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EFFECT OF CO-ENZYME Q10 IN RECOVERY OF HISTOLOGICAL CHANGES OF LIVER IN RABBITS TREATED WITH IVERMECTIN

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Abstract

The present study was designed to investigate the potential protective and prophylatic effect of Coenzyme Q10 against the Liver tissues affected by Ivermectin administration to rabbits . Forty-eight Healthy adult male albino rabbits approximately 13-14weeks old, ranging in weight from 1350 - 1800 grams were used in this study . The groups divided into six identical groups of 8 animals .group A = control. group B , C and D all rabbits receiving Ivermectin 2mg/kg weekly for 8 weeks , then after stopping Ivermectin B = Direct tissue slicing ,C = administer adaily dose of Coenzym q 10 10mg/kg for 30 days , D = rabbits Leave 30 days for self-healing . E =Ivermectin 2mg/kg weekly + Coenzym q10 10mg/kg daily for 8 weeks, F =only Coenzym q10 10mg/kg for 30 days. Results showed normal liver tissue in group A , C , E and F . Histopathlogical observations of group B and D showed damage in liver such as sever cell swelling with sever necrosis of hepatocytes ,heperplasia of epithelial cells lining bile ducts and congestion of blood vessels. The present study suggests firstable caution must be considered for Ivermectin administration. Second The Coenzym q10 almeliorate liver damage due to Ivermectin toxicity.

Keywords: Ivermectin, Co-enzyme Q10, Kidney, liver.

INTRODUCTION

Ivermectin is a broad-spectrum antihelminthic medication used in sheep and goats to control ectoparasites and endoparasites (Gunn and Sadd, 1994) . In agriculture as plant protection agents (Zanoli et al., 2012). In humans, ivermectin is used to treat onchocerciasis (river blindness) and is also effective against stronglyloidiasis, ascaraisis, trichuriasis, filariasis, entrobiasis, and scabies (Banerjee et al., 2009 and Del Giudice et al., 2003). Ivermectin is metabolized mostly by the oxidative pathway, and it has a high affinity for protein binding, which can reach up to 93 percent. Ivermectin or its metabolites are also reported to be eliminated almost entirely in the feces, but only 12 days later and with fewer than 5% of the administered doses eliminated in the urine (Klotz et al., 1990 and Plumb et al.,2008)

Additionally, Trailovic and Varagic (2007) added that most prominent recorded clinical sings of (IVM) poisoning in domestic and wild animals appeared in the form of C.N.S depression, coma and may be ended by death. Ming et al. (2013) stated that ivermectin induced pathological changes as neuronal degeneration and necrosis on pigeon brain tissues after sub chronic exposure to different doses of AVM

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at different periods. Also Al-Jassim et al. (2015) reported that repeated administration of different doses of ivermectin induced pathological changes in hepatic tissue of female rabbits as vacuolation of hepatocytes and fibrosis. The severity of lesion depending on dose of administration.

Frederick Crane of Wisconsin, USA, was the first to isolate CoQ10, a 1,4-benzoquinone with a 50-carbon isoprenoid side chain, from beef heart mitochondria in 1957..(FL et al.,1957). is a lipid-soluble endogenous benzo-quinonone molecule that serves as a diffusible electron carrier in the mitochondrial respiratory chain. (Lenaz et al.,2007), Then ATP synthesis acts as an antioxidant and aids in the regeneration of other antioxidants, impacting membrane stability and permeability, as well as boosting cell growth and suppressing cell death. (Crane ,2001 and Jones et al.,2002). CoQ10 impacts the operation of all cells in the body due to its role in ATP generation, making it necessary for the health of all human tissues and organs. The heart, immune system, gingiva, and gastric mucosa are among the cells that are most metabolically active. (johnston , 1998)

MATERIALS AND METHODS

The Ivermectin 1% purchased from local market (VET Product Office, Vabco Company, Jordn), and Co_enzym q10 (PHARMACY, Poland).

Experimental Animals Forty-eight Healthy adult male albino rabbits approximately 13- 14weeks old, ranging in weight from 1350-1800 grams, obtained from the animal house of Experimental Research Unit, College of Veterinary Medicine, University of Mosul, Mosul, Iraq were used in the present study. provided with chow and frish water. Experimental Design After one week of adapting to feed, housing and the surrounding environment, the experimental rabbits were randomly divided into six identical groups of 8 animals . Group A : control receiving D.W Sc Twenty four rabbits receiving ivermectin Sc to cause harm in organs (Arise et al., 2012) . 2mg/kg weekly were prolonged for 8 weeks. (Al-Jassim et al.,2016) .and then divided to B ,C and D groups. Group B : 8 rabbits Direct tissue slicing after stopping Ivermectin. Group C :Animal of this group receive Coenzyme q10 (10 mg/kg b.w) orally for 30 days (Abdel-Hady et al., 2011) after stopping Ivermectin. Group D : 8 rabbits Leave 30 days for self-healing after stopping Ivermectin Group E : Ivermectin (weekly) + Coenzyme Q10(daily) for 8 weeks Group F : Coenzym Q10 only (daily) for 30 days

RESULTS

Macroscopic Results

The liver was normal in size and appearance and reddish brown in colour in the control group (Group A),while The liver appears red_ brown slightly to dark in color, flappy texture , congestion , with few Petechial hemorrhage in (Group B).Group C and E have normal apparent .in Group D general appearance of the liver and kidney was similar to that in section of group B.

Microscopic Results

The examination of the liver of control rabbits revealed normal parts were typically divided into lobules with central hepatic venules, into which a converging set of sinusoidal channels surrounded by

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interconnecting plates of hepatocytes that runs between the central terminal hepatic venules and the liver's periphery exhausts (Figure 1) . In Group B which treated with ivermectin (2mg/Kg) revealed sever vacuolar degeneration of hepatocytes with necrosis of some hepatocytes, hyperplasia of epithelial cells lining bile ducts , congestion of blood vessels (Fig 2,3) . (Group C) that received Coenzyme Q10 (10 mg/kg b.w) orally for 30 days, after stopping Ivermectin administration shows normal architecture representing by central vein, hepatocytes and sinusoids with accumulation of few inflammatory cells and fibroblasts in portal area (Fig.4) . (D group) These animal kept without treatment for a month for self-healing (recovery) after stopping Ivermectin shows pathological changes in portal area representing by fibrosis, hyperplasia of epithelial cells lining bile duct, infiltration of inflammatory cells and congestion of blood vessel. Fig. 5,6 . (E group) receive Ivermectin (weekly)+ Coenzyme Q10(daily) at the same time for 8 week shows mild cloudy degeneration of few hepatocytes and mild dilation of sinusoids (Fig.7,8) .(F group) receive Coenzym Q10 only for 30 days shows normal architecture of liver tissue representing by central vein , portal vein , hepatocytes and sinusoids (Fig.9 ,10) .

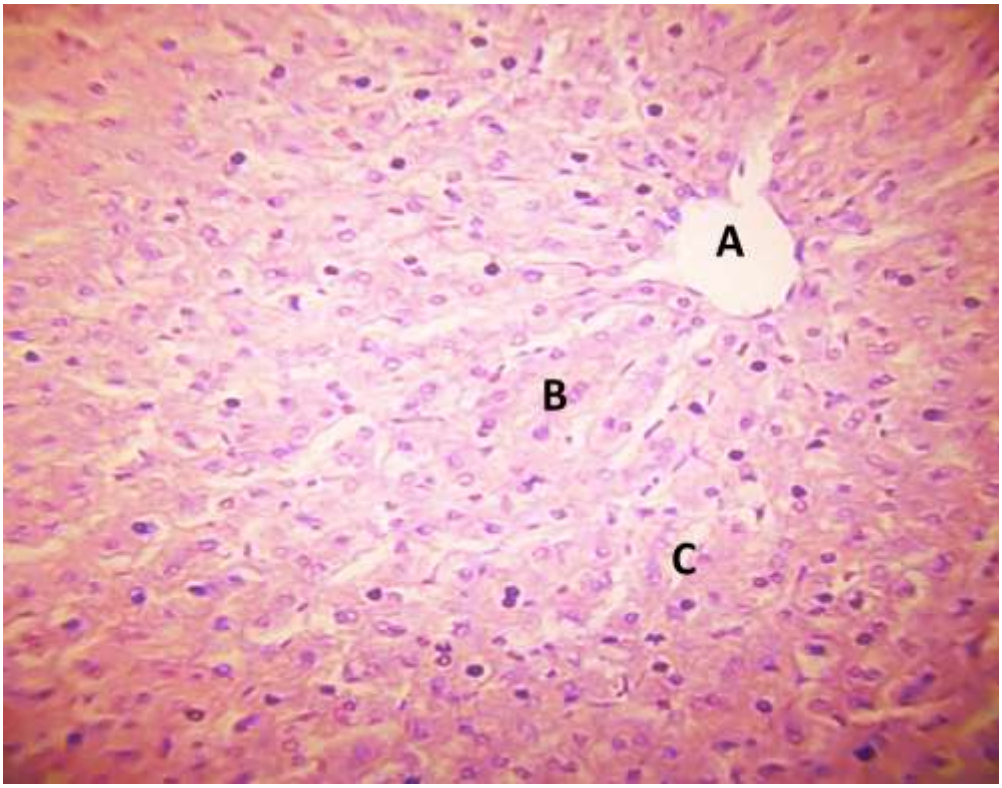

Fig. 1: Photomicrograph of liver at (control A group) shows normal architecture representing by central vein (A), hepatocytes (B) and sinusoids (C). H&E stain. 200X.

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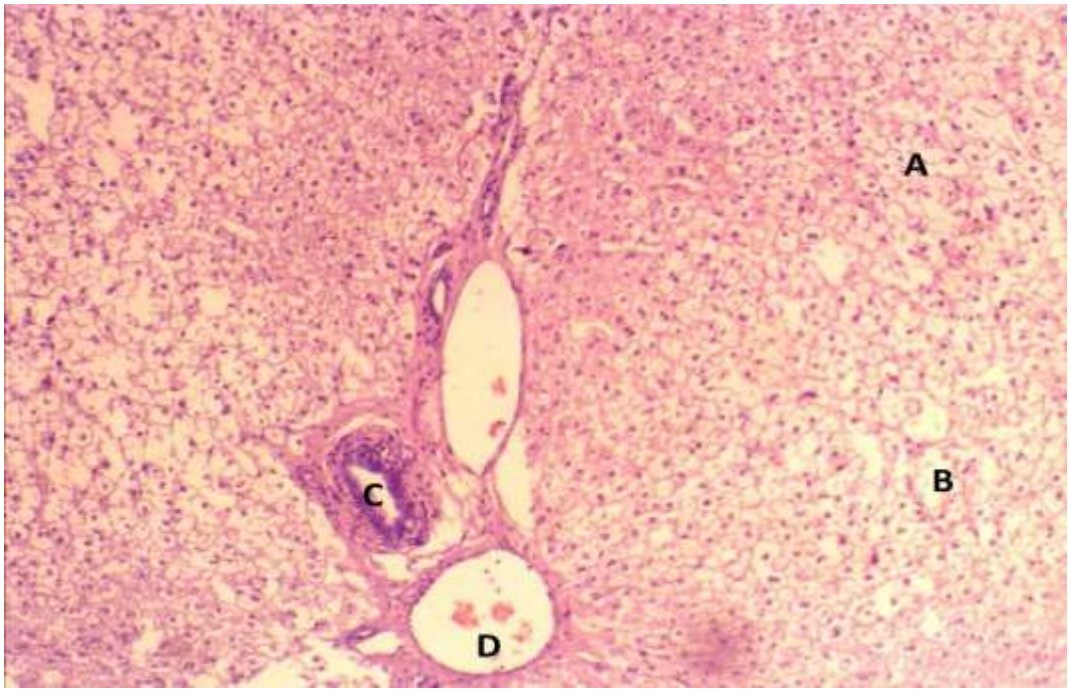

Fig 2: Photomicrograph of liver at (B Group) Sever vacuolar degeneration of hepatocytes(A) with necrosis of some hepatocytes(B), hyperplasia of epithelial cells lining bile ducts (C), congestion of blood vessels (D). H&E stain 100x

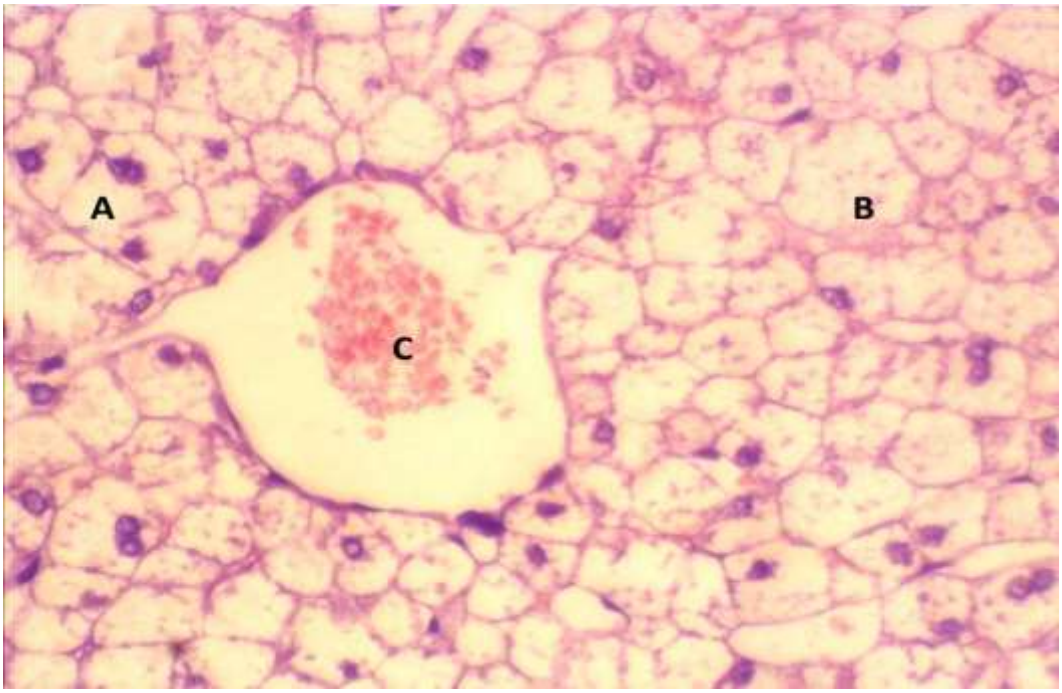

Fig 3: Photomicrograph of Liver at (B Group) Severe cell swelling and vacuolar degeneration of hepatocytes (A) necrosis of some hepatocytes(B)and congestion of central vein(C) H&E stain 400x

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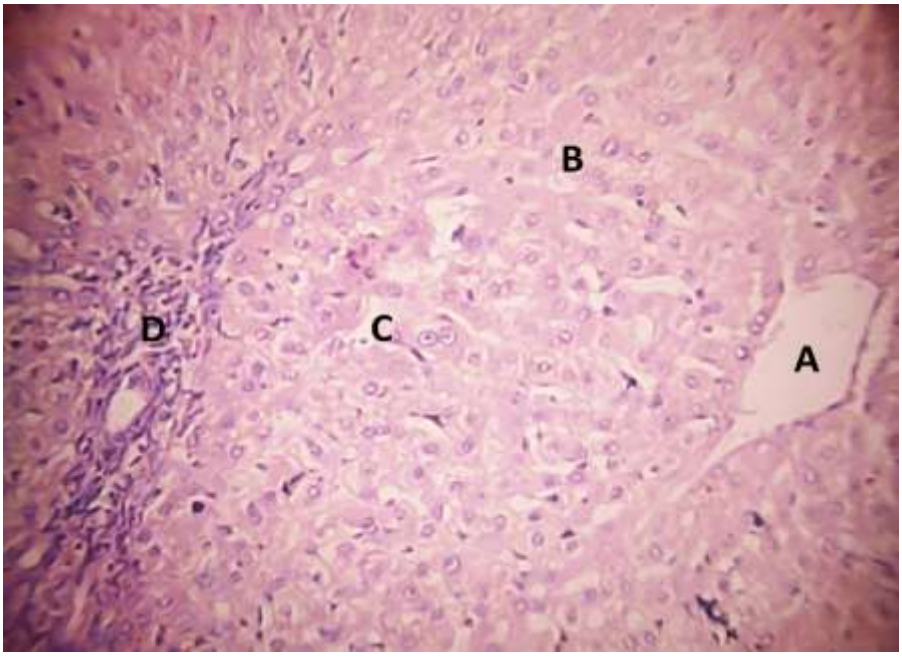

Fig.4: Photomicrograph of liver of (C group) shows normal architecture representing by central vein (A), hepatocytes (B) and sinusoids (C) with accumulation of few inflammatory cells and fibroblasts in portal area (D). H&E stain. 200X.

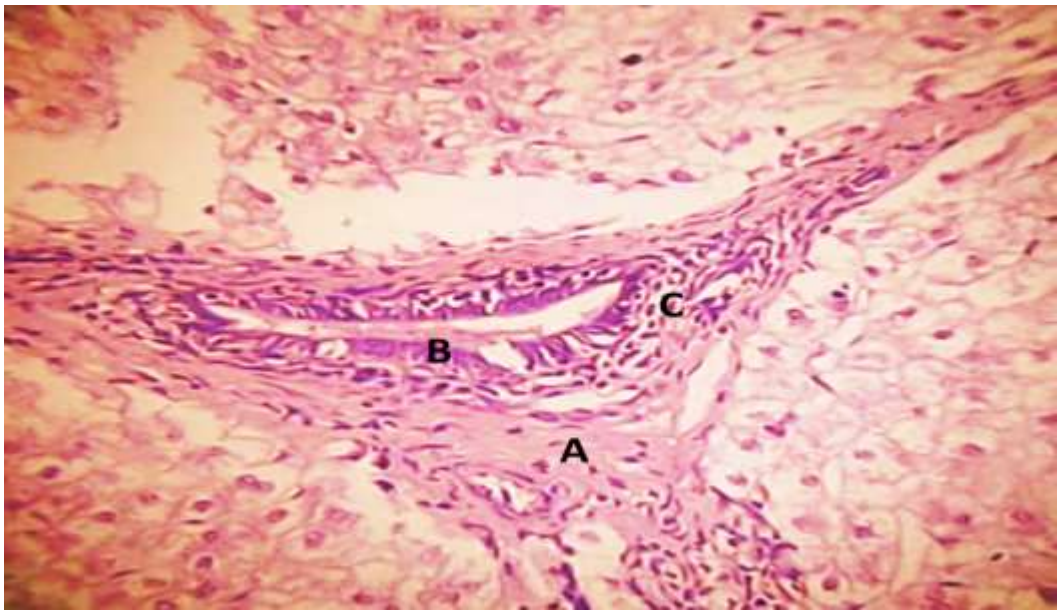

Fig.5 : photomicrograph of liver of(D group) shows pathological changes in portal area representing by fibrosis(A), hyperplasia of epithelial cells lining bile duct (B), infiltration of inflammatory cells (C) H&E stain. 200X.

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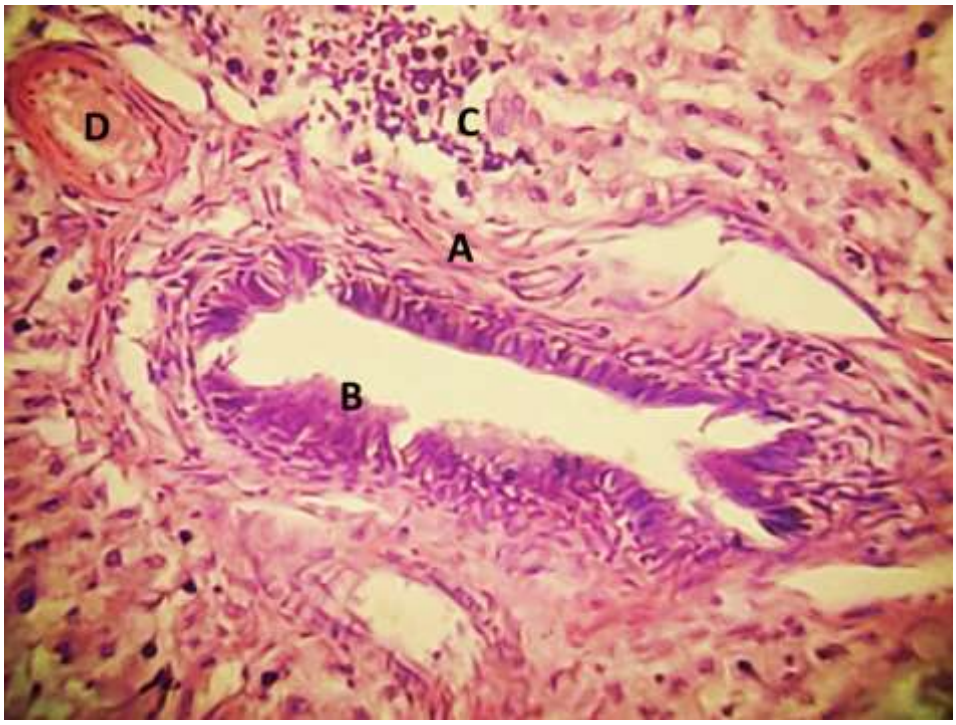

Fig. 6: Photomicrograph of liver of (D group) shows pathological changes in portal area representing by fibrosis(A), hyperplasia of epithelial cells lining bile duct (B), infiltration of inflammatory cells (C) and congestion of blood vessel (D). H&E stain. 200X

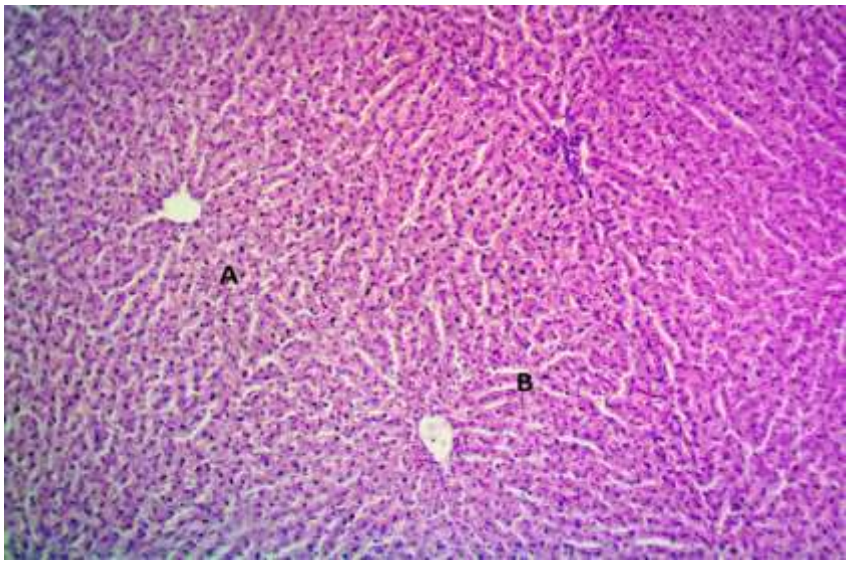

Fig.7: Photomicrograph of liver of (E group) shows mild cloudy degeneration of few hepatocytes (A) and mild dilation of sinusoids (D). H&E stain, 100X.

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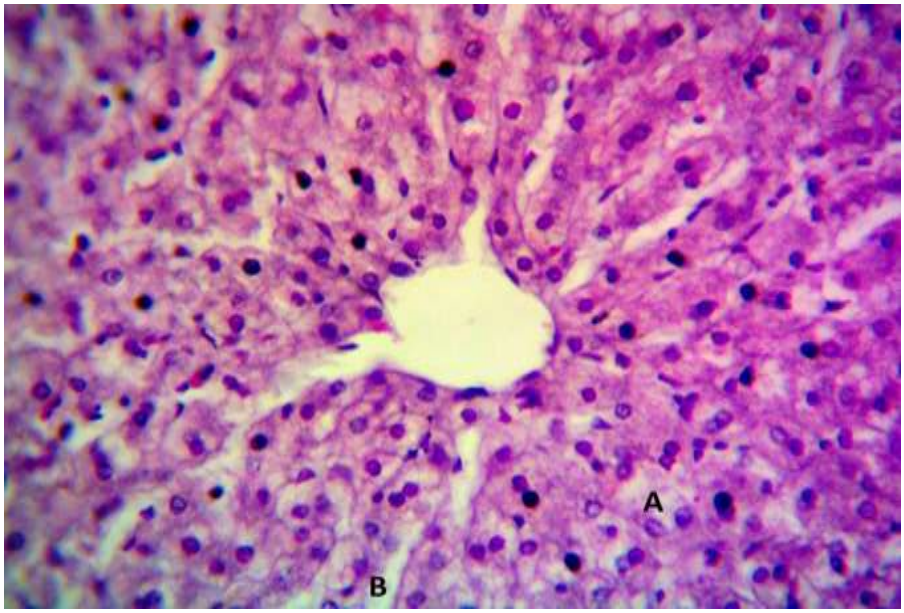

Fig.8: Photomicrograph of liver of (E group) shows mild cloudy degeneration of few hepatocytes (A) and mild dilation of sinusoids (D). H&E stain, 400X.

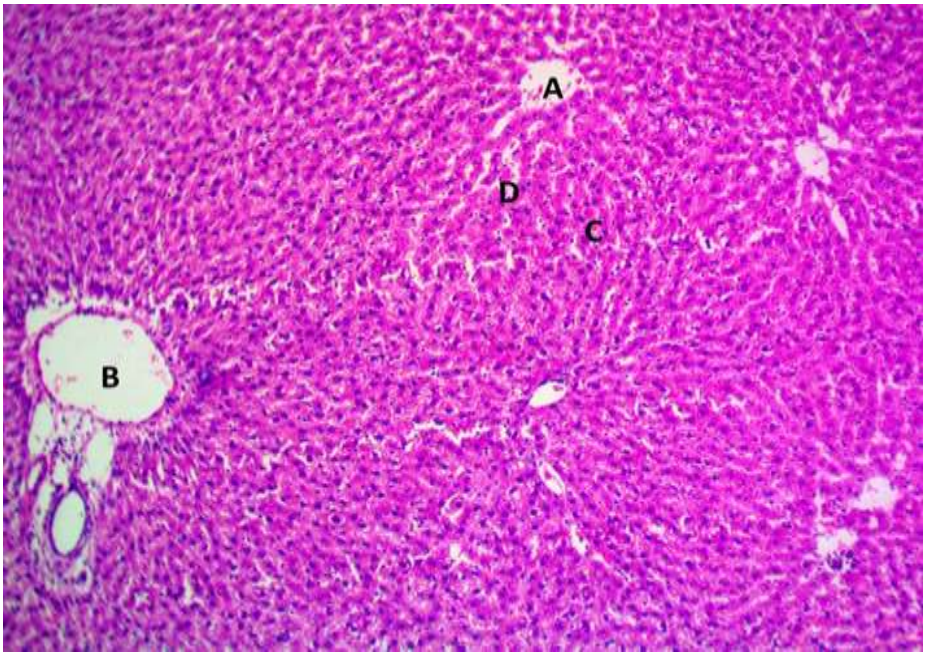

Fig.9: Photomicrograph of liver of (F group) shows normal architecture of liver tissue representing by central vein (A), portal vein (B), hepatocytes (C) and sinusoids (D). H&E stain, 100X.

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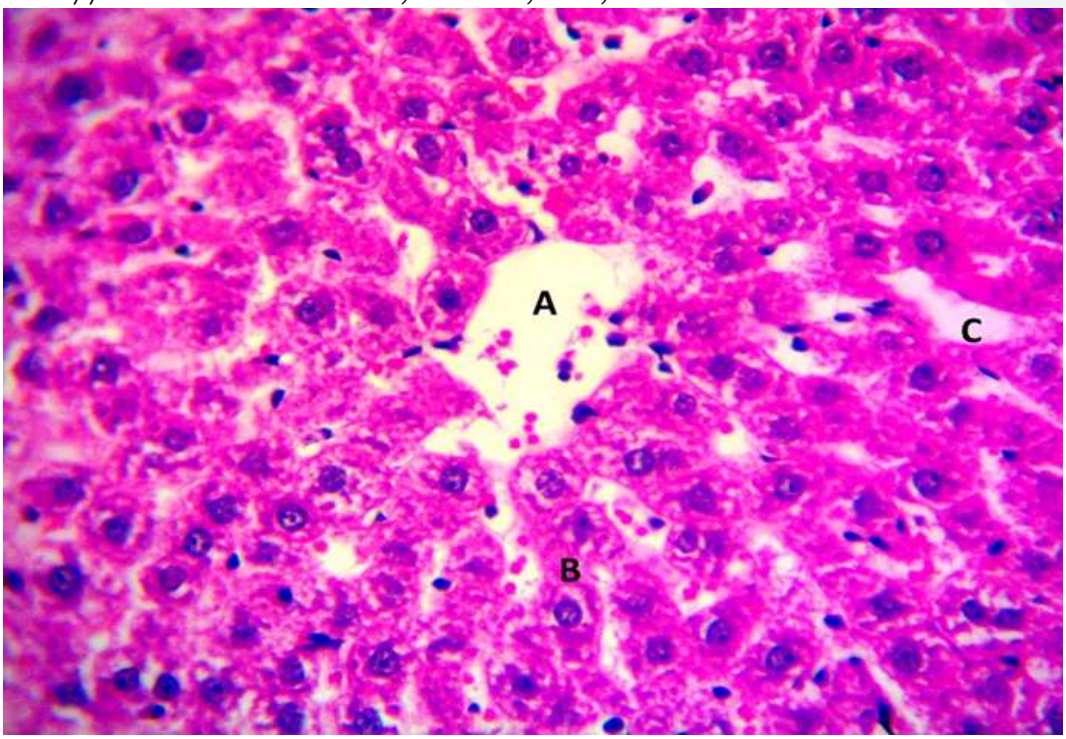

Fig.10: Photomicrograph of liver of (F group) shows normal architecture of liver tissue representing by central vein (A), hepatocytes (B) and sinusoids (C). H&E stain, 400X.

Discussion

Ivermectin was metabolized in the liver which is conceded the most important organ in drug metabolism, as the hepatocyte receives the high drug concentration of the drug itself or its metabolites, which are metabolized by the enzyme cytochrome P 450(Zhang& Tang2018). Furthermore, medicines are typically concentrated in the renal tubules during the water reabsorption process, exposing the renal tubules to a concentrated action from the drug(Liu et al.,2019). Toxins produced by pharmaceuticals or their metabolites are known to cause cellular damage and necrosis, as well as programmed death in the chronic stages of exposure to toxins, and drug metabolites have similar interactions with target molecules, resulting in alterations in these molecules (Perazella, 2019) . Equivalent reactions effect direct toxicity with the target molecules, but non-equivalent reactions include super oxidation of fats, the generation of harmful oxygen radicals, glutathione depletion, and enzyme sulfhydryl group modification(Chorna et al., 2019). Our findings discovered that ivermectin injections alone weekly for 8 weeks of treatment at a dose of 2 mg/kg Sc, resulted in histopathological effects on the liver tissue, including severe swelling and necrosis of some liver cells, hyperplasia of the epithelial cells lining the bile ducts, vascular congestion, and hydropic degeneration of hepatocytes. these findings are consistent with those of another study, which found pathological alterations in the livers cells of ivermectin-treated mice(Nashat et al., 2018). Because the liver is sensitive to harm from direct exposure to toxic chemicals and plays a role in detoxifying metabolic by products and xenobiotics, such changes were a common response to the bodily tissues experiencing any of the negative consequences(Di Giulioet al.,

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2020). These findings were supported by a number of studies that found that giving rats 5 mg/kg ivermectin caused an increase in AST and ALT, which could imply hepatic cell injury as well as a qualitative and quantitative alteration of protein synthesis in the liver. Changes in the activities of liver enzymes due to dysfunction, with a resulting decrease in enzyme biosynthesis and a change in the permeability of the membrane to allow enzyme leakage into the blood, as well as a record of hypoalbuminemia, a liver disorder thought to be caused by a decrease in hepatic albumin synthesis as a result of ivermectin administration(Ogueji et al., 2020).

According to the findings of our study, ivermectin caused this histopathological changes by causing oxidative stress in liver cells, as these histopathological changes in the liver were greatly reduced and the animals returned to normal activity when given ivermectin with coenzyme Q10 10 mg/kg of body weight orally for 30 days after stopping the administration(Group C)

Based on our findings, we believe that the oxidative stress induced by ivermectin administration is related to the occurrence of these pathological changes, as the super-oxidation of unsaturated fats can be triggered by active metabolites or the emergence of free oxygen radicals, as Lipid peroxidase can produce Lipid peroxy radical, which works to create more free oxygen radicals. This mechanism, which involves the interaction of membrane proteins with lipid oxidation products, alters membrane lipids and leads to cell breakdown and death as a result of affecting the integrity of the cell membrane(Flores-Romeroet al., 2020).

Glutathione depletion may play a role in this because it causes oxidative stress, which can occur naturally as a result of metabolite accumulation or as a result of interactions with toxic substances and medications (García-Caparrós et al.,2020).

When glutathione levels fall below 20-30% of normal, oxidative toxins accumulate, resulting in a variety of degenerative alterations that eventually lead to cell necrosis and death (Azouz&Korany, 2020).

In line with everything that has been said, we note that our results in the group D of rabbits that were left for a month after stopping ivermectin treatment revealed the presence of fibrosis, hyperplasia of epithelial cells lining the bile duct, infiltration of inflammatory cells, congestion of blood vessels, and pathological changes in the entrance area, which represent hepatocyte necrosis are all examples of pathological changes. This finding indicates that ivermectin has histopathological effects on the liver that are not pathologically reversible in the longer term, as evidenced by the presence of fibrosis in the liver tissues, as well as necrosis and inflammation that persisted for a month after stopping ivermectin treatment. This could be explained by the depletion of antioxidant mechanisms in animal bodies to counteract ivermectin-induced oxidative stress, as the humans' and animals bodies have defense mechanisms such as glutathione peroxidase and vitamin E, as well as many other substances, including coenzyme Q10, that can protect against this damage. As a result, the presence of oxidants without the presence of antioxidants causes cell death(Farouk et al., 2021).

The mechanisms described above explain why rabbits developed histopathological changes after receiving ivermectin, and why therapy with coenzyme Q10 10 mg/kg (Group E) resulted in evident beneficial changes in liver tissues. Because of its role in the electron and proton transport chain in mitochondrial membranes during aerobic cellular respiration, as well as participating in electron

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transport outside mitochondria (plasma membranes, lysosomes), adequate amounts of CoQ10 are required for cellular respiration and ATP production(Rodick et al., 2018). The impact of mitochondria, one of the organelles whose impact leads to a disturbance in the production of energy that affects the activity of the cell and its ability to perform its function properly, (Filadi et al., 2018). Because mitochondria are more vulnerable to external factors, failure of mitochondrial cellular metabolism leads to necrosis. Vacuoles occur in the cytoplasm as a result of intracellular sodium and the osmotic impact inside the injured cell many studies show that cytoplasmic vacuoles is a common morphological phenomenon and is considered a protective physiological adaptive and reactionary state. This study also considered that exposure to some drugs, toxic substances, and even viruses and bacteria as inducers of cytoplasmic vacuolation is generally considered an early form of degeneration, and many studies show that cytoplasmic vacuoles is a common morphological phenomenon and is considered a protective physiological adaptive and reactionary state(Kim et al., 2020).

CoQ10 supplementation decreases inflammatory mediator levels of C-reactive protein (CRP), interleukin-6 (IL-6), and necrosis factor-alpha (TNF-) through a complimentary impact on nuclear transcription factor NF kappa beta, according to clinical research(Farsi et al .,2019). CoQ10 decreases the development of degenerative illnesses through these methods, as well as participating in DNA repair replication (through its position as an important cofactor in pyrimidine synthesis), regulating the physicochemical properties of cellular membranes, and regulating gene expression (Abiri&Vafa, 2021). Dietary supplementation that affects CoQ10 levels in the body has been shown to have a cytoprotective effect, which can be explained by its significant effect on the expression of several genes that are primarily involved in cell signaling, as mediators of metabolism, transport, transcriptional control, and inflammation, implying that CoQ10 plays an important role as a pow liver is the primary site for CoQ10 synthesis, it is impacted, as evidenced by one study that found a decrease in CoQ10 production in liver patients. This is consistent with our previous findings, as damage to the liver tissue causes a decrease in CoQ10 levels, which results in histopathological effects on the liver (Abdeen et al., 2020)erful genetic regulator (Guescini et al., 2017).

Through CoQ10's ability to protect liver tissue against induced free radicals, a number of studies in animal models have demonstrated the ability of CoQ10 to reduce or prevent the development of cirrhosis after treatment with a variety of toxic metabolites, including medicinal drugs, toxic chemicals, and parasitic microorganisms(Mantle& Hargreaves, 2020).

Supplementation with CoQ10 also slowed the evolution of cirrhosis in mice prone to nonalcoholic fatty liver disease by reducing symptoms of free radical-induced oxidative stress, inflammation, and liver damage(Zhang et al., 2021).

We conclude that injecting ivermectin at a dose of 2 mg/kg subcutaneously and as a single dose for an 8-week period caused histological effects in liver and kidney tissues, and that administering CoQ10 at a dose of 10 mg/kg orally managed to counteract the histopathological effects caused by ivermectin treatment. Oxidative stress is the cause of these degenerative effects, and CoQ10's antioxidant capacity plays a direct role in the partial repair of liver tissues.

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CONCLUSION

1.Ivermectin given in 2mg/kg weekly for 8 weeks have toxic effects on liver characterized by sever cell swelling or vacuolar degeneration, with necrosis of periportal hepatocytes , dilation of sinusoids , congestion of central vein and portal vein.

2. Coenzym q10 in 10 mg/kg for 30 days after stopping Ivermectin has healing effect on liver where the histological appear obvious ameliorate characterized by disappear of most lesion.

3. Ivermectin (2mg/kg weekly) + Coenzyme Q10 (10 mg/kg daily) for 8 weeks did not show any significant histological changes ,Therefore, coenzyme Q10 has a prophylactic effect on the liver from pathological change.

4. Rabbits that were left to self-heal for a month after stopping ivermectin did not show significant improvement in liver sections. This confirms that coenzym q10 has a healing and protective effect.

5. Coenzyme q10 alone given in 10mg/kg daily for 30 days has not shown any histopathological changes or abnormal clinical sings so it has no side effect.

على تحسين التغيرات النسيجية في كبد وكلى االرانب المعالجة باليفرمكتين Q10 تأثير االنزيم المساعد

محمد طيب طاهر صهيب اسماعيل

كلية طب الموصل

جامعة الموصل

الخلاصة

ضد أنسجة الكبد والكلى المتأثرة بإعطاء عقار الإيفرمكتين Q10صُممت الدراسة الحالية لدراسة التأثير العلاجي والوقائي المحتمل لمركب الإنزيم للأرانب. تم استخدام ثمانية وأربعين من الذكور البالغين الأصحاء من الأرانب البيضاء التي تتراوح أعمارهم بين 13 و 14 أسبوعًا ، وتتراوح أوزانهم بين 1350 و 1800 جرامًا في هذه الدراسة. تم تقسيم المجموعات إلى ست مجموعات متطابقة من 8 حيوانات. المجموعات B و C و D = تقطيع مباشر للأنسجة ، Bجميع الأرانب حقنت بمادة الإيفرمكتين 2 مجم / كجم تحت الجلد أسبوعياً لمدة 8 أسابيع ، ثم بعد إيقاف الايفرمكتين ، E = السيطرة ، A = تركت الارانب 30 يومًا للشفاء الذاتي. D (1 0 مجم / كجم) لمدة 30 يومًا ، Q10 = إعطاء جرعة يومية من الإنزيم C (1 0 مجم / كجم) لمدة Q10 30 = فقط الانزيم F (1 0 مجم / كجم) يوميًا لمدة 8 أسابيع ، Q10ايفرمكتين 2 مجم / كجم أسبوعيًا +الانزيم تلفًا في D و B. أظهرت الملاحظات النسيجية للمجموعة F و E و C و Aيومًا. أظهرت النتائج أن أنسجة الكبد والكلى طبيعية في المجموعات الكبد والكلى مثل انتفاخ الخلايا في الكبد مع نخر شديد لخلايا الكبد ، وتضخم الخلايا الظهارية المبطنة للقنوات الصفراوية واحتقان الأوعية الدموية بينما في الكلى ضمور الكبيبات ، والتكيسات الكلوية ونخر الخلايا الظهارية المبطنة للأنابيب الكلوية وارتشاح الخلايا الالتهابية. تقترح الدراسة على تحسين تلف الكبد والكلى الناتج عن تسمم Q10الحالية ضرورة : اولا توخي الحذر عند تناول عقار الإيفرمكتين. ثانيًا ، يعمل الإنزيم الإيفرمكتين.

,الكبد,الكلىq10مفاتيح الاستدلال: الايفرمكتين, الانزيم المساعد

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