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RESEARCH ARTICLE

POTENTIAL AMELIORATIVE EFFECT OF PROPOLIS AGAINST THE DEVELOPMENTAL TOXICITY INDUCED BY OXALIPLATIN IN ALBINO RATS PRIOR AND DURING PREGNANCY

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ABSTRACT

Oxaliplatin (OXA), belongs to the class of platinum-based antitumor drugs. Among the standard chemotherapeutic agents, OXA succeeded in the treatment of different tumors. However, using of OXA prior or during pregnancy constitutes health challenge to mothers and their offspring owing to cumulative outcome. Propolis (PRO) is a resinous product collected by the bee "*Apis mellifera*" from plants to cement the beehives, and has a protective efficiency against many medication-toxicity. The present study aimed to appreciate the protective effect of PRO against OXA-induced toxicity on the mothers and their neonates. Thirty-five adult female Sprague-Dawley rats were equally divided into seven groups: the control pregnant group received distilled water; however, the groups 2, 3, and 4 received PRO (200 mg/kg body weight, orally/daily), OXA (3 mg/kg body weight, intravenous injection, three times/week), OXA+PRO, respectively, for 21 days pre-pregnancy; while, the groups 5, 6, and 7 received the same treatments and doses for 21 days during pregnancy. The results of the current study showed that – as compared to the OXA-induced renal and splenic toxicity in maternal rats and their neonates – co-administration of PRO with OXA either prior or during pregnancy conferred a crucial protective role to overwhelm the OXA-induced histopathological alterations in the renal and spleen tissues.

INTRODUCTION

Cancer is the most common chronic disease; the information about the occurrence and the possibility of cancer therapy during pregnancy is increasing nowadays[1]. A variety of theses chemotherapeutic drugs was in a concomitant with significant toxic manifestations[2]. The kidney is crucial organ for the major function of the body. It plays essential part in an elimination of the drugs, toxins, and the metabolic products. Thus, kidney might become susceptible to damage and injury caused by several nephrotoxic agents[3]. Chemo-

therapeutic drugs can attack any part of the kidney, resulting in kidney damage with glomerulonephritis and interstitial inflammation[4].

The platinum-dependent drugs, which comprised cisplatin, oxaliplatin (OXA), and carboplatin, are exceedingly used as anti-neoplastic therapy[5]. The OXA, a third-generation platinum-based analogue, has been devoted for the remedies of the colon, pancreatic, and gastrointestinal tumors nowadays. The OXA other than other platinum agents was claimed to own a reduced risk of tissues toxicity[6]. However, the cumulative dose-dependent side effect is a characteristic of OXA-induced toxicity[7]. Several cases of OXA-induced renal dysfunction have been reported[6]. Nephrotoxicity is a primary hazardous issue as complication resultant of the platinum-based drugs therapy. Insufficiency in the kidney functions, fundamentally serum creatinine level, is an accurate marker for kidney injuries[8]. The OXA-induced nephrotoxicity confirmed by renal biopsy[6]; histopathologically, it was linked with tubular necrosis and acute interstitial nephritis. Therefore, monitoring for kidney function aberrations should be kept in attendance during OXA chemo-therapy.

Regarding to the immune system, the spleen represents the greatest lymphoid tissue that plays a critical part in the functioning of the immune body[9]. Accordingly, splenic dysfunction deterio-rates a variable numbers of the bio-logical body functions. Correspondingly, OXA is dose-dependent, unexpectedly induced splenomegaly in the patients with significant baseline platelet count. Myelo-suppressive reaction, immune-mediated response, and splenic sequestration of platelets are considered the main three mechanisms have been suggested OXA-induced thrombocytopenia[10].

It is well recognized that antineoplastic drugs were capable of induction of the oxidative stress through reactive oxygen species (ROS) leading to disturb the functioning of the normal cells and cell apoptosis[11]. The OXA could induce oxidative stress in mice, as reflected by a significant increment in the malondi-aldehyde (MDA) level accompanied by significant reduction in the antioxidants "catalase (CAT), superoxide dismutase (SOD), and reduced glutathione (GSH)[12]. This could be because of OXA was able to the formation of DNA adducts which lead to intracellular generation of ROS following mitochondrial lesions[13]. ROS could directly promote tissues damage by oxidative modifying fatty acid constituents of the phospholipid content leading to lipid peroxidation and formation of MDA[14].

It is not surprised that none of the chemotherapeutic drugs is quite risk-free during the pregnancy; as exposure timing and transplacental transfer properties are deleteriously influence the fetus. The OXA has the susceptibility to pass through the placental blood barrier and confirms the effect on the offspring following the administration[15]. In spite of the shortage in the management of pregnancy-associated cancer, plenty of earlier studies mentioned the possible fetal side effects of anti-neoplastic medicine during pregnancy[16]. Accordingly, the cases of birth of a neonate small was reported[17]. Latterly, a rising attention has been paid towards herbals and natural products in the treatment of the different toxicological issues and various diseases[18].

Propolis (PRO) is a collected natural mixture from living plants via honeybees[19]. The PRO has clearly turned into to exert a substantial role of alternative medicine attributed to its biological effects. It incites anti-inflammatory, anti-tumor, antioxidant, anti-microbial, anti-ulcer, and carcinostatic activities. Wherefore, varying researches were conducted on the chemotherapeutic agents by using the PRO to attenuate their most toxic manifestations[20]. The PRO could alleviate drugs-induced oxidative stress in the tissues notably the kidney *via* the ability to scavenge the liberated free radicals to avoid the lipid peroxidation. This

alleviation is manifested by significant improvement in the antioxidant parameters of the kidney such as the level of SOD, glutathione peroxidase, and malondialdehyde[21].

Therefore, it was necessitated to reduce the side effects of OXA in a possible enhancement of its anti-cancer efficacy, which can occur *via* combination OXA with natural products notably PRO. Thereby, this work was designed to minimize the hazardous effects because of OXA therapy through PRO combinatorial treatment.

MATERIAL AND METHODS

Drugs and chemicals

The OXA was purchased from Mylan Institutional LLC (Morgantown, WV, USA) packed as a fluid injected as a singular intravenous dosage. The PRO was obtained from Elhassan Bee House located in Qena Governorate, Egypt. According to Salleh *et al*.[22], the crude PRO was extracted by distilled water (1:5 mass/volume) in the flask, and stirred for 5 minutes at 70^{o}C then left overnight in a dark room. After that, the mixture was filtered using Whatman number 1.0 filter paper; and freshly used for the experiments.

Characterization of aqueous PRO extract ingredients by using gas chromatography-mass spectrometry (GC-MS) analysis

According to the method of Abd El-Kareem *et al*.[23], the main components of aqueous PRO extract were determined using Trace GC-TSQ mass spectrometer (Thermo Scientific, Austin, TX, USA) with a direct capillary column TG–5MS (30 m × 0.25 mm × 0.25 µm film thickness). Temperature was initially held at 50°C and then increased by 5°C/minute to 250°C. Finally, the temperature was increased to 300°C by 30°C/minute and hold for 2 min. The injector and MS transfer line temperatures were kept at 270°C and 260°C, respectively; Helium was used as a carrier gas at a constant flow rate of 1 mL/minute. The peak area percentage was used to determine the aqueous PRO extract relative concentration of various components. The components of aqueous PRO extract were identified by comparison of their mass spectra with those of WILEY (Wiley Registry of Mass Spectral Data, 9th Edition) and NIST (National Institute of Standards and Technology 14th Edition).

Experimental animals and experimental design

A total of thirty-five Sprague-Dawley female albino rats (*Rattus norvegicus*) weighted about 80-220 g with 5-6 months old were obtained from laboratory animal house belonging to Sohag University (Sohag Governorate, Egypt). Rats housed in plastic cages in room under suitable environmental conditions of temperature and humidity. Animals kept in the experimental place for about two weeks to be adapted to the surrounding environment. Along over the experiment, the animals were given standard diet and clean water.

The animals were randomly classified into seven groups, five for each. The control pregnant group, where animals were orally given distilled water. The other six animal groups were dosed with OXA and PRO prior or during the pregnancy for 21 days as following: the rats of the PRO group received orally and daily 200 mg PRO/kg body weight[24], the rats of the OXA group received intravenously injected three times per week with 3 mg OXA/kg body weight[15], and the rats of the OXA+PRO group received a combine dose of OXA and PRO. The experimental procedures were complying with the guidelines with the Care and Use of Laboratory Animals and approved by the Institutional Animal Care Unit Committee, Faculty of Science, South Valley University, Qena, Egypt (agreement number**:** 019/03/2023).

Body and kidney weights

Body weight of the pregnant female rats was consecutively measured during experiment at 0, 6th, 12th, 18th and 20th day of pregnancy. Kidney weight of the mother was assessed too after necropsy; besides this, body weight

of the neonatal was soon evaluated at the time of birth.

Biochemical assay

At time of parturition; the mothers rats of all groups were euthanized under general anesthesia management *via* diethyl ether. Fully enzymatic determination of blood urea and creatinine was done using standard measuring kits purchased from Bio-diagnostic Company (Giza, Egypt) in agreement with the producer's commands. Kidneys were immediately dissected and kidney tissue specimens were homogenate in PBS (phosphate buffered saline) solution, pH 7.4 containing 0.16 mg/mL heparin then cold centrifuged at 2325 ×*g* for 15 minutes at 4°C according to Ghanbari *et al*.[25]. Renal MDA level and CAT activity were assessed in the different experimental groups using ideal measuring kits from Biodiagnostic Company in agreement with the producer's commands.

Histopathology studies

For histological screening, maternal and fetal kidneys and spleen of the different groups were extracted and then fixed in 10% neutral buffered formalin solution for 24 hours at the minimal level. Kidney and spleen specimens were consecutively processed by mean of washing with distilled water followed by serial dilutions of ethanol for dehydration, clearance in xylene, and embedding at 60°C melted in paraffin waxes as expressed by Larson *et al*.[26]. The obtained tissue sections of about 4-5 µm thickness were deparaffinized and eventually stained with hematoxylin and eosin (H&E) and Masson's trichrome to be inspected under light microscopy for histopathological examinations.

Statistical analysis

All the described data for each group were in the form of mean values ± standard deviation (SD). Statistical analysis was conducted with SPSS program using one way analysis of variance (ANOVA) followed by *post-hoc* Scheffe's test, and statistically being considered significant when $P<0.05$[27].

RESULTS

Characterization of the bioactive components of aqueous PRO extract

Figure "1" showed the GC-MS chromatogram of the bioactive compositions presented in aqueous PRO extract. The major components were hexadecanoic acid (11.41%), oleic acid (11.19%), vaccenic acid (11.19%), 9-octadecenoic acid (11.19%), 10-octadecenoic acid methyl ester (9.50%), pentadecanoic acid (5.65%), cyclopentanetrideanoic acid methyl ester (5.65%), hi-oleic safflower oil (4.61%), linoleic acid ethyl ester (4.27%), and erucic acid (2.21%). Other components represent less than 2%. The major phyto-chemical components of aqueous PRO extract, identified by retention time, peak area percentage, molecular weight, and chemical formula were summarized in Table "1".

Effect of OXA and PRO on body and kidney weights of maternal Sprague-Dawley rats and their neonates

The PRO, OXA, and OXA+PRO treated rats prior pregnancy or during pregnancy had non-significant changes ($P\geq0.05$) in the maternal body weights compared with the control animals (Table 2). Likewise, the same results were recorded among the maternal kidney weights of the treated rats prior and during pregnancy in comparison with the control animals (Table 3). Conversely, a significant decrease ($P<0.05$) fulfilled in neonatal weights of the OXA-treated rats prior pregnancy as compared with the control animals. Moreover, uses of PRO improved and reversed the body weights of newborns, which reduced because of OXA therapy, to the control value (Table 3). Non-significant changes ($P\geq0.05$) were detected among the PRO, OXA, and OXA+PRO treated animals during pregnancy in comparison with the control animals (Table 3).

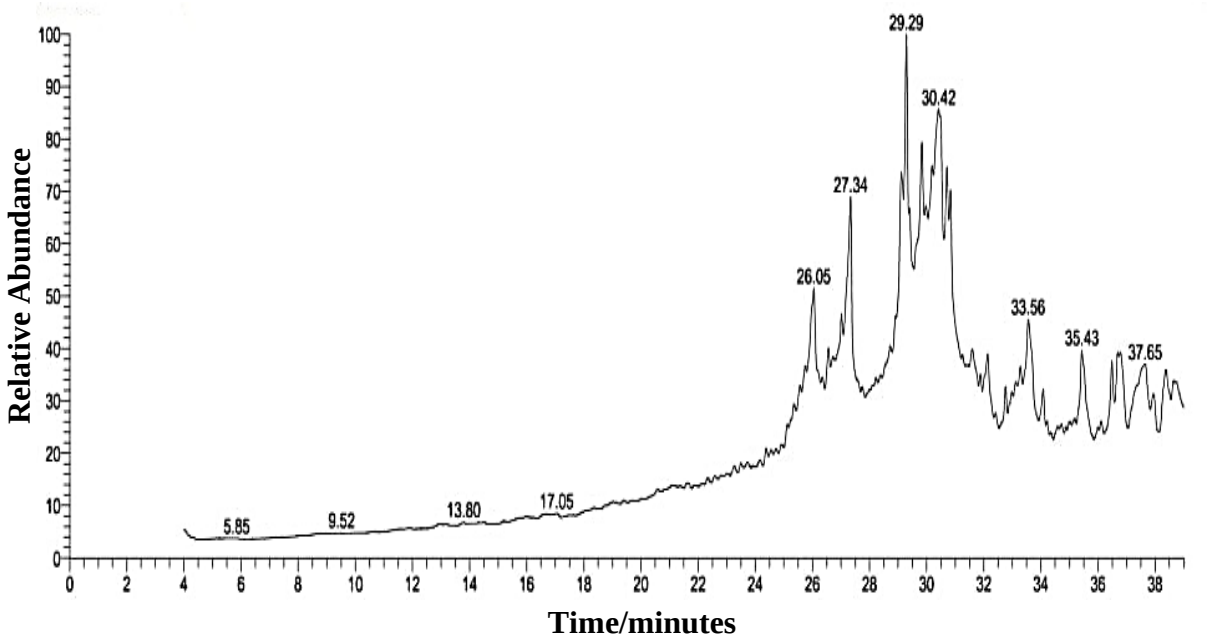

Figure 1. GC-MS chromatogram of the bioactive compounds identified in aqueous PRO extract.

Table 1: Phytochemical analysis of aqueous propolis extract by gas chromatography-mass spectrometry (GC-MS).

Number	Compound Name	Retention Time (minutes)	Area (%)	Molecular Weight	Molecular Formula
1	Hexadecanoic acid	27.34	11.41	296	$C_{16}H_{32}O_2$
2	Oleic acid	30.49	11.19	282	$C_{18}H_{34}O_2$
3	Cis-Vaccenic acid	30.49	11.19	282	$C_{18}H_{34}O_2$
4	9-octadecenoic acid	30.49	11.19	282	$C_{18}H_{34}O_2$
5	10-Octadecenoic acid, methyl ester	29.29	9.50	296	$C_{19}H_{36}O_2$
6	Pentadecanoic acid	26.05	5.65	242	$C_{15}H_{30}O_2$
7	Cyclopentanetrideanoic acid, methyl ester	26.05	5.65	296	$C_{19}H_{36}O_2$
8	Hi-oleic safflower oil	32.13	4.61	450	$C_{21}H_{22}O_{11}$
9	Linoleic acid ethyl ester	29.10	4.27	308	$C_{20}H_{36}O_2$
10	Erucic acid	36.68	2.21	338	$C_{22}H_{42}O_2$

Effect of OXA and PRO on biochemical parameters of pregnant Sprague-Dawley rats

Our results illustrated that the level of urea in treated groups prior and during pregnancy in comparison with the control rats, showed a significant increase (P<0.05) in the OXA and OXA+PRO treated rats. Meanwhile, the PRO-treated rats prior and during pregnancy illustrated non-significant changes (P≥0.05) when compared with the control animals (Table 4). However, the combination of OXA with PRO diminished significantly (P<0.05) the elevated urea level in comparison with the OXA-treated groups prior and during pregnancy.

Regarding to creatinine, there was a significant increase (P<0.05) in the OXA

and OXA+PRO treated groups prior or during the pregnancy as compared with the control rats. On the other hand, treatment with combination of PRO with OXA prior or during the pregnancy led to a non-significant reduction ($P \geq 0.05$) in the creatinine level when compared with the OXA-treated rats (Table 4).

Table 2: Effect of OXA and PRO on the maternal body weight (g, mean ± standard deviation) of Sprague-Dawley rats.

		GD (0)	GD (6^{th})	GD (12^{th})	GD (18^{th})	GD (20^{th})
Prior pregnancy	Control	181.0±17.0	185.3±18.5	192.3±21.5	199.0±24.1	203.3±24.5
	PRO	196.0±2.6	197.6±2.1	207.0±1.0	213.3±4.2	224.0±3.6
	OXA	211.3±25.7	215.6±26.8	227.6±29.8	235.6±16.9	240.3±14.2
	OXA+PRO	172.0±2.0	177.3±3.7	190.6±4.9	210.0±3.6	222.3±4.0
During pregnancy	PRO	189.3±11.5	198.6±14.7	206.6±18.6	217.0±22.2	225.0±23.8
	OXA	179.6±18.5	175.3±23.1	182.0±22.5	196.6±20.2	205.4±17.2
	OXA+PRO	183.6±5.5	189.6±7.4	192.3±4.9	202.6±6.4	209.3±5.8

GD: gestational day, OXA: oxaliplatin, PRO: propolis.

Table 3: Effect of OXA and PRO on the weights (g) of maternal kidney and newborns (mean ± standard deviation) of Sprague-Dawley rats.

		Maternal kidney weight (g)	Fetal weight (g)
Prior pregnancy	Control	1.6±0.4	5.3±0.6
	PRO	1.4±0.4	5.6±0.6
	OXA	1.2±0.4	3.3±0.6[a]
	OXA+PRO	1.4±0.6	5.3±0.6[b]
During pregnancy	PRO	1.6±0.2	5.3±0.6
	OXA	0.8±0.3	3.9±0.1
	OXA+PRO	1.0±0.2	4.5±0.5

[a]$P<0.05$ compared with the control group, [b]$P<0.05$ compared with the OXA-treated group, OXA: oxaliplatin, PRO: propolis.

The OXA-treated rats prior pregnancy, revealed a significant increase ($P<0.05$) in the lipid peroxidation marker "MDA level" when compared with the control rats. On contrary the MDA level of the OXA-treated rats during pregnancy didn't exhibit significant changes ($P \geq 0.05$) when compared with control rats. Nevertheless, the PRO administration in the OXA-treated rats prior and during pregnancy had reduced significantly ($P<0.05$) the MDA level as compared with the OXA-treated rats (Table 4). Furthermore, CAT activity was decreased significantly ($P<0.05$) in the OXA-treated rats prior and during pregnancy in comparison with the control rats. While, a significant increase ($P<0.05$) was noticed in the CAT activity in the OXA+PRO-treated rats prior pregnancy in comparison with the OXA-treated rats. However, during pregnancy the OXA+PRO-treated rats didn't exhibit significant changes ($P \geq 0.05$) when compared with the control and OXA-treated rats (Table 4).

Table 4: Effect of OXA and PRO on the kidney functions and renal oxidative stress markers (mean ± standard deviation) of pregnant Sprague-Dawley rats.

		Urea (mg/dL)	Creatinine (mg/dL)	Malondialdehyde (nmol/g tissue)	Catalase (U/g tissue)
Prior pregnancy	Control	52.0±2.0	1.0±0.2	3.7±0.2	37.3±1.8
	PRO	57.6±2.5	1.2±0.2	3.3±0.3	36.3±1.5
	OXA	110.6±4.0[a]	2.5±0.4[a]	4.0±0.2[a]	28.8±1.0[a]
	OXA+PRO	62.6±3.0[ab]	2.2±0.2[a]	2.9±0.1[b]	35.2±2.3[b]
During pregnancy	PRO	59.0±2.0	1.3±0.3	3.2±0.2	36.0±1.0
	OXA	130.0±3.0[a]	2.8±0.2[a]	3.8±0.2	27.5±0.5[a]
	OXA+PRO	64.0±2.0[ab]	2.3±0.3[a]	3.3±0.3[b]	34.3±3.1

[a]$P<0.05$ compared with the control group, [b]$P<0.05$ compared with the oxaliplatin-treated group, OXA: oxaliplatin, PRO: propolis.

Histopathological alterations in kidney tissues induced by OXA and PRO in maternal Sprague-Dawley rats and their neonates

Histological findings listed in Table "5" indicated that administration of OXA prior or during pregnancy was accompanied with violent histological deteriorations evident in the renal and splenic tissues of the mother and their neonates. Even though, co-administration of PRO with OXA resulted in diminished and attenuated the histological damage compared to those in the OXA-treated group. Such histological changes were confirmed by fibrosis *via* Masson's trichrome stain.

The histological analysis of hematoxylin and eosin staining sections of maternal kidneys of the control rats detected normal architecture of the nephrons, composed of healthy glomerulus and tubules (Figure 2A and B). According to the results of the treatment prior pregnancy, the PRO-treated rats showed normal architecture of the kidney parenchyma (Figure 2C). Contrariwise, pronounced histological changes were observed in the OXA-treated rats, where the renal tissues exhibited distinct necrosis of the renal tubules with hypercellularity of the glomeruli, severely dilated and congested blood vessels, besides sharp aggregation of mononuclear cells that mainly consisted of lymphocytes (Figure 2D and E). Even though, PRO minified the histological alterations induced by OXA therapy and decreased the congestion in the blood vessels (Figure 2F). Likewise, the treatment during pregnancy indicated that the PRO-treated rats had intact histology of the kidney tissues (Figure 2G); while, the OXA-treated rats showed inflammatory cells replaced necrotic tissues and obviously accumulated at the interstitium, as well severe engorgement of the blood vessels with stagnant red blood cells (Figure 2H and I). However, in the OXA+PRO-treated rats, regeneration in some renal tubules was clearly detected (Figure 2J).

The histological analysis of Masson's trichrome staining sections of maternal kidneys of the control rats showed ill-defined fibrous tissues (Figure 3A and B). According to the results of the treatment prior pregnancy, the PRO-treated rats showed minimally distributed collagen fibers at the capsular tissues (Figure 3C); while, in the OXA-treated animals the fibrous tissues were markedly infiltrated around the blood vessels (Figure 3D and E). However, the OXA+PRO-treated rats showed slightly infiltrated collagen fibers (Figure 3F). Likewise, the treatment during pregnancy indicated that the PRO-treated

Table 5: Histological scoring of kidney and spleen of the control and treated groups categorized depending on the severity of lesion.

	Control	Prior pregnancy			During pregnancy		
		PRO	OXA	OXA+PRO	PRO	OXA	OXA+PRO
			Kidney				
Necrosis of the renal tubules	-	-	++	+	-	+++	+
Degenerative changes of the tubules	-	-	+++	+	-	+++	+
Cytoplasmic vacuolation	-	-	+++	+	-	+++	+
Interstitial fibrosis	-	-	+++	+	-	+++	+
Inflammatory cells infiltration	-	-	+++	+	-	+++	+
Glomerular hypercellularity	-	-	+++	+	+	+++	+
Congestion of glomeruli	+	-	+++	+	-	+++	+
Dilatation and congestion of the blood vessels	-	-	+++	+	-	+++	+
Thickening of the blood vessels wall	-	-	+++	+	-	+++	+
			Spleen				
Depletion of the white pulp	-	-	+++	++	-	+++	++
Splenic fibrosis	-	-	+++	+	-	+++	+
Hemorrhage of the red pulps	-	-	+++	+	-	+++	+
Congestion and dilatation of blood vessels	-	-	+++	++	-	+++	++
Thickening of the splenic capsule	-	-	++	+	-	+++	+

Absent (-), mild (+), moderate (++), sever (+++), OXA: oxaliplatin, PRO: propolis.

rats showed credible degree of the interstitial fibrosis in kidneys of pregnant rats (Figure 2G). The renal perivascular fibrosis was characterized by noticeable infiltration of the fibrous tissues after OXA administration (Figure 3H and I). However, animals received OXA and PRO revealed slight perivascular fibrosis in kidneys of pregnant rats (Figure 3J).

The histological analysis of hematoxylin and eosin staining sections of the fetal kidneys of the control rats displayed normal nephritic tissues (Figure 4A and B). The treatment prior pregnancy revealed that the fetal kidneys of the PRO-treated rats had normal histological structures of the glomeruli and renal tubules (Figure 4C); while, the fetal kidney tissue of the OXA-treated rat was distinguished by intense infiltration of the inflammatory cells, also destructive damage and necrosis of the renal tubules was identified (Figure 4D and E). Otherwise, mild degeneration of the epithelium lining renal tubules and insubstantial glomerular congestion was seen in the fetal kidneys of the OXA+ PRO-treated rats (Figure 4F). Furthermore, the treatment during pregnancy indicated that the fetal kidneys of the PRO-treated group was characterized by intact nephritic tissues with healthy glomeruli and tubules (Figure 4G). Characteristic features of necrosis with sloughing and desquamation of the renal tubules were indicative by

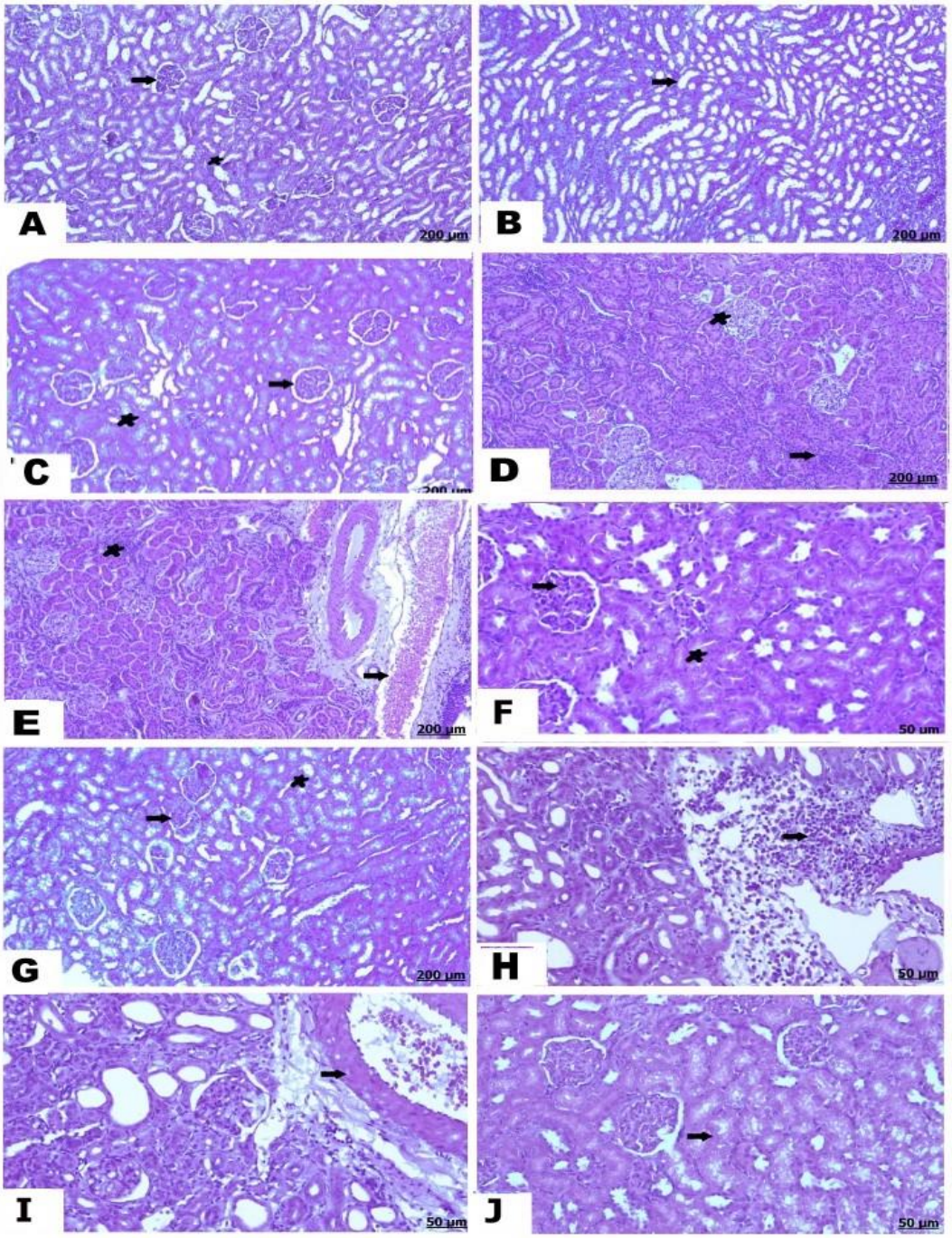

Figure 2: Photomicrograph of maternal kidney of control rat **(A & B)**; PRO **(C)**, OXA **(D & E)**, and OXA+PRO **(F)** treated rats prior pregnancy; and PRO **(G)**, OXA **(H & I)**, and OXA+PRO **(J)** treated rats during pregnancy. **(A)** Arrangement of the nephrons in a good manner with intact glomerulus (arrow) and normal convoluted tubules (star). (**B)** Normally arranged of convoluted tubules. **(C)** Normal renal parenchyma comprised healthy glomeruli (arrow) and normal renal tubules (star). **(D)** Renal tubules necrosis (arrow) and hypercellularity of the glomeruli (star). (**E)** Severely congestion of blood vessels (arrow), focal aggregation of mononuclear cells (star). (**F)** Mild congestion of the glomeruli (arrow), besides regeneration in some renal tubules (star). (**G)** Normal glomeruli (arrow) and normal renal tubules (star). (**H)** Prominent accumulation of inflammatory cells replaced necrotic tissues (arrow). **(I)** Severely dilated and congested blood vessels (arrow). (**J)** Renal tubules regeneration (star). Hematoxylin and eosin stain; **A-E**, and **G** scale bar = 200 µm; **F** and **H-J** scale bar = 50 µm.

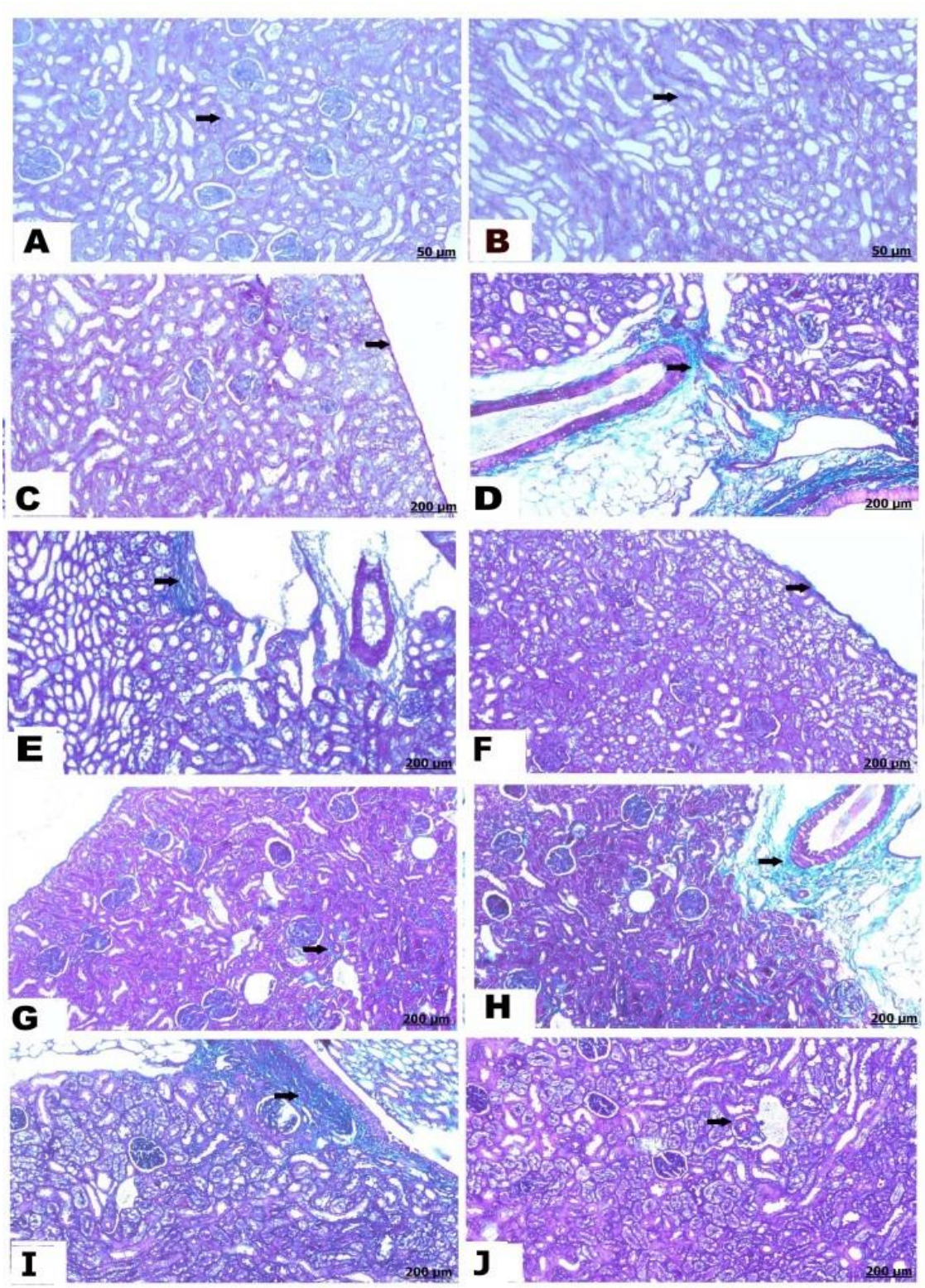

Figure 3: Photomicrograph of maternal kidney of control rats **(A & B)**; PRO **(C)**, OXA **(D & E)**, and OXA+PRO **(F)** treated rats prior pregnancy; and PRO **(G)**, OXA **(H & I)**, and OXA+PRO **(J)** treated rats during pregnancy. **(A & B)** Fibrous tissues were scantly infiltrated. **(C)** Minimally distributed collagen fibers. **(D & E)** Prominent fibrosis with remarkable infiltration of the collagen fibers. (**F)** Slightly infiltrated collagen fibers. **(G)** Moderate degree of the interstitial fibrosis. **(H & I)** Remarkable perivascular fibrosis. (**J)** Slightly deposited collagen fibers around blood vessels. Masson trichrome stain; **A** and **B** scale bar = 50 µm; **C-J** scale bar = 200 µm.

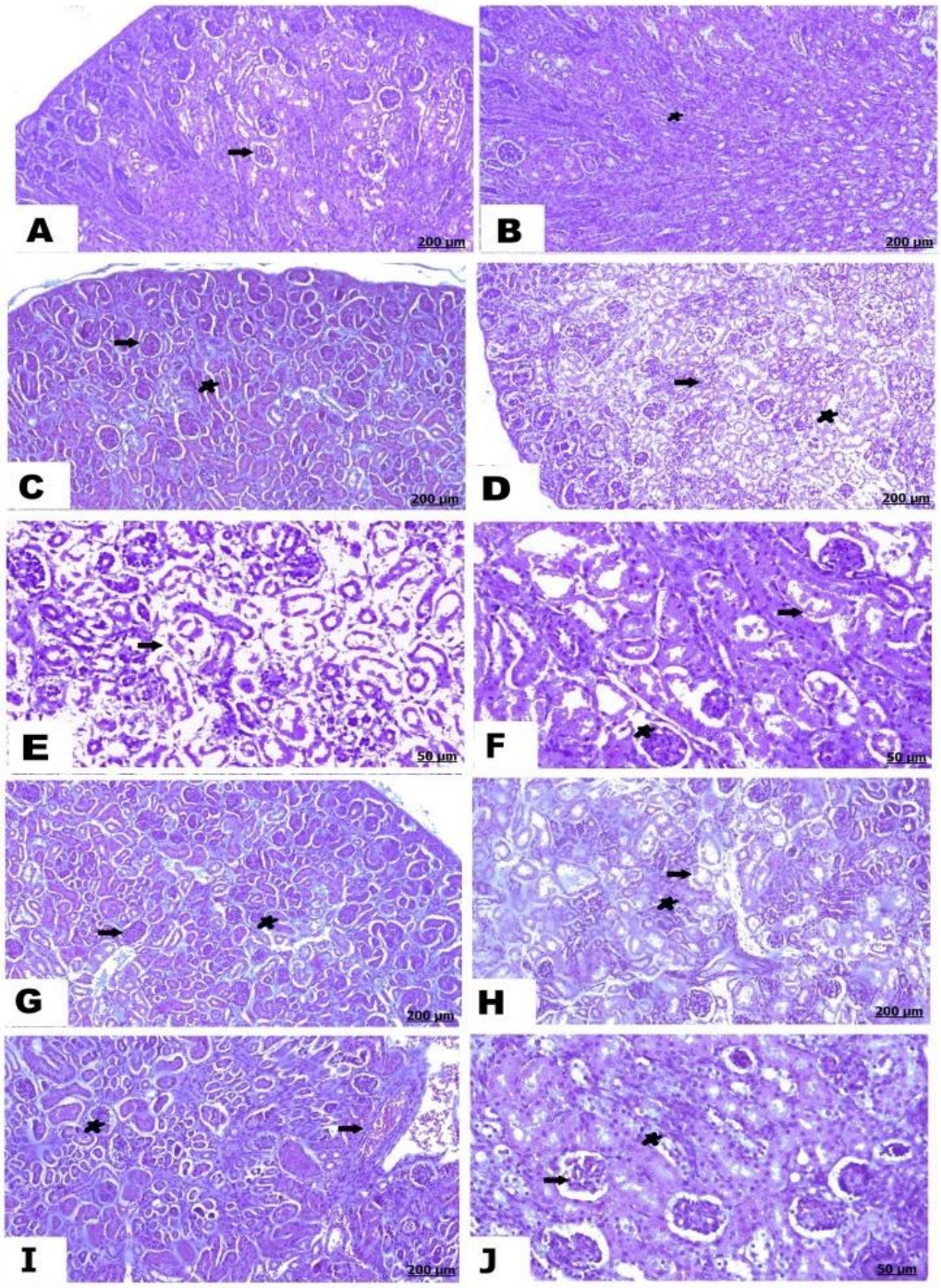

Figure 4: Photomicrograph of fetal kidney of control rats **(A & B)**; PRO **(C)**, OXA **(D & E)**, and OXA+PRO **(F)** treated rats prior pregnancy; and PRO **(G)**, OXA **(H & I)**, and OXA+PRO **(J)** treated rats during pregnancy. (**A)** Normal glomeruli. (**B)** Renal tubules coordinated in a good manner. (**C)** Normal glomeruli (arrow) and normal renal tubules (star). **(D)** Remarkable infiltration of the inflammatory cells (arrow) and necrosed tubules (star). (**E)** Destructive damage of the renal tubules. **(F)** Mild degeneration of the renal tubular epithelium (arrow) and slight congestion of the glomeruli (star). **(G)** Healthy nephritic tissues comprised healthy glomeruli (arrow) and tubules (star). **(H)** Necrosis with sloughing of the epithelial lining tubules (arrow) and interstitial inflammation (star). (**I)** Blood vessels engorged with blood (arrow) and glomerular hypercellularity (star). **(J)** Mild congestion of glomeruli (arrow) and slight degree of the cytoplasmic vacuolation (star). Hematoxylin and eosin stain; **A-D** and **G-I** scale bar = 200 µm; **E, F,** and **J** scale bar = 50 µm.

discrete mononuclear infiltration in fetal kidneys after OXA-treatment. Moreover, congestion of the blood vessels with hypercellularity of the glomeruli of fetal kidneys was cruelly disseminated in the OXA-treated rats (Figure 4H and I). The treatment with OXA+PRO led to ill-identified histological changes in fetal kidneys characteristic by inconsiderable congestion of the blood vessels with weak degenerative changes mainly cytoplasmic vacuolation (Figure 4J).

The histological analysis of Masson's trichrome staining sections of fetal kidneys of the control rats showed weak detectable fibrosis (Figure 5A and B). The treatment prior pregnancy revealed that the PRO-treated rats had faint distribution of the fibrous tissues in fetal kidneys (Figure 5C). The fetal kidneys of the OXA-treated rats pronounced heavy fibrosis, which was indicative by sharp infiltration of the fibrous tissues (Figure 5D and E). Interestingly, administration of OXA+PRO minified the fetal kidney fibrosis (Figure 5F). The treatment during pregnancy indicated that less fibrosis were observed in the fetal kidneys of the PRO-treated rats (Figure 5G), while fibrous tissues were markedly distributed perivascular in fetal kidneys of the OXA-treated rats (Figure 5H and I). Contrariwise, the OXA+PRO-treated rats showed obviously reduced in the amount of fibrous tissue in fetal kidneys (Figure 5J).

Histopathological alterations in spleen tissues induced by OXA and PRO in maternal Sprague-Dawley rats and their neonates

The histological investigation of hematoxylin and eosin staining of maternal spleen sections of the control rats demonstrated a normal, well-defined splenic pulps (Figure 6A and B). According to the results of the treatment prior pregnancy, the PRO-treated group showed normal parenchyma of white and red pulps (Figure 6C). However, the OXA-treated group had irregular histology; whereby spleen suffered from sharp depletion of the white pulps in addition to lucid distension of the blood vessels (Figure 6D and E). Even though, the treatment with PRO diminished the destructive damage induced by OXA treatment (Figure 6F). The treatment during pregnancy showed that normal histology of the splenic tissues was more detectable after PRO treatment (Figure 6G). The OXA-treated rats showed vascular dilatation of the splenic vessels and cytoplasmic vacuolation of splenic pulps (Figure 6H and I). With regards to OXA+PRO-treated animals, mild protrusion of the splenic trabeculae was shown (Figure 6J).

The histological investigation of Masson's trichrome staining sections of maternal spleen of the control rats showed less distinguished collagen fibers (Figure 7A and B). The treatment prior pregnancy indicated that the treatment with PRO induced a minimal deposition of the collagen fibers in the spleen of maternal rats (Figure 7C); while, the OXA-treated rats showed a considerable spleen fibrosis (Figure 7D and E). The group treated with OXA+PRO showed mild to moderate degree of the splenic interstitial fibrosis (Figure 7F). The treatment during pregnancy indicated that the splenic tissues of the PRO-treated animals had non-significant infiltration of fibrous tissues (Figure 7G). At the same time, there was a distinguished dense layer of fibrosis after the OXA treatment (Figure 7H and I). Though, a minimal degree of fibrous tissues infiltration was shown in maternal spleen of OXA+PRO-treated group (Figure 7J).

The histological investigation of hematoxylin and eosin staining sections of fetal spleen from the control rats indicated that the splenic pulps were normal and well organized (Figure 8A and B). The treatment prior pregnancy indicated that the fetal spleen of the PRO-treated rats exhibited visibly demarcated splenic regions (Figure 8C). Meanwhile, the fetal spleen of the OXA-treated rats showed depletion of the white follicles; cytoplasmic vacuolation and blood vessels were appeared severely

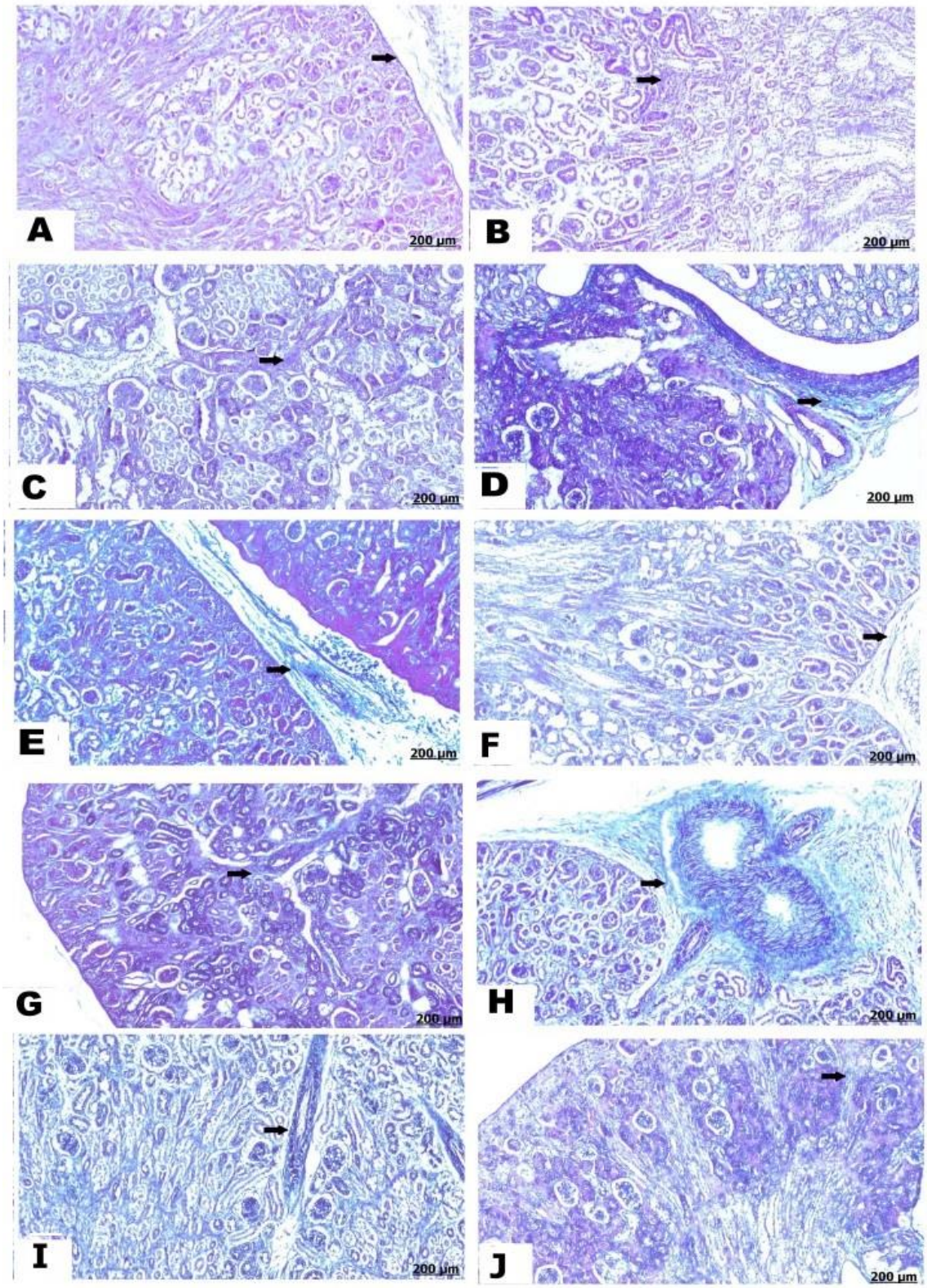

Figure 5: Photomicrograph of fetal kidney of control rats **(A & B)**; PRO **(C)**, OXA **(D & E)**, and OXA+PRO **(F)** treated rats prior pregnancy; and PRO **(G)**, OXA **(H & I)**, and OXA+PRO **(J)** treated rats during pregnancy. (**A & B)** Distribution of the fibrous tissues in a normal manner. **(C)** Slight interstitial fibrosis. **(D & E)** Heavily infiltrated collagen fibers. (**F)** Minimal distribution of the collagen fibers. (**G)** Few collagen fibers. **(H & I)** Well defined perivascular fibrosis. (**J)** Less infiltration of the collagen fibers. Masson trichrome stain; **A-J** scale bar = 200 µm.

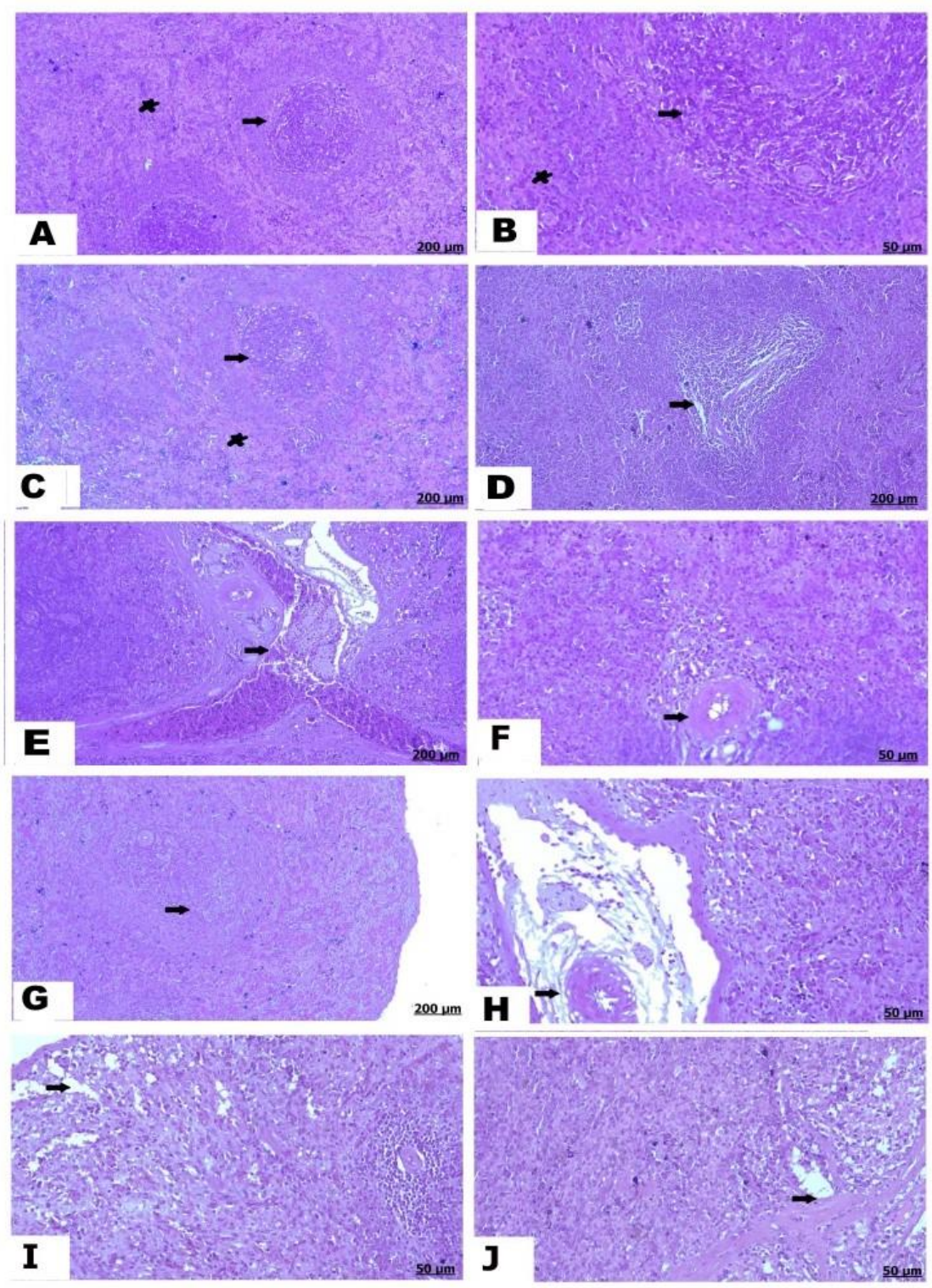

Figure 6: Photomicrograph of maternal spleen of control rat **(A & B)**; PRO **(C),** OXA **(D & E)**, and OXA+PRO **(F)** treated rats prior pregnancy; and PRO **(G)**, OXA **(H & I)**, and OXA+PRO **(J)** treated rats during pregnancy. (**A & B)** Normal architecture of the splenic tissues with normal lymphoid follicles (arrow) and normal red pulp (star). **(C)** Well defined white (arrow) and red pulps (star). (**D)** Depletion of the lymphoid follicles. (**E)** Severely distended blood vessels with blood. (**F)** Minimally dilated central arteriole. (**G)** Normal histology of the spleen. (**H)** Dilated blood vessels. (**I)** Intense vacuolation of the splenic tissues. (**J)** Minimally protruded of the splenic trabeculae. Hematoxylin and eosin stain; **A, C-E, G** scale bar = 200 µm; **B, F,** and **H-J** scale bar = 50 µm.

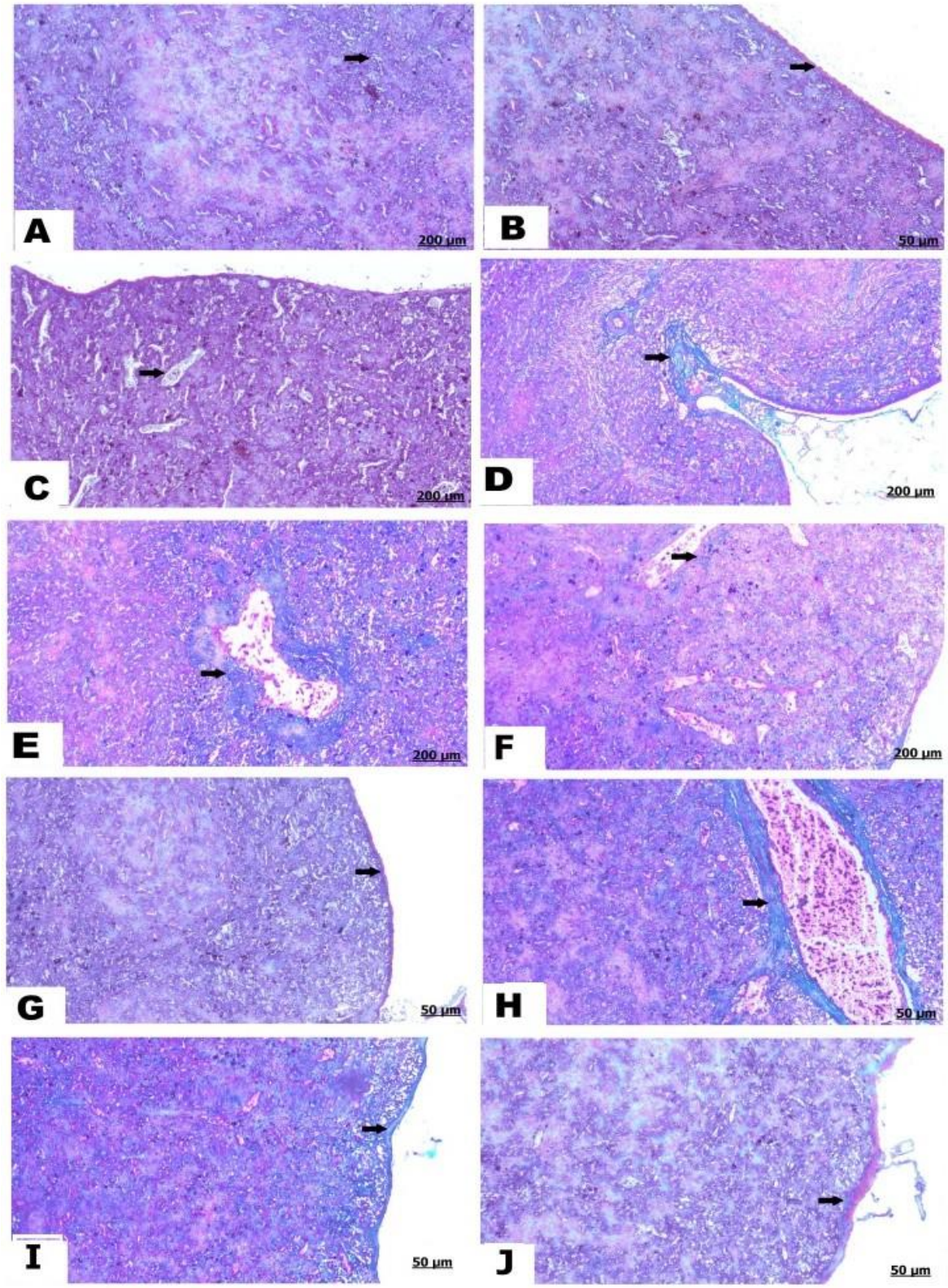

Figure 7: Photomicrograph of maternal spleen of control rat **(A & B)**, PRO **(C),** OXA **(D & E)**, and OXA+PRO **(F)** treated rats prior pregnancy; and PRO **(G)**, OXA **(H & I)**, and OXA+PRO **(J)** during pregnancy. **(A & B)** Less distinguished collagen fibers. (**C)** Less defined collagen fibers. **(D & E)** Intense fibrosis. (**F)** Minimal to moderate interstitial fibrosis. **(G)** Normal infiltration of the fibrous tissues. **(H & I)** Sharp layer of collagen fibers. (**J)** Minimal fibrosis. Masson trichrome stain; **A** and **C-F** scale bar = 200 µm; **B** and **G-J** scale bar = 50 µm.

congested (Figure 8D and E). The treatment with PRO attenuated the histological alterations caused by OXA; thereby minimal lesions in the blood vessels were more evident (Figure 8F). The treatment during pregnancy indicated that the treatment by PRO was accompanied by normal parenchyma of the spleen (Figure 8G). Notably, the OXA-treated group manifested clearly depleted white pulp and noticeable degree of the congestion of blood vessels (Figure 8H and I). Congestion of blood vessels in a mild manner was a characteristic feature of spleen tissue after co-administration of PRO with OXA (Figure 8J).

The histological investigation of Masson's trichrome staining section of fetal spleen of the control rats exhibited lack of interstitial fibrosis (Figure 9A and B). The treatment prior pregnancy showed that the fetal spleen of the PRO-treated rats had less detectable fibrous tissues (Figure 9C). Nevertheless, the OXA-treated rats manifested characteristic histology of the splenic fibrosis (Figure 9D and E), which were reduced in OXA+PRO-treated rats (Figure 9F). The treatment during pregnancy showed that the PRO-treated rats explained infrequent infiltration of fibrous tissues (Figure 9G), while acceptable degree of the splenic fibrosis was identified by a sharp layer of the fibrous tissues in the fetal splenic tissues of the OXA-treated rats (Figure 9H and I). In the contrast, the OXA+PRO-treated rats displayed minimal splenic fibrosis with ill-defined fibrous tissues (Figure 9J).

DISCUSSION

Not only cancer is a public health disease, but also may have profound implications for immune defense[28]. However, chemotherapy used for cancer treatment has associated with varying profound side effects[2]. OXA, cisplatin, and carboplatin are the major platinum compound used in cancer chemotherapy[29]. Accordingly, chemotherapy with OXA is appointed for a broad range of malignancies. Dissimilar to other platinum compounds, OXA afford minimal nephrotoxicity. Unfortunately, variable forms of toxicity related to OXA were recorded in the past decade[30]. Changes in the body weight due to the chemotherapy are commonly observed[31]. However, few data have assessed the relationship between body weight change and chemotherapeutic drugs[32]. Currently, the OXA-treated animals prior pregnancy exhibited reduction in the fetal body weight gain. The OXA therapy can directly disturb skeletal muscle homeostasis and enhance muscle loss through upregulation of myopathy-associated genes[33].

The current data revealed that significant increases (P<0.05) in serum urea and creatinine, which is a diagnostic tool for the nephrotoxicity, induced post OXA administration prior and during pregnancy. Gaspari *et al*.[34] also reported the renal toxicity of cisplatin (another platinum-based chemotherapy). Kidney injury is frequently incident in the chemotherapeutic patients[35]. Antineoplastic drugs can harm the glomeruli, renal tubules, and blood vessels and obviously associated with an elevation in the level of serum creatinine[36]. There was a close relationship between the OXA therapy and renal failure occurrence; kidney biopsy demonstrated severe renal necrosis[37]. Severe toxicity emitted from OXA treatment is a dose-limiting side effect[38]. Therefore, in platinum-induced nephrotoxicity; DNA damage response, the generation of reactive oxygen species (ROS), cell apoptosis, and inflammatory response are considerable causes participating to in kidney cells[39]. Moreover, the binding to the intracellular thiol-containing molecule glutathione probably developed the nephrotoxic conditions[40]. Kidney pathologies in OXA-induced cases were confirmed by renal biopsy[41]. Since, the shown data recorded degenerative changes and necrosis of the renal tubules compensated with inflammatory cells infiltration, glomerular hypercellularity, and congestion in the blood vessels. OXA was associated with

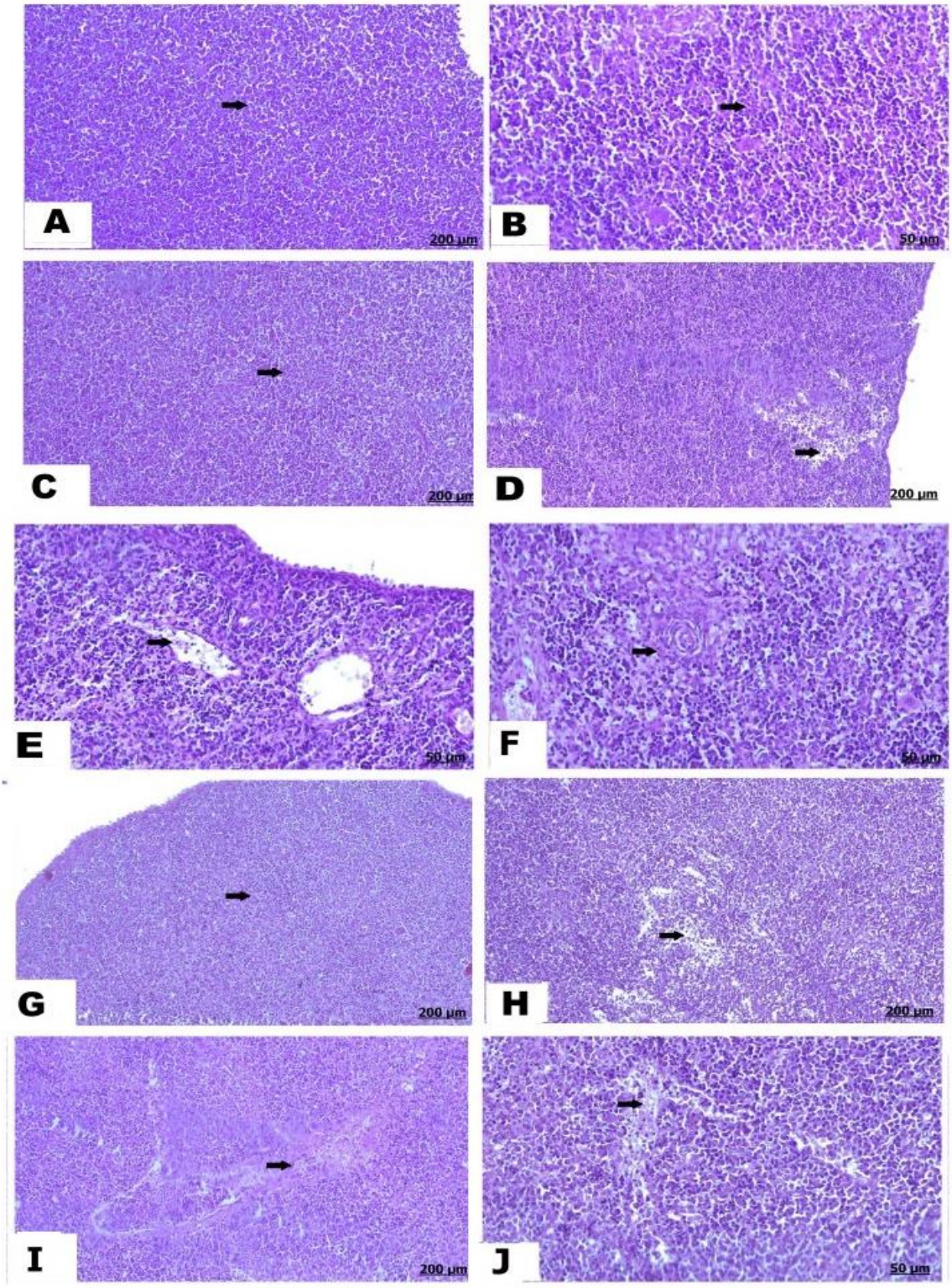

Figure 8: Photomicrograph of fetal spleen of control rat **(A & B)**; PRO **(C)**, OXA **(D & E)**, and OXA+PRO **(F)** treated rats prior pregnancy; and PRO **(G)**, OXA **(H & I)**, and OXA+PRO **(J)** treated rats during pregnancy. **(A & B)** Normal arrangement of splenic tissues. (**C)** Normal view of the splenic pulps. (**D)** Depletion with vacuolation of the splenic tissues. (**E)** Severely dilated blood vessels. (**F)** Mild congestion of the blood vessels. (**G)** Healthy splenic parenchyma. (**H)** Marked depletion of the white pulp. (**I)** Obviously congested blood vessels. (**J)** Slight congestion of blood vessels. Hematoxylin and eosin stain; **A, C, D and G-I** scale bar = 200 µm; **B, E, F,** and **J** scale bar = 50 µm.

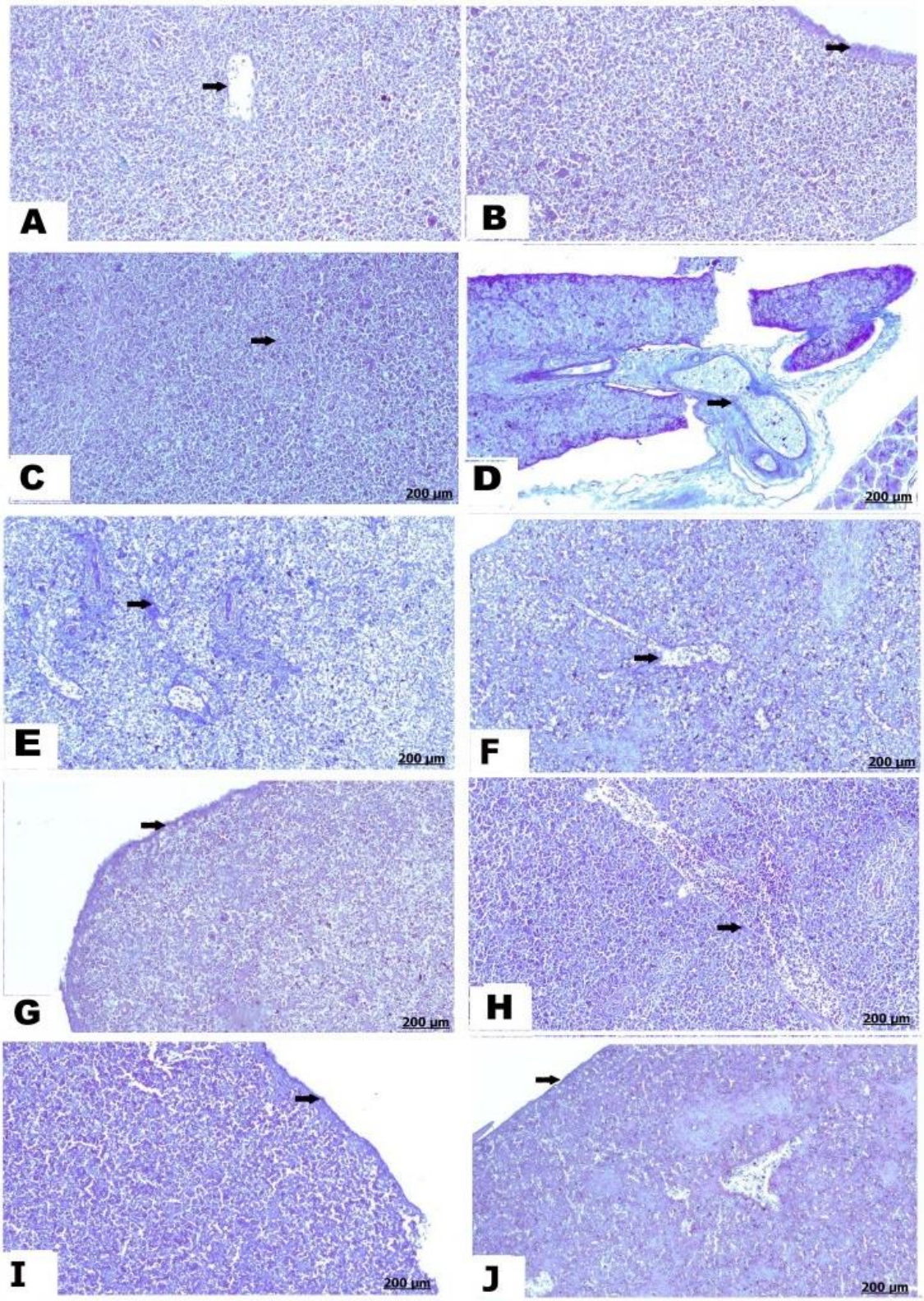

Figure 9: Photomicrograph of fetal spleen of control rat **(A & B)**; PRO **(C)**, OXA **(D & E)**, and OXA+PRO **(F)** treated rats prior pregnancy; and PRO **(G)**, OXA **(H & I)**, and OXA+PRO **(J)** treated rats during pregnancy. (**A & B)** Less definitive fibrous tissues. (**C)** Little amount of the interstitial collagen fibers. **(D & E)** Prominent perivascular fibrosis. (**F)** Slight perivascular fibrous tissues infiltration. (**G)** Collagen fibers minimally infiltrated**. (H & I)** Considerable layer from the fibrous tissues. (**J)** Thin layer of fibrosis. Masson trichrome stain; **A**-I scale bar = 200 µm.

tubular necrosis and acute interstitial nephritis[6]. Also, it was correlated with OXA therapy the renal necrosis and tubular acidosis[42]. Moreover, it can assist different forms of nephrotoxicity identified by cytoplasmic vacuolization, renal necrosis, and acidosis, secondary to hematological toxicity [43].

Moreover, OXA has been implicated in confined issues of immunity[44]. OXA induced splenomegaly that was the common irreversible deleterious effect of OXA therapy in colon cancer patients[10]. However, the current study reported vacuolation in spleen, which was attributed to lymphoid depletion, besides congestion of the blood vessels. Interestingly, the pathophysiological mechanism of OXA induced splenic dysfunction is not completely understood. However, the developed inflammation was contributed to potent cytotoxic immune response, apoptosis, and splenic injury in OXA-treated rats[45]. Oxidative stress is one of the important mechanisms in OXA-induced tissues injury. The OXA has been known to induce oxidative damage; hence it is not only responsible for an increasing lipid peroxidation, but also for lowering the activity of various anti-oxidant enzymes, leading to an imbalance between the oxidative and antioxidative mechanism, and substantially cell injury[12].

The protective role induced by PRO against the altered parameters and histo-architecture changes in the kidney and spleen may be turned to its bioactive contents like hexadecanoic acid, oleic acid, vaccenic acid, 10-octadecenoic acid, penta-decanoic acid, and cyclopentanetrideanoic acid, methyl ester. Synergistic effect of oleic acid on health, occurring through inhibition of tumor cells proliferation, lowering inflammation, decreasing leuko-cytes activity, modulation of physiological functions, and decreasing blood pressure[46]. Also, presence of pentadecanoic acid in PRO has ability to arrest tumor cells and induce cell apoptosis[47]. Animal-derived trans fatty acids found in PRO mainly vaccenic acid are suggesting its beneficial effect[48].

Herein, the treatment with OXA in combination of PRO corrected the altered kidney functions and the renal histological structure induced by a virtue of OXA. Other scientists reported that the PRO offered a critical role in amelioration of the toxicity owing to the chemotherapy "doxorubicin"[49]. The PRO can normalize the renal biochemical levels such as urea and creatinine in a concomitant with attenuation in the toxic renal histo-pathological changes[50]. The protective role of PRO may be attributed to its antioxida-tive activity; hence PRO could protect the renal tissues from superoxide-induced damages[51]. As well, PRO could ameliorate drugs-induced lipid peroxidation in the kidney[21]. Furthermore, PRO can minimize lipid peroxidation in the renal tissues preventing the renal oxidative damages that induced by the toxic reactive metabolites[49].

In conclusion, it could be clarified that concomitant administration of PRO with OXA either prior or during pregnancy can significantly reduce the OXA-induced histopathological alterations in renal and spleen tissues, potentially owing to its antioxidant influence. Further studies are required to investigate the protective role of PRO against the OXA-induced toxicity in a cancer model, as well as to investigate the bioactivity of different compounds of aqueous PRO extract against OXA-induced toxicity and cancer cells.

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CONFLICT OF INTEREST
The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTIONS
DAMZ, and ZK jointly developed the hypothesis and concept of the study and contributed to the chemical and material preparations, as well as the techniques performed. For this research and scientific paper, ZK, ZAA, and AAM were involved

in the experimental procedures and analyses. ZK reviewed, revised, and edited the final version of the paper. All authors have read and approved the final manuscript.

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التأثير المُحَسن المحتمل لصمغ النحل ضد تسمم النمو المُستحث بالأوكساليبلاتين في الجِرذان المهقاء قبل وأثناء الحمل

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ينتمي أوكساليبلاتين إلى فئة الأدوية المضادة للأورام القائمة على البلاتين. ومن بين عوامل العلاج الكيميائي القياسية، حقق الأوكساليبلاتين نجاحًا في علاج الأورام المختلفة. ومع ذلك، فإن استخدامات الأوكساليبلاتين قبل أو أثناء الحمل يشكل تحديًا صحيًا للأمهات وذرياتهن بسبب تراكمه في الجسم. وصمغ النحل (العكْبر) هو منتج راتنجي تجمعه النحلة "*Apis mellifera*" من النباتات لتدعيم خلايا النحل، وله كفاءة وقائية ضد العديد من سُميات الأدوية. هدفت الدراسة الحالية إلي تقدير التأثير الوقائي لصمغ النحل ضد السُمية المُستحثة بالأوكساليبلاتين على الأمهات وحديثي الولادة. تم توزيع خمسة وثلاثين من إناث الجِرذان البالغة من سلالة "Sprague-Dawley" بالتساوي إلى سبع مجموعات: تلقت مجموعة الجِرذان الحوامل الضابطة ماء مقطر؛ وتلقت المجموعات "2 و 3 و 4" صمغ النحل (200 ملجم/كجم من وزن الجسم يوميا عن طريق الفم)، الأوكساليبلاتين (3 ملجم/كجم من وزن الجسم ثلاث مرات أسبوعيًا عن طريق الحقن الوريدي)، الأوكساليبلاتين + صمغ النحل، على التوالي، لمدة 21 يومًا قبل الحمل؛ بينما تلقت المجموعات "5 و 6 و 7" العلاجات والجرعات نفسها لمدة 21 يومًا خلال فترة الحمل. أظهرت نتائج الدراسة الحالية أنه بالمقارنة مع السُمية الكُلوية والطحال الناجمة عن الأوكساليبلاتين في أمهات الجِرذان وحديثي الولادة، فإن المعاملة المشتركة بصمغ النحل مع الأوكساليبلاتين سواء قبل أو أثناء الحمل يمنح دورًا وقائيًا فعالًا في التغلب على الأضرار النسيجية المُستحثة بالأوكساليبلاتين في أنسجة الكُلى والطحال.