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A comparative study on the cardiopulmonary protective effect of propolis versus coenzyme Q10 on paclitaxel-induced toxicity

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ABSTRACT

Paclitaxel (PTX) is one of the most commercially and clinically effective chemotherapeutics, but its toxicity causes significant problems with its administration. Consequently, it was intended in the current research to explore the potential activity of coenzyme Q10 (CoQ10) and propolis against PTX-induced cardiopulmonary damage. Thirty male albino rats were divided equally into six groups: control group; given saline, CoQ10 group; given CoQ10 (100 mg/kg b.wt daily), propolis group; given propolis (200 mg/kg b.wt daily), PTX group; given PTX (7.5 mg/kg b.wt i.p.), CoQ10+PTX group; given CoQ10 (100 mg/kg b.wt daily) before PTX (7.5 mg/kg b.wt) and propolis+PTX group; given propolis (200 mg/kg b.wt) before PTX (7.5 mg/kg b.wt). All treatments were received for 4 weeks. The PTX group had significantly higher serum concentrations of CK-MB and LDH. This result was concomitant with histopathological changes that represented by cardiac necrosis and degeneration together with congestion, edema and hemorrhage in the heart. Lung injury induced by PTX was characterized by perivascular hemorrhage, inflammatory cell infiltrates, bronchiolestenosis, hyperplasia and/or desquamation of the bronchiolar epithelium, alveolar emphysema, congestion, interstitial edema and fibrinoid necrosis of blood vessels walls. Besides, pulmonary fibrosis was confirmed by Van Gieson stain. Immunohistochemical staining for IL-1β revealed positive immunoexpression in heart and lung tissue. Treatment with CoQ10 and propolis ameliorated the cardiopulmonary toxicity induced by PTX indicated by improved microscopic picture of heart and lungs, serum biochemical parameters and decrease IL-1β immunoreactivity in heart and lung tissues. In conclusion, CoQ10 could be the best choice to counteract the cardiopulmonary toxicity produced by PTX exposure.

Introduction

Chemotherapy is the delivery of cytotoxic agents that have cell-killing activities to kill or destroy cancer cells, so it interferes with the growth of tumors. Although chemotherapy is generally regarded PTX as an effective agent in cancer treatment, it has serious side effects since it can damage either healthy cells or tissues (Wang *et al*., 2018). Therefore, many patients were unable to complete their chemotherapy treatment due to its toxic side effects, resulting in failure of treatment (Park *et al*., 2012).

The high effectiveness of PTX is diminished by the association with several side effects that lead to serious impairments in the quality of life (Rowinsky *et al*., 1991). As a result of the side effects of chemotherapeutic treatments, particularly PTX, supporting medications and/or dietary supplements must be added to chemotherapy regimens immediately. It is possible to employ a variety of natural medicinal products with antioxidant capacity to treat PTX-related side effects (El-Sayed *et al*., 2016).

Coenzyme Q10 is a 1, 4-benzoquinone, with the letter "Q" indicating the quinone group and the number "10" referring to the isoprenyl units at the end. CoQ10 plays a substantial role as an electron carrier in the mitochondrial electron transport chain, resulting in the synthesis of ATP (Bhagavan and Chopra, 2006), In addition, CoQ10 possesses powerful free radical scavenging activity that helps to maintain the mitochondrial membrane potential thus, it can conserve cell function as opposed to oxidative stress (Noh *et al*., 2013). CoQ10 has been experimentally used in the treatment of inflammatory diseases (Zhai *et al*., 2017), heart failure (Jafari *et al*., 2018), diabetes, breast cancer, hypertension and as a nutritional supplement for cancer patients receiving chemotherapy (Madmani *et al*., 2014; Yeung *et al*., 2015).

Natural therapeutics with antioxidant and anti-inflammatory properties will be a hopeful strategy to counteract, and prevent the side effects of anticancer drugs and aim to maximize their efficacies by minimizing their toxicity (Şengül *et al*., 2017). Propolis is a natural product collected by honeybees from various plants and exhibits broad biological activities as free radical scavenging, antioxidant (Rivero-Cruz *et al*., 2020), anti-inflammatory, immunoregulatory, antibacterial, antifungal, antiviral, and antitumor activity (Sameni *et al*., 2016). Two main immunopotent components in propolis are caffeic acid phenethyl ester (CAPE) and artepillin C (Zaccaria *et al*., 2017).

Accordingly, this study was carried out to compare the protective action of CoQ10 versus propolis against PTX-induced cardiopulmonary toxicity.

Materials and methods

Chemicals

Paclitaxel (Unitaxel®) was obtained from the Hikma pharmaceutical company, Cairo, Egypt. Propolis (BioPropolis®) each capsule contains 400 mg pure Propolis and was purchased from Sigma Pharmaceutical Industries, Cairo, Egypt. CoQ10 (Coenzyme Q 10®) each capsule contains 30 mg CoQ10 was purchased from MEPACO, Cairo, Egypt.

Experimental Animals

Thirty adult male albino rats with weights of 125–140 g was obtained from the Center of Laboratory Animal, Faculty of Veterinary Medicine, Za-

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gazig University, Egypt. In order to rule out any concurrent infections, the rats were housed in stainless-steel wire cages and watched for one week before the beginning of the experiment. Rats were housed at a standard air temperature of (25±5°C), humidity 60±5% with a 12-hour light cycle. Animals had free access to water and received a sufficiently balanced ration ad libitum.

Experimental design

In this study, thirty adult male albino rats were divided equally into six groups, five rats per each group. Group 1 (Control group): each rat injected with 0.5 ml of 0.9% saline once weekly. Group 2 (CoQ10 group): rats were administrated CoQ10 orally at a dose of 100 mg /kg body weight (b.wt) daily (Ulla *et al*., 2017). Group 3 (Propolis administrated group): rats were administered propolis orally at a dose of 200 mg/kg b.wt daily (Ali *et al*., 2020). Group 4 (PTX group): rats were injected PTX intraperitoneally at a dose of 7.5 mg/kg b.wt once weekly (Malekinejad *et al*., 2016). Group 5 (CoQ10+PTX group): rats were administered PTX intraperitoneally (7.5 mg/kg b.wt once weekly) and CoQ10 (100 mg/kg b.wt every day). Group 6 (propolis+PTX group): rats were injected PTX intraperitoneally (7.5 mg/kg b.wt once weekly) and received propolis orally (200 mg/kg b.wt).

All experimental procedures continued for 28 consecutive days and were performed in accordance with the international guidelines for the care and use of experimental animals and approved by the Ethics Committee, Faculty of Veterinary Medicine, Benha University, Egypt (Ethical Approval Number: BUFVTM32-09-22).

Serum biochemical analysis

At the end of the experiment, all rats were fasted overnight, blood samples were collected from each animal's orbital sinus into gel and clot activator tubes, allowed to coagulate at room temperature. Then samples were centrifuged at 3,000 rpm for 10 min. non-hemolyzed sera were aspirated quickly in an Eppendorf tube and kept at -20°C until needed for biochemical testing. Biomarkers for heart function including creatine kinase-Myocardial Band (CK-MB) and lactate dehydrogenase (LDH) were assessed in serum using diagnostic kits purchased from spectrum diagnostic company, Egypt-IFUFCC46. Measurement was assessed as described previously by Young (1995) using Semi-auto chemistry analyzer.

Histopathological examination

Rats were euthanized after 28 days by cervical dislocation and small lung and heart tissue specimens were rapidly collected during necropsy and preserved in neutral-buffered formalin (10%). The tissues were washed with water and dehydrated in a series of ethyl alcohol dilutions (50%, 70%, 90%, 95%, 100%). Specimens were cleared with xylene before being embedded in paraffin wax. Five µm sections in thickness were cut from paraffin tissue blocks with a sliding microtome. The tissue sections were stained with hematoxylin and eosin stain (Bancroft and Layton, 2019a). Histopathological images were photographed using a Nikon Eclipse E800 microscope (Melville, NY, USA) equipped with a camera.

According to the severity of the histopathological lesions, all specimens were examined and classified on a modified semi-quantitative scale of Gibson-Corley *et al*., (2013) into none (-), mild (+), moderate (++) and severe (+++). Each lesion was graded as follows: (-) normal histology, (+) with up to 1/3 of the examined section exhibiting the evaluated lesion, (++) in which greater than 1/3 to 2/3 of the inspected section revealed the pathological change, while (+++) means greater than 2/3 of the assessed section showed the pathological alteration.

Van Gieson staining technique

Collagen deposition was evaluated using Van Gieson stain. Tissue sections incubated in 1% acid fuchsin in aqueous saturated picric acid for 2 minutes. Sections were dehydrated and mounted using DPX. Collagen fibers appear pink to red after staining, while muscle appears yellow (Bancroft and Layton, 2019b).

Immunohistochemical examination

Five µm thick paraffin-embedded tissue sections were preheated and dewaxed in xylene followed by dehydration in ethanol. The tissue sections were incubated with antigen retrieval solution (Dako, Carpinteria, CA, USA) for 40 minutes using a steamer followed by a cooling step (for 30 minutes at room temperature). The tissue sections were treated with 3% hydrogen peroxide to block endogenous peroxidase activity and washed, and 10% bovine serum albumin was added to block non-specific immunoreactivity. The slides were incubated overnight with anti–IL-1β (1:400, NBP1-19532, Novus, Centennial, CO, USA). On the next day, slides were washed three times and incubated with the corresponding biotinylated secondary antibody diluted in phosphate buffer saline (PBS) for 1 hour at 25°C, followed by three PBS washes. The slides were incubated with diaminobenzidine tetrahydrochloride (DAB). solution for 10 minutes. The slides were washed three times in distilled water and counter stained with hematoxylin. Tissue sections were finally dehydrated using graded alcohols and xylene and then covered with a glass slip. DAB staining (brown color) was recorded as a positive result.

Statistical analysis

The statistical analysis was carried out using One-way ANOVA using SPSS, ver. 27 (IBM Corp. Released 2013). Data were treated as a complete randomization design according to Steel and Torrie (1980). Multiple comparisons were carried out by applying Duncun test as a post hock test. The significance level was set at $P < 0.05$.

Results

Serum biochemical analysis

Serum biochemical analysis revealed a significant elevation ($P < 0.05$) in the cardiac function biomarkers (CK-MB, and LDH) levels was recorded in the PTX group compared with the control group. On the other hand, treatment with CoQ10 or propolis substantially reduced the increased serum CK-MB and LDH levels compared with PTX group. However, as compared to the propolis+PTX group, CoQ10+PTX group slightly reversed elevated levels of CK-MB and LDH (Table 1).

Table 1. Levels of CK-MB and LDH in control and treated groups in long-term PTX toxicity.

Group	CK-MB (U/L)	LDH (U/L)
Control	8.20±0.58^{c}	372.60±25.24^{c}
CoQ10	8.60±1.21^{c}	399.00±22.25^{c}
Propolis	9.40±0.93^{c}	408.20±23.65^{c}
PTX	33.25±1.75^{a}	1196.25±98.52^{a}
CoQ10+PTX	16.80±1.28^{b}	650.60±44.56^{b}
Propolis+PTX	18.80±1.59^{b}	680.20±47.64^{b}

Values are expressed as the mean ± SE (n = 5). A statistically significant difference ($P \leq 0.05$) is indicated by superscript letters in the same column.

Histopathological findings

Heart

Normal cardiomyocytes with their centrally placed vesicular nuclei were detected in the cardiac tissue obtained from control, CoQ10 and

propolis groups (Fig. 1A, B and C). Administration of PTX produced severe vascular alterations including marked congestion of myocardial blood vessels, perivascular edema and hemorrhage in association with mononuclear leukocytic infiltration as well as vacuolation in the blood vessels walls (Fig. 1D). Multifocally, Extravasated RBCs was also noticed in-between cardiac muscles (Fig. 1E). Accidentally, discrete clear vacuoles of varying size scattered within cardiomyocytes were observed (Fig. 1F). Necrosis of cardiac muscles characterized by nuclear pyknosis and hyperesinophilic cytoplasm was also seen (Fig. 1G).

The histological structure of the heart in rats of CoQ10+PTX group was nearly identical to that of the control (Fig. 1H), with only slight degenerative changes in the cardiac muscle of a few examined heart sections (Fig. 1I). Meanwhile, propolis+PTX group showed only mild congestion of myocardial blood capillaries (Fig. 1J) and focal myocardial hyalinosis (Fig. 1K). However, propolis+PTX treatment was not as effective as CoQ10+PTX treatment in reducing PTX-induced heart damage.

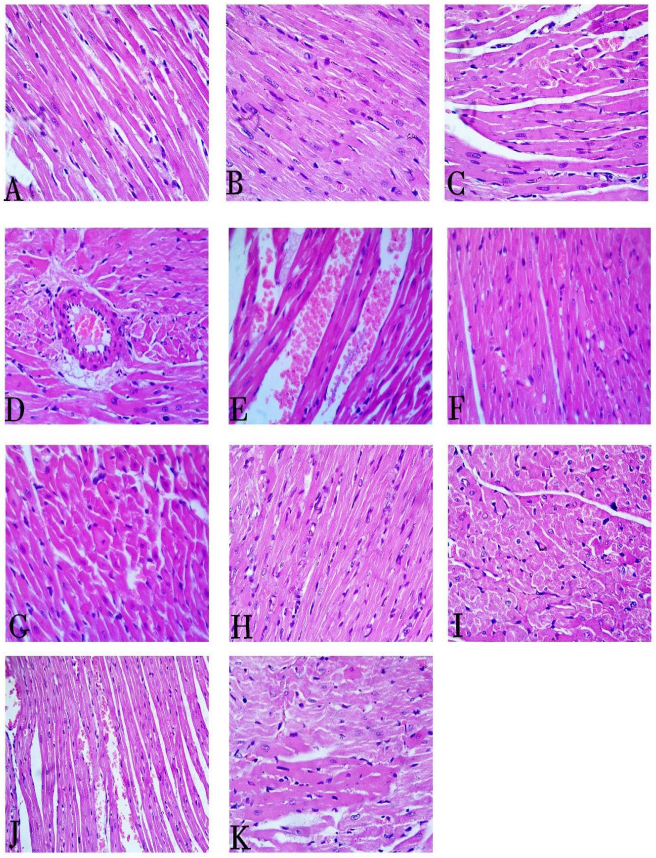

Fig. 1. Photomicrographs of heart sections stained with H&E stain. Control (A), CoQ10 (B) and propolis (C) groups show normal histological structure of cardiac muscles x200. PTX group (D-G) D-Perivascular edema with vacuolation in the blood vessels wall x200, E-Intermuscular hemorrhage x400, F-Cytoplasmic vacuolation x200, G-Myocardial necrosis x200. CoQ10+PTX group (H-I) H-Normal cardiac histoarchitecture x200, I-Mild myocardial degeneration x200. Propolis+PTX group (J-L) J-Mild congestion of myocardial blood capillaries x100, K-Focal myocardial hyalinosis x200.

The histopathological alterations in the hearts in control and experimental groups were represented as a score. The PTX group had the highest score for these lesions, showing that PTX caused substantial heart damage. Treatment with CoQ10+PTX or propolis+PTX was related with a reduction in these scores, showing that these substances provided effective cardiac protection against PTX-induced heart injury (Table 2).

Lung

In control, CoQ10 and propolis groups, almost all the lung sections had normal histological architecture, clear empty alveoli and thin interalveolar septa. with patent bronchioles lined with simple columnar epithelium (Fig. 2A, B, C). In the lung sections of PTX-intoxicated rats, severe distortion of pulmonary architecture with hypertrophy of tunica media of pulmonary arteries were seen (Fig. 2D). Congestion of peribronchiolar blood vessel and interalveolar capillaries, hemorrhage were the main pronounced vascular alterations in the pulmonary tissue. Additionally, fibrinoid necrosis of pulmonary blood vessels wall with perivascular mononuclear leukocytic infiltrations were seen (Fig. 2E). Extensive perivascular hemorrhage (Fig. 2F) and perivascular inflammatory cell infiltrates, including lymphocytes and macrophages with nearly obliteration of pulmonary blood vessel lumen were also detected in some examined cases (Fig. 2G). Peribronchial, perivascular and interstitial fibrosis were detected in most lung sections (Fig. 2I, H). Additionally, alveolar septal thickening with extensive mononuclear inflammatory cells infiltration in the interalveolar space was also observed. Meanwhile, multiple areas of pulmonary emphysema were seen. Multifocally, some alveoli were filled with foamy macrophages (Fig. 2J). As well as, bronchiolestenosis was observed as a result of hyperplasia of peribronchiolar lymphoid tissue (Fig. 2K). While other bronchioles were suffered from hyperplasia of their lining epithelium with the presence of desquamated intraluminal cells and peribronchial edema (Fig. 2L).

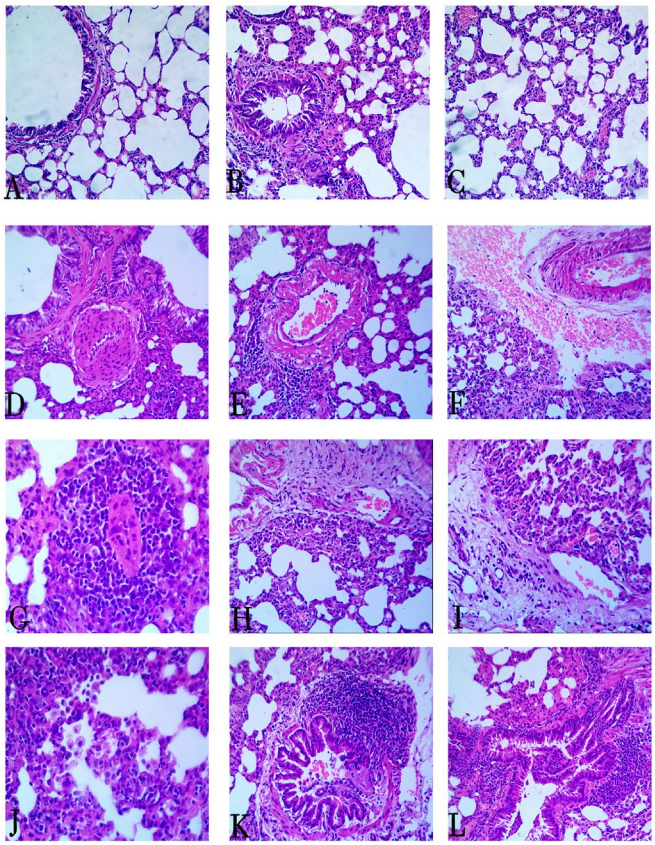

Fig. 2. Photomicrographs of lungs sections stained with H&E stain. Control (A), CoQ10 (B) and propolis (C) groups normal respiratory bronchioles and alveoli x200. PTX group (D-L) D-Hypertrophy of tunica media of pulmonary vessel x200, E-Fibrinoid necrosis of blood vessel x200 (E), F-Perivascular edema and hemorrhage x200, G- perivascular inflammatory cellular infiltration x400, H, I-Pulmonary fibrosis x200, J-Alveolar macrophages x400, K-Bronchiole stenosis x200, L-Hyperplasia and desquamation of bronchiolar epithelium x200.

Apparent amelioration of histopathological alterations induced by PTX was detected in the pulmonary tissue obtained from CoQ10 or propolis treated groups compared to the PTX group. The examined lungs in CoQ10+PTX group showed mild perivascular leukocytic cellular infiltration (Fig. 3A). Most bronchioles lined by nearly normal simple columnar epithelium with few disrupted and desquamated epithelium (Fig. 3B). While the desquamation of the bronchiolar epithelial cells was also seen in few examined lungs (Fig. 3C). In contrast, lungs of propolis+PTX group revealed mild thickening of interalveolar septa in association with mild mononuclear leukocytic cellular aggregations and alveolar emphysema

(Fig. 3D). Interestingly, mild peribronchial lymphoid hyperplasia was detected in some cases (Fig. 3E). While other cases showed desquamation of the bronchiolar epithelium admixed with eosinophilic secretion (Fig. 3F).

Table 2. Lesions scores of various cardiac histopathological changes in long-term PTX toxicity.

	Control, CoQ10, Propolis	PTX	CoQ10+PTX	Propolis+PTX
Lesion score				
Congestion	-	+++	-	+
Hemorrhage	-	+++	-	-
Edema	-	++	-	-
Necrosis	-	+++	-	-
Degeneration	-	+++	+	++

(–): normal histology; (+): up to 1/3 of the examined section exhibiting the evaluated lesion; (++): greater than 1/3 to 2/3 of the inspected section revealed the estimated pathological change; (+++): greater than 2/3 of the assessed section showed the estimated pathological alteration.

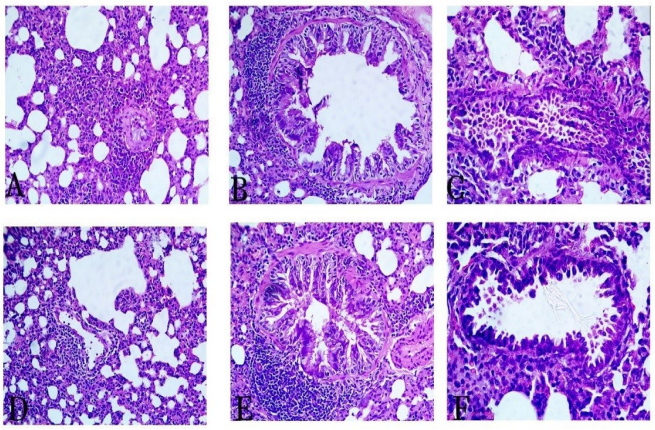

Fig. 3. Photomicrographs of lungs sections stained with H&E stain. CoQ10 + PTX group (A-C) A-Perivascular leukocytic cellular infiltration, B- Epithelial disruption and desquamation, C-Desquamation of bronchiolar epithelium. Propolis + PTX group (D-F), D-Interstitial mononuclear cell infiltration with alveolar emphysema, E-Peribronchiolar lymphoid hyperplasia, F-Desquamation of few bronchiolar epithelium. (x200).

Van Gieson staining

Van Gieson stain was used to assess the anti-fibrotic effects of CoQ10 and propolis against pulmonary fibrosis induced by PTX. Control, CoQ10 and propolis groups have only a thin layer of pink-stained collagen fibers in the tunica adventitia of pulmonary blood vessels and wall of bronchioles (Fig.4 A, B, C). On the other hand, in PTX-intoxicated rats, multifocal areas of tightly packed pink-stained collagen fibers were seen around bronchioles and replacing damaged lung parenchyma (Fig. 4D). Additionally, severe positive reaction of pink-stained collagen fibers was seen around blood vessels (Fig. 4E). The pulmonary tissues of the CoQ10+ PTX group have weak positive reaction of pink-stained collagen fibers nearly similar to the negative control group (Fig. 4F). Also, the lungs in the propolis+PTX group showed moderate positive reaction of Van Gieson stain for collagen fibers around bronchioles and blood vessels (Fig. 4G). However, treatment with CoQ10+PTX has better anti-fibrotic action than treatment with propolis+PTX.

The histopathological alterations in the lungs in control and experimental groups were represented as a score. The PTX group had the highest score for these lesions, showing that PTX caused substantial lung injury. Treatment with CoQ10+PTX or propolis+PTX was related with a reduction in these scores, showing that these substances provided effective protection against PTX-induced pulmonary damage (Table 3).

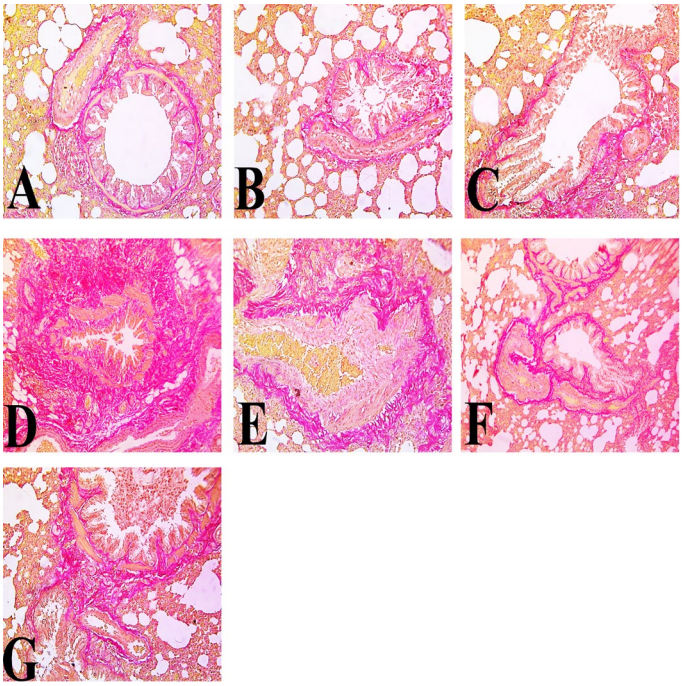

Fig. 4. Photomicrographs of Van Gieson stain of pulmonary tissues. Control (A), CoQ10 (B) and propolis (C) groups thin strands of pink-stained collagen fibers around bronchiole and blood vessel, PTX group (D, E) severe positive reaction of Van Gieson-stained collagen fibers in: D-peribronchiolar tissue, E-perivascular area, CoQ10+PTX (F)-Weak positive reaction of pink-stained collagen fibers, Propolis+PTX group (G)-Moderate positive reaction of collagen fibers (x100).

Immunohistochemistry

The anti-inflammatory effects of CoQ10 and propolis were evaluated using IL-1β expression. Low IL-1β expressions restricted only to endothelial cells of myocardial blood capillaries was recorded in the heart of rats

Table 3. Lesions scores of various pulmonary histopathological changes in long-term PTX toxicity

	Control, CoQ10, Propolis	PTX	CoQ10+PTX	Propolis+PTX
Lesion score				
Hemorrhage	-	+++	-	-
Leukocytic infiltrations	-	+++	+	+
Fibrosis	-	+++	+	++
Alveolar emphysema	-	++	-	+
Peribronchial lymphoid hyperplasia	-	+++	-	+
Hyperplasia of bronchiolar epithelium	-	+++	-	-
Desquamation of bronchiolar epithelium	-	+++	++	+

(–): normal histology; (+): up to 1/3 of the examined section exhibiting the evaluated lesion; (++): greater than 1/3 to 2/3 of the inspected section revealed the estimated pathological change; (+++): greater than 2/3 of the assessed section showed the estimated pathological alteration.

in the control, CoQ10 and propolis groups (Fig. 5A). While the examined heart of rats in the PTX group showed strong positive IL-1β immunoexpression in many cardiomyocytes (Fig. 5B). Compared with PTX group, CoQ10+PTX group associated with low IL-1β immunoexpresion and the immunoreactivity was limited to few cardiomyocytes (Fig. 3C). Likewise, IL-1β expression was restricted to endothelial cells of myocardial blood capillaries and few cardiac muscles of rats in propolis+PTX group (Fig. 5D).

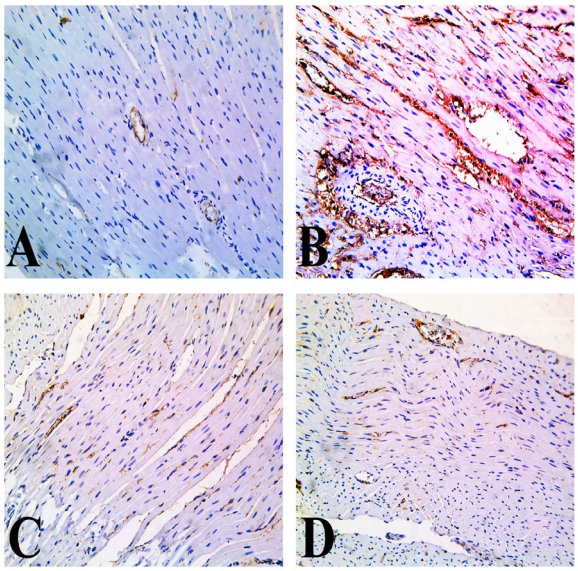

Fig. 5. Immunohistochemical reaction for IL-1β expression in cardiac tissue in control group (A)-Very mild expression of IL-1β expression restricted to endothelium of myocardial blood vessel, PTX group (B)-Strong expression of IL-1β in most cardiomyocytes, CoQ10+PTX group (C)- Mild expression of IL-1β, propolis+PTX group (D)-Mild expression of IL-1β in few cardiac cardiomyocytes (x200).

Immunohistochemical results for IL-1β in pulmonary tissues were summarized in Fig. 6. Immunohistochemical staining was negative for IL-1β in the control, CoQ10 and propolis groups (Fig. 6 A, B, C). While very severe immunoexpression for IL-1β in PTX group particularly in interstitial tissues (Fig. 6D), bronchial epithelial cells (Figure 6E) and in perivascular area (Fig. 6F). Compared with PTX group, CoQ10+PTX group associated with very mild IL-1β immunoexpression in interstitial (Fig. 6G), peribronchiolar (Fig. 6H) and perivascular tissues (Fig. 6I). Similarly, IL-1β expression in the lungs of rats in propolis+PTX group was representedby mild immunoreactivity in interstitial (Fig. 6J), peribronchiolar (Fig. 6K) and perivascular tissues (Fig. 6L).

Discussion

PTX, a powerful chemotherapeutic drug, is approved by the Food and Drug Administration (FDA) and has several toxic side effects (Alavi and Nokhodchi, 2022). The most well-known side effect of PTX is peripheral neuropathy (Klein and Lehmann, 2021). However, there is not sufficient publication for its cardiopulmonary toxicities. Accordingly, in this study, a potential therapeutic agent including CoQ10 and propolis were evaluated for prevention of PTX-induced cardiopulmonary toxicity in rat model.

In the current research, PTX-induced cardiac damage is evidenced biochemically via increasing serum cardiac markers CK-MB and LDH. In the same manner, previous researchers found that PTX caused cardiac damage resulting in loss of functional integrity based on a significant increase in serum CK-MB and LDH levels (Ali *et al*., 2023).

The histopathological examination in the present study of the cardiac tissue obtained from PTX-intoxicated rats demonstrated vascular damage in form of perivascular edema, hemorrhage and perivascular inflammatory cellular infiltration. These results might be attributed to PTX impairs endothelial function in vivo (Vassilakopoulou *et al*., 2010). Additionally, the obtained histopathological findings in the current study approved that PTX-induced cardiotoxicity was manifested by cardiac vacuolation, necrosis, hemorrhage and edema that is also identical to the findings in previous studies (Malekinejad *et al*., 2016; Khaled *et al*., 2022). paclitaxel-induced cardiac damage either indirect following a massive histamine release or direct via its effect on cellular organelles (Schimmel *et al*., 2004; Herrmann *et al*., 2016).

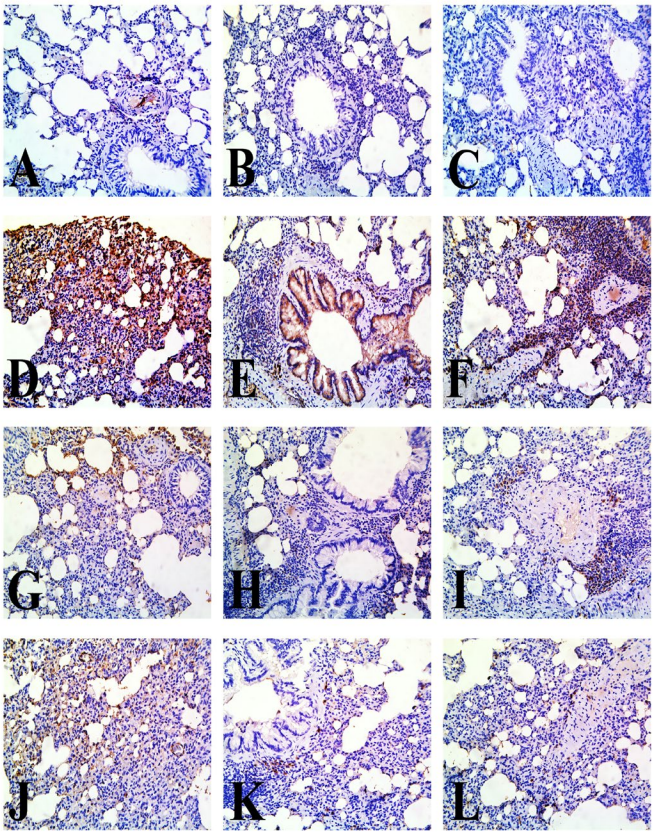

Fig. 6. Immunohistochemical reaction for IL-1β expression in pulmonary tissue. Control (A), CoQ10 (B) and propolis (C)-Null expression of IL-1β, PTX group (D-F)-Strong immunoexpression of IL-1β in: D-interstitial tissue, E-bronchiolar epithelium, F-perivascular area, CoQ10+PTX group (G-I) mild expression in: G-interstitial tissue, H-peribronchial tissue, I-perivascular area, Propolis +PTX group (J-L) mild expression of IL-1β in: J-interstitial tissue, K-peribronchial tissue, L-perivascular area (x200).

In the current research, the lungs of PTX-intoxicated rats showed various histopathological alterations as activation of alveolar macrophages, inflammatory response, pulmonary edema and fibrosis. These findings matched with Ostoros *et al.* (2006) and Liu *et al.* (2015). Pulmonary edema could be attributed to PTX-induced alveolar capillary leakage (Jacob and Gaver, 2012). Additionally, paclitaxel induced necrosis and desquamation of bronchial epithelium which might attributable to oxidative stress induced by PTX (Sarıözkan *et al*., 2017). In the current work, marked positive immunoreaction for IL-1β was detected in heart and lung tissues. paclitaxel induced severe inflammatory reactions which may be due to the abnormal expression of a pro-inflammatory factor and activating a cascade of inflammatory reactions (Jacob and Gaver, 2012). The induction of fibrosis by chemotherapy including PTX may be the consequences of cytokines secreted from alveolar macrophages following lung injury (Chandler, 1990) as cytokines promote fibroblast proliferation and stimulate the abnormal extracellular matrix production leading to fibrosis (Reinert *et al*., 2013).

CoQ10+PTX group revealed a significant decrease in the serum levels of CK-MB and LDH as well as it improved most histopathological alterations induced by PTX in cardiac and pulmonary tissues. This result confirmed that CoQ10 increased the stabilization of cardiomyocyte cell membranes (Mustafa *et al*., 2017). Additionally, CoQ10 significantly decreased the fibrous tissue deposition and inflammatory cell infiltrate in the lung which was matched with the previous study of Lim *et al.* (2010). However, the anti-inflammatory action of CoQ10 was confirmed immunohistochemically in the current study as very mild immunoexpression for IL-1β was demonstrated. It could be hypothesized that therapeutic mechanisms of CoQ10 action involve inhibiting inflammation (Cirilli *et al*., 2021) and protecting cellular DNA, lipids, and protein from oxidative damage (Garrido-Maraver *et al*., 2014).

In the present study, propolis reduced both CK-MB and LDH levels and the histopathological alteration induced by PTX in the heart and lung tissues. These results are also supported by Mohamed *et al*., (2021) who showed that propolis can reduced CK-MB and LDH activity in doxorubicin-induced cardiac toxicity. Interestingly, propolis is rich in various flavo-

noids and phenolic substances that are responsible for its antioxidant and anti-inflammatory properties (Huang *et al*., 2014) and these properties prevent the progression of lung fibrosis via decreasing different inflammatory mediators such as tumor necrosis factor-α (TNF-α), tumor growth factor-β (TGF-β) in lung tissues (Tarry-Adkins *et al*., 2016). The anti-inflammatory effect of propolis was established immunohistochemically in the present study as a mild immunoexpression for IL-1β in cardiopulmonary tissues was detected. Anti-inflammatory action of propolis attributed to CAPE blocks the release of proinflammatory cytokines IL-1β, and IL-6, increases the secretion of anti-inflammatory cytokines and decreases leukocytic cellular infiltration such as neutrophils and monocytes (Zaccaria *et al*., 2017; Franchin *et al*., 2018; Asgharpour *et al*., 2019). Also, propolis has protective and curative effects against epirubicin-induced cardiotoxicity in Wister rats (Chaa *et al*., 2021) and cyclophosphamide-induced acute lung injury in mice (Abdulrahman Hamdan Almaeen; Mahrous Abd El-Basset Ibrahim, 2018).

Conclusion

PTX caused noteworthy heart and lung damage, as evidenced by severe histopathological alterations in heart and lung, as well as increases in CK-MB and LDH levels and the release of IL-1β proinflammatory cytokine. Treatment with CoQ10 or propolis significantly attenuate PTX-induced cardiopulmonary toxicity. Currently, CoQ10 supplementation has a more effective protection than propolis in lowering the deleterious action of PTX on heart and lung tissues.

Acknowledgments

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Conflict of interest

The authors declare that they have no conflict of interest.

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