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Original Article / Özgün Araştırma

The Protective Effects of Receptor-Interactive Protein Kinase-3 Inhibitor - Dabrafenib on Cisplatin Induced Nephrotoxicity

Mehmet Küçüköner[1], Zeynep Erdoğmuş Ozgen[2], Fesih Aktar[3], Ulas Alabalık[4], Meryem Şeyda Kaya[2], Levent Erdinç[5], İlker Kelle[2], Meral Erdinç[2]

1. Department of Medical Oncology, Dicle University Faculty of Medicine, Diyarbakır, Türkiye

2. Department of Pharmacology, Dicle University Faculty of Medicine, Diyarbakır, Türkiye

3. Department of Pediatrics, Dicle University Faculty of Medicine, Diyarbakır, Türkiye

4. Department of Pathology, Dicle University Faculty of Medicine, Diyarbakır, Türkiye

5. Department of Biochemistry, Dicle University Faculty of Medicine, Diyarbakır, Türkiye

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Abstract

Objective: The aim of this study is to investigate the protective effects of dabrafenib, a receptor-interacting kinase-3 enzyme inhibitor, against necroptosis which has an important role in Cisplatin-induced nephrotoxicity.

Methods: 32 male Sprague-Dawley rats were divided into 4 groups. A single dose of i.p. saline was given to the first group. In the second group, a single dose of cisplatin (5 mg/kg i.p.) was given. In the third group, 10mg/kg i.p injections of Dabrafenib began a day before injection of a single dose of 5 mg/kg, i.p. cisplatin for 7 days. In the forth group 10mg/kg Dabrafnib was injected i.p. for 7 days. After 7 days, in all groups rats were anesthetized and with a laparotomy left kidneys were isolated. Histopathological examinations, Western-Blot analyses (expression levels of RIP1, RIP3, and MLKL proteins), and malondialdehyde (MDA) measurements were performed on the isolated kidney tissues

Results: In the biochemical evaluation of the study, it was observed that MDA levels in the kidney tissue increased significantly in the Cisplatin group compared to the control group ($p<0.05$). This increase was evaluated as an important indicator of oxidative stress. On the other hand, a significant decrease was detected in MDA levels in the group administered Dabrafenib + Cisplatin. This decrease was found to be substantial when compared to the Cisplatin group ($p<0.05$). Histopathological analysis revealed that cisplatin caused serious kidney damage, but its administration with dabrafenib significantly reduced this damage and provided a protective effect ($p<0.05$). In addition, the expression levels of RIP1, RIP3, and MLKL proteins, which are associated with necroptosis, were examined by Western Blot analyses. Significant increases were observed in the expression levels of these proteins in the Cisplatin group compared to the control group ($p<0.05$). However, a significant decrease was observed in the expression levels of these proteins in Cisplatin + Dabrafenib group ($p<0.05$). This decrease indicates the inhibitory effect of Dabrafenib on the necroptotic pathway.

Conclusion: This study suggests that the use of Dabrafenib with Cisplatin can be considered as a potential strategic agent to reduce chemotherapy-induced nephrotoxicity. However, advanced preclinical and clinical studies are needed before clinical practice.

Keywords: Cisplatin, Nephrotoxicity, Dabrafenib

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Correspondence / Yazışma Adresi: *Mehmet Küçüköner, Dicle University Faculty of Medicine, Department of Medical Oncology Diyarbakır, Türkiye e-mail: drmehmetonko@hotmail.com*

Reseptör Etkileşimli Protein Kinaz-3 Inhibitörü Dabrafenib'in Sisplatin Nefrotoksisitesi Üzerine Koruyucu Etkileri1

Öz

Amaç: Bu çalışma reseptör etkileşimli kinaz-3 enzim inhibitörü olan dabrafenibin sisplatin tarafından tetiklenen nefrotoksisitede oluşan nekroptoza karşı koruyucu etkilerini araştırmaktır.

Yöntemler: 32 adet Sprague-Dawley cinsi erkek rat 4 gruba ayrıldı. 1.gruba tek doz i.p. salin verildi. 2.gruba 5 mg/kg tek doz sisplatin i.p. olarak verildi. 3.gruba tek doz sisplatin (5 mg/kg,i.p) enjeksiyonundan bir gün önce başlanarak 7 gün boyunca Dabrafenib günde 10 mg/kg,i.p olarak verildi. 4. Gruba 7 gün boyunca Dabrafenib günde 10 mg/kg, i.p olarak verildi. Tüm gruplarda 7. Günün sonunda anestezi altında laparotomi yapılarak börekler izole edildi. Alınan böbrek dokularında histopatolojik incelemeler, Western-Blot analizleri (RIP1, RIP3, ve MLKL proteinlerinin ekspresyon seviyeleri) ve malondialdehit (MDA) ölçümler yapıldı.

Bulgular: Çalışmada MDA düzeyleri değerlendirildiğinde, sisplatin uygulanan grupta kontrol grubuna kıyasla böbrek dokusundaki MDA düzeylerinin anlamlı düzeyde arttığı gözlendi ($p<0,05$). Bu artış oksidatif stresin önemli bir göstergesi olarak değerlendirildi. Buna karşın sisplatin+ dabrafenib uygulanan grupta ise MDA düzeylerinde anlamlı bir azalma saptandı ve bu azalma sisplatin grubu ile kıyaslandığında anlamlı bulundu ($p<0,05$). Bu durum, dabrafenibin oksidatif hasar üzerindeki hafifletici etkisini göstermektedir. Nekroptozis ile ilişkili olan RIP1, RIP3 ve MLKL proteinlerinin ekspresyon seviyeleri Western Blot analizleri ile incelendi. Sisplatin verilen grupta, kontrol grubuna göre bu proteinlerin ekspresyon düzeylerinde anlamlı artışlar görüldü ($p<0,05$). Bu bulgular sisplatinin nekroptozu indüklediğini göstermektedir. Ancak sisplatin+dabrafenib grubunda, bu proteinlerin ekspresyon düzeylerinde anlamlı bir azalma görüldü ($p<0,05$). Bu azalma da Dabrafenibin nekroptotik yolağı inhibe edici etkisine işaret etmektedir.

Sonuç: Bu çalışma sisplatin ile birlikte Dabrafenib kullanımının kemoterapiye bağlı nefrotoksisiteyi azaltmak amacıyla potansiyel bir stratejik ajan olarak değerlendirilebileceğini düşündürmektedir. Ancak bu verilerin klinik uygulamaya yansıması için ileri düzeyde preklinik ve klinik çalışmalara ihtiyaç duyulmaktadır.

Anahtar kelimeler: Sisplatin, Dabrafenib, Nefrotoksisite.

INTRODUCTION

Cisplatin, a platinum-derived chemotherapeutic agent, is widely used to treat many types of solid tumors, particularly ovarian, testicular, and lung cancers[1]. However, its clinical use is limited by serious side effects, such as nephrotoxicity. Nephrotoxicity often requires a reduction in the dosage of cisplatin treatment and may lead to its discontinuation in some patients. Approximately one-third of treated patients experience cisplatin-induced acute kidney injury (AKI), and there is still no approved nephroprotective agent[2]. Multiple mechanisms, such as oxidative stress, mitochondrial dysfunction, DNA damage, inflammation, and regulated cell death pathways (apoptosis, necroptosis, and pyroptosis), play a role in the pathogenesis of cisplatin nephrotoxicity[3,4]. This side effect's basic pathophysiology is related to the drug's accumulation in proximal tubule cells and increased production of reactive oxygen species (ROS) in these cells. This leads to mitochondrial dysfunction, DNA damage, and cell death[3].

Among these mechanisms, necroptosis is a type of cell death that has recently become the focus of significant research. It has been reported to play a decisive role in cisplatin-induced nephrotoxicity[4]. Necroptosis is considered to be the most studied type of regulated necrosis, especially in recent years, and its molecular mechanisms have been revealed in detail[5]. Various kinases, including RIPK1 (receptor-interacting protein kinase 1), RIPK3, and MLKL (mixed lineage kinase domain-like protein), have been identified as playing critical roles in this pathway[6]. Necroptosis can be triggered by various endogenous and exogenous stimuli, including anticancer agents, metabolic disorders, ischemia/reperfusion injury, and especially activation of tumor necrosis factor-α (TNF-α), and interferon receptors[7]. Among these stimuli, TNF-α is the best defined and probably the most important necroptosis

initiation agent[8]. The initiation of necroptosis results in the disruption of plasma membrane integrity and the subsequent release of damage-associated molecular patterns (DAMPs) into the extracellular space, thereby further increasing inflammation in the kidney tissue. In contrast to apoptosis, necroptosis is a type of inflammatory cell death, thereby significantly contributing to the enhancement of cisplatin-induced renal damage[9]. Consequently, the targeting of key molecules within this pathway is regarded as a promising therapeutic strategy for the prevention of cisplatin-induced AKI.

Dabrafenib, a selective BRAF kinase inhibitor, has been approved by the FDA for the treatment of malignant melanomas with the BRAF V600E mutation. In recent years, this drug has been the focus of research investigating new targets in non-cancer diseases. It has been reported that the drug can also function as a RIPK3 inhibitor. As discussed in the literature, dabrafenib has been shown to suppress necroptosis by inhibiting RIPK3 phosphorylation and to provide a protective effect in paracetamol-induced liver damage[10]. These findings suggest that dabrafenib may also function as a protective agent against nephrotoxic stress. Dabrafenib has been claimed to suppress necroptosis and provide a kidney-protective effect by inhibiting RIPK3 phosphorylation[11]. Furthermore, dabrafenib has demonstrated protective effects not only in kidney tissue but also in tissues with a high concentration of postmitotic cells, such as the cochlea. Its efficacy has been demonstrated in models of cisplatin-induced hearing loss[12].

Consequently, dabrafenib is considered a promising candidate in the treatment of cisplatin-induced multiple tissue damage due to its targeting of both the MAPK/ERK signaling pathway and the necroptosis pathway. In this preclinical study, the protective effects of dabrafenib in the cisplatin-induced nephrotoxicity model were evaluated histopathologically and biochemically. The investigation focused on determining whether this effect occurred through the inhibition of the necroptosis mechanism.

METHODS

Animals and Experimental Design: Thirty-two adult male Rats weighing between 200 and 250 grams were used in this study. The rats were kept in a standard laboratory environment with access to food and water at all times. The rats were randomly divided into four groups of eight rats each. Ethical approval for the study was obtained from the Institutional Animal Ethics Committee, decision number 1, dated January 27, 2022. The Dicle University Scientific Research Projects Unit supported this project with the grant number TIP.22.012.

1. Control group: Received 1 ml of a single dose of physiological saline intraperitoneally(i.p).

2. Cisplatin group: Received a single dose of cisplatin(5 mg/kg,i.p)

3. Cisplatin + Dabrafenib group: Received a single injection of cisplatin(5 mg/kg i.p) and 10mg/kg i.p injections of Dabrafenib began a day before injection of cisplatin and lasted for seven days.

4. Dabrafenib group: Received daily injection 10 mg/kg of Dabrafenib intraperitoneally for seven days.

After seven days, in all groups rats were anesthetized and with a laparotomy kidneys were isolated and used for analysis.

Biochemical Analysis

Serum samples were collected to evaluate kidney function by measuring urea and creatinine levels with an automated biochemical analyzer. Renal oxidative stress was evaluated by measuring malondialdehyde (MDA) levels in kidney tissue homogenates using thiobarbituric acid.

Histopathological Evaluation

Kidney tissue samples were collected for evaluation. Any foreign tissue residues and blood were removed and the tissue was washed with saline. Then, the tissue was placed in plastic containers containing a 10% formaldehyde solution. The tissue samples were fixed in 10% formalin for 48 hours, embedded in paraffin, and cut into 5-mm sections. The sections were examined under a light microscope (Olympus BX53) at 200x magnification using the hematoxylin and eosin staining method. A pathologist blinded to the groups evaluated the degree of kidney damage using a standard scoring system[13].

Western blot analysis

Renal tissue lysates were prepared to detect RIP1, RIP3, and MLKL protein levels. Equal amounts of protein were separated using SDS-PAGE and transferred to PVDF membranes. The membranes were then incubated with primary antibodies against RIP1, RIP3, MLKL, and β-actin (as a loading control), followed by incubation with HRP-conjugated secondary antibodies. Bands were visualized using chemiluminescence, and densitometric analyses were conducted.

Statistical Analysis

Data are expressed as median (range) or mean ± standard deviation, as appropriate. Statistical significance between groups was assessed using the Kruskal–Wallis test, followed by the Mann–Whitney U test for pairwise comparisons. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Biochemical Findings: A significant difference in urea levels was found between the groups ($p<0.005$) as a result of the statistical analysis test (Figure 1). The median urea value was 41.5 (39–47) mg/dL in the control group, 44.5 (39–56) mg/dL in the dabrafenib group, 129.5 (53–372) mg/dL in the cisplatin group, and 117.5 (89–244) mg/dL in the cisplatin + dabrafenib group. Pairwise comparisons using the Mann-Whitney U test revealed significant differences in urea levels between the cisplatin group and the control group ($p = 0.005$) and between the dabrafenib group ($p = 0.004$). The urea level in the cisplatin + dabrafenib group was also significantly higher than in the control ($p = 0.004$) and dabrafenib ($p = 0.005$) groups.

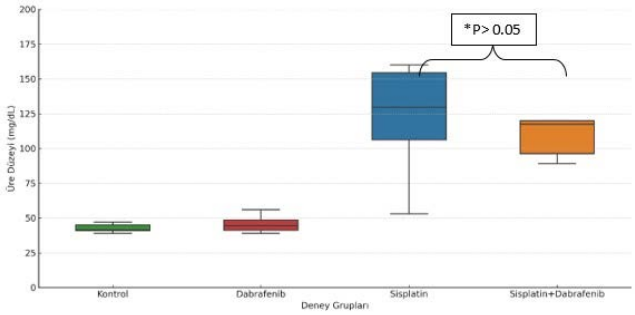

Figure 1: Change in urea levels in all groups (in mg/dL).

A statistical analysis of creatinine levels revealed significant differences among the groups ($p < 0.005$) (Figure 2). The median creatinine values were 0.265 (0.24–0.30) mg/dL in the control group, 0.245 (0.21–0.30) mg/dL in the dabrafenib group, 0.810 (0.25–4.30) mg/dL in the cisplatin group, and 0.745 (0.49–4.10) mg/dL in the cisplatin + dabrafenib group. According to the Mann-Whitney U test, the creatinine level in the cisplatin group was significantly higher than in the control ($p = 0.03$) and dabrafenib ($p = 0.01$) groups. Similarly, the creatinine level in the cisplatin + dabrafenib group was significantly higher than in the control ($p < 0.05$) and dabrafenib ($p < 0.05$) groups.

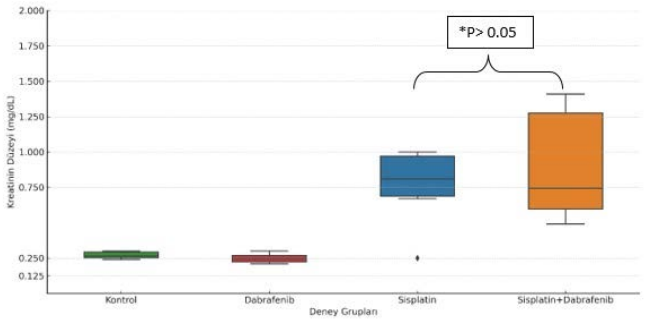

Figure 2: Change in creatinine levels in all groups (mg/dL)

The MDA levels measured in kidney tissues increased statistically significantly in the cisplatin group compared to the control group ($p < 0.05$) (Figure 3). In the cisplatin + dabrafenib group, MDA levels decreased significantly compared to the cisplatin group ($p < 0.05$), showing the oxidative damage-alleviating effect of dabrafenib. No significant difference was detected in the group administered dabrafenib alone compared to the control group ($p > 0.05$).

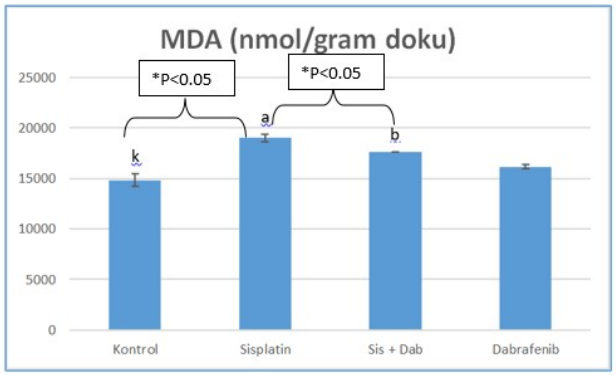

Figure 3: Tissue Malondialdehyde (MDA) levels (nmol/gram tissue) measured in all groups

Histopathological Findings

Normal histological structures were observed in the examination of the control group. Kidney tissue with a grade 0 structure was observed, along with a histologically normal glomerular structure, proximal and distal tubules, and preserved brush border structures (Figure 4).

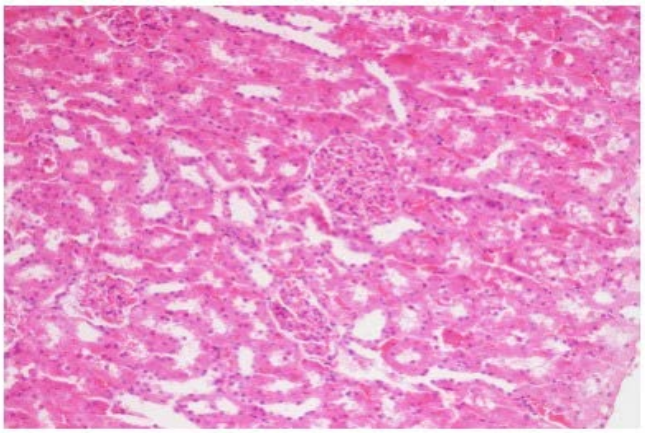

Figure 4: Normal kidney tissue appearance in Control group (H&E, 400X).

In the examination of the cisplatin group, impaired kidney integrity was observed. Grade 2 kidney structure was observed, characterized by prenecrotic changes, including loss of brush border, local tubule epithelial cell thickening, significant regenerative changes in tubule epithelial cell nuclei, and cellular swelling and loss of multiple nuclei (Figure 5).

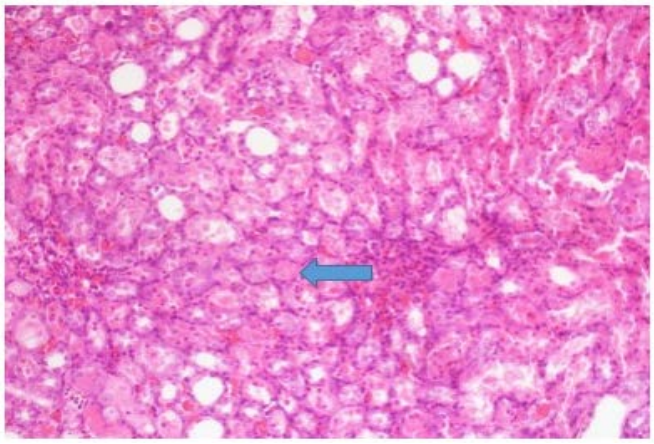

Figure 5: Interstitial inflammation, multiple nucleus loss and tubular necrosis in a rat in the cisplatin group (arrows) (H&E, 200x)

In studies performed with cisplatin and dabrafenib, it was observed that dabrafenib protected the integrity disrupted by cisplatin in both groups. Compared to the Cisplatin group, the following changes were observed in the groups: mild eosinophilic degeneration, mild hydropic degeneration, and mild tubular dilatation in the tubular epithelium and kidney

tissue with grade-1 changes, decreased brush border loss in the tubules, decreased nuclear loss, and preserved epithelial cells and tubular organization (Figure 6).

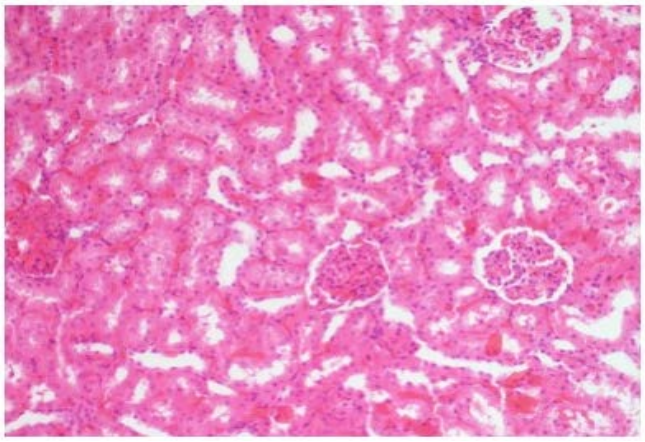

Figure 6: Normal kidney tissue appearance in Cisplatin+Dabrafenib group (H&E, 400X).

Statistical analysis showed a significant difference ($p < 0.05$) between the groups regarding histopathological scores (Figure 7). The control group had much lower scores in terms of cell structure and function than the other groups. The cisplatin group showed a significant difference compared to all the other groups, reflecting severe kidney damage. The group that received a combination of cisplatin and Dabrafenib had a protective effect and scored much lower than the group that received cisplatin alone.

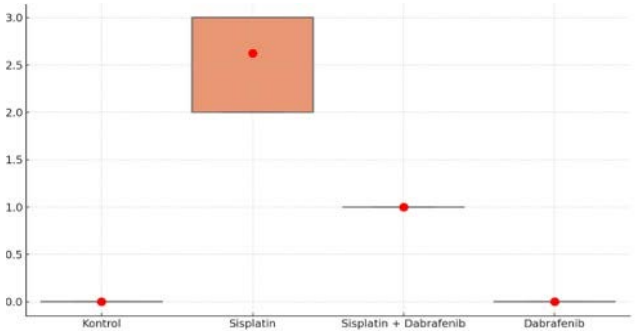

Figure 7: Kidney Histopathology scores of the groups

Western Blotting Findings: Subsequent Western Blot analyses revealed that the levels of RIP1, RIP3, and MLKL, which are the fundamental proteins of necroptosis pathways, exhibited a marked increase in the Cisplatin group compared to the control group ($p < 0.05$) (Figure 8). This finding indicates that the application of cisplatin instigates necroptotic cell death in renal tissue. In the group where Dabrafenib was applied in conjunction with Cisplatin, the expression levels of these proteins were significantly decreased compared to the Cisplatin group ($p < 0.05$), indicating that Dabrafenib may have a suppressive effect on necroptosis.

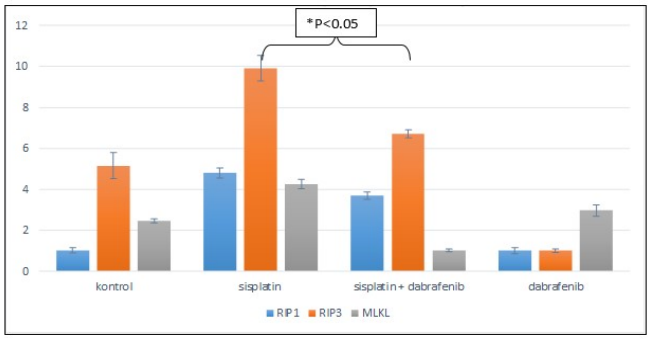

Figure 8: Tissue protein expression levels according to groups.

In the Cisplatin group, a significant increase in the band intensities of RIP1, RIP3, and MLKL proteins was observed in comparison to the control group (Figure 9). This increase indicates that cisplatin activates necroptosis pathways and triggers cell death processes in the tissue. In the Cisplatin + Dabrafenib group, the intensity of the bands belonging to these three proteins is observed to be weaker compared to the Cisplatin group. This finding indicates that Dabrafenib exerts a suppressive effect on necroptotic pathways, thereby attenuating Cisplatin-induced cell death. In the Dabrafenib alone group, the RIP1, RIP3, and MLKL band intensities were found to be nearly equivalent to those observed in the control group. This result demonstrates that Dabrafenib, when administered as a monotherapy, exerts minimal influence on the necroptosis mechanism and does not induce a deleterious side effect on the tissue. The intensity of Beta-Actin was found to be consistent across all groups, thereby

substantiating the hypothesis that the bands are comparable in terms of loading control.

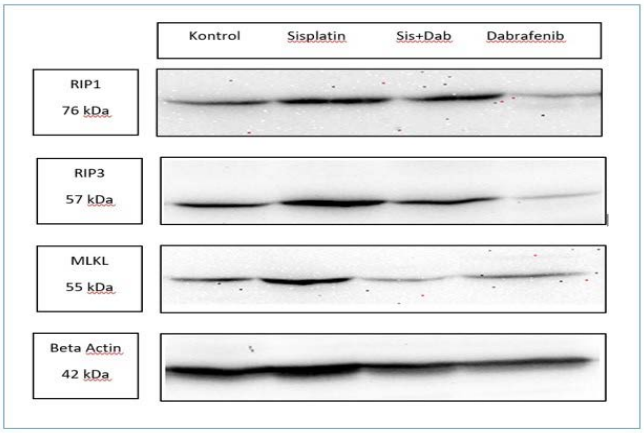

Figure 9: Western Blot band images of the proteins studied in all groups.

DISCUSSION

The present study observed that the administration of cisplatin led to a significant increase in renal malondialdehyde (MDA) levels and the expression of necroptosis-related proteins, including RIP1, RIP3, and MLKL. Concurrently, the study noted substantial histopathological kidney damage. The co-administration of dabrafenib and cisplatin led to a significant reduction in oxidative stress markers, a decrease in necroptosis protein expression, and an improvement in renal tissue injury. These findings suggest a protective effect of the combination therapy.

This study is one of the limited number of experimental studies evaluating the biochemical, histopathological and molecular protective effects of BRAF inhibitors in a cisplatin-induced nephrotoxicity model. The wide range of clinical use of cisplatin and its serious renal toxicity increase the need for new and safe strategies that can reduce this side effect[14]. In this context, the nephroprotective potential of dabrafenib, a drug currently used in melanoma treatment, was experimentally tested in our study, obtaining promising results.

We observed that histopathological examinations revealed structural damages, including widespread tubular degeneration, brush border loss, and nuclear pyroptosis, in the cisplatin group. These damages were significantly reduced in cisplatin+ dabrafenib group. The regression in histological scores indicates that the dabrafenib provides significant protection at the structural level. These findings were also confirmed in a similar study by Pushpan et al[11]. The present study examined the protective effects of dabrafenib on acute kidney injury induced by cisplatin. In an another study, Ingersoll et al. demonstrated that dabrafenib exhibited a protective effect against cisplatin-induced hearing loss[12]. In this that study, also dabrafenib demonstrated had a protective effect on the auditory system in mouse models and it was also shown to reduce cochlear cell death by inhibiting the pERK signal that leads to hearing loss[12]. Pushpan et al. expanded these findings and reported that dabrafenib also provides similar protective effects in kidney tissue[11]. Interestingly, the BRAF–MEK–ERK signaling pathway is a common target in both studies; similar mechanisms are seen to be effective in reducing cellular damage in different organ systems (kidney and cochlea). However, as an important difference, Ingersoll's study focused on postmitotic stress signaling in cochlear support cells; whereas our study emphasized the suppression of necroptotic and pyroptotic processes in tubular cells. The findings of these studies suggest that dabrafenib should be evaluated as a broad-spectrum protective agent with the potential to be effective in multiple organ systems[11,12].

In the present study, we observed that the expression levels of RIP1, RIP3, and MLKL, which are the primary indicators of necroptosis, were considerably elevated in animals treated with cisplatin. This finding indicates that cisplatin primarily activates necroptosis as a

cell death mechanism[5,15]. In this context, our study supports the mechanisms proposed by Tang et al.[1] Necroptosis is activated by RIPK1 and RIPK3-mediated activation of the MLKL[16]. The expression of RIPK1, RIPK3, and MLKL increased in the kidneys of mice treated with cisplatin[17]. Genetic deletion of Ripk3 or Mlkl, as well as inhibition of RIPK1, reduced cisplatin-induced proximal tubule damage, suggesting an important role for necroptosis in cisplatin-induced acute kidney injury[18].

It is important to stop necroptosis to prevent damage caused by a drug called cisplatin. Dabrafenib has been described as a RIP3 inhibitor in the literature, and our study directly demonstrated this effect in renal tissue[10]. Furthermore, a substantial impact of dabrafenib on signaling pathways associated with cellular stress was observed. It was determined that pERK1/2 expression increased with cisplatin application and that this increase was suppressed by dabrafenib. This finding suggests that suppression of the inflammation-related ERK pathway may play a role in the nephroprotective effect. In this regard, it may be feasible to reduce both inflammation and cell death, particularly by suppressing the BRAF-MEK-ERK axis[11,19].

In addition to BRAF inhibitors, another step in the same signaling pathway, MEK kinases, is also considered an important target in cisplatin-induced kidney damage. A study on the subject demonstrated that trametinib, an FDA-approved MEK inhibitor, exhibited a significant protective effect against cisplatin-induced acute kidney injury[20]. In the groups treated with trametinib, a decrease was observed in renal injury biomarkers, including blood urea nitrogen, creatinine, and NGAL. Additionally, renal histological deterioration was significantly reduced. At the molecular level, trametinib suppressed both MEK1/2 and ERK1/2 phosphorylation, as well as reduced macrophage infiltration and proinflammatory cytokine expression. The study demonstrated a reduction in lipid peroxidation products, an enhancement in glutathione redox balance, and a suppression in NADPH oxidase 4 expression. Notably, inhibitory effects were observed on both apoptosis and necroptosis. The results of the study suggest that trametinib provides an integrated nephroprotective effect by suppressing nephrotoxicity not only at the signaling pathway level but also through inflammation, oxidative stress, and cell death mechanisms.

In summary, the development of strategies to mitigate the adverse effects of commonly used nephrotoxic agents, such as cisplatin, is of critical importance in clinical practice. The evaluation of agents with well-defined toxic profiles, such as Dabrafenib, which are already in clinical use, as nephroprotective agents in new indications appears to be highly valuable from a translational perspective. The findings of these studies indicate that inflammatory cell death pathways, such as necroptosis, play a significant role in kidney injury and should be targeted for therapeutic intervention. It is recommended that future studies clarify their effects on different necroptotic signaling pathways.

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Conflict of Interest: The authors declared no conflicts of interest.

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