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RESEARCH ARTICLE

HISTOLOGICAL STUDIES ON LIVERS OF RATS' MOTHERS AND THEIR OFFSPRING FOLLOWING OXALIPLATIN TREATMENT, AND THE POSSIBLE PROTECTIVE ROLE OF PROPOLIS

Zeinab Kamal[1*]; Ebnalwaled A. Ahmed[2]; Dorreia A. M. Zaghloul[3]; Zeinab Al-Amgad[4]; Amany A. Mohamed[1]; Seham A. Mobarak[1]

[1]Zoology Department, Faculty of Science, South Valley University, Qena, Egypt
[2]Electronic and Nano Devises Lab, Faculty of Science, South Valley University, Qena, Egypt
[3]Human Anatomy and Embryology Department, Faculty of Medicine, Assiut University, Assiut, Egypt
[4]General Authority for Veterinary Services, Qena Veterinary Directorate, Qena, Egypt

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***Correspondence:**
Zeinab Kamal
Zoology Department
Faculty of Science
South Valley University
Qena, Egypt
E-mail:
zinabmostafa@sci.svu.edu.eg

ABSTRACT

Knowledge about the possibility of chemotherapy during pregnancy is increasing. Oxaliplatin, a third-generation of platinum drug, is the main agent for treatment of many cancers. It causes abnormal changes in the cells of the vital organs, especially those responsible for detoxification such as the liver. The present study focused on the evaluation of the possible alleviative role of propolis against the hepato-toxicity induced by oxaliplatin in the rats' mothers before and during the period of pregnancy, and their offspring. A total of 35 adult female albino Sprague-Dawley rats were randomly divided into seven groups (n=5). Group "1" (the control group) received distilled water during the experimental period. Group "2" received a daily oral dose of propolis 200 mg/kg body weight (bw), group "3" received an intravenous dose of 3 mg/kg bw of oxaliplatin three times per week, and group "4" received oxaliplatin with propolis in a combination for 21 days before pregnancy. Similarly, groups 5-7 received the same treatment and doses as groups 2-4, respectively, during the period of pregnancy. The results of the current study demonstrated that the oxaliplatin treatment before and after pregnancy induced degeneration and fibrosis in the maternal and fetal liver tissues. Nevertheless, the results demonstrated that the combined administration of oxaliplatin with propolis alleviated the hepatotoxicity associated with oxaliplatin treatment either before or during pregnancy, indicating the promising potential role of propolis as anti-toxic of natural origin.

INTRODUCTION

The incidence of cancer is in a persistent growing to encompass 26 million in 2040. Chemotherapy is one of the most pre-dominant medications exerts for therapeutic cancer. The growing in cancer cases is projected to raise the demand for chemo-therapy as a cancer treatment[1]. A broad variety of drugs visibly linked with side effects notably hepatotoxicity as well, conventional chemotherapy have noticeable identified hepatotoxic impacts[2].

Cisplatin and its analogs, oxaliplatin, is a potent chemotherapeutic drug of platinum derivatives that confers effective treatment against several cancers[3]. Oxaliplatin is differ from other platinum analogue drugs that has been proved to offer anticarcinogenic efficacy, but of minimal toxicological profile[4]. It has been related with distinct adverse effects such as sinusoidal obstruction syndrome, which is a form of hepatic toxicity distinguished by damage to hepatic blood vessels leading to obstruction of the terminal hepatic vessels notably blood sinusoids[5]. Oxaliplatin, in a particulate, is frequently applied for many malignancies that commonly occur during pregnancy[6]. Correspondingly, utero exposure has been correlated with pathologically growth restriction for offspring during chemotherapy[7]. Hepatotoxicity correlated with chemotherapy administration distinguished by elevation in liver enzymes, veno-occlusive disease, steatohepatitis, and also with possible hepatic fibrosis and chronic liver failure[8]. Hepatotoxicity has been occurred in the treated patients with chemotherapy, perhaps due to cumulative outcome emitted in the liver resulted in remarkable hepatic toxicity inducing common histological findings in form of disorganization of hepatic cords, necrosis, and focal inflammation[9]. Platinum drugs correlated with increased formation of hydrogen peroxide, hydroxyl radical and superoxide radical would ultimately participate in liver damage, hepatic apoptosis, and liver failure[10]. Additionally, oxidative stress afforded an effective role in hepatotoxicity because the detrimental effect of reactive oxygen species (ROS) through suppression of antioxidant enzymes system and increase of malondialdehyde in hepatic tissues[11].

Natural antioxidants have grown considerable regard of researchers greatly on adverse toxicological proceedings of some synthetic drugs and also attracted consciousness among consumers[12]. In the past decade, there is a trend for finding efficacious therapeutic agents with little side effects for liver toxicity; indeed some of natural products showed hepatoprotective potential[11,13,14]. Honeybee products, such as propolis (bee glue), had been much familiar as traditional medicine for human health worldwide[15]. Propolis was suggested to treat cure diabetes, cardiac diseases, and even cancer. Propolis occupies vital pharmacological characteristics including anti-inflammatory, antioxidant, and antibacterial, besides malignant cell arrest had also been recognized[16].

Liver is the best and cheap example for recycling system and comprises an array of cardinal functions as favor support metabolism, detoxification of chemical substances, digestion and immunity. The clearance processes involve both parenchymal and nonparenchymal liver cells[17]. Owing to such the vital importance of liver function in the human body[17], and given what propolis successfully achieved in amelioration of reno-splenic deteriorations and liver toxicity induced by oxaliplatin and doxorubicin in our previous investigation and the study of Omar *et al*.[18,19], respectively. Therefore, it was necessary to study the combinatorial treated effect of propolis with oxaliplatin against liver damages emitted by oxaliplatin. Moreover, protective effect of propolis stay inadequately recognized against *in vivo* liver damage. In the current study, an attempt was made to fulfill this gap *via* the detection of the morphological effects of oxaliplatin chemotherapy on the liver parenchyma and the appreciation of the protective role of the propolis on the development of hepatotoxicity induced by oxaliplatin. The used aqueous extract of propolis was analyzed by gas chromatography-mass spectrometry in our previous study. The main bioactive components were hexadecanoic acid, oleic acid, vaccenic acid, 9-octadecenoic acid, and pentadecanoic acid[18].

MATERIAL AND METHODS

Chemicals and propolis extraction

Oxaliplatin was provided for single intravenous dosage from Mylan Institutional

LLC (Morgantown, WV, USA). Crude propolis was purchased from Elhassan Bee House in Qena City, Egypt. Aqueous extract of propolis was prepared as described previously[18,20].

Experimental animals and design

In this study, 35 female Sprague-Dawley albino rats (*Rattus norvegicus*) weighing 180-220g were purchased from the Animal House belonging to Sohag University (Sohag Governorate, Egypt). Rats were permitted a 2-weeks period of acclimation in cages to the rat room environment before performing the experiments. Rats were supplied with standard diet and fresh water. Rats were randomly divided into seven experimental groups (n=5). The group "1" considered the control group and was orally supplied with distilled water. The groups "2, 3, and 4" were designed for prior-pregnancy treatment. The group "2" treated daily with propolis (200 mg/kg body weight "bw")[21] *via* gastric tube every day for 21 days. Meanwhile, in group "3" oxaliplatin was intravenously administered at 3 mg/kg bw three times per week[22]. The group "4" received oxaliplatin along with propolis as demonstrated above. The remainder female animals (15 female rats) were designed for during the period of pregnancy treatment and caged with mature males in a ratio of 3 females: 1 male. Once, pregnancy had occurred, animals were immediately divided into groups "5, 6, and 7" and then administrated the same previous treatments at similar doses during the period of pregnancy. After parturition, all mothers were euthanized using diethyl ether solution. The livers of mothers and their offspring were taken from all existing groups for further histological studies. All the procedures regarding this study were approved and conducted according to the ethical guidelines for the use of animals in laboratory experiments of the Faculty of Science, South Valley University, Qena, Egypt (permit number: 019/03/2023).

Histopathology

For histological examination, the maternal and fetal liver were sliced and fixed in 10% neutral buffered formalin. The standard histological procedures for hematoxylin and eosin staining were followed as described by Larson *et al*.[23]. Furthermore, the paraffin embedded livers of 5 μm thickness intended for Masson's trichrome stain for detection of the hepatic fibrosis and viewed under the light microscope.

RESULTS

Histopathological changes in the liver tissues induced by oxaliplatin and propolis in mothers and their offspring

Histological results of the maternal liver sections with hematoxylin and eosin staining clarified that administration of oxaliplatin before or during the period of pregnancy induced prominent histological observations, which extremely attenuated after co-administration of propolis with oxaliplatin, as detailed in Table "1". Correspondingly, normal architecture of the hepatic tissues of the control female animals was shown; where the hepatic cords were arranged in good manner and few hepatocytes under-gone hepatic vacuolation (Figure 1A & B).

The results of the treatment before pregnancy, with comparison with the control group, showed that liver tissues of the propolis-treated rats was similar to that in the control rats, where they exhibited normal histology of the hepatocytes with slight vacuolation (Figure 1C). Contrariwise, the oxaliplatin-treated rats showed severe histopathological alterations with severe hepatic damage comprising fatty infiltration of hepatocytes, severely congested blood vessels, cytoplasmic vacuolation, and agg-ressive aggregation of inflammatory cells (Figure 1D & E). Whereas, combination of propolis with oxaliplatin improved the histological damage induced by oxaliplatin, besides regeneration in some hepatocytes and minimal infiltration of leukocytes was noticed (Figure 1F). Likewise, the adminis-tration of propolis during the period of pregnancy induced less detectable cyto-plasmic vacuolation (Figure 2A). Mean-while, the oxaliplatin-treated rats showed

Table 1: Histological lesions scoring of the maternal liver tissues of the control and treated groups.

	Control	Before pregnancy			During pregnancy		
		Propolis	Oxaliplatin	Oxaliplatin + propolis	Propolis	Oxaliplatin	Oxaliplatin + propolis
Hepatocytes necrosis	-	-	++	+	-	++	+
Hepatic fibrosis	-	-	+++	+	-	+++	+
Cytoplasmic vacuolation	+	+	+++	+	+	+++	+
Fatty infiltration	+	-	+++	+	-	+++	+
Lymphocytes infiltration	-	++	+++	+	+	+++	+
Perivascular inflammation	-	-	++	+	-	++	+
Congestion and dilatation of vasculatures	+	-	++	+	-	+++	+

Absent (-), mild (+), moderate (++), sever (+++)

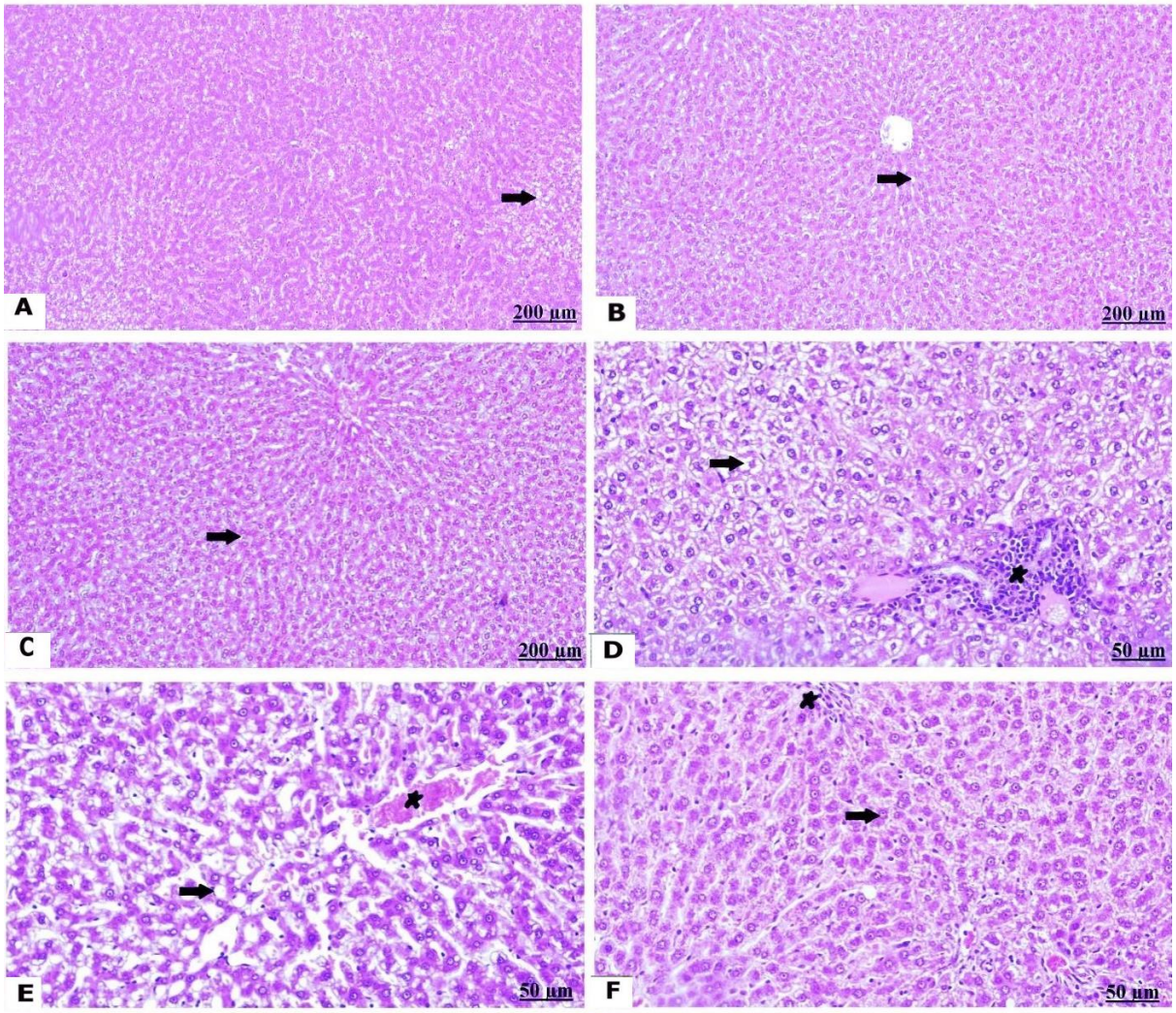

Figure 1: Histological sections (with hematoxylin and eosin stain) of the maternal liver of the control group **(A & B)** and the treated groups before pregnancy with propolis **(C)**, oxaliplatin **(D & E)**, and oxaliplatin+propolis **(F)**. **(A & B)** Showing normal arrangement of the hepatocytes and suffered with mild vacuolation (arrows). **(C)** Showing normal architecture of the hepatic tissues with slight vacuolation (arrow). **(D)** Showing cytoplasmic vacuolation (arrow) and focal aggregation of inflammatory cells (star). **(E)** Showing fatty infiltration of hepatocytes (arrow), and severely congested blood vessels (star). **(F)** Showing regenerated hepatocytes (arrow), besides minimally infiltrated inflammatory cells (star).

degenerative changes of the liver tissues with formation of clear fatty vacuoles, and central vein appeared sharply congested (Figure 2B & C). However, in the oxaliplatin+propolis-treated rats, less fatty degeneration and regeneration in some hepatocytes were observed (Figure 2D).

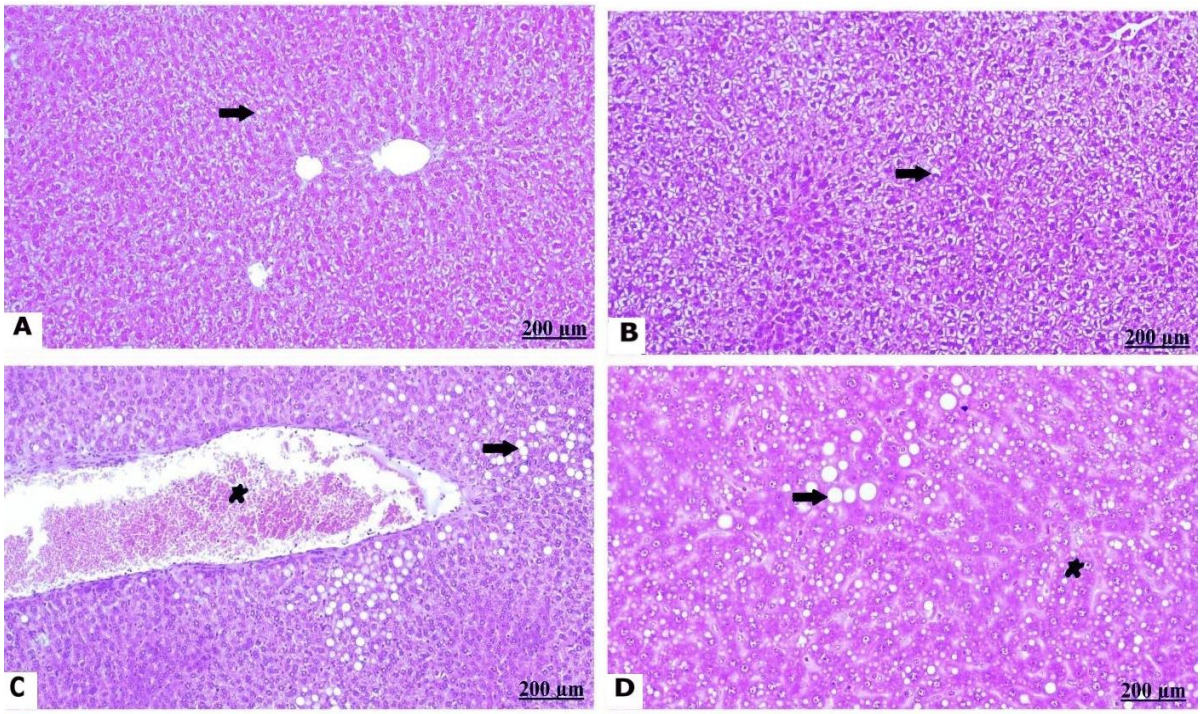

Figure 2: Histological sections (with hematoxylin and eosin stain) of the liver of the treated mothers with propolis **(A)**, oxaliplatin **(B & C)**, and oxaliplatin+propolis **(D)** during the period of pregnancy. (**A)** Showing less degree of cytoplasmic vacuolation (arrow). **(B)** Showing degenerative changes of the hepatocytes (arrow). (**C)** Showing clear fatty vacuoles (arrow) and severe congestion of the central vein (star). **(D)** Showing minimally aggregated vacuolated fats (arrow) with regeneration in some hepatocytes (star).

The histological structure of the embryonic liver of the control rats' mothers affords slight congestion and few cytoplasmic vacuolation (Figure 3A & B). Treatment before pregnancy demonstrated that liver of fetus of the propolis-treated rats' mothers had noticeable degree of interstitial inflammation and lymphocytes infiltration (Figure 3C). However, oxaliplatin treatment caused fetal hepatic injury, which was differentiated by distinct hepatocytes vacuolization and more severely congested blood vessels with stagnant blood (Figure 3D & E). Fortunately, the treatment with oxaliplatin+propolis alleviated the histological alterations induced by oxaliplatin treatment (Figure 3F). Furthermore, the histological changes of the fetal liver of the propolis-treated rats during the period of pregnancy showed mild interstitial inflammation consisted of lymphocytes infiltration (Figure 4A). Moreover, the histological alterations of fetal liver induced by oxaliplatin were distinguished by remarkable cytoplasmic vacuolation, and the blood vessels were strongly dilated and intensely engorged with stagnant erythrocytes (Figure 4B & C). The treatment of oxaliplatin plus propolis reduced histological changes in the hepatocytes of fetal liver (Figure 4D).

Concerning to the histological examination of the liver sections stained with Masson's trichrome stain. In the control group, the maternal liver showed fewer fibrous tissues incidence (Figure 5A & B). Moreover, liver tissues of the propolis-treated group prior to the pregnancy disclosed normal criteria of the liver cells

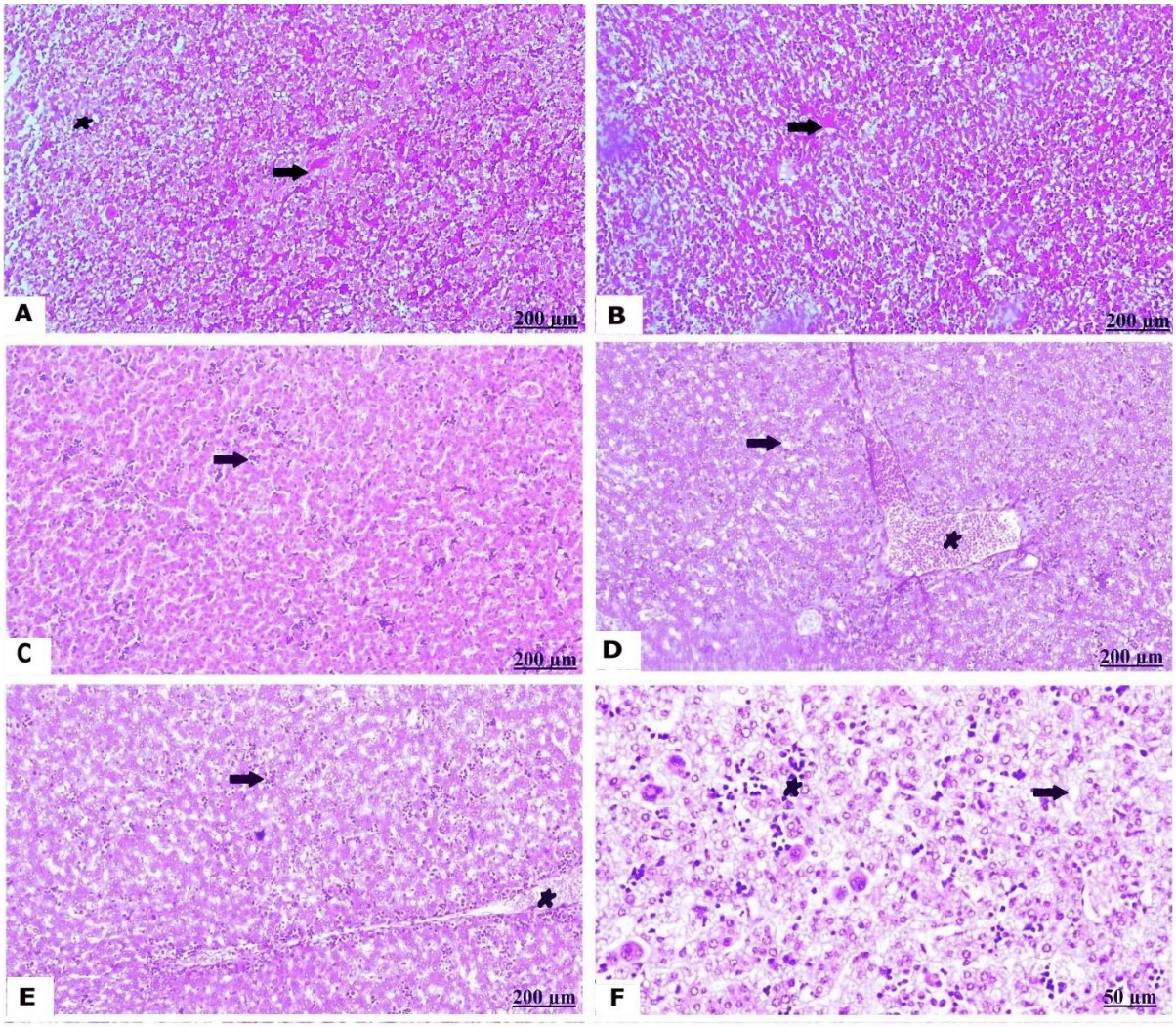

Figure 3: Histological sections (with hematoxylin and eosin stain) of the fetal liver of the control group **(A & B)** and the treated groups before pregnancy with propolis **(C)**, oxaliplatin **(D & E)**, and oxaliplatin+propolis **(F)**. **(A & B)** Showing slightly congested central vein (arrows) with mild clear vacuoles (stars). **(C)** Showing interstitial lymphocytic infiltration. **(D & E)** Showing distinct vacuoles (arrows) and severe engorgement of the blood vessels (stars). **(F)** Showing hepatocytes vacuolation (arrow), besides lymphocytes infiltration (star).

without fibrosis (Figure 5C). Nevertheless, liver tissues of the oxaliplatin-treated group showed significant liver fibrosis identified by a large amount of collagen fibers in the liver of maternal rats (Figure 5D & E). Even though, the oxaliplatin and propolis-treated group showed diminish in the severity degree of hepatic fibrosis (Figure 5F). Similarly, the rats treated with propolis during the period of pregnancy implied small amount of pale stained fibrous tissues at the hepatic parenchyma (Figure 6A). Even though, oxaliplatin therapy led to significant hepatic fibrosis with extensive accumulation of the fibrous tissues around blood vessels (Figure 6B & C). Whilst the fibrous tissue of maternal liver was scant proliferated with pale stain in the oxaliplatin+propolis-treated rats (Figure 6D).

The examination of Masson's trichrome section of fetal hepatic tissues of the control rats' mothers displayed a mild expression of perivascular fibrosis (Figure 7A & B). Meanwhile, the fetal liver of the propolis-treated group before pregnancy showed ill-detectable fibrosis (Figure 7C). On the other hand, notable hepatic fibrosis with distinguished blue coloration almost observed in the fetal liver from the oxaliplatin-treated group (Figure 7D & E). Substantially,

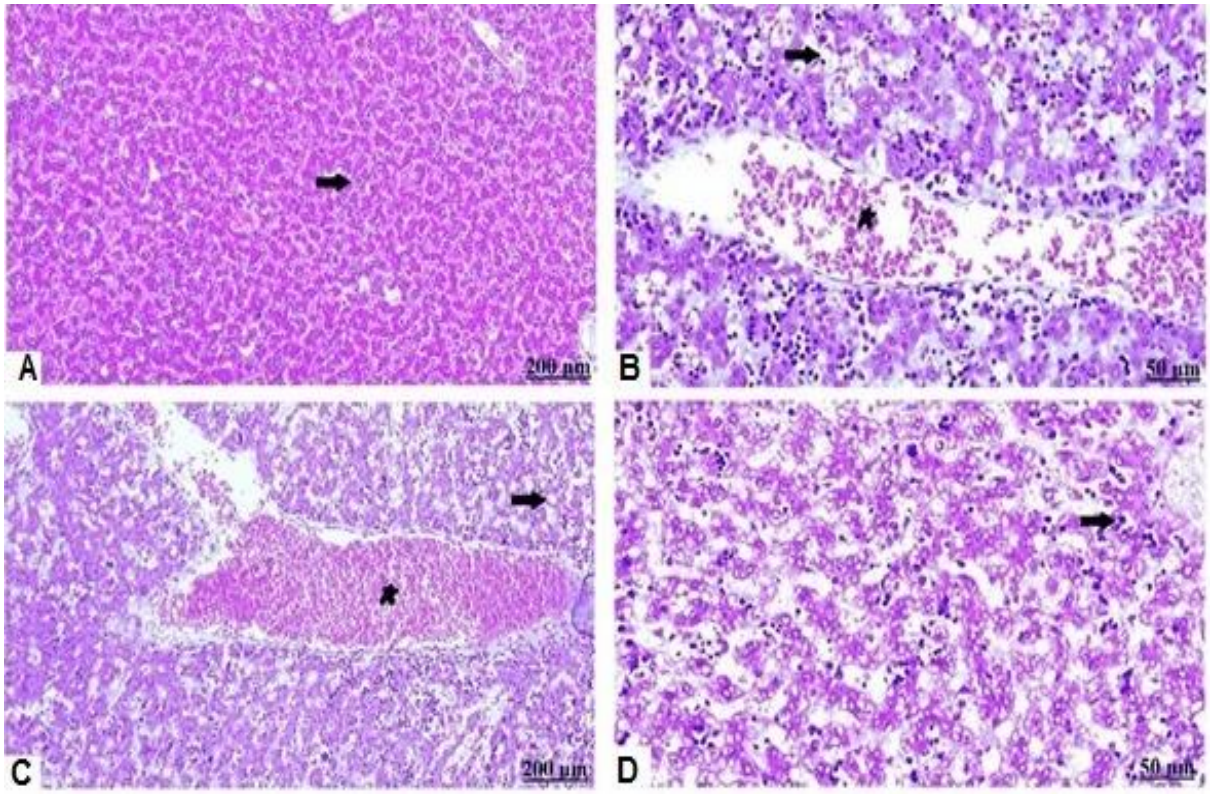

Figure 4: Histological sections (with hematoxylin and eosin stain) of the fetal liver of the rats' mothers treated with propolis **(A)**, oxaliplatin **(B & C)**, and oxaliplatin+propolis **(D)** during the period of pregnancy. (**A)** Showing mild lymphocytic infiltration (arrow). **(B & C)** Showing prominent cytoplasmic vacuolation (arrows) and intense engorgement of the blood vessels with erythrocytes (stars). **(D)** Showing mononuclear cells infiltration (star).

hepatic fibrosis emitted by oxaliplatin treatment was lowered by the administration of propolis after oxaliplatin therapy (Figure 7F). The treatment during the period of pregnancy showed that the administration of propolis alone induced a prominent reduction in liver fibrosis (Figure 8A). Whereas, thick detectable layer of fibrous tissues proliferated perivascular was observed in fetal liver of the oxaliplatin-treated animals (Figure 8B & C). Contrari-wise, the incorporation of propolis with oxaliplatin reduced liver fibrosis in the oxaliplatin-treated rats (Figure 8D).

DISCUSSION

With increased chemotherapy purposes, there has been greater knowledge of a broad range of hepatic-toxic agents linked with the usage of systemic chemotherapy[24]. The hazards of such therapies involve liver toxicity; whereas, on chemotherapy consequent splenomegaly and selection of resistant cancer clones were noticed[25]. As such, longer exposure of chemotherapy is correlated with possible hepatic toxicity[26].

The liver confers an important role in the metabolism of variable drugs and toxins and thus is predominately liable to damage caused by drugs comprising cyto-toxic chemotherapy regimens[27]. Hepato-toxicity is one of the major reasons comes beyond drugs withdrawal. Recorded cases of acute liver failures and hospital admittance are in association with drug-induced hepatotoxicity[28]. Disorder to the liver leads to unfavorable consequences[29]. Thence, it can damage liver structures like blood sinusoids, hepatocytes, and bile ducts[27]; resulted in deterioration of metabolic functions of the liver associated with hepatocytes necrosis, cell fibrosis, and increased lipid peroxidation process that accompanied with depletion of antioxidant levels.

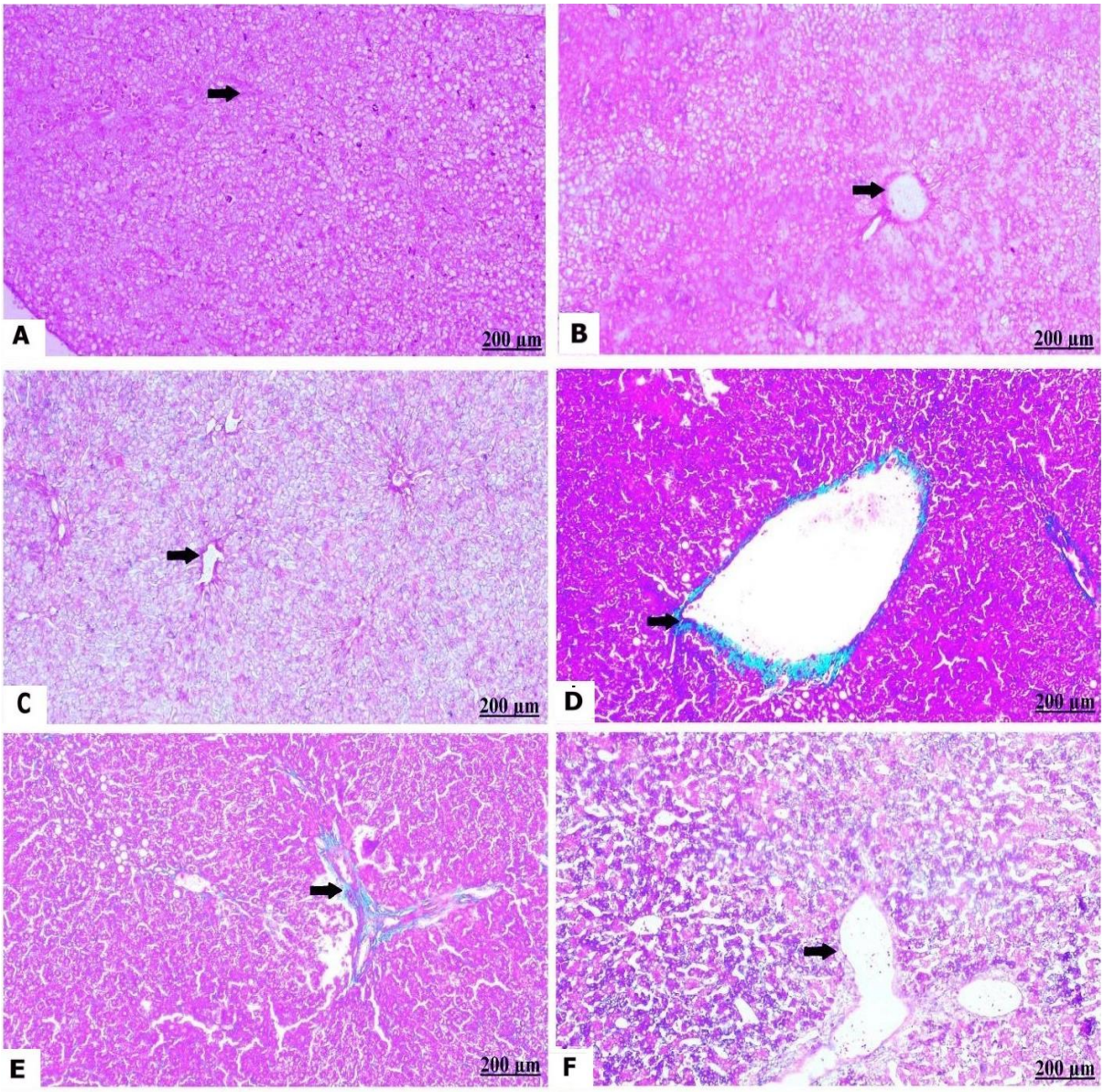

Figure 5: Histological sections (with Masson's trichrome stain) of the maternal liver of the control group **(A & B)** and the treated groups before pregnancy with propolis **(C)**, oxaliplatin **(D & E)**, and oxaliplatin+propolis **(F)**. **(A & B)** Showing normally deposited collagen fibers (arrows). **(C)** Showing less invaded fibrous tissues (arrow). **(D & E)** Showing significant infiltration of the fibrous tissues (arrows). **(F)** Showing weak fibrous tissues infiltration (arrow).

At the same time, propolis offered powerful hepatoprotective effect through attenuation of oxaliplatin-induced hepatotoxicity. Our histopathological lesions were defined by severe inflammation, excessive fibrosis, hepatic degeneration and prominent congestion in the vasculatures. In consistent with Rubbia-Brandt *et al.*[30] who appreciated histological findings in oxaliplatin-induced liver injury were hepatic necrosis and perivascular fibrosis, interstitial hemorrhage and damage of blood sinusoidal endothelial. Oxaliplatin was developed liver injury in a mouse model, and was characterized by disruption in the hepatic architecture, collagen fibers infiltration and dilatation in blood sinusoid[31]. In the current study, oxaliplatin developed hepatic fibrosis, with increase deposition of collagen fiber in the liver. Oxaliplatin plays an essential role in upregulation of the expression of collagen I and transforming growth factor-β (TGFβ)[32]. Hence, increased TGFβ level found in both the early and late stages of

oxaliplatin-induced hepatic injury. TGFβ is the potent proinflammatory cytokine share in liver fibrosis, as it can enhance synthesis of mass collagen and gradual precipitation of extracellular matrix[32].

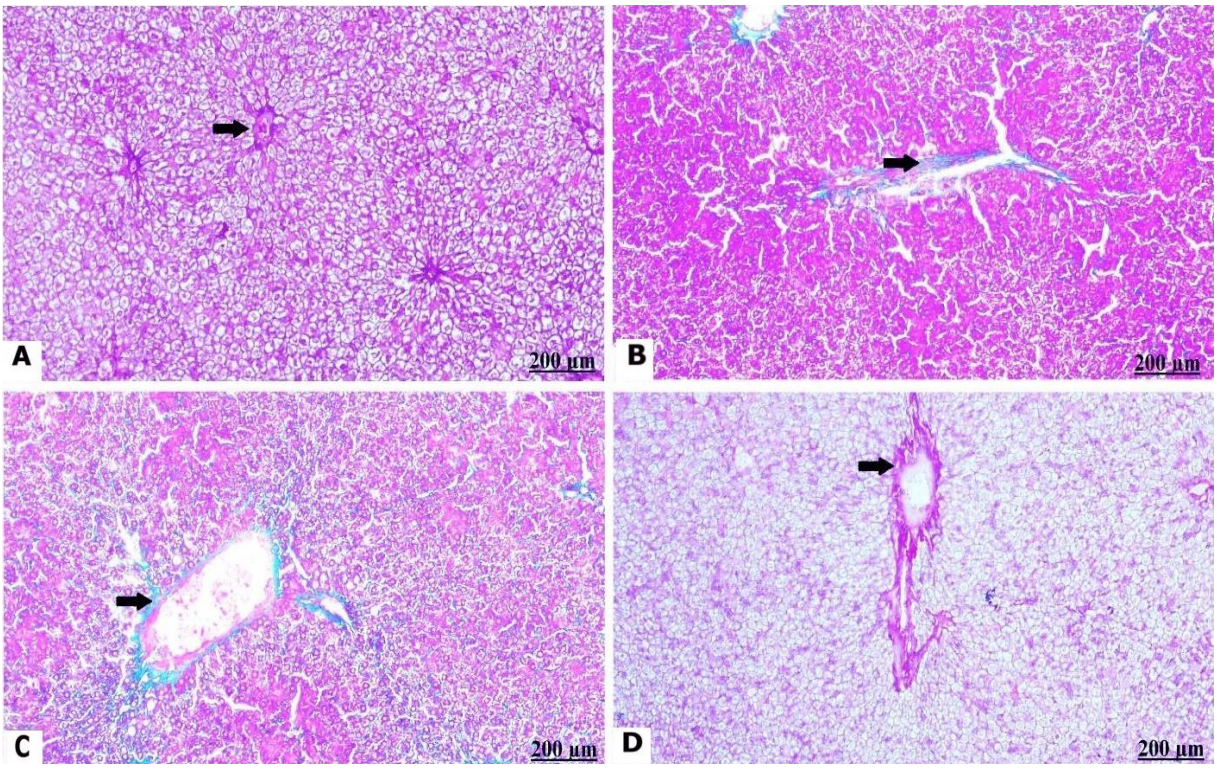

Figure 6: Histological sections (with Masson's trichrome stain) of the maternal liver of the treated rats' mothers with propolis **(A)**, oxaliplatin **(B & C)**, and oxaliplatin+propolis **(D)** during the period of pregnancy. **(A)** Showing normal distribution of the fibrous tissues (arrow). **(B & C)** Showing significant hepatic fibrosis (arrows). **(D)** Showing minimally infiltrated fibrous tissues (arrow).

Oxaliplatin-based chemotherapy is often used as adjuvant therapy in colon and rectal cancer[33]. Oxaliplatin, is a third generation platinum anticarcinogenic; frequently known as chemotherapy-associated liver injury[34]. Sinusoidal obstruction syndrome is side complication of oxaliplatin toxicity, in which histological screening of the liver is characterized by a series of pathological lesions included expansion of blood sinusoid, hemorrhage, and nodular hyperplasia[5,30,31].

Oxaliplatin promotes liver injury through aggravates the oxidative stress, inflammation and fibrosis[34]. Oxaliplatin induced liver oxidative stress response by generation of excess ROS that eventually caused spectrum of reactions like oxidative damage of hepatocytes mitochondria and edematous changes of the blood sinusoidal endothelium[26]. Oxidative stress is a condition reflects disturbance between the ROS and cellular antioxidant system due to activated ROS generation[35]. The enhanced ROS are in charge of toxic effects in the body resulted in tissue damages. ROS comprised in-between others hydroxyl radicals, peroxyl radicals, singlet oxygen, and peroxynitrite, which produced from nitrogen oxide, all these atoms act as a unit and termed free radical. Free radicals such as peroxyl, alkoxyl, and aldehyde are formed owing to subsequent lipid peroxidation, which can damage all components of the cell such as comprehensive proteins, lipids, and DNA[35]. So that, when plasma membrane of the liver cell is damaged, a variety of normally located enzymes in the cytosol are leaked into the blood circulation[24].

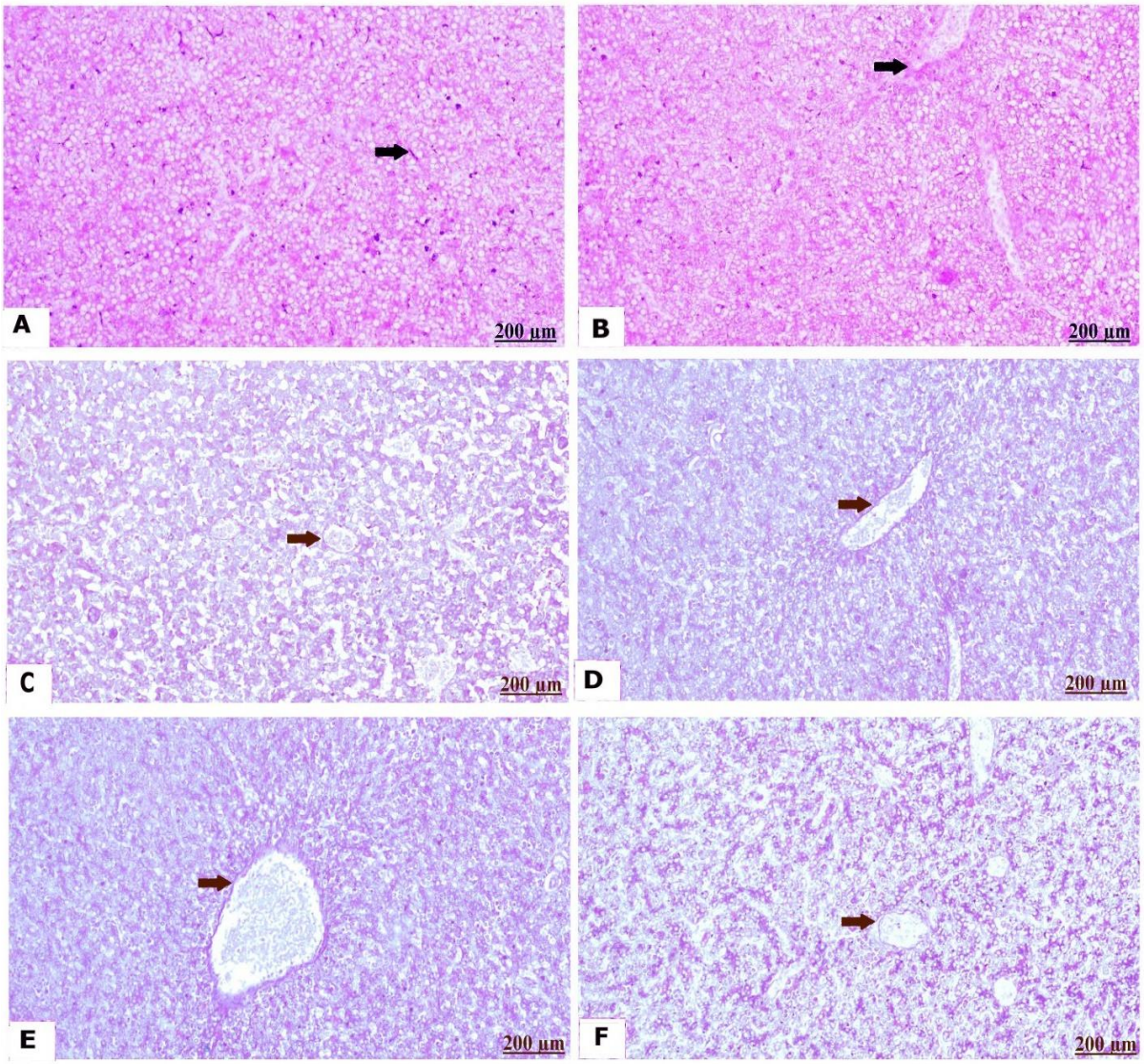

Figure 7: Histological sections (with Masson's trichrome stain) of the fetal liver of the control group **(A & B)** and the treated groups before pregnancy with propolis **(C)**, oxaliplatin **(D & E)**, and oxaliplatin+propolis **(F)**. **(A & B)** Showing less distinct collagen fibers (arrows). **(C)** Showing fair-detectable fibrosis (arrow). **(D & E)** Showing acceptable degree of perivascular fibrosis (arrows). **(F)** Showing slightly perivascular allocated fibrous tissues (arrow).

Process of fetal development is complicated and presumably affected by teratogenic drugs at varying stages. Chemotherapeutic drugs can go across the placenta at variable amounts. During pregnancy, cancer therapy makes the fetus more susceptible to considerable toxic agents that impact cell division[36]. In which pathological processes were restricted to offspring[37]. Propolis enclosed more than 108 active compounds of phenolic origin with antioxidants activity such as poly-phenol and flavonoids[38]. Additionally, the biological role of propolis is frequently through presence of flavonoids, which are known as various influences on health[39]. The GC-MS analysis of the used propolis extract in the current study identified the major classes of the bioactive compounds in propolis perhaps are responsible for favorable health activity as hexadecanoic acid, oleic acid, and pentadecanoic acid[18]. Zulhendri *et al*.[40] reported that the bioactive compounds in propolis possess a wide range of biological activities including hepato-protective, antitumor, antioxidative, and anti-inflammatory effects.

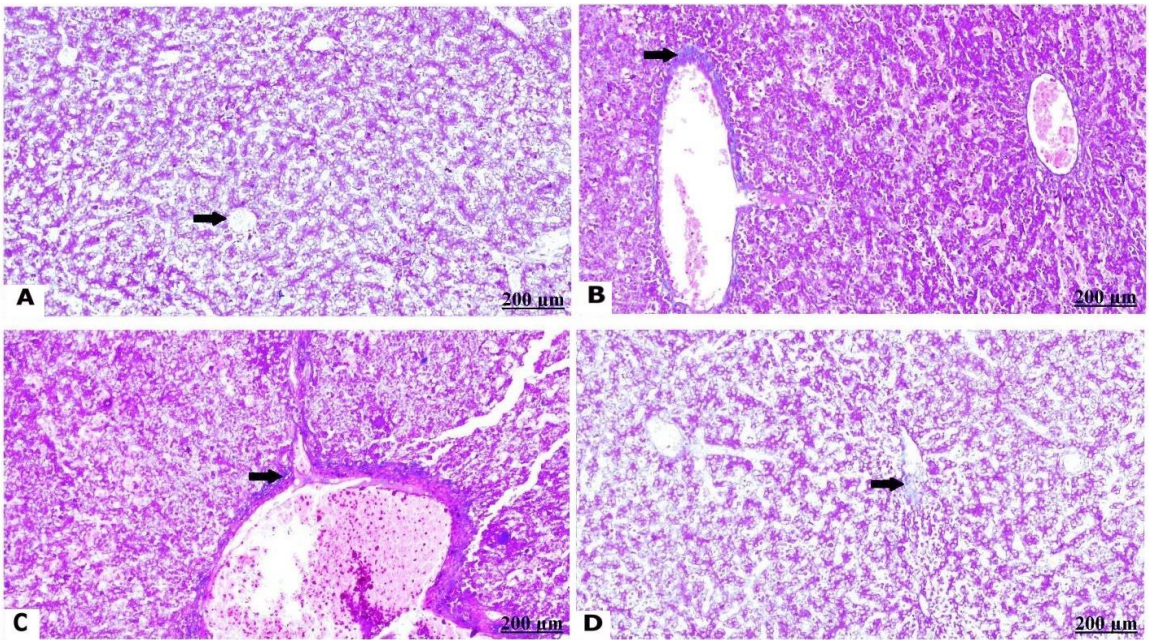

Figure 8: Histological sections (with Masson's trichrome stain) of the fetal liver of the treated rats' mothers with propolis **(A)**, oxaliplatin **(B & C)**, and oxaliplatin+propolis **(D)** during the period of pregnancy. **(A)** Showing normally defined fibrous tissues (arrow). **(B & C)** Showing heavily demarcated fibrous tissues around blood vessels (arrows). (**D)** Showing slight degree of hepatic fibrosis (arrow).

Depending on our data, it could be concluded that propolis markedly alleviated the extent of hepatic damage and fibrosis induced by oxaliplatin in female rats and their offspring, which might related to the antioxidant activity of propolis that required further studies to prove it.

AUTHORS' CONTRIBUTIONS

EAA, DAMZ, and ZK jointly developed the hypothesis of the study and methodology. For this manuscript, ZK, ZAA, SAM and AAM were involved in the experimental procedures and analyses. ZK edited and revised final version of the manuscript. All authors have approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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دراسات نسيجية على أكباد أمهات الجِرذان وذرياتهن بعد المعاملة بالأوكساليبلاتين والدور الوقائي المحتمل لصمغ النحل

زينب كمال[1]، خالد بن الوليد عبدالفتاح أحمد[2]، درية عبدالله محمد زغلول[3]، زينب الأمجد[4]، أماني أيمن محمد[1]، سهام علي مبارك[1]

[1]قسم علم الحيوان، كلية العلوم، جامعة جنوب الوادي، قنا، جمهورية مصر العربية
[2]معمل الإلكترونيات والأجهزة النانومترية، كلية العلوم، جامعة جنوب الوادي، قنا، جمهورية مصر العربية
[3]قسم التشريح الآدمي والأجنة، كلية الطب، جامعة أسيوط، أسيوط، جمهورية مصر العربية
[4]الهيئة العامة للخدمات البيطرية، مديرية الطب البيطري بقنا، جمهورية مصر العربية

تتزايد المعرفة حول إمكانية العلاج الكيميائي أثناء الحمل. عقار الأوكساليبلاتين – الجيل الثالث من عقار البلاتين – هو العامل الرئيسي لعلاج العديد من الأورام السرطانية. ويسبب الأوكساليبلاتين تغيرات مَرَضية لخلايا الأعضاء الحيوية، خاصة تلك المسؤولة عن إزالة السموم مثل الكبد. ركزت الدراسة الحالية على تقييم الدور المُخفف المحتمل لصمغ النحل ضد تسمم الكبد المُستحث بالأوكساليبلاتين في أمهات الجِرذان وذرياتهن قبل وفي أثناء فترة الحمل. تم توزيع "35" من إناث الجِرذان البالغة من سلالة "Sprague-Dawley" إلى سبع مجموعات (ن = 5). تلقت المجموعة "1" (المجموعة الضابطة) ماء مقطر خلال فترة التجربة. وتلقت المجموعة "2" جَرعة من صمغ النحل "200 ملجم/كجم من وزن الجسم" يوميًا عن طريق الفم، والمجموعة "3" تلقت جرعة "3 ملجم/كجم من وزن الجسم" من الأوكساليبلاتين بالحقن الوريدي ثلاث مرات أسبوعيًا، وتلقت المجموعة "4" الأوكساليبلاتين وصمغ النحل معًا، وذلك لمدة 21 يومًا قبل الحمل. بالمثل تلقت المجموعات "5-7" المعاملات والجرعات نفسها كما في المجموعات "2-4"، علي التوالي، خلال فترة الحمل. وأظهرت نتائج الدراسة الحالية أن المعاملة بالأوكساليبلاتين قبل وبعد الحمل أدت إلي ضرر وتليف في أنسجة أكباد الأمهات والأجنة. كما أظهرت النتائج أن المعاملة المشتركة بالأوكساليبلاتين وصمغ النحل خففت من سُمية الكبد المرتبطة بالمعاملة بالأوكساليبلاتين سواء قبل أو في أثناء فترة الحمل، مما يشير إلي الدور الواعد لصمغ النحل كمضاد للسموم من أصل طبيعي.