Archives of Pharmaceutical Sciences Ain Shams University 2025; Vol. 9(1): 120-151

OPEN ACCESS

Clinical Pharmacy

Review Article

The Impact of Genetic Polymorphisms on Cisplatin-Induced Acute Kidney Injury: A Systematic Review

Israa G. A. Abdelbar[a*], Lamia M. El-Wakeel[b], Diaa Eldin M. Sherif[c], Amal A. Elkholy[b]

[a]*Department of Clinical Pharmacy Practice, Faculty of Pharmacy, The British University in Egypt, Cairo, Egypt*
[b]*Department of Clinical Pharmacy, Faculty of Pharmacy, Ain Shams University, Cairo, 11566, Egypt*
[c]*Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Ain Shams University, Cairo, Egypt*

ABSTRACT

Cisplatin is a widely used chemotherapeutic agent effective against various solid tumors, including testicular, ovarian, lung, and bladder cancers. However, its clinical use is often limited by dose-dependent toxicities, with nephrotoxicity being the most concerning side effect. Patients undergoing multiple cycles of cisplatin chemotherapy frequently experience a sustained subclinical reduction in glomerular filtration rate (GFR), which can lead to acute kidney injury (AKI) and negatively impact patient outcomes. According to recent research, genetic variability, specifically, single nucleotide polymorphisms (SNPs), may contribute to interindividual differences in susceptibility to cisplatin-induced nephrotoxicity. This review summarizes current research on SNPs across key genes implicated in cisplatin metabolism, transport, and detoxification processes. It examines the association between specific genetic variations and the incidence and severity of nephrotoxicity in patients undergoing cisplatin therapy. Understanding the intricate molecular pathways and genetic variations associated with cisplatin nephrotoxicity is essential to prevent this adverse effect and guide personalized cisplatin treatment approaches. Further research is essential to validate these SNPs as predictive markers and to explore their potential role in guiding tailored cisplatin therapies.

Keywords: *Cisplatin; Single-nucleotide polymorphism; Nephrotoxicity; Acute kidney injury; Pharmacogenomics*.

***Correspondence** | Israa G. A. Abdelbar; Department of Clinical Pharmacy Practice, Faculty of Pharmacy, The British University in Egypt, Cairo, Egypt. Email: israa.aly@bue.edu.eg

Citation | Abdelbar IGA, El-Wakeel LM, Sherif DM, Elkholy AA, 2025. The Impact of Genetic Polymorphisms on Cisplatin-Induced Acute Kidney Injury: A Systematic Review. Arch Pharm Sci ASU 9(1): 120-151
DOI: 10.21608/aps.2024.333177.1206
Print ISSN: 2356-8380. **Online ISSN**: 2356-8399.
Received 17 November 2024. **Accepted** 05 December 2024.

Published by: Ain Shams University, Faculty of Pharmacy

1. Introduction

Recent epidemiological studies have shown that nephrotoxicity is the third most common cause of acute kidney disease (AKD), raising serious clinical concerns. This rise is closely associated with the increasing use of various pharmaceuticals that can potentially harm renal function **[1]**. Drug-induced nephrotoxicity is responsible for a substantial proportion of acute kidney injury (AKI) cases in hospital settings, contributing to approximately 60% of all AKI occurrences. This condition is characterized by a rapid decline in the kidney's excretory function, leading to the accumulation of waste products from protein metabolism, such as urea, nitrogen, and creatinine **[2]**. As the incidence of drug-induced AKI continues to escalate, clinicians need to be aware of the risk factors for nephrotoxicity. These risk factors encompass urinary tract obstructions, polymorphic genetic variations, the concomitant use of nephrotoxic agents, intravascular hypovolemia, prior radiation therapy, and any pre-existing renal disease **[3]**.

Identifying patients at higher risk can be crucial in preventing or mitigating the severity of nephrotoxicity and its related adverse outcomes. Diagnostic criteria for AKI include an increase in serum creatinine (SCr) levels by at least 0.3 mg/dl (≥26.5 μmol/L) within 48 hours, a 1.5-fold increase from baseline within seven days, or oliguria lasting six hours or more. For AKD, a new glomerular filtration rate (GFR) lower than 60 mL/min/1.73 m² lasting not more than three months, a decline in GFR of at least thirty-five percent, or a more than fifty percent increase in SCr from baseline within three months are diagnostic indicators **[4, 5]**.

Kidneys are essential in eliminating a wide range of chemicals from the body, including chemotherapeutic agents. Chemotherapy-induced acute kidney injury is a complex condition that is not fully understood. It involves a combination of direct damage to the kidneys, changes in blood flow, and immune reactions. Chemotherapy does not only target cancer cells, but it can also harm the kidneys, leading to oxidative stress, inflammation, and damage to kidney cells. Acute tubular injury (ATI) is the primary cause of AKI in conventional chemotherapy; however, the mechanism of renal injury differs depending on the chemotherapeutic drug. Antimetabolites and antitumor antibiotics were found to be more likely to cause thrombotic microangiopathy (TMA), whereas interstitial nephritis occurs mostly in Oxaliplatin. Certain medications under study exhibit vasoconstriction, altered intraglomerular hemodynamics, and crystal deposition **[6]**. Among the numerous anticancer agents linked to nephrotoxicity, platinum-based chemotherapeutic agents play a pivotal role in treating various solid tumors **[7]**. Cisplatin is a first-generation platinum derivative that is very useful in treating several cancers, including lung, stomach, pancreatic, esophageal, and testicular cancers **[8]**. However, nephrotoxic side effects are frequent and affect between 28% to 36% of cisplatin-treated patients. In addition to temporary AKI, toxic consequences are linked to the advancement of CKD, which raises co-morbidity **[9, 10]**. Cisplatin exerts its antineoplastic effects by forming a crosslink with the DNA's purine nucleotides, which prevents cell division and encourages apoptosis **[6]**. However, its nephrotoxic effects stem from elevated concentrations causing renal inflammation, oxidative damage, and apoptosis **[6]**. Factors contributing to the risk of cisplatin-induced acute kidney injury (CIAKI) include the cumulative dose of cisplatin, prior exposure, baseline renal function, and concurrent health conditions such as diabetes and hypertension indicators **[4]**. Consequently, clinicians must prioritize effective management strategies to monitor and address potential nephrotoxic risks associated with cisplatin therapy, including appropriate hydration protocols, dosage adjustments, and careful patient selection.

Given the high incidence of nephrotoxicity and its serious implications for patient outcomes, this review aims to elucidate the mechanisms underlying drug-induced renal injury, particularly focusing on cisplatin's nephrotoxic profile, its clinical manifestations, risk factors, and the critical importance of careful monitoring in cancer patients undergoing cisplatin-based chemotherapy.

2. Materials and methods

This review comprised clinical studies, systematic reviews, and literature reviews. **Fig. 1** shows the article selection process. Medical subject headings (MeSH) were used to create a search technique that queried the MEDLINE and PubMed databases. The MeSH terms included cisplatin, kidney damage, genetic variants, DNA repair, cellular uptake, efflux transporters, and detoxification enzymes. We focused on studies published between 2009 and 2022, emphasizing

the most recent findings on the effects of genetic variants on cisplatin-related kidney impairment **(Table 1)**. The following requirements had to be met by all studies to be included: (1) genetic association studies; (2) cisplatin-containing treatment; (3) nephrotoxicity as an undesirable result (by any definition); (4) English-language publications; (5) research involving cancer patients. To find more research papers, the reference sections of the listed publications were also reviewed.

Table 1. Criteria for Inclusion in Search Strategy

Parameter	Criterion
Trials and studies	Studies on genetic associations that include cancer patients published in English
Protocol	Chemotherapy protocols based on cisplatin
Outcome	Any definition of nephrotoxicity
Setting	All healthcare settings

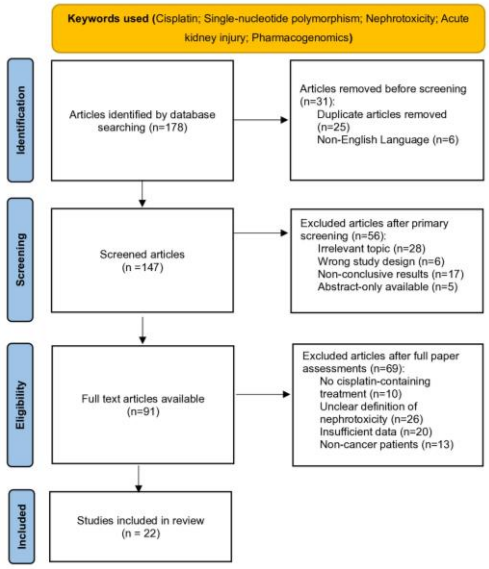

Fig. 1. Flowchart of the articles selection process. This flow diagram is created following PRISMA guidelines.

1. Results and Discussion

1.1. Nephrotoxicity

Epidemiological study indicates that nephrotoxicity, the third most common cause of AKD, has gotten worse recently because of a rise in the use of drugs that potentially harm the kidneys **[1]**. Around 1.7 million fatalities globally are attributed to AKI each year. AKI can also lead to end-stage renal disease (ESRD) and chronic kidney disease (CKD). As of right now, dialysis and supportive care are the only available therapy options **[11]**. Nephrotoxicity is caused by a rapid decline in the kidney's excretory function, which leads to the accumulation of waste products from protein metabolism, such as urea, nitrogen, and creatinine **[2]**. Various factors influence kidney function, including environmental, socioeconomic, and care-related factors, along with acute exposures and patient-specific conditions. Environmental factors such as poor hygiene, inadequate healthcare, and

infections have a major impact. Certain patient-related factors, like dehydration, nephrotoxic drugs, and radiation therapy are modifiable, while other factors are non-modifiable, like diabetes, chronic illnesses, genetic polymorphism, or inherited disorders. Other major risks include severe infections, sepsis, trauma, surgeries, hospitalization, chemotherapy, autoimmune disorders, and urinary obstructions **[5]**. One of the many factors that cause AKI is drug-induced nephrotoxicity, which affects around 25% of patients with AKI and is particularly common with chemotherapeutic drugs like cisplatin **[12, 13]**. This happens because of the kidneys' vital function in the removal of several chemical substances through tubular secretion and glomerular filtration, including antineoplastic drugs and their metabolites, which impact various segments of the nephron and its microvasculature **[6]**. Substances are typically transported by solute carrier (SLC) transporters either in the direction of or against their concentration gradients. Organic anion transporters (like OAT1 and OAT3), organic cation transporters (like OCT2), and multidrug and toxin extrusion proteins (MATE1) are examples of the vital multi-specific SLC transporters in the kidney **[14]**. Multidrug-Related Resistance Proteins 2 and 4 (MRP2 and MRP4) are the main ATP-Binding Cassette (ABC) transporter proteins, which use energy produced by ATP hydrolysis to move molecules across cell membranes **[15]**. Together, these efflux transporters, which are found in the apical membrane, and uptake transporters, which are found in the basolateral membrane, make up the paths of renal tubular secretion **[16]**. Consequently, this led to a range of clinical issues, including microvasculature, acute and chronic interstitial nephritis, glomerulopathy, proteinuria, hypertension, and electrolyte abnormalities. AKI, and potentially chronic kidney disease (CKD). Thus, drug-induced AKI has emerged as a prominent concern in clinical practice **[6]**. AKI is defined as an increase in SCr by at least 50% within 7 days, or an increase of more than or equal to 0.3 mg/dL (26.5 µmol/L) within 2 days, or oliguria lasting 6 hours or more. While AKD is identified as AKI, or a new GFR below 60 ml/min/1.73 m^2, or a GFR reduction of 35% or more from baseline, or an SCr increase exceeding 50% from baseline, lasting not more than three months **[5]**. Since AKI can be life-threatening, often requires kidney replacement therapy, particularly in critically ill patients with a poor prognosis. Furthermore, the long-term consequences of AKI and acute kidney disease (AKD), such as chronic kidney disease (CKD) and cardiovascular complications highlight the importance of early detection. Therefore, identifying patients at risk for nephrotoxicity is essential to prevent or minimize the severity and progression of AKI **[3]**.

1.2. Cisplatin

Platinum-based chemotherapeutic agents, including cisplatin, carboplatin, and oxaliplatin, play a crucial role in the treatment of various solid tumors **[17]**. In 1845, Michele Peyrone created cisplatin, the first-generation platinum-based anticancer medication, which was initially known as Peyrone's chloride **[8]**. In the 1960s, the cisplatin's cytotoxic effect was discovered by serendipity. Biophysicist Barnett Rosenberg noted that Escherichia coli bacteria changed from their usual short rod shape to long filaments when exposed to an electrical field generated by platinum electrodes. Once the electrical field's effect was ruled out, it was found that platinum compounds, including cisplatin, were responsible for inhibiting cell division and altering bacterial morphology **[7]**. Years later, Subsequent research demonstrated that these compounds had notable anticancer effects in tumor-bearing mice. Given the urgency and importance of this treatment, clinical trials were conducted promptly, leading

to the FDA's approval of cisplatin in the 1970s **[18]**. Its remarkable effectiveness, when used alone or in conjunction with other treatments, cisplatin has become the standard treatment for cancer, including non-small cell lung, stomach, esophageal, bladder, and head and neck malignancies **[19]**. This is largely due to its wide spectrum of anticancer effects, affordability, and strong clinical evidence supporting its use **[8]**. Cisplatinum or cis-diamminedichloroplatinum (II) are other names for the compound. Cisplatin ($Cl_2H_6N_2Pt$) has a square planar structure, with two chloride ions and two ammonia molecules acting as ligands, coordinated to a central platinum atom **[20]**. Its antineoplastic activity happens once it enters the cell, where it interacts with the N7 position of purine residues in DNA, creating interstrand and intra-strand crosslinks that irreversibly damage the DNA, as shown in **Fig. 2.** This disruption hinders DNA replication, preventing the division of rapidly proliferating cancer cells and inducing apoptosis **[21]**. Despite being widely used, cisplatin has several short- and long-term side effects including neurotoxicity, hepatotoxicity, gastrointestinal toxicity, retinal toxicity, ototoxicity, and nephrotoxicity **[22, 23]**. Among these, CIAKI is the most concerning dose-limiting side effect. Although cisplatin's effectiveness is dose-dependent, using greater dosages that could increase its antitumor impact is frequently restricted due to the substantial risk of nephrotoxicity. Furthermore, platinum may stay in cancer patients' plasma for up to 20 years after cisplatin-based chemotherapy is stopped **[24]**. Patients undergoing multiple cycles of cisplatin chemotherapy were shown to experience a sustained subclinical reduction in GFR **[24]**. Nearly 20% to 30% of patients undergoing cisplatin therapy experience kidney function deterioration, either shortly after treatment initiation or following multiple chemotherapy cycles, making this adverse effect a significant limitation in the use of cisplatin for cancer treatment **[25]**.

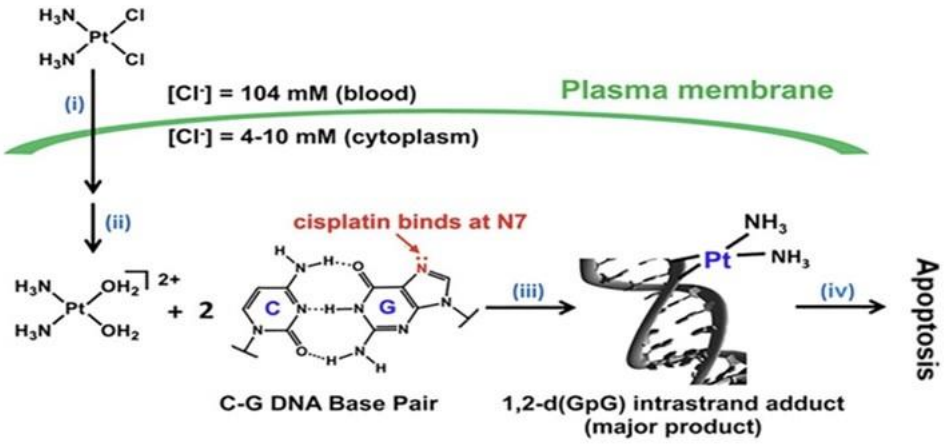

Fig. 2: Cisplatin Mechanism (i) Cellular uptake, (ii) Aquation/activation, (iii) DNA binding, and (iv) Cellular response leading to apoptosis **[92]**.

1.3. Cisplatin Nephrotoxicity

Cisplatin-induced nephrotoxicity (CIN) was first reported in 1971, with histopathological changes linked to acute tubular necrosis (ATN) and azotemia in mice. At that time, CIAKI was observed in 14 to 100% of patients treated, depending on the cumulative dose. But, with appropriate hydration and diuresis during

cisplatin treatment, the incidence has reduced to 20-30% **[25]**. Salt-wasting, glomerular filtration rate (GFR) decline, and acute kidney injury (AKI) are common indicators of CIN and can raise the risk of hypocalcemia and hypomagnesemia. Furthermore, AKI makes chronic kidney disease worse, which might result in fatal renal disease. Even with extensive electrolyte and hydration management after cisplatin delivery, avoiding cisplatin-induced AKI is still a major therapeutic challenge **[26]**. It takes around 2 days for the kidneys to eliminate up to 50% of cisplatin, with the intestines and bile excreting very little of the drug **[20]**. Research indicates that doses exceeding 50 mg/m² are more likely to cause CIAKI **[27]**, though clinically; AKI can develop even with low-dose cisplatin administration **[19]**. Elevated cisplatin concentrations have been found to directly induce renal inflammation, oxidative damage, apoptosis, and eventually renal toxicity coupled with changes in renal transport pathways **[20]**. The long-term impact of cisplatin on renal function is not completely understood, but it is believed that cisplatin administration can lead to either subclinical or permanent reductions in the GFR **[21]**. While cisplatin-induced nephrotoxicity can present in various forms, ATN is the most common manifestation. Even with better outcomes after stopping diuretics to encourage volume expansion and hydration, the occurrence of CIAKI remains significant.

Several risk factors for CIAKI in cancer patients have been well-established. These include cumulative dose, prior exposure to cisplatin, age, baseline eGFR, ECOG performance status (PS), coexisting conditions (such as diabetes, hypertension, and cardiovascular disease), concurrent medications, pre-hydration treatment, hypoalbuminemia, and magnesium supplementation **[4]**. Female sex and smoking were also mentioned among the risk factors for developing CIAKI. Investigations are currently ongoing to determine how diabetes affects the risk of AKI **[25]**.

Elevations in SCr levels and blood urea nitrogen (BUN), along with a decreased GFR, typically occur within 10 days of cisplatin treatment, indicating renal insufficiency **[21]**. Proximal tubular dysfunction may be evident through reduced urine output, glucosuria, and proteinuria. Additionally, hypomagnesemia and hypokalemia can signal kidney deterioration even when GFR remains normal after cisplatin administration. Proper hydration and dose adjustments for patients with preexisting renal impairment are crucial for preventing nephrotoxicity induced by cisplatin **[3]**.

1.4. Mechanism of cisplatin nephrotoxicity

Cisplatin is a neutral, low molecular weight compound that is freely filtered by the glomerulus and primarily excreted through urine. The toxic effects of cisplatin are triggered by its uptake into proximal tubular epithelial cells (PTEC). Cisplatin consists of a central platinum atom bonded to two chlorine atoms and two ammonia groups, forming a square planar structure. The two chlorine atoms are positioned on the same side of the molecule **[28]**. In the bloodstream, cisplatin remains resistant to hydrolysis because of the high concentration of chloride ions (around 100 mM) **(Fig. 2)**.

Cisplatin can enter the proximal tubule of the nephron through membrane transporters such as the organic cation transporter (OCT2) and the high-affinity copper transporter 1 (CTR1), which are located on the basolateral membrane of proximal tubule cells, leading to intracellular accumulation **[29] (Fig. 4)**. After entering the cells, water molecules take the place of the cisplatin's chloride ions to create an aquatic version. This hydrolyzed form is a potent electrophile that can react with a variety of

nucleophiles, such as nitrogen atoms in nucleic acids and sulfhydryl groups on proteins. Subsequently, DNA crosslinks form both within and across strands, preventing transcription and DNA replication **[30] (Fig. 2)**. As a result, cisplatin primarily targets proximal tubular epithelial cells (PTECs), and membrane transporters regulate how the drug passes through PTEC membranes GFR **[24]**. Cisplatin causes tubular damage and renal failure through a very complicated mechanism that involves many interconnected biomolecules and processes. Acute renal insufficiency due to tubular necrosis and fluid and electrolyte imbalances are frequently the outcomes of cisplatin-induced tubular toxicity, which is mostly caused by direct damage to epithelial cells, as illustrated in **Fig. 3**. Additionally, cisplatin causes tubular cells to produce more TNF-α, which triggers a potent inflammatory response that exacerbates cell damage and death. Cisplatin can also harm renal blood vessels, which lowers GFR by triggering ischemia cell death in the tubules **[21]**. Besides, cisplatin causes glomerular injury, which, while less frequent compared to other nephropathies, can lead to proteinuria, hematuria, nephrotic syndrome, and/or edema. Finally, it also led to interstitial injury, particularly with chronic use of cisplatin, where fibrosis represents the signs of chronic kidney disease. This can potentially progress to CKD **[31]**. These combined effects result in acute kidney failure.

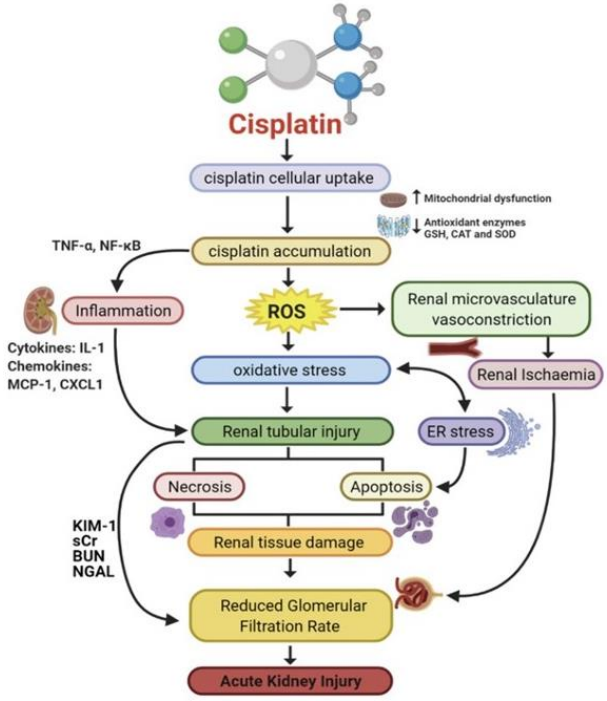

Fig. 3. Pathophysiological Pathways in Acute Kidney Injury Caused by Cisplatin: Mechanisms of Nephrotoxicity and Inflammatory Response.

In this figure, the complexity of the mechanisms contributing to CIAKI is highlighted, particularly the effect of platinum buildup in renal tissue. This build-up is associated with elevated levels of tumor necrosis factor-alpha (TNF-α) and reactive oxygen species (ROS), which together stimulate inflammatory responses, oxidative stress, vascular damage, and apoptotic pathways. These apoptotic mechanisms contribute to renal tissue injury, culminating in the clinical manifestation of nephrotoxicity characterized by a reduction in glomerular filtration rate (GFR). Key abbreviations used in the figure include GSH (glutathione), CAT (catalase), SOD (superoxide dismutase), TNF-α (tumor necrosis factor-alpha), ROS (reactive oxygen species), ER stress (endoplasmic reticulum stress), IL-1 (interleukin 1), MCP-1 (monocyte chemoattractant protein 1), CXCL1 (C-X-C motif chemokine ligand 1), KIM-1 (kidney injury molecule 1), SCr (serum creatinine), BUN (blood urea nitrogen), and NGAL (neutrophil gelatinase-associated lipocalin) **[19]**.

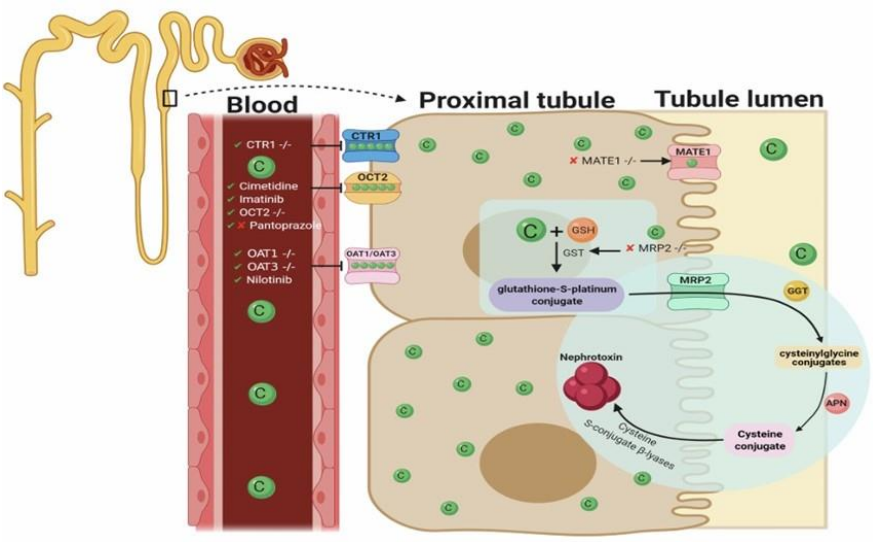

Fig. 4: Cisplatin Transport Mechanisms and Therapeutic Interventions Targeting Nephrotoxicity in Proximal Tubule Epithelial Cells (PTECs).

The figure illustrates essential transporters that facilitate the cisplatin uptake from blood into PTECs, resulting in higher platinum concentrations within these cells compared to blood levels. It highlights various interventions that have been trialed for mitigating cisplatin-induced acute kidney injury (CIAKI) and evaluates their effectiveness. Furthermore, the figure shows the cellular processes that lead to the absorption, efflux, and metabolic conversion of cisplatin into a reactive thiol molecule, all of which contribute to nephrotoxicity. Important chemicals and pathways linked to these processes are cited in the literature **[19]**.

An elevated risk of nephrotoxicity has been associated with variations in genes linked to organic transporter proteins, DNA-repairing enzymes, tumor suppression genes, and the metabolic enzymes that detoxify platinum. Currently, there is no comprehensive list of all the genetic variations that are consistently connected to cisplatin-based chemotherapy-induced nephrotoxicity, even though several genetic variations have been reported to influence cisplatin-induced nephrotoxicity in cancer patients. The objective of our review article was to determine which genetic variations in cancer patients were consistently linked to cisplatin-induced nephrotoxicity and to assess the clinical value of these variants in directing cisplatin treatment **(Table 2)**.

Table 2. Pharmacogenetic Studies of Cisplatin-Induced Renal Damage

RFID	Study, Publication year, Country	Subjects	Chemotherapy protocol	Nephrotoxicity definition	Outcomes	Ref.
OCT2 (SLC22A2)						
rs316019	Filipski et al., 2009, Netherland.	Not specified, malignant solid tumors	Cisplatin-based protocols	Serum creatinine variations following the first cycle.	Following cisplatin treatment, there was no change in serum creatinine in patients having a copy of this SNP (n=10; 13%) (p=	**[32]**

		patients.			0.12). On the other hand, patients with the wild-type genotype had significantly higher serum creatinine levels (n= 68; p= 0.0009).	
rs316019	Iwata et al., 2012, Japan.	53 patients with advanced cancer, ages ranging from 68.0±9.7 years.	Cisplatin-based regimens, dose 60–80 mg/m^2.	The Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 criteria was used to calculate the toxicity grade.	The OCT2 gene's genetic polymorphism (SNP rs316019) seemed to offer protection against kidney damage brought on by cisplatin. While no significant difference was found in other metrics including eGFR and BUN, the differences between SCr wildtype GG and GT were 0.34±0.12 vs. 0.34±0.33, P= 0.04.	**[33]**
rs316019	Zhang et al., 2012, China.	123 patients with malignant solid tumors at any stage, ages ranging from 54.62±10.	Cisplatin monotherapy or cisplatin is given with docetaxel and etoposide.	Changes in BUN, cystatin C, and SCr, are indicators of renal function.	Changes in BUN and SCr levels did not significantly differ across the groups based on genotypes (P > 0.05). However, patients with the mutant genotype (GT/TT) showed a smaller increase in cystatin C levels compared to those with the wild genotype (GG) (P < 0.05). Among cisplatin patients not treated with cimetidine, the increase in cystatin C levels was significantly smaller for those with the mutant genotype (GT/TT) than for those with the wild genotype (GG) (P = 0.043). Thus, The SLC22A2 gene mutation (808G/T) may reduce cisplatin-induced nephrotoxicity.	**[34]**
rs316019	Hinai et al., 2013, Japan.	95 patients with esophageal cancer Stage II-IV.	5-fluorouracil and cisplatin.	(Pre-chemotherapy value - post-chemotherapy value) / Pre-chemotherapy value is the eGFR change rate.	Patients with the SLC22A2 808GG genotype (n = 70) and those with the 808GT+TT genotype (n = 25) had mean change rates of eGFR following FP chemotherapy of 27.9% and 27.8%, respectively, with no significant difference.	**[35]**
rs316019	Tzvetkov et al., 2011, Germany.	79 patients with various late-stage cancers, age range (22–76).	Cisplatin-containing chemotherapy.	NCI-CTCAE (version unspecified) divided patients into those in grade 0 and those in grade 1. Before and three to eight days after cisplatin treatment, serum creatinine and cystatin C levels were measured. Nephrotoxicity was	The surrogate markers serum creatinine and cystatin C, as well as the cisplatin-induced decline in eGFR, were not significantly affected by the polymorphism.	**[36]**

				determined by calculating the relative decrease in eGFR.		
rs316019	Zazuli et al., 2019, Canada.	282 patients with testicular-cancer patients, age>17.	100 mg/m^2 cisplatin per cycle	Adjusted Acute Kidney Injury, CTCAE-AKI grading, SCr and eGFR	An elevated incidence of cisplatin nephrotoxicity was associated with the presence of allele A at SLC22A2 rs316019 (adjusted OR = 4.41; 95% CI: 1.96–9.88; p < 0.001). Furthermore, compared to the CC genotype, the AC genotype was linked to an even higher risk (adjusted OR = 5.06; 95% CI: 1.69–15.16; p = 0.004)	**[37]**
rs316019	Khrunin et al., 2010, Russia.	104-woman patient with epithelial ovarian cancer, aged 23–65.	Cisplatin, 100 mg/m^2 + cyclophosphamide, 600 mg/m^2 for 3 weeks each, including anti emetic drugs (dexamethasone + blockers of 5HT3 receptors) and water load. 6 cycles	Nephrotoxicity, defined as a drop in creatinine clearance to less than 60 milliliters per minute, was one of the most used markers for cisplatin dosage reduction.	The fact that ovarian cancer patients' cisplatin-induced nephrotoxicity did not correlate with genetic differences in OCT2 implies that the function of these genes in cisplatin metabolism is more complicated than theoretical models have suggested.	**[38]**
rs316019	Oda et al., 2020, Japan.	28 Patients	cisplatin (≥50 mg/m^2) -containing chemotherapy	Relationships with AKI (CTCAE v4.0), impact the average deviations from the baseline eGFR following the first chemotherapy cycle.	The OCT2 rs316019 variant, previously linked to renal injury, showed no association with CIAKI (P= 0.667). Other OCT2 gene variants also lacked any association with AKI.	**[39]**
rs316019, rs596881, rs312757 rs227946	Chang et al., 2017, USA.	206 patients with various types of cancer, Age group: 53 ± 14 years.	Various cisplatin-based combination	alterations in the protein biomarkers (such as albumin, B2M, cystatin C, NGAL, osteopontin, TFF3, calbindin, clusterin, KIM-1, GST-pi, IL-18, and MCP-1)	1. Patients with the wild-type CC genotype of the SLC22A2 polymorphism rs596881 maintained their eGFR levels, while those with the CT genotype improved their eGFR (p=0.01). Furthermore, compared to individuals with the wild-type CC genotype, those with the CT genotype in the SLC22A2 mutation rs596881 showed a substantial rise in osteopontin and a decrease in beta-2-microglobulin (B2M) on Day 3 following cisplatin treatment. 2. Urinary fold increases in KIM-1 were greater in those with the AC genotype for the SLC22A2 rs316019 polymorphism at baseline	**[27]**

					(p = 0.02), Day 3 (p = 0.03), and Day 10 (p = 0.046) than in those with the wild-type CC genotype. 3. The SLC22A2 mutations rs3127573 and rs2279463 are linked to higher beta-2-microglobulin (B2M) levels on Day 3 following cisplatin therapy. Increased OCT2 activity has also been connected to the rs3127573 variation, which could affect cisplatin toxicity and absorption.	
CTR1						
rs12686377 rs7851395	Chang et al., 2017, USA.	206 patients with various types of cancer, Age group 53 ± 14 years.	Various cisplatin-based combination	alterations in the protein biomarkers (such as albumin, B2M, cystatin C, NGAL, osteopontin, TFF3, calbindin, clusterin, KIM-1, GST-pi, IL-18, and MCP-1)	In contrast to those that possess the wildtype genotypes AA (rs12686377) and CC (rs7851395), respectively, patients with the GG (rs12686377) and AA (rs7851395) variant genotypes showed improvements in eGFR. Additionally, on Day 3 following cisplatin therapy, patients with the GG variation in rs7851395 showed elevated urine osteopontin levels. Although this may signal early kidney impairment, the overall improvement in eGFR shows that these variants could have a protective effect on kidney health.	**[27]**
rs10981694	Xiaojing Xu et al., 2012, China.	204 patients with NSCLC patients.	Cisplatin-based regimens.	two cycles of platinum-based chemotherapy, Intravenous cisplatin (100 mg/m^2)	The rs10981694 polymorphism and nephrotoxicity did not significantly correlate.	**[40]**
MATE						
rs2289669	Iwata et al., 2012, Japan.	53 patients with a variety of advanced cancers, Ages ranging from 68.0±9.7 years.	Cisplatin-based regimens, dose 60–80 mg/m^2.	CTCAE version 4.0 criteria were used to calculate the toxicity grade.	rs2289669 polymorphism did not significantly affect cisplatin toxicity	**[33]**
rs2289669	Chang et al., 2017, USA.	206 patients with various types of cancer, Age group: 53 ± 14 years.	Various cisplatin-based combination	alterations in the protein biomarkers (such as albumin, B2M, cystatin C, NGAL, osteopontin, TFF3, calbindin, clusterin, KIM-1, GST-	The urine biomarkers KIM-1 and MCP-1 were shown to be considerably elevated in response to polymorphisms in the SLC47A1/MATE1 rs2289669 variation.	**[27]**

				pi, IL-18, and MCP-1)		
MRP (ABCC2)						
rs3740066 rs717620 rs2273697	Chang et al., 2017, USA.	206 patients with various types of cancer, Age group: 53 ± 14 years.	Various cisplatin-based combination	alterations in the protein biomarkers (such as albumin, B2M, cystatin C, NGAL, osteopontin, TFF3, calbindin, clusterin, KIM-1, GST-pi, IL-18, and MCP-1)	Following cisplatin treatment, Patients carrying the ABCC2 rs2273697 mutation showed statistically significant increases in KIM 1 at baseline (p = 0.02), Day 3 (p = 0.03), and Day 10 (p = 0.046). The ABCC2 variant rs3740066 was specifically associated with a substantial rise in the amounts of calbindin, clusterin, cystatin C, and NGAL in urine. Clusterin and cystatin C levels were likewise greater in patients with the CT genotype for the rs717620 ABCC2 variation than in those with the wildtype CC genotype. A small number of patients with homozygous genotypes for rs3740066 or rs717620, however, did not exhibit any meaningful correlations.	**[27]**
7 SNPS, not mentioned	Sprowl et al., 2012, the country not mentioned.	112 patients.	Several cisplatin-based treatment plans	Variations in SCr.	None of the common genotypes were significantly correlated with changes in serum creatinine levels.	**[41]**
ERCC1						
rs11615	Chen et al., 2010, China.	95 patients with advanced NSCLC (stages IIIB–IV), median age 58.	Cisplatin+gemcitabine Cisplatin+vinorelbine Cisplatin+taxane	WHO toxicity criteria (1979).	P > 0.05 revealed no significant correlation between the risk of nephrotoxicity and the ERCC1 gene polymorphism rs11615.	**[42]**
rs3212986	Zazuli et al., 2021, Canada.	The sensitivity cohort of 608 patients & validation cohort of 149 patients, Aged>18	(75 mg/m2) cisplatin single or in combination	eGFR	A higher risk of cisplatin-induced nephrotoxicity was linked to the rs3212986 mutation in the 3' UTR of ERCC1, as observed in a validation cohort for non-small cell lung cancer (NSCLC).	**[43]**
rs11615 rs3212986	Khrunin et al., 2010, Russia.	104 Russian women, with epithelial ovarian cancer (stages I–IV)	Cisplatin+cyclophosphamide	NCI-CTCAE (no version specified). Divided into grade 0 and ≥1 groups.	Patients with the heterozygous T/C genotype at rs11615 (46.7%; OR = 2.51, 95% CI: 1.09–5.57, p = 0.037) and heterozygous C/A genotype at rs3212986 (52.8%; OR = 3.29, 95% CI: 1.40–7.73, p = 0.009) of the ERCC1 gene were more likely to experience cases of renal dysfunction than patients with homozygous	**[38]**

					variants.	
rs3212986 rs11615	Tzvetkov et al., 2011, Germany.	79 Caucasian patients with a range of late-stage malignancies, ages 22 to 76	Cisplatin-containing chemotherapy.	Serum creatinine, cystatin C, and NCI-CTCAE (version unidentified) levels were measured before and three to eight days following cisplatin treatment. Nephrotoxicity was measured by the relative change in eGFR.	The cisplatin-induced nephrotoxicity was not observed in homozygous carriers of the rare A allele of the 8092C>A ERCC1 gene polymorphism (rs3212986), with a mean change in eGFR of AA = 24 ± 3.4 ml/min/1.73 m², CA = −10.2 ± 2.6 ml/min/1.73 m², and CC = −12.6 ± 2.5 ml/min/1.73 m² (P = 0.0002). The Asn118Asn ERCC1 gene polymorphism's homozygous carriers, who had mean changes in eGFR of CC = 6.91 ± 9.1 ml/min/1.73 m², CT = −11.8 ± 1.7 ml/min/1.73 m², and TT = −12.8 ± 4.2 ml/min/1.73 m² (P = 0.004), also demonstrated protection against cisplatin-induced nephrotoxicity.	**[36]**
rs3212986	KimCurran et al., 2011, China.	300 patients with NSCLC, median age of 60 years.	Cisplatin-based regimen	Grade 0 against Grades 1–4 on the NCI-CTCAE v3.0	The polymorphism and nephrotoxicity were not significantly correlated (p = 0.311).	**[44]**
rs11615 rs3212986	Erculj et al., 2012, Slovenia.	113 patients, median age 60 years.	Cisplatin-based regimen	NCI-CTCAEv2.0Grade0vs. Grade1–4	None of the polymorphisms studied had any effect on the occurrence of nephrotoxicity.	**[45]**
rs3212986 rs11615	Windsor et al., 2012, UK.	50 patients with Osteosarcoma , older than 16 years old.	MAP	Version 3.0 of NCI-CTCAE divided into grade 0 and grade 1–4 groups	The incidence of nephrotoxicity was unaffected by any of the SNPs that were investigated.	**[46]**
XPD (ERCC2)						
rs13181 rs1799793	Powrozek et al., 2016, Poland.	55 Caucasian patients with locally progressed, advanced NSCLC (IIIB and IV), ages ranging from 51–77 years.	The combination of vinorelbine and platinum compounds	NCI-CTCAE v4.03	The risk of early severe nephrotoxicity (after the 2nd chemotherapy cycle) was significantly lower in carriers of the C allele of the XPD gene (rs13181, 2251A > C, OR = 0.07, 95% CI 0.02–0.31, P < 0.0001) compared to those with the A allele. Similarly, the risk of severe nephrotoxicity after the 4th cycle was significantly lower in carriers of the C allele (rs13181, 2251A > C, OR = 0.24, 95% CI 0.07–0.81, P = 0.017) and the A allele (rs1799793, 934G > A, OR = 0.26, 95% CI 0.07–0.90, P = 0.029) of the XPD gene, compared to patients with the A or G allele.	**[47]**

rs13181 rs1799787 rs238405 rs238415 rs238416 rs3916874 rs50871 rs50872	Kim et al., 2012, South Korea.	129 Korean patients with unresectable NSCLC stage III-IV, age median: 63 years.	Cisplatin and carboplatin-based regimens	Not specified, using a grade range of 0 to 4. divided into grades 0–2 and grades 3–4.	Nephrotoxicity and infection were substantially correlated with rs238405 ($p < 0.05$). Significant correlations were also discovered between rs238416 and nephrotoxicity and asthenia ($p < 0.05$) and between rs238415 and nephrotoxicity ($p < 0.05$).	**[48]**
rs13181	Windsor et al., 2012, UK.	50 Patients with osteosarcoma, aged >16 years.	MAP	Version 3.0 of NCI-CTCAE divided into grade 0 and grade 1–4 groups.	ERCC2 p.Lys751Gln (rs13181) c.2251A>C: When comparing the genotypes AC/CC to AA, the OR was 4.4 (95% CI: 1–18.8, P = 0.044), and the GFR decreased by 23 mL/min/1.73 m^2 as opposed to 4 mL/min/1.73 m^2 ($p < 0.05$).	**[46]**
rs1799793 rs13181	Erculj et al., 2012, Slovenia.	113 patients with an average age of 60.	Cisplatin-based regimen	NCI-CTCAEv2.0Grade0vs. Grade1–4	None of the polymorphisms studied had any effect on the occurrence of nephrotoxicity.	**[45]**
rs1799793 rs13181	Goekkurt et al., 2009, Germany.	63 Patients with advanced gastric cancer (AGC), mean age 64 years.	FLP protocol (fluorouracil-leucovorin-cisplatin)	A 0–4 grading system was applied, and the grades were divided into groups of 0–2 and 3–4.	Significant associations were observed between the XPD-Asn312Gln and XPD-Lys751Gln (rs1799793-rs13181) haplotype and nephrotoxicity, with an odds ratio of 2.27 (95% CI: 1.28–4.0, P = 0.005).	**[49]**
GGT						
rs2236626 rs5751901	Khrunin et al., 2010, Russia	104-woman patient, aged 23–65 with epithelial ovarian cancer	Cisplatin, 100 mg/m2 + cyclophos phamide, 600 mg/m2 for 3 weeks each, including anti-emetic drugs (dexamethasone + blockers of 5HT3 receptors) and water load. 6 cycles	Nephrotoxicity, defined as a drop in creatinine clearance to less than 60 milliliters per minute, was one of the most utilized markers for cisplatin dosage reduction.	Patients with the homozygous GGT1 T/T genotype (rs5751901) had a higher risk of nephrotoxicity.	**[50]**
GSTP1						
rs1695	Chang et al., 2017, USA.	206 patients with various types of cancer, Age range of 53 ± 14 years.	Various cisplatin-based combination	alterations in the protein biomarkers (such as albumin, B2M, cystatin C, NGAL, osteopontin, TFF3, calbindin, clusterin, KIM-1, GST-pi, IL-18, and MCP-1)	Significant correlations were found between GSTP1 polymorphisms and elevated urine excretion of novel AKI biomarkers, namely KIM-1, NGAL, IL, and calbindin.	**[27]**

BACH2						
rs4388268	Zazuli et al., 2021, Canada.	Sensitivity cohort of 608 patients & validation cohort of 149 patients, with head and neck and esophageal cancer, Aged>18.	(75 mg/m2) cisplatin single or in combination	eGFR	BACH2 rs4388268 was associated with a decreased eGFR in the discovery cohort, showing a genome-wide significant association (β = -8.4, 95% CI -11.4 to -5.4, $p = 3.9 \times 10^{-8}$). It was also linked to a higher risk of AKI-CTCAE, with a suggestive association (OR = 3.9, 95% CI 2.3–6.7, $p = 7.4 \times 10^{-7}$). BACH2 was further tested in the validation cohort. Although no statistically significant association was confirmed, the BACH2 rs4388268 variant showed a similar trend to that observed in the discovery cohort for both AKI-CTCAE (OR = 1.7, 95% CI 0.8–3.5) and eGFR outcomes (β = -1.5, 95% CI -5.3 to 2.4; Table 4).	**[43]**
rs4388268	Klumpers et al., 2022, Netherland.	249 patients, including 102 adults with head-neck tumors and 147 children with brain tumors.	Cisplatin and/or carboplatin	AKI-CTCAE and eGFR.	With a p-value of 0.443, the BACH2 variant rs4388268 did not show any correlation with the drop in eGFR in the study's cohort.	**[51]**

2.1. Genetic polymorphisms associated with cisplatin-induced nephrotoxicity

2.1.1. Organic Cation Transporters (OCT)

Organic cation drugs, which account for 40% of medications with a net positive charge at biological pH, often rely on organic cation transporters (OCTs) to cross cell membranes due to their hydrophilic nature **[52]**. The Solute carrier 2, member 22 (SLC22A2) family genes include three isoforms, OCT1, OCT2 and OCT3. These isoforms share structure and function similarities but differ in their location among the tissues. OCT1 and OCT2 are highly expressed in the kidney tissues of rodents. While in humans, OCT1 is primarily found in the liver as opposed to other tissues, this explains the absence of an association between OCT1 and cisplatin nephrotoxicity **[19]**. Human OCT3 is highly distributed among different tissues including skeletal muscles, the adrenal gland, the heart, salivary glands, and the placenta. However, their distribution within the kidney tissues is minimal showing a weak correlation between OCT3 and CIAKI **[19]**. On the contrary, it has been reported that 30% of the CIAKI are directly influenced by OCT2. This can be explained by the kidneys' high OCT2 expression in contrast to OCT1 and OCT3 **[19]**. Illustrated in **Fig. 4**, OCT2 is mostly found on the renal basolateral membrane mediating the cisplatin cellular uptake into the proximal tubule cells causing cisplatin accumulation. Transfected hOCT2 embryonic kidney (HEK293) cells provided the first proof of

cisplatin transport by human OCT2 (hOCT2). When compared to wild-type HEK293 cells, hOCT2 expression was linked to higher cisplatin accumulation **[53]**.

A natural substance called wedelolactone inhibits OCT2 and has been shown to decrease cisplatin-induced nephrotoxicity by blocking OCT2 activity in HEK293 cells **[54]**. Furthermore, it has been demonstrated that cimetidine, another OCT2 inhibitor, can decrease the nephrotoxicity caused by cisplatin in wild-type mice to a degree similar to that seen in OCT1/2 (-/-) animals given cisplatin **[55, 56] (Fig. 4)**. A recent study found that L-tetrahydropalmatine (L-THP) selectively inhibits OCT2, reducing cisplatin accumulation and alleviating cisplatin-induced cytotoxicity in human primary renal tubular cells **[57]**. In addition, Liraglutide and/or rabeprazole treatment before cisplatin preserved kidney function and shape by significantly inhibiting OCT2 and reducing cisplatin renal absorption **[58]**. This implies that protection against cisplatin-induced nephrotoxicity may be provided by reduced activity of the kidney's cisplatin uptake transporters **[59]**. Kidneys retain more cisplatin than other organs, with the proximal tubules being the renal structures most damaged. These tubules are also the primary sites of OCT2 expression. Subsequently, this cisplatin aggregation among the tubular cells will increase the cytotoxic potency of cisplatin, including mitochondrial and nuclear DNA destruction, as well as reactive oxygen species production, which activates apoptosis and necrosis pathways **[25] (Fig. 3)**. The unique localization of OCT2 in the kidney tissue makes it an important target for studying platinum-induced nephrotoxicity. Consequently, researchers have focused on how missense mutation in OCT2 would influence the cisplatin effect on kidneys **[20]**.

An investigation using mice by Filipski et al. observed that OCT1/2 (-/-) mice had a reduced cisplatin excretion in comparison with the wildtype, which validates that OCT2 is important in the cisplatin renal excretion. Additionally, Filipski et al. discovered that cisplatin-treated wild-type mice developed dilated tubules that contained protein clumps, cellular debris, and dead tubular cells. The glomeruli, which do not express Oct1 or Oct2, seemed to be unaffected, though. However, after receiving cisplatin, OCT1/2 (-/-) mice did not exhibit any renal injury **[32]**. This was verified in human studies that showed increased SCr post cisplatin treatment for those demonstrating a wild GG genotype of rs316019 than those with the GT variant ($P<0.05$) **[32]**. Matching results were presented in a study by Zhang et al. where wildtype GG carriers developed elevated cystatin C than mutant (GT/TT) Carriers ($P= 0.0009$), but changes of SCr and BUN demonstrated no significant variations **[34]**. Additionally, in research by Tzvetkov et al., BUN and eGFR were likewise elevated in patients with the GG wild genotype, however, this did not achieve statistical significance **[36]**. Another study conducted on American Caucasian patients by Chang et al. reported that at day three after cisplatin administration, patients with the AC genotype had higher levels of kidney injury molecule-1 (KIM-1), in contrast to the wild type **[27]**. Similarly, Zazuli et al. observed that an elevated risk of cisplatin nephrotoxicity was connected to the presence of allele A at SLC22A2 rs316019 **[37]**. Another three studies found no correlation between rs316019 and cisplatin nephrotoxicity, but these studies were underpowered and involved various cancer types **[35, 39, 50]**. Furthermore, Chang et al. evaluated the SLC22A2 polymorphism rs596881, rs312757, and rs227946 and found that patients with the rs596881 CT genotype exhibited eGFR significant improvements in contrast to those who possess the wild-type CC genotype ($p =$

0.01) **[27]**. This discovery raises the possibility that rs596881 polymorphism is connected to renal function preservation and protection against cisplatin-induced nephrotoxicity. Besides, SLC22A2 variants rs3127573 and rs2279463 are associated with higher levels of β2-microglobulin (B2M) three days after cisplatin treatment. Furthermore, the rs3127573 variant is connected to increased OCT2 activity, potentially affecting cisplatin uptake and toxicity **[36, 38]**. It's interesting to note that mice deficient in the ortholog genes OCT1 (SlC22A1) and OCT2 (SlC22A2) only partially display renal tubular damage linked to cisplatin, indicating that cisplatin-induced kidney damage involves a separate mechanism that operates independently of Oct1/Oct2-mediated drug uptake **[60]**.

2.1.2. Copper Transporters (CTR)

The primary plasma membrane transporter has been identified as the copper transporter family. ATPase, Cu2+ transporting beta polypeptide (ATP7B), copper-transporting ATPase 1 (ATP7A), copper transporter 1 (CTR1), sometimes referred to as solute carrier family 31, member 1 (SLC31A1), copper transporter 2, and solute carrier family 31, member 2 (SLC31A2) are all members of this family **[61]**. Copper transporters are essential for promoting cisplatin's cellular absorption. CTR1 plays a role in copper ion transport. Nevertheless, it also demonstrated a strong affinity for cisplatin. Through an enhanced diffusion process, cisplatin reaches the cell via CTR1-mediated transport **[62]**. CTR1 performs a crucial physiological function by providing copper to the cells, an important nutrient necessary for a wide array of enzymatic reactions. Cisplatin binds to the methionine-rich extracellular domain of CTR1, just like Cu^{+} does. Since CTR1 is localized on the basolateral side of both proximal and distal tubular cells in the kidney, it is involved in the accumulation of cisplatin in the kidney, as demonstrated in mice **[63] (Fig. 4)**. Studies conducted in vitro as well as in vivo have confirmed this **[61]**. For example, mouse cell lines with one or both copies of the CTR1 gene alleles absent exhibited less cisplatin accumulation and increased resistance to cisplatin. These results imply that CTR1 functions as a cisplatin transporter in mouse cells, and an analogous function is probably played by the human form of CTR1 (hCtr1), which is 92% identical to the mouse form of CTR1 (mCtr1). Therefore, lowering CTR1 expression in healthy cells might provide a means of minimizing nephrotoxicity brought on by cisplatin **[64]**. The presence of CTR1 primarily on the basolateral side of the proximal and distal tubules was confirmed by another investigation by Pablo et al. additionally, cisplatin absorption in renal tubular cells was reduced and cisplatin-induced renal cell death was prevented by CTR1 knockdown using small interfering (si) RNA **[65]**. Furthermore, Nieskens et al. explored the significance of influx transporters in cisplatin-induced toxicity by treating ciPTEC-parent cells with cisplatin and the CTR1 substrate ($CuSO_4$) for 24 h. Cisplatin toxicity was considerably decreased by the copper substrate, indicating that CTR1 is essential for cisplatin absorption and contributes to its nephrotoxicity. According to this research, blocking CTR1 may lessen the negative effects of cisplatin on the kidneys **[66]**.

Limited studies have explored the correlation between genetic polymorphisms in CTR1 and CIAKI. Research by Xu et al. found the absence of a correlation between rs10981694 polymorphism in CTR1 and cisplatin nephrotoxicity **[40]**. While another study examined two more specific polymorphisms, CTR1 rs12686377 and rs7851395, and revealed GG genotype patients (rs12686377) and AA genotype (rs7851395) experienced significant improvements in eGFR ($p = 0.01$ and $p = 0.04$)

relative to those with the wild-type genotypes (AA and CC, respectively). Additionally, patients with these variants showed increased levels of a urinary biomarker, osteopontin, at Day 3 post-treatment. While this might suggest initial kidney injury, the overall positive effect on eGFR indicates that these variants may serve a protective function in kidney health **[27]**. While inhibiting CTR1 seems to offer protection against cisplatin-induced nephrotoxicity, it may also compromise the drug's anticancer effectiveness. Since CTR1 is crucial for cisplatin uptake in tumor cells, there is concern that targeting this transporter to protect the kidneys could unintentionally reduce cisplatin's anti-tumor activity **[59, 67]**.

Complete loss of CTR1 expression caused only a 31% reduction in whole-cell copper accumulation after 1 hour, suggesting the existence of an additional pathway for copper uptake beyond CTR1. CTR2 shares a similar structure with CTR1 and is primarily located in late endosomes and lysosomes **[68]**. Research conducted on CTR2-deficient mice indicates that CTR2 stabilizes the cleaved version of CTR1, which lacks metal-binding methionine and histidine motifs, reducing the uptake of copper and cisplatin. This shows that CTR2 indirectly controls intracellular distribution and copper uptake **[69]**. High CTR2 expression has been linked to resistance to cisplatin's cytotoxic effects **[68]**, while CTR2 knockdown increases cisplatin accumulation and toxicity **[68, 70]**. Independent of CTR1 expression, CTR2 knockdown increased whole-cell platinum accumulation and DNA adduct formation by 2.1–3.5 times. The spike in cytotoxicity was accompanied by an increase in platinum accumulation and DNA adduct formation, suggesting that increased accumulation was directly linked to the hypersensitivity brought on by CTR2 deletion **[68]**.

While CTR1 and CTR2 are involved in the uptake of copper into the cell, the cellular efflux of copper is facilitated by the two P-types ATPases, ATP7A and ATP7B **[70]**. Both P-type ATPases, ATP7A and ATP7B, are copper-transporting proteins that exhibit structural and functional similarities. ATP7A is expressed in most tissues except the liver, whereas ATP7B is predominantly found in the liver, with additional expression in the kidneys, placenta, and lower levels in the brain, heart, and lungs **[71]**. Most studies focused on the copper efflux transporters' effect on cisplatin resistance showing that overexpression of ATP7A and ATP7B leads to tumor resistance to cisplatin. This can be attributed to their action in increasing the cisplatin efflux from the cells **[67]**. Given the copper transporter’s role in cisplatin cellular accumulation, Studies are needed to investigate whether mutation in these transporters may influence cisplatin-induced nephrotoxicity.

2.1.3. Organic Anion Transporters (OAT)

The most abundant organic anion transporters in the kidneys are OAT1 (SLC22A6) and OAT3 (Slc22a8). OAT1 and OAT3 are found at the proximal tubules' basolateral membrane and are crucial for the removal of organic anions, such as endogenous uremic toxins and various medications **[15] (Fig. 4)**. The secretion of organic anions occurs through unidirectional transcellular transport, involving the uptake of organic anion compounds from the blood across the basolateral membrane and their subsequent exit across the brush border membrane into the luminal fluid **[72]**. According to research on rodents, OAT1 is widely distributed in the basolateral plasma membrane of the proximal tubules' S2 segment. OAT3, on the other hand, is dispersed throughout the body, originating from the proximal tubule and stretching into the connecting tubules, the cortical and medullary parts of the collecting system, and

the cortical and medullary thick ascending limb of Henle's loop **[72]**. In contrast to control cells, a rodent investigation showed that cells overexpressing the transporters OAT1 and OAT3 promote the formation of a nephrotoxic mercapturic acid metabolite of cisplatin (NAC-1) **[60]**. The kidneys produce NAC-1 by a sequence of enzymatic processes that include the conjugation of cisplatin and glutathione. Following its entry into kidney cells by OAT1 and OAT3, it undergoes further metabolism to produce a highly reactive thiol that damages renal cells. Reduced cisplatin-induced nephrotoxicity may result from blocking the enzymes that generate NAC-1 or from inhibiting the OAT1 and OAT3 transporters **[60]**. Using a C57BL/6 mouse model with OAT1 and OAT3 gene deletions, researchers examined the function of the organic anion transporters OAT1 and OAT3 in cisplatin toxicity. While OAT3 was almost nonexistent in OAT1 (–/–) mice, OAT1 expression was lower in OAT3 (–/–) animals. The study found that BUN and creatinine levels, indicators of acute renal tubular necrosis, significantly increased in wild-type mice within 1–3 days post-cisplatin administration, whereas OAT1 (–/–) mice did not exhibit these increases. Besides, histological examination of cisplatin-treated wild-type mice revealed dilated tubules with necrotic cells and debris, while the glomeruli remained normal. In addition, OAT3 (–/–) mice showed similar but more severe kidney injuries than OAT1 (–/–) mice **[19]**. Jacobs et al. used Probenecid along with cisplatin and reported that Probenecid reduced the renal clearance of cisplatin and protected patients from nephrotoxicity by competitively inhibiting OAT-mediated transport **[73, 74]**. Accordingly, OAT1 mutant mice and wild-type mice co-treated with probenecid showed decreased cisplatin clearance and notable protection against renal injury **[60, 75]**. Also, Hu et al. examined giving nilotinib (OAT inhibitor) along with cisplatin which shows a renoprotective effect against cisplatin **[60] (Fig. 4)**. Another research study found that suppressing OAT1 and OAT3 expression in rats might prevent kidney damage-induced by cisplatin and the accumulation of uremic toxin **[76]**. Additionally, rats were given cisplatin and nano ellagic acid, which helped to reverse the effects of cisplatin on renal tissue atrophy, oxidative stress indicators, and kidney damage by inhibiting the organic anion transporters found in the kidney **[77]**. These findings support the theory that the organic anion transporter controls the nephrotoxicity brought on by cisplatin.

Contradictory results were found in various studies. These investigations showed that cisplatin inhibits the expression of organic anion transporters, and this contributes to the nephrotoxicity caused by cisplatin. Therefore, various substances known to restore the OAT expression were tested to confirm if high OAT expression might protect the kidney against CIAKI. Thymoquinone's ability to regulate renal organic anion transporters in cisplatin-induced nephrotoxicity was assessed in an animal investigation and found that thymoquinone increased OAT1 and OAT3 expression that was suppressed by cisplatin when given in concomitant with cisplatin, indicating that Thymoquinone could be used as a nephroprotective against the kidney damage caused by cisplatin upregulation of the OAT **[78]**. Cordyceps cicadae mycelia, a Chinese mycelia extract that was used to protect the kidney, decreased cisplatin kidney damage by increasing organic anion transport expression **[79]**. Another study demonstrated that rats received dual treatment of lycopene (antioxidant), and cisplatin caused an increase in the expression of OAT1 in contrast to giving monotherapy of cisplatin suggesting that lycopene counteracted the cisplatin suppression which subsequently saved the kidneys **[80]**. Knowing the involvement of organic anion transporters in cisplatin

nephrotoxicity handling proposes the need for further studies to identify the correlation between these transporters' polymorphisms and CIAKI.

2.1.4. Multidrug and Toxin Extrusion Protein (MATE)

Human MATE1 was first identified as an efflux transporter of organic cations and is primarily expressed in the liver, kidney, adrenal gland, and skeletal muscle. In the kidney, MATE1 is located at the apical membrane of renal proximal tubule cells, working alongside MATE2 and MATE2-K, which are also confined to the apical membrane of these cells. MATEs are proton/organic cation exchangers, using a proton gradient to drive the exchange of protons for organic cations **[52]**. Cisplatin is a substrate for efflux transporters multidrug and toxin extrusion 1 (MATE1, SLC47A1), and to a lesser extent MATE2-K (SLC47A2) **[81]**. The balance between influx and efflux transporters determines the accumulation of cisplatin, which is closely related to its nephrotoxic effects **[59]**. Evidence shows that MATE1 facilitates cisplatin secretion into the urine, and mice lacking MATE1 exhibit increased sensitivity to cisplatin-induced nephrotoxicity **[81] (Fig. 4)**. Similarly, a recent study using MATE1-deficient mice demonstrated significantly elevated BUN and plasma creatinine levels compared to wild-type mice, along with a 20-fold increase in renal platinum concentration, indicating a key role for MATE1 in preventing CIAKI **[19]**.

Increased SCr and BUN were also observed in MATE1 pharmacological inhibition studies. Ondansetron, a potent MATE1 and MATE2-K inhibitor, significantly increases the tissue accumulation and renal toxicity of cisplatin, as shown by elevated SCr, BUN levels, and severe kidney damage in mice. This suggests that ondansetron's inhibition of MATE1 enhances cisplatin-induced nephrotoxicity **[59]**. Co-administration of cisplatin and pyrimethamine, another MATE 1 inhibitor, had similar effects, further emphasizing MATE1's role in cisplatin elimination **[81]**. Since OCT and MATE transporters share common substrates and inhibitors, drugs like pazopanib, which inhibits OCT2, MATE1, and MATE2, can limit cisplatin uptake and reduce its cytotoxic effects in vitro **[57]**.

While single-nucleotide polymorphisms (SNPs) affecting MATE1 function have been identified, few studies have directly connected these variations to cisplatin toxicity. Recent findings suggest that genetic differences in MATE transporters may impact cisplatin-induced nephrotoxicity, emphasizing their role in ensuring active clearance and preventing drug accumulation in the proximal tubules **[27, 82]**. A study by Chang et al. revealed a relationship existed between the SLC47A1 rs2289669 variation and increased urinary levels of KIM-1 and MCP-1, indicating potential kidney damage. This suggests that genetic variations that decrease SLC47A1 function could enhance drug efficacy, reduce kidney clearance, and increase kidney toxicity for medications that are substrates of MATE1 **[27]**. However, another study found no association between the MATE1 SNP rs2289669 G > A and cisplatin-induced toxicity, though it did not evaluate MATE2 isoforms (MATE2-K and MATE2-BK) **[33]**. Furthermore, diabetic individuals with reduced MATE1 expression, caused by advanced glycation end-products, were found to be more susceptible to kidney damage **[83]**. The conflicting findings from these studies emphasize the necessity for additional research to clarify the potential association between MATE1 Polymorphism and CIAKI.

2.1.5. Multidrug Resistance-Associated Protein (MRP)

Multidrug resistance-associated proteins (MRPs) facilitate the ATP-dependent export of organic anions, which includes cytotoxic and

antiviral drugs. These MRPs belong to a subfamily of ABC transporters and function as membrane glycoproteins (MRP/ABCC). ABC transporters are efflux transporters that export drugs out of cells by utilizing ATP as driving energy. Among the primary efflux transporters in the kidney are MRP2 and MRP4. Multidrug resistance protein 2 (MRP2) is encoded by the ATP-binding cassette subfamily C member 2 (ABCC2) gene, a crucial ABC efflux transporter that is widely expressed in hepatocytes and the apical membrane of proximal tubules in human kidneys **[84] (Fig. 4)**. MRPs, especially MRP2, are crucial for mediating the efflux of cisplatin and its nephrotoxic conjugates from kidney cells, which helps mitigate cisplatin-induced nephrotoxicity **[85]**. While the substrate specificity of MRP4 remains unclear, it may act as an efflux pump for cAMP and cGMP. Increased expression of MRPs has been shown to reduce cisplatin accumulation within renal cells, thus providing a protective effect against kidney damage **[85]**. However, studies in rats with acute renal failure revealed significant upregulation of MRP2 after 72 h of cisplatin treatment, while MRP4 levels showed only minor increases **[86]**. MRPs are believed to facilitate the elimination of glutathione-s-platinum conjugates that contribute to nephrotoxicity **[86]**. In experiments with MRP2-deficient mice, enhanced platinum accumulation and proximal tubular injury were observed, indicating MRP2 role in regulating platinum levels and excreting nephrotoxic substances **[19]**. Increased levels of AKI-associated urine biomarkers have been linked to variations in the ABCC2 gene, according to recent research. Following cisplatin treatment, a notable rise in the amounts of calbindin, clusterin, cystatin C, and NGAL in urine was notably associated with the ABCC2 variation rs3740066. Clusterin and cystatin C levels were likewise greater in patients with the CT genotype for the rs717620 ABCC2 variation than in those with the wildtype CC genotype. However, a small number of patients with homozygous genotypes for rs3740066 or rs717620 did not exhibit any significant relationships **[27]**. Oppositely, a study by Sprowl examined seven common single-nucleotide polymorphisms (SNPs) in ABCC2 due to their established link to reduced transport of other ABCC2 substrates and their relatively high allele frequency in the target populations. This study found no significant association between any of the common ABCC2 genotypes and either the clearance of unbound cisplatin or changes in serum creatinine levels after treatment, which served as a marker for nephrotoxicity **[41]**. This suggests that genetic variations affecting transporter function may influence the kidney's response to cisplatin treatment, further underscoring the relevance of MRPs in renal pharmacology and nephrotoxicity. Overall, MRPs, through their efflux functions, are critical in protecting the kidneys from the adverse effects of cisplatin while also indicating a need for further research to understand the underlying mechanisms of their regulation in the context of nephrotoxicity **[19]**.

2.1.6. Excision repair cross-complementation group 1 (ERCC1).

Nucleotide excision repair is essential for cellular maintenance. ERCC1 is crucial for the nucleotide excision repair process, and polymorphisms in this gene can influence their DNA repair functions. This may impact the kidneys' ability to repair damage caused by platinum-based agents and influence patient responses **[87]**. Inadequate repair of cisplatin-induced DNA damage can result in cell death **[88]**. The most extensively studied SNPs concerning cisplatin-induced nephrotoxicity are ERCC1 rs11615 and rs3212986, both located in the 3' UTR. In a study by Khrunin et al., kidney damage was more frequently observed in patients with the heterozygous rs11615 TC genotype

(46.7%), with an odds ratio (OR) of 2.51 (95% CI 1.09–5.57; P = 0.037), and in those with the rs3212986 CA genotype (52.8%), showing an OR of 3.29 (95% CI 1.40–7.73; P = 0.009) when compared to patients with the homozygous variant genotype **[38]**. Tzvetkov et al. provided support for these findings, by demonstrating a substantial correlation (P < 0.05) between both SNP variations and a decline in eGFR among different late-stage cancer patients. It is crucial to remember that many patients included in the previous study (n = 47, 58.0%) had previously received therapy with cisplatin. This could have affected their initial eGFR levels, which varied from 40 to 167 mL/min/1.73 m², thus adding bias to the findings **[36]**. According to the NCI-CTCAE classification, Khrunin et al. defined nephrotoxicity as a grade ≥1, but Tzvetkov et al. evaluated relative changes in eGFR **[36, 38]**. Nevertheless, other studies revealed no conclusive connection between cisplatin nephrotoxicity and ERCC1 polymorphisms **[42, 44, 45]**. Furthermore, the ERCC1 (rs11615 and rs3212986) SNPs in cohorts of head and neck and esophageal cancer were not supported by a recent study by Zazuli et al. However, in line with earlier studies, the rs3212986 variant was linked to a higher risk of cisplatin-induced nephrotoxicity in a validation cohort for non-small cell lung cancer (NSCLC); yet this association lost statistical significance after multiple testing adjustments were made **[43]**. Factors such as insufficient study power, inconsistent definitions of outcomes, variations in cancer types, and population stratification may account for the absence of associations for these SNPs.

2.1.7. Xeroderma pigmentosum group D protein (XPD)

Excision repair cross-complementing group 2 (ERCC2), also known as xeroderma pigmentosum group D (XPD), plays a crucial role in nucleotide excision repair, a pathway responsible for repairing DNA damage. Four studies identified significant associations between ERCC2 variants and nephrotoxicity. These studies varied in design, with some focusing on European populations and others on East Asian patients. The definitions of nephrotoxicity were also not uniform throughout the investigations; two studies used distinct NCI-CTCAE criterion thresholds (≥grade 2 vs. ≥grade 1), while the other studies did not provide a definition **[46–49]**. Out of the six SNPs examined, only rs13181 could be replicated effectively. The C allele of the XPD gene (rs13181, 2251A > C) had a significantly lower risk of early severe nephrotoxicity (OR = 0.07, P < 0.0001) after the second cycle, according to Powrozek et al. study. Likewise, a significant decrease in nephrotoxicity following the 4th cycle chemotherapy was seen in C allele carriers (OR = 0.24, P = 0.017) and the A allele (rs1799793, 934G > A; OR = 0.26, P = 0.029) **[47]**. Moreover, there was a strong correlation (p < 0.05) between rs238405 and nephrotoxicity and infection **[48]**. In addition, rs238415 and nephrotoxicity as well as rs238416, nephrotoxicity, and asthenia were revealed to be significantly correlated (p < 0.05) **[48]**. The ERCC2 haplotype (rs1799793 and rs13181) was found to be significantly associated with nephrotoxicity by Goekkurt et al., but Windsor et al. found that the AA genotype of ERCC2 rs13181 was linked to a decreased risk of nephrotoxicity and lesser declines of eGFR **[46, 49]** However, Erculj et al. analysis revealed no connection between CIAKI, rs1799793, or rs13181 **[45]**. Conflicting results draw attention to the need for more research to clarify ERCC2's role in cisplatin nephrotoxicity.

2.1.8. Glutathione S-Transferases (GSTs) & Gamma-Glutamyl Transferase (GGT)

Glutathione S-transferases (GSTs) are

involved in metabolizing platinum-based chemotherapeutics, including cisplatin. The enzymes glutathione S-transferase pi-1 (GSTP1) and gamma-glutamyltransferase 1 (GGT1) break down cisplatin in the proximal tubule cells. These enzymes' actions may also be a factor in the nephrotoxicity brought on by cisplatin. A cisplatin-glutathione substrate is created by the GST metabolism of cisplatin and is released from the proximal tubule cells. GGT1 then processes this substrate extracellularly at the apical brush border membrane. Aminopeptidase subsequently transforms the resultant substrate, a cisplatin-cysteinyl-glycine compound, into cisplatin-cysteine, which is subsequently reabsorbed by the proximal tubule cells. These cells' additional metabolic activities produce a reactive thiol, which worsens nephrotoxicity **[27]**. Previous research found that acivicin effectively prevents cisplatin-induced nephrotoxicity in rats. Acivicin inhibits gamma-glutamyl transferase (GGT) **[89]**. This finding is supported by research showing protection against cisplatin-induced kidney damage in animals lacking GGT. In contrast, wild-type mice exhibited increased levels of blood urea nitrogen, serum creatinine, and renal tubular necrosis, regardless of N-acetyl cysteine (NAC) supplementation. No differences were observed in platinum excretion or renal platinum accumulation between wild-type and GGT-deficient mice. These findings suggest that renal toxicity from cisplatin relies on GGT activity, supporting the hypothesis that cisplatin nephrotoxicity occurs through a GGT-dependent metabolic pathway **[90]**.

A noticeable trend related to the C/T polymorphism in intron 1 of the GGT1 gene (rs5751901), became more apparent when looking at the frequency of specific genotypes. The T/T genotype was discovered in 50% of the cases with renal failure, while its occurrence in patients with normal renal function was only 31% (OR = 2.19, 95% CI 0.953–5.038; p = 0.088) [50]. In contrast, other studies have reported no correlation between GGT activity and cisplatin-induced nephrotoxicity **[38, 46, 49, 91]**. Since GGT1-dependent metabolism of cisplatin in the kidneys is thought to play a role in at least one pathway leading to nephrotoxicity, assessing GGT1 polymorphism could potentially help in deciding whether to include cisplatin in treatment regimens **[50]**.

Furthermore, following cisplatin chemotherapy, correlations were discovered between the GSTP1 mutation (rs1695) with notable increases in urine biomarkers, such as KIM-1, Calbindin, and NGAL at Day 3 and IL-18 at Day 10. Although polymorphisms in GST metabolism genes appear to influence biomarker changes, further research is needed **[27]**.

2.1.9. BTB and CNC Homology 2 (BACH2)

BACH2 rs4388268 is a common intronic variant on chromosome 6, with minor allele frequencies of 0.29 globally. BACH2 variations may contribute to cisplatin-induced kidney damage because the drug is primarily eliminated by the kidneys; however, more investigation is needed to determine the exact mechanism, which may include cell proliferation, DNA damage, or autoimmune. With genome-wide significance for the eGFR outcome and suggestive connection for AKI-CTCAE, BACH2 rs4388268 is the SNP most consistently linked to an elevated risk of cisplatin-induced nephrotoxicity across both outcomes and genotyping platforms **[43]**. Only a few studies suggest that the rs4388268 variant in the BACH2 gene is linked to an increased risk of kidney damage in patients treated with cisplatin. A recent genome-wide association study (GWAS) investigated the relationship between CIAKI and genetic variations throughout the genome in adult cancer patients. This study identified five novel variants, one of which was in the BACH2 gene, and this association was further confirmed in a second validation cohort.

In the initial group (discovery cohort), the rs4388268 variant was strongly associated with a decreased eGFR. The variant also correlated with a higher likelihood of developing AKI, as classified by CTCAE. The associations observed were statistically significant, suggesting a true link between the variant and the risk of nephrotoxicity. There is a pattern indicating that patients with more copies of the A allele experienced worse kidney outcomes. For instance, in the discovery cohort, the risk of AKI increased progressively from GG (no A allele) to AG to AA genotypes. In a separate group (validation cohort), the trend of the rs4388268 variant associated with worse kidney outcomes was observed consistent with the findings of the discovery cohort, but it wasn't statistically significant, possibly due to sample size or variability. Concluding that, across both cohorts, carriers of the A allele had more significant declines in eGFR, with AA genotype patients showing the most substantial reductions in kidney function. For each genotype (GG, AG, AA), the incidence rates of kidney damage were higher in allele carriers **[43]**. Another study by Klumpers et al. did not show a significant association between rs4388268 BACH2 with eGFR decline, with p-values of 0.443. However, the direction of the effect sizes was consistent with the initial discovery study, indicating an increased risk for A-allele carriers of the BACH2 variant. Despite this, the study was unable to replicate the findings from Zazuli et al. as the primary association between the BACH2 variant and cisplatin-induced eGFR reduction observed in adult cancer cohorts was not found in this study, although the effect direction remained similar. Thus, validation in a separate cohort is needed before these results can be applied to customize cisplatin treatment for patients **[51]**.

Conclusion

A significant rise in pharmacogenomics research on cisplatin-induced nephrotoxicity has been observed throughout the last ten years. This review has identified various genes that may influence the risk of developing nephrotoxicity from cisplatin. However, concerns persist regarding study design limitations, the reproducibility of findings, and the overall quality of research conducted. Beyond transporter genes, further investigation into DNA repair genes, metabolism genes, and inflammation and stress response genes is needed to understand their potential role in cisplatin nephrotoxicity. The genome-wide approaches may help overcome the limitations of current research and move us closer to implementing personalized and precision medicine for cancer patients receiving cisplatin treatment.

Declarations

Ethics Approval and Consent to Participate

Not applicable.

Consent to Participate

Not applicable.

Consent for publication

Not applicable.

Availability of the data and Material

All data generated or analyzed during this study are included in this article.

Competing interests

The authors declare that there is no conflict of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contribution

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by Israa Gamal Aly Abdelbar, Amal Abdel Moneim

Elkholy, Diaa Eldin Mousa Sherif, and Lamia Mohamed El-Wakeel. The first draft of the manuscript was written by Israa Gamal Aly Abdelbar and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Acknowledgment

The authors would like to acknowledge all colleagues and heads in the Clinical Department, The British University in Egypt, and Ain Shams University for their support.

3. References

[1] Sales GTM, Foresto RD. Drug-induced nephrotoxicity. Rev Assoc Med Bras 2020;66:82–90. https://doi.org/10.1590/1806-9282.66.S1.82.

[2] Mody H, Ramakrishnan V, Chaar M, Lezeau J, Rump A, Taha K, et al. A Review on Drug-Induced Nephrotoxicity: Pathophysiological Mechanisms, Drug Classes, Clinical Management, and Recent Advances in Mathematical Modeling and Simulation Approaches. Clin Pharmacol Drug Dev 2020;9:896–909. https://doi.org/10.1002/cpdd.879.

[3] Santos MLC, Brito BB de, Silva FAF da, Botelho AC dos S, Melo FF de. Nephrotoxicity in cancer treatment: An overview. World J Clin Oncol 2020;11:190–204. https://doi.org/10.5306/wjco.v11.i4.190.

[4] Patimarattananan T, Nongnuch A, Pattaranutaporn P, Unwanatham N, Jiarpinitnun C, Ngamphaiboon N. Risk and impact of delayed renal impairment in patients with locally advanced head and neck squamous cell carcinoma receiving chemoradiotherapy with cisplatin. Supportive Care in Cancer 2021;29:877–87. https://doi.org/10.1007/s00520-020-05566-y.

[5] Kellum JA, Romagnani P, Ashuntantang G, Ronco C, Zarbock A, Anders HJ. Acute kidney injury. Nat Rev Dis Primers 2021;7. https://doi.org/10.1038/s41572-021-00284-z.

[6] Lyrio RM da C, Rocha BRA, Corrêa ALRM, Mascarenhas MGS, Santos FL, Maia R da H, et al. Chemotherapy-induced acute kidney injury: epidemiology, pathophysiology, and therapeutic approaches. Frontiers in Nephrology 2024;4. https://doi.org/10.3389/fneph.2024.1436896.

[7] Jin Z, Zhao-Xia L, Fan-Ke P, Wen-Juan Z, Min-Li W, Han-Yi Z. Progress in the study of reproductive toxicity of platinum-based antitumor drugs and their means of prevention. Front Pharmacol 2024;15. https://doi.org/10.3389/fphar.2024.1327502.

[8] Duan ZY, Cai GY, Li JJ, Chen XM. Cisplatin-induced renal toxicity in elderly people. Ther Adv Med Oncol 2020;12. https://doi.org/10.1177/1758835920923430.

[9] Bork T, Hernando-Erhard C, Liang W, Tian Z, Yamahara K, Huber TB. Cisplatin Nephrotoxicity Is Critically Mediated by the Availability of BECLIN1. Int J Mol Sci 2024;25. https://doi.org/10.3390/ijms25052560.

[10] Hucke A, Schröter R, Ceresa C, Chiorazzi A, Canta A, Semperboni S, et al. Role of Mouse Organic Cation Transporter 2 for Nephro- and Peripheral Neurotoxicity Induced by Chemotherapeutic Treatment with Cisplatin. Int J Mol Sci 2023;24. https://doi.org/10.3390/ijms241411486.

[11] Li P, Li D, Lu Y, Pan S, Cheng F, Li S, et al. GSTT1/GSTM1 deficiency aggravated cisplatin-induced acute kidney injury via ROS-triggered ferroptosis. Front Immunol 2024;15:1457230. https://doi.org/10.3389/fimmu.2024.1457230.

[12] Karimzadeh I, Barreto EF, Kellum JA, Awdishu L, Murray PT, Ostermann M, et al. Moving toward a contemporary classification of drug-induced kidney disease. Crit Care 2023;27. https://doi.org/10.1186/s13054-023-04720-2.

[13] Zhang M, Li Y, Ma Y, Jin Y, Gou X, Yuan Y, et al. The toxicity of cisplatin derives from effects on renal organic ion transporters expression and serum endogenous substance levels. Food and Chemical Toxicology 2024;192. https://doi.org/10.1016/j.fct.2024.114949.

[14] Caetano-Pinto P, Stahl SH. Renal Organic Anion Transporters 1 and 3 In Vitro: Gone but Not Forgotten. Int J Mol Sci 2023;24. https://doi.org/10.3390/ijms242015419.

[15] Nigam SK, Wu W, Bush KT, Hoenig MP, Blantz RC, Bhatnagar V. Handling of drugs, metabolites, and uremic toxins by kidney proximal tubule drug transporters. Clinical Journal of the American Society of Nephrology 2015;10:2039–49. https://doi.org/10.2215/CJN.02440314.

[16] Ma Y, Ran F, Xin M, Gou X, Wang X, Wu X. Albumin-bound kynurenic acid is an appropriate endogenous biomarker for assessment of the renal tubular OATs-MRP4 channel. J Pharm Anal 2023;13:1205–20. https://doi.org/10.1016/j.jpha.2023.05.007.

[17] Duan M, Leng S, Mao P. Cisplatin in the era of PARP inhibitors and immunotherapy. Pharmacol Ther 2024;258. https://doi.org/10.1016/j.pharmthera.2024.108642.

[18] Kelland L. The resurgence of platinum-based cancer chemotherapy. Nat Rev Cancer 2007;7:573–84. https://doi.org/10.1038/nrc2167.

[19] McSweeney KR, Gadanec LK, Qaradakhi T, Ali BA, Zulli A, Apostolopoulos V. Mechanisms of cisplatin-induced acute kidney injury: Pathological mechanisms, pharmacological interventions, and genetic mitigations. Cancers (Basel) 2021;13. https://doi.org/10.3390/cancers13071572.

[20] Zazuli Z, Vijverberg S, Slob E, Liu G, Carleton B, Veltman J, et al. Genetic variations and cisplatin nephrotoxicity: A systematic review. Front Pharmacol 2018;9. https://doi.org/10.3389/fphar.2018.01111.

[21] Pabla N, Dong Z. Cisplatin nephrotoxicity: Mechanisms and renoprotective strategies. Kidney Int 2008;73:994–1007. https://doi.org/10.1038/sj.ki.5002786.

[22] Tan WJT, Vlajkovic SM. Molecular Characteristics of Cisplatin-Induced Ototoxicity and Therapeutic Interventions. Int J Mol Sci 2023;24. https://doi.org/10.3390/ijms242216545.

[23] Nagasaki T, Maeda H, Yanagisawa H, Nishida K, Kobayashi K, Wada N, et al. Carbon Monoxide-Loaded Red Blood Cell Prevents the Onset of Cisplatin-Induced Acute Kidney Injury. Antioxidants 2023;12. https://doi.org/10.3390/antiox12091705.

[24] Tang C, Livingston MJ, Safirstein R, Dong Z. Cisplatin nephrotoxicity: new insights and therapeutic implications. Nat Rev Nephrol 2023;19:53–72. https://doi.org/10.1038/s41581-022-00631-7.

[25] Miller RP, Tadagavadi RK, Ramesh G, Reeves WB. Mechanisms of cisplatin nephrotoxicity. Toxins (Basel) 2010;2:2490–518. https://doi.org/10.3390/toxins2112490.

[26] Mehrab H, Sharifi M, Akhavan A, Aarabi M-H, Mansourian M, Mosavi E, et al. Curcumin supplementation prevents cisplatin-induced nephrotoxicity: a randomized, double-blinded, and placebo-controlled trial. vol. 18. 2023. https://doi.org/10.4103/1735-5362.389952

[27] Chang C, Hu Y, Hogan SL, Mercke N, Gomez M, O'Bryant C, et al. Pharmacogenomic variants may influence the urinary excretion of novel kidney injury biomarkers in patients receiving cisplatin. Int J Mol Sci 2017;18. https://doi.org/10.3390/ijms18071333.

[28] Qi L, Luo Q, Zhang Y, Jia F, Zhao Y, Wang F. Advances in Toxicological Research of the Anticancer Drug Cisplatin. Chem Res Toxicol 2019;32:1469–86. https://doi.org/10.1021/acs.chemrestox.9b00204.

[29] Karasawa T, Steyger PS. An integrated view of cisplatin-induced nephrotoxicity and ototoxicity. Toxicol Lett 2015;237:219–27. https://doi.org/10.1016/j.toxlet.2015.06.012.

[30] Tchounwou PB, Dasari S, Noubissi FK, Ray P, Kumar S. Advances in our understanding of the molecular mechanisms of action of cisplatin in cancer therapy. J Exp Pharmacol 2021;13:303–28. https://doi.org/10.2147/JEP.S267383.

[31] Snchez-Gonzlez PD, López-Hernández FJ, López-Novoa JM, Morales AI. An integrative view of the pathophysiological events leading to cisplatin nephrotoxicity. Crit Rev Toxicol 2011;41:803–21. https://doi.org/10.3109/10408444.2011.602662.

[32] Filipski KK, Mathijssen RH, Mikkelsen TS, Schinkel AH, Sparreboom A. Contribution of organic cation transporter 2 (OCT2) to cisplatin-induced nephrotoxicity. Clin Pharmacol Ther 2009;86:396–402. https://doi.org/10.1038/clpt.2009.139.

[33] Iwata K, Aizawa K, Kamitsu S, Jingami S, Fukunaga E, Yoshida M, et al. Effects of genetic variants in SLC22A2 organic cation transporter 2 and SLC47A1 multidrug and toxin extrusion 1 transporter on cisplatin-induced adverse events. Clin Exp Nephrol 2012;16:843–51. https://doi.org/10.1007/S10157-012-0638-Y.

[34] Zhang J, Zhou W. Ameliorative effects of SLC22A2 gene polymorphism 808 G/T and cimetidine on cisplatin-induced nephrotoxicity in Chinese cancer patients. Food and Chemical Toxicology 2012;50:2289–93. https://doi.org/10.1016/j.fct.2012.03.077.

[35] Hinai Y, Motoyama S, Niioka T, Miura M. Absence of effect of SLC22A2 genotype on cisplatin-induced nephrotoxicity in oesophageal cancer patients receiving cisplatin and 5-fluorouracil: Report of results discordant with those of earlier studies. J Clin Pharm Ther 2013;38:498–503. https://doi.org/10.1111/jcpt.12097.

[36] Tzvetkov M V., Behrens G, O'Brien VP, Hohloch K, Brockmöller J, Benhr P. Pharmacogenetic analyses of cisplatin-induced nephrotoxicity indicate a renoprotective effect of ERCC1 polymorphisms. Pharmacogenomics 2011;12:1417–27. https://doi.org/10.2217/pgs.11.93.

[37] Zazuli Z, Otten LS, Drögemöller BI, Medeiros M, Monzon JG, Wright GEB, et al. Outcome definition influences the relationship between genetic polymorphisms of ERCC1, ERCC2, SLC22A2 and cisplatin nephrotoxicity in adult testicular cancer patients. Genes (Basel) 2019;10. https://doi.org/10.3390/genes10050364.

[38] Khrunin A V., Moisseev A, Gorbunova V, Limborska S. Genetic polymorphisms and the efficacy and toxicity of cisplatin-based chemotherapy in ovarian cancer patients. Pharmacogenomics Journal 2010;10:54–61. https://doi.org/10.1038/tpj.2009.45.

[39] Oda H, Mizuno T, Ikejiri M, Nakamura M, Tsunoda A, Ishihara M, et al. Risk factors for cisplatin-induced acute kidney injury: A pilot study on the usefulness of genetic variants for predicting nephrotoxicity in clinical practice. Mol Clin Oncol 2020;13:1–6. https://doi.org/10.3892/mco.2020.2127.

[40] Xu X, Ren H, Zhou B, Zhao Y, Yuan R, Ma R, et al. Prediction of copper transport protein 1 (CTR1) genotype on severe cisplatin induced toxicity in non-small cell lung cancer (NSCLC) patients. Lung Cancer 2012;77:438–

42. https://doi.org/10.1016/j.lungcan.2012.03.023.

[41] Sprowl JA, Gregorc V, Lazzari C, Mathijssen RH, Loos WJ, Sparreboom A. Associations between ABCC2 polymorphisms and cisplatin disposition and efficacy. Clin Pharmacol Ther 2012;91:1022–6. https://doi.org/10.1038/CLPT.2011.330.

[42] Chen S, Huo X, Lin Y, Ban H, Lin Y, Li W, et al. Association of MDR1 and ERCC1 polymorphisms with response and toxicity to cisplatin-based chemotherapy in non-small-cell lung cancer patients. Int J Hyg Environ Health 2010;213:140–5. https://doi.org/10.1016/j.ijheh.2010.01.004.

[43] Zazuli Z, de Jong C, Xu W, Vijverberg SJH, Masereeuw R, Patel D, et al. Association between Genetic Variants and Cisplatin-Induced Nephrotoxicity: A Genome-Wide Approach and Validation Study. J Pers Med 2021;11. https://doi.org/10.3390/JPM11111233.

[44] Kimcurran V, Zhou C, Schmid-Bindert G, Shengxiang R, Zhou S, Zhang L, et al. Lack of correlation between ERCC1 (C8092A) single nucleotide polymorphism and efficacy/toxicity of platinum based chemotherapy in Chinese patients with advanced non-small cell lung cancer. Adv Med Sci 2011;56:30–8. https://doi.org/10.2478/v10039-011-0013-3.

[45] Erčulj N, Kovač V, Hmeljak J, Dolžan V. The influence of platinum pathway polymorphisms on the outcome in patients with malignant mesothelioma. Annals of Oncology 2012;23:961–7. https://doi.org/10.1093/ANNONC/MDR324.

[46] Windsor RE, Strauss SJ, Kallis C, Wood NE, Whelan JS. Germline genetic polymorphisms may influence chemotherapy response and disease outcome in osteosarcoma: a pilot study. Cancer 2012;118:1856–67. https://doi.org/10.1002/CNCR.26472.

[47] Powrózek T, Mlak R, Krawczyk P, Homa I, Ciesielka M, Kozioł P, et al. The relationship between polymorphisms of genes regulating DNA repair or cell division and the toxicity of platinum and vinorelbine chemotherapy in advanced NSCLC patients. Clinical and Translational Oncology 2016;18:125–31. https://doi.org/10.1007/S12094-015-1343-6/TABLES/3.

[48] Kim SH, Lee GW, Lee MJ, Cho YJ, Jeong YY, Kim HC, et al. Clinical significance of ERCC2 haplotype-tagging single nucleotide polymorphisms in patients with unresectable non-small cell lung cancer treated with first-line platinum-based chemotherapy. Lung Cancer 2012;77:578–84. https://doi.org/10.1016/J.LUNGCAN.2012.04.016.

[49] Goekkurt E, Al-Batran SE, Hartmann JT, Mogck U, Schuch G, Kramer M, et al. Pharmacogenetic analyses of a phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil and leucovorin plus either oxaliplatin or cisplatin: a study of the arbeitsgemeinschaft internistische onkologie. Journal of Clinical Oncology 2009;27:2863–73. https://doi.org/10.1200/JCO.2008.19.1718.

[50] Khrunin A V., Moiseev AA, Khokhrin D V., Gorbunova VA, Limborska SA. Polymorphisms of OCT2, GGT1, HO1, and DNASE1 genes and nephrotoxicity of cysplatin in ovarian cancer patients. Molecular Genetics, Microbiology and Virology 2010;25:163–6. https://doi.org/10.3103/S089141681004004X.

[51] Klumpers MJ, De Witte W, Gattuso G, Schiavello E, Terenziani M, Massimino M, et al. Genome-Wide Analyses of Nephrotoxicity in Platinum-Treated Cancer Patients Identify Association with Genetic Variant in RBMS3 and Acute Kidney Injury. J Pers Med 2022;12. https://doi.org/10.3390/jpm12060892.

[52] Wagner DJ, Hu T, Wang J. Polyspecific organic cation transporters and their impact on drug intracellular levels and pharmacodynamics. Pharmacol Res 2016;111:237–46. https://doi.org/10.1016/j.phrs.2016.06.002.

[53] Ciarimboli G, Ludwig T, Lang D, Pavenstä H, Koepsell H, Rgen Piechota H-J, et al. Cisplatin Nephrotoxicity Is Critically Mediated via the Human Organic Cation Transporter 2. vol. 167. 2005. https://doi.org/10.1016/S0002-9440(10)61234-5.

[54] Wang G, Bi Y, Xiong H, Bo T, Han L, Zhou L, et al. Wedelolactone protects against cisplatin-induced nephrotoxicity in mice via inhibition of organic cation transporter 2. Hum Exp Toxicol 2021;40:S447–59. https://doi.org/10.1177/09603271211047915.

[55] Fang C yan, Lou D yong, Zhou L qin, Wang J cheng, Yang B, He Q jun, et al. Natural products: potential treatments for cisplatin-induced nephrotoxicity. Acta Pharmacol Sin 2021;42:1951–69. https://doi.org/10.1038/s41401-021-00620-9.

[56] Mody H, Vaidya TR, Lesko LJ, Ait-Oudhia S. Pharmacodynamic Modeling to Evaluate the Impact of Cimetidine, an OCT2 Inhibitor, on the Anticancer Effects of Cisplatin. Cells 2023;12. https://doi.org/10.3390/cells12010057.

[57] Li C, Li L, Yi Y, Wang W, Yuan J, Tan F, et al. L-tetrahydropalmatine attenuates cisplatin-induced nephrotoxicity via selective inhibition of organic cation transporter 2 without impairing its antitumor efficacy. Biochem Pharmacol 2020;177. https://doi.org/10.1016/j.bcp.2020.114021.

[58] Sharaf G, El EM, El-Sayed EK. Augmented nephroprotective effect of liraglutide and rabeprazole via inhibition of OCT2 transporter in cisplatin-induced nephrotoxicity in rats. Life Sci 2023;321. https://doi.org/10.1016/j.lfs.2023.121609.

[59] Li Q, Guo D, Dong Z, Zhang W, Zhang L, Huang SM, et al. Ondansetron can enhance cisplatin-induced nephrotoxicity via inhibition of multiple toxin and extrusion proteins (MATEs). Toxicol Appl Pharmacol 2013;273:100–9. https://doi.org/10.1016/j.taap.2013.08.024.

[60] Hu S, Leblanc AF, Gibson AA, Hong KW, Kim JY, Janke LJ, et al. Identification of OAT1/OAT3 as Contributors to Cisplatin Toxicity. Clin Transl Sci 2017;10:412–20. https://doi.org/10.1111/cts.12480.

[61] Xu X, Duan L, Zhou B, Ma R, Zhou H, Liu Z. Genetic polymorphism of copper transporter protein 1 is related to platinum resistance in Chinese non-small cell lung carcinoma patients. Clin Exp Pharmacol Physiol 2012;39:786–92. https://doi.org/10.1111/j.1440-1681.2012.05741.x.

[62] Elmorsy EA, Saber S, Hamad RS, Abdel-Reheim MA, El-kott AF, AlShehri MA, et al. Advances in understanding cisplatin-induced toxicity: Molecular mechanisms and protective strategies. European Journal of Pharmaceutical Sciences 2024;203. https://doi.org/10.1016/j.ejps.2024.106939.

[63] Skvortsov AN, Zatulovskiy EA, Puchkova L V. Structure-functional organization of eukaryotic high-affinity copper importer CTR1 determines its ability to transport copper, silver, and cisplatin. Mol Biol 2012;46:304–15. https://doi.org/10.1134/S0026893312010219.

[64] Ishida S, Lee J, Thiele DJ, Herskowitz I. Uptake of the anticancer drug cisplatin mediated by the copper transporter Ctr1 in yeast and mammals. n.d. https://doi.org/10.1073/pnas.162491399

[65] Pabla N, Murphy RF, Liu K, Dong Z. The

copper transporter Ctr1 contributes to cisplatin uptake by renal tubular cells during cisplatin nephrotoxicity. Am J Physiol Renal Physiol 2009;296:505–11. https://doi.org/10.1152/ajprenal.90545.2008.

[66] Nieskens TTG, Peters JGP, Dabaghie D, Korte D, Jansen K, Van Asbeck AH, et al. Expression of Organic Anion Transporter 1 or 3 in Human Kidney Proximal Tubule Cells Reduces Cisplatin Sensitivity. Drug Metabolism and Disposition 2018;46:592–9. https://doi.org/10.1124/dmd.117.079384.

[67] Manohar S, Leung N. Cisplatin nephrotoxicity: a review of the literature. J Nephrol 2018;31:15–25. https://doi.org/10.1007/s40620-017-0392-z.

[68] Blair BG, Larson C, Safaei R, Howell SB. Copper transporter 2 regulates the cellular accumulation and cytotoxicity of cisplatin and carboplatin. Clinical Cancer Research 2009;15:4312–21. https://doi.org/10.1158/1078-0432.CCR-09-0311.

[69] Öhrvik H, Thiele DJ. The role of Ctr1 and Ctr2 in mammalian copper homeostasis and platinum-based chemotherapy. Journal of Trace Elements in Medicine and Biology 2015;31:178–82. https://doi.org/10.1016/j.jtemb.2014.03.006.

[70] Blair BG, Larson CA, Adams PL, Abada PB, Pesce CE, Safaei R, et al. Copper transporter 2 regulates endocytosis and controls tumor growth and sensitivity to cisplatin in vivo. Mol Pharmacol 2011;79:157–66. https://doi.org/10.1124/mol.110.068411.

[71] La Fontaine S, Mercer JFB. Trafficking of the copper-ATPases, ATP7A and ATP7B: Role in copper homeostasis. Arch Biochem Biophys 2007;463:149–67. https://doi.org/10.1016/j.abb.2007.04.021.

[72] Villar SR, Brandoni A, Anzai N, Endou H, Torres AM. Altered expression of rat renal cortical OAT1 and OAT3 in response to bilateral ureteral obstruction. Kidney Int 2005;68:2704–13. https://doi.org/10.1111/j.1523-1755.2005.00741.x.

[73] Jacobs C, Coleman CN, Rich L, Hirst K, Weiner MW. Inhibition of c/s-Diamminedichloroplatinum Secretion by the Human Kidney with Probenecid1. vol. 44. 1984.

[74] Jacobs C, Kaubisch S, Halsey J, Lum BL, Gosland M, Coleman CN, et al. The use of probenecid as a chemoprotector against cisplatin nephrotoxicity. Cancer 1991;67:1518–24. https://doi.org/10.1002/1097-0142(19910315)67:6<1518::AID-CNCR2820670610>3.0.CO;2-3.

[75] Wu W, Bush KT, Nigam SK. Key Role for the Organic Anion Transporters, OAT1 and OAT3, in the in vivo Handling of Uremic Toxins and Solutes. Sci Rep 2017;7. https://doi.org/10.1038/s41598-017-04949-2.

[76] Liu T, Meng Q, Wang C, Liu Q, Guo X, Sun H, et al. Changes in expression of renal Oat1, Oat3 and Mrp2 in cisplatin-induced acute renal failure after treatment of JBP485 in rats. Toxicol Appl Pharmacol 2012;264:423–30. https://doi.org/10.1016/j.taap.2012.08.019.

[77] Neamatallah T, El-Shitany N, Abbas A, Eid BG, Harakeh S, Ali S, et al. Nano ellagic acid counteracts cisplatin-induced upregulation in OAT1 and OAT3: A possible nephroprotection mechanism. Molecules 2020;25. https://doi.org/10.3390/molecules25133031.

[78] Ulu R, Dogukan A, Tuzcu M, Gencoglu H, Ulas M, Ilhan N, et al. Regulation of renal organic anion and cation transporters by thymoquinone in cisplatin induced kidney

injury. Food and Chemical Toxicology 2012;50:1675–9. https://doi.org/10.1016/J.FCT.2012.02.082.

[79] Deng JS, Jiang WP, Chen CC, Lee LY, Li PY, Huang WC, et al. Cordyceps cicadae Mycelia Ameliorate Cisplatin-Induced Acute Kidney Injury by Suppressing the TLR4/NF-κB/MAPK and Activating the HO-1/Nrf2 and Sirt-1/AMPK Pathways in Mice. Oxid Med Cell Longev 2020;2020:17. https://doi.org/10.1155/2020/7912763.

[80] Erman F, Tuzcu M, Orhan C, Sahin N, Sahin K. Effect of lycopene against cisplatin-induced acute renal injury in rats: Organic anion and cation transporters evaluation. Biol Trace Elem Res 2014;158:90–5. https://doi.org/10.1007/s12011-014-9914-x.

[81] Nakamura T, Yonezawa A, Hashimoto S, Katsura T, Inui KI. Disruption of multidrug and toxin extrusion MATE1 potentiates cisplatin-induced nephrotoxicity. Biochem Pharmacol 2010;80:1762–7. https://doi.org/10.1016/j.bcp.2010.08.019.

[82] Sauzay C, White-Koning M, Hennebelle I, Deluche T, Delmas C, Imbs DC, et al. Inhibition of OCT2, MATE1 and MATE2-K as a possible mechanism of drug interaction between pazopanib and cisplatin. Pharmacol Res 2016;110:89–95. https://doi.org/10.1016/J.PHRS.2016.05.012.

[83] Mizuno T, Sato W, Ishikawa K, Terao Y, Takahashi K, Noda Y, et al. OncoTargets and Therapy Dovepress Significance of downregulation of renal organic cation transporter (SLC47A1) in cisplatin-induced proximal tubular injury. Onco Targets Ther 2015;8:1701–6. https://doi.org/10.2147/OTT.S86743.

[84] Schaub TP, Kartenbeck J, König J, Spring H, Dörsam J, Staehler G, et al. Expression of the MRP2 gene-encoded conjugate export pump in human kidney proximal tubules and in renal cell carcinoma. J Am Soc Nephrol 1999;10:1159–69. https://doi.org/10.1681/ASN.V1061159.

[85] Li X, Wang H, Wang J, Chen Y, Yin X, Shi G, et al. Emodin enhances cisplatin-induced cytotoxicity in human bladder cancer cells through ROS elevation and MRP1 downregulation. BMC Cancer 2016;16. https://doi.org/10.1186/S12885-016-2640-3.

[86] Mbatchi LC, Gassiot M, Pourquier P, Goberna A, Mahammedi H, Mourey L, et al. Association of NR1I2, CYP3A5 and ABCB1 genetic polymorphisms with variability of temsirolimus pharmacokinetics and toxicity in patients with metastatic bladder cancer. Cancer Chemother Pharmacol 2017;80:653–9. https://doi.org/10.1007/S00280-017-3379-5/METRICS.

[87] Cheng J, Ha M, Wang Y, Sun J, Chen J, Wang Y, et al. A C118T polymorphism of ERCC1 and response to cisplatin chemotherapy in patients with late-stage non-small cell lung cancer. J Cancer Res Clin Oncol 2012;138:231–8. https://doi.org/10.1007/S00432-011-1090-1.

[88] Garcia SL, Lauritsen J, Zhang Z, Bandak M, Dalgaard MD, Nielsen RL, et al. Prediction of Nephrotoxicity Associated with Cisplatin-Based Chemotherapy in Testicular Cancer Patients. JNCI Cancer Spectr 2020;4. https://doi.org/10.1093/JNCICS/PKAA032.

[89] Capraro MA, Hughey RP. Use of acivicin in the determination of rate constants for turnover of rat renal gamma-glutamyltranspeptidase. J Biol Chem 1985;260:3408–12. https://doi.org/10.1016/s0021-9258(19)83636-0.

[90] Hanigan MH, Lykissa ED, Townsend DM, Ou CN, Barrios R, Lieberman MW. Gamma-glutamyl transpeptidase-deficient mice are resistant to the nephrotoxic effects of cisplatin.

Am J Pathol 2001;159:1889–94. https://doi.org/10.1016/S0002-9440(10)63035-0.

[91] Khrunin A, Ivanova F, Moisseev A, Khokhrin D, Sleptsova Y, Gorbunova V, et al. Pharmacogenomics of Cisplatin-Based Chemotherapy in Ovarian Cancer Patients of Different Ethnic Origins. Pharmacogenomics 2012;13:171–8. https://doi.org/10.2217/PGS.11.140.

[92] Zhang C, Xu C, Gao X, Yao Q. Platinum-based drugs for cancer therapy and anti-tumor strategies. Theranostics 2022;12:2115–32. https://doi.org/10.7150/thno.69424.