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Analysis of Renal Platinum Content as a Novel Approach to Protect against Cisplatin Nephrotoxicity: A Review

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Cisplatin (cis-diamine-dichloroplatinum (II), CDDP) is a prominent member of the effective broad-spectrum antitumor drugs. However, its clinical usage is restricted due to serious side effects particularly nephrotoxicity. The vulnerability of the kidney to CDDP is almost certainly related to its primary role in the excretion of the drug as intact CDDP and its platinum containing products are excreted mainly in the urine. There is a correlation between the level of platinum in urine and nephrotoxicity because of renal uptake of the drug. Some analytical methods were applied for the determination of platinum content in biological fluids such as plasma, urine, serum, and peritoneal fluid. Studies have not documented a strong correlation between the renoprotective mechanism and the diminution of renal platinum content.

Keywords: Amino acids; cisplatin; HPLC; nephrotoxicity; novel renoprotective; renal uptake.

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1. INTRODUCTION

All molecules containing platinum produce a hazardous effect on health because of the heavy poisonous metal, it is accumulated and not biodegradable by the human body [1,2]. Cisplatin (cis-diamine-dichloroplatinum (II), CDDP) is a prominent member of the broad-spectrum antitumor drugs. However, it is blamed for its prominent nephrotoxicity [3,4]. Acute and cumulative renal toxicity associated with histological damage has been shown in-vivo [5,6], in humans [7], and rat kidney slices model [8]. CDDP produces nephrotoxicity shortly after initiation of therapy or after long-term administration. In general, renal toxicity can be divided into two phases, an acute phase and a chronic phase [9]. The acute toxicity of CDDP is characterized by hypomagnesemia, hypokalemia, acute reduction in glomerular filtration rate, and high serum creatinine [10]. The chronic phase of renal dysfunction is characterized by low creatinine clearance with or without increment in serum creatinine [11]. Several studies have reported the devastating effects of CDDP as one of the most effective antineoplastic agents [3,4,6,8]. Indeed, the role of platinum uptake by the kidneys has been documented, however, the implication of CDDP-uptake in the renoprotective mechanism has not been fully clarified [12]. This review explored the main analytical methods which have been approved and used for CDDP analysis in biological fluids. In addition, the review aimed to elaborate the contribution of diminution of renal CDDP content as one of the mechanisms involved for the renoprotection of antioxidants and amino acids.

1.1 Mechanisms of Cisplatin Renal Tubules Damage

1.1.1 Oxidative stress and deoxyribonucleic acid (DNA) adduct formation

Histologically, the renal damage is mainly situated in the S3 segment of the proximal tubules in the outer stripe of the outer medulla and occurring rarely in the glomeruli [13]. Several in-vitro and in-vivo studies have suggested that CDDP-induced kidney injury is linked to the production of oxidative stress [12, 14], lipid peroxidation [15] and reduction in the concentration of protein thiol [16] play a role in this toxicity. Two serial studies found that high lipid peroxides level is not mediated by direct membrane lipids peroxidation but was attributed to a reduction of antioxidant enzymes [17, 18]. CDDP induced depletion of renal reduced glutathione GSH [16] and inhibition of antioxidant enzymes activity such as glutathione-S-transferase, glutathione peroxidase, catalase, and Cu-, Zn-superoxide dismutase in renal tissue, which shifts the cellular redox status resulting in an imbalance between free radicals and endogenous antioxidants occur leading to oxidative damage of membrane lipids [15, 19]. Also, selective inhibition of glutathione biosynthesis by buthionine sulfoximine is known to enhance CDDP nephrotoxicity [20], while glutathione ester coadministration along with CDDP protects against CDDP-induced nephrotoxicity [21, 22].

Another theory is based on a correlation of nephrotoxicity with structural changes in nuclear DNA of tubular cells through CDDP-induced interstrand and intrastrand DNA adducts as well as the adduct level in the kidney cells [23,24]. CDDP-induced renal toxicity is known to be of tubular origin [25], because the highest levels of CDDP -DNA adducts were seen in the renal tubules [26]. In addition, there is a good correlation between DNA adduct levels and drug efficacy as well as sensitivity in-vitro and in-vivo [27].

1.1.2 Renal uptake of cisplatin

The exact mechanism of CDDP nephrotoxicity is unclear. The vulnerability of the kidney to CDDP is linked to its crucial role in the excretion of both the intact drug and its platinum containing products [28]. CDDP is cleared by both glomerular filtration and tubular secretion [3], and the lower urinary excretion of CDDP might be due to a tubular reabsorptive process [29]. Thus, CDDP concentrations within the kidney exceed those in blood, which indicates accumulation of drug by renal parenchymal cells. In 1999, a strong correlation between the level of platinum in urine and nephrotoxicity because of reabsorption of the drug into the nephron was reported [30].

Moreover, there are two different membrane transporters capable of transporting CDDP into cells: Ctr1 and hOCT2 [31]. Ctr1; copper transporter which was also shown to mediate CDDP uptake into renal tubular [12]. hOCT2; the human organic cation transporter 2 isoform is the critical transporter for CDDP uptake in proximal tubules [32]. A problem was detected with these studies on the transporter-mediated distribution of CDDP is the use of strong nucleophiles as

competitors which might confound the results by chemically interacting with CDDP [33]. Two examples are copper sulfate [34] and Cimetidine, an OCT2 substrate, reduced CDDP uptake and cytotoxicity in vitro [35,36], and CDDP-induced nephrotoxicity in vivo [37]. Therefore, caution is warranted when interpreting the results of such studies.

2. ANALYTICAL METHODS FOR RENAL CISPLATIN CONTENT

Several analytical separating techniques are used for the determination of CDDP content such as flow injection chemiluminescence [38], inductively coupled plasma atomic emission spectrometry, gas chromatography, high-performance liquid chromatography (HPLC), and mass spectrometry [39-41].

2.1 Mass Spectrometry Technique

Several analytical methods were applied for the determination of platinum content in biological fluids such as plasma, urine, serum, and peritoneal fluid. One of these methods used is the inductively coupled plasma mass spectrometry technique [42]. The detection of platinum was achieved in the linear range of 0.01–100 ng/mL, with inter-and intraday precision and accuracy (≤15%), recovery, robustness and stability. It was found that the quantification limit was 18.0 ng/mL platinum in plasma, 8.0 ng/mL platinum in ultrafiltrate and 6.1 ng/mL in urine as well as the peritoneal fluid. The spectroscopic method was proposed for the detection of CDDP in the urine, but it has some disadvantages as the time required for derivatizing is 24 hours [43]. Cisplatin was determined in the urine and plasma by quenched phosphorescence in the range 5×10−7 to 5×10−5M. [44], while the interaction between CDDP and G-quadruplex DNA was used to detect CDDP by using the fluorescence method [45].

2.2 Atomic Absorption Spectrometry

The atomic absorption spectrometry technique was applied to assess CDDP and monohydrated form in plasma. The linearity was 60–600 and 87.5–700 nM for CDDP and monohydrated CDDP in deproteinized plasma, respectively. The lower limits of quantification of both CDDP and the monohydrated CDDP were 60 and 87.5 nM, respectively. The samples were taken from the patient who received 75mgm^{-2} cisplatin as a 1-h intravenous infusion. [46]. Accurate and sensitive Atomic Absorption Spectrometry (AAS) methods coated with graphite tube were developed by [47, 48] for analysis of CDDP in tissue and serum. Cisplatin was quantified using AAS by measuring the complex formed from its reaction with diethyldithiocarbamic acid, the complex was extracted into methylene chloride then mixed with acetonitrile to release the platinum which determined by Zeeman atomic absorption (AA) spectrophotometer [49].

An in vitro experiment to investigate the distribution of liposomal encapsulated CDDP in blood was developed by Meerum and coworkers [50]. In this method, total platinum concentration including the liposomal encapsulated platinum, protein-bound platinum released from the liposomes as well as the free platinum were assessed in plasma. In addition, a fraction of CDDP released from the liposomal carrier and the free platinum was measured in plasma ultrafiltrate by graphite furnace atomic absorption spectrometry (GF-AAS). As well CDDP was detected in the liposome and other biological fluids by (CE-ICP-MS) method [51] and by using HPLC [52] while the separation of the free CDDP from liposomal encapsulated and protein-bound was achieved by using a capillary electrophoresis inductively coupled plasma mass spectrometry (CE–ICP–MS) [53]. The electro analytical method was created for analysis of CDDP, the method based upon the replacement of mercury electrode by metallothionein and the determination of cisplatin were performed by adsorptive transfer stripping technique and differential pulse voltammetry [54].

Coupled plasma atomic emission spectrometric method was applied for the analysis of both CDDP and its hydrolysis products in addition to the two methionine–platinum complexes in aqueous solutions [55]. Moreover, A number of inductively coupled plasma– mass spectrometric methods were reported for the determination of CDDP [56-71]. From the aforementioned studies, modifications have been done to increase the accuracy of CDDP analysis in the biological fluids as well as purification of the platinum being analyzed.

2.3 High-performance Liquid Chromatography (HPLC)

HPLC methods are used for the separation of CDDP and its hydrolysis products using C18 column and a mobile phase composed of 3% (v/v) methanol, 0.05mMsodium dodecyl sulfate,

and pH 2.5 (adjusted with triflic acid) [72]. Two methods were reported. One needs a pre-treatment procedure and the detection wavelength is 210 nm [73]. The other needs an automated column switching technique [74]. Liquid chromatography post-column derivatization assay in plasma was proposed by Farrish et al., [75] who suggested that in order to increase the CDDP stability before being analyzed on a chemically generated anion exchange column, samples were treated with acetonitrile and a citrate buffer. The reaction forms a complex which is used for isolated of CDDP on an anion-exchange column using 0.125M succinic acid–sodium hydroxide buffer pH 5.2 and methanol (2:3, v/v) as a mobile phase at 344 nm [28] or its reaction with sodium bisulfite to give products which have enhanced absorptivity at 280–300 nm. Detection limit at 290 nm was 20 nM for CDDP [76]. However, while drugs containing platinum are not easy to be determined spectrophotometrically, post-column derivatization technique is used [77-79]. Unchanged CDDP and its metabolites were determined by HPLC with post-column derivatization [80].

Selective HPLC methods are applied for detection of CDDP either with its toxic impurities using 4-methyl-2-thiouracil at 315 nm [81], or by chelating with diethyldithiocarbamate and detection at 260 nm [82] or by pre-column derivatization of platinum with a mobile phase such as bis (salicylaldehyde) tetramethylethylenediimine methanol–acetonitrile–water and detection at 254 nm [83]. Two HPLC methods for quantization of CDDP using pre-column derivatization were proposed, the first based on the reaction of platinum with 2-acetylpyridine-4-phenyl-3-thiosemicarbazone to form a complex which extracted in chloroform and detected at 380 nm while the second method based on chelation of Pt(II) with N, N'-bis(salicylidene)-1,2-propanediamine and extraction of the neutral platinum complex, and detection at 254 nm [84,85]

A method was developed for the analysis of CDDP in plasma, cancer cell and tumor samples by Lopez et al. [86], the separation was carried out using methanol–acetonitrile–water as mobile phase with flow rate 1.6mLmin^{-1} and detection at 254 nm. Gradient elution on a reversed-phase column is used for the determination of CDDP with other anticancer drugs. [87]. To detect CDDP in plasma, A hexadecyltrimethylammonium loaded reversed-phase HPLC column with a 5mM citrate-buffered eluent (pH 6.5) is used in anion-exchange chromatography with on-line reductive electrochemical technique [88].

Liquid chromatography-mass assay was established for quantitation of CDDP in human [89] and in rat plasma and urine [90, 91] as well the same technique was used to study the effect of CDDP on liver and kidney [92] and the CDDP-water interaction was studied by [93] moreover the detection in blood was take placed by [94]. Indeed, a study has reported that Liquid chromatography-electro spray ionization tandem mass spectrometric (LC/ESI-MS/MS) was used to identify and characterize in-vivo metabolites of CDDP in rat kidneys [95], while Bandu and coworkers [96] used the same technique to study the distribution of CDDP. It could be concluded that HPLC is one of the most prominent methods used for the analysis of CDDP in renal or cancer tissues either to assess the nephrotoxicity or cytotoxicity indices of CDDP, respectively.

2.4 Mass Spectroscopy

The use of the mass spectroscopy is one of the most selective and sensitive techniques used for the analysis of platinum-containing drugs, CDDP was separated with its mono and dehydrated complexes using high-field asymmetric waveform ion mobility spectrometry (FAIMS) [97]. A combination of both size exclusion chromatography–ICP–MS (SEC–ICP–MS) and ESI-MS technique have been used to detect structural information of CDDP metabolites which react with metallothionein and GSH resulting in CDDP-mediated side effects [98]. Peleg-Shulman studied the interaction between platinum and the protein by using either ubiquitin or myoglobin as model protein and identified platinum–protein adducts [99], while other studies reported the binding of CDDP to transferrin [100,101]. Moreover, the same technique was used for quantitative analysis of phospholipid alteration in resistant and sensitive cancer cells to CDDP [102]. One of the methods was applied for comparison of different methods for determination of platinum – DNA interaction and study the advantages and disadvantages of these methods [103].

Determination of platinum was established by the colorimetric method. It was based on the change of the red color result from the binding of platinum with gold nanoparticles (AuNPs) to blue, this binding prevents aggregation of AuNPs in

the presence of cationic polymer. The absorbances were measured at 610 and 520 nm and the linearity was 0.24–2 μM [104].

2.5 Miscellaneous Methods

Because of the low solubility and non-volatile nature of CDDP, it is very difficult to determine it by the usual methods, and so it needs to use ESI-MS especially when it is used with the HPLC technique. Cui and his colleagues [105] applied this method to test the characteristics of CDDP and identify three hydrolysis products. Determination of CDDP in the pharmaceutical preparation and in blood samples of patients with cancer was carried out by using gas chromatography [106], the method based on the complex formation between platinum and bis(isovalerylacetone) ethylenediimine then extraction with chloroform.

Many methods were reported for analysis of CDDP by capillary electrophoresis, one of them applied to examine the behaviors of CDDP in sodium chloride solution, The reagent used for detection was 4-nitrosodimethylaniline [107], some of these methods used for separation the hydrolysis products of CDDP originated because physiological stimulation [108] as well two methods used micellar electrokinetic capillary chromatography were applied for separation of platinum in aqueous solution [109,110], and in tumor tissues [111]. Capillary electrophoresis is either used to validate the interaction between CDDP and human serum albumin [112] or to investigate the interaction between CDDP and other anticancer drugs and nucleotides [113-115], the absorption bands of the formed adducts were shifted compared to unmodified nucleotides.

3. NOVEL RENOPROTECTIVE STRATEGIES

As the anti-tumor activity and renal toxicity in CDDP-based chemotherapy are mediated in part by different mechanisms, selective inhibition of its nephrotoxicity might be achieved while retaining the antineoplastic activity [116]. Ibrahim and coworkers have stated that “continued aggressive high-dose CDDP necessitates investigating newer measures of preventing dose-limiting nephrotoxicity, that inhibit the administration of CDDP at tumoricidal doses” [117]. In recent years, newer therapeutic strategies are being investigated aimed at minimizing CDDP-induced nephrotoxicity while increasing its antitumor efficacy through the simultaneous supplementation of preventive agents. Such strategies may include 1) inhibition of pathways leading to activation of CDDP to a nephrotoxin, 2) reduction of renal uptake of platinum, 3) use of antioxidants to counter the effect of reactive oxygen molecules, 4) inhibition of CDDP-induced cell injury, MAPKs inhibitors, 5) inhibition of the inflammatory response by IL-10 and specific suppression of TNF-α can, 6) target inhibition of apoptotic mechanism activated by CDDP specifically in kidney cells, 7) uses of cytoprotective agents that can protect normal cells, but not tumor cells, from CDDP, 8) uses of agents that enhance cell proliferation and differentiation and finally, uses of novel therapies like serum thymic factor and amino acids.

3.1 Antioxidants and Renal Uptake of Cisplatin

Several studies have documented the importance of ROS in CDDP -induced renal cell apoptosis [5,118]. For example, ROS can induce Fas [119], activate p53 [120,121], alter mitochondrial permeability [122,123], release cytochrome c into the cytosol [124] and even directly activate caspases [125]. Thus, several studies have investigated the antiapoptotic effect of many antioxidants such as dimethylthiourea (DMTU), Indole 3 carbinol, N-acetly cysteine (NAC), sodiumthiosulfate (STS), carvedilol and coenzyme Q specifically provide partial protection against CDDP-induced apoptosis [126-130]. The question with many studies concerning the antiapoptotic effect of antioxidants is if the antiapoptotic effect is secondary to antioxidative stress and/or has an independent mechanism. Another question to consider is can the antioxidants reduce the platinum uptake by the kidney and how much the effect will be? It was found by El Naga and Mahran that Indole-3-carbinol ameliorated the CDDP induced-nephrotoxicity through antioxidant effect without altering the cellular uptake of CDDP [130], another older study by Hannemann and coworkers reported that the antioxidant N,N'diphenyl-p-phenylenediamine (DPPD) did not reduce the uptake of platinum compounds in rat renal cortical slices [131]. Conclusively, we suggested that there was no strong evidence that the antioxidants might have their renoprotection through suppression of renal platinum uptake. Therefore, further investigation is warranted to elaborate on the involvement of renal platinum uptake in the nephroprotection mechanism.

3.2 Amino Acids and Renal Uptake of Platinum

From two decades, it had been proved that amino acids and protein-derived peptides possess vasodilatory effects on renal vessels and improve glomerular filtration rate (GFR) [132, 133]. They increase RBF and GFR through an important renal vasodilator which is NO. Alanine [134], glycine, and glutathione [135] are reported to protect renal proximal tubules from hypoxic/anoxic injury.

The mechanisms involved in the cytoprotective effect of amino acids are not clarified. A study conducted by Weinberg & coworkers reported the cytoprotective effect of small amino acid including; glycine, D-alanine, L-alanine, and β-alanine [136]. It was proposed that the cytoprotective effect of neutral small amino acids is attributed to their ability to influence the tertiary protein structure of renal cell membranes. They could be accumulated within the cell without disrupting pH or binding to reactive sites on intracellular proteins, and so they would correct the membrane-damaging actions of cytotoxic agents [137].

In the last years, certain amino acids have been shown to prevent CDDP-induced nephrotoxicity in vivo: L-cysteine [138], L-methionine [139]), N-acetylcysteine [126], glycine [140], L-arginine [141], N-benzoyl-b-alanine [137] and glutamine [142]. However, the nephroprotective mechanisms are not well understood. Modulation of CDDP uptake in renal tissues by sulfur-amino acids had been suggested [143], Kroning and coworkers suggested that these amino acids such as N-acetylcysteine, cysteine, methionine, and DL-homocysteine might have prevented the CDDP-induced cytotoxicity in the kidney because of their inhibition of CDDP uptake in the cultured S1, S3, and DCT cells. They also suggested the structural element R-CH(NH2)-[CH2]1 2-S-R that might play a significant role in blocking the transport of CDDP.

Besides the sulfur-containing amino acids, few studies investigated the nephroprotective effect of glycine and L-arginine through a hemodynamic and non-hemodynamic nephroprotective mechanism that involves NO production [15, 141]. A study by Mahran et al. [8] has suggested for the first time the non-hemodynamic mechanisms of glycine and L-arginine nephroprotection against CDDP in rat renal cortical slices through the restoration of the antioxidant cellular defense mechanism. In addition, they added another new mechanism for L-arginine nephroprotection through lowering the platinum uptake by the kidney tissue.

Furthermore, the role of organic cation transporter 2 (OCT2) has been known in the nephroprotective mechanism of some amino acids and their derivatives. The human organic cation transporter 2 (hOCT2) is highly expressed in the renal proximal tubules and plays a crucial role in the secretion of platinum cation molecules. It was discovered that a single nucleotide polymorphism in hOCT2 gene (Ala270Ser) significantly reduced the platinum transport as well as the CDDP-induced toxicity compared to the wild-type hOCT2 [144]. A study by Kim and colleagues documented that glutamine inhibited the CDDP-induced expression of OCT2 which in turn inhibiting the CDDP accumulation and thus nephrotoxicity [145].

4. CONCLUSION

Several studies have reported the devastating effects of CDDP as one of the most effective antineoplastic agents. Indeed, the role of platinum uptake by the kidneys has been documented, however, the implication of CDDP-uptake in the renoprotective mechanism has not been fully clarified. Moreover, a number of analytical methods have been approved and used for CDDP analysis in biological fluids while studying the nephroprotective effect of several agents. In this context, we did not find a strong correlation between the renoprotection and the diminution of renal platinum content.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Besse J-P, Latour J-F, Garric J. Anticancer drugs in surface waters: what can we say about the occurrence and environmental

significance of cytotoxic, cytostatic and endocrine therapy drugs? Environment International. 2012;39(1):73-86.
2. Verma N, Singh M. Biosensors for heavy metals. Biometals. 2005;18(2):121-129.
3. Yao X, Panichpisal K, Kurtzman N, Nugent K. Cisplatin nephrotoxicity: A review. The American Journal of the Medical Sciences. 2007;334(2):115-124.
4. Ibrahim MY AA, Ibrahim TAT, AbdelWahab SI, Elhassan MM, Mohan S. Attenuation of cisplatin-induced nephrotoxicity in rats using zerumbone. African Journal of Biotechnology. 2010;9(28):4434-4441.
5. Mahran YF. New insights into the protection of growth hormone in cisplatin-induced nephrotoxicity: The impact of IGF-1 on the Keap1-Nrf2/HO-1 signaling. Life sciences. 2020;253:117581.
6. Hassan YFMaHM. Ganoderma lucidum prevents cisplatin-induced nephrotoxicity through inhibition of epidermal growth factor receptor signaling and autophagy-mediated apoptosis. Oxidative Medicine and Cellualar Longevity; 2020. In Press.
7. Vickers AEM RK, Fisher R, Saulnier M, Sahota P, Bentley P. Kidney slices of human and rat to characterize cisplatin-induced injury on cellular pathways and morphology. Toxicologic Pathol. 2004;32:577–590.
8. Mahran YFK KA, El-Demerdash E. A comparative study of protective mechanisms of glycine and L-arginine against cisplatin-induced nephrotoxicity in rat renal cotitoxicity in rat renal cotical slices. Drug Discoveries and Therapeutics; 2010.
9. Massry G. Textbook of Nephrology, edn 3 edn: Baltimore: Williams & Wilkins; 1995.
10. Arany I, Safirstein RL. Cisplatin nephrotoxicity. Seminars in Nephrology. 2003;23(5):460-464.
11. Pinzani V BF, Haug IJ, Galtier M, Blayac JP, Balmès P. Cisplatin-induced renal toxicity and toxicity-modulating strategies: A review. Cancer Chemother Pharmacol. 1994;35(1):1-9.
12. Pabla N, Dong Z. Cisplatin nephrotoxicity: mechanisms and renoprotective strategies. Kidney International. 2008;73(9):994-1007.
13. Cristofori P ZE, Fregona D, Piaia A, Trevisan A. Renal proximal tubule segment-specific nephrotoxicity: An overview on biomarkers and histopathology. Toxicologic Pathol. 2007; 35:270–275.
14. Kuhlmann M, Burkhardt G, Köhler H. Insights into potential cellular mechanisms of cisplatin nephrotoxicity and their clinical application. Nephrology, dialysis, transplantation: Official publication of the European dialysis and transplant association-european renal association 1997;12(12):2478-2480.
15. Saleh S, El-Demerdash E. Protective effects of l-arginine against cisplatin-induced renal oxidative stress and toxicity: role of nitric oxide. Basic & Clinical Pharmacology & Toxicology 2005; 97(2):91-97.
16. Ray S, Roy K. Evaluation of protective effects of water extract of Spirulina platensis (blue green algae) on cisplatin-induced lipid peroxidation. Indian Journal of Pharmaceutical Sciences. 2007; 69(3):378.
17. Yasuyuki S, Takahiro S, Yoshio T. Change of lipid peroxide levels in rat tissues after cisplatin administration. Toxicology Letters. 1991;57(2):159-166.
18. Yasuyuki S, Takahiro S, Yoshio T. Mechanism of the increase in lipid peroxide induced by cisplatin in the kidneys of rats. Toxicology Letters. 1992;62(2):293-300.
19. Ateşşahín A, Çeríbaşi AO, Yuce A, Bulmus Ö, Çikim G. Role of ellagic acid against cisplatin-induced nephrotoxicity and oxidative stress in rats. Basic & Clinical Pharmacology & Toxicology. 2007;100(2):121-126.
20. Li X-M, Filipski E, Lévi F. Pharmacological modulation of cisplatin toxicity rhythms with buthionine sulfoximine in mice bearing pancreatic adenocarcinoma (PO3). Chronobiology International. 1998;15(4):323-335.
21. Babu E, Gopalakrishnan V, Sriganth INP, Gopalakrishnan R, Sakthisekaran D. Cisplatin induced nephrotoxicity and the modulating effect of glutathione ester. Molecular and Cellular Biochemistry. 1995;144(1):7-11.
22. Babu E, Ebrahim AS, Chandramohan N, Sakthisekaran D. Case report: Rehabilitating role of glutathione ester on cisplatin induced nephrotoxicity. Renal Failure. 1999;21(2):209-217.
23. Poirier MC, Reed E, Litterst CL, Katz D, Gupta-Burt S. Persistence of platinum-ammine-DNA adducts in gonads and kidneys of rats and multiple tissues from

cancer patients. Cancer Research. 1992;52(1):149-153.

24. Yoshida M, Khokhar AR, Kido Y, Ali-Osman F, Siddik ZH. Correlation of total and interstrand DNA adducts in tumor and kidney with antitumor efficacies and differential nephrotoxicities of cis-ammine/cyclohexylamine-dichloroplatinum (II) and cisplatin. Biochemical Pharmacology 1994;48(4):793-799.
25. Brady H, Zeidel M, Kone B, Giebisch G, Gullans S. Differential actions of cisplatin on renal proximal tubule and inner medullary collecting duct cells. Journal of Pharmacology and Experimental Therapeutics. 1993;265(3):1421-1428.
26. Johnsson A, Olsson C, Nygren O, Nilsson M, Seiving B, Cavallin-Stahl E. Pharmacokinetics and tissue distribution of cisplatin in nude mice: platinum levels and cisplatin-DNA adducts. Cancer Chemotherapy and Pharmacology. 1995;37(1-2):23-31.
27. Welters M, Fichtinger-Schepman A, Baan R, Jacobs-Bergmans A, Kegel A, Van Der Vijgh W, Braakhuis B. Pharmacodynamics of cisplatin in human head and neck cancer: correlation between platinum content, DNA adduct levels and drug sensitivity in vitro and in vivo. British Journal of Cancer. 1999;79(1):82.
28. Andersson A, Fagerberg J, Lewensohn R, Ehrsson H. Pharmacokinetics of cisplatin and its monohydrated complex in humans. Journal of Pharmaceutical Sciences. 1996;85(8):824-827.
29. Daley-Yates PT MD: Nephrotoxicity, Assessment and Pathogenesis: Wiley, Chichester; 1982.
30. Kroning R, Katz D, Lichtenstein AK, Nagami GT. Differential effects of cisplatin in proximal and distal renal tubule epithelial cell lines. British Journal of Cancer. 1999;79(2):293-299.
31. Miller RP, Tadagavadi RK, Ramesh G, Reeves WB. Mechanisms of cisplatin nephrotoxicity. Toxins. 2010;2(11):2490-2518.
32. Filipski KK, Loos WJ, Verweij J, Sparreboom A. Interaction of Cisplatin with the human organic cation transporter 2. *Clinical Cancer Research : An Official Journal of the American Association for Cancer Research.* 2008;14(12):3875-3880.
33. Ehrsson H, Wallin I. Cimetidine as an organic cation transporter antagonist. The American Journal of Pathology. 2010;177(3):1573-1574; author reply 1574.
34. More SS, Akil O, Ianculescu AG, Geier EG, Lustig LR, Giacomini KM: Role of the copper transporter, CTR1, in platinum-induced ototoxicity. The Journal of neuroscience : The Official Journal of the Society for Neuroscience. 2010;30(28):9500-9509.
35. Pabla N MR, 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:F505–F511.
36. Ciarimboli G, Ludwig T, Lang D, Pavenstädt H, Koepsell H, Piechota H-J, Haier J, Jaehde U, Zisowsky J, Schlatter E. Cisplatin Nephrotoxicity Is Critically Mediated via the Human Organic Cation Transporter 2. The American Journal of Pathology. 2005;167(6):1477-1484.
37. Ciarimboli G, Deuster D, Knief A, Sperling M, Holtkamp M, Edemir B, Pavenstädt H, Lanvers-Kaminsky C, am Zehnhoff-Dinnesen A, Schinkel AH. Organic cation transporter 2 mediates cisplatin-induced oto-and nephrotoxicity and is a target for protective interventions. The American Journal of Pathology. 2010; 176(3):1169-1180.
38. Wang X, Yin X, Cheng H. Microflow injection chemiluminescence system with spiral microchannel for the determination of cisplatin in human serum. Analytica Chimica Acta. 2010; 678(2):135-139.
39. Verschraagen M, van der Born K, Zwiers TU, van der Vijgh WJ. Simultaneous determination of intact cisplatin and its metabolite monohydrated cisplatin in human plasma. Journal of Chromatography B. 2002;772(2):273-281.
40. Bosch ME, Sánchez AR, Rojas FS, Ojeda CB. Analytical methodologies for the determination of cisplatin. Journal of Pharmaceutical and Biomedical Analysis. 2008;47(3):451-459.
41. Ye L, Xiang M, Lu Y, Gao Y, Pang P. Electrochemical determination of cisplatin in serum at graphene oxide/multi-walled carbon nanotubes modified glassy carbon electrode. Int J Electrochem Sci. 2014;9:1537-1546.
42. Lemoine L, Thijssen E, Noben J-P, Adriaensens P, Carleer R, Van der Speeten K. A validated inductively coupled plasma mass spectrometry (ICP-MS)

method for the quantification of total platinum content in plasma, plasma ultrafiltrate, urine and peritoneal fluid. Journal of Pharmaceutical and Biomedical Analysis. 2018;152:39-46.
43. Inagaki K, Yonehara S, Kidani Y. Direct determination of cis-dichlorodiammineplatinum (II) in urine by derivative spectroscopy. Chemical and Pharmaceutical Bulletin. 1985;33(8):3369-3374.
44. Baumann R, Gooijer C, Velthorst N, Frei R, Klein I, Van der Vijgh W. Quantitative determination of cisplatin in body fluids by liquid chromatography with quenched phosphorescence detection. Journal of Pharmaceutical and Biomedical Analysis. 1987;5(2):165-170.
45. Yang H, Cui H, Wang L, Yan L, Qian Y, Zheng XE, Wei W, Zhao J. A label-free G-quadruplex DNA-based fluorescence method for highly sensitive, direct detection of cisplatin. Sensors and Actuators B: Chemical. 2014;202:714-720.
46. Verschraagen KV M, Zwiers THU, Van der Vijgh. WJF J Chromatogr B: Anal Technol Biomed Life Sci. 2002;772:273–281.
47. Bu XS HF, Dou HM. Chin Pharm Bull. 1999;15:380–381.
48. Xiao M, Huang Z, Cai J, Jia J, Zhang Y, Dong W, Wang Z. Comparison of different sample preparation methods for platinum determination in cultured cells by graphite furnace atomic absorption spectrometry. PeerJ. 2017;5:e2873.
49. Raghavan R, Mulligan JA. Low-level (PPB) determination of cisplatin in cleaning validation (rinse water) samples. I. An atomic absorption spectrophotometric method. Drug Dev Ind Pharm. 2000;26(4):423-428.
50. Meerum Terwogt MMT JM, Welbank H, Schellens JHM, Beijnen JH. Fresenius J Anal Chem. 2000;366:298–302.
51. Nguyen TT, Østergaard J, Stürup S, Gammelgaard B. Determination of platinum drug release and liposome stability in human plasma by CE-ICP-MS. International Journal of Pharmaceutics 2013;449(1-2):95-102.
52. Toro-Córdova A, Ledezma-Gallegos F, Mondragon-Fuentes L, Jurado R, Medina LA, Pérez-Rojas JM, Garcia-Lopez P. Determination of liposomal cisplatin by high-performance liquid chromatography and its application in pharmacokinetic studies. Journal of Chromatographic Science. 2016;54(6):1016-1021.
53. Nguyen TT, Østergaard J, Stürup S, Gammelgaard B. Metallomics in drug development: characterization of a liposomal cisplatin drug formulation in human plasma by CE–ICP–MS. Analytical and bioanalytical chemistry. 2013;405(6):1845-1854.
54. J. Petrlova DP, J. Zehnalek, B. Sures, V. Adam, L. Trnkova, R., Kizek. Electrochim Acta. 2006;51:5169–5173.
55. de Waal WA, Maessen FJ, Kraak JC. Analysis of platinum species originating from cis-diamminedichloroplatinum(II) (cisplatin) in human and rat plasma by high-performance liquid chromatography with on-line inductively coupled plasma atomic emission spectrometric detection. Journal of Chromatography. 1987;407:253-272.
56. Bell DN, Liu JJ, Tingle MD, McKeage MJ. Specific determination of intact cisplatin and monohydrated cisplatin in human plasma and culture medium ultrafiltrates using HPLC on-line with inductively coupled plasma mass spectrometry. Journal of chromatography B, Analytical Technologies in the Biomedical and Life Sciences. 2006;837(1-2):29-34.
57. Cairns WR, Ebdon L, Hill SJ. A high performance liquid chromatography - inductively coupled plasma-mass spectrometry interface employing desolvation for speciation studies of platinum in chemotherapy drugs. Anal Bioanal Chem. 1996;355(3-4):202-208.
58. Esteban-Fernandez D, Gomez-Gomez MM, Canas B, Verdaguer JM, Ramirez R, Palacios MA. Speciation analysis of platinum antitumoral drugs in impacted tissues. Talanta. 2007;72(2):768-773.
59. Falter R, Wilken RD. Determination of carboplatinum and cisplatinum by interfacing HPLC with ICP-MS using ultrasonic nebulisation. The Science of the total environment. 1999;225(1-2):167-176.
60. Hahn M, Kleine M, Sheldrick WS. Interaction of cisplatin with methionine- and histidine-containing peptides: competition between backbone binding, macrochelation and peptide cleavage. Journal of Biological Inorganic Chemistry : JBIC : A Publication of the Society of Biological Inorganic Chemistry. 2001;6(5-6):556-566.

61. Hann S, Stefanka Z, Lenz K, Stingeder G. Novel separation method for highly sensitive speciation of cancerostatic platinum compounds by HPLC-ICP-MS. Anal Bioanal Chem. 2005; 381(2):405-412.
62. Hann S, Zenker A, Galanski M, Bereuter TL, Stingeder G, Keppler BK. HPIC-UV-ICP-SFMS study of the interaction of cisplatin with guanosine monophosphate. Fresenius' Journal of Analytical Chemistry. 2001;370(5):581-586.
63. Inagaki K, Sawaki K. Reaction of (1R,2S,3S)-3-methylcyclohexanediamineplatinum(II) with DNA: isolation and characterization of the platinum-nucleotide adducts by means of HPLC and NMR spectroscopy. Chemical & Pharmaceutical Bulletin. 1995;43(2):183-188.
64. Heudi AC O, Allain P. Chromatographia. 1997;44:19–24.
65. Da Col LS R, Baiocchi C, Giacosa D, Viano I. J Chromatogr. 1993;633:119–128.
66. Reeder F, Guo Z, Murdoch PD, Corazza A, Hambley TW, Berners-Price SJ, Chottard JC, Sadler PJ. Platination of a GG site on single-stranded and double-stranded forms of a 14-base oligonucleotide with diaqua cisplatin followed by NMR and HPLC -- influence of the platinum ligands and base sequence on 5'-G versus 3'-G platination selectivity. European Journal of Biochemistry. 1997;249(2):370-382.
67. S. Hann GK, Zs. Stefanka, G. Stingeder, M. F¨urhacker, W., Buchberger RMM. J Anal Spectrom. 2003;18:1391–1395.
68. Zhao Z, Tepperman K, Dorsey JG, Elder RC. Determination of cisplatin and some possible metabolites by ion-pairing chromatography with inductively coupled plasma mass spectrometric detection. Journal of Chromatography. 1993;615(1):83-89.
69. Wagle SA, Jain D, Rathod S, Athawale R, Bajaj A. Development and validation of inductively coupled plasma atomic emission spectroscopy [icp-aes] analytical method for estimation of cisplatin in biological samples. Indian Journal Of Pharmaceutical Education And Research. 2017;51(4):S783-S789.
70. Torres MG, Torres CM, Torres AM, Munoz SV, Talavera RR, Ruiz-Baltazar AdJ, Brostow W. Validation of a method to quantify platinum in cisplatin by inductively-coupled plasma. Chemistry & Chemical Technology. 2017;11(4):437-444.
71. Hermann G, Heffeter P, Falta T, Berger W, Hann S, Koellensperger G. *In vitro* studies on cisplatin focusing on kinetic aspects of intracellular chemistry by LC-ICP-MS. Metallomics 2013; 5(6):636-647.
72. El-Khateeb M, Appleton TG, Charles BG, Gahan LR. Development of HPLC conditions for valid determination of hydrolysis products of cisplatin. Journal of Pharmaceutical Sciences. 1999;88(3):319-326.
73. Kizu R, Higashi S, Miyazaki M. A method for determining cis-dichlorodiammineplatinum(II) in plasma and urine by high performance liquid chromatography with direct ultraviolet detection. Chemical & Pharmaceutical Bulletin. 1985;33(10):4614-4617.
74. Riley CM, Sternson LA, Repta AJ, Siegler RW. High-performance liquid chromatography of platinum complexes on solvent generated anion exchangers. III. Application to the analysis of cisplatin in urine using automated column switching. Journal of Chromatography. 1982; 229(2):373-386.
75. Farrish HH, Hsyu PH, Pritchard JF, Brouwer KR, Jarrett J. Validation of a liquid chromatography post-column derivatization assay for the determination of cisplatin in plasma. J Pharm Biomed Anal. 1994;12(2):265-271.
76. Kizu R, Yamamoto T, Yokoyama T, Tanaka M, Miyazaki M. A sensitive postcolumn derivatization/UV detection system for HPLC determination of antitumor divalent and quadrivalent platinum complexes. Chemical & pharmaceutical bulletin. 1995;43(1):108-114.
77. Kinoshita M, Yoshimura N, Ogata H, Tsujino D, Takahashi T, Takahashi S, Wada Y, Someya K, Ohno T, Masuhara K et al. High-performance liquid chromatographic analysis of unchanged cis-diamminedichloroplatinum (cisplatin) in plasma and urine with post-column derivatization. Journal of Chromatography. 1990;529(2):462-467.
78. Hanada K, Mukasa Y, Nomizo Y, Ogata H. Effect of buthionine sulphoximine, glutathione and methimazole on the renal disposition of cisplatin and on cisplatin-induced nephrotoxicity in rats: pharmacokinetic-toxicodynamic analysis. The Journal of Pharmacy and Pharmacology. 2000;52(12):1483-1490.

79. Hanada K, Ninomiya K, Ogata H. Pharmacokinetics and toxicodynamics of cisplatin and its metabolites in rats: relationship between renal handling and nephrotoxicity of cisplatin. *The Journal of pharmacy and pharmacology* 2000, 52(11):1345-1353.
80. Hanada K, Nagai N, Ogata H: Quantitative determination of unchanged cisplatin in rat kidney and liver by high-performance liquid chromatography. Journal of Chromatography B, Biomedical Applications. 1995;663(1):181-186.
81. Ari¨oz GYı F, D¨olen E. Chromatographia. 1999;49:562–566.
82. Augey V, Cociglio M, Galtier M, Yearoo R, Pinsani V, Bressolle F. High-performance liquid chromatographic determination of cis-dichlorodiammineplatinum(II) in plasma ultrafiltrate. J Pharm Biomed Anal. 1995;13(9):1173-1178.
83. Khuhawar MY, Lanjwani SN, Memon SA. High-performance liquid chromatographic determination of cisplatin as platinum(II) in a pharmaceutical preparation and blood samples of cancer patients. Journal of Chromatography B, Biomedical Sciences and Applications. 1997; 693(1):175-179.
84. Khuhawar MY, Arain GM. Liquid chromatographic determination of cis-platin as platinum(II) in pharmaceutical preparation, serum and urine samples of cancer patients. Talanta. 2005;66(1):34-39.
85. Lanjwani SN, Zhu R, Khuhawar MY, Ding Z. High performance liquid chromatographic determination of platinum in blood and urine samples of cancer patients after administration of cisplatin drug using solvent extraction and N,N'-bis(salicylidene)-1,2-propanediamine as complexation reagent. J Pharm Biomed Anal. 2006;40(4):833-839.
86. Lopez-Flores A, Jurado R, Garcia-Lopez P: A high-performance liquid chromatographic assay for determination of cisplatin in plasma, cancer cell, and tumor samples. Journal of Pharmacological and Toxicological methods. 2005;52(3):366-372.
87. Macka M, Borak J, Kiss F. Separation of some platinum(II) complexes by ionic strength gradient on a solvent-generated ion-exchange sorbent. Journal of Chromatography. 1991;586(2):291-295.
88. Treskes JDJ M, Leeuwenkamp OR, Van Der Vijgh WJF. J Liquid Chromatogr. 1990;13:1321–1338.
89. Gerina-Berzina A, Hasnere S, Kolesovs A, Umbrashko S, Muceniece R, Nakurte I. Determination of cisplatin in human blood plasma and urine using liquid chromatography-mass spectrometry for oncological patients with a variety of fatty tissue mass for prediction of toxicity. Experimental Oncology. 2017;39(2):124-130.
90. Shaik AN, Altomare DA, Lesko LJ, Trame MN. Development and validation of a LC–MS/MS assay for quantification of cisplatin in rat plasma and urine. Journal of Chromatography B. 2017;1046:243-249.
91. Xia H, Zhang W, Li Y, Yu C. High performance liquid chromatography: Tandem mass spectrometric determination of cisplatin levels in different visceral pleura layers of rats. *Oncology letters* 2015, 9(5):2388-2392.
92. Katanić J, Matić S, Pferschy-Wenzig E-M, Kretschmer N, Boroja T, Mihailović V, Stanković V, Stanković N, Mladenović M, Stanić S. Filipendula ulmaria extracts attenuate cisplatin-induced liver and kidney oxidative stress in rats: *In vivo* investigation and LC-MS analysis. Food and Chemical Toxicology. 2017;99:86-102.
93. Vidmar J, Martinčič A, Milačič R, Ščančar J. Speciation of cisplatin in environmental water samples by hydrophilic interaction liquid chromatography coupled to inductively coupled plasma mass spectrometry. Talanta. 2015;138:1-7.
94. Yaroshenko D, Grigoriev A, Sidorova A, Kartsova L. Determination of cisplatin in blood plasma by liquid chromatography with mass spectrometry detection. Journal of Analytical Chemistry. 2013;68(2):156-160.
95. Bandu R, Ahn HS, Lee JW, Kim YW, Choi SH, Kim HJ, Kim KP. Liquid chromatography electrospray ionization tandem mass spectrometric (LC/ESI-MS/MS) study for the identification and characterization of in vivo metabolites of cisplatin in rat kidney cancer tissues: Online hydrogen/deuterium (H/D) exchange study. PloS one. 2015;10(8):e0134027.
96. Bandu R, Ahn HS, Lee JW, Kim YW, Choi SH, Kim HJ, Kim KP. Distribution study of cisplatin in rat kidney and liver cancer tissues by using liquid chromatography

electrospray ionization tandem mass spectrometry. Journal of Mass Spectrometry. 2015;50(6):844-853.
97. Cui M, Ding L, Mester Z. Separation of cisplatin and its hydrolysis products using electrospray ionization high-field asymmetric waveform ion mobility spectrometry coupled with ion trap mass spectrometry. Analytical Chemistry. 2003;75(21):5847-5853.
98. D. Esteban-Fern´andez BCn, I. Pizarro, M.A. Palacios, M.M. G´omez-, G´omez. J Anal At Spectrom. 2007;22:1113–1121.
99. Peleg-Shulman T, Gibson D. Cisplatin-protein adducts are efficiently removed by glutathione but not by 5'-guanosine monophosphate. Journal of the American Chemical Society. 2001;123(13):3171-3172.
100. Khalaila I, Allardyce CS, Verma CS, Dyson PJ. A mass spectrometric and molecular modelling study of cisplatin binding to transferrin. Chem Bio Chem. 2005;6(10):1788-1795.
101. Allardyce CS, Dyson PJ, Coffey J, Johnson N. Determination of drug binding sites to proteins by electrospray ionisation mass spectrometry: the interaction of cisplatin with transferrin. Rapid communications in mass spectrometry : RCM. 2002;16(10):933-935.
102. Cadoni E, Vanhara P, Valletta E, Pinna E, Vascellari S, Caddeo G, Isaia F, Pani A, Havel J, Pivetta T. Mass spectrometry discrimination of phospholipid patterns in cisplatin-resistant and sensitive cancer cells. Rapid Communications in Mass Spectrometry; 2018.
103. Sar DG, Montes-Bayón M, Blanco-González E, Sanz-Medel A. Quantitative methods for studying DNA interactions with chemotherapeutic cisplatin. TrAC Trends in Analytical Chemistry. 2010;29(11):1390-1398.
104. Sang F, Liu J, Zhang X, Pan J. An aptamer-based colorimetric Pt (II) assay based on the use of gold nanoparticles and a cationic polymer. Microchimica Acta. 2018;185:1-8.
105. Cui M, Mester Z. Electrospray ionization mass spectrometry coupled to liquid chromatography for detection of cisplatin and its hydrated complexes. Rapid Communications in Mass Spectrometry : RCM. 2003;17(14):1517-1527.
106. MY Khuhawar AAM, Bhanger MI. Chromatographia. 1999;49:249–252.
107. M. Lederer EL-P. Anal Chim Acta. 1998;358:61–68.
108. Zenker A, Galanski M, Bereuter TL, Keppler BK, Lindner W. Kinetics of binding properties of 5'-GMP with cisplatin under simulated physiological conditions by capillary electrophoresis. Journal of chromatography B, Biomedical Sciences and Applications. 2000;745(1):211-219.
109. B.W. Wenclawiak MW. J Chromatogr A. 1996;724:317–326.
110. Huang Z, Timerbaev AR, Keppler BK, Hirokawa T. Determination of cisplatin and its hydrolytic metabolite in human serum by capillary electrophoresis techniques. Journal of Chromatography A. 2006;1106(1-2):75-79.
111. El-Attug M, Ammar A, Elhamili A, Kamour R, Almog T, Saad S, Van Schepdael A: Development and validation of a micellar electrokinetic capil-lary chromatography method for determination of cisplatin in tumor tissue. *J Chem Pharm Res* 2013, 5:308-313.
112. Timerbaev AR, Aleksenko SS, Polec-Pawlak K, Ruzik R, Semenova O, Hartinger CG, Oszwaldowski S, Galanski M, Jarosz M, Keppler BK. Platinum metallodrug-protein binding studies by capillary electrophoresis-inductively coupled plasma-mass spectrometry: characterization of interactions between Pt(II) complexes and human serum albumin. Electrophoresis. 2004;25(13):1988-1995.
113. Kung A, Strickmann DB, Galanski M, Keppler BK. Comparison of the binding behavior of oxaliplatin, cisplatin and analogues to 5'-GMP in the presence of sulfur-containing molecules by means of capillary electrophoresis and electrospray mass spectrometry. Journal of Inorganic Biochemistr. 2001;86(4):691-698.
114. Zenker A, Galanski M, Bereuter TL, Keppler BK, Lindner W. Capillary electrophoretic study of cisplatin interaction with nucleoside monophosphates, di- and trinucleotides. Journal of Chromatography A.1999;852(1):337-346.
115. Zenker A, Galanski M, Bereuter TL, Keppler BK, Lindner W. Time-dependent interactions of platinum(II) complexes with 5'-GMP under simulated physiological conditions studies by capillary electrophoresis. Journal of Biological

Inorganic Chemistry : JBIC : a Publication of the Society of Biological Inorganic Chemistry. 2000;5(4):498-504.

116. Leonetti C, Biroccio A, Gabellini C, Scarsella M, Maresca V, Flori E, Bove L, Pace A, Stoppacciaro A, Zupi G. α-tocopherol protects against cisplatin-induced toxicity without interfering with antitumor efficacy. International Journal of Cancer. 2003;104(2):243-250.
117. Ibrahim MA, Ashour OM, Ibrahim YF, El-Bitar HI, Gomaa W, Abdel-Rahim SR. Angiotensin-converting enzyme inhibition and angiotensin AT1-receptor antagonism equally improve doxorubicin-induced cardiotoxicity and nephrotoxicity. Pharmacological Research. 2009;60(5):373-381.
118. Xiao T, Choudhary S, Zhang W, Ansari N, Salahudeen A. Possible involvement of oxidative stress in cisplatin-induced apoptosis in LLC-PK1 cells. Journal of Toxicology and Environmental Health Part A. 2003;66(5):469-479.
119. Bauer MK, Vogt M, Los M, Siegel J, Wesselborg S, Schulze-Osthoff K. Role of reactive oxygen intermediates in activation-induced CD95 (APO-1/Fas) ligand expression. Journal of Biological Chemistry. 1998;273(14):8048-8055.
120. Chandel NS, Vander Heiden MG, Thompson CB, Schumacker PT. Redox regulation of p53 during hypoxia. Oncogene. 2000;19(34):3840.
121. Hassan HM, Al-Wahaibi LH, Elmorsy MA, Mahran YF. Suppression of cisplatin-induced hepatic injury in rats through alarmin high-mobility group box-1 pathway by *Ganoderma lucidum*: Theoretical and experimental study. Drug design, development and therapy 2020;14:2335-2353.
122. Kruidering M, Van De Water B, De Heer E, Mulder GJ, Nagelkerke JF. Cisplatin-induced nephrotoxicity in porcine proximal tubular cells: mitochondrial dysfunction by inhibition of complexes I to IV of the respiratory chain. Journal of Pharmacology and Experimental Therapeutics. 1997;280(2):638-649.
123. Nowak G. PKC-α and ERK1/2 mediate mitochondrial dysfunction, decreases in active Na+ transport, and cisplatin-induced apoptosis in renal cells. Journal of Biological Chemistry; 2002.
124. Reed JC. Cytochrome c: can't live with it—can't live without it. Cell 1997;91(5):559-562.
125. Higuchi M, Honda T, Proske RJ, Yeh ET. Regulation of reactive oxygen species-induced apoptosis and necrosis by caspase 3-like proteases. Oncogene. 1998;17(21):2753.
126. Dickey DT, Wu YJ, Muldoon LL, Neuwelt EA. Protection against cisplatin-induced toxicities by N-acetylcysteine and sodium thiosulfate as assessed at the molecular, cellular, and in vivo levels. Journal of Pharmacology and Experimental Therapeutics. 2005;314(3):1052-1058.
127. Tsuji T, Kato A, Yasuda H, Miyaji T, Luo J, Sakao Y, Ito H, Fujigaki Y, Hishida A. The dimethylthiourea-induced attenuation of cisplatin nephrotoxicity is associated with the augmented induction of heat shock proteins. Toxicology and Applied Pharmacology. 2009;234(2):202-208.
128. Fouad AA, Al-Sultan AI, Refaie SM, Yacoubi MT. Coenzyme Q10 treatment ameliorates acute cisplatin nephrotoxicity in mice. Toxicology. 2010;274(1-3):49-56.
129. Rodrigues MC, Rodrigues J, Martins N, Barbosa F, Curti C, Santos N, Santos A. Carvedilol protects against cisplatin-induced oxidative stress, redox state unbalance and apoptosis in rat kidney mitochondria. Chemico-Biological Interactions. 2011;189(1-2):45-51.
130. El-Naga RN, Mahran YF. Indole-3-carbinol protects against cisplatin-induced acute nephrotoxicity: role of calcitonin gene-related peptide and insulin-like growth factor-1. Scientific Report. 2016;6:29857.
131. Hannemann J, Baumann K. Nephrotoxicity of cisplatin, carboplatin and transplatin. A comparative in vitro study. Archives of Toxicology. 1990;64(5):393-400.
132. Brezis M, Silva P, Epstein F. Amino acids induce renal vasodilatation in isolated perfused kidney: coupling to oxidative metabolism. American Journal of Physiology-Heart and Circulatory Physiology. 1984;247(6):H999-H1004.
133. Rodríguez-Iturbe B, Herrera J, García R. Relationship between glomerular filtration rate and renal blood flow at different levels of protein-induced hyperfiltration in man. Clinical Science. 1988;74(1):11-15.
134. Garza-Quintero R, Ortega-Lopez J, Stein J, Venkatachalam MA. Alanine protects rabbit proximal tubules against anoxic injury in vitro. American Journal of

Physiology-Renal Physiology. 1990;258(4):F1075-F1083.
135. Weinberg JM, Davis JA, Abarzua M, Rajan T. Cytoprotective effects of glycine and glutathione against hypoxic injury to renal tubules. The Journal of Clinical Investigation. 1987;80(5):1446-1454.
136. Weinberg JM, Davis JA, Abarzua M, Smith RK, Kunkel R. Ouabain-induced lethal proximal tubule cell injury is prevented by glycine. American Journal of Physiology-Renal Physiology.1990;258(2):F346-F355.
137. Tokunaga J KM, Nakamura C, Kitagawa A, Arimori K, Nakano M. Protective effect of N-benzoyl-beta-alanine against cisplatin nephrotoxicity in rats. Ren Fail. 1996;18(2):225-240.
138. El Daly ES. Protective effect of cysteine and vitamin E, Crocus sativus and Nigella sativa extracts on cisplatin-induced toxicity in rats. Journal De Pharmacie De Belgique. 1998;53(2):87.
139. Basinger MA JM, Holscher MA. Effect of glycine on cisplatin nephrotoxicity and heat-shock protein 70 expression in the rat kidney. Toxicol Appl Pharmacol. 1990;103(1):1-15.
140. Musio F, Carome MA, Bohen EM, Sabnis S, Yuan CM. Effect of glycine on cisplatin nephrotoxicity and heat-shock protein 70 expression in the rat kidney. Renal Failure. 1997; 19(1):33-46.
141. Quan L, Bowmer CJ, Yates MS. Effect of arginine on cisplatin-induced acute renal failure in the rat. Biochemical Pharmacology. 1994;47(12):2298-2301.
142. de Oliveira Mora L, Antunes LMG, Francescato HsDC, Bianchi MdLP. The effects of oral glutamine on cisplatin-induced nephrotoxicity in rats. Pharmacological Research. 2003;47(6):517-522.
143. Kröning R, Lichtenstein A, Nagami G. Sulfur-containing amino acids decrease cisplatin cytotoxicity and uptake in renal tubule epithelial cell lines. Cancer Chemotherapy and Pharmacology. 2000;45(1):43-49.
144. Frenzel D, Köppen C, Bauer OB, Karst U, Schröter R, Tzvetkov MV, Ciarimboli G. Effects of single nucleotide polymorphism ala270ser (rs316019) on the function and regulation of hOCT2. Biomolecules. 2019;9(10).
145. Kim HJ, Park DJ, Kim JH, Jeong EY, Jung MH, Kim TH, Yang JI, Lee GW, Chung HJ, Chang SH. Glutamine protects against cisplatin-induced nephrotoxicity by decreasing cisplatin accumulation. Journal of Pharmacological Sciences. 2015;127(1): 117-126.

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