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Comparative Protective Effect between Vitamin-E and Royal Jelly on the Liver Injury of Adult Male Albino Rats Induced by Cisplatin (Histological and Ultrastructural Study)

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ABSTRACT
Background: Cisplatin (CP) is an alkylating agent with antitumor properties. It has a wide range of adverse effects including hepatotoxicity. **Objective:** Evaluating the effectiveness of CPon the rat's liver architecture as well as the comparative protective role of vitamin E and Royal Jelly (RJ).
Material and Methods: Two sets of forty adult male albino rats with average body weights of 200–250 g each were created at random. Thirty rats were provided as the treated group (group2) divided into three equal subgroups (a, b and c), and ten rats were served as the control group (group1). Ten rats were in subgroup (a), and they received CP treatment. Ten rats from subgroup (b) were administered CP and vitamin E. Ten rats from subgroup (c) were administered CP and RJ. The rat's liver was removed and histologically prepared for evaluation under the light and electron microscopes.
Results: Administration of CP to rats produced harmful hepatotoxic effect, these effects relatively improved by administration of vitamin E and RJ, but RJ was observed that had a more potent protective effect on the rat's liver than vitamin E. **Conclusion:** CP induced hepatotoxicity in animal model while, RJ has a great protective effect against the liver toxicity. Furthermore, vitamin E plays a healing role in the liver damage caused by CP.
Keywords: Cisplatin – Vitamin E - Royal jelly – Hepatotoxicity - Albino rat.

INTRODUCTION
The liver is a key organ, since it is essential for the detoxification and metabolism of most medicines and poisons [(1)]. Alkylating drugs are used in chemotherapy to inhibit the proliferation of cancer cells; however, they do not differentiate between normal and malignant cells[(2)]. CP is an effective alkylating and antineoplastic agent that used in solid tumors treatment[(3)]. Although CP has strong anticancer properties, its practical application is followed by cytotoxic side effects that reduce its effectiveness[(4)]. However, hepatotoxicity is significantly related to CP injection [(5)], as shown by changes in molecular, biochemical, and histological markers[(6)].

In animals administration of vitamin E can protect against many drugs, chemicals and metals through initiation of free radicals formation[(7)].

RJ is a milky food produced by bee worker, it has immune modulator properties in rat and mice models though its compositing of proteins, vitamins, free fatty acids and vital minerals beside its bacteriostatic activity[(8)].

Free radicals are produced from the hepatotoxicity that alkylating drugs cause by acting cytotoxically on cancer cells [(9)].So, the study was aimed to compare the potential role of vitamin E and RJ on the liver induced toxicity byCP.

MATERIALANDMETHODS
Type of study: Experimental study.
Experimental Animals:

Forty male albino rats, ranged from 200 to 250 gm were used in this study obtained from the breeding unit of Helwan farm of experimental animals, VACSERA, Egypt. They were housed in a room temperature at 25 ± 2°C and light-controlled room (12-h light/dark cycle) with free access to standard diet pellets and tap water. Rats were left for one week to acclimatize before starting the experiment. All the experimental procedures conform to the principles laid down according to the Guide for the Care and Use of Laboratory Animals.

Rats randomly divided and assigned into two experimental groups; the negative control group have (10) rats and the treated group, which was separated into three equal subgroups (a, b and c), each subgroup has the same number (10 rats).

Chemicals:

- **Cisplatine:** was obtained from a pharmacy in the form of solution 50 mg/50ml. The drug obtained to Egypt from Mylan S.A.S. - 117Allee des Parcs 69800 Saint-Priest – France.
- **Vitamin E:** It was obtained from Pharco Pharmaceuticals, Cairo, Egypt, in the form of soft gelatin capsules; each capsule contains 400 mg of vitamin E.
- **Royal jelly:** It was obtained from PharcoPharmaceuticals, Cairo, Egypt, in the form of soft gelatin capsules; each capsule contains 1000 mg of royal jelly.

Experimental design:
Group 1: Control group (10 rats) that was administrated intraperitoneally saline solution daily at the dose of 1 ml/kg body weight for 7 days.
Group 2: Treated group consists of thirty rats that divided into three equal subgroups (10 rats in each subgroup).

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Subgroup (2a): Rats injected cisplatin in a single dose of 50 mg/kg body weight intraperitoneally[10].

Subgroup (2b): Rats injected cisplatin a single dose of 50 mg/kg body weight intraperitoneally followed by administration of vitamin E at dose of 200 IU/kg body weight/day orally, started with the for 7 days after.

Subgroup (2c): Rats injected cisplatin a single dose of 50 mg/kg body weight intraperitoneally followed by administration of royal jelly in a dose of 1000 µg/kg body weight/day orally, started with the for 7 days after.

After 7 days, rats, fasted for 12 hr, all animals sacrificed under diethyl ether anesthesia. Then the livers were carefully extracted and processed for light microscopy (LM) (hematoxylin and eosin stain) and transmission electron microscopy (TEM).

Histological Studies:

Liver tissue samples were taken from rats in different groups for histological analysis according to Carleton's histological technique[11]**.** Light microscope combined with a photo camera which used for cross section analysis (magnification 400×). Finally, the ultrastructure of the hepatocytes was observed by transmission electron microscopy after staining with uranium acetate and lead citrate.

Ethical Approval:

All experimental procedures were carried out according to principles and guidelines of ethics committee of Faculty of Medicine, Al-Azhar University, Assiut, Egypt conformed to Guide for the care and use of laboratory animals for the use and welfare of experimental animals health (NIH publication No. 85-23, 1996).

RESULTS

Histopathological examination

Under the light microscopic examination, liver tissues from the control group displayed a typical classic hepatic tissue architecture known as the hepatic lobule, which was made up of regular polygonal shaped cells arranged in cords of hepatocytes. Each of these cords emanated from a normal central vein and was encircled by a regular thin basement membrane. There are typical blood sinusoids between the cords of hepatocytes, and these sinusoids' perimeter contains Von Kupffer cells. There was a typical portal triad at the edge of the hepatic lobule, consisting of hepatic artery, portal vein and one or more bile ductules (Figs. 1 &2).

Rat's liver of the treated group (2a) showed a disarrangement of hepatic cords with markedly distorted hepatocytes that had different shapes and irregular thick outlines. Most of the hepatocytes showed many vacuoles, scanty cytoplasmic organelles and in some ways disappearance or shrinkage of their nucleus that become mostly eccentric at its position. Most of the central veins and the portal tracts appeared congested with an increased number of mononuclear cellular infiltrations. In between the hepatic cords, there was an area of hemorrhage in the irregular dilated blood sinusoids(Figs. 3, 4 &5).

The hepatic cords of the treated group (2b) rats were examined in sections, and the results revealed that most of the hepatic cords had regular shapes, almost normal architecture, and some vacuolated hepatocyte. Numerous mononuclear cellular infiltrations were present, along with some congestion in the majority of the central veins and portal tracts. There were typical blood sinusoids in the space between the hepatic cords (Figs. 6 &7).

The rat's liver of treated group (2c) showed that the majority of the hepatic cords had regular outlines; they showed nearly the normal architecture. Most of the central veins and the portal triads appeared non-congested but had a number of mononuclear cellular infiltrations. In between the hepatic cords, there were regular blood sinusoids (Figs. 8 &9).

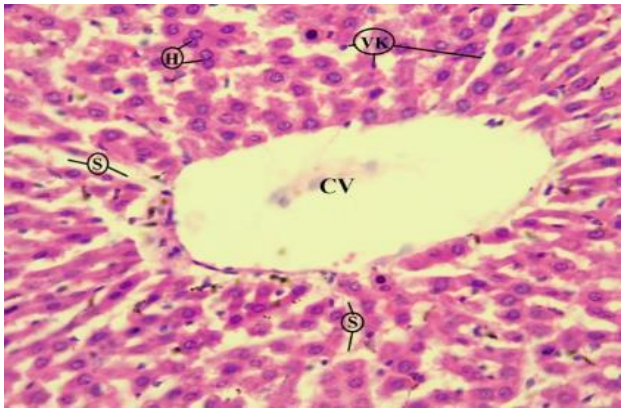


Figure (1): Light microscopic photograph of liver section of rat from group 1 showing: normal histological structure of the hepatic cords radiating from the central veins (CV), hepatocytes (H) separated by normal blood sinusoids (S) containing Von Kupffer cells (VK) at the periphery of the blood sinusoids **(H&E X 400).**

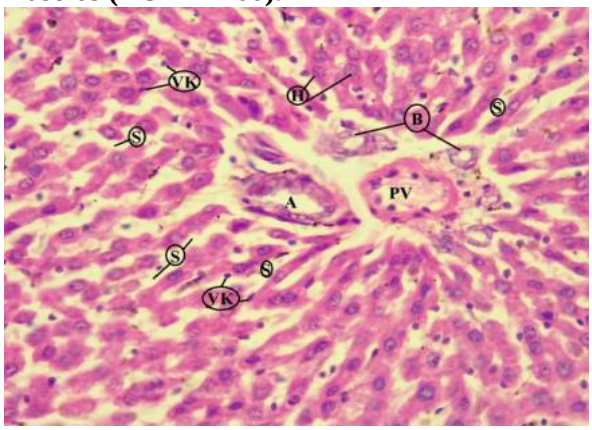


Figure (2): Light microscopic photograph of liver section of rat from group 1 showing: normal histological structure of hepatocytes (H), normal blood sinusoids (S) containing Von Kupffer cells (VK), normal branches of portal vein (PV), hepatic artery (A) and bile ductules (B)
(H&E X 400).

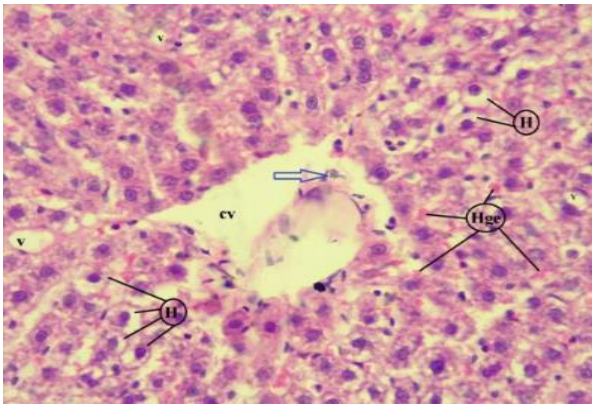
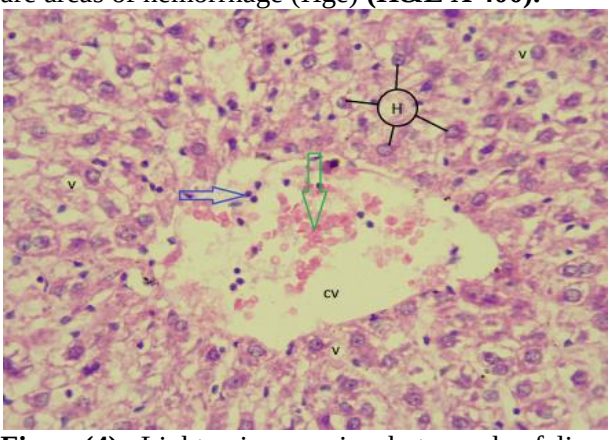


Figure (3): Light microscopic photograph of liver section of rat from group (2a) showing: disarrangement of the histological structure of the hepatic cords radiating from congested central veins (CV) with an infiltration of inflammatory cells (blue arrow), hepatocytes (H) appeared vacuolated (v) with eccentric nuclei. In between hepatocytes there are areas of hemorrhage (Hge) **(H&E X 400).**



Figure(4): Light microscopic photograph of liver section of rat from group (2a) showing: disarrangement of the histological structure of the hepatic cords radiating from slightlycongested (green arrow) central veins (CV) infiltratedby inflammatory cells (blue arrow). The hepatocytes (H) were vacuolated (v) with eccentric nuclei **(H&E X 400).**

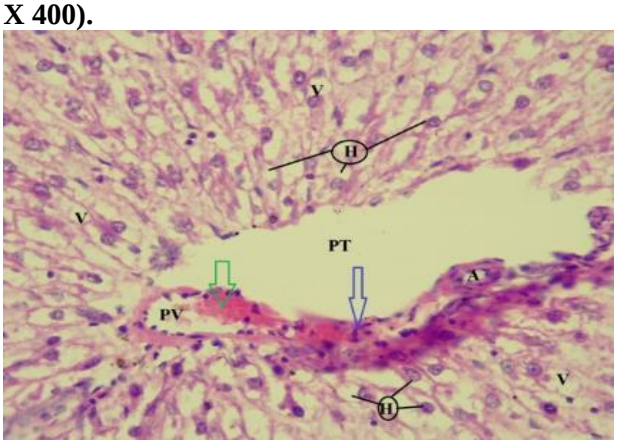


Figure (5): Light microscopic photograph of liver section of rat from group (2a) treated with CP showing: hepatic cords radiating from congested (green arrow) portal vein (PV) and hepatic artery (A) branches with an infiltration of inflammatory cells (blue arrow) at the portal triad (PT). The hepatocytes (H) were highly vacuolated (v) with eccentric nuclei **(H&E X 400).**

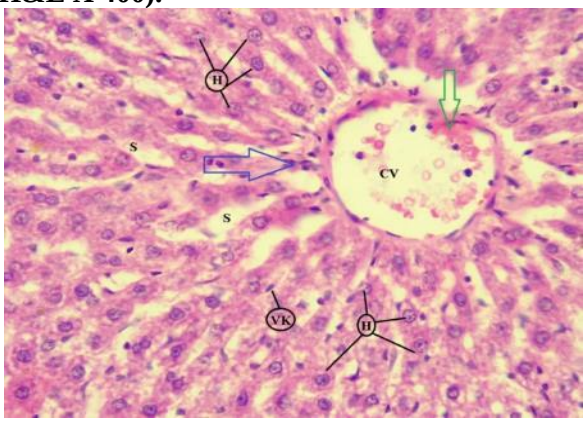


Figure (6): Light microscopic photograph of liver section of rat from group (2b) showing: hepatic cords nearly in similar to the control group radiating from slightly congested (green arrow) central veins (CV) with an infiltration of inflammatory cells (blue arrow). The hepatocytes (H) appeared nearly normal but some cells vacuolated (V) with eccentric nuclei, and the hepatic cords separated by normal blood sinusoids (S). Von Kupffer cells (VK) scattered at the periphery of the blood sinusoids **(H&E X400).**

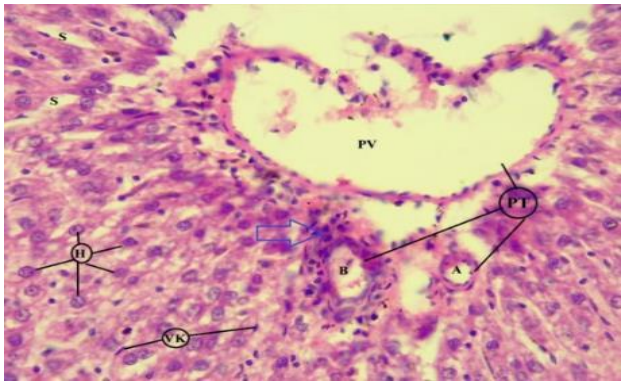


Figure (7): Light microscopic photograph of liver section of rat from group (2b) showing: hepatic cords nearly similar to control group hepatocytes (H) appeared nearly normal and normal blood sinusoids (S). Von Kupffer cells (VK) scattered at the periphery of the blood sinusoids but showing portal vein (PV) hepatic artery (A) branches and bile ductile (B) with an infiltration of inflammatory cells (blue arrow) at the portal triad (PT) **(H&E X400).**

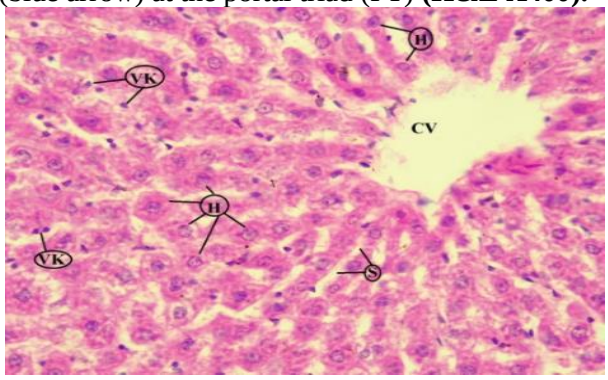


Figure (8): Light microscopic photograph of liver section of rat from group (2c) showing: normal histological structures of the hepatic cords radiating from normal central veins (CV), normal hepatocytes

(H), hepatic cords are separated by normal blood sinusoids (S). Von Kupffer cells (VK) scattered at the periphery of the sinusoids **(H&E X 400).**

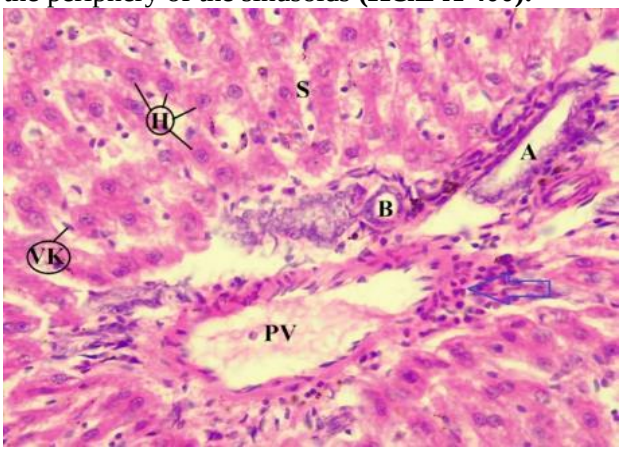


Figure (9): Light microscopic photograph of liver section of rat from group (2c) showing: normal histological structure of the hepatic cords, hepatocytes (H) appeared nearly normal, and the hepatic cords separated by normal blood sinusoids (S). Von Kupffer cells scattered at the periphery of these sinusoids. The hepatic artery (A) branches, portal vein (PV) and bile ductule (B) showed an infiltration by inflammatory cells (blue arrow) **(H&E X400).**

Electron microscopic examination

The livers of group (1) revealed normal hepatocyte architecture that had cytoplasm contained normal numerous organelles mostly oval or sphericalmitochondria and endoplasmic reticulum. The nucleus appeared oval in shape with irregular indentationsand regular intact nuclear membrane,located in the central region of the cell, contained a fine granular chromatin material and a prominent nucleolus. Von Kupffer cells were seen between the hepatocytes at the peripheryblood sinusoids. They revealed regularly elongated in shape. Their nuclei were seen vesicular with fine indentations, and each had a thin peripheral interrupted rim of chromatin material (Figs. 10 &11). Thelivers of group (2a) rats revealed abnormal hepatocyte architecture that hadcytoplasm contains scanty organelles and diffuse cytoplasmic vacuoles. The nucleus appeared small in size, shrunk, apoptotic, or karyolytic with irregular indentations and irregular nuclear membrane. The nucleus contained a fine granular chromatin material and maycontain nucleolus. In between the hepatocytes there were red blood cells and inflammatory cells. Hypertrophied Von Kupffer cells were seen between the hepatocytes at the periphery blood sinusoids. They are irregularly elongated in shape. Their nuclei were seen vesicular with fine indentations, with a thick peripheral interrupted rim of chromatin material (Figs. 12, 13 &14). The changes observed in the rat's livers of group (2b) rats showed that their cytoplasm contained many rounded mitochondria, less rough endoplasmic reticulum, and no empty spaces but containing numerous lipid droplets. The cell had more oval nucleus with a regular nuclear membrane, and a prominent nucleolus. In between hepatocytes there is a normal Von Kupffer cell with an appearance of mononuclear inflammatory cell in the congested blood sinusoid(Figs. 15, 16 & 17).

The livers of group (2c) rats did not exhibit the same abnormalities as those seen in group (2a) rats, although electron microscopic analysis did show a significant degree of healing from the harmful effects of CP. More spherical mitochondria with evident cisterns and an abundance of rough endoplasmic reticulum were present in the cytoplasm. The nucleus had a normal nuclear membrane, a conspicuous nucleolus, regions of chromatin material, and a spherical appearance. A typical Von Kupffer cell with the appearance of a mononuclear inflammatory cell was present between the hepatocytes in a mildly clogged blood sinusoid (Figs. 18 &19).

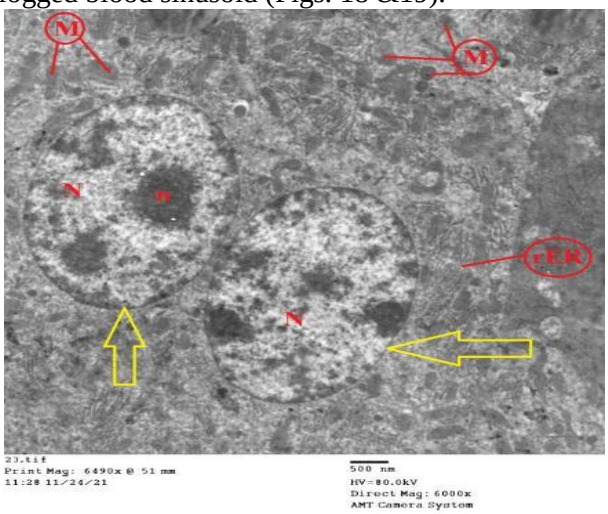


Figure (10): Electron photomicrograph of a liver section of the control group showing: a hepatocyte with two rounded nuclei (N), prominent nucleolus (Nu) with regular intact nuclear membrane (yellow arrow). The cytoplasm contains many normal scattered mitochondria (M) and rough endoplasmic reticulum (rER) **(TEM x6000).**

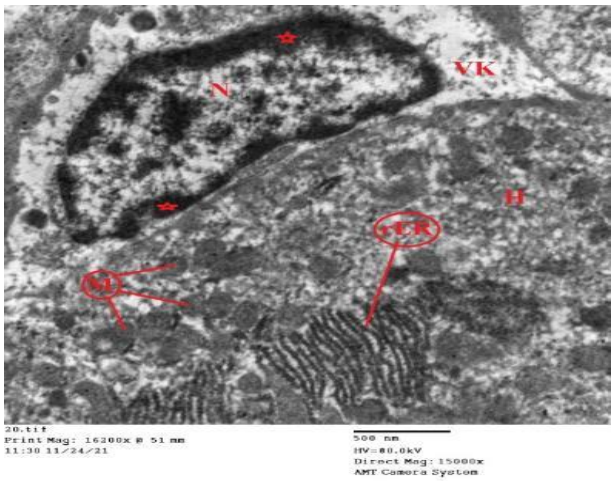


Figure (11): Electron photomicrograph of a liver section of the control group showing: hepatocyte cytoplasm contains normal abundant mitochondria (M) and rough endoplasmic reticulum (rER), also

showing normal Von Kupffer (VK) cell with fusiform nucleus (N) with fine indentations, with a thin peripheral interrupted rim of chromatin material (*) **(TEM x15000).**

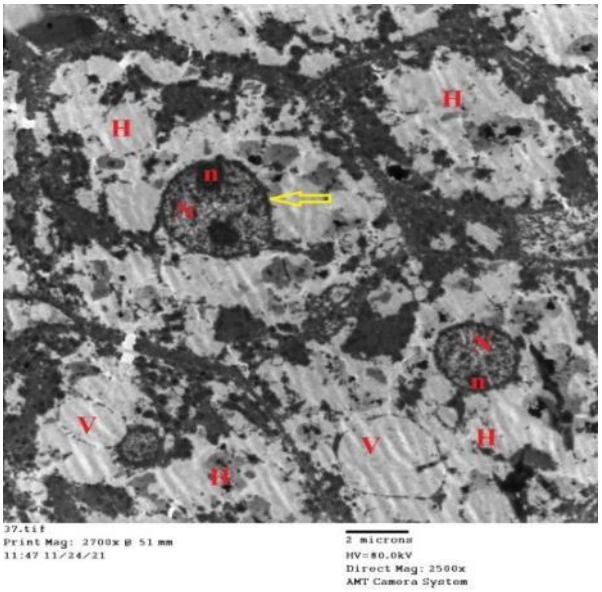


Figure (12): Electron photomicrograph of a liver section of CP treated group (2a) showing: many hepatocytes (H) which contain scanty cytoplasmic organelles that replaced by diffuse degenerated vacuoles (V), pyknotic nucleus (N) with a prominent nucleolus (n) and an irregular thick nuclear membrane (yellow arrow) **(TEM x2500).**

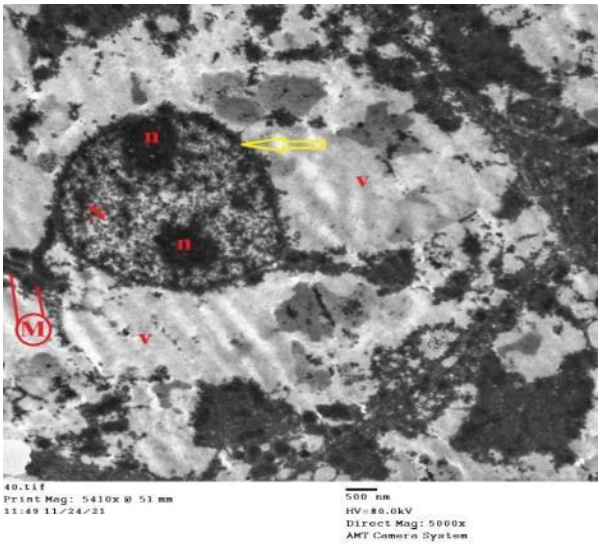


Figure (13): A magnified electron photomicrograph of Fig. 12showing: hepatocyte (H) contain scanty cytoplasmic organelles like mitochondria (M) that replaced by diffuse degenerated vacuoles (V), pyknotic nucleus (N) with a prominent nucleolus (n) and irregular thick nuclear membrane (yellow arrow) **(TEM x5000).**

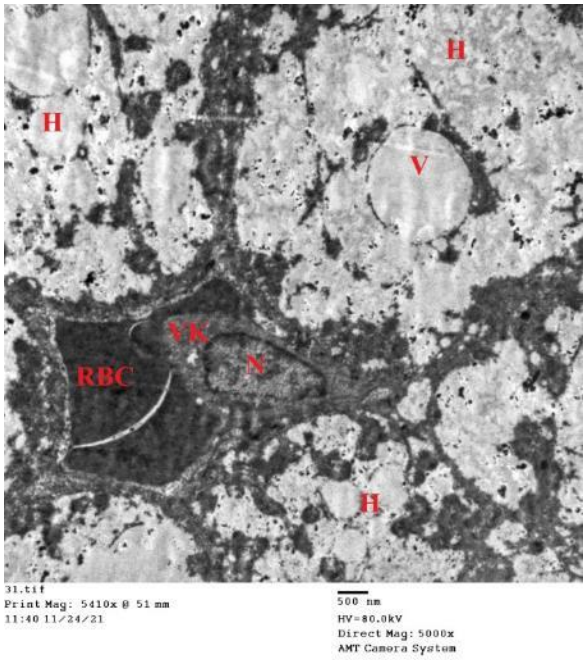


Figure (14): Electron photomicrograph of a liver section of the cisplatin treated group (2a) showing: many hepatocytes (H) contain scanty cytoplasmic organelles that replaced by diffuse degenerated vacuoles (V), and also showing space in between hepatocytes containing Von Kupffer (VK) cell that has elongated nuclei (N) and red blood cells beside (RBC) **(TEM x5000).**

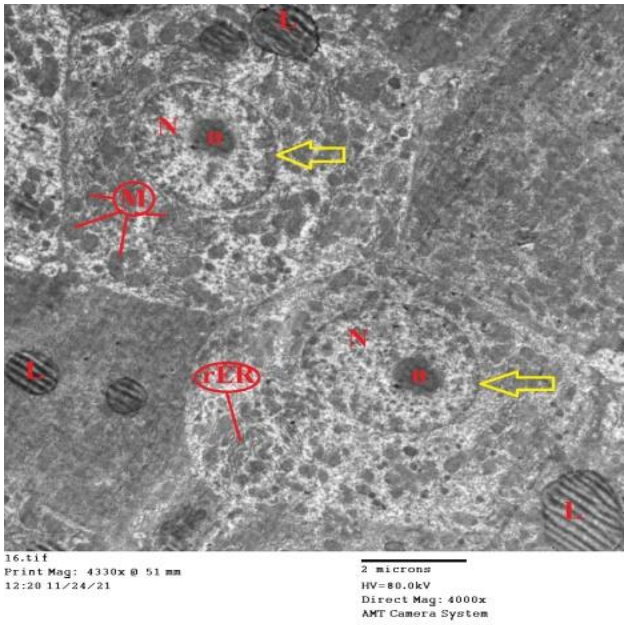


Figure (15): Electron photomicrograph of a liver section of group (2b) showing: Two hepatocytes contained many rounded mitochondria (M), less rough endoplasmic reticulum (rER), and no empty spaces but containing numerous lipid droplets (L). The cell had a regular nuclear membrane (yellow arrow), with an oval nucleus (N) and a prominent nucleolus (n) **(TEM x4000).**

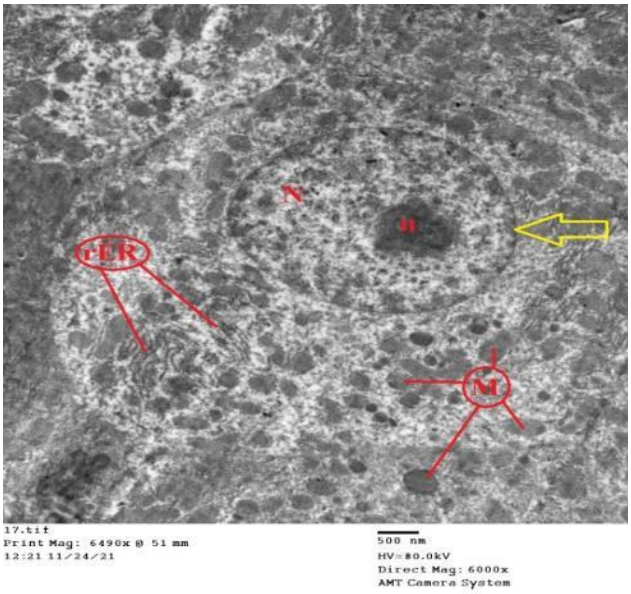


Figure (16): A magnified electron photomicrograph of Fig. 15 showing: hepatocyte cytoplasm contained less rough endoplasmic reticulum (rER), many rounded mitochondria (M). The cell had more oval nucleus (N) with a regular nuclear membrane (yellow arrow), and a prominent nucleolus (n) **(TEM x6000).**

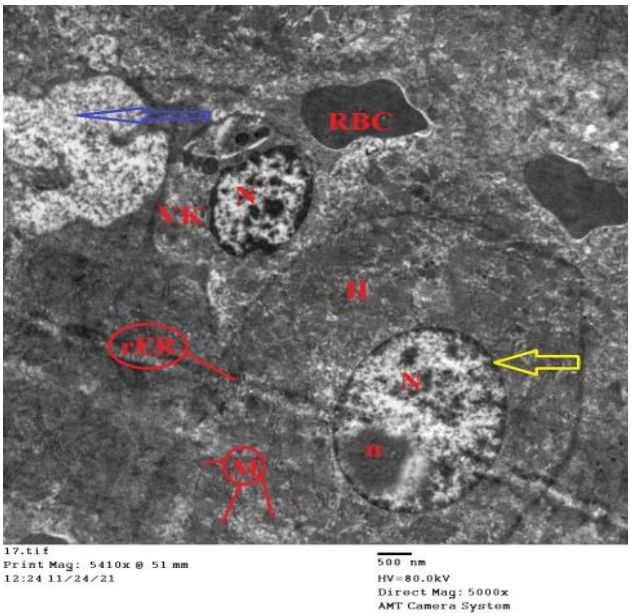


Figure (17): Electron photomicrograph of a liver section of the treated group (2b) showing: hepatocyte contained less rough endoplasmic reticulum (rER), many rounded mitochondria (M). The cell had a regular nuclear membrane (yellow arrow) with an oval nucleus (N), and prominent nucleolus (n). In between hepatocytes the blood sinusoid appeared slightly congested containing red blood cells (RBC), there was normal Von Kupffer cell (VK) with fusiform nucleus (N), also appearance of mononuclear inflammatory cell (blue arrow) **(TEM x5000).**

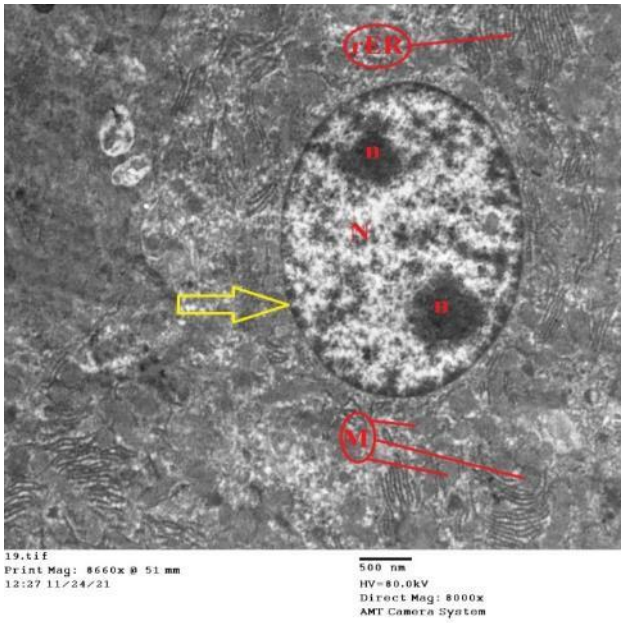


Figure (18): Electron photomicrograph of a liver section of the treated group (2c) showing: hepatocyte contained many rounded mitochondria (M), and rough endoplasmic reticulum (rER). The cell had a regular nuclear membrane (yellow arrow), and an oval nucleus (N) with a prominent nucleolus (n)**(TEM x8000).**

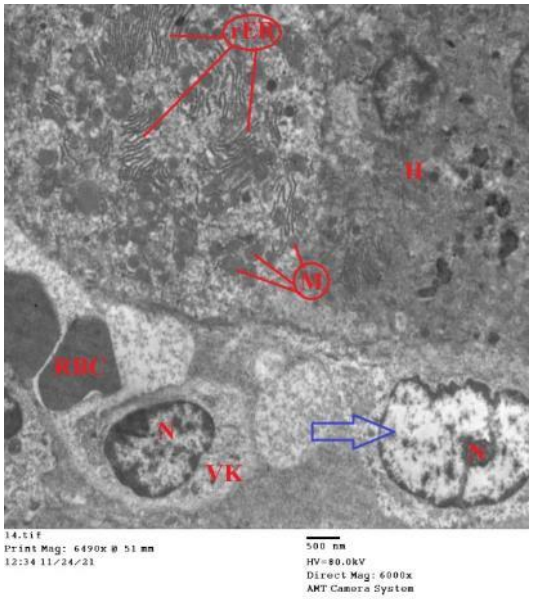


Figure (19): Electron photomicrograph of a liver section of group (2c) showing: hepatocyte contained rough endoplasmic reticulum (rER) and many rounded mitochondria (M). In between hepatocytes the blood sinusoid appeared slightly congested containing red blood cells (RBC). There was a normal Von Kupffer cell (VK) with a fusiform nucleus (N). Also a mononuclear inflammatory cell (blue arrow) was seen**(TEM x6000).**

DISCUSSION

The route intraperitoneal injection of CP was selected for this study because it is more trustworthy in animals and is equal to the intravenous route, which is the standard way to administer CP to humans [12].

Injection of CP in the current investigation resulted in noticeable light and electron histological degenerative alterations of liver tissue.

The present study was in agreement with those of **Abdullah*et al.*** [13] they observed that administration of CP revealed variable histological changes. Some sections showed thatthe blood sinusoids were highly dilated. Some hepatocytes showed vacuolation with fragmented nuclei which appeared with peripheral margination of chromatin granules with inflammatory cells infiltration in between the hepatocytes. By electron microscopic examination of animals treated with CP, the cytoplasm of hepatocytes showed clumps of cellular organelles with large areas of rarified cytoplasm were observed in between these cellular organelles.

Under electron microscopy, the cytoplasm of animals given CP indicated mitochondria with poorly differentiated cisternae and displayed vesiculated rough endoplasmic reticulum (RER). The tissue showed inflammatory cellular infiltration into the gaps between the liver cells. Our results corroborated those of **El-Sayyad*et al.*** [14], who asserted that CP-treated livers showed that the majority of hepatic cords were abnormal, displaying a vacuolebetweenhepatic strands related to necrotic hepatocytes, focal inflammatory cellularinfiltration as well as periportal fibrosis demonstrated by endothelial lining cells corresponding to membrane changes.

These results are consistent with CP-induced hepatotoxicity, which was described by **Huang *et al.*** [15] and showed up as severe haemorrhage, hepatocyte vacuolation, infiltration by inflammatory cells, and cytoplasmic degeneration.

The present results were also agreed with those of **Mohsen*et al.*** [16]who reported that evaluation of histological liver slides of CP treated ratsin a dose of2.5mg/kg showed, congestion, inflammation andsinusoidal dilation. Some hepatocytes had pyknotic nucleus and disorganized hepatic architecture. Also, in evaluation of histological liver slides of CP treated rats in a dose of 5mg/kg showed, congestion and sinusoidal dilation with abnormal endothelial cells appearance, the number of hepatocytes with pyknotic nucleus was elevated.

Similar to this, **Banoand Najam**[17] found that CP therapy resulted in substantial hepatotoxicity in rats, resulting in the development of obvious cystic lesions with mostly inflammatory borders and focally dilated and congested blood vessels. The nucleus of certain hepatocytes was abnormally enlarged and pyknotic.

Additionally, the current findings concurred with those of **Hesham and Ghobara**[18], who noted that CP-induced hepatotoxicity was characterised by vacuolization of hepatocytes, blood sinusoidal congestion, more number of Von Kupffer cells, and inflammatory cell infiltration.

Abdelmeguid*et al.* [19] also noted hepatic histological abnormalities, such as inflammatory cell infiltration, hepatic cord disorganisation that manifested as dilated blood sinusoids and empty vacuoles.These results in agreement with our study, **Liao *et al.*** [20] mentioned that CP treatment was associated with hepatotoxicity manifested by massive histological abnormalities.

In addition, **Kambleand Bhiwgade**[21] came to the conclusion that CP treatment resulted in significant modification at the histological level, exhibiting vacuolated hepatocytes and increased portal spaces, heterochromatin condensation along the nucleolar edge, and a tiny conspicuous nucleus.

The current findings also concurred with those of **Hesham and Ghobara**[18], who noted that ultrastructural analysis revealed hepatocytes with irregular nuclei, large cytoplasmic vacuoles, vesiculated endoplasmic reticulum, decreased mitochondria size with poorly differentiated cisternae as well asincreased number of Von Kupffer cells.

Furthermore,**Stewart *et al.*** [22]found that liver slices had a dense cluster of inflammatory cells, as well as mitochondria with poorly defined cisternae and a dilated rough endoplasmic reticulum in the cytoplasm.On the other hand,**Leite*et al.*** [23]reported that following treatment with CP, no histological modification regard to hepatotoxicity.

Vitamins having antioxidant qualities can ameliorate the levels of reactive oxygen species in the body meanwhile stop oxidative cell damage that can result in cellular death through a variety of processes [24].

Vitamin E is considered as one of the most important chain-breaking antioxidants, according to **Debbabi*et al.*** [25].By controlling cell damage, cellular signaling, inflammatory response, and cellular proliferation in addition to its antioxidative properties, it has therapeutic effects that can delay hepatic fibrosis and possibly prevent cirrhosis [26].

The livers of adult male albino rats demonstrated a reorganisation of hepatic cords and a reduced incidence of inflammatory infiltration when vitamin E alleviated oxidative stress and inflammation.Similar findings were reported by **Miguel *et al.*** [27], who examined the histology of the vitamin E-treated group and found that there was less necrosis or inflammatory infiltration. Also,**BeytutandAksakal**[28] demonstrated that selenium and vitamin E supplementation were successful in decreasing liver damage in glucocorticoid-treated Westar rats.Additionally, according to **NaziroğluÇay (2000)**[29] research, selenium and vitamin E have considerable anti-oxidative protective effects on the blood, liver, and

muscle. However, **Poli *et al.*[30]** found that administration of vitamin E was ineffective in preventing fatty liver.

Many organic compounds were employed to lessen the mutagenic effects of chemotherapy medicines. These chemicals boosted the effectiveness of the therapy rather than induce any harmful effects on normal cells since they had an anticancer effect in addition to their protective properties **[31].**

The protective effect of RJ was related to its antioxidant component as, vitamins A, B complex, C, D and E **[32].**In addition to being an antioxidant and anti-cancer agent, royal jelly offers several medicinal benefits **[33].**

The results observed that RJ have great protective effect on liver structure with no vacuolation of hepatocytes and most of central veins and portal triads appear non-congested but still show number of mononuclear cellular infiltration. This study, agree to the study of **Yildirim*et al.*[34]**showed the normal structures of liver tissues that had takenfrom the RJ treated group.

The represented findings agree with the results of**Mostafa *et al.*[35]** reported that RJ supplement was significantly showed improvement in hepatic histopathological picture, with low inflammatory cellularinfiltration being seen in the portal area. These results demonstrated that RJ significantly provided hepatic protective effects.

The histological architecture of the liver cells in the group of rats that received both RJ and CP treatment was almost normal. These results are in accordance with **Cemek*et al.*[36]** who found that giving cadmium tetrachloride (CCl4) to rats causes severe hepatotoxicity. The therapy with RJ successfully prevents the severe acute hepatic affection brought on by CCl4.

The results indicated that, liver tissue from subgroup (2c) showed hepatic lesions, as the central vein was restored to a normal structure and both blood sinusoids as well as hepatocytes nearly to control after Royall Jelly administration. The results in accordance with**Abdul-Hamid *et al.*[37]**, reported that, RJ is a hepatoprotective agent against liver toxicity.

CONCLUSION

Liver histology changes are brought on by CP. RJ may be clinically helpful because it is a more effective antioxidant than vitamin E against the toxicity of this drug to the liver. When CP causes hepatic damage, vitamin E can help repair the damage.

RECOMMENDATION

1- In clinical practice, CP adverse effects must be taken in consideration for fear of hepatic toxicity.
2- The therapeutic doses of CP and periods of administrations must be carefully adjusted.
3- The current investigation showed that the use of antioxidants such RJ and vitamin E could be a successful preventative measure for CP-induced hepatotoxicity.
4- More research must be done on RJ before its use in therapeutic settings is advised.
5- Additional research on vitamin E dosage and therapy duration in humans is needed.

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