

Histological Study of the Preventive and Therapeutic Role of The Aqueous Extract of Ziziphus Jujba Fruits Against the Effects Induced by Dexamethasone and Risedronate Sodium in Liver of Male Rats.

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Abstract: The present study was designed to examine the preventive and therapeutic effects of the hot aqueous extract of jujube fruit on liver histological changes of albino male rats administered the hot aqueous extract of jujube fruit, dexamethasone and risedronate sodium. The experiment was carried out inside the animal house of the College of Science, University of Kufa, starting from the start of July 2024 till the end of April 2025. This experiment used 30 male rats (9-11) weeks old with a weight of (200-250) grams. They were divided into 6 groups (5 rats per group) Experimental Details: The experiment was conducted over a period of 30-days. The first cohort served as the control cohort and received no treatment except for food and water. A second group received a dose of the anti-inflammatory dexamethasone of 0.05 mg/kg of body weight. The 3rd group received risedronate sodium (5 mg/kg) daily by way of oral administration. The fourth group was administered a daily aqueous extract of jujube plant as 3000 mg/kg, The fifth group was dosed with 0.05 mg/kg of body weight dexamethasone and subsequently a daily oral dose of risedronate sodium as 5 mg/kg. The sixth group was administered jujube plant aqueous extract at a concentration of 3000 mg/kg orally daily and after one hour, 0.05 mg/kg oral dexamethasone and considered as preventive group, the seventh group received orally 0.05 mg/kg daily dexamethasone one hour after, was dosed with 3000 mg/kg of the aqueous extract of the jujube plant and was assigned to treatment group. The livers were harvested post-mortem for histological analyses In the current study, the results of the histological examination of the liver of male rats in the control group proved that the tissue composition of the liver was normal and no pathological changes were observed in it, while the histological sections of the liver of rats treated with dexamethasone at a dose of (0.05) mg/kg of body weight and those treated with risedronate sodium at a dose of (5) mg/kg of body weight and group treated with dexamethasone at a dose of (0.05) mg/kg of body weight + risedronate sodium at a dose of (5) mg/kg of body weight for (30) days showed histopathological effects were represented by calcification and necrosis of hepatic cells, dilatation of sinusoids, infiltration of inflammatory cells, destruction of the hepatic vein wall, atrophy of the hepatic vein and separation of the hepatic vein from its base compared to the control group against which showed histopathological composition of the liver wild rats that was normal or close to normal. In the group that received dexamethasone with risedronate sodium for 30 days (dexamethasone 0.05 mg/kg + risedronate sodium 5 mg/kg) and the group treated similarly with hot aqueous extract of jujube plant (3000 mg/kg) + dexamethasone (0.05 mg/kg) for 30 days; The group treated with dexamethasone + hot aqueous extract of jujube plant (3000 mg/kg) was only observed detachment of lining the hepatic vein compared to the control group for 30 days (Fig. 2). In conclusion: We think calcareous extract of the jujube herb can workaround to prevent and cure adverse histopathological effects on liver tissue induced by administration of dexamethasone and risedronate sodium.

Keywords: dexamethazone, risedronate sodium, liver, Zizphus jujuba.

INTRODUCTION

The jujube plant (*Ziziphus jujba*) is a member of the Rhamnaceae family. Chinese red dates are the fifth most important nutritive fruit, and there is a belief in China that regularly consuming Chinese red dates can enhance mental cognition and improve sleep (Chen et al., 2014). Previous studies reported calming and hepatoprotective properties of jujube fruits, immunomodulatory and antioxidant activities and anti-inflammatory effects (Wojdyło et al., 2016). This could be due to the rich chemical composition of jujube, such as vitamin C,

sugars, amino acids, flavonoids, saponins, phenolic compounds, alkaloids, proteins, lipids, calcium, potassium, phosphates, iron, triterpenoid acids and nucleosides (Elaloui et al., 2016). As one of the most abundant constituents of jujube fruits, polysaccharides are considered the predominant bioactive component (Ji et al., 2019). They possess a variety of immunomodulatory (Cao et al., 2016), antioxidant (Alqarni et al., 2020), antitumor (Bernaola et al., 2021), hepatoprotective (Zou et al., 2018; Li et al., 2021), hypoglycemic (Zhu et al., 2019; Real et al., 2021), and

gastrointestinal protective effects (Gao et al., 2021). Also the major protective activity of jujube fruit are antioxidant, anti-wound, anti-burn, anti-allergic, and anti-asthma, which is due to flavonoids, saponins, and steroids of jujube (Pourahmadi et al., 2023). Jujube is well-distributed in tropical and subtropical areas in Asia and European nations and is largely cultivated in China (Ji et al., 2020). There are 46 species of polysaccharides successfully extracted from jujube fruits, several of which possess biochemical activities including such therapeutic functions as antioxidant, anti-fatigue, anti-inflammatory, and liver-protective activities (Park et al. They also include monosaccharides, for instance, uronic acid, galactose, xylose, arabinose, and galacturonic acid (Ji et al., 2019). But some studies report that there are no harmful reactions to the consumption of jujube fruits due to their ability to counter with oxidative stress (Sabzghabae et al., 2013).

Dexamethasone is a manmade glucocorticoid commonly prescribed for a number of disorders including inflammatory, immune, and rheumatic conditions (Coutinho and Chapman, 2011). Although dexamethasone is extremely beneficial for therapy, long-term treatment with dexamethasone results in adverse effects such as osteoporosis. Other studies have found that osteoblast activity decreased, and osteoblast activity increased. Although the activity of osteoblasts is reduced by glucocorticosteroids, and in particular dexamethasone (Hsu and Nanes, 2017), the chronic treatment with dexamethasone or high doses induces serious adverse effects including hyperglycemia, central obesity, myopathy, hypertension, osteoporosis and impaired immune function (Clark and Belvisi, 2012). Due to both local and systemic effects, the mechanisms underlying dexamethasone-induced osteoporosis remain elusive. Hepatitis and hepatocellular injury may occur following high doses of dexamethasone (nih.gov, 2021). Corticosteroids act to reduce vasodilation and capillary permeability in the short-term and have delayed-effect on the changes till the binding with the GC receptor and CNT (change in gene expression) occurs, leading to a multiplative and prolonged effects lasting from hours to days (Yasir and Sonthalia, 2023). Corticosteroids have an anti-inflammatory effect in lower doses, and at higher doses, they exert immunosuppressive, salt-retaining, and hypokalemic actions (Yasir and Sonthalia, 2023).

Risedronate sodium is in the bisphosphonates family of medications, which is widely used in osteoporosis treatment and its associated fracture prevention. By influencing osteoclasts, it inhibits the osteoclastic activity from the required formation of ovarian hormones, which is therefore associated with lower levels of bone resorption, leading to a subsequent indirect enhancement of bone mineral density (Velde et al. 2017). The most developed of the nitrogen-containing class is the third-generation pyridinyl, risedronate sodium. The cytoprotective effects of alendronate on osteoclasts are primarily mediated through the inhibition

of farnesyl pyrophosphate synthase (FPPS), an enzyme that plays an essential role in promoting osteoclast adhesion to bone. This leads to the disassociation of osteoclasts from the surface of the bone which inhibits bone resorption (Ebetino et al., 2011). Read this information carefully before you take risedronate. Serious side effects: Stop taking risedronate and contact your doctor immediately if you experience heartburn, difficulty, or pain on swallowing risedronate. These could be signs of an ulcer in the esophagus. Also, some studies also reported an increased risk of esophageal cancer with Risedronate use (Sun et al., 2013).

MATERIALS AND METHODS

Animals:

The experimental (30) white male rats of *Rattus rattus* species were divided into (10) rats, aged from (9-11) weeks and weight between (200-250) grams. The animals were sourced from the animal house of the Department of Life Sciences; College of Science; University of Kufa. The creatures were put into special plastic cages and were covered with metal covers made for such cases Wooden shavings were strewn over the cages' floor. Their cages were always clean, and sterilized and the shavings were constantly changed out. They also maintained cleanliness of the irrigation bottles and of the housing room. All the experimental animals were housed in similar laboratory conditions of (25) degrees Celsius, acceptable ventilation and duration of light (12 h light: 12 h dark). During the experiment period, the experimental animals were supplied for drinking with rat water and food. The animals were allowed to acclimate to condition for 2 weeks prior to the experiments and checked free from disease.

Deisgen of the experiment.

Thirty animals were allocated in 6 groups with (5) animals in each group The groups are treated in the following manner; The first group (control group) received orally water and food. The other group were given dexamethasone at a concentration of 0.05 mg/kg. The third group received risedronate sodium at a dose of 5 mg/kg of body weight orally once a day. The fourth group was treated with aqueous extract of jujube plant in the daily oral dose of 3000 mg/kg. The fifth group received treatment with dexamethasone at 0.05 mg/kg body weight daily and then received daily oral risedronate sodium at a dose of 5 mg/kg. Aqueous extract of jujube plant: Sixth group was given daily 3000 mg/kg oral aqueous extract of jujube plant, after an hour were given 0.05 mg/kg oral dexamethasone and was known as preventive group, Seventh group was treated with 0.05 mg/kg dexamethasone then were given 3000 mg/kg oral aqueous extract of the jujube plant (an hour later) and was assigned to the treatment group. Animals in all groups received the treatment for duration of 30 days.

Preparing a Hot Aqueous Extract of Jujube:

Dried jujube fruits without the seeds were blended in an electric blender into powder. They had been sealed in

plastic bags to keep them dry and uncontaminated until needed. In a glass beaker, 100 g of dry powder from jujube fruit powder (ground to pass through a No. 25 mesh sieve) is dispersed in 1 L of hot distilled water.

Clean the mixture and incubate it at room temperature on a magnetic stereo device for 24 hours. Then it is sampled, put into boxes and into a centrifuge with 4500 rpm for 30 minutes. Filter through filter paper. Subsequently the filtrate is taken and poured into large glass dishes to dry fast in an electric oven. The powder is then position in clean containers and kept in the refrigerator until ready to use (Irshad et al. 2020).

Dexamethasone dose:

This study used dexamethasone, which was obtained in tablet form at a dose of 0.5 mg daily from pharmacies in Najaf Governorate. This drug is used to induce osteoporosis. From this dose for humans, the required dose was prepared for this study, adapted to the weights of male rats.

Risedronate sodium dose:

This study used Risedronate sodium which was obtained in tablet form at a dose of 5 mg daily from pharmacies in Najaf Governorate (produced in Canada by PMS), and is used to treat osteoporosis. The dose required for this study was then prepared to suit the weights of male rats.

Animal dissection

Male rats were given daily doses for 30 days after the end of the experiment. The animals were presented for slaughter under chloroform anesthesia. They were placed on a dissection tray secured with dissection staples, and the peritoneal cavity was opened and livers were extracted after removing the surrounding fatty and connective tissue. The livers were placed in a 10% formalin solution for histological preparation.

Preparation, examination and imaging of liver tissue sections.

Liver histological sections of male rats were prepared using the steps for preparing liver histological sections (Suvana *et al.*, 2018), then examined using an Olympus compound light microscope at 40x power and then liver histological images were photographed using a digital camera attached to the examination microscope.

RESULTS AND DISCUSSION

Histological study of the control group's livers in the present study showed that the liver tissue composition was normal, with no pathological change seen in the male rats in (Figure 1). The hepatic sections of rats treated with dexamethasone for 30 days (Figs. t in this study showed significant histopathological alterations being calcification and necrosis of hepatic cells, dilation of sinusoids, inflammation of inflammatory tissue, rupture of the wall of the hepatic vein, atrophy of the hepatic vein and separation of the hepatic vein from it's base (Figs.(1) and (2) compare to the control group and these histopathological changes induced by dexamethasone were similar to the study of Safaei *et al.*, (2012) who showed that dexamethasone leads to necrosis, infiltration of inflamed tissue and, severe erosion of hepatocyte. Dexamethasone is known to decrease hepatocyte proliferative activity and therefore, described regenerative capacity (Mikiewicz *et al.*, 2017). Kimura *et al.*, (2011) found that at high doses, Dexamethasone inhibited the expression of hepatocyte growth factor via reduced expression in mesenchymal stem cell proliferation. Hepatocyte-related morphological changes were accompanied by the dilatation of the nasal sinus and central vein. The immunosuppressive, and anti-inflammatory glucocorticoid, dexamethasone, trigger free radicals that could contribute to oxidative stress, skeletal muscle atrophy and insulin resistance (Zanchi *et al.*, 2012). This study suggests that excess liver damage is caused by dexamethasone as a result of overproduction of free radicals and oxidative stress, as shown by Hasona and Morsi (2018) and Subramaniam *et al.* The liver is a vital organ that has a significant role in the metabolism and detoxification of many exogenous and endogenous substances and if there is any damage—due to either a disease or an unfavorable agent (exogenous or endogenous)—to liver, it will affect many other functions of the body (Montenegro *et al.* 2015). These functions become distorted leading to liver damage. That's metabolic, and dexamethasone treatment heart connected liver injury-inductor liver function enzymes are aggrandized.

While the hepatic vein wall destruction, hepatic vein atrophy and separation from basis hepatic vein, Histological has pathological changes of the them Histological structure of the livers As for hepatic tissue of rats treated with dexamethasone at a dose of 0.05 (/Kg body weight) + risedronate sodium at concentrations of 5 (/Kg/day) shown in Fhgure (7) compared with the control group were shown in Histological sections of group treated With risedronate sodium at 5 mg/kg (30days) (4,5)they histopathological effects were apparent manifested by calcified & necrosed hepatic cells, dilation of sinusoids, mixed type of inflammatory cellular infiltration, destruction of vein wall & vein obliteration as for the risedronate sodium causes mild to moderate hepatitis, which generally resolves shortly after its discontinuation. The adverse event profile specifically attributed to risedronate sodium on the gastrointestinal tract were dyspepsia, abdominal pain, gastritis, and esophagitis (Taggart *et al.*, 2002). It also leads to these symptoms: headache, musculoskeletal pain, and glossitis. Patients treated with risedronate sodium may have experienced mild, transient decreases in serum calcium and phosphate levels and hepatocellular lysis test abnormalities. Annual Academy of Orthopaedic Surgeons85:723-731, 1994:**Some have associated clinically apparent acute liver injury with mild jaundice with risedronate sodium use. Patients usually suffered from discomfort in the abdomen and nausea and sometimes later from jaundice. Characteristically, serum enzymes were elevated in a hepatocellular pattern, and liver histology showed acute toxic hepatitis. Most reported cases were mild to

moderate in severity, and most published cases resolved on discontinuation of the drug but full recovery was not always rapid (Zimmerman, 2018).

Histological slides of the livers of rats treated the hot aqueous extract of jujube at a concentration of 3000 mg/kg as in Figure (6) and treated with both the hot aqueous extract of jujube at a concentration of 3000 mg/kg + dexamethasone at a concentration of 0.05 mg/kg for 30 days, as in Figure (8), and the group treated with dexamethasone at a concentration of 0.05 mg/kg + hot aqueous extract of jujube at a concentration of 3000 mg/kg for 30 days as in Figure (9), compared to the control group were characterized by detachment of the cells lining the hepatic vein compared to the control group for the same treatment period. The variety of nutrients and active substances, including polyphenols, polysaccharides, nucleotides, ascorbic acid and the triterpenoid acids in a jujube fruit, confirmed the extent of a preventive and therapeutic role of the plant extract. The active constituents of jujube fruits exhibit a multitude of biological effects, including anticancer, antioxidant and anti-inflammatory activities, hepatoprotective, neuroprotective and antiviral properties and immune function enhancement, among others (Ji., 2017). A study by Liu et al. The extract may also contain elements that assist the liver in converting and eliminating toxins to reduce the toxic load on this vital organ (2016). The principle detoxification processes performed by the liver is a multi-step enzymatic process that renders toxic substances water soluble and readily excrete-able from the body. The extract is a rich source of antioxidants that are capable of quenching free radicals and protecting liver cells from oxidative damage (Zhang et al., (2021) as oxidative stress due to an imbalance between free radicals and functioning antioxidants is a major process in liver injury and contributes to the development and progression of various liver disorders. JuJube fruit extract may have the potential to ameliorate oxidative stress-related risk factors affecting the liver. In this regard, Mojgan et., (2018) concluded that Jujube fruit extract has a positive effect to relieve alcoholic liver disease and Zhang and Mao-dong (2006) also reported that jujube fruit could reduce a chemical induced liver injury.

Figure(1) A cross section of liver tissue from the control group for 30 days. (A) A central vein (B) A hepatic artery (C) A hepatic portal vein (Hematoxylin-Eosin 400x).

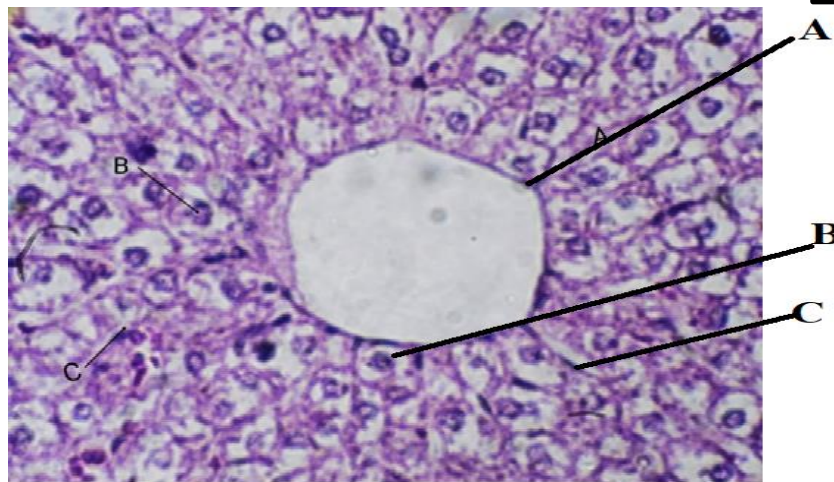


Figure (2) A transverse histological section of the liver of a male rat from the group treated with dexamethasone at a concentration of 0.05 mg/kg for 30 days. It shows: (A) thickened hepatic vein wall (B) Degeneration of hepatocytes (C) Dilation of sinusoids and infiltration of inflammatory cells (Hematoxylin and Eosin stain, 40x magnification).

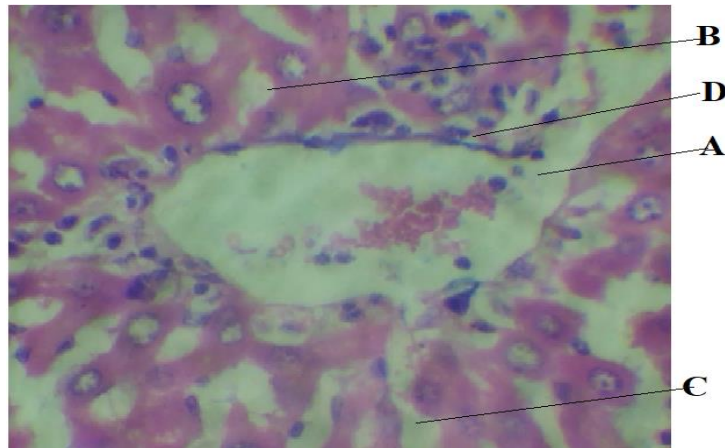


Figure (3) A transverse histological section of the liver of a male rat from the group treated with the aqueous extract of Ziziphus Jujuba fruits at a concentration of 0.05 mg/kg for 30 days. It shows: (A) separation of the hepatic vein wall (B) degeneration of hepatocytes (C) dilation of sinusoids and infiltration of inflammatory cells (Hematoxylin and Eosin stain, 40x magnification).

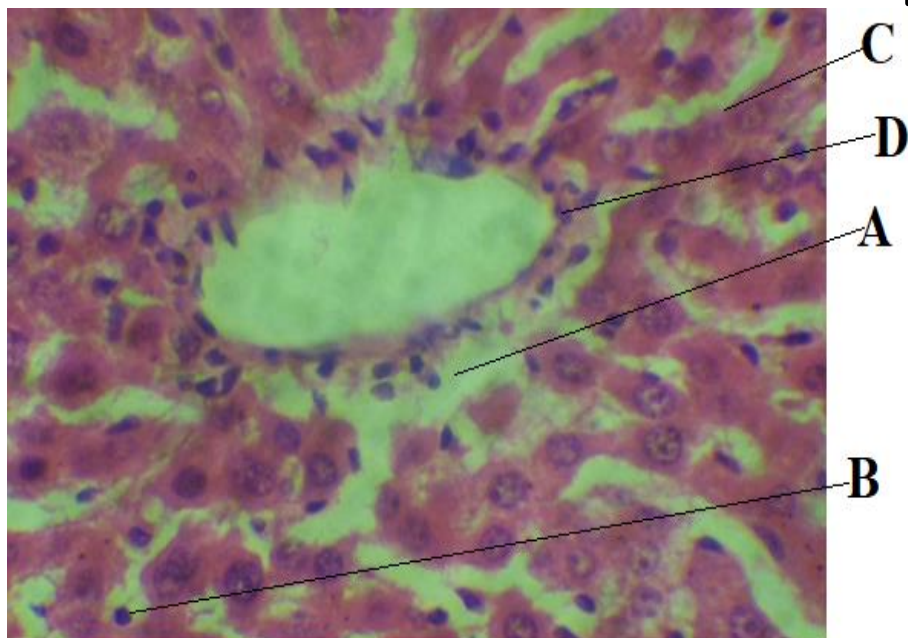


Figure (4) A transverse histo liver of a male rat from the risedronate sodium at a conc for 30 days. It shows: (A) Ne (B) Dilation of sinusoids inflammatory cells (D) Necr (Hematoxylin-Eosin 400x).

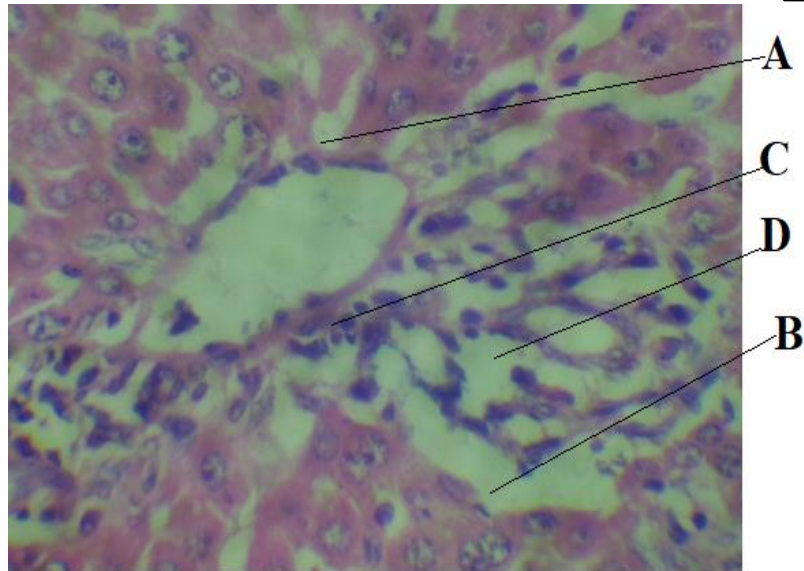


Figure (5) A transverse histo liver of a male rat from the mg/kg sodium risedronate for Congestion into the hepatic hepatic cells (C) Dilation Infiltration of hepatic cells 400x).

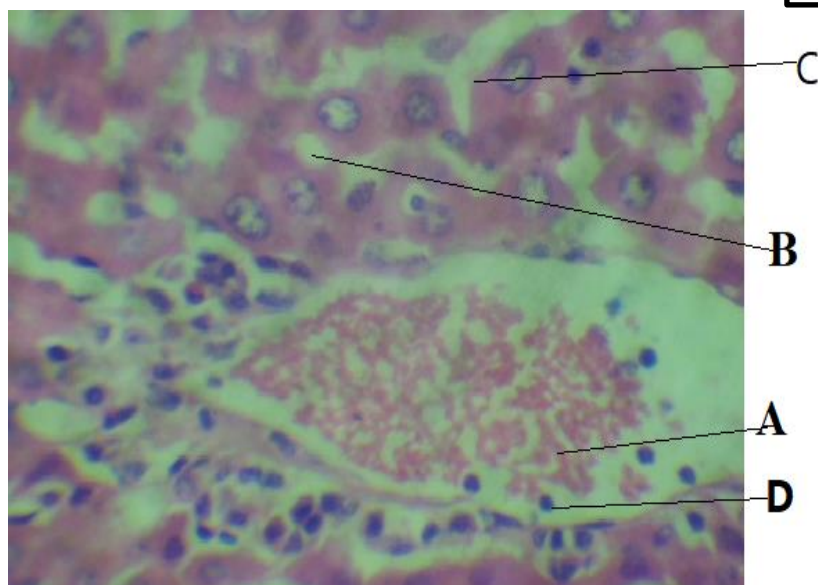


Figure (6) A transverse tissue section of the liver of a male rat from the group treated with the aqueous extract of jujube fruit at a dose of 2000 mg/kg for 30 days. It shows: (A) Central vein, (B) Hepatocytes, (C) Glomeruli (Hematoxylin-Eosin 400x).

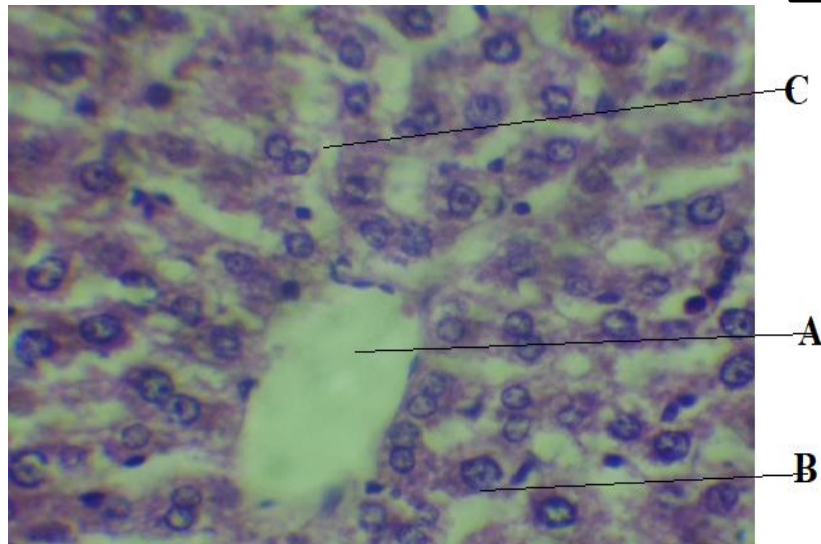


Figure (7) A transverse histological section of the liver of a male rat from the group treated with dexamethasone at a concentration of 1 mg/kg and sodium risedronate at a concentration of 10 mg/kg for 30 days. It shows: (A) Central vein, (B) Necrosis of hepatocytes, (C) Infiltration of inflammatory cells, (D) Infiltration of sinusoids (Hematoxylin-Eosin 400x).

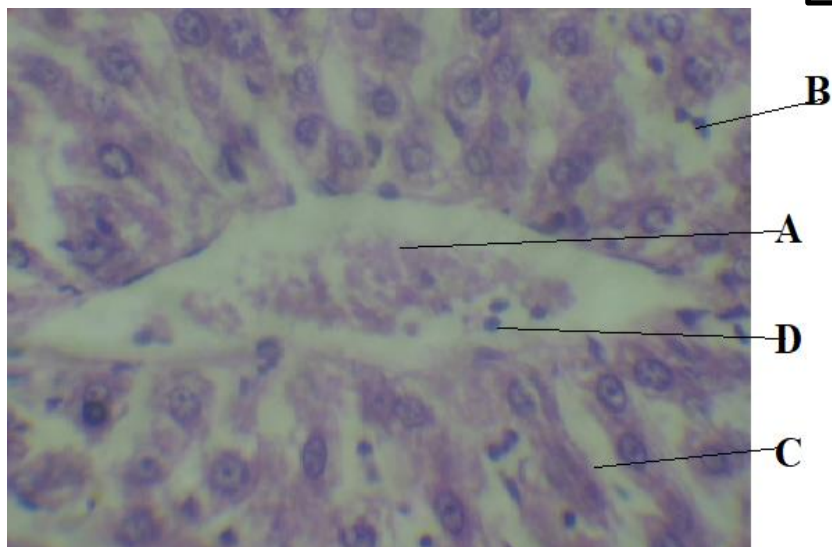


Figure (8) A transverse histological section of the liver of a male rat from the group treated with the hot aqueous extract of jujube fruit at a concentration of 3000 mg/l + dexamethasone at a concentration of 30 days. It shows: (A) Hepatocellular necrosis of hepatocytes (Hematoxylin-Eosin 400x).

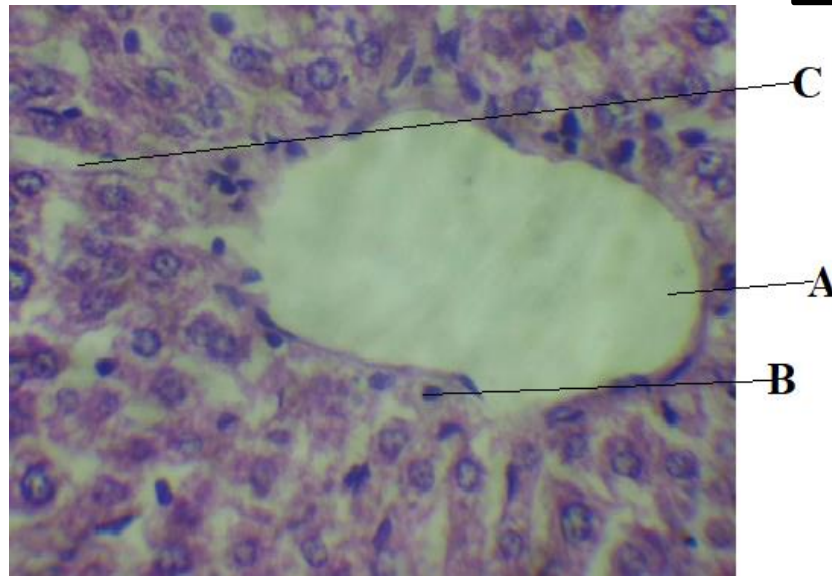
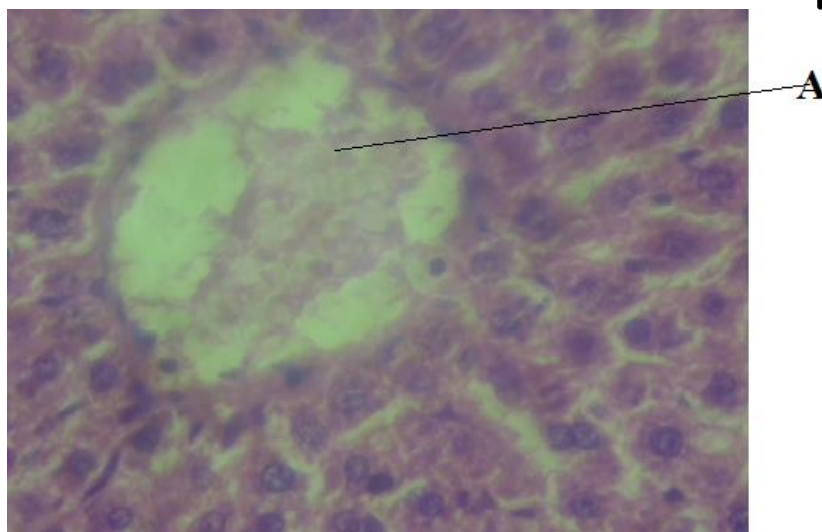


Figure (9) A transverse histological section of the liver of a male rat from the group treated with dexamethasone + 3000 mg/l jujube fruit for 30 days. It shows: (A) Hepatocellular necrosis of the central vein, (B) Hepatocellular necrosis of the central vein (Hematoxylin-Eosin 400x).



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