

## Cisplatin Nephrotoxicity and Treatment Approaches

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### ABSTRACT:

Cancer is one of the most important health problem in the world. Cisplatin is an effective chemotherapeutic drug that is widely used in many cancer types such as lung, cervical, head and neck cancer, stomach cancer, testicular, ovarian, breast cancer. However, the clinical use of cisplatin is limited due to serious side effects and drug-induced resistance. Acute kidney injury (AKI) develops in 20-35% of patients after cisplatin administration. Long-term use of cisplatin results in tubular kidney damage, acute kidney failure, and chronic kidney disease in patients. Mechanisms of kidney injury induced by cisplatin use include proximal tubular damage, oxidative stress, ER stress, apoptosis, and inflammation in the kidneys. There is no completely effective drug or method for kidney damage due to cisplatin use. In vitro and in vivo studies have proven that many natural products and chemicals are effective against cisplatin-induced kidney damage in recent years. In this review, the molecular mechanisms of nephrotoxicity due to the use of cisplatin are described and the findings on current treatment approaches against cisplatin-induced kidney injury are summarized.

**Keywords:** Cisplatin, nephrotoxicity, apoptosis, oxidative stress, inflammation.

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## 1. INTRODUCTION

Cancer is one of the important problem that threaten human health and result in high rates of death. Today, it is reported that one out of every four people has a lifetime risk of cancer and cancer cases are over 19 million worldwide [1-3]. Cisplatin is an effective chemotherapeutic drug that has been used for a long time in the treatment of cancer [4,5]. Cisplatin is a platinum compound that is in the form of a white or dark yellow crystalline powder at room temperature, also called cis-diamminedichloroplatinum (II). It was first synthesized in 1844 by M. Peyrone and its chemical structure was elucidated by Alfred Werner, and Rosenberg drew attention to the possible use of platinum-based compounds in cancer chemotherapy. Cisplatin shows anticancer activity in a variety of tumors, including ovarian cancer, testicular, head and neck solid tumors. In 1978 it became the first FDA-approved platinum compound for the treatment of testicular and bladder cancer [6].

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Since the discovery of cisplatin, five platinum drugs such as carboplatin, oxaliplatin, nedaplatin, lobaplatin and heptaplatin have been approved in more diverse countries [7]. The mechanism of the anticancer activity of cisplatin is not fully understood. It is generally thought to exert its anticancer effect by binding to DNA. When cisplatin enters cells, hydrolyzed products with a strongly electrophilic structure are formed, which can react with DNA bases. Interaction of cisplatin with DNA; It has many effects such as inhibition of DNA replication and transcription, disruption of protein production, necrosis and apoptosis [4,8]. Although cisplatin has been used in many cancer types for many years, there are two important factors limiting its clinical use. The first is the serious side effects caused by the use of cisplatin, the second is the resistance to cisplatin [6,9]. Cisplatin has many side effects that limit its use in cancer patients. These are ototoxicity, nephrotoxicity, hepatotoxicity, neurotoxicity [10]. The most common side effect of cisplatin in clinical use is nephrotoxicity [4]. Nephrotoxicity may vary depending on the dose used, and the rate of development of nephrotoxicity in patients is 30-40%. Cisplatin nephrotoxicity initially shows symptoms such as hypocalcemia, hypomagnesemia, and acute kidney injury. It then manifests in various forms such as proximal tubular damage and chronic renal failure. Patients who develop kidney damage have a decrease in renal plasma flow and glomerular filtration rate (GFR). At the same time, serum creatinine (Cr) and blood urea nitrogen (BUN) concentrations increase [8,11].

Many methods have been developed to combat the side effects that limit the use of cisplatin, such as developing cisplatin analogues with lower toxicity and hydrating patients during cisplatin treatment. Despite these precautions, especially nephrotoxicity remains a serious side effect that limits the use of cisplatin.

### ***1.1. Nephrotoxicity Mechanisms of Cisplatin***

Cisplatin is taken into the cell by the copper transporter 1 (CTR1) and organic cation transporter 2 (OCT2) located in the plasma membrane. These transporter proteins are localized in the kidney, so cisplatin tends to accumulate in the kidneys at higher concentrations, particularly in the proximal tubule [12,13]. The toxicity of cisplatin in the kidney is due to its accumulation in high concentrations in the proximal tubules. Even doses that would not normally cause toxicity can reach toxic levels in the kidney tubules and cause damage [8]. Clinically, the development of nephrotoxicity occurs within 10 days after cisplatin administration [4] and is manifested by disturbances in electrolyte balance and abnormalities in renal function tests [14].

Cisplatin, which causes tubular cell damage, achieves this effect by activating many signaling pathways [4]. Cisplatin tends to bind to mitochondrial DNA in the cell. Cisplatin tends to bind to mitochondrial DNA in the cell. The renal proximal tubule is the region with the highest mitochondria density in the kidney, so it is more susceptible to cisplatin toxicity [15].

The mechanisms of nephrotoxicity caused by cisplatin are quite complex. Many pathways are activated simultaneously. Activated pathways mainly include oxidative stress, inflammation, and apoptosis. It is stated that cisplatin doses that cause kidney damage cause an increase in necrosis and apoptosis in the tubules [16,17]. In the nephrotoxicity of cisplatin, apoptotic pathways activated by tumor necrosis factor receptors 1 and 2 (TNFR1 and TNFR2) or death receptors such as Fas and intrinsic pathways such as mitochondrial and endoplasmic reticulum (ER) stress pathway have been identified [15]. In caspase-independent pathways, a nuclear factor responsible for DNA regulation activates a factor on the mitochondrial membrane and apoptosis is induced. The apoptotic response can also be activated by Bcl/Bax and caspases. Bax travels to the mitochondria and induces the release of cytochrome c, then activation of caspase-3 and 9 occurs for activation of apoptosis [14].

Cisplatin-induced apoptosis can also be triggered by ER stress (ERS). As a result of physiological and pathological events, unfolded and/or misfolded proteins accumulate in the ER lumen. ERS activates the unfolded protein response (UPR) to prevent protein aggregation and maintain homeostasis. If ER stress continues for a long time, the UPR leads to apoptosis [18]. In vitro study showed activation of GRP78/BiP and PERK pathways after cisplatin treatment [19]. Another study found that CHOP, GRP94 and GRP78 were upregulated in cisplatin-treated rats [20]. Oxidative stress caused by reactive oxygen species (ROS) is one of the critical mechanisms underlying cisplatin nephrotoxicity. Oxidative stress occurs due to the deteriorated balance of oxidant and antioxidant production in the body [21]. ROS can attack and alter multiple target molecules such as lipids, proteins, and DNA, creating cellular stress. In cisplatin-induced nephrotoxicity, ROS molecules activate apoptotic pathways and important signaling pathways that lead to cell death. NADPH oxidase, cytochrome P450 system and electron transport system can cause oxidative stress by generating ROS in the cell [22].

Inflammation is an important mechanism in the pathogenesis of many diseases [23] and plays an active role in the nephrotoxicity mechanisms of cisplatin. Proinflammatory cytokines play an important role in many inflammatory diseases. It has been determined that cytokines accompanying inflammation such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), IL-1 $\beta$ , transforming growth factor-beta 1 (TGF- $\beta$ ), RANTES, MIP2 and MCP1 are increased in cisplatin-induced kidney damage [22]. Studies show that TNF- $\alpha$  plays an important role in the pathogenesis of cisplatin nephrotoxicity. TNF- $\alpha$  triggers the inflammatory response in cisplatin-induced nephrotoxicity [24,25]. After cisplatin administration, oxidative stress pathways are activated and ROS is induced. In addition, the transcription factor NF- $\kappa$ B is activated and TNF- $\alpha$  is induced. TNF- $\alpha$  and ROS are two inducers that affect each other's activation [22]. In addition, p53, a tumor suppressor protein, has been reported to be a contributing factor to cisplatin's renal damage. In the experiment performed on rabbits, it

was determined that p53 played a role in apoptosis due to tubular damage caused by cisplatin, and pifithrin- $\alpha$ , a pharmacological inhibitor of p53, suppressed apoptosis [26].

### ***1.2. Renoprotective Treatment Approaches for the Cisplatin Nephrotoxicity***

Low glomerular filtration rate, decreased serum magnesium and potassium levels, and elevated serum Cr occur after 10 days of use in cancer patients using cisplatin. In addition, loss of sodium, potassium, and magnesium causes tubular damage and tubular dysfunction [27]. Patients treated with high-dose cisplatin are treated with hydration, magnesium supplementation, or mannitol-induced forced diuresis to alleviate or prevent nephrotoxicity [16]. However, a sufficient level of effect cannot be seen with these treatment approaches. In clinical practice, hydration and diuresis increase cisplatin excretion and decrease renal exposure. However, this method has a disadvantage. Intravenous administration of large volumes (3–6 L per day) of isotonic saline is required before and after cisplatin use to reduce nephrotoxicity [28]. Many pathways are activated when cisplatin produces toxicity. Therefore, blocking only one of these pathways does not provide a full protective effect for the target tissue. Many potential therapeutic approaches have been developed against cisplatin nephrotoxicity. These approaches aim to reduce cisplatin uptake, inhibit its bioactivation, regulate the mitochondrial system, inhibit oxidative stress, reduce inflammation, regulate ER stress and UPR, inhibit apoptosis and/or regulated necrosis [18]. In a study examining the protective effects of cimetidine against cisplatin nephrotoxicity, it was shown that high-dose and continuous infusion of cimetidine reduced nephrotoxicity. It has been reported that cimetidine competitively inhibits OCT2-mediated cisplatin transport and affects cell toxicity [29]. In another study, cilastatin, a renal dehydropeptidase-I inhibitor, was found to have protective effects in vitro and in vivo against cisplatin-induced kidney injury by inhibiting apoptosis and oxidation. [30] In addition, studies have shown that  $\beta$ -adrenoceptor blockers (carvedilol, propranolol) reduce cisplatin toxicity by preventing oxidative stress [31,32].

*Nigella sativa* (*N. sativa*) is a plant known as black cumin and used in the treatment of a wide variety of diseases. In the study, the protective effects of *N. sativa* and Vitamin E on cisplatin-induced nephrotoxicity in rats were evaluated. It has been observed that *N. sativa* extract and Vitamin E weaken nephrotoxicity and reduce oxidative stress [33]. Hesperetin is a flavonoid found in citrus fruits. Kidney damage was induced in rats using cisplatin, and the protective effect of Hesperetin was investigated. It has been observed that Hesperetin treatment normalizes kidney function by reducing oxidative stress, lipid peroxidation and inflammatory cytokines formed in renal tubules [34]. In another study, it was shown that administration of gallic acid (GA), an antioxidant substance, decreased the expression of Bcl-2, Bax and caspase-3 in cisplatin-induced nephrotoxicity in rats. Likewise, TAC level increased and kidney malondialdehyde (MDA) content decreased with GA administration. GA also reduced levels of inflammatory factors, including IL-1 $\beta$  and TNF- $\alpha$ . In addition, GA reduced plasma BUN and Cr, leading to amelioration of renal

dysfunction [35]. Studies have evaluated the effects of Curcumin on cisplatin-induced nephrotoxicity in rats. The polyphenol Curcumin has pharmacological effects with antioxidant, anti-inflammatory and anti-cancer properties. Curcumin treatment prevented the elevation of serum BUN, Cr and renal MDA levels [36]. Curcumin nanoparticles caused significant increases in bilirubin, urea, uric acid and Cr levels with aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) activities. In addition, MDA, nitric oxide and serum TNF- $\alpha$  levels were also increased [37]. The protective activity of linalool, an essential oil, against cisplatin-induced nephrotoxicity was investigated. According to biochemical results and molecular studies, linalool has been found to reduce oxidative stress and have an antioxidant effect. In addition, linalool reduced inflammatory cytokine levels induced in the kidney and attenuated cisplatin-induced apoptotic markers. These data showed that linalool may protect against the nephrotoxic effects of cisplatin and against tissue damage [38]. In another study, the protective effects of Phloretin (PH) and its glycosylated form Phloridzin (PZ), which are natural compounds found in apple fruit, for nephrotoxicity caused by cisplatin were evaluated. They are compounds with high antioxidant properties thanks to the hydroxyl group in their PH and PZ structures. PH and PZ ameliorated cisplatin-induced renal dysfunction. It was also found that it reduced oxidative stress and protected the kidneys from the toxic effects of cisplatin by suppressing the inflammatory response [39].

One of the important side effects of the use of chemotherapy drugs in cancer patients is vomiting. Aprepitant, which is used as an antiemetic drug in patients treated with cisplatin in the clinic, is a selective neurokinin 1 receptor antagonist (NK1RA) drug. A study was conducted to investigate the protective effects of Aprepitant on nephrotoxicity and hepatotoxicity in patients using cisplatin. According to this study, it was determined that Aprepitant reduced cisplatin-induced kidney and liver damage by reducing oxidative stress, inflammatory cytokines such as TNF- $\alpha$  and NF- $\kappa$ B, and serum levels of ALT, AST, ALP, BUN and Cr [40]. Only natural compounds have not been tested on cisplatin nephrotoxicity. Platelet-rich plasma (PRP) has curative properties that have been used for many diseases. PRP is obtained from blood and has a rich content of active growth factors. PRP is obtained by centrifuging the blood sample and isolating the supernatant. In this study, PRP was administered to rats with cisplatin-induced nephrotoxicity by subcapsular renal injection. According to the results, Cr, BUN and N-acetyl glucosaminidase levels were decreased. In addition, while PRP increases epidermal growth factor, intercellular adhesion molecule-1 (ICAM-1), kidney injury molecule-1 (KIM-1), caspase-3 and TGF- $\beta$ 1 levels suppressed. According to these data, PRP showed protective effects in cisplatin-induced kidney damage in rats. It has been shown that PRP application can also be used to reduce the side effects of cisplatin [41]. These treatment approaches under development should not harm the anticancer activity of cisplatin. Therefore, further studies are needed

to evaluate the effects of the kidney-protecting agents cisplatin on anticancer therapy in animals with cancer.

## **2. CONCLUSIONS**

Cisplatin is widely used in the treatment of various types of cancer, but its clinical use is limited due to its side effects. The most important side effect of cisplatin is nephrotoxicity. Many studies on this subject have tried to elucidate the cellular and molecular mechanisms of cisplatin nephrotoxicity. Cisplatin generally acts through many mechanisms such as DNA damage, mitochondrial dysfunction, oxidative stress, ERS, inflammation and apoptosis. More research is needed to determine the activation pathways of these mechanisms that cause severe renal damage and to determine the roles of critical molecules involved in cisplatin nephrotoxicity. Many potential therapeutic approaches for cisplatin nephrotoxicity have been tried to be described. The effects of these developed renoprotective approaches on the anticancer activity of cisplatin need to be comprehensively evaluated. Further studies on cisplatin nephrotoxicity will protect the kidney without reducing its chemotherapeutic efficacy.

### **Conflict of Interest**

The authors of the article declare that there is no conflict of interest.

### **Author Contributions**

The authors declare that they have contributed equally to the article.

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