Ameliorative effects of propolis and coenzyme Q10 against short-term paclitaxel associated cardiopulmonary toxicity: histopathological and immunohistochemical evaluation

Eman Aly, Abdel-Baset I. El-Mashad*, Ahmed A. Tantawy, Aziza A. Amin
Department of Pathology, Faculty of Veterinary Medicine, Benha University, Toukh 13736, Egypt.

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ABSTRACT

This study aimed to assess the protective effects of Coenzyme Q10 (CoQ10) and propolis on paclitaxel (PTX)-induced cardiopulmonary toxicity. Thirty male albino rats were divided into six equal groups. Group I (control), group II (CoQ10), group III (propolis), group IV (PTX), group V (CoQ10+ PTX) and group VI (propolis+ PTX). Intraperitoneal injection of PTX-induced myocardial hyalinosis and necrosis associated with focal hemorrhages, swelling and damage of the endothelium lining the myocardial blood vessels with perivascular edema and mononuclear cells infiltration. Also, PTX significantly elevated serum CK-MB and LDH levels. Furthermore, PTX causes focal hemorrhage, perivascular edema, mononuclear cell infiltrations and fibrinoid necrotizing vasculitis in the lungs with hyperplasia and desquamation of the bronchial epithelium. Strong positive immunoreactivity of TNF-α and low expression of Bcl-2 were recorded in the heart and lungs of rats in the PTX group. Pretreatment with propolis or CoQ10 markedly improved the microscopic pictures of the heart and lungs confirmed by significantly mild immunoreaction of TNF-α and moderate expression of Bcl-2 in the hearts and lungs and reversed the elevated CK-MB and LDH levels. In conclusion, pretreatment with CoQ10 or propolis had a significant protective effect against PTX-induced cardiopulmonary toxicity through attenuation of proinflammatory cytokines and the apoptotic pathway.

1. INTRODUCTION

Paclitaxel is one of the most potent chemotherapeutic agents extracted from the bark of Taxus brevifolia and possesses broad-spectrum antineoplastic activity. The anticancer action of PTX by stabilizing microtubules during mitosis, preventing the formation of spindle fiber and promoting Bcl-2 phosphorylation which leads to the arrest of the cell cycle, and induces tumor cell death (Alves et al., 2018). Despite its powerful antitumor activities, PTX produces severe side effects, including peripheral neuropathy (Park, 2014), inflammatory reaction, immunosuppression (Feio et al., 2017), cardiovascular toxicity (Malekinejad et al., 2016; Vassilakopoulou et al., 2010) and lung injury (Liu et al., 2015), which limit its efficacy. Antioxidant agents have been extensively used for the prevention of damage induced by oxidative stress (El-Sayed et al., 2016). Thus, agents with anti-inflammatory, antioxidant, anti-apoptotic and immunomodulatory action may attenuate PTX toxicity. Coenzyme Q10 (CoQ10) is a naturally occurring fat-soluble benzoquinone, a vitamin-like substance that is obtained from meat, poultry, fish, vegetables and fruits (Lee et al., 2012). CoQ10 found everywhere in the body where biosynthesis takes place in the mitochondria of vital organs with high-energy requirements such as brain, heart, liver and muscles (Acosta et al., 2016). The antioxidant and anti-inflammatory action of CoQ10 was reported to be beneficial for diseases such as congestive heart failure (Acosta et al., 2016), cardiomyopathy (Rahmanifard et al., 2021) and lung injury (Lim et al., 2010).

Propolis is a valuable bee lipophilic resinous product produced by different types of bees as Apis mellifera and contains active constituents such as flavonoids, phenolic acid and their esters, artempillin C, caffeic acid phenethyl ester (CAPE). It has a broad spectrum of biological and therapeutic properties such as anti-inflammatory, antioxidant and immunomodulatory agents as well as treatment of cardiovascular diseases, chronic obstruct pulmonary diseases and respiratory tract-related diseases (Zullikfiee et al., 2022). Hence, this study aimed to evaluate the protective role of CoQ10 and propolis against PTX-induced cardiopulmonary toxicity.

2. MATERIAL AND METHODS

2.1. Drugs:

Paclitaxel (6 mg/ml) with the brand name Unitaxel was purchased from Hikma specialized pharmaceuticals Company (Cairo, Egypt). Propolis capsules (each contains 400 mg pure Propolis) with a brand name BioPropolis was purchased from Sigma Pharmaceutical Industries (Cairo, Egypt). Coenzyme-Q 10 capsules (each contains 30 mg CoQ10) was purchased from MEPACO, Cairo, Egypt.

* Correspondence to: ABDELBASET.ALMASHAD@fvtm.bu.edu.eg
2.2. Experimental animals:

Rats weighing 140-200 gm were obtained from the Center of Laboratory Animal, Faculty of Veterinary Medicine, Zagazig University, Egypt. Rats were housed in stainless-steel wire cages. Prior to the experiment, rats were acclimated for one week at temperature approximately 25±5 °C, humidity 60±5% with a 12 h light/dark cycle and were given a standard rat ration and water ad libitum.

2.3. Experimental design:

Thirty male albino rats were randomly divided into six equal groups. In Group I (control group) rats were injected intraperitoneally (i.p.) with 0.5 ml of 0.9% saline. While in Group II (CoQ10 group) rats were administrated CoQ10 orally at a dose of 200 mg/kg body weight (b.wt) every day (Mustafa et al., 2017). In Group III (propolis group) rats were received propolis orally at dose (250 mg/kg b.wt/day) by gastric tube (Barary et al., 2022) and in Group IV (PTX group) rats were injected i.p. with PTX (2mg/kg diluted in 0.9% saline solution) at alternate day (Liu et al., 2015). In Group V (CoQ10+ PTX group) rats were received CoQ10 (200 mg/kg b.wt) 2 hours before PTX (2mg/kg b.wt) at alternate day and in Group V (propolis+ PTX group) rats were received propolis (250 mg/kg b.wt/day) 2 hours before PTX (2mg/kg b.wt) at alternate day. All experimental procedure continued for 14 days. All animal-related procedures were performed, complying with the recommendations and instructions of the Ethics Committee of the Faculty of Veterinary Medicine, Benha University, Egypt (Ethical Approval Number BUFVTM31-09-22).

2.4. Serum biochemical analysis:

At the end of the experiment, all rats were fasted overnight then blood samples were collected from orbital sinus of each rat into gel and clot activator tubes, allowed to coagulate at room temperature, and then centrifuged at 3,000 rpm for 15 min to obtain serum. The serum samples were stored at -20 °C until used. Biomarkers for heart function including creatine kinase-myocardial band (CK-MB) and lactate dehydrogenase (LDH) were assessed using diagnostic kits purchased from spectrum Company, Egypt-IFUFCC46. Measurement was performed according to Young, (1995) using Semi-auto chemistry analyzer.

2.5. Histopathological study:

After collection of blood sample, rats were sacrificed by cervical decapitation. Small tissue specimens were collected from heart and lungs, rinsed in saline and immediately fixed in 10 % neutral buffered formalin. Then the fixed specimens were washed with water and dehydrated in a series of ascending grades of ethyl alcohol. Then Specimens were cleared in xylene before being embedded in paraffin wax. Five microns sections were cut from paraffin wax tissue blocks and stained with hematoxylin and eosin (Bancroft and Layton, 2019).

According to the severity of the histopathological lesions, all specimens were examined and classified on a modified semi-quantitative scale of Bagheri et al., (2011) into none (-), mild (+), moderate (+++) and severe (++++) . Each lesion was graded as follow: (-) normal histology, (+) with up 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.

2.6. Immunohistochemical examination:

Tissue sections were deparaffinized and dehydrated using a descending ethanol series. For antigen retrieval, sections were heated at 80 °C with citrate acid solution for 5 min, cooled, and immersed in 3% hydrogen peroxide (H2O2) for 10 minute to inhibit endogenous peroxidases. Subsequently, 5% bovine serum albumin (BSA) solution was added as a blocking agent for 20 min. The following diluted primary antibodies were used as follows: Anti-tumor necrosis factor (TNF-α), anti-B-cell lymphoma-2 (Bcl-2). The staining was visualized using an avidin-biotin complex with a one-hour incubation at approximately 37 °C (Akishima et al., 2005). The final visualization was produced by 3,3-diaminobenzidine tetrahydrochloride (DAB) reaction, and the slides were counterstained with Mayer’s hematoxylin.

2.7. Statistical analysis:

Statistical analysis of serum CK-MB and LDH levels was carried out using SPSS, Ver. 27. Statistical difference among groups was determined using one way analysis of variance (ANOVA) followed by Duncun test as the post hoc test. All values were expressed as mean ± SE, with a P-value of < 0.05 considered statically significant.

3. RESULTS

CoQ10 or propolis alleviated PTX induced cardiopulmonary damage

Histopathological examination of hearts of rats in the control, CoQ10 and propolis groups revealed normal cardiomyocytes with centrally located nuclei and normal myocardial blood vessels (Fig. 1A, B & C). PTX induced severe cardiac damage in form of hyalinosis, cytoplasmic vacuolation (Fig. 1D) and necrosis of the cardiac muscle characterized by hypereosinophilic cytoplasm with small round pyknotic nuclei (Fig. 1E). Mononuclear inflammatory cell aggregations in between degenerated and necrotic cardiac muscles were seen (Fig. 1F). In addition to these lesions, PTX injection was associated with blood vessel damage characterized by injury of the endothelium with hypertrophy and degeneration of the muscular layer. Besides, congestion of the cardiac blood vessels and intermuscular capillaries, perivascular edema and mononuclear inflammatory cells aggregations (Fig. 1G) with focal myocardial hemorrhage were also seen (Fig. 1H).

Pretreatment with CoQ10 before PTX injection attenuated this cardiac damage where normal histological structure of the cardiac muscles (Fig. 1I) and perivascular aggregation of a few mononuclear leukocytic cells with intermuscular edema (Fig. 1J) were the major microscopic changes of the examined hearts. However, minimal intermuscular hemorrhage and a few small vacuoles in the sarcoplasm of some cardiac muscles were seen in some examined hearts. Furthermore, propolis pretreatment reduced the cardiac damage caused by PTX where the most examined heart showed mild perivascular edema intermixed with a few erythrocytes as well as mild congestion of some myocardial blood vessels (Fig. 1K) with normal cardiac architecture similar to the control group (Fig. 1L). In addition, A mild degree of degenerative changes which manifested by vesiculation in the sarcoplasm of myocardium with few mononuclear leukocytic infiltrations were seen in a few examined heart sections.
Aly et al. (2023)

Fig. 1. Representative Photomicrographs of heart sections stained with H&E stain. Control (A), CoQ10 (B) and propolis (C) groups-normal histological structure of cardiac muscles. PTX group (D-H) D-Cytoplasmic vacuolation of cardiac muscles (arrow), E-Myocardial necrosis, F- Intermuscular mononuclear leukocytic aggregation (arrowhead), G-Endothelial damage and muscular hypertrophy of blood vessel with perivascular edema, H-Intermuscular hemorrhage (asterisk), CoQ10+PTX group (I-J) I-Normal cardiac histoarchitecture, J-Few perivascular mononuclear leukocytic infiltration. Propolis+PTX group (K-L) K-Congestion of intermuscular capillaries (arrow), L-More or less normal cardiac muscles. (x400)

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. Pretreatment with CoQ10 or propolis was related with a reduction in these scores, showing that these substances provided effective cardioprotection against PTX-induced heart injury (table 1).

Table (1): Lesions scores of various histopathological alterations in the cardiac tissue:

<table>
<thead>
<tr>
<th>Lesion score</th>
<th>Control</th>
<th>CoQ10</th>
<th>Propolis</th>
<th>PTX</th>
<th>CoQ10+PTX</th>
<th>Propolis+ PTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vacuolar degeneration</td>
<td>-</td>
<td>+++</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Necrosis</td>
<td>-</td>
<td>+++</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Leukocytic cellular infiltrations</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Congestion</td>
<td>-</td>
<td>+++</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Blood vessels wall damage</td>
<td>-</td>
<td>+++</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Edema</td>
<td>-</td>
<td>+++</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>-</td>
<td>+++</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

(-): normal histology,  
(++) up to 1/3 of the examined section exhibiting the evaluated lesion  
(++) greater than 2/3 of the assessed section showed the estimated pathological alteration
Moreover, serum biochemical analysis confirmed these histopathological findings where significant elevation ($P < 0.05$) in the cardiac function biomarkers (CK-MB, and LDH) levels were recorded in PTX group compared with control group. On the other hand, pretreatment with CoQ10 or propolis substantially reduced the increased serum CK-MB and LDH levels comparing with PTX group. However, as compared to the propolis-treated group, pretreatment with CoQ10 slightly reverse elevated level of CK-MB, and LDH. (Table 2).

Table 2: Serum analysis of CK-MB and LDH levels in control and treated groups

<table>
<thead>
<tr>
<th>Group</th>
<th>CK-MB (U/L)</th>
<th>LDH (U/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>7.60±0.51c</td>
<td>628.00±40.52c</td>
</tr>
<tr>
<td>CoQ10</td>
<td>7.80±0.37c</td>
<td>662.80±67.44c</td>
</tr>
<tr>
<td>Propolis</td>
<td>8.90±1.49c</td>
<td>672.80±51.26c</td>
</tr>
<tr>
<td>PTX</td>
<td>27.00±9.71a</td>
<td>1246.00±5.05a</td>
</tr>
<tr>
<td>CoQ10+PTX</td>
<td>20.20±1.39b</td>
<td>913.60±43.15b</td>
</tr>
<tr>
<td>Propolis+PTX</td>
<td>21.00±0.71b</td>
<td>1026.60±14.25b</td>
</tr>
</tbody>
</table>

All 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.

The histological structure of bronchioles, pulmonary blood vessels, interalveolar blood capillaries, and alveoli were normal in the control, CoQ10, and propolis groups (Fig. 2A, B, and C). In PTX group, the lungs revealed severe congestion of the pulmonary blood vessels and interalveolar blood capillaries with multifocal hemorrhages replacing the pulmonary tissue and intermixed with deteriorated alveoli (Fig. 2D). Perivascular edema and hemorrhage intermixed with few mononuclear leukocytic infiltrations were also prevalent in all examined lungs (Fig. 2E). The pulmonary blood vessels mostly displayed proliferation of the lining endothelial cells with vesiculation in the sarcoplasm of muscular layers (Fig. 2F). In addition, fibrinoid necrotizing vasculitis was seen (Fig. 2G). Furthermore, severe thickening of the blood vessels walls owing to muscular hypertrophy was detected. Multiple mononuclear leucocytic cell aggregations were scattered throughout the pulmonary tissues notably surrounding blood vessels (Fig. 2H). Severe hyperplasia and/or desquamation of the bronchiolar epithelium with some erythrocytes in the bronchial lumen were detected.

Administration of CoQ10 prior to PTX injections improved pulmonary histological alterations induced by PTX where there were mild congestion of the pulmonary blood vessels and interalveolar blood capillaries together with mild perivascular edema. Moreover, the bronchioles showed only mild epithelial hyperplasia (Fig. 2I) and desquamation with an albuminous faint eosinophilic substance in their lumens (Fig. 2J). Also, pretreatment with propolis restores lung histological structure where mild perivascular mononuclear cellular infiltration as well as congestion of pulmonary blood vessels with necrosis of endothelium lining pulmonary blood vessels along with vesiculation of sarcoplasma of the muscular layers were also seen (Fig. 2K). Nearly normal bronchiolar epithelium with mild interalveolar congestion were recorded (Fig. 2L).

Fig. 2. Representative photomicrographs of lungs sections stained with H&E stain. Control (A), CoQ10 (B) and propolis (C) groups-normal histological structure of bronchioles and alveoli. PTX group (D–H) D-Focal pulmonary hemorrhage (asterisk). E-Perivascular hemorrhage (asterisk). F-Vesiculation of pulmonary blood vessels wall (arrow) and hypertrophy of its muscular layer with narrowing of lumen. G-Fibrinoid necrotizing vasculitis. H-Perivascular mononuclear leukocytic cellular infiltration. CoQ10+PTX group (I–J) I-Mild hyperplasia of bronchiolar epithelium. J-Mild desquamation of bronchiolar epithelium. Propolis+PTX group (K–L) K-Congestion of pulmonary blood vessel (asterisk) with necrosis of endothelial cell lining. L-mild interalveolar congestion. (x400)
PTX caused substantial lung injury. Pretreatment with CoQ10 or propolis was related with a reduction in these scores, showing that these substances provided effective protection against PTX-induced pulmonary damage (table 3).

Table 3. Lesions scores of various histopathological changes in the pulmonary tissues

<table>
<thead>
<tr>
<th>Lesion score</th>
<th>Control</th>
<th>CoQ10, Propolis</th>
<th>PTX</th>
<th>+PTX</th>
<th>+ Propolis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestion</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>-</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Perivascular edema</td>
<td>-</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Blood vessels wall damage</td>
<td>-</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Leukocytic cellular infiltrations</td>
<td>-</td>
<td>+++</td>
<td>-</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Deterioration of alveolar structure</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Hyperplasia and desquamation of bronchial epithelium</td>
<td>-</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

(-): normal histology.
(+): up to 1/3 of the examined section exhibiting the evaluated lesion.
(++): up to 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.

CoQ10 and propolis attenuated PTX induced cardiopulmonary inflammation

The anti-inflammatory effects of CoQ10 and propolis were evaluated using TNF-α expression which related to the increasing of inflammatory reaction in the heart and lungs. Low TNF-α expressions restricted only to endothelial cells of myocardial blood capillaries were detected in the heart of rats in the control, CoQ10 and propolis groups (Fig. 3A). While the examined heart of rats in the PTX group showed high TNF-α immunoexpression mainly in many cardiomyocytes (Fig. 3B). Compared with PTX group, pretreatment with CoQ10 resulted in markedly lower the TNF-α immunoexpression where the immunoreactivity was limited to few cardiomyocytes (Figs. 3C). Likewise, TNF-α expression was also reduced in the cardiac muscles of rats pretreated with propolis (Fig. 3D).

Fig. 3. Photomicrographs showing immunohistochemical expression of TNF-α in heart of rats in A: Control group. B: PTX group. C: CoQ10 +PTX group. D: Propolis + PTX group X 200.

Low TNF-α expression was recorded in the lungs of rats in the control, CoQ10 and propolis groups compared to other groups (Fig.4A). However, marked TNF-α immunoexpression was seen in the lungs of rats in the PTX group. TNF-α immunopositivity was found in endothelial cells of pulmonary blood vessels and perivascular areas (Figs. 4B and C). TNF-α immunoexpression was also seen in the vicinity of inflammatory cells in both interstitial and peribronchial tissues (Figs. 4D and F). Furthermore, the desquamated bronchial epithelium was immunopositive for TNF-α (Fig.4E). Pretreatment with CoQ10 resulted in marked decrease in TNF-α immunoexpression, with immunoreactivity limited to the bronchial and bronchiolar epithelium, as well as the in inflammatory cells in the peribronchial areas (Fig.4G). Similarly, TNF-α expression was also reduced in the lungs of rats pretreated with propolis compared with the PTX group (Fig.4H).

Fig. 4. Effects of CoQ10 and propolis on TNF-α expression after PTX intoxication in the lung. A: Control groups. B-F: PTX group. G: CoQ10 +PTX group. H: Propolis +PTX group X 200.

CoQ10 and propolis ameliorate PTX-induced cardiopulmonary apoptosis:

Expression of Bcl-2 was assessed to evaluate the protective effects of propolis and CoQ10 on PTX induced apoptosis. Control, CoQ10 and propolis groups revealed positive cytoplasmic immunoreactivity of Bcl-2 in many cardiomyocytes (Fig. 5A). Comparing with these groups, Low Bcl-2 immunoexpression was recorded in PTX group (Fig. 5B). In contrast, pretreatment with CoQ10 was associated with marked immunoreactivity in most cardiac muscle fibers (Fig. 5C). Similarly, Bcl-2 immunoreactivity also moderately increased in the heart of rats pretreated with propolis (Fig. 5D).

Fig. 5. Photomicrographs showing the immunohistochemical expression of Bcl-2 in heart of rats in A: Control group. B: PTX group. C: CoQ10 +PTX group. D: Propolis + PTX group X 200.
Similarly, there was high expression of Bcl-2 in the lungs of rats in the control, CoQ10 and propolis groups (Fig.6A). In contrast, null to mild immunexpression of Bcl-2 was recorded in the pulmonary tissue of rats in PTX group (Fig. 6B). Comparing with the PTX group, moderate Bcl-2 expression was detected in the lung tissue of rats pretreated with CoQ10 (Fig.6C). Also, pretreatment with propolis accompanied with moderate Bcl-2 immunexpression (Fig D6).

Figure 6: Photomicrographs showing immunohistochemical expression of Bcl-2 in lungs of rats in A: Control group. B: PTX group. C: CoQ10 +PTX group. D: Propolis +PTX group X 200.

4. DISCUSSION

Paclitaxel is recognized worldwide as one of the most effective chemotherapeutic drugs used in the treatment of many types of solid cancers. Unfortunately, its mechanism of action operates in cancer and normal cells (Rowinsky et al., 1993). Consistence with prior studies, in the present work various histopathological cardiac lesions were observed in PTX-administered rats such as congestion, hemorrhage, hyaline degeneration, necrosis and cytoplasmic vacuolation (Li et al., 2015; Razzaq et al., 2021). Paclitaxel-induced myocardial damage directly via an effect on subcellular organelles or indirectly following a massive histamine release (Schimmel et al., 2004; Herrmann et al., 2016). Furthermore, the lung of rats in the PTX group showed hemorrhage, diffuse perivascular cuffing and degenerated alveoli as well as hyperplasia and desquamation of the bronchial epithelium. Similar microscopic findings were reported (Utreja et al., 2011; Liu et al., 2015). These results might attributable to PTX causes pulmonary alveolar-capillary leakage (Jacob and Gaver III, 2012). Paclitaxel-induced vascular damage was characterized by damage of the endothelium with perivascular edema which might be attributable to PTX impairs endothelial function in vivo (Vassilakopoulou et al., 2010).

Paclitaxel induced a significantly increases in serum CK-MB and LDH levels. The recorded cardiac necrosis associated with increase the permeability or rupture of the cell membrane, causing leakage of these enzymes into the blood so increasing their serum concentrations (Mohamed et al., 2021). Additionally, increase in LDH activities recorded in patients treated with PTX attributed to its oxidative injury (Simão et al., 2006). TNF-α is one of the proinflammatory cytokines, produced chiefly by activated macrophages or many other inflammatory cells. In the current work, PTX was associated with high TNF-α immunoreactivity and a null expression of antiapoptotic member Bcl-2 in cardiac and pulmonary tissues in PTX-intoxicated rats. Similar findings were also reported (Ilterturk et al., 2023). Paclitaxel-induced cytotoxicity occurs through stabilizing microtubules by synthesis of free radicals, increase inflammation parameters including TNF-α, and phosphorylation of Bcl-2 proteins (Doyle et al., 2012; Park, 2014; Starobova and Vetter, 2017).

Pretreatment with CoQ10 improved hearts and lungs histopathological changes induced by PTX and caused reduction in the levels of CK-MB and LDH. In previous studies, CoQ10 has a protective action against cardiac remodeling induced by isoprenaline (Ulla et al., 2017) and lung injury induced by cyclophosphamide and methotrexate in rat models (Olama et al., 2018; Mohamed et al., 2019). These findings account for being endogenous antioxidants and anti-inflammatory agent (Sifuentes-Franco et al., 2022). Besides, CoQ10 protects myocardial integrity through preservation of ATP levels which is essential for proper heart functioning (Zozina et al., 2018). Low expressions of TNF-α in the heart and lungs tissues were detected in PTX-pretreated rats with CoQ10. These results were in agreement with previous study which indicated the anti-inflammatory activity of CoQ10 via decreasing the proinflammatory cytokines TNF-α (Ali-Johani et al., 2022). Moreover, moderately increased Bcl-2 expression was found in the heart and lung tissues of rats pretreated with CoQ10 that inhibited apoptosis via increasing the level of Bcl-2 gene (Mahmoud et al., 2019; Jafarvand et al., 2016).

Pretreatment with propolis substantially improved heart and lung histopathological alterations induced by PTX and also reduced the elevated CK-MB and LDH. These results were in agreement with Mohamed et al., (2021). These results may be the consequence of the synergistic action of propolis various components as CAPE which is a bioactive compound that has been extracted from propolis (Larki, Harchegani et al., 2013). Furthermore, low expressions of TNF-α were recorded in the heart and lungs tissues of the PTX group pretreated with propolis. This finding was in a harmony with these findings of Khaled et al., (2022). Low TNF-α expression might be attributable to the potential antioxidant and anti-inflammatory role of propolis through inhibiting pro-inflammatory cytokines such as TNF-α (Zulhendri et al., 2022). On the other hand, moderate Bcl-2 immunoreactivity was observed in the cardiopulmonary tissues of the PTX group pretreated with propolis. Soliman and Noya, (2023) mentioned that concomitant administration of propolis with bisphenol A in rats was associated with strong positive cytoplasmic immunoreactivity for Bcl-2 in the lung.

5. CONCLUSIONS

Paclitaxel induced noteworthy heart and lung damage as indicated by severe histopathological alterations and elevated serum CK-MB and LDH levels. Pretreatment with CoQ10 or propolis ameliorates PTX-induced cardio-pulmonary toxicity due to inflammation and apoptosis by...
down regulation of TNF-α production and up regulation of Bcl-2 expression.

6. REFERENCES


