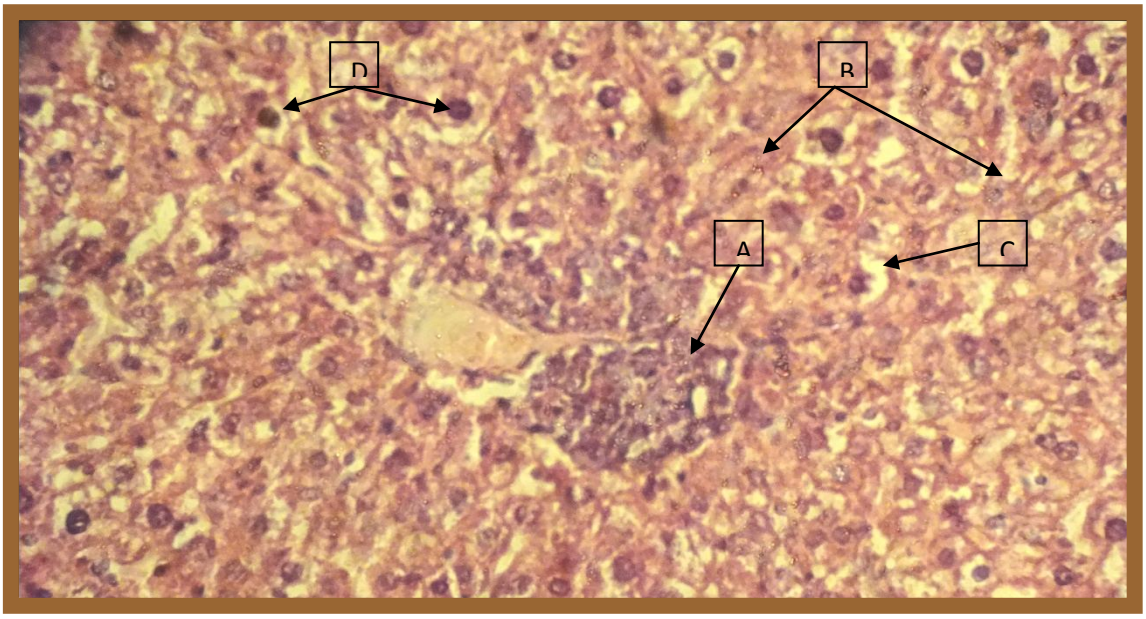


**Figure 11:** The effect of *peganum harmala* extract on the liver tissue at the concentration 100 mg/ kg shows A- mononuclear polymorph infiltration B-fibrosis (cirrhosis) C- widening in some of hepatic sinusoids D- pyknotic and vesiculation of hepatic cells H & E 40 X.

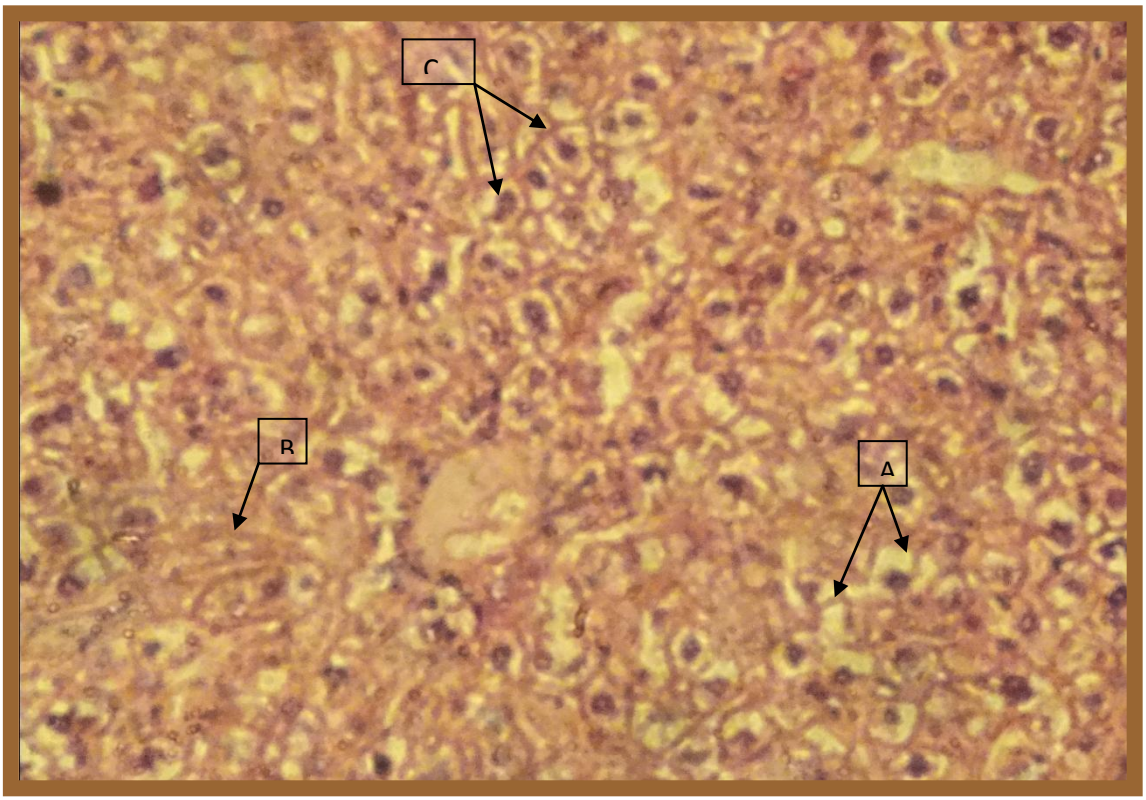


**Figure 12:** The effect of *peganum harmala* extract on the liver tissue at the concentration 100 mg/ kg shows A- vesiculation in cytoplasm of hepatic cells B-fibrosis (proliferation) of reticular fibers C- pyknotic in the nuclei of hepatic cells H & E 40 X.

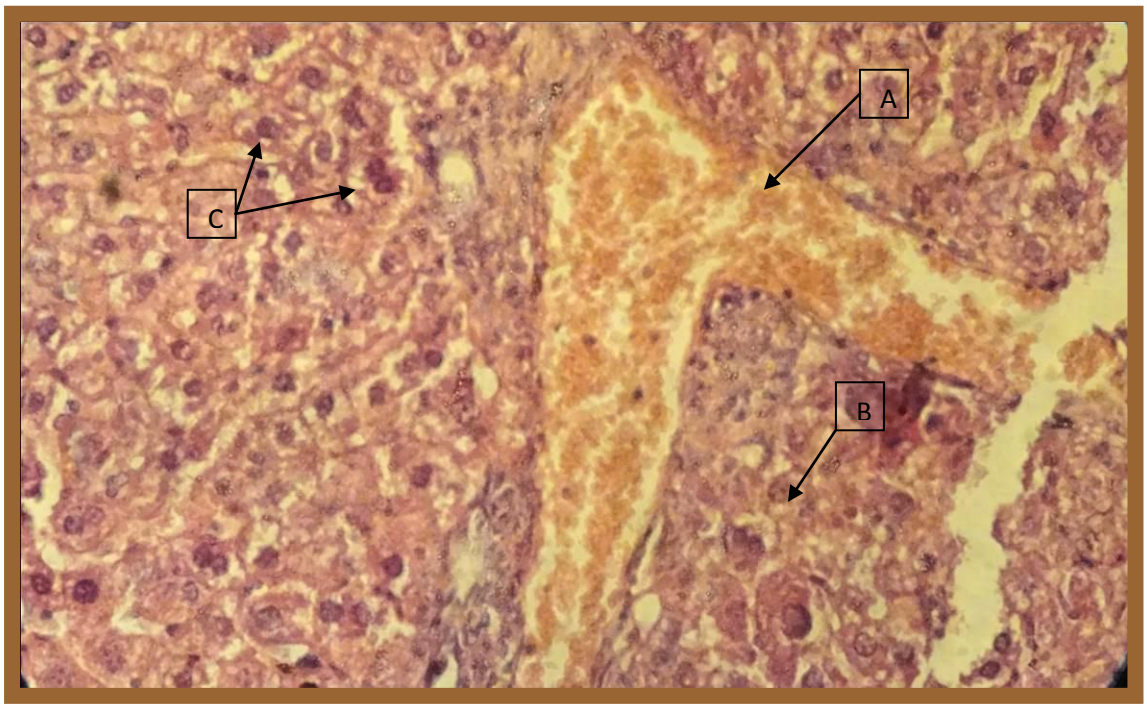


**Figure 13:** The effect of *peganum harmala* extract on the liver tissue at the concentration 100 mg/ kg shows A- congestion and hemorrhage in branch of portal vein B-hypertrophy in hepatic cells C- Pyknotic in some of hepatic cells nuclei H & E 40 X.

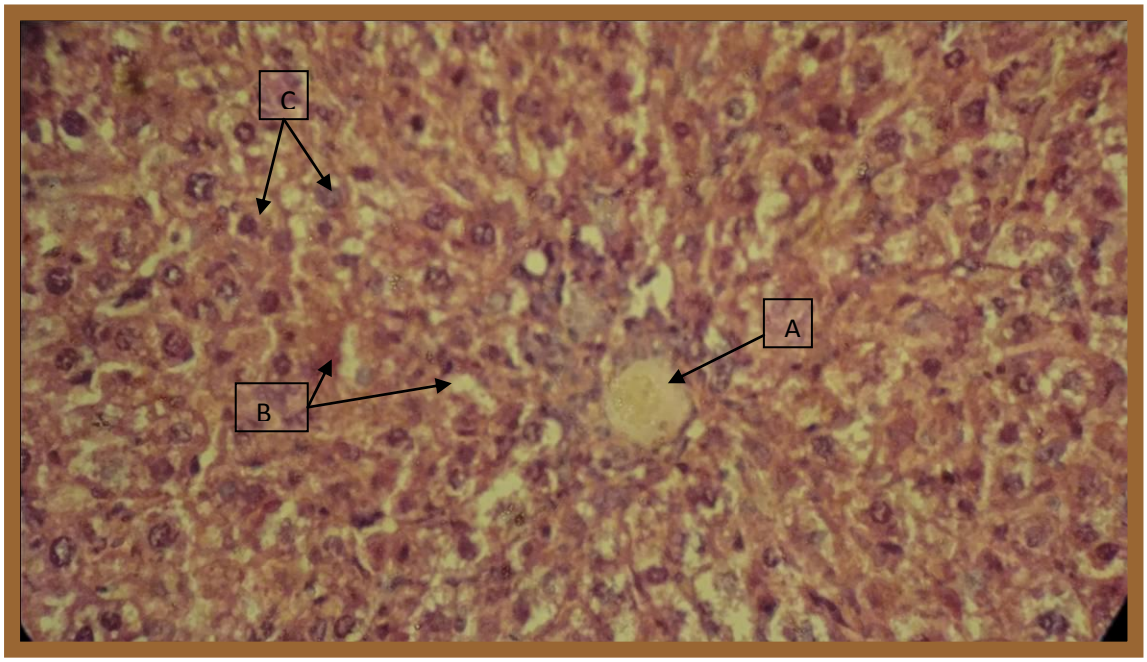


**Figure 14:** The effect of *peganum harmala* extract on the liver tissue at the concentration 75 mg/ kg shows A- destruction in central vein B- vesiculation in cytoplasm of hepatic cells C- pyknotic in of cytoplasmic nuclei of hepatic cells H & E 40 X.

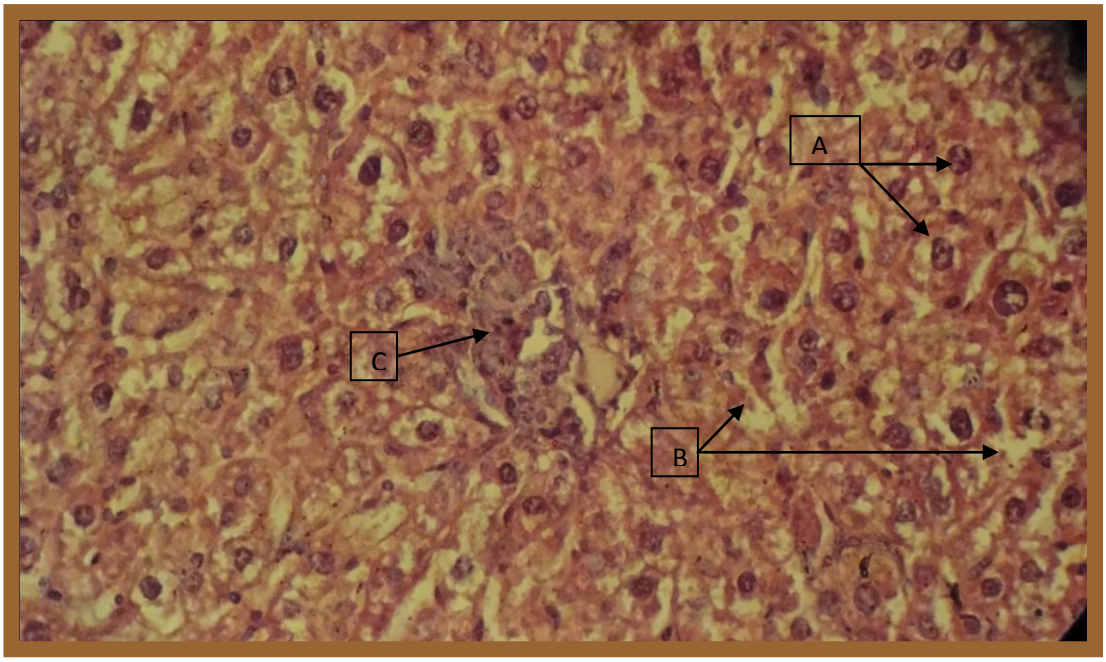


**Figure 15:** The effect of *peganum harmala* extract on the liver tissue at the concentration 75 mg/ kg shows A-pyknotic of cytoplasmic nuclei of hepatic cells B-vesiculation in hepatic cells C- hypertrophy and necrosis in hepatic cells H & E 40 X.

## Discussion

The present study demonstrated dose-related histological changes in the kidney and liver following repeated administration of peganum harmala seed extract. Significant histo-pathological alterations in the kidney and liver occurred in all dose groups. Peganum harmala seed extract induced hemorrhage in the interstitial connective tissue of kidney, degeneration, necrosis in the kidney tubules. In addition, our results revealed severe changes in the liver parenchyma following different doses of alcoholic extract of harmala seeds, which were manifested by hypertrophy of hepatic cells, congestion and hemorrhage in the blood vessels. These histo-pathological observations are in agreement with previous studies.[1, 27]

In chicks fed diets containing (10 %) of peganum harmala leaves for period of two week, the histological changes noticed in the kidney and liver, were degeneration of the epithelial cells of the renal proximal convoluted tubules and mild fatty degeneration in the liver whereas findings of the present study showed, a vesiculation in the cytoplasm of hepatic cells due to fatty liver degeneration. However, other findings such as congestion or hemorrhage and necrosis of the centrilobular hepatic cells were similar to the present study.

Our histo-pathological observations in the kidney and liver are not in agreement with recent study in mice injected s/c with aqueous extract of Iraqi peganum harmala, no apparent toxic effects on the liver and kidney were noted, but treatment resulted in a significant increase in the number of leucocytes (neutrophils, lymphocytes) and macrophages, as demonstrated in this study.

However our observations were revealed histo-pathological changes occurred in the livers and kidneys of mice, these changes represented, fatty degeneration, necrosis, fibrosis, congestion of blood vessels, hemorrhage in the liver structures, from other hand, numerous histological alterations were happened in the cortex and medulla of mice kidneys, these were glomerulonephritis, interstitial hemorrhage, degeneration and necrosis in the kidney tubules have been ranged from moderate to severe signs, these our results ensure that causes signs of intoxication due to injection of harmala extract, the present study was identical with previous

studies conducted on the large animals such as sheep and horse[19] and cattle[17], in the cattle after postmortem examination of animal, no distinctive lesions were observed, rapid rigor mort has been observed, the renal and gastrointestinal system were noticed to be congested and sub- capsular hemorrhage in the liver has been manifested.

The harmala has traditionally been in the public medicine as abortifacient and emmenagogue agents.[28] Human toxicity has been occurred and reported in a patient with over dose of harmala plant seeds who has taken 50 gram of seeds for treatment of amenorrhea.[29]

The signs of harmala over dose comprised of hallucinations and neuro-sensorial syndromes, bradycardia and gastrointestinal disturbances such as nausea and vomiting para- clinical tests showed the function of liver and kidney to be normal and the patient had a normal hematological picture, she was discharged from hospital few hours later after the signs of intoxication had disappeared. A case report was recorded by 3, they mentioned a 35 year old male patient, he took around 150 gram of peganum harmala seeds, after that vomited blood and gastrointestinal distress, endoscopy showed a 2.5 cm gastric ulcer at location of internal region.

The symptoms of peganum harmala toxicity experienced in the patients were similar to what had been reported for animal (30), and over dose of peganum harmala led to the damage and ulceration of the organs tissues such as liver, kidney especially in the epithelial cells that lined the kidney tubules and the blood vessels, and hepatic cells in hepatic cords, these our observations came to ensure the previous reports about peganum harmala intoxication.[18, 30]

In conclusion, these results, suggest that peganum harmala exerted a potent toxic effect on tissues of liver and kidney at dose of 100 and above. In view of its toxicity, harmaline may not be used in food of human and other animals.

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