DOI:10.34108/eujhs.1580627

SAĞLIK BİLİMLERİ DERGİSİ
JOURNAL OF HEALTH SCIENCES
Erciyes Üniversitesi Sağlık Bilimleri Enstitüsü Yayın Organıdır

Araştırma 2025; 34(1): 1-7

MYRICETIN REDUCES CISPLATIN-INDUCED LUNG INJURY BY REGULATING OXIDATIVE STRESS AND HYPOXIA INDUCIBLE FACTOR-1α LEVELS
MİRİSETİN OKSİDATİF STRESİ VE HİPOKSİ İNDÜKLENEBİLİR FAKTÖR-1α DÜZEYLERİNİ DÜZENLEYEREK SİSPLATİN KAYNAKLI AKCİĞER HASARINI AZALTIR

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ABSTRACT

Cisplatin is an anticancer agent that is frequently used in the treatment of solid tumors. However, widespread organ toxicity is the most important factor limiting its use. Lung toxicity has also become an increasing concern in recent years. This study aimed to evaluate the protective roles of myricetin, a natural antioxidant found in plants, in cisplatin-induced lung injury. For this purpose, twenty-eight male Wistar rats were randomly assigned to four equal groups (n=7): control, myricetin, cisplatin, and myricetin+cisplatin. The control group received physiological saline; the myricetin group was given myricetin (10 mg/kg) intraperitoneally for seven consecutive days. The cisplatin group was given a single dose of cisplatin (7.5 mg/kg) intraperitoneally on the seventh day. The myricetin+cisplatin group was treated with myricetin for seven consecutive days, and at the end of the seventh day, cisplatin was administered. One day later, the rats were sacrificed, and their lungs were removed. The sections obtained from the lungs were stained with hematoxylin & eosin, and histopathological damage was evaluated. Biochemical analyses were performed using total oxidant status, total antioxidant status, and hypoxia-inducible factor-1α. In results, significant inflammatory cell infiltration, cellular deterioration, and loss of tissue integrity were observed in the

ÖZ

Sisplatin, katı tümörlerin tedavisinde sıklıkla kullanılan bir antikanser ajandır. Ancak yaygın organ toksisitesi kullanımını kısıtlayan en önemli faktördür. Akciğer toksisitesi de son yıllarda giderek artan bir endişe haline gelmiştir. Bu çalışmada bitkilerde bulunan doğal bir antioksidan olan mirisetinin sisplatin kaynaklı akciğer hasarında koruyucu rolünün değerlendirilmesi amaçlandı. Bu amaçla 28 adet erkek Wistar sıçanı rastgele dört eşit gruba (n=7) ayrıldı: kontrol, mirisetin, sisplatin ve mirisetin+sisplatin. Kontrol grubuna fizyolojik salin verildi; mirisetin grubuna artarda yedi gün boyunca periton içinden mirisetin (10 mg/kg) verildi. Sisplatin grubuna yedinci gün tek doz sisplatin (7.5 mg/kg) intraperitoneal olarak verildi. Mirisetin+sisplatin grubuna art arda yedi gün boyunca mirisetin tedavisi uygulandı ve yedinci günün sonunda sisplatin uygulandı. Bir gün sonra sıçanlar sakrifiye edildi ve akciğerleri çıkarıldı. Akciğerlerden alınan kesitler hematoksilen&eozin ile boyanarak histopatolojik hasar değerlendirildi. Biyokimyasal analizler toplam oksidan durumu, toplam antioksidan durumu ve hipoksi ile indüklenebilir faktör-1α kullanılarak yapıldı. Sonuç olarak sisplatin grubunda belirgin inflamatuar hücre infiltrasyonu, hücresel bozulma ve doku bütünlüğünde kayıp gözlendi. Buna karşılık mirisetin+sisplatin grubunda hücresel yapı ve alveoler

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Makale Geliş Tarihi : 11.11.2024
Makale Kabul Tarihi: 26.12.2024

cisplatin group. In contrast, in the myricetin+cisplatin group, the cellular structure and alveolar order were largely preserved, and inflammatory infiltration was minimal. Pretreatment with myricetin reduced total oxidant status and hypoxia-inducible factor-1α while increasing total antioxidant status levels. Taken together, this study indicates that pretreatment of myricetin could serve therapeutic purposes in cisplatin-induced lung injury.

Keywords: Cisplatin, HIF-1 alpha, lung injury, myricetin, oxidative stress.

düzen büyük ölçüde korunmuş, inflamatuar infiltrasyon ise minimal düzeyde kalmıştır. Mirisetin ile ön tedavi toplam oksidan statusu ve hipoksi ile indüklenebilir faktör-1α'yı azaltırken toplam antioksidan status seviyelerini arttırdı. Birlikte ele alındığında bu çalışma, mirisetin ön tedavisinin sisplatin kaynaklı akciğer hasarında terapötik amaçlara hizmet edebileceğini göstermektedir.

Anahtar kelimeler: Sisplatin, HIF-1 alfa, akciğer hasarı, mirisetin, oksidatif stress.

INTRODUCTION

Cisplatin (Cis-diamminedicholoroplatinum II), one of the most effective antineoplastic drugs, has been widely used in the treatment of several neoplasms, primarily targeting testicular, ovarian, head and neck, cervical, breast, and pulmonary cancers. The United States Food and Drug Administration (FDA) approved cisplatin in 1978, and it is currently included in the World Health Organization's list of essential medicines.[1]

Cisplatin related antineoplastic mechanism involves its reactivity and binding to deoxyribonucleic acid (DNA) in cells. This interaction results in both intra- and inter-strand DNA crosslinks, inhibiting further DNA replication and transcription activities and, eventually, initiates programmed cell death, which includes apoptosis.[1,2] However, its cytotoxic processes which generate complications such as vomiting, gastro-intestinal disorders, and toxic manifestations influencing multiple organs and systems, restrict its clinical usefulness.[3] Although the kidneys are the most vulnerable organs to cisplatin toxicity, especially in recent years lung toxicity has been demonstrated.[4-6] The lungs are essential organs that meet the organism's basic metabolic demand for oxygen. Lung damage due to any reason, often results in inflammatory alterations in the lungs, which, if uncontrolled, can progress to acute respiratory distress syndrome, a severe and widespread symptom and cause of increased mortality.[7]

There are various components to the development of cisplatin toxicity. The first stems from cisplatin's basic action, binding to DNA, while the other main aspects are the development of oxidative stress via free radical production and the rise of inflammatory mediators by cisplatin.[1]Similar pathways have been observed in cisplatin-induced lung damage.[8,9] Due to the lack of effective preventive and therapeutic approaches against cisplatin-induced organ toxicity, this issue has been and continues to be investigated for many years.[2] Several studies have revealed favorable benefits on cisplatin-induced lung damage with various agents.[4-6] However to the best of our knowledge no research has been conducted on the use of myricetin, a natural substance, as a treatment agent for cisplatin induced lung injury.

Myricetin (3, 5, 7, 3′, 4′, 5′-hexahydroxyflavone) is a significant polyhydroxy flavonol found primarily in fruits as glycosides (O-glycosides).[10] It plays a function in cancer prevention by modulating inflammation, angiogenesis, and cell cycle arrest. Furthermore, myricetin enhances the chemotherapeutic potential of other anticancer medicines by modulating the activity of cell signaling molecules.[10,11] Due to its potent anti-inflammatory and antioxidant properties,[12] myricetin, have been investigated as a potential preventive agent against to cisplatin induced organ damage. It has been shown to be effective in cisplatin-induced kidney damage, and in improving cisplatin-induced liver damage in a study conducted by our colleagues.[13-15]

In conclusion, the effect of myricetin on the development of cisplatin-induced lung injury was investigated in this study. In addition to the histological analysis, lung tissue total antioxidant status (TAS) and total oxidant status (TOS) levels, and hypoxia inducible factor-1α (HIF-1α), which has been shown to play important roles in the response to oxidative stress and inflammation in the lungs,[16,17] were also investigated in this study.

MATERIALS AND METHODS

Animals and Experimental Procedures

Twenty-eight male Wistar rats aged nine weeks, 220-240 g weighted (Erciyes University Experimental and Clinical Research Center, Türkiye) were included in the study. The animals were acclimatized seven days before the experiment. They were housed in cages at room temperature, fed a standard pellet diet, and given tap water under a 12-hour light/dark cycle at 23 ± 2 °C.

The animals were randomly divided into four experimental groups (n=7). Throughout the experiment, the control group received a daily injection of 0.5 mL 0.9% saline. On the seventh day, the cisplatin group (Cis) received 7.5 mg/kg of cisplatin (Koçak Farma®, Istanbul, Türkiye).The myricetin group (Myr) was administered 10 mg/kg myricetin (Sigma-Aldrich®, St. Gallen, Switzerland) forseven days. The myricetin+cisplatin group (Myr+Cis) administered myricetin (10 mg/kg) for seven days, and at the end of the seventh day, a single dose of cisplatin (7.5 mg/kg) was injected.[15] Both myricetin and cisplatin were injected intraperitoneally in 0.9% saline.

Twenty-four hours after the last treatment all animals were anesthetized with ketamine (Ketalar®, 75 mg/kg) + xylazine (Rompun®,10 mg/kg) and both lungs were removed for tissue biochemical (frozen and stored at –80°C) and histological (fixated in 10% buffered formalin) analyses.

Histological Analysis

Tissue samples fixed in formalin were further processed following standard histopathological procedures and tissue was embedded in paraffin. Sections of 5-6 µm thickness were cut from the paraffin blocks and mounted on slides. For general morphological evaluation, the sections were stained with hematoxylin and

eosin (H&E), then cleared through ascending alcohol series and finally with xylene. The sections were examined under a light microscope (Olympus BX53 microscope), and histological changes were assessed and scored.[18] The scoring was conducted by two independent histologists to ensure unbiased results.

The following parameters were evaluated:

Cell Infiltration: The presence of inflammatory cells within the lung parenchyma.

Edema: The accumulation of fluid with in the interstitial spaces.

Detached Cells: The presence of cells that have detached from the alveolar walls.

Disorientation: The disruption of the normal lung architecture.

Each parameter was scored on a scale of 0 to 3, where: 0 = None (no presence of the parameter); 1 = Mild (slight presence); 2 = Moderate (noticeable presence); 3 = Severe (extensive presence).

Biochemical Analysis

Frozen tissue samples were melted and then washed with phosphate buffered saline (PBS). After they weighed, homogenized in cold 0.015 M, 1/10 (w/v) PBS. The homogenization process was carried out with a teflon-tipped homogenizer (Ultra-Turrax T25 Basic IKA Werke; 17500 rpm, 30 seconds, 6 strokes for each sample) in ice. The homogenates centrifuged (20.000 g, 15 min at 4°C) to obtain a clear supernatant that was further used for the determination of tissue biochemical parameters. At the end of the process, tissue samples were diluted with PBS 40-fold for HIF-1α.

Tissue HIF-1α levels were determined using USCNK brand ELISA kits (Cloude-Clone Corp, USA; Catalog No: SEA798Ra).

TOS and TAS levels in the lung tissue supernatants were measured with Rel Assay Diagnostics (Gaziantep-Türkiye, Catalog No: RL0024 and RL0017, respectively) brand kit.

The protein content in lung tissue homogenate was determined using albumin standard curve at 280 nm. All measurements made in the tissue were given in proportion to the amount of protein.

Statistical Analysis

Statistical analysis was carried out using the IBM-SPSS version 23.0 for Windows. The normality of sample distribution was evaluated using the Shapiro-Wilk test. Continuous variables with normal and abnormal distributions were reported as mean with standard deviation (SD) and median (25%-75%), respectively. Differences among the experimental groups were tested by one-way ANOVA and Kruskal Wallis tests followed by post-hoc tests (Tukey's multiple comparison test and Mann Whitney U test, respectively). The p value of <0.05 was considered statistically significant.

RESULTS

Histological Analysis Results

Lung tissue H&E staining of all groups are shown in Figure 1. In the control group, the cellular morphology appears orderly and structurally intact. Cell boundaries are distinct, and the arrangement of cells is well-maintained. The nuclei are of normal size and evenly distributed, showing no signs of condensation or fragmentation. The alveolar structures are regular, preserving their integrity, with alveolar spaces of normal dimensions. The cellular morphology in the Myr group is identical to that of the control group, apart from limited apoptosis and inflammatory cell infiltration (Figure 1).

In the Cis group, there are irregularities and morphological disruptions among the cells, with indistinct cell boundaries. The nuclei exhibit condensation and fragmentation (pyknosis). There is significant loss of alveolar tissue, indicating impaired tissue integrity. There is prominent inflammatory cell infiltration. The intercellular junctions are weakened, and the cellular structure is disrupted (Figure 1). In the Myr+Cis group, cellular morphology is relatively orderly and structurally intact, with distinct cell boundaries and well-maintained cellular arrangement. The nuclei are of normal size and evenly distributed. The alveolar structures are regular, preserving their integrity, with alveolar spaces of normal dimensions. Inflammatory cell infiltration is minimal (Figure 1).

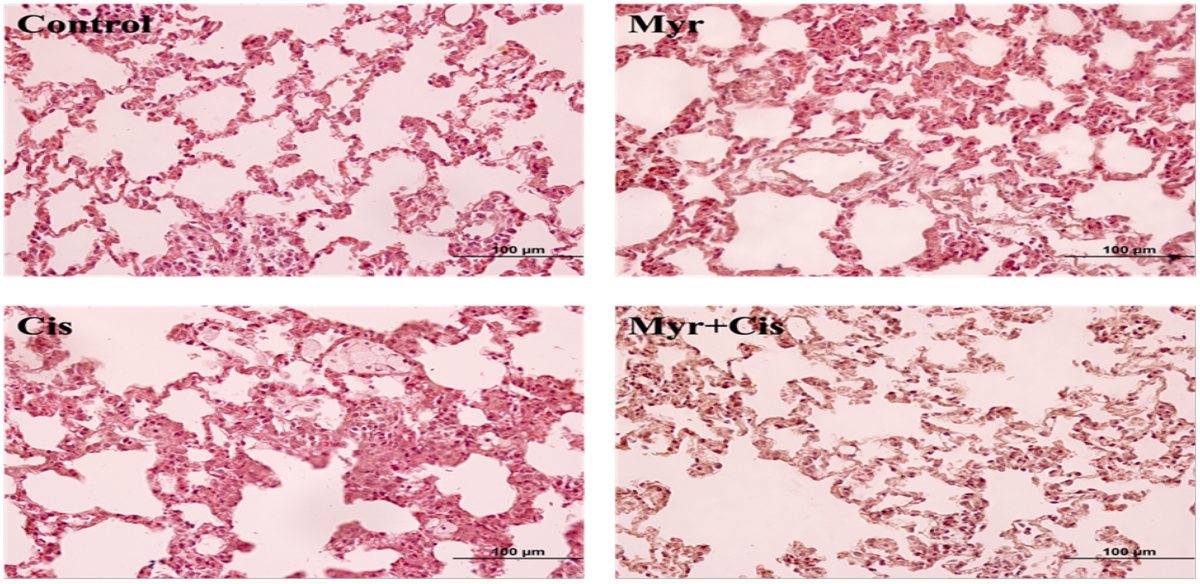

Figure 1: Lung tissue H&E staining of all groups. Scale bar 100 µm.

Histological analyses indicated that cell infiltration, edema, sloughed cells, and disorientation were minimal in the control group. The Myr group exhibited mild edema and disorientation compared to the control group, but these differences were not statistically significant (p>0.05). In the Cis group, there was a significant increase in cell infiltration, edema, detached cells, and disorientation compared to the control group. These findings suggest that cisplatin induces substantial histopathological damage in lung tissue. In the myricetin and cisplatin combination group (Myr+Cis), a significant decrease in all variables was observed compared to the cisplatin alone group (Table 1). These findings suggest that myricetin may reduce the damage caused by cisplatin to lung tissue and potentially exhibit a protective effect.

According to Table 2, while HIF-1α values increased significantly in the cisplatin-administered group, no change was observed in the animals administered myricetin. In animals that were administered cisplatin following myricetin administration, HIF-1α levels were found to decrease similarly to the control (Table 2).

DISCUSSION

The current study, which examined the protective effects of myricetin in cisplatin-induced lung damage, found that myricetin protects against oxidative stress and lung injury, with a focus on the contribution of HIF-1α.

Histological research revealed that cisplatin induced lung injury in the current study, as evidenced by cell infiltration, edema, detached cells, and disorientation. Similarly, in previous investigations have demonstrated that cisplatin promotes edema, interalveolar septa thickening, neutrophil and lymphoid cell infiltration in the lungs.[9,19]

Over the years, many factors have been identified that are related to cisplatin causing cellular damage, and among these, oxidative stress has received the most attention.[6,9] Oxidative stress is defined as the disruption of the balance between free radicals and antioxidants in favor of radicals. The uncontrolled increase of radicals not only results in their chemical attack on biomolecules but also plays a role as a cellular signal and causes the activation of cellular pathways such as inflammation, apoptosis and necrosis.[1] In the present study, the increased in TOS levels and decreased in TAS levels demonstrate the presence of oxidative stress. TOS and TAS measurements were preferred in this study because they are easy to apply and reliable methods in terms of both sample preparation and measurement. However, there are also studies in the literature showing lipid peroxidation, protein and DNA oxidation with specific parameters in case of cisplatin-induced oxidative stress.[6,20]

In the present study, the lung tissues of rats administered myricetin before cisplatin showed a considerable decrease in TOS levels and an increase in TAS levels, indicating that myricetin is a potent antioxidant. Furthermore, histologically, myricetin therapy showed damage-reduction effects while maintaining cellular shape and tissue integrity. These findings support the protective and therapeutic potential of myricetin for lung tissue. Two mechanisms have been proposed for the role of myricetin in suppressing oxidative stress: (1) a direct scavenging effect on free radicals, and chelating metal ions due to possible metal binding sites (2) an indirect effect via the induction of antioxidant enzymes

Table 1. Histological assessment scores of study groups (n:7 per-group)

	Control	Cis	Myr	Myr+Cis	p
Cell Infiltration	0 (0-0)	1 (1-1)*	0 (0-0) [a]	0 (0-1)[a]	0.003
Edema	0 (0-0)	1 (1-2) *	0 (0-1) [a]	1 (0-1) [a]	0.004
Detached Cells	0 (0-0)	1 (1-2) *	0 (0-0) [a]	1 (0-1) [a]	0.002
Disorientation	0 (0-0)	2 (1-2) *	0 (0-1) [a]	1 (0-1) [a]	0.001

Data are presented as median (25%-75%). p <0.05 was considered statistically significant*; indicates the comparisons of the Control group with the others; [a]; indicates the result of the comparison of Cis group with the others.

Table 2. Lung Tissue TOS, TAS and HIF-1α levels of study groups (n:7 per-group)

	Control	Cis	Myr	Myr+Cis	p
TOS (μmol H_2O_2 Eq/g protein)	109.81±9.71	135.55±9.12*	111.08±6.82 [a]	112.61±11.36 [a]	<0.001
TAS (mmol Trolox Eq/g protein)	25.49±3.60	17.53±2.13*	25.55±1.51 [a]	20.28±5.96 *,[a]	0.001
HIF-1α (ng/mg protein)	114.47±18.27	205.12±29.54*	120.42±12.96[a]	135.14±26.25 [a]	0.001

Data are presented as mean ± standard deviation values. p <0.05 was considered statistically significant. *; In the comparisons of the Control group with the other groups; [a]; indicates the result of the comparison of Cis group with the others.

activities.[21]

Another significant finding in the present work is the elevated intracellular HIF-1α levels in lung tissues subjected to cisplatin-induced damage, indicating a potential relevance between lung injury and HIF-1α.

HIF-1 is a transcriptionally active nuclear protein that is expressed under hypoxic conditions and regulates hypoxic genes and critical metabolic pathways such as angiogenesis, erythropoiesis, and glycolysis. It consists of two subunits: HIF-1α and HIF-1β. HIF-1α, an active member of HIF-1, is a key regulator of hypoxia due to its high sensitivity to oxygen.[22] Previous studies have shown that HIF-1 is associated with lung damage caused by different pathological conditions.[16,17] Although no study has been found investigating HIF-1α levels in cisplatin-induced lung injury, it has been shown that cisplatin administration causes an increase in HIF-1α levels in kidney tissues.[23,24] Schödel et al.,[25] have shown cisplatin suppress prolyl hydroxylases levels which plays a role in controlling HIF-1α levels in the cell, and these findings may explain the elevated HIF-1α levels observed in the current investigation. Contrary to these findings, some studies have shown that the increase in HIF-1α acts as a protective mechanism to prevent cisplatin-induced nephrotoxicity by suppressing apoptosis by preserving mitochondrial integrity.[26,27] Although these results are confusing, when assessing the results of these studies, the effect of the route and amount of cisplatin administration, the kind of tissue studied, and, most significantly, the time passed after cisplatin administration should be taken into consideration.[28]

Additionally, HIF-1 is considered one of the redox-sensitive transcriptional factors and as a result its expression is modulated by free radicals.[29] Therefore, the increase in HIF-1α levels shown in this study may have occurred in the early periods of cisplatin administration in response to increased oxidative stress. In particular, the demonstration of an increase in radicals and inflammatory mediators due to an increase in HIF-1α in lung injury supports our findings.[30]

Myricetin has been shown to reduce HIF-1α accumulation in adipose tissue in hypoxic conditions.[31] Similarly, in the current investigation, myricetin therapy delivered prior to cisplatin injection prevented the release of HIF-1α.Although our experiments are unable to confirm this conclusively, it is possible that myricetin's high antioxidant activity reduces free radical-mediated HIF-1α release, as evidenced by improved TAS, decreased TOS, and histological improvements in the Myr+Cis group. Also, aside from its antioxidant properties, myricetin has also recently been shown to inhibit HIF-1α in tumor cells by directly binding to it.[32]

CONCLUSION

The current study's findings indicate that cisplatin imposes significant damage to the lungs, with the damage caused by oxidative stress and HIF-1α. Myricetin applied before cisplatin protects the lungs from this damage mostly by reducing oxidative stress. Further research on this topic may offer a foundation for clinical trials and provide more precise instructions on the usage of myricetin. It can be suggested that the cause-and-effect relationship can be revealed more precisely by studying the prominent parameters of different oxidative stress pathways in more detail in a similar experimental model.

Ethics Committee Approval: Ethics committee approval was received for this study from the Animal Experiments Local Ethics Committee of Erciyes University, Türkiye (Approvalnumber:23/130, Date: June 2023).

Informed Consent: Written and/or verbal consent was obtained from all authors participating in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept-IG, SA, NK, CY, BY; Design-IG, NK, CY; Supervision-IG, CY, BY; Resources-IG, NK, DK; Materials-IG, NK, SA, ND, DK; Data Collection and/or Processing-IG, NK, SA, ND, CY, DK; Analysis and/or Interpretation- IG, NK, SA, ND, CY, DK Literature Search- IG, NK, SA, ND; Writing Manuscript- IG, NK, DK; Critical Review- IG, NK, CY, DK, BY

Declaration of Interests: The authors declare that there is no conflict of interest.

Funding: This research did not receive support from any funding agency/industry.

Etik Komite Onayı: Bu çalışma için Erciyes Üniversitesi Hayvan Deneyleri Yerel Etik Kurulundan (Tarih: Haziran 2023, Sayı: 23/130) onay alınmıştır.

Bilgilendirilmiş onam: Çalışmaya katılan tüm yazarlardan yazılı ve/veya sözlü onam alınmıştır.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir-İG, SA, NK, CY, BY; Tasarım-İG, NK, CY; Denetleme-İG, CY, BY; Kaynaklar-İG, NK, DK; Malzemeler-İG, NK, SA, ND, DK; Veri Toplanması ve/veya işlenmesi-İG, NK, SA, ND, CY, DK; Analiz ve/veya yorum- İG, NK, SA, ND, CY, DK Literatür taraması- İG, NK, SA, ND; Yazıyı yazan- İG, NK, DK; Eleştirel inceleme-İG, NK, CY, DK, BY.

Çıkar Çatışması: Yazarlar arasında herhangi bir çıkar çatışması bulunmamaktadır.

Finansal Destek: Bu araştırma herhangi bir finansman kuruluşundan/sektörden destek almamıştır.

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