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Research Article

Antioxidant Role of Beta-glucan on Cisplatin-induced Liver Injury in Rats

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Abstract

Objective: Cisplatin (cisdiamminedichloridoplatinum II [CDDP]) is an antineoplastic cancer drug frequently used in the treatment of a wide variety of cancers. In addition to its positive effects, it may have toxic effects in tissues such as hepatoxicity. In this study, we investigated the reparative effects of beta-glucan, a potent antioxidant, on cisplatin-induced hepatoxicity.

Method: In this study, 40 Wistar Albino rats were randomly divided into 2 groups according to the time of sacrifice, 3rd day and 5th day (n=20 in each group). Each group was divided into four groups as control, Beta-glucan (100 mg/kg/bw), cisplatin (10 mg/kg/bw), cisplatin+beta-glucan (n=5 in each group). The rats were sacrificed 3 days and 5 days after the last injections and liver tissue samples were taken for routine tissue follow-up for histopathologic examination under light microscope. Paraffin blocks were sectioned and stained with Hemaoxylin-Eosin.

Results: Histopathological examination revealed different degrees of hydropic degeneration, sinusoidal expansion, disorganization of hepatic cords, inflammatory cell foci and changes in the density of Kupffer cells in cisplatin 3rd day and cisplatin 5th day groups compared to the control group. When cisplatin was administered together with beta-glucan, cell damage was found to be minimal in cisplatin+beta-glucan 3rd and cisplatin+beta-glucan 5th day groups.

Conclusion: Light microscopic findings suggest that beta-glucan may have protective effects on cisplatin-induced liver injury.

Keywords: Antioxidant, Beta-glucan, Cisplatin, Liver Injury.

INTRODUCTION

Cisplatin (cisdiamminedichloridoplatinum II [CDDP]) is a platinum-derived antineoplastic agent (Güleç et al., 2004) used in the treatment of many solid tumors such as head, neck, ovarian, bladder, breast, lung and cervical cancers (Abdel-Daim et al., 2020). Cisplatin, like many other chemotherapeutic agents, does not discriminate whether the cell is cancerous or non-cancerous while exerting its antineoplastic effect, and therefore many side effects have been recorded in chemotherapeutic treatment (El-Hak et al., 2022). The most important dose-limiting side effect in the clinic is nephrotoxicity (Fouad et al., 2008). Another toxicity is dose-dependent hepatotoxicity due to accumulation in the liver during metabolism (Al-Majed, 2007; Mansour, 2006).

The liver is one of the organs involved in the metabolism of drugs. Hepatic blood flow and the capacity of the enzyme system play an important role in the metabolism of drugs by the liver. Many drugs such as cisplatin are biotransformed in the liver by the use of cytochrome P450 enzyme complex. Toxic metabolites of drugs may be released during biotransformation by the use of this enzyme complex (Kesim, 2001). Cisplatin rapidly diffuses into various tissues after injection and reaches higher concentrations in the liver. Cisplatin enters the cell via passive transport and hepatic metabolism is mediated by the enzyme cytochrome P450 2E1 (CYP2E1). Several studies have shown that the enzyme P450 2E1 (CYP2E1) may play a role in hepatotoxicity (Rashid et al., 2021). Cisplatin stops the cell cycle in G2 phase by forming deoxyribo nucleic acid (DNA) adducts and shows antineoplastic mechanism of action by triggering apoptosis. Although there is insufficient information about the hepatoxicity caused by cisplatin, it is thought that DNA adducts are the cause of this condition. Severel studies have shown that oxidative stress plays an important role in cisplatin hepatoxicity (Topcu Tarladaçalışır et al., 2005). Cisplatin decreases the level of antioxidant enzymes, leading to the accumulation of reactive oxygen species (ROS) in cells and the formation of oxidative stress, leading to toxic cell damage, heart diseases and many pathogenic diseases (Ekinci-Akdemir et al., 2020). Cisplatin damages mitochondrial protein by targeting it. This inhibits calcium uptake and decreases the potential of the mitochondrial membrane, triggering lipid peroxidation and apoptosis (El-Hak et al., 2022).

Therefore, various antioxidants such as vitamin E, selenium, vitamin C, glutamine, caffeic acid ester (CAPE), aminoguanidine and erdostein were used together to reduce the toxic effects of cisplatin treatment (Söğüt et al., 2004; Yılmaz et al., 2004). β-glucan (β-glucan) is a polysaccharide that forms the structural component of the cell walls of yeast, bacteria, fungi and cereals such as oats and barley. Since β-glucans differ structurally according to the source, their mechanism of action may also be different. Among these polysaccharides, the one obtained from baker's yeast (Saccharomyces cerevisia) is the type with high biological effects on which many studies have been conducted (Şener et al., 2007). β-glucan is a powerful antioxidant and immunomodulator (Akaras et al., 2019). The biological activities of beta-glucan are to regenerate damaged tissue and modulate inflammation (Gardiner, 2000). β-glucans protect DNA against oxidative damage with its free radical scavenging effect. Many studies have shown that it has beneficial effects against various diseases and disorders such as spinal cord injury, sepsis, post-menopausal brain injury, periodontal diseases, respiratory problems, ischaemia/reperfusion induced lung injury (Kaya et al., 2019). β-glucan exerts its effect on the immune system by binding to

special glucan receptors in monocytes, leukocytes and macrophages, releasing cytokinins and creating an immune response (Tatlı Seven et al., 2021), thus defending against bacteria, viruses, fungi and parasites, as well as preventing tumor development and showing protective effects against radiation (Şener et al., 2007).

In the light of this information, we aimed to reveal the protective effects of β-glucan, a potent antioxidant, against cisplatin-induced cell damage in the liver histopathologically.

METHOD

The injectable form of cisplatin (50 mg/50 ml) was purchased from Mayne Pharma Plc (Warwickshire, United Kingdom) and β-glucan (50 mg capsule Imuneks®) was obtained from Mustafa Nevzat Pharmaceutical Company (Turkey). All other chemicals were purchased from Sigma-Aldrich Chemical Company (St. Louis, MO, USA).

Wistar albino rats used in this study were obtained from Samsun Ondokuz Mayıs University Experimental Animals Research and Application Center. Six-eight week-old male Wistar albino rats of the same generation, weighing 200-300 g, were housed in plastic cages and fed standard chow and given unlimited water. The rats were kept in a controlled environment with a room temperature of 20-250 C and a 12-hour light/dark cycle.

The study was conducted with the approval of the ethics committee obtained from Ondokuz Mayıs University Samsun Clinical Research Ethics Committee (2009/83).

Experimental Design

Forty Wistar albino rats were randomly divided into two groups as 3rd day (n:20) and 5th day (n:20) according to the time of sacrifice. Both groups were divided into 4 subgroups with 5 rats in each group: Control, cisplatin, β-glucan, cisplatin+β-glucan. Control groups did not receive any injection. Cisplatin (10 mg/kg/bw) (Palipoch and Punsawad, 2013) was administered intraperitoneally (i.p.) as a single dose on the first day of the study. β-glucan (100 mg/kg/bw) (Tohamy et al., 2003) was administered intraperitoneally (i.p.) to β-glucan groups and cisplatin+β-glucan groups every day until the last day of the study. On the 3rd and 5th days, one day after the last injections in the groups, the rats were deeply anesthetized by intramuscular administration of a mixture of ketamine (40 mg/kg/bw) and xylazine (10 mg/kg/bw). The removed liver tissues were fixed in 10% neutral-buffered formalin for 48 hours. Samples were embedded in paraffin blocks after routine tissue tracking procedure. Then, 5µm thick sections were taken from the paraffin blocks with a microtome (Leica RM 2135; Nussloch, Germany). The sections were stained with Hematoxylin-Eosin (Mansouret et al., 2006) for light microscopic examination (Leica DM 1000). The sections were photographed using a digital camera (Leica DFC 290).

Histological Assessment

In the histological evaluation of the liver tissue, hydropic degeneration, sinusoidal expansion, disorganization of hepatic cords, inflammatory cell foci and Kupffer cells were observed in all groups. Accordingly, liver injury was evaluated using semiquantitative scale. The scores given for the damaged tissue in the semiquantitative scale were determined as follows: 0, normal; 1 (minimal), <25%; 2 (mild), <50%; 3 (moderate), <75%; 4 (severe), >75% of damaged area. Under light microscopy at 40x magnification, 10 areas of each group were examined and scored. The scoring of the sections was done blindly. The scores were then averaged and evaluated (Hamad et al. 2015).

Statistical Analysis

All statistical analyses were conducted by using SPSS 21.0 program. Non-parametric tests The Mann-Whitney U and Wilcoxon Rank Sum were used for the comparison of groups and $p<0.05$ was considered as statistically significant.

RESULTS

Light microscopic evaluation of the control and β-glucan groups revealed normal histologic appearance of the liver tissue (Figure 1 A, B). Hepatocytes were large polygonal shaped, nuclei were located in the center of the cell with single or sometimes double nuclei. Hepatocytes were arranged in a regular lobule structure with radial and radial arrangement around the central vein (V. centrolobularis). The branches of the portal vein (V. porta) and hepatic artery (A. hepatica) and the gallbladder ducts were normal.

Light microscopic evaluation of the cisplatin treated groups revealed significant cell damage in the liver tissue in both day groups. Sinusoidal expansion, hydropic degeneration in hepatocytes, disorganization in hepatic cords, inflammation foci and Kupffer cell activation were evaluated as cell damage markers. Both cisplatin groups showed remarkable histopathologic changes in general appearance compared to the control group (Figure 1 C, D). In the cisplatin 3rd day group, mild hydropic degeneration was observed in hepatocytes, especially around the central vein and portal area, as well as enlargement of sinusoids, disorganization of hepatic cords, inflammation foci and increase in Kupffer cells. In the cisplatin 5th day group, hydropic degeneration in hepatocytes was found to spread throughout the whole liver tissue and this was found to be more moderate compared to the 3rd day group (Table 1).

Table 1. Cell damage scores of cisplatin treated groups

Data	n	Control	3rd day	5th day
Hydropic degenerasyon	5	0	3	3
Sinuzoidal expansion	5	0	2	3
Disorganization of hepatic cords	5	0	2	3
Inflammatory cell foci	5	0	2	3
Kupffer cells	5	0	2	3

0, normal; 1 (minimal), <25%; 2 (mild), <50%; 3 (moderate), <75%; 4 (severe), >75% of damaged area.

Expansion of sinusoids, disorganization of hepatic cords, increase in the distribution of inflammation foci and increase in Kupffer cells were detected. When 3rd day and 5th day groups treated with cisplatin were compared with each other, no statistically significant changes were found in terms of hydropic degeneration and sinusoidal expansion ($p>0.05$; $p=0.650$; $p=0.142$, respectively), but statistically significant differences were found in terms of disorganisation of hepatic cords, inflammatory cell foci and Kupffer cells ($p<0.05$; $p=0.042$; $p=0.005$; $p=0.042$, respectively) (Table 2).

In the examination performed in the cisplatin+β-glucan 3rd day group, it was determined that the histological damage observed in the cisplatin 3rd day group decreased and decreased to a minimal level (Table 3).

Table 2. Statistical comparison of cisplatin 3rd day 5th day groups

Data	n	3rd day Mean rank	5th day Mean rank	p
Hydropic degenerasyon	5	5,10	5,90	0,650
Sinuzoidal expansion	5	4,20	6,80	0,142
Disorganization of hepatic cords	5	3,80	7,20	**0,042***
Inflammatory cell foci	5	3,00	8,00	**0,005***
Kupffer cells	5	3,80	7,20	**0,042***

p=significance level; If p<0.05 is significant between groups.

In the cisplatin+β-glucan 5th day group, it was determined that the damage decreased even more than the cislatin 5th day group and decreased to a minimal level (Figure 1 E-F). This shows that β-glucan played a more effective role in this group. β-glucan can reduce tissue damage when applied for a longer period of time.

Table 3. Cell damage scores of cisplatin+β-glucan treated groups

Data	Control	3rd day	5th day
Hydropic hepatosit degenerasyon	0	1	1
Sinuzoidal congestion	0	1	1
Disorganization of hepatic cords	0	1	1
Inflammatory cell foci	0	1	1
Kupffer cells	0	1	1

0, normal; 1 (minimal), <25%; 2 (mild), <50%; 3 (moderate), <75%; 4 (severe), >75% of damaged area.

When 3rd day and 5th day groups treated with cisplatin and β-glucan were compared with each other, no statistically significant change was detected in terms of Hydropic degeneration, Sinusoidal expansion, Disorganisation of hepatic cords, Inflammatory cell foci and Kupffer cells (p>0.05; p=0.549; p=0.513; p=0.134; p=0.317; p=1, respectively) (Table 4).

Table 4. Statistical comparison of cisplatin+β-glucan 3rd day 5th day groups

Data	n	3rd day Mean rank	5th day Mean rank	p
Hydropic degenerasyon	5	6,00	5,00	0,549
Sinuzoidal expansion	5	6,00	5,00	0,513
Disorganization of hepatic cords	5	6,50	4,50	0,134
Inflammatory cell foci	5	6,00	5,00	0,317
Kupffer cells	5	5,50	5,50	1,000

p=significance level; If p<0.05 is significant between groups.

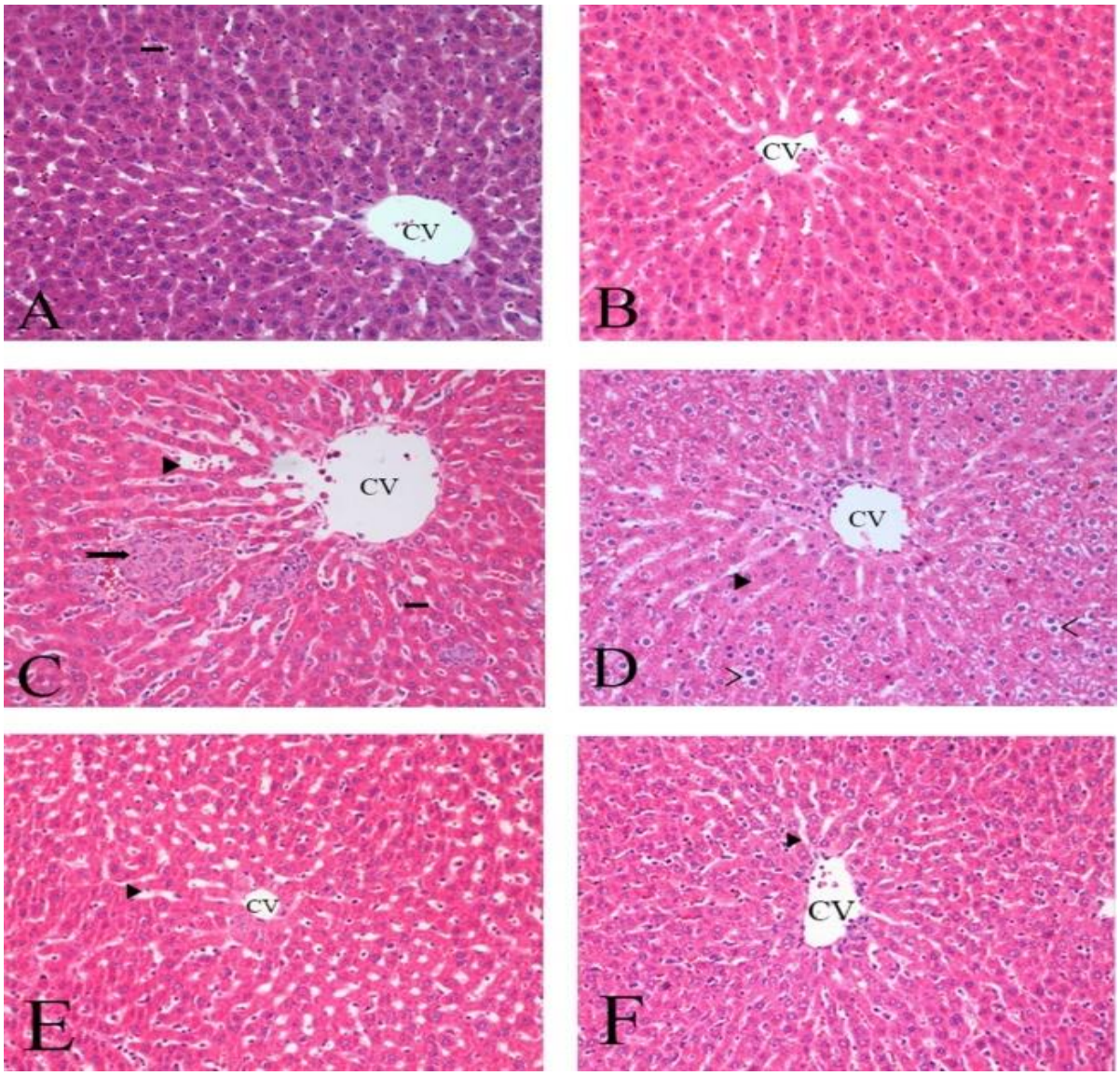

Figure 1. Histological observations of liver tissue in rat. A: Control, B: β-glukan 3rd day group, C: Cisplatin 3rd day group, D: Cisplatin 5th day group, E: Cisplatin+β-glukan 3rd day group, F: Cisplatin+β-glukan 5rd day group. Central ven (Cv), sinuzoidal congestion (arrowhead), inflammatory cell foci (notched arrow), hydropic hepatosit degenerasyon (<). Kuppfer cells (arrow). Hematoxylin&eosin x200.

DISCUSSION

The liver is an organ with an important role in the removal of toxic substances and detoxification of drugs. Therefore, liver tissue is exposed to the effects of many substances (Zhang et al., 2017). Although cisplatin is the most widely used antineoplastic drug, it causes unwanted side effects in the liver and many other tissues (İşeri et al., 2007). Cisplatin easily passes through the cell membrane, reaches the cell nucleus and changes the structure of DNA. Cisplatin causes hepatotoxicity in tissue by causing oxidative stress and apoptosis (Rady et al., 2023). It is recommended to use antioxidants with cisplatin to reduce hepatotoxicity caused by cisplatin (Kaymak et al., 2022; Pınar et al., 2019). In this study, toxic effects were examined in rat liver tissue on two different days (3rd day and 5th day) of cisplatin administration and the antioxidant activity of β-glucan was evaluated on these toxic effects.

Many studies have shown that cisplatin causes oxidative stress in the liver due to the formation of reactive oxygen species (ROS) such as superoxide and hydroxyl radicals (Avcı et al., 2008; Kurt et al., 2021). Removal of reactive oxygen species (ROS) from the cell is performed by endogenous antioxidants such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) and non-enzymatic exogenous antioxidants such as transferrin, vitamin C, alpha-tocopherol (Ekinci-Akdemir et al., 2020; Valko et al., 2006,). Oxidative stress caused by accumulation of ROS and decrease in antioxidant defense system is an important factor in the formation of liver damage (Sherif et al., 2014). In a study, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), uric acid, urea, creatinine and interleukin-6 (IL-6) levels increased in cisplatin-treated rats. Malondialdehyde (MDA) and nitrogen monoxide (NO) levels were also significantly increased in hepatic tissue. In addition, glutathione (GSH) levels, SOD and CAT activities were decreased. These data cause histopathological changes in liver tissue (Abdel-Daim et al., 2020). In a study by Ekinci-Akdemir et al. (2020), liver damage was detected in rats administered 12 mg/kg cisplatin after 72 hours with an increase in MDA level and a remarkable decrease in GSH, GPx, SOD and CAT activities due to oxidative stress. Histopathological evaluation revealed coagulation necrosis, hydropic degeneration, sinusoidal dilatation and hyperemia. Studies have shown that cisplatin causes inflammatory cell infiltration, hyperplasia, periportal fibrosis, dilated blood sinusoids. In addition, karyomegaly and pyknotic nuclei were observed in hepatocytes (Abdel-Daim et al., 2020; El-Sayyad et al., 2009;). An electron microscopic examination showed that cisplatin 7 caused degeneration of cellular organs in rat liver, such as vesicular enlargement in the rough endoplasmic reticulum, especially mitochondria (Nasr et al., 2013).

In another study, the presence of inflammatory cells detected in liver tissue was attributed to the interaction of cisplatin with enzymes and proteins of interstitial liver tissue. As a result, cisplatin may interfere with the antioxidant defense mechanism and cause the formation of reactive oxygen species (Hakiminia et al., 2019). Cisplatin caused focal necrosis in some hepatocytes, which may be due to DNA inhibition (El-Hak et al., 2022). Kaymak et al. (2022) observed numerous hemorrhagic areas and necrotic cells in the cisplatin (7 mg/kg) group. In addition, while the histopathologic score was significantly higher in the cisplatin group, it was found that the score was insignificant in the group administered melatonin with cisplatin. Pınar et al. (2019) investigated the toxic effects of cisplatin (5 mg/kg) in rat liver and found significant perivenule sinusoid dilation, karyomegaly, pyknotic and karyolytic cells, central vein congestion, parenchymal inflammation, mildbileduct proliferation and periportal sinusoid dilation in an 11-day study. When the antioxidant Alpha lipoic acid was administered with cisplatin, this toxic damage was reduced. Rady et al. (2023) detected the toxic effects of cisplatin (7,5 mg) in liver tissue as hepatic structure disruption, congestion in central hepatic veins, lymphocytic infiltration, perivascular edema, hepatic cords disturbance, vacuolated cells, cellular necrotic area with condensed pyknotic nuclei.

As a result of the 3-day study conducted by Avcı et al. (2008), enlargement of sinusoids, hydropic degeneration and irregularities in hepatocytes, fibrosis around the central vein and enlarged periportal areas were observed in the group given cisplatin (10 mg/kg). In in previous study

where cisplatin was administered as a single dose (10 mg/kg, IP), hepatic function, histological changes, oxidative stress, inflammation, and apoptotic markers were detected in the examination of liver tissue (Habib et., 2020a). In our study, in parallel with these findings, mild hydropic degeneration in hepatocytes, especially around the central vein and portal area, as well as enlargement of sinusoids, disorganization in hepatic cords, inflammation foci and increase in Kupffer cells were detected in the cisplatin day 3 group. In a study by Koc et al. (2005), structural changes in the parenchyma around the central vein and hepatocellular vacuolization in these cells were observed in light microscopic images in the liver of the 5-day-old group given only cisplatin (10 mg/kg). Expansion in the sinusoids, formation of cell communities around the portal region, most of which consisted of plasma cells and lymphocytes, were clearly visible changes when the control group was compared with the cisplatin group. In the study conducted by İşeri et al. (2007), vacuolization in hepatocytes, degenerated hepatocytes, pyknotic nuclei, activation of Kupffer cells and dilated sinusoids were taken as criteria for liver damage caused by cisplatin. In our study, we found that hydropic degeneration in hepatocytes in the CP 5th day group spread throughout the whole liver tissue and this was found to be at a more moderate level compared to the 3rd day group. In addition, enlargement in sinusoids, disorganization in hepatic cords, increase in the distribution of inflammation foci and increase in Kupffer cells were found to be at a more moderate level compared to the 3rd day group.

In a study by Demirel Yılmaz et al. (2024), it was shown that liver damage caused by cisplatin started at mild level on day 2, increased on day 7 and started to decrease on day 14. In addition to these findings, in our study, there was a moderate change in hydropic degeneration on the 3rd day and cell damage was generally mild. In addition Demirel Yılmaz et al. (2024) found severe sinusoidal congestion on the 7th day in their study. The damage increase in on 5th day compared to 3rd day in our study shows that it will continue to increase in the following days. These and similar studies show that cisplatin causes oxidative stress, induces the release of free oxygen species and ultimately causes damage. İn addition these findings Habib et al. (2021b) found that cisplatin caused a major inflammatory response in liver tissues.

In order to withstand the adverse effects of cisplatin, many mechanisms have been proposed, including reducing drug accumulation, enhancing repair of damaged tissue and increasing detoxification factors (Beretta et al. 2008). The most appropriate method to reduce oxidative stress is the use of antioxidant substances (Quiles et al., 2002). A wide variety of antioxidant applications have been shown in studies to reduce and manage cisplatin toxicity (Rashid et. al. 2021).

In line with this information, the most effective dose of 100 mg/kg of β-glucan was used as an antioxidant substance in our study (Tohamy et al., 2003). No significant toxic effect was observed in the livers of rats injected with β-glucan by light microscopy. In the sisplatin+β-glucan 3rd day group, an almost normal image was obtained in the liver. In the examination, minimal inflammation foci, decrease in hydropic degeneration around the central veins, sinusoids close to normal appearance, and minimal increase in kupffers were determined. On sisplatin+β-glucan 5th day group, a histologic appearance close to normal was determined by decreasing the enlargement of sinusoids, hydropic degeneration, infiltrating cells, which were at moderate level compared to cisplatin 5th day group. In a study investigating the

antioxidant effects of β-Glucan on the biochemical and histopathological damages of ciplatin, it was found that β-Glucan reduces the oxidative and histopathological effects (Kaya et. al. 2024). These findings are parallel to our study.

According to these results, we can say that β-glucan, as a powerful antioxidant, reduces the damage caused by cisplatin in the liver. In a study conducted by Tohamy et al. (2003), it was determined that cisplatin, an anticancer drug, caused the formation of excessive amounts of reactive oxygen species in the cellular environment, which are not normally present in the cellular environment, and the antioxidant β-glucan scavenged these reactive oxygen species. In a study investigating the effects of β-glucan on the toxicity of the environmental pollutant 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD), β-glucan (50 mg/kg/day) was applied for 3 weeks. As a result of histopathological and biochemical findings, it was determined that the toxicity caused by TCDD in the brain and liver tissue was improved by β-glucan application (Turkmen et.al. 2022). In addition, it has been shown in previous studies that β-glucan may protect tissues against oxidative damage with its effect of scavenging free radicals (Demirel Yılmaz et al., 2024; Karaduman et al., 2010; Şener et al., 2006).

CONCLUSION

In the light of our findings, it was shown that cisplatin induced histopathological changes in the tissues by stimulating the production of free oxygen radicals in two different day groups (3rd day and 5th day). On this histopathologic change, β-glucan was found to reduce the damage caused by cisplatin by scavenging free oxygen radicals in both day groups.

The role of β-glucan on the molecular and histological changes induced by cisplatin on tissues can be supported by further studies on rats by applying different combinations.

Declaration of Interests: The authors have no conflict of interest to declare.

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Ethical Approval: The study was conducted with the approval of the ethics committee obtained from Ondokuz Mayıs University Samsun Clinical Research Ethics Committee (2009/83).

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