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Effects of royal jelly on liver paraoxonase activity in rats treated with cisplatin

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Aim: To evaluate the protective effects of royal jelly (RJ) on the changes caused by cisplatin in paraoxonase-1 (PON-1) and arylesterase (ARE) activities.

Materials and methods: Twenty-four Sprague-Dawley rats were divided into 4 groups of 6: control, royal jelly (300 mg kg^{-1} day^{-1}), cisplatin (7 mg kg^{-1} body weight), and royal jelly (300 mg kg^{-1} day^{-1}) plus a single dose of cisplatin (7 mg kg^{-1} body weight). After the experimental procedures, blood and liver tissue samples were taken from each animal. The effects of RJ and cisplatin were evaluated by PON-1, ARE (in liver homogenates), and serum alanine aminotransferase measurements. The liver tissue was also histologically examined.

Results: Administration of cisplatin reduced the PON-1 and ARE activities in the liver. However, in the rats given a pretreatment with RJ before the injection of cisplatin, the reduction caused by the cisplatin in the PON-1 and ARE activities was prevented at a significant level. These biochemical observations were supported by histological findings and suggested that RJ restored the cisplatin-induced structural alterations in the liver tissue by the way of its antioxidant, radical scavenging, and antiapoptotic effects.

Conclusion: RJ may be a potential preventive agent against the hepatic toxicity associated with cisplatin therapy.

Key words: Arylesterase, cisplatin, oxidative stress, paraoxonase, royal jelly

Sisplatin ile tedavi edilen sıçanlarda karaciğer paraoksonaz aktivitesi üzerine arı sütünün etkileri

Amaç: Sisplatinin neden olduğu paraoksonaz-1 (PON-1) ve arilesteraz (ARE) aktivitelerindeki değişiklikler üzerinde arı sütünün koruyucu etkilerini değerlendirmek.

Yöntem ve gereç: Yirmi dört Sprague-Dawley sıçan, 6'şarlı 4 gruba bölündü: Kontrol; arı sütü (300 mg kg^{-1} $gün^{-1}$); sisplatin (7 mg kg^{-1} vücut ağırlığı) ve arı sütü (300 mg kg^{-1} $gün^{-1}$) + tek doz sisplatin (7 mg kg^{-1} vücut ağırlığı). Tüm hayvanlardan deneyler sonrası karaciğer dokusu ve serum örnekleri alındı. Arı sütü ve sisplatinin etkileri PON-1, ARE (karaciğer homojenatında) ve serum alanin aminotransferaz ölçümleriyle değerlendirildi. Ayrıca karaciğer dokusu histolojik olarak incelendi.

Bulgular: Sisplatin uygulaması, karaciğer dokusunda PON-1 ve ARE aktivitelerini azalttı. Bununla birlikte sisplatin enjeksiyonu öncesi arı sütü uygulanan hayvanlarda, sisplatinin neden olduğu PON-1 ve ARE aktivitelerindeki azalmanın anlamlı düzeyde önlendiği görüldü. Ayrıca bu biyokimyasal gözlemler, histolojik bulgularla da desteklendi ve

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antioksidan, radikal toplayıcı ve antiapopitotik etkileriyle arı sütünün, sisplatinin neden olduğu karaciğer dokusundaki yapısal değişiklikleri engellediği görüldü.

Sonuç: Arı sütü, sisplatin tedavisiyle ilgili oluşan karaciğer toksisitesine karşı potansiyel koruyucu ilaç olarak kullanılabilir.

Anahtar sözcükler: Arilesteraz, sisplatin, oksidatif stres, paraoksonaz, arı sütü

Introduction

Royal jelly (RJ), a food item secreted by worker honeybees, is a mixture that contains protein, glucose, lipid, vitamins, and minerals (1). RJ is widely used as a commercial medical product. Previous studies have shown that RJ has a number of physiological effects, such as antiinflammatory, antitumor, antiallergic, and antioxidant activities (2). Şimşek et al. (3) reported in their study on rats that an oral RJ application of 300 mg kg^{-1} day^{-1} increases the number of erythrocytes and their diameters; therefore, it could be used as a supportive antioxidant molecule in anemic patients. Guo et al. (2) stated that RJ peptides have a protective effect against lipid peroxidation caused by free radicals, both under in vivo and in vitro conditions.

Cisplatin (cis-diamine-dichloroplatinum) is one of the major drugs used in the treatment of cancer. It is commonly used in the treatment of such cancers as lung, ovarian, and testicular cancer (4,5). However, cisplatin may lead to serious adverse effects if used in high doses. Clinical use is limited by its toxic side effects, which occur primarily in the liver and then in the bone marrow, kidneys, and other organs (6,7). Cisplatin toxicity may occur with different mechanisms. Different studies performed so far have shown that cisplatin leads to the formation of reactive oxygen species, lipid peroxidation, and DNA damage (8). Therefore, one of the issues with which one should be careful in cancer treatment is the prevention of the oxidative stress caused by cisplatin.

The paraoxonase (PON) multigene family is composed of 3 members: PON-1, PON-2, and PON-3 (9). PON-1 is a calcium-dependent ester hydrolase that has both PON and arylesterase (ARE) activities. The PON-1 enzyme, synthesized mainly in the liver, is a protein that possesses a hydrolytic effect on many substrates, including organophosphates, aryl esters, and lactones (10,11). Similar to PON-1, PON-3 is expressed mostly in the liver and secreted into the blood, but it is approximately 2 orders of magnitude less abundant than PON-1. PON-2 is not detectable in serum, although it is expressed in many tissues, including brain, liver, kidney, and testis.

It has been reported in many studies that PON-1 has an antioxidant effect against the lipid peroxidation caused by free radicals on cell membranes and lipoproteins (12-14). The purpose of this study was to examine the probable protective effects of RJ on the oxidative organ damage caused by cisplatin. To this end, the antioxidant effects of RJ were analyzed with PON-1 and ARE enzyme activities measured in liver tissues, as well as histological changes.

Materials and methods

Animals and experimental procedure

This experimental study was conducted with the approval of the local ethics board for animal experiments at Atatürk University. Twenty-four female adult Sprague-Dawley rats (about 200 g) were used. During the study, the rats were kept in metal cages at 22-24 °C with a L/D photoperiod of 12:12, and they were fed commercial standard rat food and tap water. They were divided into 4 groups of 6, as follows: the control group (Group C), the group that was given RJ (Group RJ), the group that was given cisplatin (Group CP), and the group that was given RJ + cisplatin (Group RJ + CP). The rats in Group C were fed standard rat food and tap water, while Group RJ rats were given RJ at 300 mg kg^{-1} day^{-1} (Balen Royal Jelly, 300 mg capsule, Arı Mühendislik, Ankara, Turkey) through an orogastric tube for 15 days. Group CP rats were given a single dose of CP [7 mg kg^{-1} body weight, intraperitoneally (i.p.)]. Group RJ + CP rats were given RJ at 300 mg kg^{-1} day^{-1} through an orogastric tube for 15 days, and were then given a single dose of cisplatin (7 mg kg^{-1}, i.p.). The doses of cisplatin and RJ used in this study were selected in accordance with previous studies (15,16).

Taking of tissue and blood samples and biochemical measures

The animals in the control and experimental groups were anaesthetized 24 h after the end of the study with an injection of sodium pentobarbitone 60 mg kg^{-1} of body weight, i.p. The rats were then killed by taking blood samples from the intracardiac site, and liver tissues were immediately removed.

Blood samples were centrifuged for 5 min at 3500 × *g* and their sera were separated and stored at –80 °C until analysis. Tissue samples were cleaned using an ice-cold solution of isotonic NaCl for the removal of blood spots, and they were then dried with blotting paper. Approximately 300 mg of liver tissue from each rat was weighed and homogenized within the ice-cold buffer solution (50 mM Tris-HCl buffer, pH 8.0, containing 2 mM $CaCl_2$) (OMNI TH homogenizer, OMNI, Warrenton, VA, USA). Tissue homogenates were centrifuged at 15,000 × *g* for 15 min (4 °C) and the supernatant was kept at –80 °C for biochemical analysis. Tissue protein levels were determined via the Bradford method (17), and the serum alanine aminotransferase (ALT) level was determined with a Roche Cobas biochemical autoanalyzer using a commercial kit (Roche Diagnostics, Mannheim, Germany) and was expressed as U L^{-1}.

Measurement of PON-1 and ARE activities

PON-1 and ARE activities were assessed by methods described previously (18,19), with some modifications. The original method was semiautomatized with the adaptation of a 96-well microplate; thus, analysis of a multitude of samples was made possible in a short time. Kinetic measurements were conducted with the use of a spectrophotometric microplate reader (PowerWave XS, Bio-Tek Instruments, Inc., Winooski, VT, USA) and its software program (KC Junior software, Bio-Tek Inc.). The PON-1 measurement was taken at 405 nm and the ARE measurement was taken at 270 nm. As the ARE measurements were made at an ultraviolet wavelength (270 nm), a 96-well UV plate was used for the assays. For the measurements of PON-1 and ARE activities, diethyl-p-nitrophenyl phosphate (Sigma, St. Louis, MO, USA) and phenyl acetate (Sigma) were used as the substrates, respectively (19). Molar absorption coefficients were used in the calculation of the PON-1 and ARE activities (17100 M^{-1} cm^{-1} and 1310 M^{-1} cm^{-1}, respectively). One unit of PON-1 activity was defined as 1 nmol 4-nitrophenol mL $serum^{-1}$ min^{-1} and 1 unit of ARE activity was defined as 1 mmol phenol mL $serum^{-1}$ min^{-1}. Tissue-specific activities of PON-1 and ARE in the liver were calculated and the results were expressed as U mg $protein^{-1}$.

Histological procedure

Liver tissue samples were fixed in 10% buffered neutral formalin and embedded in paraffin. The paraffin blocks were cut to thicknesses of 5-7 μm and stained with Mallory's triple staining technique, as modified by Crossman. Stained specimens were examined under a Nikon i50 light microscope. Apoptotic cells were determined immunohistochemically as pyknotic, hyperchromatic nuclei, and caspase-3-positive reactions. For the immunohistochemistry examination, primary antibody monoclonal caspase-3 (dilution: 1/25, BioVision-3015-100, BioVision, Milpitas, CA, USA) and biotinylated secondary antibody (Universal LSAB Kit-K0690, Dako, Glostrup, Denmark) were used. The antibody binding sites were visualized with diaminobenzidine (Sigma) and evaluated by high-power light microscopic examination (Nikon i50). All of the apoptotic staining cells were estimated with an image processing system (Kameram SLR, 1.6.1.0, Mikro Sistem Ltd. Şti., İstanbul, Turkey) in 4 different areas of 0.2 mm^2 at 20× objective. Damaged cells were not evaluated. The marked cells were counted automatically with the same image analysis program.

Statistical analysis

The results were expressed as means ± standard deviation (SD). Differences among the groups were assessed with one-way ANOVA following Tukey's post hoc multiple comparison test. $P \leq 0.05$ was statistically significant. SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for these analyses.

Results

Effects of cisplatin and RJ on serum ALT levels

When compared with Group C, cisplatin led to a significant increase in the serum ALT levels. While ALT activity was 32.8 ± 4.5 U L^{-1} in Group C, it was 50.4 ± 5.7 U L^{-1} in Group CP ($P < 0.001$). This increase in ALT activity was partially prevented by

pretreatment with RJ. ALT activity was 47.9 ± 4.7 U L^{-1} in Group RJ + CP, but this decrease in ALT activity did not show statistically significant differences compared with Group CP ($P > 0.05$). These results are shown in Figure 1.

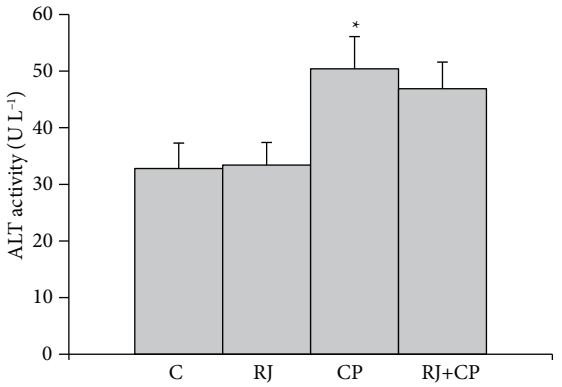

Figure 1. Serum ALT activities in all of the groups. *P < 0.001 vs. Group C and Group RJ. C, control (Group C); RJ, royal jelly (Group RJ); CP, cisplatin (Group CP).

Cisplatin reduces the activities of liver PON-1 and ARE

PON-1 and ARE activities were measured in liver homogenates. When compared with Group C, a dose of cisplatin administration (Group CP) was observed to significantly decrease the PON-1 enzyme activities in the liver tissue (Figure 2). While liver PON-1 activity was 8.1 ± 1.6 U mg $protein^{-1}$ in Group C, it was 5.2 ± 1.1 U mg $protein^{-1}$ in Group CP ($P < 0.005$). Similarly, ARE activity was lower in Group CP (4.1 ± 0.7 U mg $protein^{-1}$) when compared with Group C (6.5 ± 0.4 U mg $protein^{-1}$) ($P < 0.001$). Data concerning the PON-1 and ARE activities measured in the study groups are presented in Figures 2 and 3.

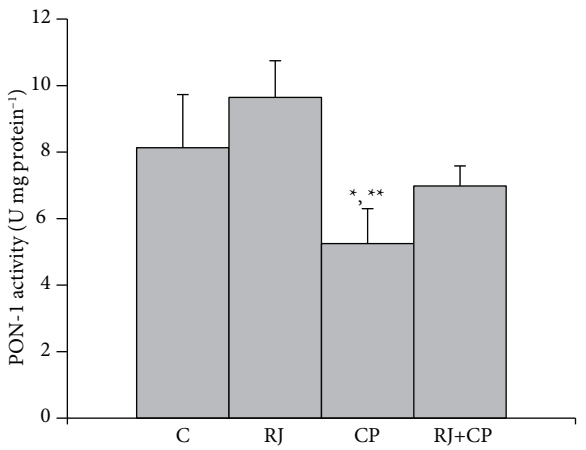

Figure 2. Liver tissue PON-1 activities in all groups. *P < 0.005 vs. Group C and **P < 0.001 vs. Group RJ.

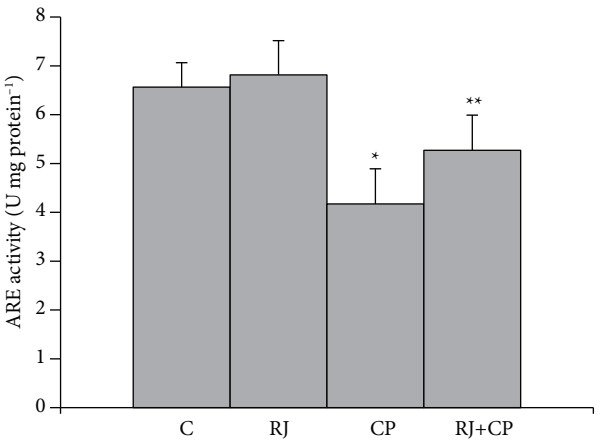

Figure 3. Liver tissue ARE activities in all of the groups. *P < 0.001 vs. both Group C and Group RJ and **P < 0.05 vs. Group C.

Protective effect of RJ on the hepatotoxicity

While cisplatin decreased the antioxidant PON enzyme activities in the liver, 300 mg kg^{-1} RJ (in Group RJ + CP) administered orally for 15 days was observed to significantly prevent the decrease in PON-1 and ARE activities caused by cisplatin. However, when compared with the other groups, the highest PON-1 and ARE activities were measured only in Group RJ. Data concerning these results are shown in Figures 2 and 3.

Histological results

For histological evaluation, although the livers of Group C and Group RJ showed normal histological structure (Figures 4A and 4B), histological alterations were observed only in Group RJ + CP and Group CP. Microscopic changes were characterized by sinusoidal dilatation, mononuclear cell infiltrations, congestion and hepatocellular degeneration, and apoptosis (Figures 4C-4E). In Group RJ + CP, interesting decreases in the cytoplasmic alteration of the hepatocytes or sinusoidal dilatations around the central vein were found in comparison to

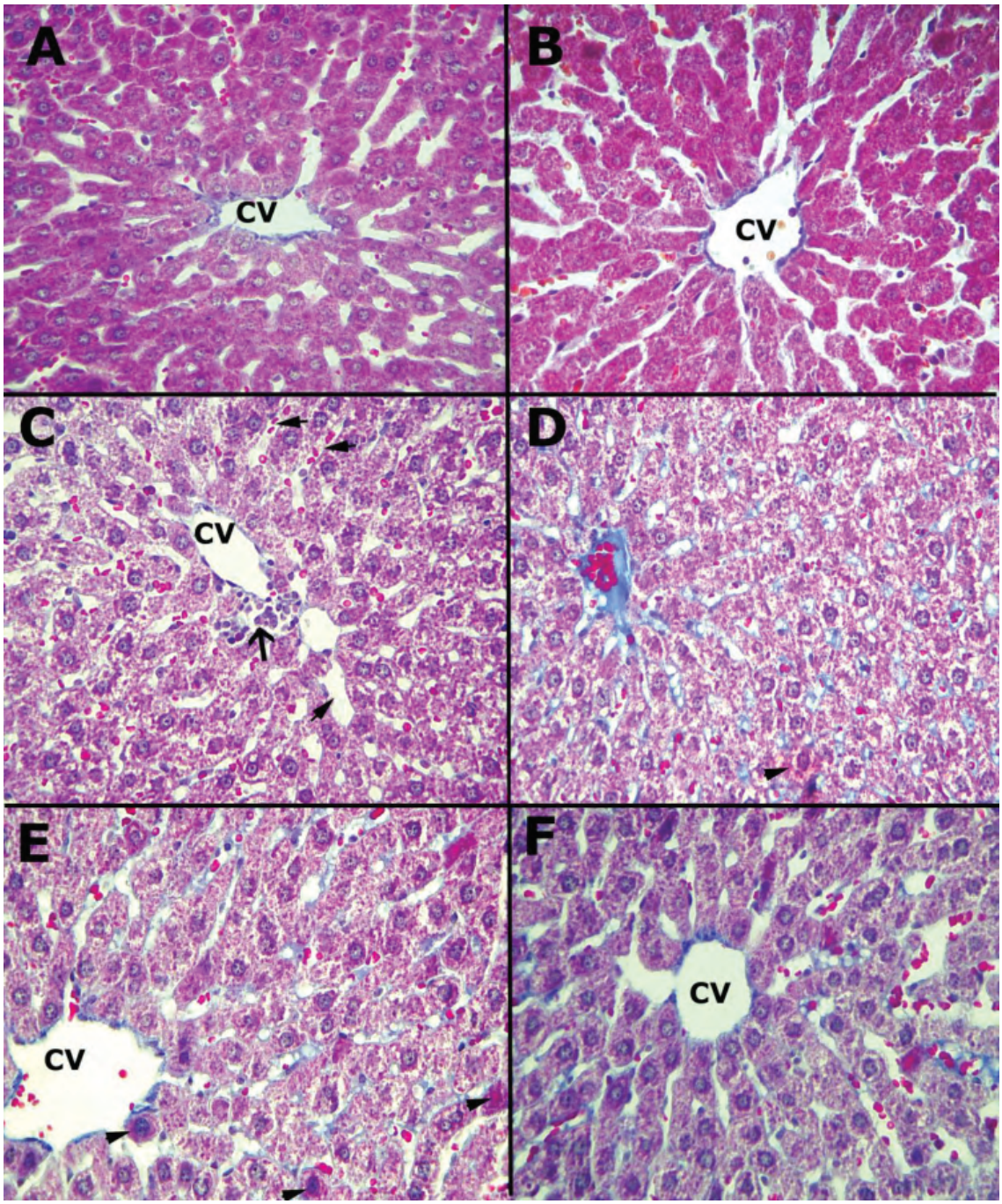

Figure 4. A) Group C, B) Group RJ, C-E) Group CP, and F) Group RJ + CP: mononuclear cell infiltrations are obvious in portal areas (open arrow), sinusoidal congestion and dilatations (arrows), and apoptotic cells (arrow heads). Light micrograph of a transverse section of the liver stained with triple stain modified by Crossman, 625×, CV = central vein.

Group CP (Figure 4F). Furthermore, in this study, apoptotic immunopositive reactions in the liver were investigated with caspase-3 antibody. Apoptotic activity comparisons of the groups are shown in Figure 5. Caspase-3-immunoreactive cells were intensely observed around the central vein of the liver in Group CP (Figure 5A) and throughout the lobules (Figure 5B). We saw that the number of apoptotic cells were increased in the liver tissue of Group CP when compared with Group RJ + CP, which showed significantly decreased apoptotic cell numbers ($P < 0.05$, Figures 5C and 5D).

Discussion

Cisplatin is one of the most effective chemotherapeutic agents in cancer treatment. It is used in the treatment of malign cancers of several tissues and organs, such as lung, testis, ovary, bladder, and head-neck (7). However, the side effects of cisplatin restrict its use

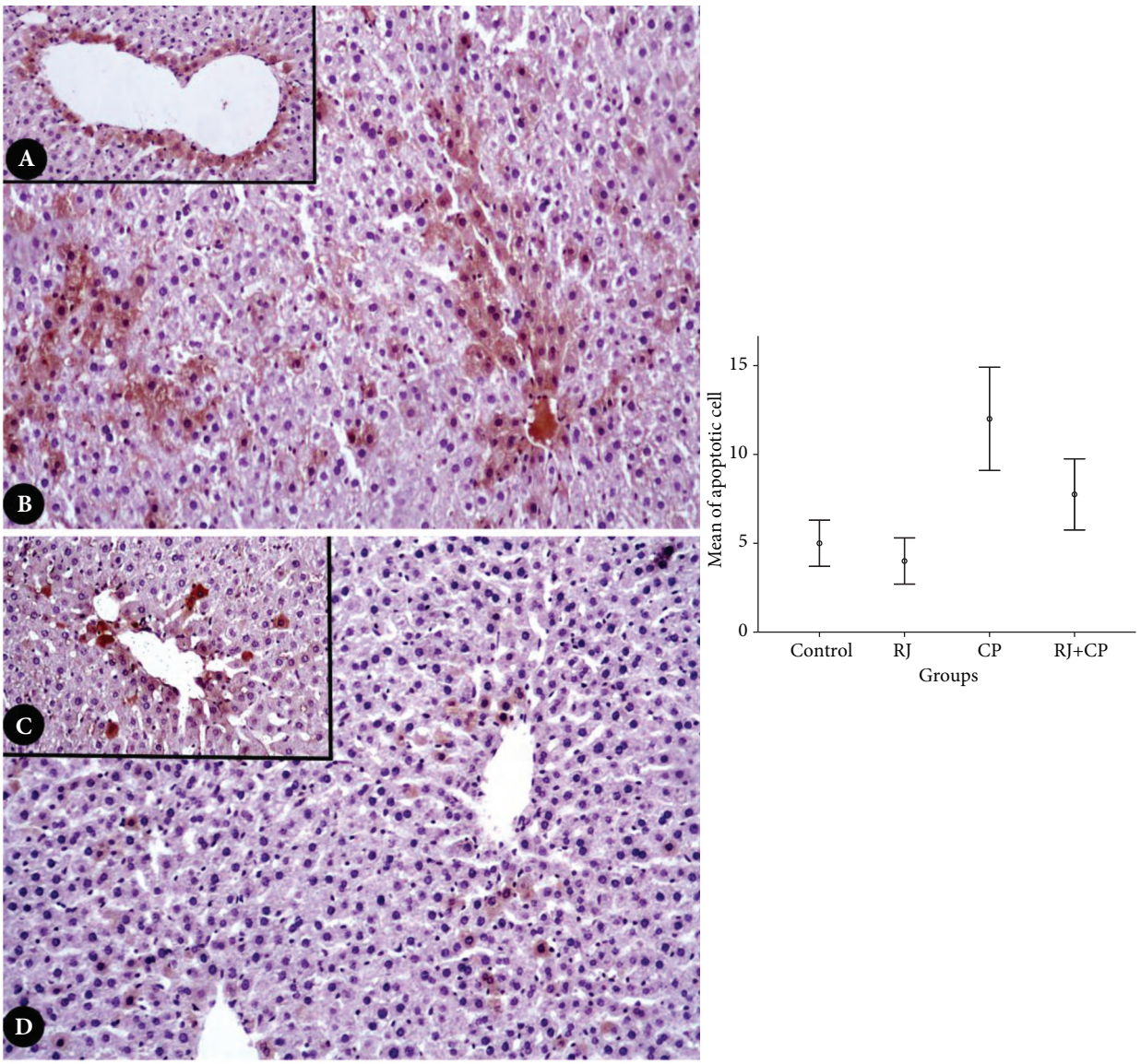

Figure 5. Apoptotic cell numbers (n 0.2 mm^{-2}) in all of the groups and caspase-3-positive cells in Group CP (A and B) and Group RJ + CP (C and D) by streptavidin biotin peroxidase stain (275×). The numbers of apoptotic cells in the unit area in Group C and Group RJ were statistically significant compared with those of Group CP and Group RJ + CP ($P < 0.05$). The numbers of apoptotic cells in Group RJ + CP were significantly decreased compared with Group CP ($P < 0.005$).

and effectiveness. Hepatotoxicity, nephrotoxicity, neurotoxicity, hair loss, nausea, and vomiting are common side effects (6,7,20). Its toxic effects on various organs, including the liver, make it necessary to carefully regulate the dosage of cisplatin (6).

Recent studies have largely focused on the ways to protect against cisplatin hepatotoxicity (21,22). To the best of our knowledge, this study is the first to research the protective effect of RJ against cisplatin hepatotoxicity. It has already been stated in the literature that some antioxidant molecules that are influential as scavengers or prevent the formation of reactive oxygen species eliminate the hepatotoxicity caused by cisplatin (21). Therefore, in this study, focus was placed on the probable protective effects of RJ on the oxidative hepatic damage caused by cisplatin.

An injection of cisplatin, if at a high dosage (>30 mg kg^{-1}), may lead to death. In this study, intraperitoneal injections of cisplatin in rats led to a significant increase in the serum ALT activity. Hepatotoxicity caused by cisplatin was evaluated with PON-1 and ARE activities measured in the liver tissue and serum ALT activity. As the liver plays a key role in the synthesis of serum paraoxonase, it was reported in previous studies that the measurement of PON-1 activity could be used as a liver function test (23,24). In this study, the existence of hepatotoxicity in the rats to which cisplatin was administered was proven by the increased serum ALT and decreased hepatic tissue PON-1 and ARE activities. Increased serum ALT activity in the cisplatin hepatotoxicity in the experimental animals was also reported by Liao et al. (6) and Kart et al. (21).

Many studies have been conducted so far on the role of the PON-1 enzyme in the pathogenesis of various diseases (25), and most have focused on cardiovascular diseases (26,27). Although serum PON-1 enzyme is primarily synthesized in the liver (23), there are a limited number of studies on the PON-1 activity of the liver.

PON-1 is an enzyme that has an antioxidant quality, and thus it has been reported that PON-1 serum and/or tissue activity changes in cases of oxidative stress (12,26). In their comparative study on human and rat liver tissue, Trudel et al. (28) reported that PON-1 expression decreases in the case of acute oxidative stress caused by the iron-ascorbate oxygen-generating system. This case shows that PON-1 responds to acute damage (23). Moreover, Ferré et al. (24) stated that PON-1 activity in chronic liver illness is associated with the degree of hepatic dysfunction. Similar to the results of Trudel et al. (28), we observed that 24 h after the administration of cisplatin, namely in the acute period, PON activities decreased in the hepatic tissue samples. Considering these results, we are of the opinion that measurement of PON-1 and ARE activities may be used as a helping biomarker of acute hepatotoxicity.

As there is not a study that assesses the relationship between cisplatin hepatotoxicity and PON-1/ARE activities, it was difficult to compare our results to others. Therefore, we found it best to have a look at other studies that examine the oxidant/antioxidant status in cisplatin hepatotoxicity. Even though the underlying mechanisms of the hepatotoxicity caused by cisplatin have not been understood exactly, it has been reported that it might be related to oxidative stress (6,29).

A decrease was reported in the oxidative stress (30) and enzymatic (31) and nonenzymatic (32) antioxidant defense system that was caused by the increase in the reactive oxygen species, and major changes were observed in cisplatin toxicity. In the present study, the activity of PON (both PON-1 and ARE), which is an antioxidant enzyme, decreased significantly in cisplatin-injected rats. This result seems to confirm the literature information regarding the effect of a decreased enzymatic antioxidant defense system in cisplatin hepatotoxicity. However, we have not been able to decide exactly whether the decreased PON-1 and ARE activities observed in cisplatin hepatotoxicity are a cause or a result.

In this study, the in vivo protective effects of RJ against cisplatin hepatotoxicity were examined. As seen in Figure 2, both tissue and serum PON-1 and ARE activities decreased significantly after the intraperitoneal cisplatin injection. However, a 15-day-long administration of RJ was observed to significantly prevent the decrease in liver paraoxonase enzyme activities caused by cisplatin (Figure 2). This effect is probably related to the antioxidant quality of RJ. As stated above, increased oxidative stress and/or a decreased enzymatic antioxidant defense system plays an important role in cisplatin toxicity

(6,29). Furthermore, recent research shows that RJ peptides have a strong hydroxyl radical scavenging quality. Accordingly, RJ peptides show antioxidant activity, preventing lipid peroxidation (2). Therefore, it is probable that RJ cures PON-1 and ARE activities through antioxidative effect mechanisms. That is, RJ probably inactivates the hydroxyl radicals, which are indeed very reactive (2), thus protecting the PON-1 and ARE enzymes from the harmful effects of free radicals.

The above biochemical results correlated well with the histological results from the liver tissue, which revealed sinusoidal dilatation, mononuclear cell infiltration, congestion and hepatocellular degeneration, and apoptosis. The histological pictures and evaluations of apoptosis are presented in Figures 4 and 5. The livers of Group C and Group RJ showed normal histological views (Figures 4A and 4B). However, rats given cisplatin alone, had hepatocellular degeneration and inflammatory infiltrations in the liver sections (Figures 4C and 4E). The liver is known to accumulate significant amounts of cisplatin, and thus hepatotoxicity can be associated with cisplatin treatment (6). Cisplatin is thought to kill cells primarily by forming DNA adducts, causing G2 arrest in the cell cycle and triggering apoptosis (33). Apoptosis is a common feature of hepatotoxicity induced by many chemicals; it may precede necrosis, as in the hepatotoxicity induced by cisplatin (34). On the other hand, the liver cells in Group RJ + CP rats were nearly normal in histological architecture. Similar findings were also reported by Kart et al. (21) and Yüce et al. (35), demonstrating the structural changes in the liver tissue of cisplatin-treated animals and its reverse action by different agents such as caffeic acid, phenethyl ester, or ellagic acid.

As a result, cisplatin decreases the liver PON-1 and ARE activities in rats. A combination of RJ and cisplatin prevents this decrease significantly. This result shows that RJ has a potential effect on paraoxonase enzyme activity; therefore, RJ can be used as a protective natural product against the hepatotoxicity caused by cisplatin.

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