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Original article

Protective Role of Selenium against Diclofenac Sodium Induced Hepatotoxicity in Female Rats

Samah Khalifa, Ensaf Abdalwahed, Marfoua Ali*, Nura Al-Zail, Salema Elwiegha

Department of Zoology, Faculty of Science, Omar Al-Mukhtar University, Albaidah, Libya

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Corresponding Email. *marfouas@yahoo.com*

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ABSTRACT

***Background and aims**. Selenium is an essential trace mineral found in soil, water, and some foods. It increases antioxidant effects in the body. Diclofenac sodium is one of the world's most commonly prescribed non-steroidal anti-inflammatory drugs (NSAIDs). This study aimed to evaluate the histological changes induced by diclofenac sodium on the liver of adult female rat and evaluating the possible ameliorative role of selenium. **Methods**. Healthy female rat 4-month-old weighting 140-235g were divided equally into four groups. The first group was received only distilled water and considered as control group. The second group animals were received selenium at a dose of 0.25 mg/kg b/w by oral gavage daily for 21 days. Third group were receiving diclofenac sodium at dose of 10mg/kg b/w by oral gavage daily for 14 days. The fourth group contains animals given same dose of selenium for 7 days, during the next two weeks, animals given same dose of diclofenac sodium. **Results**. Histological examinations revealed that administration of diclofenac sodium only caused congestion of the central vein and granular degeneration of hepatocytes with granular cytoplasm around central vein hemorrhage in hepatocyte cells. In contrast, administration of selenium along with diclofenac sodium induced the protective role of selenium against diclofenac sodium, ameliorating the change in hepatic tissue of the diclofenac sodium-intoxicated rat. **Conclusion**. Selenium can hinder the progression and severity of liver injury during acute inflammatory episodes.*

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INTRODUCTION

The liver is an important organ that performs various functions in the body, including the production of proteins, the production of triglycerides and cholesterol, the synthesis of glycogen, and the formation of bile. The liver is involved in the metabolism of various toxins, including chemicals, drugs, and natural products [1]. Millions of people around the world suffer from inflammatory diseases and consume large amounts of anti-inflammatory drugs (e.g., diclofenac, a non-selective cyclooxygenase [COX] inhibitor) for many years. However, severe side effects and induced intolerance to anti-inflammatory drugs have prompted a search for ways to reduce their effective doses and improve safety measures [2]. Non-steroidal anti-inflammatory drugs (NSAIDs) are a variety of chemical drugs with similar properties that are used to control inflammation and pain. Normal doses of NSAIDs only cause gastrointestinal distress. However, consuming high doses of these drugs (such as ibuprofen, diclofenac, and naproxen) can lead to toxicity [3]. Diclofenac sodium belongs to the NSAID family that causes liver damage at high doses. It is used for medical complications such as rheumatoid

arthritis, inflammation, trauma, osteoarthritis, dysmenorrhea, and surgical pain [4]. It also acts on reduces prostaglandin synthesis by inhibiting of cyclooxygenase enzymes and diminishing apoptosis [5,6]. This drug is listed in the Food and drug administration's black box warning for its liver toxicity [7]. The mechanism of diclofenac sodium-induced hepatotoxicity is partially related to mitochondrial damage [8], an impaired antioxidant defense system [9], impairment of covalent protein integrity by reactive metabolites [10] and dysfunction of the immune system [11]. Moreover, it involves the production of reactive oxygen species that lead to oxidative stress and genomic DNA fragmentation [12]. Diclofenac sodium is a derivative of phenylacetic acid well known for its analgesic and anti-inflammatory properties [13]. In addition, its antipyretic and antibacterial effects have been reported [14]. Diclofenac sodium is used in humans and animals to treat and control inflammation, fever, and pain associated with disease or injury in livestock and humans. It has been used by humans for many years. It is indicated for the treatment of pain due to osteoarthritis/rheumatoid arthritis, various inflammatory and degenerative disorders following trauma, as well as preoperative treatment including vitrectomy [15]. Despite these beneficial effects, there is strong evidence that drug-induced oxidative stress is a mechanism of toxicity in many tissues. Several studies conducted around the world indicate that diclofenac sodium may be associated with adverse effects on the kidney [16] and liver [17-19].

Previous work indicates that drug is cytotoxic to the liver via cytochrome P-450 (CYP)-mediated metabolism [20]. ROS affects the most important cellular targets, namely DNA, lipid and protein macromolecules. ROS can damage these critical cellular components at the molecular level, resulting in cell survival effects mediated by kinase cascades. These factors may play a key role in triggering cell death in response to oxidative damage [21]. Diclofenac sodium had shown deleterious hematopathological and histopathological effects in the rats. The hematopathological changes could cause and reflect tissue damage involving the kidney and the lung [22].

Selenium (Se) is an essential trace element of fundamental importance for humans and animals [23]. It acts at the active sites of a large number of selenium-dependent enzymes, such as glutathione peroxidase (GPX), and serves as an integral part of several important metabolic pathways, including thyroid hormone metabolism, antioxidant defense systems, and immune system function [24]. The importance of selenium is based on the requirement for selenocysteine, which is genetically encoded in certain selenoproteins and is known as the 21st essential amino acid [25]. Selenium can be non-specifically incorporated into proteins as selenomethionine [26]. It is an essential trace mineral in the diet that acts as an antioxidant, which plays as an integral part of many proteins with catalytic and structural functions. Nutrient deficiency of selenium leads to muscular dystrophy, deadly endemic cardiomyopathy (Keshan disease) and chronic degenerative diseases in humans, which can be prevented by selenium supplementation alone or in combination [27]. The most important metabolic roles of selenium in mammalian cells arise from its function in the active site of many antioxidant enzymes, such as thioredoxin reductase and GPX [28]. The GPX enzyme was the first known selenoenzyme capable of preventing oxidative damage to cell membranes. Furthermore, GPX not only protects cells from free radical damage, but also protects membrane lipids from peroxide-induced oxidation and allows regeneration of membrane lipid molecules through reacylation [29,30]. Therefore, there is a growing need for exogenous sources of antioxidants such as trace elements which have various biological activities and to perform many investigations regarding the hepatotoxicity induced by different drugs and the possible hepatoprotective effects of therapeutic strategies from the alternative or complementary medicine. Therefore, the present study examined the possible protective effects of selenium on diclofenac sodium-induced hepatic changes in female albino rats.

METHODS

Diclofenac sodium 50mg tablets (votrex company) and selenium 200 mcg capsules that used in this study were obtained from local pharmacy. Experimental animals and treatment healthy female adult albino rats (4-month-old and weighing 140-235g) were obtained from the animal breeding house of faculty of veterinary medicine, Omar Al-Mukhtar University, Al Bayda-Libya. They were housed in the laboratory animal room in clean plastic cages (7 rats/ cage). The animals were maintained on standard commercial pellet diet and clear drinking water. The rats were acclimatized for a 2 week prior to the start of experiments.

The rats were divided equally into 4 equal groups of seven rats each and subjected to the following treatments: The first group were received only standard diet and clear drinking water and considered as control group. The second group (selenium group), the animals were received selenium at a dose of 0.25 mg/kg body weight by oral gavage daily for 21 days at early morning [31]. Third group were received diclofenac sodium at a dose of 10mg/kg body weight by oral gavage daily for 14 days [32]. The fourth group the protective group (selenium and diclofenac sodium). The animals were given selenium at a dose of 0.25 mg\kg body weight by oral gavage daily for 7 days. Then at next two weeks, animals

were given selenium at a dose of 0.25 mg/ kg orally in the early morning after two hours. The animals were given diclofenac sodium at a dose of 10 mg/ kg orally.

Histopathological study

At the end of the experimental period the animals from both control and experimental groups were dissected after sacrificed by cervical dislocation. For the light microscopic examination, the Liver samples were collected from both control and experimental animals and immediately fixed in aqueous Formaldehyde 10% fixative, dehydrated in ascending grades of ethyl alcohol, cleared in xylol, impregnated in paraffin wax (melting point between 56°C and 58°C), sectioned with rotary microtome (Leica RM 2125) at 5 µm thicknesses and stained with Harri's Hematoxylin and Eosin according to [33]. Stained sections were examined under light microscope and histopathological changes were recognized.

RESULTS

Figures 1-3 show the normal histologic architecture of the liver. Normal hepatocytes arranged in a trabecular manner around a normal central vein were observed in the liver of the control. Normal hepatocytes are the main cell type in the parenchyma, with large, round euchromatic nuclei and one or more nucleoli bi-nucleate cells (paired nuclei). Figures 4 and 5 present sections from the second group. In comparison, the opposite situation was found in the liver sections of rats treated with diclofenac sodium, with congestion of the central vein, degeneration of hepatocytes, and granular cytoplasm around the central vein.

Hemorrhage in hepatocyte cells and hemorrhage in sinusoids (pyknotic) were also observed. Sections from the third group were presented in figures 6 and 7. No detectable histopathological lesions in liver sections of rats treated only with selenium for 21 days were found. Histological sections of the liver showed regular structure with a well-normal histologic architecture of the liver. Normal hepatocytes arranged in a trabecular manner around a normal central vein were observed in the liver.

In the fourth group, the main characteristic abnormalities were the appearance of degeneration and hepatocytes with diffuse hydropic degeneration and vacuolation. Necrosis in the cells and inflammatory cells around the central vein were also observed. While administration of selenium with diclofenac sodium induced marked improvement in the histological structure of the liver in comparison to the diclofenac sodium only treated group, see figures 8 and 9.

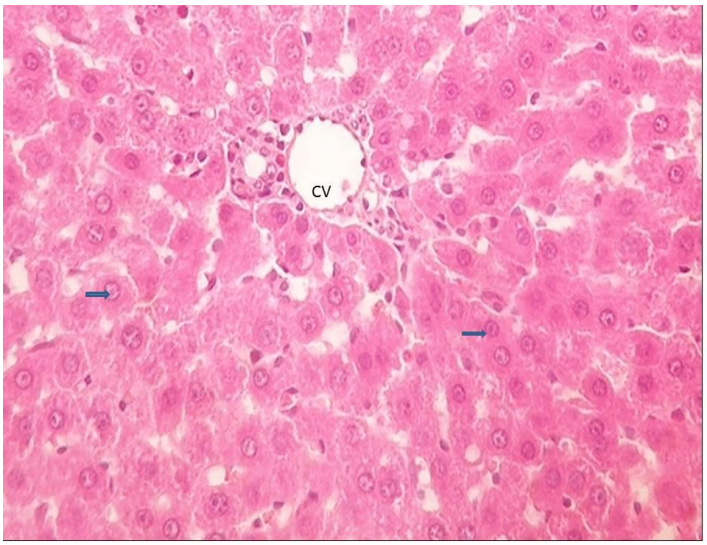

Figure 1. Photomicrographs of liver tissue of control rats showing normal hepatic cells (Arrow), with central vein (CV) (H&E stain, X 400).

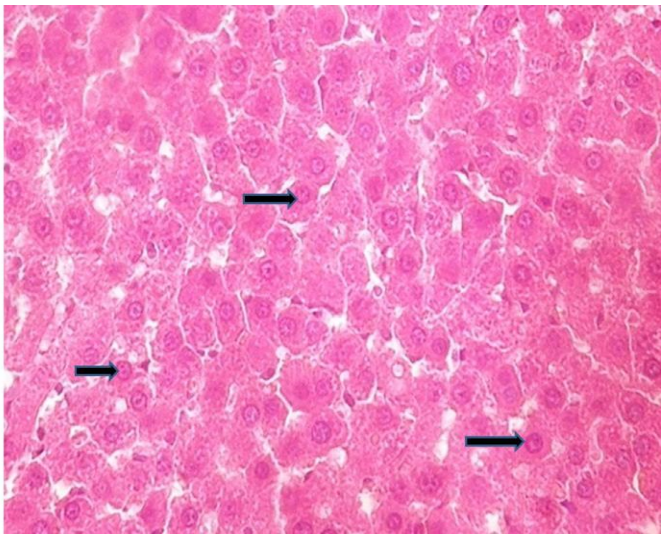

Figure 2. Photomicrographs of liver tissue of control rats showing normal hepatic cells hepatocytes: main cell type in the parenchyma, have large, round euchromatic nuclei, and one or more nucleoli binucleate cell s are common (paired nuclei (Arrow), (H&E stain, X 400).

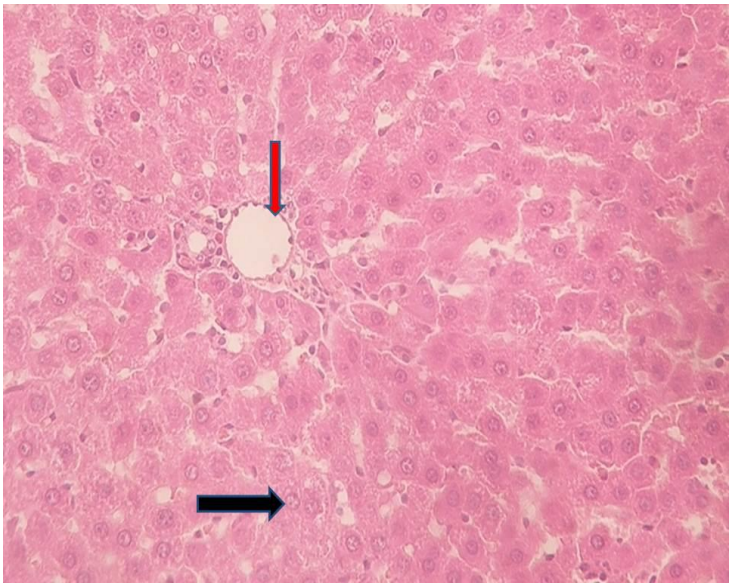

Figure 3. Photomicrographs of liver tissue of control rats showing normal Central vein (Red Arrow) and hepatic cells with hepatic cords and sinusoids around (Black Arrow) (H&E stain, X400).

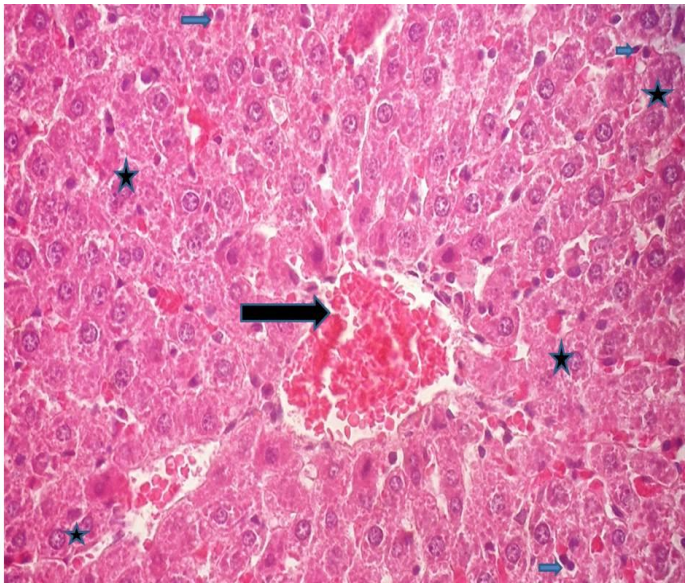

Figure 4. Photomicrographs of liver tissue of rat treat with diclofenac sodium for 3 weeks showing congestion of central vein (Black Arrow) and degeneration of hepatocytes with granular cytoplasm around central vein, Hemorrhage in hepatocytes cells (Star) and Hemorrhage in sinusoids, pyknotic (Blue Arrow), (H&E stain, X 400).

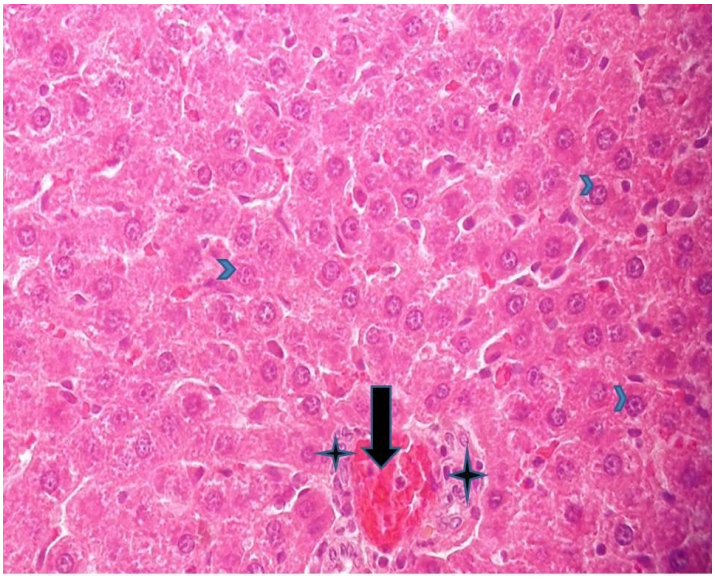

Figure 5. Photomicrographs of liver tissue of rat treat with diclofenac sodium for 3 weeks showing congestion of central vein (Black Arrow), degeneration of hepatocytes (Head Arrow), inflammatory cells (Star), (H&E stain, X 400).

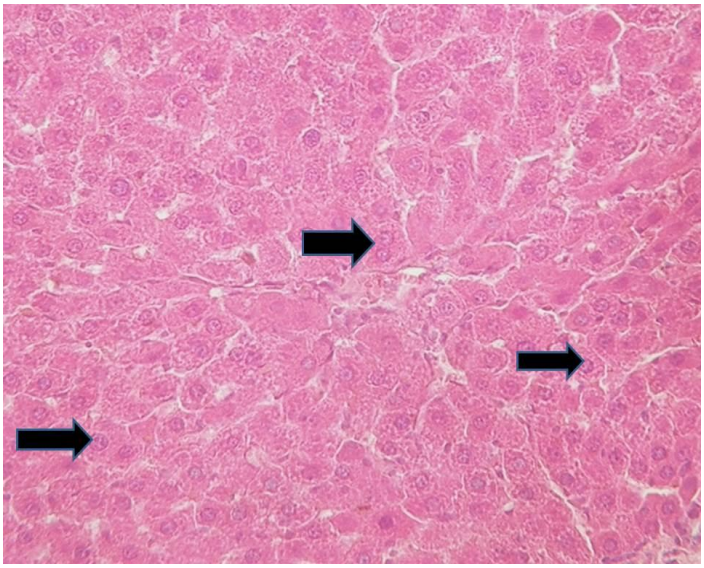

Figure 6. Photomicrographs of liver tissue of rat treat with selenium for 3 weeks showing normal hepatic cells and hepatic cords and sinusoids around (Black Arrow) (H&E stain, X400).

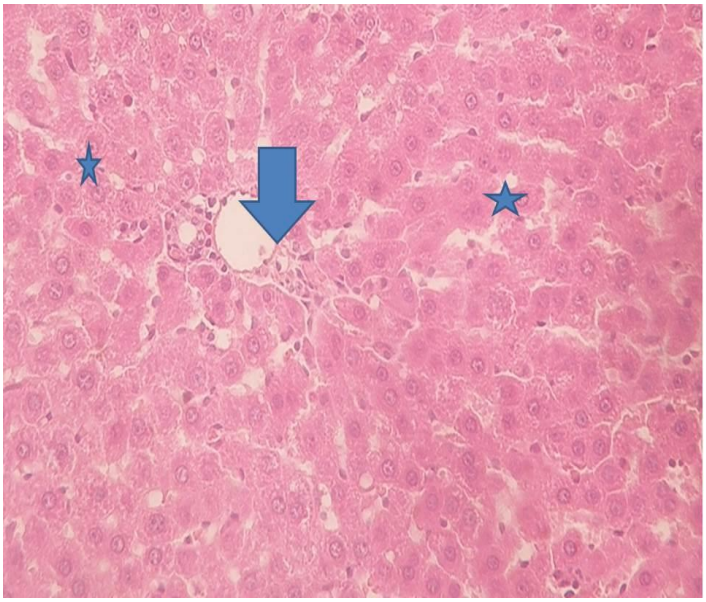

Figure 7. Photomicrographs of liver tissue of rat treat with selenium for 3 weeks showing normal Central vein ((blue Arrow) and showing normal hepatic cells Hepatocytes (Star), (H&E stain, X400).

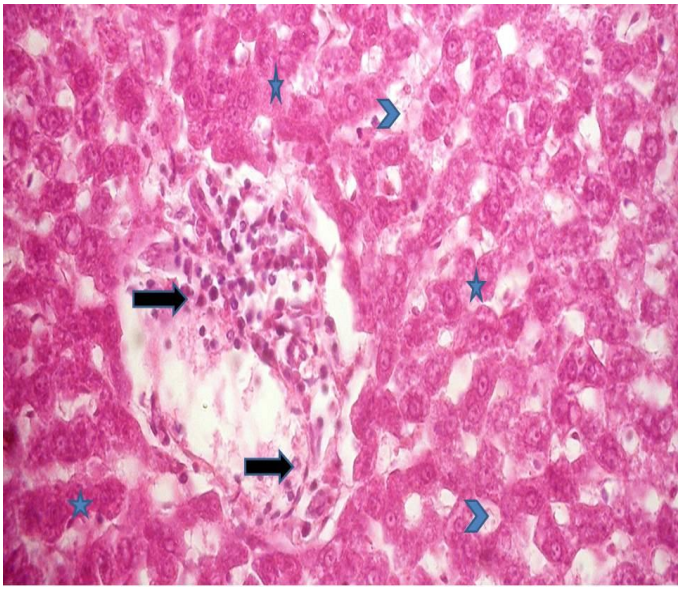

Figure 8. Photomicrographs of liver tissue of rat treat with diclofenac sodium and selenium for 3 weeks showing degeneration and Hepatocyte with diffuse hydropic degeneration (Star), and vacuolation. (Head Arrow), Showing inflammatory cells in the central vein, (Black Arrow), (H&E stain, X 400)

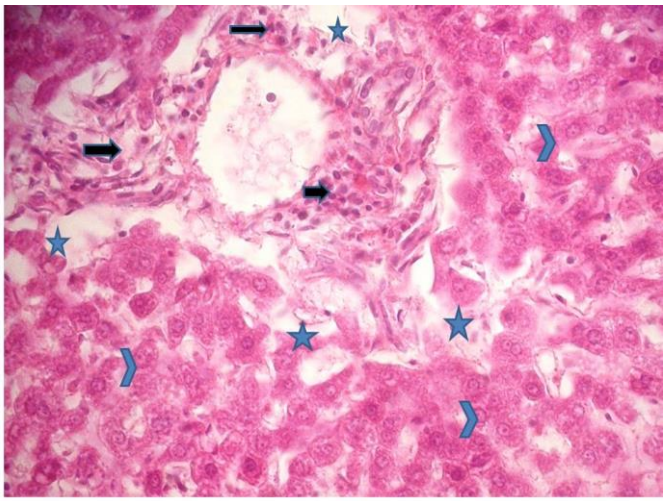

Figure 9: Photomicrographs of liver tissue of rat treat with diclofenac sodium and selenium for 3 weeks showing degeneration of the hepatocyte (Head Arrow), necrosis (Star), and showing inflammatory cells around central vein (Black Arrow), (H&E stain, X 400)

DISCUSSION

The liver is one of the most important organs in the body. It is the main site for protein synthesis, xenobiotic detoxification and the synthesis of enzymes necessary for digestion. Since the liver is the primary organ for the metabolism of xenobiotics, it is exposed to high concentrations of many toxins. Hepatocytes make up the largest number of hepatocytes and are also the main site for drug metabolism, protein synthesis, bile salt production, and glycogen storage [1]. In the present study, histological changes were seen in the liver tissue samples. These findings suggest that a diclofenac sodium causes irreversible cell death, as well as cell damage and these observations were in contrast with previous studies that used different doses of diclofenac sodium in rats [18, 34].

Diclofenac sodium is metabolized in liver tissue and so is toxic to liver cells [35]. The toxic effects of diclofenac could be acute or reversible [36]. Several investigators have attempted to clarify the mechanism of diclofenac-sodium-induced hepatotoxicity. It has been reported that the damage in hepatocytes induced by diclofenac sodium was associated with an idiosyncratic reaction [37]. Recent study also showed that giving diclofenac sodium at a dose of (5 mg/kg/day) for 21 days led to displaying congestion in sinusoids with inflammatory cell infiltration in the portal are and central vein congestion and congestion and dilation in blood sinusoids in rats [22]. Some experimental results suggest that the toxic effect of diclofenac on hepatocytes may be caused by drug-induced mitochondrial impairment together with a futile consumption of nicotinamide adenine dinucleotide phosphate (NADPH) [38]. Mitochondrial damage and NADPH deficiency are thought to be responsible for diclofenac sodium hepatotoxicity [39]. During diclofenac sodium metabolism the number of reactive oxygen species can be increased. These products induced prooxidative damage in renal tissue as reported in other studies [16,18-19].

This study was conducted to investigate the protective potential of selenium against the damage caused by diclofenac sodium to the liver showing congestion of central vein, granular degeneration of hepatocytes with granular cytoplasm around central vein, and hepatocytes with diffuse hydropic degeneration and vacuolation. These observations were in similar with Eucalyptus Globulus protects against diclofenac sodium that induced hepatorenal toxicity in male rats [4]. Moreover, the pre-administration of omega-3 fatty acids, preferably at a low dose, could reduce hepatotoxicity that could result from subsequent exposure to diclofenac sodium [8]. Selenium supplementation mitigated diclofenac sodium -induced oxidative stress, inflammation, and hematological abnormalities in the liver and kidney of treated rats [40].

Despite the various clinical benefits of non-steroidal anti-inflammatory drugs, their frequent and prolonged use has led to numerous health risks, including hepatotoxicity. Selenium supplementation, on the other hand, relieved diclofenac sodium -induced hepatic toxicity. Decreased hepatic tissue injuries was observed in rats co-treated with selenium.

CONCLUSION

Patho-histological examinations showed toxicological changes of the liver of female rats treated with diclofenac sodium and these results for the recognition of the histopathologic events and disease in the course of diclofenac sodium cytotoxicity. It can be concluded that selenium supplementation can help in mitigating drug-induced hepatic injury and improve drug safety.

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الدور الوقائي للسيلينيوم ضد التسمم الكبدي الناتج عن ديكلوفيناك الصوديوم في إناث الجرذان

سماح خليفة، إنصاف عبدالواحد، مرفوعة علي *، نورا الزاعل، سليمة الويغة

قسم علم الحيوان، كلية العلوم، جامعة عمر المختار، البيضاء، ليبيا

المستخلص.

الخلفية والأهداف. السيلينيوم هو معدن أساسي موجود في التربة والمياه وبعض الأطعمة. يزيد من تأثير مضادات الأكسدة في الجسم. يعد ديكلوفيناك الصوديوم أحد أكثر الأدوية المضادة للالتهابات غير الستيرويدية الموصوفة شيوعًا في العالم. هدفت هذه الدراسة إلى تقييم التغيرات النسيجية التي يحدثها ديكلوفيناك الصوديوم على كبد إناث الجرذان البالغة وتقييم الدور التحسيني المحتمل للسيلينيوم. **طُرق الدراسة**. تم تقسيم أنثى الفئران السليمة عمرها 4 أشهر بوزن 140-235 جرام بالتساوي إلى أربع مجموعات. تلقت المجموعة الأولى الماء المقطر فقط واعتبرت مجموعة ضابطة. تم إعطاء حيوانات المجموعة الثانية السيلينيوم بجرعة 0.25 ملغم / كغم من وزن الجسم عن طريق الفم يومياً لمدة 21 يوماً. المجموعة الثالثة تم إعطاؤها ديكلوفيناك الصوديوم بجرعة 10 ملغم/كغم من وزن الجسم عن طريق الفم يومياً لمدة 14 يوماً. المجموعة الرابعة تحتوي على حيوانات أعطيت نفس الجرعة من السيلينيوم لمدة 7 أيام، وخلال الأسبوعين التاليين أعطيت نفس الجرعة من ديكلوفيناك الصوديوم. **النتائج**. كشفت الفحوصات النسيجية أن إعطاء ديكلوفيناك الصوديوم يسبب فقط احتقان الوريد المركزي وتنكس حبيبي لخلايا الكبد مع السيتوبلازم الحبيبي حول نزيف الوريد المركزي في خلايا الكبد. في المقابل، أدى إعطاء السيلينيوم مع ديكلوفيناك الصوديوم إلى تحفيز الدور الوقائي للسيلينيوم ضد ديكلوفيناك الصوديوم، مما أدى إلى تحسين التغير في الأنسجة الكبدية لدى الفئران المسكرة بديكلوفيناك الصوديوم. **الخاتمة**. يمكن أن يعيق السيلينيوم تطور وشدة إصابة الكبد أثناء نوبات الالتهاب الحادة.

الكلمات الدالة. السيلينيوم، ديكلوفيناك الصوديوم، التشريح المرضي، الكبد، أنثى الجرذ.