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Antioxidants and cisplatin nephrotoxicity; an updated review on current knowledge

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ABSTRACT

Cisplatin is a first-line antitumor drug which is applied in the therapeutic field of numerous kinds of cancers. The main dose-dependent adverse effect of cisplatin is nephrotoxicity in approximately one-third of patients, who received this drug during their treatment. Oxidative stress is one of the most significant mechanisms in cisplatin nephrotoxicity. Cisplatin-induced oxidative stress stimulates apoptosis, inflammation, mitochondrial damage within cells, and endoplasmic reticulum (ER) stress. The administration of an antioxidant in this context could be a suitable approach for preventing of cisplatin nephrotoxicity. Antioxidants are categorized into four classes: dietary antioxidants, free radical scavengers, thiol-containing compounds, and iron chelators.

Keywords: Cisplatin, Oxidative stress, Cancer, Nephrotoxicity, Reactive oxygen species, Antioxidants, Renoprotection

Implication for health policy/practice/research/medical education:
Cisplatin cytotoxicity is mediated by reactive oxygen species generation, reducing antioxidant enzymes and activation of apoptosis and inflammation pathways significantly.

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Introduction

Cancer is a significant global illness burden and the second leading cause of death in the world. Cisplatin is one of the first-line antitumor drugs applied in the therapy of numerous types of cancers. However, side effects of this drug, including nephrotoxicity, ototoxicity, gastrointestinal toxicity, neurotoxicity, and allergic reactions limit its use significantly. The main dose-dependent adverse effect of cisplatin is nephrotoxicity (1). Cisplatin nephrotoxicity happens in around one-third of patients, who receive this treatment. Proximal tubular epithelial cells are the primary cells for cisplatin excretion source since renal cytotoxicity persists even with hydration and dose modification.

Cisplatin nephrotoxicity can be mitigated or prevented on multiple levels, such as; intervening in the transport of cisplatin to the renal epithelial cells, aggressive hydration, forced diuresis, chelating agents to diminish cell death, blockade of cyclin-dependent kinase, mitogen-activated protein kinase (MAPK), inhibition of p53 activation, antioxidants supplementation and inflammation blockage (2,3).

Search strategy

For this review, we searched PubMed/Medline, DOAJ (Directory of Open Access Journals), Embase, Web of Science, EBSCO, Scopus, and Google Scholar,

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using various keywords including cisplatin, oxidative stress, cancer, nephrotoxicity, reactive oxygen species, antioxidants and renoprotection.

Mechanisms of cisplatin nephrotoxicity

Oxidative stress is one of the main mechanisms of cisplatin nephrotoxicity. Cisplatin-induced oxidative stress stimulates apoptosis, inflammation, mitochondrial damage, and endoplasmic reticulum (ER) stress. Therefore, the administration of antioxidants in this context could be a reasonable option to prevent cisplatin nephrotoxicity. The principal target for cisplatin-induced oxidative stress in mitochondria leads to damage of mitochondrial thiol proteins, blockade of calcium absorption, and a decrease of the physiological function of the respiratory chain to produce energy and subsequent cytochrome c release (4).

Reactive oxygen species (ROS) seem to attack numerous cellular constituents, such as lipids, proteins, and DNA, which trigger multiple signaling pathways within cells/body. Severe damages to these cellular constituents trigger the activation of p53, which is responsible for the transcription of multiple proapoptotic proteins, including two intrinsic and extrinsic apoptotic proteins. The generation of the ROS increases apoptosis via increased expression of the genes that encode the extrinsic apoptotic proteins such as Fas, FasL and subsequently, increases caspase eight and tumor necrosis factor-alpha (TNF-α) (extrinsic approach) and facilitates Bak/Bax activation and also cytochrome c release (intrinsic approach) (1,4).

Cisplatin-induced acute kidney injury is associated with mitochondrial dysfunction as indicated by lipid peroxidation, reduction of essential antioxidants, variations in transmembrane electric potential, variations in calcium uptake, caspase three activations, and apoptosis (5). There are three mechanisms for ROS production during cisplatin nephrotoxicity; a) reduction of related antioxidants such as glutathione peroxidase, glutathione reductase, catalase (CAT), superoxide dismutase (SOD), and glutathione transferase, b) increase in ROS generation by the disruption of the mitochondrial respiratory chain reactions such as increased malondialdehyde levels, increased 8-hydroxy-2'-deoxyguanosine content, increased 4-hydroxynonenal content, and increased lipid peroxides content and c) interaction of microsomal cytochrome P450 (a group of heme proteins) with antitumor platinum complexes (6,7).

Pathways of antioxidants

The nuclear factor E2-related factor 2 (Nrf2) is a transcription factor that responds to oxidative stress. Nrf2 regulates the expression of the antioxidant response element (ARE) dependent genes. ARE genes are regulating the antioxidant enzymes and protein synthesis to adjust the cellular oxidant level and oxidant signaling. ARE genes also influence specific cellular functions, for example, autophagy, inflammation, inflammasome signaling, ER stress, apoptosis, and mitochondrial biogenesis (8). Additionally, the absence of Nrf2 leads to the aggravation of cisplatin nephrotoxicity. Meanwhile, activated Nrf2 mitigates the cytotoxic effects and associated with chemotherapy.

Heme oxygenase-1 (HO-1) is one of the genes regulated through Nrf2, which catalyzes the degradation of heme into biliverdin, iron ions, and carbon monoxide, while HO-1 and their derivatives prevent oxidative damage (9).

It has been proposed that several antioxidants such as galangin, Wuzhi tablet, melatonin, and sinapic acid exert antioxidant mechanisms via Nrf2/HO-1 signaling pathway.

Suppression of ROS by free radical scavengers, such as dimethyl thiourea (DMTU) and N-acetylcysteine, attenuated p53 activation, shields the tubular cells from apoptosis, and conserves kidney function. Besides ATR-dependent activation of checkpoint kinase 2 (Chk2), other protein kinases and p38 have been involved in p53 activation through cancer treatment. Furthermore, nuclear factor-κB (NF-κB) is another agent that may link ROS with p53 to control cisplatin nephrotoxicity. Thus, antioxidants can cause weak NF-κB activation and protect the kidney from toxicity related to cisplatin (10).

Recently, antioxidants were classified into four classes: dietary antioxidants, free radical scavengers, thiol-containing compounds, and iron chelators (11). In a previous review study, dietary antioxidants are categorized into 11 classes by Gómez-Sierra et al. The classless include capsaicin, curcumin, ellagic acid, epigallocatechin 3-gallate, alpha-lipoic acid, lycopene, quercetin, resveratrol, sulforaphane, tannins, and vitamins. These compounds not only show some nephroprotective effects but also have intensified cisplatin antineoplastic effect, therefore, it could be considered a potential option as an adjuvant therapy with cisplatin (12) (Table 1).

Plant-derived agents

Antioxidant extracts from natural plants have been of interest recently. Notably, natural antioxidants may attenuate ROS from kidneys, without influencing the anticancer effects of cisplatin. It has been shown that the utilization of multiple plant-based agents can protect kidneys against cisplatin nephrotoxicity (13,14). It has also been observed that females are associated with a lesser risk of cisplatin nephrotoxicity. Furthermore, plant-based estrogen may mitigate the risk of cisplatin nephrotoxicity significantly (15).

New antioxidants

Several antioxidants have been shown to diminish oxidative stress. Antioxidant phytochemicals including tocopherols, flavonoids, carotenoids, and phenolic compounds can act as reducing agents that prevent oxidation induced by iron ions and free radicals. Antioxidants protect biomolecules from injury induced by both reactive oxygen and nitrogen

Table 1. The types of antioxidants

Antioxidant	Published before	Recently years
Dietary antioxidants	Selenium, some vitamins, and some flavonoids (such as quercetin and Silibinin), and Licochalcone A	Dietary antioxidants in 11 classes (12)
Free radical scavengers	dimethylthiourea (DMTU), dimethyl sulfoxide (DMSO), and edaravone	Edarabone, N N'-diphenyl-1, 4-phenylenediamine (DPPD)
Thiol-containing compounds	N -acetylcysteine, sodium thiosulphate, Lipoic acid, Amifostine	D-methionine S-allylmercaptocysteine
Iron chelators	Deferrioxamine (DFO), 1,10-phenanthroline, 2,3-dihydroxybenzoic, 20-tetrakis(4-sulfonatophenyl) porphyrinatoiron(III) (FeTPPS)	-

species (ROS and RNS). Intracellular effects of cisplatin nephrotoxicity cause a decrease in sodium, potassium, and magnesium and lead to the increment of calcium in the plasma. Magnesium supplementation through chemotherapy with cisplatin has a nephroprotective effect without reduction of antitumor efficiency. Antioxidants and their effective pathways are presented in Table 2.

For instance, astaxanthin shows antioxidant activities via the scavenging of free radicals and protection against chain reactions. The astaxanthin is easily found in natural or synthetic sources in nutritional supplements (28). Likewise, galangin increases anti-oxidative enzyme activity like SOD and CAT in the renal tissue in addition to inhibition of TNF-alpha and interleukin-6 (IL-6) in mice model (18).

During an experimental study, the administration of methanolic leaf extract of *Apodytes dimidiata* was able to prevent acute renal toxicity in a rat model after exposure to cisplatin by scavenging ROS and RNS. It is possible that the nephroprotective effect of *Apodytes dimidiata* might be related to multiple ROS scavengers such as saponins, tannins, steroids, polyphenols and flavonoids also metal chelators due to the existence of numerous hydroxyl groups (29).

It has also been shown that melatonin has a role in the inhibition of cisplatin nephrotoxicity. This protective effect of melatonin is referred to as its antioxidant, anti-inflammation and anti-apoptosis effects. Melatonin counteracts free radicals through complex formation, proton transmission, and donation/acceptance of electrons and finally reduction oxidative stress and rise the anti-oxidant enzymes level via Nrf2 activation (25).

A retrospective cohort study presented that concurrent use of proton pump inhibitors with cisplatin may improve nephrotoxicity (30). It is clearly demonstrated that Omeprazole, a proton pump inhibitor, has a nephroprotective effect against cisplatin nephrotoxicity by reducing oxidative stress, inflammation, and apoptosis (20). In an experimental model, venlafaxine reduced the sensitivity of kidneys and bladder to cisplatin. This effect was mediated by decreasing renal oxidative stress and increasing renal nitric oxide and its derivatives (19). Based on another report, the renoprotective properties of the methanol leaf extract of *Delonix regia* was observed. This extract reduced the induced mATPase activity and works as a result decreased additional ATP hydrolysis (21).

Astilbin powerfully caused Nrf2 activation and induced the expression of Nrf2-mediated antioxidant genes such

Table 2. Recently published antioxidants

Antioxidants	Reference	Pathway
American ginseng berry extract	16	Activation of MAPK and NF-κB signaling pathways
Wuzhi tablet	17	Nrf2-mediated pathway
Galangin	18	Via inhibition of ERK and NF-κB signaling
Venlafaxine	19	Protects the urinary bladder from hypersensitivity to acetylcholine
Omeprazole	20	Transporter function NF-κB and JAK-STAT3/6
Delonix regia leaves	21	Suppression of mATPase activity, reduced release of cytochrome c and caspase 3 activation
Rutin	22	Inhibitor for the ROS/JNK/TNF/P38 MAPK signaling pathways
Sinapic acid	23	Nrf2/HO-1 pathway
Zingerone	24	Suppression of oxidative stress and inflammation
Melatonin	25	Nrf-2/HO-1 pathway
Danshen	26	Nrf2-mediated Pathway
Astilbin	27	Nrf2 mediated pathway
Astaxanthin	28	scavenge of free radicals and protection against chain reactions
Apodytes dimidiata	29	ROS scavengers and metal chelators

as glutamate-cysteine ligase modifier in cisplatin-induced human embryonic kidney 293 cells (27).

Organosulfur compound

Over the years, it has been shown that compounds containing sulfur such as glutathione have an impact on the metabolism of platinum-based therapies. Amifostine and dimesna (external analogs) lessen the nephrotoxicity of platinum-based therapies (31).

S-allylmercaptocysteine, one of the garlic-derived organosulfur compounds, has antioxidant, anti-inflammatory function and anti-apoptotic effect and decreases NF-κB activity from one side/hand, and increased Nrf2 and NAD(P)H from the other side/hand: quinone oxidoreductase 1 (NQO1) gene expression and decreased inflammatory cytokine levels (32).

D-methionine is an organosulfur amino acid and has complex properties for scavenging free radicals. Oral D-methionine showed some antioxidant efficiency by blockage of malondialdehyde leading to increasing glutathione concentration and CAT activity in kidney homogenate. Co-administration of D-methionine along with cisplatin may intensify chemoprotection characteristics (33).

Iron chelators

It has been shown that cisplatin induces a substantial increase in iron release in kidney cells while iron chelator supplementation like deferoxamine (DFO), and 2,3-dihydroxybenzoic acid, considerably weaken the cytotoxicity of cisplatin (7). These iron chelator effects are independent of antioxidant properties. Increased iron levels catalyze ROS/RNS reactions involved in different renal diseases. DFO decreases renal damage and lipid peroxidation induced by cisplatin; while at the same time increasing non-protein thiol group concentrations such as SOD within the kidney tissue (15).

Conclusion

In summary, cisplatin cytotoxicity is mediated by ROS generation, reducing antioxidant enzymes and activation of apoptosis and inflammation pathways significantly. Administration of an antioxidant in this context could be a suitable approach for the prevention of cisplatin nephrotoxicity. Using antioxidants as adjuvant therapy to increase the antineoplastic effect and reduce nephrotoxicity is recommended.

Authors' contribution

Conceptualization: MK, RT and RT. Validation: MK, RT, RT, FD and TS. Research and resources: MK, RT and RT. Data curation: MK, RT, RT, OFBM and TS. Writing—original draft preparation: MK, RT, RT and TS. Writing—reviewing and editing: VF, PP, SS, OFBM and LM. Visualization and funding acquisition: MK. Supervision: MK, RT, RT and LM. Project management: MK, LM and RT.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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