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Histological Evaluation of the Protective Role of β-glucan Against Cisplatin-Induced Hepatotoxicity

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Abstract

Cisplatin is a commonly used chemotherapeutic agent in the treatment of many cancers. The most important dose-limiting side effect is hepatotoxicity. Some studies have shown that antioxidant treatment with cisplatin reduces the toxic effect. In the present study, we were aimed to investigate the protective effects of antioxidant β-glucan on histological injury caused by cisplatin treatment in the liver. Wistar rats were randomly divided into three groups according to time of sacrifice, 7th day and 14th day (n=20 rats each). Both groups were then divided into four sub-groups Control, Cisplatin (10 mg/kg bw), β-glucan (100 mg/kg bw) and cisplatin+β-glucan (n=5 in each group). The rats were sacrificed at the 7th day and 14th day after the last injection. The liver sections were evaluated under a light microscope after the histological procedure. Histological injury caused by cisplatin in different days were evaluated as as sinusoidal congestion, hydropic degeneration, disorganization of hepatic cords, and mononuclear cellular infiltration in liver. When β-glucan was administered with cisplatin, it was determined that cellular damage caused by cisplatin decreased considerably in the liver in the different days groups. The light microscopic examination showed that the antioxidant beta-glucan protects against hepatotoxicity caused by cisplatin with its free radical scavenging effect. In conclusion, β-glucan may improve patients' quality of life by reducing cisplatin's toxicity on the liver.

Key Words: Cisplatin, β-glucan, Liver, Histopathology

Sisplatinin Neden Olduğu Hepatotoksisite Üzerine β-glukanın Koruyucu Rolünün Histopatolojik Olarak Değerlendirilmesi

Öz

Sisplatin pek çok kanserin tedavisinde sıklıkla kullanılan kemoterapötik bir ajandır. En önemli doz sınırlayıcı yan etkisi hepatotoksisitedir. Bu çalışmada, sisplatin tedavisinin karaciğerde neden olduğu histolojik hasar üzerinde antioksidan β-glukanın etkilerinin araştırılması amaçlandı. Wistar ratlar sakrifiye edilecek zamana göre rastgele dört gruba ayrıldılar. Bu gruplar 1. gün, 2. gün, 7. ve 14. gün (n=20 her grupta 20 rat) olarak belirlendi. Her grupta kendi içinde Kontrol, Sisplatin (10 mg/kg), β-glukan (100 mg/kg) ve Sisplatin+β-glukan (n=5 her grupta) olmak üzere dört alt gruba ayrıldı. Ratlar son enjeksiyondan sonraki 1. gün, 2. gün, 7. gün ve 14. günde sakrifiye edildi. Histolojik prosedürün ardından karaciğer kesitleri ışık mikroskobik incelendi. Sisplatinin farklı günlerde oluşturduğu histolojik hasar sinüzoidal konjesyon, hidropik dejenerasyon, hepatik kordlarda düzensizlik ve karaciğerde mononükleer hücre infiltrasyonu olarak değerlendirildi. Sisplatin ile birlikte β-glukan uygulandığında farklı gün gruplarında sisplatinin karaciğerde neden olduğu hücresel hasarın önemli ölçüde azaldığı belirlendi. Işık mikroskobik incelemede antioksidan β-glukanın serbest radikal temizleyici etkisi ile sisplatinin neden olduğu hepatotoksisiteye karşı koruma sağladığı görüldü. Sonuç olarak β-glukan, sisplatinin karaciğer üzerindeki toksisitesini azaltarak hastaların yaşam kalitesini arttırabilir.

Anahtar Kelimeler: Sisplatin, β-glukan, Karaciğer, Histopatoloji

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1. INTRODUCTION

With the use of chemotherapeutic drugs in the treatment of cancer, which is one of the most common diseases nowadays, both the quality of life of cancer patients have increased and new possibilities for treatment have emerged. In spite of its success, some of the most effective cancer advanced treatments cause undesirable toxicities (Tohamy et al. 2023).

The liver has an important role in the breakthrough and detoxification of toxic chemical substances and other materials, and at the same time is the first target of toxins. Cisplatin accumulates in the liver, and hepatotoxicity occurs in high doses (Grant 1991). Nowadays, cisplatin (cis-diamminedichloroplatium (II), cis-platinum (II) or cis-DDP) is one of the important cytostatic agents used in the treatment of many cancer types such as ovarian, testicular, bladder, head, neck, lung, cervix and endometrial cancers as well as solid tumors (Sindhu et al. 2015; İşeri et al. 2007). However, the clinical application of cisplatin is often restricted with severe side effects on many organs and systems, such as hepatotoxicity, nephrotoxicity, ototoxicity, and neurotoxicity (Kaya et al. 2016). The underlying mechanism of hepatotoxicity induced by cisplatin remains incompletely understood (Palipoch and Punsawad 2013); for this reason, many studies are carried out nowadays to prevent cisplatin toxicity. According to the results obtained from experimental studies, the toxicity of cisplatin in cells is attributed to its inhibition of both DNA replication and RNA transcription by acting on DNA and forming inter-helix and intra-helix adducts (Rabik and Dolan 2007). Cisplatin initiates the process leading to apoptosis by damaging mitochondria in cells, inhibiting the cell cycle and ATPase activity, negatively affecting cellular transport systems (Mansour el al. 2006). The induction of apoptosis based on the anticancer action mechanism of cisplatin is also the basis of the toxicity mechanism (Florea and Busselberg 2011). Moreover, cisplatin causes reactive oxygen species (ROS) such as superoxide dismutase hydroxyl radical formation in tissues, inhibiting the activity of antioxidant enzymes in liver tissues and decreasing glutathione levels (Avcı et al. 2008). Reactive oxygen species can cause cell damage and necrosis due to peroxidation of lipids in the cell membrane, protein denaturation, and DNA damage (Tohamy et al. 2016).

Studies are needed to reduce the dose-limiting side effects that prevent the administration of high-dose cisplatin, which is necessary for tumor destruction in chemotherapy (Liao et al. 2008). In this direction, many studies have been conducted on the simultaneous addition of protective agents to prevent the side effects of cisplatin (Simsek et al, 2016; Soliman et al. 2016). Some compounds such as superoxide dismutase (SOD), glutathione, flavoids, vitamin E, selenium, vitamin C, glutamine, caffeic acid phenethyl ester (CAPE) and Nigella sativa extract and carotenoids, adenosine antagonists, L-histodinol, aminoguanidine, nifedipine, erdosteine, have been used with cisplatin in support of its protective effect against the oxidative damage caused by cisplatin (Yılmaz et al. 2004; Söğüt et al. 2004).

In this study, β-glucan, which we used to reduce the side effects of cisplatin, is a carbohydrate consisting of glucose polymers found in the cell walls of cereals such as yeast, mushrooms, barley, and oats. The active role of the β-glucan molecule in the immune system and the absence of toxic or any side effects cause studies to focus on this molecule (Toklu et al. 2006; Sener et al. 2007). It is currently approved as one of the most powerful immune-response modifiers (Brown and Gordon 2003). The main immunopharmacological activities of β-glucan include an increase of the host resistance to bacterial, viral, fungal, and parasitic infections, an anti-tumor effect and prevention of carcinogenesis, radioprotective activity and adjuvant effects, and enhancement of the phagocytic and proliferative activity of the reticulo-endothelial system (Tohamy et al. 1991). Among the many features of the β-glucan molecule that are claimed to be protective, the most striking feature is the antioxidant effect of the molecule (Toklu et al. 2006; Aydogan et al. 2016). Many studies have shown that β-glucan is an effective free radical scavenger (Kayali et al. 2005; Akaras et al. 2020). This activity of β-glucan was significantly higher than that of various polymers used as food additives (Kofuji et al. 2012).

In light of these observations, we aimed to investigate the possible protective effects of β-glucan against cisplatin-induced oxidative liver damage evaluated by histopathological.

2. MATERIAL AND METHOD

2.1. Chemicals

The injectable form of cisplatin (50 mg/50 ml) was purchased from Mayne Pharma Plc (Warwickshire, United Kingdom). β-glucan (50 mg capsule Imuneks® Mustafa Nevzat Drug Company, Turkey), prepared from the yeast Saccharomyces cerevisiae (1,3-1,6-beta-D-glucan), was dissolved in saline. All other chemicals were obtained from Sigma-Aldrich Chemical Company (St. Louis, MO, US).

2.2. Animals

In the present study, we used 80 male Wistar albino rats obtained from Experimental Animals Implementation and Research Center of the Ondokuz Mayıs University, Samsun, Turkey. Ethics committee approval was received

for this study from Samsun Clinical Research Ethics Committee of Ondokuz Mayıs University (2009/83). The rats were fed in plastic cages with the standard pellet food and given ad libitum supply of water. The animals were kept at room temperature (25 0C), and 12-hour cycles of light and dark was provided. The rats, chosen from the same generation (6-8 weeks old), 200-300 g body weight.

2.3. Experimental Design

Eighty male Wistar albino rats were randomly divided into four groups according to time of sacrifice, first day, second day, seventh day, and 14th day (n=20 rats each). Both groups were then divided into four sub-groups as (i) Control (C), (ii) Cisplatin (CP), (iii) β-glucan (βg), and (iv) cisplatin+β-glucan (CP+βg) (n= 5 in each group). Cisplatin (10 mg/kg body weight) (Palipoch and Punsawad 2013) was administered intraperitoneally (i.p.) as a single dose on the first day of the study. β-glucan and cisplatin+β-glucan groups were administered β-glucan (100 mg/kg body weight) (Beretta et al. 2018) everyday. No injections were performed on the control groups. After the last injection, on 1st day, 2nd day, 7th day, and 14th days, the rats were deeply anesthetized with a mixture of ketamine (40 mg/kg body weight) and xylazine (10 mg/kg body weight) administered intramuscularly. Then, liver tissues were removed and taken in 10% neutral-buffered formalin for histopathological processing.

2.4. Liver Histology

For examination under light microscope, liver tissues were fixed in %10 neutral-buffered formalin for 48 hours, and samples were then routinely processed and embedded in paraffin blocks. After embedding, 5-µm thick sections were taken using a microtome (Leica RM 2135; Nussloch, Germany). Sections were stained with Hematoxylin-eozin (Mansour et al. 2006). Sections were examined under a light microscope (Leica DM 1000) and photographed by using a digital camera (Leica DFC 290).

At the histological evaluation, all groups' injury in the liver section was investigated based on sinusoidal congestion, hydropic degeneration, disorganization of hepatic cords, and mononuclear cellular infiltration in the liver. Hepatic injury was assessed using a semiquantitative scale which was assigned a score: 0, normal; 1 (minimal),< 25%; 2 (mild), <50%; 3 (moderate), < 75%; 4 (severe), > 75% of the affected area. Ten fields of each group were examined with 40x magnification and took average. The slides were scored and identified as blind (Hamad et al. 2015).

3. RESULTS

3.1. Histopathological Results of The Liver

Light microscopic evaluation revealed that the general structure of the liver in control and β-glucan groups was in normal histological appearance. These groups showed hepatic lobules separated by interlobular septa transversed by portal vein. The liver parenchymal cell (hepatocyte) is a polygonal cell with a central nucleus (fig. 1 A). The cisplatin groups demonstrated histopathological changes, such as sinusoidal congestion, hydropic degeneration, disorganization of hepatic cords, and mononuclear cellular infiltration. Histopathological liver injury in cisplatin groups began on days 2, and injury was most pronounced on day 7. On the 14th day, it was observed that the effect of the damage continued to a mild level (tab. 1). In all groups of the cisplatin+β-glucan, liver injury was significantly reduced (tab. 2).

Table 1. Histopathological score for rat liver tissues treated with cisplatin.

Group Data	Control	2st day	1st day	7th day	14th day
Sinusoidal congestion	0	2	1	4	3
Hydropic hepatocyte degeneration	0	2	0	3	2
Disorganization of hepatic cords	0	2	1	3	2
Mononuclear cellular infiltration	0	1	0	3	2

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

Table 2. Histopathological score for rat liver tissues treated with cisplatin+β-glucan.

Group Data	Control	1st day	2st day	7th day	14th day
Sinusoidal congestion	0	0	1	2	1
Hydropic hepatocyte degeneration	0	0	1	1	1
Disorganization of hepatic cords	0	0	1	2	1
Mononuclear cellular infiltration	0	0	1	1	1

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

There were no significant histologic changes in the β-glucan all days group and cisplatin 1st days group compared to the control group (fig.1 B-C). In the 2nd days group of cisplatin, moderate sinusoidal congestion, hypertrophic hepatocyte degeneration, disorganization of hepatic cords, inflammatory cell infiltrates, and cell foci were observed compared to the control group (fig. 1 D). On the first and second days groups of cisplatin+β-glucan, it was observed that histological changes were not observed in the 1st days group, but in the 2nd days group histological changes were observed to be at a minimal level (fig. 1 G, H).

When compared to cisplatin 7th days group control and other cisplatin groups, it was determined that severe histological damage occurred. Sinusoidal congestion, hydropic degeneration, disorganization of hepatic cords, and mononuclear cellular infiltration were more severe in the centrilobular area around the central ven in 7th days group. Mononuclear cells usually spread in portal areas, these cells formed aggregates (foci) in parenchyma (fig.1 E; tab. 1). Cisplatin+β-glucan group on the 7th days had sinusoidal congestion, hydropic degeneration, disorganization of hepatic cords, and mononuclear cellular

infiltration were mild in comparison to the cisplatin 7th day group (fig. 1 I; tab. 2).

In the cisplatin 14th days group, less histological changes were observed compared to 7th days group of cisplatin (fig 1 F; tab. 1). The cisplatin+β-glucan 14th days group nearly it showed normal histological structure, when compared with the control group (fig.1 J; tab. 2).

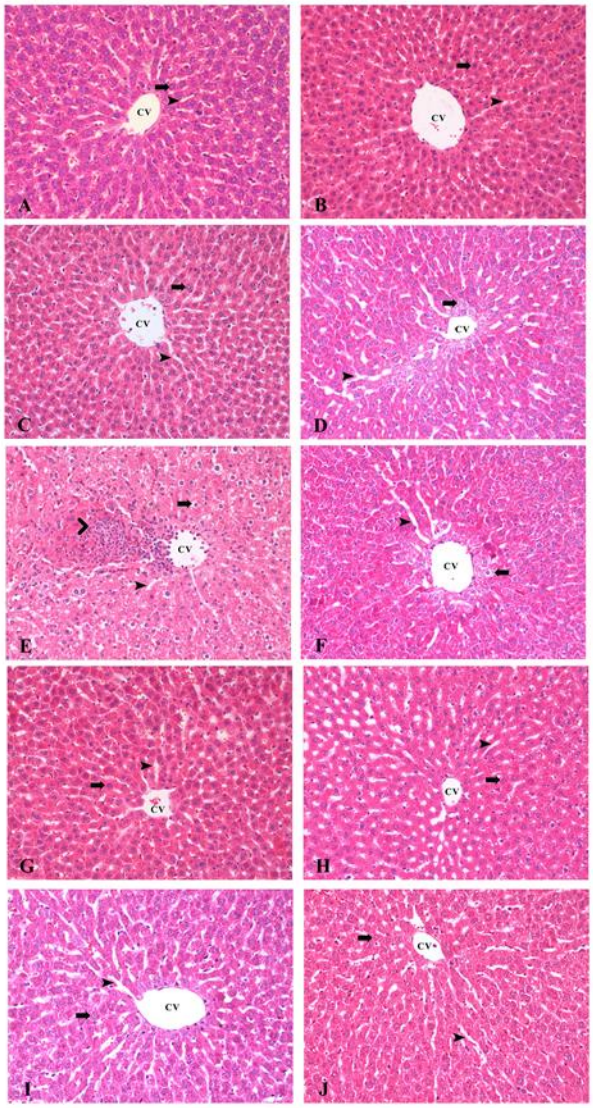

Fig. 1. Light microscopic image of rat liver in the C group (A), βg 2th days group (B), CP 1st day group (C), CP 2nd days group (D), CP 7th days group (E), CP 14th days group (F), CP+βg 1st day group (G), CP+βg 2nd days group (H), CP+βg 7th days grous (I) and CP+βg 14th days group (J). Central ven (Cv), Hepatocyte (arrow), Sinusoid (arrowhead), Mononuclear cellular infiltration (>). Stain: Hematoxylin-eosin x200.

4. DISCUSSION AND CONCLUSION

Cisplatin is the most commonly used chemotherapy drug. However, high doses of cisplatin cause damage to many different tissues, such as the liver, kidney, and testes (Atessahin et al. 2005). The liver has many basic physiological functions such as balancing blood glucose and lipoprotein synthesis, bile acid synthesis and secretion, detoxifying and storing vitamins. Therefore, any dysfunction that may occur in the liver can affect all systems in the body (Rajendrakumar 2020). In light of this information, we aimed to observe the effects of antioxidant beta-glucan on the negative effects of cisplatin on the liver, an important organ.

Some reports have shown that cisplatin induces oxidative stress, causing damage due to the release of free oxygen species (Mansour et al. 2006; Soliman et al. 2016). Recently many studies have shown that cisplatin induces a decrease in endogenous antioxidant SOD, catalase (CAT), and glutathione peroxidase (GSH-Px) levels in the liver due to the formation of free radicals and it has been shown to induce lipid peroxidation as a result of an increase in MDA level, which is indicative of damage (Pınar et al. 2019; Abbasi et al. 2020)—in addition to Kaymak et al. (2022) demonstrated that alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and albumin levels in the serum were significantly increased in liver Cis (7 mg/kg) group on the eighth day. This study determined that the severity of liver damage varied on different days (7th and 14th days). It was observed that the damage started on the 7th day due to oxidative stress, and the damage was nearly mild on the 14th day. The liver can explain the decrease in cell damage on the 14th day has regenerative properties can repair itself within a few weeks in cases of significant tissue injury (Adam et al. 2012).

We were showed many histopathological abnormalities in the cisplatin treatment rat liver, including sinusoidal congestion, hydropic degeneration, disorganization of hepatic cords, and mononuclear cellular infiltration. In parallel with our findings, histopathological damage such as structural modifications (Zicca et al. 2002), hepatic vacuolization, degenerated hepatocytes, kupffer cells, and enlarged sinusoids (İşeri et al. 2007) mononuclear cell infiltration (Rajendrakumar et al. 2020) were detected in some studies. Koc et al. (2005) showed that structural changes in the liver, central parenchyma around the central vein, hepatocellular vacuolization, enlargement of the sinusoids, majority of the plasma cells around the portal region, and lymphocytes in the liver five days after treatment with cisplatin (10 mg/kg body weight). In addition, Avcı et al. (2008) reported that 3 days of cisplatin (10 mg/kg body weight) treatment caused that enlargement of sinusoids, intense hepatocyte irregularity with hydropic degeneration, fibrosis around the central venous and enlarged periportal areas.

Several mechanisms have been proposed to relieve the adverse effects of cisplatin, such as reducing drug accumulation, increasing repair of damaged tissue, and increasing detoxification factors (Beretta et al. 2008). This suggests that serious side effects of cisplatin treatment, including nephrotoxicity and hepatotoxicity, are reduced by antioxidant treatment (Tohamy et al. 2016). In light of this information, we examined the protective effects of β-glucan on cisplatin injury.

This study demonstrated the effect of β-glucan antioxidant co-administered with cisplatin in the liver by reducing

histological damage. Cisplatin+β-glucan in the seventh day group, it was determined that the severity of the damage was at a mild level compared to the 7th day group. β-glucan is a potent antioxidant, especially on the 7th days, by reducing free radical-induced cellular damage. Cisplatin+β-glucan 14th day group showed minimal cellular damage. These results suggest that β-glucan acts as an antioxidant and an immunomonitor, reducing the cellular damage cisplatin produces in the liver. A study paralleling our findings stated that cisplatin caused an unusual, excessive amount of reactive oxygen species in the cellular environment, and antioxidant β-glucan swept these reactive oxygen species (Tohamy et al. 2003). The combination of β-glucan with chemotherapy agents can be administered to human cancer patients because it can serve as an immunomodulator for many side effects of cancer chemotherapy drugs (Wakui et al. 1986). In addition, previous studies have shown that glucans have a protective effect against oxidative damage (Sener et al. 2006; Toklu et al. 2006; Karaduman et al. 2010).

In the present study, β-glucan was found to decrease CP-induced hepatoxicity considerably. It was concluded that co-administered cisplatin with β-glucan showed that beta-glucan was protective against cisplatin-induced hepatic injury. Potential of β-glucan to reduce oxidative stress, antioxidants and its scavenging power of free radicals may explain its therapeutic effect.

We suggest that some antioxidants, such as β-glucan may play a protective role against cisplatin-induced hepatotoxicity during treatment. More experimental and clinical studies may be conducted to investigate the therapeutic molecular mechanism of β-glucan on cisplatin-induced hepatoxicity in rats.

CONFLICT OF INTEREST

The authors declared no conflict of interest. The authors declared that this study hasn't received financial support.

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