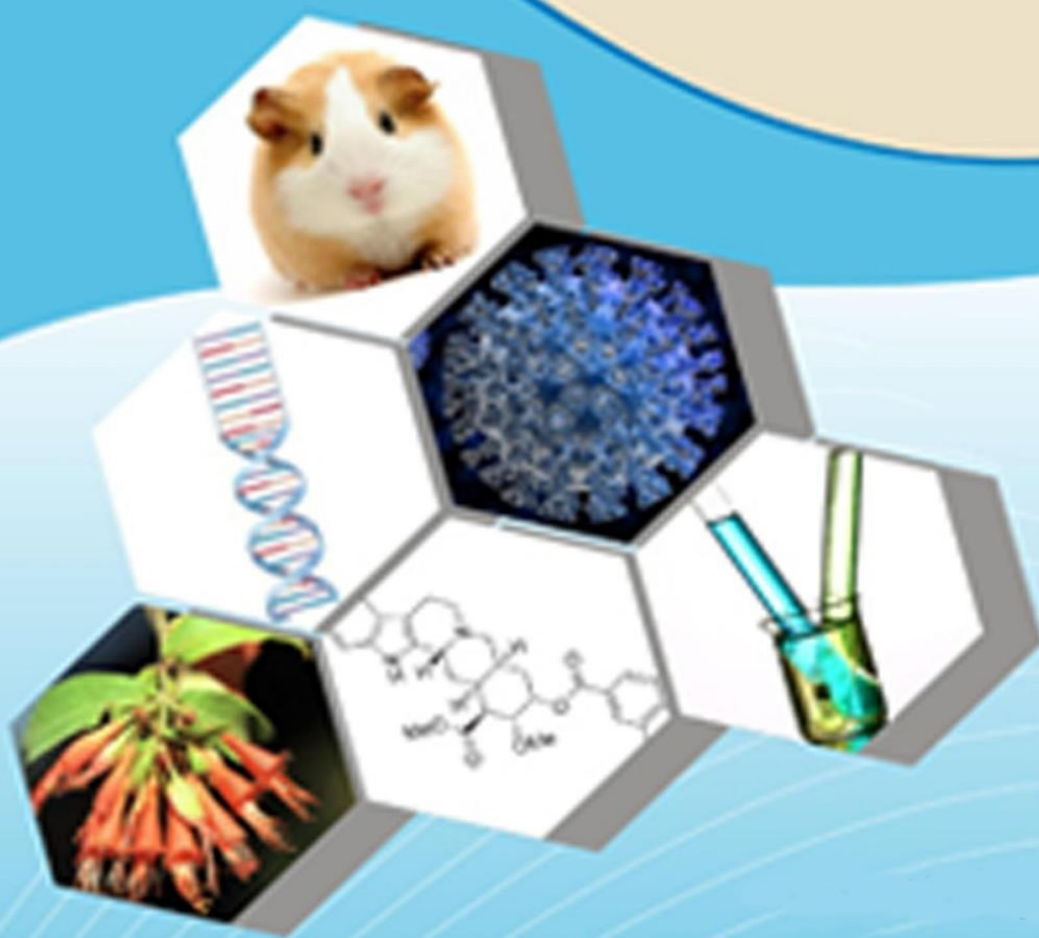




ISSN : 2347-2251

**Indo-American Journal of
Pharma and Bio Sciences**



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Protective Role of Natural Antioxidants Against Cisplatin-Induced Nephrotoxicity in Rats

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Abstract:

Nephrotoxicity is the most frequent adverse effect associated with cisplatin, which limits its clinical use. One of the upstream responses that causes varying degrees of damage to the intracellular material components in a cisplatin-induced pathological response is oxidative stress. One of the first signaling molecules that goes through a number of pathogenic responses, including necrosis and apoptosis, is reactive oxygen species (ROS). According to this review, the mechanism of cisplatin-induced intracellular ROS generation is primarily caused by the consumption of endogenous antioxidants, the breakdown of antioxidant enzymes, the induction of mitochondrial crosstalk between the endoplasmic reticulum by ROS and Ca^{2+} , and the destruction of the cytochrome P450 (CYP) system in the endoplasmic reticulum. These factors all contribute to an excessive buildup of intracellular ROS and oxidative stress. Furthermore, research showed that by lowering or even eliminating excess free radicals and also influencing other nonredox pathways, natural antioxidants may guard against cisplatin-induced nephrotoxicity. Thus, this review offers theoretical justification for the investigation and clinical use of natural antioxidants while also offering a fresh perspective on the intricate mechanism of cisplatin nephrotoxicity, potentially laying the groundwork for cisplatin's future clinical use.

1. Introduction

Cisplatin, also known as cis-diamminedichloroplatinum (II), or CDDP, is one of the most commonly used antitumor medications worldwide, particularly for the treatment of numerous solid tumors, including lung cancer [8], ovarian cancer [4, 5], bladder cancer [6], head and neck cancer [7], testicular cancer [2, 3], and uterine cancer [1]. Cisplatin has even been shown to be successful in treating testicular cancer, with a 90% or greater cure rate [3]. Cisplatin causes intra- and interchain DNA to cross-link, which may damage DNA and prevent transcription and replication [9, 10]. While substantial DNA damage may result in permanent harm and cell death, which is the basic mechanism, mildly damaged DNA can be repaired of cisplatin's cytotoxic antitumor action in cancer treatment; cancer cells that are growing are more vulnerable to DNA damage [11, 12].

Since its usage in anticancer therapy, cisplatin has garnered a lot of interest because to its possible adverse effects, including gastrointestinal responses, renal toxicity, neurotoxicity, and ototoxicity, in addition to its curative effect [13, 14]. Renal damage is the primary dose-limiting adverse effect, according to studies [15–18]. Cisplatin's renal toxicity significantly restricts both its dose and therapy duration. After receiving a single dosage of cisplatin, it is known that 25–35% of patients have a significant decline in renal function [19]. Although cisplatin nephrotoxicity involves direct effects on the renal vasculature, it primarily manifests a tubular damage pattern of dysfunction and disorder, resulting in electrolytic disturbances, acute tubular injury (ATI), and acute kidney injury (AKI), with elevated levels of plasma creatinine and urea [20,21]. In rare cases, this can lead to the development of chronic fibrotic nephropathy.



The prevalence of cisplatin-induced nephrotoxicity is still significant, despite the demonstration of preventative measures, such as hydrotherapy in clinical practice [22]. Thus, knowing the mechanism behind cisplatin-induced nephrotoxicity might aid in the exploration of new renoprotective therapies and improve defenses against such nephrotoxicity.

In research involving human participants, treatment safety is always the first priority. The optimal protective ingredient should be nontoxic, widely accessible, efficient at lower dosages, and affordable. Natural dietary agents have garnered a lot of interest from academics and the general public in recent years due to their potential to suppress malignancies and lower the incidence of cancer [23]. Additionally, using chemotherapeutic medications in conjunction with natural antioxidants may help reduce toxicities linked to medicines [24]. Additionally, natural antioxidants' antioxidant activity suggested that they may be used as a treatment for cellular pathologies linked to oxidative stress, such as cisplatin-induced nephrotoxicity. Therefore, in order to thoroughly investigate whether antioxidants may be employed for renoprotection against cisplatin toxicity, we compiled the most recent research in this review.

2. Accumulation of ROS Is the Upstream Reaction Leading to Pathological Events in Cisplatin-Induced Nephrotoxicity

Oxidative stress has been considered a significant contributor to cisplatin-induced nephrotoxicity for more than ten years [25, 26]. According to research, cisplatin primarily damages the kidneys by causing oxidative stress in the glomerular and renal tubular cells. This results in vascular dysfunction, a robust immunological response, and cell necrosis and apoptosis [27–31]. Cisplatin nephrotoxicity research has recently focused on the mechanism of apoptosis-induced renal tubular cell failure. Apoptosis has been linked to a number of pathways. The first is the extrinsic pathway, which is mediated by death receptors like Fas and the tumor necrosis factor- α (TNF- α) receptor [32]. Others include the endoplasmic reticulum (ER) stress pathway, which is primarily triggered by caspase-12 [35], the intrinsic pathway focused on mitochondria, which is related to cellular stress and causes the activation of the proapoptotic Bcl-2 family proteins Bax and Bak on the mitochondrial membrane [33, 34]. Oxidative stress and apoptosis have been frequently linked, despite the fact that cisplatin-induced apoptosis progresses via a number of specific routes. Additionally, oxidative stress and apoptosis may be directly associated since they both involve mitochondrial dysfunction. A disruption in the reduction and oxidation (redox) equilibrium between reactive and antioxidant species causes oxidative stress, a cellular stress response. The chemical process known as oxidation is a crucial component of cellular metabolism and other biological processes that permits the removal of electrons from an atom or molecule.

Excess buildup of free radicals, which are unstable and very reactive atoms or molecules with unpaired electrons, often results in oxidative stress. Reactive oxygen species (ROS), also known as oxygen-derived radicals, and reactive nitrogen species (RNS), sometimes known as nitrogen-based radicals, are the two main categories of free radicals. The superoxide anion ($O_2^{\bullet-}$), hydroxyl radical ($\bullet OH$), alkoxyl radical ($RO\bullet$), peroxy radical ($ROO\bullet$), and oxygen-centered radicals are among the oxygen-centered radicals. The oxygen-centered nonradicals, also known as nonfree radical oxygen intermediates, include hydrogen peroxide (H_2O_2) and singlet oxygen ($^1O_2$) [36, 37]. Free radicals are always present in every cell in the body. Serum, erythrocytes, and other tissues and organs contain antioxidants to guard against damage from ROS, RNS, and other free radicals. Glutathione (GSH), vitamin C, transferrin, albumin, and other antioxidant enzymes, including glutathione peroxidase (GSH-Px), are among the components that make up the antioxidant system [38]. When the delicate balance between the levels of oxidants and anti-oxidants is upset, oxidative stress results from a reduced antioxidant defense in the human body. It is important to note that cisplatin quickly causes a significant buildup of reactive oxygen species (ROS) within kidney cells, upsets the intracellular redox system's equilibrium, and aids in the release of multiple intracellular components that may result in varying degrees of harm. Additionally, ROS have the ability to target and alter a variety of cellular molecules, including proteins, DNA, and lipids, which may lead to cellular stress [28, 39]. Furthermore, during cisplatin-induced nephrotoxicity, ROS seem to play a role in the activation of many crucial signaling pathways. Numerous studies have verified that the early signaling of cisplatin-induced pathological events, including the inflammatory response and multiple apoptotic signal pathways mediated by caspases and mitogen-activated protein kinases (MAPKs), is the massive accumulation of ROS and other mitochondrial oxidative stress-induced functional disorders [40–45]. Research, on the other hand, indicates that nitrosative stress and oxidative stress together form a number of steps in the mechanism of cell damage [39, 48, 49] and that nitrosative stress plays a toxic role in cisplatin-induced nephrotoxicity by another free radical, RNS [46, 47]. The mechanism of the oxidative stress response caused by cisplatin that leads to nephrotoxicity is discussed in this review, which primarily focuses on oxidative stress and ROS.

3. How Does Cisplatin Induce Accumulation of ROS and Cause Oxidative Stress Response?

As mentioned above, excess ROS are harmful due to their oxidant species and might cause cellular dysregulation and damage to several cell structures. In this review, we classified the oxidative stress as follows: (a) lipid peroxidation assessed by the determination of malondialdehyde (MDA), 4-hydroxynonenal (4-HNE), thiobarbituric acid reactive substances, or other lipid peroxide content; (b) 8-hydroxy-



deoxy-guanosine (8-OHdG), an oxidatively modified DNA adduct; and (c) GSH and other common antioxidant depletion [39]. The major mechanisms of excessive ROS accumulation induced by cisplatin are mainly caused by the following detailed approaches (Figure 1):

- (1) Since the uptake by renal tubular epithelial and glomerulus cell, cisplatin can rapidly reduce the endogenous antioxidant substances, such as GSH and metallothionein (MTs). Although the exact mechanism of cisplatin reducing endogenous antioxidant is still unclear, cisplatin may play a role in the following ways: (a) cisplatin can reduce copper and zinc in the cell. It is acknowledged that copper and zinc are the necessary substances to synthesize superoxide dismutase (SOD) in the cytoplasm and mitochondrial inner membrane and to help take in selenium, which is necessary for the synthesis of GSH-Px [50–52]. It is known that SOD and GSH-Px are the most important enzymes that can regulate and maintain the balance of redox reactions in the cell. Therefore, cisplatin destroys the first line of defense, that is, enzymatic antioxidant defense response. When the corresponding SOD and GSH-Px are reduced, the free radical content in the body rises sharply and the redox balance is destroyed; then, oxidative stress is formed. (b) Cisplatin can directly combine with thiol-containing compounds such as GSH, MTs, GSH-Px, and SOD, resulting in a direct reduction of endogenous reducing substances that can scavenge the ROS [52–54], such as ascorbic acid and GSH; thus, cisplatin can destroy the second line of defense, that is, nonenzymatic antioxidant defense response [51]. When endogenous antioxidants are consumed excessively, the cell's redox equilibrium state is broken, which triggers the oxidative stress response and causes damage to cells and even tissues
- (2) After being transported into the cell, cisplatin enters into mitochondria and binds to mitochondrial DNA, causing mitochondrial dysfunction and increasing ROS production via the disrupted respiratory chain, which may be more important than nuclear DNA damage in cisplatin-induced cell death [55]. Cisplatin affects the normal transmission of electrons on the oxidative respiratory chain and produces a large number of free radicals that can be generated to form ROS. Meanwhile, the decrease in cytochrome c oxidase (COX) activity and the low expression of complex I-IV protein can result in ROS generation [56]. It is also reported that complex III and glycerol 3-phosphate dehydrogenase can release superoxide into the intermembrane space, suggesting that the release of mitochondrial ROS into the cytosol is important to cellular damage [57], especially the damage to endoplasmic reticulum (ER) which will result in a vicious circle between mitochondria and ER. In normal condition, calcium

(Ca^{2+}) in mitochondria can reduce ROS when complexes I and III are working as usual but can increase the ROS generation when these complexes were inhibited by pharmacological agents [58]. Since ER is a major site of calcium storage which can cause an increased release of Ca^{2+} to mitochondria, when mitochondrial ROS releases into the cytosol and targets ER-based calcium channels, a vicious circle will finally develop [59]

Besides the effect of Ca^{2+} and ROS crosstalk between ER and mitochondria, cisplatin can also reduce the activity of manganese-containing superoxide dismutase (MnSOD), glutamic dehydrogenase (GDH), succinate dehydrogenase (SDH), and mitochondrial GSH-reductase (GSH-Rd) in mitochondria directly, resulting in a sharp reduction in mitochondrial-related endogenous antioxidants, which can cause dysregulation of mitochondrial antioxidant defense systems, and finally increase ROS accumulation and oxidative stress [3, 40, 60].

- (3) Cisplatin increases the free iron by acting on the cytochrome P450 (CYP) system in the endoplasmic reticulum and microsomes, and iron ions are important catalysts in the production of ROS [61]. In the presence of iron ions and H_2O_2 , the first and second steps of the Haber–Weiss reaction will cause the excessive generation of $\cdot\text{OH}$ rapidly [62], resulting in more ROS accumulation and triggering oxidative stress response [63, 64]

4. The Protective Mechanism of Natural Antioxidants

Researches have shown that many natural products which may decrease various side effects induced by anticancer drug are available over the counter [24]. It is known that antioxidant is the substance that can put off, prevent, or twist the oxidative damage in a target molecule [65]. In addition, natural antioxidants are a group of compounds that naturally have the antioxidant properties, without excluding other biological properties [66]. Natural antioxidants can protect against mitochondrial dysfunction and inflammation [67–69]. Moreover, a large number of experimental studies showed that natural antioxidants can protect against cisplatin-induced nephrotoxicity [70]. Here, we summarized the protective mechanisms of natural antioxidants in cisplatin-induced nephrotoxicity. Besides, we used a variety of representative antioxidants to present the underlying mechanism (Figure 2 and Table 1).

4.1. Reducing the Production of ROS. Various experimental results showed that natural antioxidants can achieve protection by reducing the production of ROS. Among them, fisetin not only can reduce the migration and invasiveness of cervical cancer [71], but it can also significantly reduce the cisplatin-induced kidney damage by reducing the mitochondrial damage and ROS generation to alleviate tissue oxidative stress response [40]. Hesperidin [53], as well as

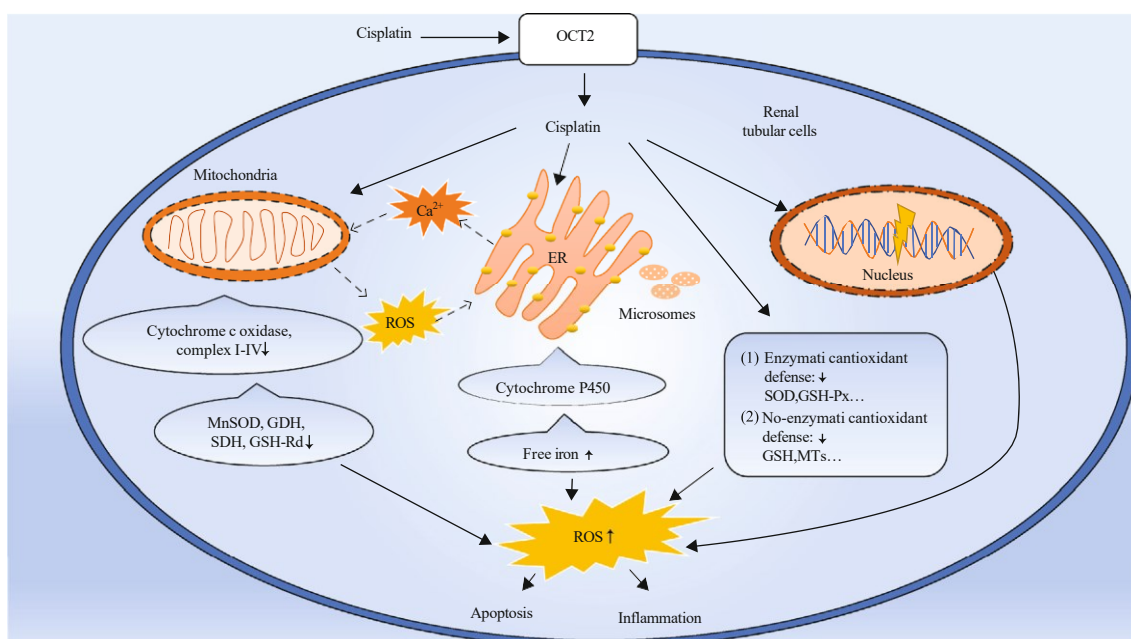


Figure 1: The major mechanism of excessive ROS generation induced by cisplatin in renal tubular cell. →: enhancement; →: circle line. The mechanism of oxidative stress induced by cisplatin is mainly from the consumption of endogenous antioxidants, destruction of antioxidant enzymes, and induction of mitochondrial damage and makes the crosstalk between mitochondria and endoplasmic reticulum (ER) by ROS and Ca^{2+} , destroys the CYP 450 system, then releases the free iron from ER, microsomes, etc., then makes the excessive accumulation of ROS in renal tubular cell, and finally results in apoptosis and inflammation. ROS: reactive oxygen species; GSH: glutathione; GSH-Px: glutathione peroxidase; SOD: synthesize superoxide dismutase; MTs: metallothionein; CYP 450: cytochrome P450; MnSOD: manganese-containing superoxide dismutase; GDH: glutamic dehydrogenase; SDH: succinate dehydrogenase; GSH-Rd: GSH-reductase.

By reviving antioxidant enzyme activity, lycopene [72] and caffeic ethanol extract (caffeic acid phenyl ester, CAPE) [73] may lower the generation of ROS (Table 1). By preventing the first line of defense from producing ROS, the restored antioxidant enzymes may shield the kidney from cisplatin-induced damage.

4.2. Eliminating Extra ROS. Twelve natural antioxidants were found to be capable of eliminating excess ROS caused by cisplatin after an analysis of pertinent experimental data (see Table 1). Hesperidin is more effective in eliminating OH and peroxide than several synthetic antioxidants, including vitamin C, butylated hydroxy-toluene (BHT), and butylated hydroxyanisole (BHA), because it may chelate with divalent iron [74] and lower the production of ROS. Additionally, additional natural antioxidants such as resveratrol [77, 78], cardamom [75], quercetin [76], naringenin [50], and Origanum majorana [27] also have an impact on eliminating excess ROS. By boosting the body's production of the endogenous antioxidant GSH, betaine may even eliminate ROS and provide protection against cisplatin nephrotoxicity [52].

4.3. Additional Nonredox Routes That Guard Against Kidney Damage. It is important to note that the majority of natural antioxidants have the capacity to withstand additional damage mechanisms brought on by cisplatin in addition to their corresponding preventive effects on lowering or eliminating ROS. For instance, it has been shown that betaine may lessen the effects of inflammation by preventing the expression of By inhibiting the activation

of nuclear factor kappa-B (NF- κ B) and exogenous apoptotic pathways, interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) [79, 80] may also directly diminish kidney damage [52]. To prevent kidney injury, fisetin and cisplatin may also prevent the inflammatory response and NF- κ B from being activated [40]. Hesperidin possesses antihypertensive, antihyperlipidemia, antioxidative, and anti-inflammatory properties, according to preclinical and clinical research [81]. Furthermore, when paired with cisplatin, hesperidin may increase neutrophil infiltration in renal tissue, decrease the nitrification stress response, and lower plasma TNF- α levels, all of which can lessen the damage that cisplatin causes to the kidneys [53]. By preventing the synthesis of several inflammatory mediators, including IL-1 β , TNF- α , NF- κ B, and inducible nitric oxide synthase (iNOS), cardamom also demonstrated a potent anti-inflammatory effect [75]. In order to prevent kidney damage caused by cisplatin, quercetin may also decrease the synthesis of NF- κ B, according to Francescato et al. [76]. Additionally, lycopene may boost the expression of nuclear factor erythroid 2-related factor (Nrf2)/heme oxygenase-1 (HO-1), which is linked to resistance to oxidative stress and the inflammatory response, and suppress the synthesis of NF- κ B [72]. Additionally, resveratrol can modify cisplatin pharmacokinetics, lowering renal accumulation and increasing plasma half-life to protect the kidney [83], and lycopene can alter the quantity and quality of transporters in the renal tubules to inhibit cisplatin uptake and improve the filtration rate of cisplatin in the kidney [82].

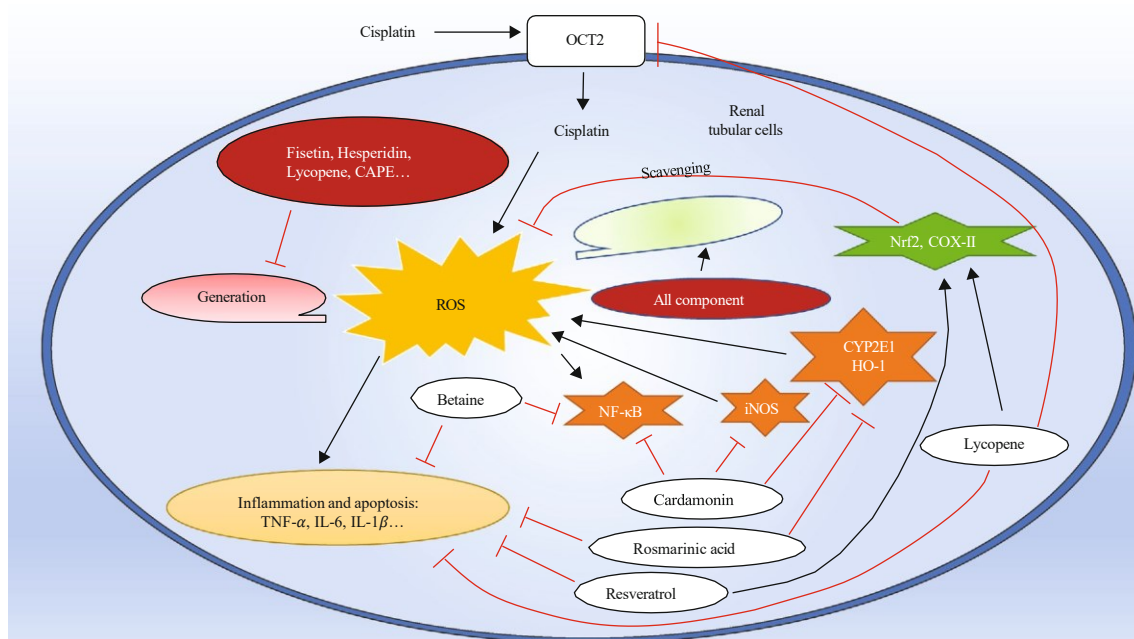


Figure 2: The major protective mechanisms of the representative natural antioxidants in cisplatin-inducing damage in renal tubular cell. →: enhancement; red left tack: inhibition. All the natural antioxidants have the ability to scavenge the accumulation of ROS induced by cisplatin. Some special can reduce the ROS generation, include Fisetin, Hesperidin, Lycopene, CAPE. Betaine, resveratrol, and cardamomin can also inhibit the inflammation of renal tubular cells by inhibiting the nuclear factor kappa-B (NF-κB) or other inflammatory factors. Cardamomin and rosmarinic acid can inhibit oxidative stress by decreasing some molecules that can induce generation of ROS via nitric oxide synthase (iNOS), cytochrome P450 2E1 (CYP2E1), and heme oxygenase-1 (HO-1). Lycopene can reduce the generation of ROS, alleviate inflammation, and also reduce the uptake of cisplatin by downregulating the expression of organic cation transporters 2 (OCT2), which are only expressed in the proximal tubules. TNF-α: tumor necrosis factor-α; IL-6: interleukin-6; IL-1β: interleukin-1β.

TABLE 1: Major natural products reducing cisplatin-induced nephrotoxicity in different experimental models.

Antioxidant	Experimental evidence		Effects on cancer therapy
	<i>In vivo</i>	<i>In vitro</i>	
Hesperidin	Mice [92], rat [53, 91, 194]	HK2 (kidney, <i>Homo sapiens</i>) [92]	Unclear
Cardamomin	Rat [75]	—	Improved [75]
Quercetin	Rat [76, 102–105]	LLC-PK1 (kidney, <i>Sus scrofa</i>) [101]	Improved [104]
Naringenin	Rat [50, 112]	—	Improved [112]
Lycopene	Rat [72, 82, 122, 123], human [125]	—	Unclear
Resveratrol	Mice [133], rat [77, 83, 134], rabbit [78]	—	Unclear
Fisetin	Rat [40]	—	Improved [141]
Caffeic acid phenethyl ester (CAPE)	Rat [73]	—	Unclear
Rosmarinic acid (RA)	Rat [158]	—	Unclear
Curcumin	Rat [165, 166]	—	Improved [167]
Origanum majorana	Rat [27]	—	Unclear
Betaine	Rat [52]	—	Unclear
Hyperin	Rat [175]	—	Unclear
Formononetin	—	LLC-PK1 (kidney, <i>Sus scrofa</i>) [176]	Unclear

In summary, natural antioxidants can reduce excess ROS because of their antioxidant properties. They can also achieve protective effects by restoring endogenous antioxidant enzyme functions and participate in the synthesis of

endogenous antioxidants. Furthermore, most natural antioxidants show a certain resistance in the damage mechanism of nonredox reactions. These mechanisms have a certain significance for future research and clinical use.



5. Research Status of the Representative Natural Antioxidants Protecting against Cisplatin Nephrotoxicity

5.1. Hesperidin. One of the most prevalent natural flavonoids, hesperetin is found in a wide variety of fruits and vegetables [84]. Citrus aurantium L. fruit peels are also a good source of hesperidin, which is hesperetin 7-rhamnoglucoside, its glycoside form. [85]. Research revealed that when hesperidin is consumed in the glycoside form, glycosidase hydrolyzes it to produce the bioactive ingredient hesperetin, which is subsequently absorbed [86,87]. Hesperetin has a wide range of biological activities, including anti-inflammatory and antioxidant properties, as shown by several in vitro and in vivo investigations [88,89]. Furthermore, hesperidin has been shown to have a neuroprotective effect in mice in a phenotypic trial [90]. Subsequent research revealed that hesperidin may also guard against nephrotoxicity caused by cisplatin. In 2014, Sahu et al. [53] discovered that hesperidin may prevent oxidative stress and lipid peroxidation, which in turn protects against acute renal damage caused by cisplatin. It can also regulate the production of ROS, the proinflammatory cytokine TNF- α , and apoptosis/necrosis. Kaltalioglu and Coskun-Cevher (2016) discovered that hesperidin may lessen the renal toxicity brought on by cisplatin and showed that the recovery of catalase (CAT) activity and the rise in GSH content are linked to the decrease of ROS. Furthermore, hesperidin may also lessen the inflammatory effect of cisplatin [91]. Hesperetin may protect against nephrotoxicity caused by cisplatin by inhibiting NADPH oxidase 4 (Nox4) in a time- and dose-dependent manner, activating the Nrf2 antioxidant signaling pathway, and activating Sirtuin 6 (SIRT6), according to Chen et al.'s study [92] using HK2 cells.

5.2. Cardamonin. For thousands of years, people have utilized cardamonin (CDN), a chalcone mostly found in the seeds of *Alpinia katsumadai* (Caodoukou in Chinese), as a medicinal plant to cure a variety of illnesses [93]. It may cause nasopharyngeal carcinoma, prostate cancer, triple-negative breast cancer, and colorectal carcinoma cells to undergo more autophagy or apoptosis [94–97]. Furthermore, cardamonin may enhance cisplatin's anticancer effects in a number of cancer types, including colon tumor cells, ovarian cancer, prostate cancer, and hepatocellular carcinoma [75, 98]. El-Naga discovered that the substantial rise in SOD and GSH, which might lessen lipid peroxidation and oxidative stress brought on by cisplatin, may be one of the underlying mechanisms of cardamonin's nephroprotective effect [75]. In summary, these investigations have shown that cardamonin may both decrease the renal toxicity of cisplatin and enhance its anticancer effect. Cardamonin may thus be very useful in medicine.

5.3. Quercetin. One important family of polyphenolic flavonoid molecules is quercetin (QE). One of the most prevalent flavonoids in the human diet, quercetin has several positive health effects, including anti-inflammatory, antiproliferative, cardioprotective, and anticancer

properties.

ties [99, 100]. According to a 1998 study by Kuhlmann et al., quercetin may prevent kidney damage from cisplatin and has anticancer properties [101]. The nephroprotective effect of quercetin may be linked to its antioxidant activity and capacity to prevent renal inflammation and tubular cell death, which may shield rats from cisplatin-induced nephrotoxicity, according to research done in 2011 by Sanchez-Gonzalez et al. Furthermore, without compromising its therapeutic anticancer potential, quercetin shields the kidneys from the renal toxic damage caused by cisplatin [102]. Almaghrabi (2015) discovered that quercetin may clearly increase the expression of the CAT, SOD, and GPx genes, improve their enzyme activities to lessen the oxidative stress brought on by cisplatin, and lessen the production of ROS by lowering the levels of MDA and protein carbonyl [103]. Because quercetin can decrease the number of aberrant crypt foci (ACF), which is a precursor to colon carcinoma in humans and rats, Li et al. (2016) also demonstrated that quercetin can lessen nephrotoxic damage and enhance the anticancer activity of cisplatin by reducing crypt multiplicity [104]. Subsequent research supported the idea that quercetin may lessen cisplatin-induced kidney damage by lowering ROS generation, having anti-inflammatory properties, and other benefits [105, 106]. Like cardamonin, quercetin may lessen cisplatin's renal toxicity without compromising its anticancer properties.

5.4. Naringenin. With a wide spectrum of biological and pharmacological actions, naringenin (NG) is a dominant flavanone found in citrus fruits [107, 108]. Naringenin has been shown in several studies to possess a variety of protective properties, including anti-inflammatory, anticarcinogenic, antioxidant, and neuroprotective effects [109–111]. Naringenin has been shown in a study conducted in early 2005 to provide significant protection against cisplatin nephrotoxicity in rats. This is primarily due to its antioxidant effect, which reduces GSH depletion, restores antioxidant enzyme activity, including SOD, CAT, and GSH-Px, and inhibits lipid peroxidation [50]. By lowering oxidative stress, Koyuncu et al. discovered that naringenin-oxime has a protective function in decreasing cisplatin-induced nephrotoxicity, indicating that its usage may amplify cisplatin's anticancer effects [112].

5.5. lycopene. Plants are the only source of lycopene, a naturally occurring pigment that gives ripe tomato fruits and tomato-based products their deep red color [113,114]. Since lycopene cannot be synthesized by humans or animals, it must be obtained via food [115, 116]. According to studies, lycopene has a number of positive health effects on people, including cardioprotective, anti-inflammatory, anti-oxidant, and anti-atherogenic effects [117–120]. Furthermore, lycopene levels in serum tissue are linked to a lower incidence and risk of prostate cancer [23,116,121]. Here, we spoke about how lycopene can lessen the kidney damage that cisplatin causes. Lycopene may prevent cisplatin-induced nephrotoxicity in rats, according to many studies [72, 122, 123]. This is



primarily because lycopene can raise GSH levels, restore Catalase, GSH-Px, and SOD are examples of antioxidative enzymes that lower ROS production while also reducing lipid peroxidation and the inflammatory response. According to a recent research, lycopene may also prevent the downregulation of organic anion and cation transporters (OATs and OCTs) brought on by cisplatin. Basolateral cation uptake in the proximal tubule, the initial stage of cation secretion, is known to be mediated by OCT1 and OCT2 [124]. This process can prevent the growth of major efflux transporters, including multidrug resistance-associated proteins (MRPs), particularly MRP2 and MRP4 [82], and enhance protection against cisplatin-induced nephrotoxicity. The glomerular filtration rate of patients almost recovered to the baseline level when they were treated with lycopene pills (25 mg) and cisplatin administration, according to Mahmoodnia et al. [125], suggesting that natural antioxidants may be used as treatment methods in the future.

5.6. Resveratrol. A phytoalexin called resveratrol (RES) is found in over 72 plant species, many of which are eaten by people, including peanuts, mulberries, and grapes [126]. Numerous in vitro and in vivo investigations have shown the diverse biological effects of resveratrol, which include immune-modulatory, anti-inflammatory, antioxidant, and anticancer effects [127]. Resveratrol is also helpful in lowering the risk of cardiovascular illnesses [128–130]. Additionally, resveratrol has been shown to scavenge OH, O₂·, and ONOO· with neuroprotective and other chemopreventive properties [131,132]. Numerous studies have shown that resveratrol may lessen the nephrotoxicity caused by cisplatin. By removing free radicals and inflammatory cell infiltrates, resveratrol may protect rats against cisplatin-induced nephrotoxicity, according to a 2008 study by Amaral et al. [77]. The same phenomenon was discovered by Cigremis et al., who demonstrated that resveratrol can boost the activities of SOD, CAT, and GSH-Px enzymes without altering the antioxidant enzymes' mRNA levels. This suggests that resveratrol can change the activities of these antioxidant enzymes at the posttranslational stage [78]. By promoting anti-inflammatory (linked to IL-1 β , TNF- α , and COX-II) and antioxidative stress (i.e., lowering renal tissue MDA and NO levels and raising GSH concentration and enzymatic activities of SOD and CAT) [133], modulating the pharmacokinetics of cisplatin [83], and activating the ERK signal pathway [134], three studies conducted in 2018 found that resveratrol reduces nephrotoxicity caused by cisplatin. But in 2019, Neag et al. tested grape pomace extract (GE) for protection against cisplatin-induced kidney injury and came to mixed results [135]. Neag et al. discovered that GE increased the harmful effect of cisplatin rather than having a protective effect on cisplatin-induced nephrotoxicity. Although the underlying mechanism is yet understood, res-veratrol may interact with copper ions to enhance ROS and create compounds that damage DNA, ultimately negating the antioxidant effect [136]. This contradiction is indeed intriguing and indicates that more investigation is required to elucidate the function of resveratrol in relation to cisplatin-induced nephrotoxicity.

5.7. Fisetin. Numerous fruits and vegetables, including cucumbers, apples, strawberries, persimmons, and onions, contain the bioactive polyphenolic flavonoid fisetin [137]. Multiple beneficial pharmacological effects of fisetin have been documented in a number of investigations, including anti-inflammatory and hypolipidemic effects in rheumatoid arthritis [138,139] and anticancer effects in cervical cancer [71]. Fisetin's physicochemical examination showed that the substance and its metabolites were highly concentrated in the kidneys of mice, suggesting that it may be used to treat renal disorders [140]. Fisetin has also shown a renoprotective effect against cisplatin-induced acute renal injury in rats when used in conjunction with cisplatin treatment. The underlying mechanism was linked to decreased oxidative stress, restored mitochondrial respiratory enzyme activities, and inhibited apoptosis in renal tissue [40]. Furthermore, a research indicated that adding fisetin to cisplatin treatment may enhance its effects by activating the mitochondrial and cell death receptor pathways.

[141], however nephrotoxicity has not been discussed. As of right now, studies have shown that fisetin may also lessen cell apo-ptosis in the kidneys of septic acute kidney injury (AKI) mice caused by lipopolysaccharide by inhibiting the kidneys' NF- κ B p65 and MAPK function [142]. According to Ren et al., fisetin may reduce renal inflammation in hyperuricemic nephropathy mice via modifying the signal transducer and activator of transcription-3 (STAT3) and transforming growth factor- β (TGF- β) signaling pathway [143]. Furthermore, a preclinical investigation shown that fisetin may be used to create an active-targeting ROS-activatable nanosystem for liver and kidney inflammation imaging and treatment [144]. The investigation of antioxidant and anti-inflammatory mechanisms, as well as drug delivery techniques, is highly encouraging and may offer some guidance for the next experimental scheme of combination with cisplatin treatment, even though these studies did not report the protective effect of fisetin in combination with cisplatin.

5.8. CAPE stands for Caffeic Acid Phenethyl Ester. Extracted from the propolis of honeybee colonies, caffeic acid phenyl ester (CAPE) is a naturally occurring bioactive molecule with several protective qualities, including anti-inflammatory, immunomodulatory, antiproliferative, and antioxidant qualities [145]. Additionally, CAPE has been shown to decrease lipid peroxidation and inhibit lipoxygenase activities [146–150]. According to a 2004 research, CAPE may lessen the kidney damage caused by cisplatin by influencing antioxidant enzymes, preventing NO synthesis, and preventing NF- κ B activation. A new reference for renal damage brought on by cisplatin may be provided by two recent articles on neurotoxicity that suggested CAPE may influence the side effects of cisplatin through particular mechanisms, such as influencing nerve growth factor (NGF) through PI3k/Akt and MAPK/ERK pathways and NGF-high-affinity receptors trkA [151,152].

5.9. Acid rosmarinic (RA). 3,4-dihydroxyphenyllactic acid, or RA, is a common natural substance that has several uses, including cosmetics and food preservation.

[153]. Numerous biological actions, including antioxidative



[154], anti-inflammatory [155], and anticancer effects [156], have been discovered for RA. Its phenolic structure, which readily donates electrons or hydrogen atoms to neutralize free radicals and enzymatically recycles the phenoxyl radicals to parent phenolic, is primarily responsible for its antioxidant action [157]. According to Domitrovic et al., RA may lessen nephrotoxicity brought on by cisplatin by inhibiting oxidative stress, the inflammatory response, and apoptotic cell death. Remarkably, Domitrovic et al. showed that RA can suppress the expression of HO-1 and cytochrome P450 2E1 (CYP2E1), which can influence the CYP family of enzymes' activity and raise the production of free radicals, thereby reducing the oxidative stress brought on by cisplatin [158].

5.10. curcumin. *Curcuma longa* L.'s rhizomes are the primary source of curcumin, a polyphenol that is insoluble in water. [159, 160] and is often used as a culinary coloring and spice. Curcumin's antibacterial, antiviral, anti-inflammatory, antioxidant, and anticarcinogenic effect capabilities have been shown in studies [161–164]. Two methoxylated phenols and one β -diketone group make up the structure of curcumin, which exhibits keto-enol tautomerism in solution and may scavenge ROS such H₂O₂, singlet oxygen (1O₂), O₂⁻, Oh, and ONOO⁻ [70]. Numerous research shown that prior to and cotreatment (15–60 mg/kg b. and 200 mg/kg b. w. p. o. w. p. o., respectively) of curcumin may mitigate kidney damage caused by cisplatin, as seen by decreased serum creatinine and BUN levels [165,166]. Its capacity to scavenge ROS by increasing the activity of antioxidant enzymes (CAT, SOD, GPx, and thioredoxin reductase), improve lipid peroxidation and anti-inflammation, and ultimately restore renal dysfunction brought on by cisplatin is the mechanism behind these protective effects. Curcumin has also been shown to increase the cytotoxicity of cisplatin in ovarian cancer cells. More in vivo studies are required to determine if curcumin may really improve the effectiveness and lessen the toxicity caused by cisplatin, even though the underlying mechanism may be because the polyphenol of curcumin can raise cisplatin cellular concentration and binding to DNA [167].

5.11. Majorana origanum. *Majorana Origanum* L. belongs to the Lamiaceae family of mints, which are mostly identified by their popular names, including sweet marjoram and oregano [168]. Numerous biological activities, including anticancer, antidiabetic, antinociceptive, antimicrobial, insecticidal, hepatoprotective, cytotoxic, and antilipase properties [169], as well as strong ferric reducing and enhanced antioxidant activity [170], can be found in origanum plants. The Food and Drug Administration considers it to be generally safe [171]. Sayed et al. confirmed the antioxidant activity of *Origanum majorana* ethanolic extract (OMEE) by blocking the DPPH (2, 2-diphenyl-1-picrylhydrazyl) free radical [168], and Soliman et al. demonstrated that OMEE can mitigate kidney damage from significant reductions in cisplatin-induced nephrotoxicity. MDA and NO levels were unable to drop, GSH levels were

rising, and SOD and CAT activity was restored [27]. Apart from cisplatin, marjoram extract may also reduce the oxidative stress and inflammation brought on by dose-dependent gentamicin [172]. By raising renal SOD, CAT, and vitamin C levels and lowering renal MDA and TNF- α gene expression, *Origanum vulgare* leaf extract, another *Origanum* species, similarly shown nephron-protective capacity against gentamicin-induced nephrotoxicity in a rat model [173]. *Origanum* species are thus prospective compounds to withstand oxidative damage caused by cisplatin, according to the aforementioned investigations. 5.12. Others. Following a thorough review of numerous studies on the protective potential of natural antioxidants against the renal toxicity of cisplatin, we discovered that, in addition to the natural antioxidants previously mentioned, a few sporadic natural antioxidants, including betaine, hyperin, formononetin, and the leaf buds of *Camellia sinensis*, also demonstrated the ability to shield the kidney from cisplatin-induced damage. However, there aren't many studies that address this topic. Plants, microbes, and other nutrient-dense foods are abundant sources of betaine, a naturally occurring component also known as trimethyl glycine [174]. According to one research, betaine may also boost GSH levels, reduce inflammation, NF- κ B activation, and apoptosis during cisplatin toxicity, and protect against oxidative stress caused by cisplatin by scavenging free radicals [52]. One of the flavonols found in the Chinese plant *Abelmoschus manihot* L. is called hyperin. Medic is mostly found in China's southern region. One research found that by blocking NF- κ B and activating Nrf2 signaling pathways, the potential mechanism of hyperinhibiting cisplatin-induced kidney damage was linked to the inhibition of oxidative and inflammatory responses [175]. One of the main substances found in red clover plants is for-mononetin, an O-methylated isoflavone. According to a study, formononetin effectively prevents cisplatin-induced cell death by preventing intracellular ROS accumulation in pig kidney epithelial LLC-PK1 cells. Its mechanism is linked to its ability to reduce ROS accumulation and antiapoptosis without compromising cisplatin's antitumor potential [176]. To lessen cisplatin-induced renal damage, *Camellia sinensis* leaf buds (CSB) and flowers (CSF) may improve renal dysfunction, decrease the level of lipid peroxidation, and boost antioxidant levels [177]. To put it briefly, there are several additional natural antioxidants that can withstand the nephrotoxicity of cisplatin and have a protective effect via a variety of pathways at various levels, which is why they merit further research.

6. The Other Toxicities Induced by Cisplatin and Its Natural Antioxidant Protection

It is commonly known that, beyond the nephrotoxicity, cisplatin can also frequently induce other side effects, such as ototoxicity and hepatotoxicity. Ototoxicity is one of the most frequent side effects in cisplatin, with the incidence of 11%-97%. It usually begins with a symmetrical and



irreversible sensorineural hearing loss, related to the dose of cisplatin used, and has a property of accumulation [178]. The exact mechanism of cisplatin-induced ototoxicity is unclear. It was reported that the transporters (e.g., OCT2), the transient receptor potential channel family members, and other calcium channels, chloride channels, as well as the excessive accumulation of ROS can lead to ototoxicity [179, 180].

Another common side effect is hepatotoxicity, which is usually observed following the administration of large cisplatin doses [181] or small repeated doses [182, 183]. The mechanism of hepatotoxicity is not accurately understood as well. Previous studies suggested that hepatotoxicity might be related to oxidative damage to cardiolipin and proteins with sulfhydryl groups and hepatic cell death by apoptosis via mitochondria as nephrotoxicity and the altered energy metabolism in the liver [184]. However, several studies demonstrated that the main dose-limiting side effect is renal toxicity [15–18], transporters related to cellular uptake of cisplatin are highly expressed in the proximal and distal tubules of the kidneys [185], and the rate of elimination of cisplatin is about 25% within just 24 h and 50% within 5 days in which more than 90% of total excretion occurs through renal excretion [186]; thus, renal excretion is the principal route of excretion of cisplatin, leading to major accumulation in the kidneys and consequent nephrotoxicity. Toxicity induced by cisplatin, excessive ROS accumulation, and the reaction in multiple organ cells have a similar mechanism. Summarizing previous researches, we observed that, besides suppressing the nephrotoxicity, several natural antioxidants also have the ability to protect against other side effects. For example, CAPE has the hepatoprotective properties on cisplatin-induced damage [181, 187], and rosmarinic acid can ameliorate the liver and testicular toxicity [188]. Our review suggests that natural products may exhibit wide use in decreasing multiple toxicity or side effects induced by cisplatin.

7. The Implications and Challenge in Clinical Trials

Following the discussion of the benefits of natural antioxidants, a few related tactics should be taken into account for therapeutic use. It is well known that cisplatin, carboplatin, and oxaliplatin are the three platinum medicines that are now often utilized in the treatment of cancer. The most widely used second-generation anticancer medications are carboplatin and cisplatin, the first platinum anticancer medication; oxaliplatin is the third. Cisplatin gained not just notoriety for its therapeutic effect but also for its serious adverse effects. The bidentate cyclobutane dicarboxylate ligand causes the second-generation platinum to have a reduced rate of aquation [189]. The neurotoxicity and ototoxicity after carboplatin administration are much less severe due to decreased responsiveness. Carboplatin is appropriate for more severe high-dose chemotherapy due to its lower toxicity profile [190]. In order to overcome resistance to carboplatin and cisplatin, the third-generation platinum was created. OCT1 and OCT2, two examples of

organic cation transporters, have been identified.

because their overexpression significantly increases the cellular accumulation of oxaliplatin but not cisplatin, suggesting that they facilitate oxaliplatin absorption. Oxaliplatin has a strong therapeutic impact on colorectal cancer because the cancer cells overexpress organic cation transporters [191]. Consequently, regardless of dose, the second generation of platinum medications may be used in conjunction with natural antioxidants to treat the condition, perhaps curing it or reducing its negative effects. Furthermore, it should be mentioned that oxaliplatin therapy and some antioxidants may both control OCT2 expression. As a result, choosing the right medication is crucial. In this case, it is important to determine if the combination of platinum and antioxidants would strengthen or lessen the therapeutic and adverse effects. The primary biological target of platinum was found to be DNA. By creating monoadducts, DNA crosslinks, and DNA adducts, as well as by triggering a number of signal-transduction pathways, including DNA damage identification and repair, cell cycle arrest, and programmed cell death/apoptosis, cisplatin disrupts normal DNA functioning [192]. An reason for the platinum drug's early anti-tumor effect is that normal and malignant cells have different DNA damage responses (DDR). Because it facilitates the error-free repair of double-strand breaks, which are very harmful to cells, the homologous recombination (HR) pathway is one of the DDR mechanisms of special interest. Platinum medications significantly improve some cancer cells that have enriched BRCA1 mutations and other HR abnormalities [193]. Since the antitumor mechanism in HR-deficient cancer cells may rely more on irreparable DNA damage and error repair than on ROS accumulation, these differences between normal kidney cells and malignant cancer cells may be a protective strategy used in cisplatin treatment in this case. It offers the best way to preserve healthy kidney cells, improve the therapeutic effects of cisplatin on cancer cells, and create disease model subtypes for the use of natural antioxidants to prevent future cisplatin-induced nephrotoxicity. As previously stated, a number of preclinical models have shown the ability of natural antioxidants to reduce the nephrotoxicity caused by cisplatin. These trials may not provide compelling evidence for the use of adjuvant clinical methods in the treatment of cisplatin. Despite the fact that preclinical models documented the use of cardamomin, quercetin, and resveratrol in conjunction with high-dose cisplatin in animals, the majority of cancer patients receiving clinical treatment receive low doses of cisplatin, and it is unknown whether the majority of these natural agents interfere with cisplatin's antitumor activity. Consequently, it is yet unknown whether these investigations can be generalized to clinical settings. However, the underlying mechanism by which a natural antioxidant might reduce cisplatin-induced nephrotoxicity is better understood thanks to these investigations. Cardamomin, quercetin, naringenin, fisetin, and curcumin (Table 1) also shown to reduce the effects of cisplatin therapy by causing kidney injury in humans [125].



shown the capacity to enhance cisplatin's anticancer effect when paired with these organic substances. Although the precise mechanism is still unknown, these early experimental findings imply that natural antioxidants can protect kidney cells while enhancing the antitumor effect of cisplatin in cancer cells. In fact, ROS is also a common factor of cisplatin therapeutic effects, and excessive accumulation of it can affect the viabilities of both normal and cancer cells. However, more high-quality pre-clinical trials are still required to confirm the effectiveness of these agents in reducing the kidney damage caused by cisplatin. These studies therefore demonstrated the effect of natural components combined with cisplatin in vivo and in vitro and discussed the possibility of adding these natural antioxidants as an adjuvant therapy in cisplatin treatment.

8. Summary

Since cisplatin's toxic and adverse effects have restricted its clinical use, reducing or eliminating these toxicities is essential to the effectiveness of therapy. Renal toxicity is the most frequent adverse effect. Studies have shown that the process of cisplatin-induced kidney injury involves apoptosis and necrosis of renal cells and tubules, as well as vascular malfunction, immunological response, and other responses. Oxidative stress and ROS buildup may be the upstream responses among the mechanisms of kidney damage. The early signaling molecules known as ROS have the ability to induce apoptosis, trigger an inflammatory response, and damage intracellular material components to varying degrees. Consumption of endogenous antioxidants, destruction of antioxidant enzymes, induction of mitochondrial damage, and destruction of the CYP system are the main mechanisms of oxidative stress caused by cisplatin. These mechanisms lead to an excessive build-up of ROS in cells (Figure 1). Natural antioxidants have been shown in experiments to have a protective effect against cisplatin nephrotoxicity damage (Table 1). In order to develop resistance to ROS caused by cisplatin, natural antioxidants can eliminate free radicals, preserve the stability of endogenous antioxidants, restore the capacity of antioxidant enzymes, and prevent mitochondrial damage. They can also enhance subsequent nonredox pathways, increase the filtration rate of cisplatin in the kidney, modify cisplatin pharmacokinetics, and ultimately shield the kidney from toxicity (Figure 2). In the meanwhile, research has shown that cisplatin's anticancer effect may be enhanced when natural antioxidants are used in conjunction with it [75, 104, 141]. In conclusion, several preclinical results supporting the clinical usage of cisplatin were obtained from experimental investigations of natural antioxidants on cisplatin nephrotoxicity, and a novel concept for the intricate mechanism of cisplatin nephrotoxicity was put forward. There is undoubtedly an urgent need for additional

preclinical and clinical research to fully examine the side effects of cisplatin and the effectiveness of these natural substances in clinical practice.

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