

# CISPLATIN INDUCED NEPHROTOXICITY AND THEIR HERBAL REMEDY: A REVIEW

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**Abstract-** Cisplatin is a major antineoplastic drug for the treatment of tumors, but it has dose-dependent renal toxicity. However, its primary dose-limiting side effect is kidney injury, which is a major clinical concern. To help understand mechanisms involved in the development of kidney injury, cisplatin rodent model has been developed. At present, there are no effective drugs or methods for cisplatin-induced kidney injury. Recent in vitro and in vivo studies show that numerous herbal remedies such as flavonoids, saponins, alkaloids, polysaccharide, phenylpropanoids, etc. have specific antioxidant, anti-inflammatory, and anti-apoptotic properties that regulate the pathways associated with cisplatin-induced kidney damage. In this review we describe the molecular mechanisms of cisplatin induced nephrotoxicity and summarize recent findings in the field of herbal remedies that determine these mechanisms to protect against cisplatin-induced kidney damage and provide potential strategies for their treatment.

**Keywords:** Cisplatin, nephrotoxicity, herbal remedy, Acute kidney injury

## INTRODUCTION

Cisplatin is highly effective anticancer drug which is used for the treatment of various tumors, such as lung cancer, stomach cancer, and ovarian cancer <sup>[1]</sup> However, nephrotoxicity is the major side effect of cisplatin administration. Clinically, the risk of nephrotoxicity in patients taking cisplatin is between 20% and 35% and leads to death in acute kidney injury (AKI) patients <sup>[2,3]</sup> In addition, pediatric patients also develop nephrotoxicity when using cisplatin <sup>[4]</sup> Most of the people suffer from the drug induced renal failure or nephrotoxicity. Most of the different category of drugs leads to nephrotoxicity while using for disease treatment which includes NSAIDs, Antibiotics such as gentamicin, Ciprofloxacin, adriamycin etc. and Immune suppressant like cyclosporine and tacrolimus produce nephrotoxicity. <sup>[5]</sup> Cisplatin is a potent antitumor drug. Cisplatin-based combination chemotherapy regimens are currently used as front-line therapy in the treatment of testicular cancer, ovarian germ cell tumors, epithelial ovarian cancer, head and neck cancer <sup>[6]</sup>

However, cisplatin is still the drug of choice in many platinum-based therapy regimens and remains one of the most commonly used chemotherapy drugs. cisplatin is toxic to the renal proximal tubules. report of accidental overdoses, all of which have lead to renal failure, confirm the potency of the cisplatin as a renal toxin in nephrotoxicity is an usual side effect of chemotherapy.

## Mechanism of Cisplatin Nephrotoxicity :

Both cisplatin and carboplatin bind DNA, killing dividing tumor cells <sup>[7]</sup> The toxicity of Cisplatin towards the renal proximal tubular cell indicates that there are at least two distinct mechanisms by which cisplatin kills the cells. Experimental evidence indicates that platinum-DNA adducts are the lesion that is toxic to dividing cells, as shown in fig.1 <sup>[8]</sup>

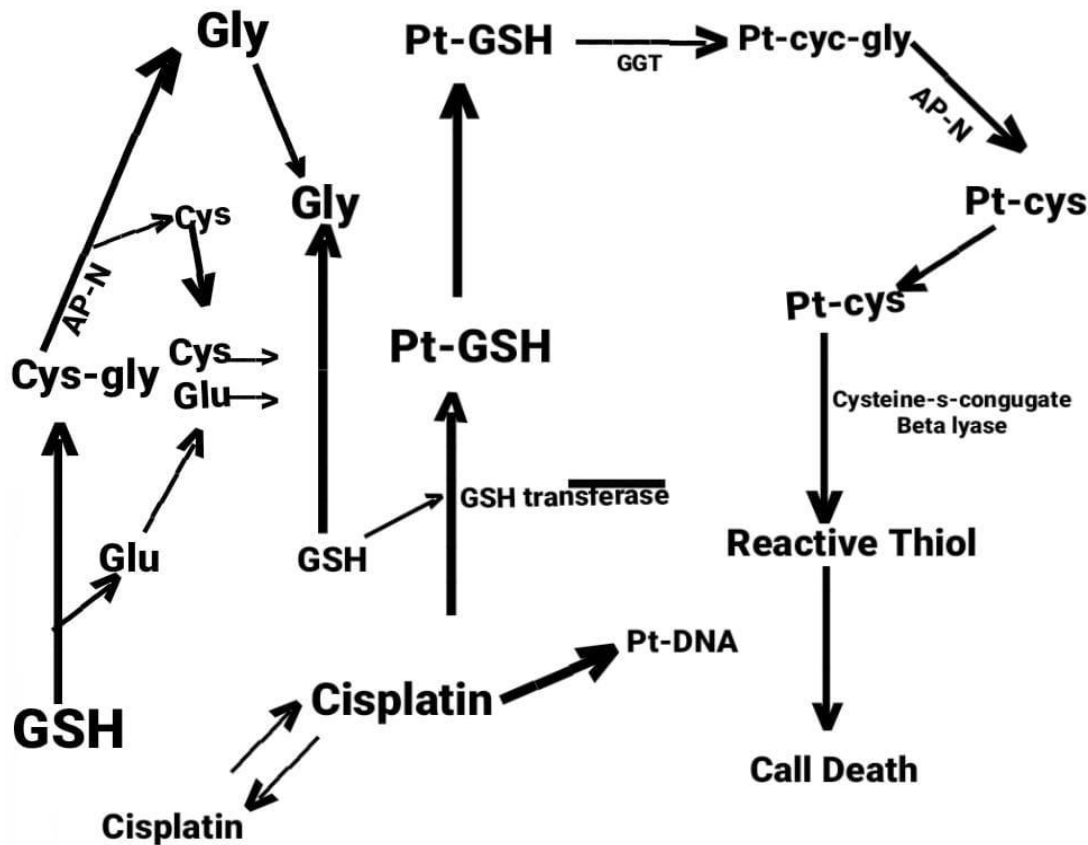


Fig.1 Proposed biochemical mechanism of cisplatin nephrotoxicity

Thiol such as the sulfur of GSH will bind to the platinum molecule, replacing one of the chloride ions and preventing binding to other cellular nucleophiles increased intracellular GSH concentration correlate with platinum-DNA in freshly isolated peripheral blood mononuclear cells. GSTs are family enzyme catalyse the conjugation of GSH to a variety of substrate.

GGTs = Gamma glutamyl transpeptidase; AP-N = aminopeptidase N <sup>[9]</sup>

A series of studies on the role of the enzyme gamma-glutamyl transpeptidase (GGT) in cisplatin toxicity reveal that the tumor cells GGT expression increased resistance to the cisplatin, while in a kidney GGT expression made the cells sensitive to cisplatin toxicity. <sup>[10,11]</sup>

GGT is a cell surface enzyme that cleaves the gamma-glutamyl bonds. GGT cleaves extracellular GSH into glutamic acid and cysteinyl-glycine (figure 1). Cysteinyl-glycine is cleaved into cysteine and glycine by diamino peptidase N. Thus, by initiating the cleavage of extracellular GSH into its constituent amino acid, GGT provides the cell with an increased in supply of cysteine. In rapidly dividing cells, cysteine can become limiting for cell growth and for intracellular GSH synthesis. In contrast, the high level of GGT expression in renal proximal tubular cells render them sensitive to cisplatin toxicity. Inhibition of GGT block the nephrotoxicity cisplatin in both rat and mice <sup>[11]</sup>

The disparate roles of GGT in the antitumor activity and nephrotoxicity of cisplatin suggest that the mechanism by which cisplatin kills tumor cells is distinct from the mechanism by which it kill the proximal tubular cells in the kidney.

### Preclinical models for nephrotoxicity

#### a) In vitro cisplatin induced nephrotoxicity

Protein kinase C (PKC) is a Ca<sup>2+</sup> + phospholipid-dependent enzyme and widely distributed in various tissues.

Changes in PKC activity have been associated with chemical-induced nephrotoxicity & renal ischaemia.

The experiments described here attempt to detect involvement of cytosolic Ca<sup>2+</sup> and PKC in the sequence of events that occur during cisplatin-induced nephrotoxicity in vitro. In this the renal cortical slices were prepared from adult rat, and incubated with cisplatin <sup>[12]</sup> This protocol allows measurement of phosphorylase a activity and PKC assay.

#### b) In vivo model-

##### Gentamicin induced nephrotoxicity in rats

Gentamicin induced nephrotoxicity is characterized by direct tubular necrosis, without morphological changes in glomerular structures <sup>[13]</sup> Gentamicin generates hydrogen peroxide in rat renal cortex mitochondria and can also enhance the generation

of reactive oxygen species (ROS) [14] Abnormal production of ROS may damage some macromolecules to induce cellular injury and necrosis via several mechanisms including peroxidation of membrane lipids, protein denaturation and DNA damage. [15,16]

The alteration in kidney functions induced by lipid peroxidation is a proximal event in the injury cascade of gentamicin mediated nephrotoxicity. [17] Gentamicin also acts as an iron chelator and the iron<sup>2+</sup>gentamicin complex is a potent catalyst of radical generation. [18]

### Cisplatin induced nephrotoxicity in rats-

The xenobiotic-induced alterations in kidney functions are characterized by signs of injury, such as changes in urine volume, creatinine clearance, in glutathione (GSH) status, increase of lipid peroxidation(LPO).

Formation of free radicals, leading to oxidative stress, has been shown to be one of the main pathogenic mechanisms of these toxicities and side effects of nephrotoxicants. CP-induced nephrotoxicity is also closely associated with an increase in LPO in the kidney tissues [19]

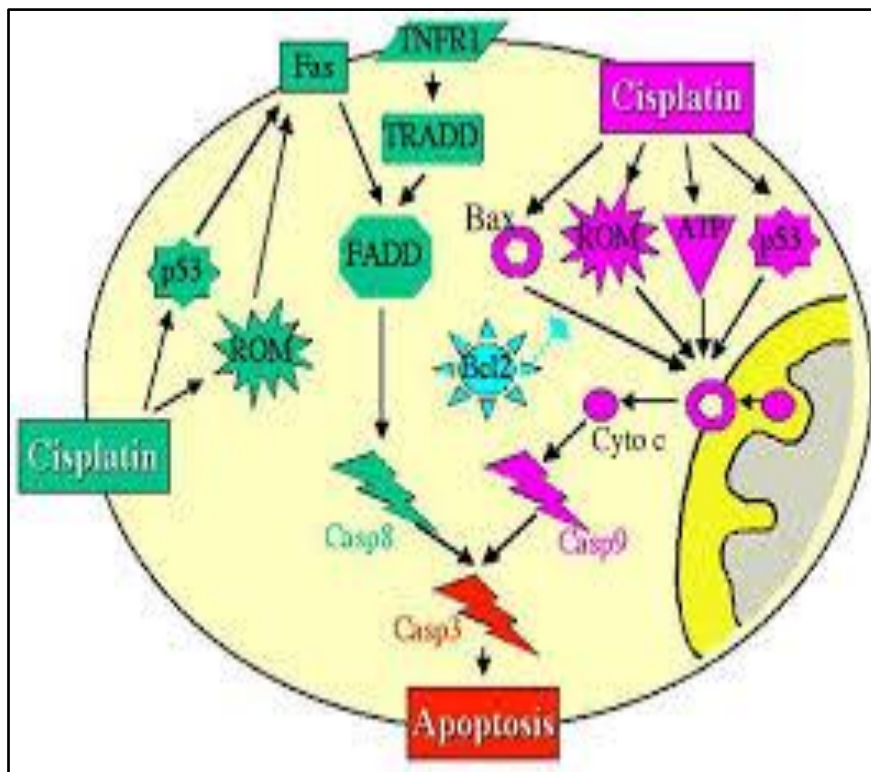
### Role of free radicals cisplatin nephrotoxicity-

Oxidative stress refers a situation of a marked imbalance between the production and removal of ROS.

This may be originated by an overproduction of these substances or by the depletion of antioxidant defenses. [20]

ROS is a collective term to oxidizing agents including free radicals and certain non-radicals, which might be turned into radicals. H<sub>2</sub>O<sub>2</sub> is not a free radical and it is able to cross membranes; it is a precursor of hydroxyl radical (OH) in a reaction catalyzed by metal ions (Fe<sup>2+</sup> or Cu<sup>+</sup>) known as **Fenton reaction**.

ROS are harmfulness due to their oxidant species, which can interrupt important cellular functions and cause damage to several cell structures.



**Fig. 2. Proposed apoptotic pathways in cisplatin nephrotoxicity**

Death receptor pathways are shown in green, and mitochondrial pathways are in purple. All arrows indicate stimulatory influences, except Bcl2 which is inhibitory.

The following are some of the most commonly used oxidative stress markers:

- Lipid peroxidation which is assessed frequently by the determination of malondialdehyde (MDA), thiobarbituric acid reactive substances or lipid peroxides content,
- 8-hydroxy-deoxyguanosine (8-OHdG)
- GSH depletion.

The formation of 3-nitrotyrosine (3-NT) is considered a nitrosative stress marker. Recently, some oxidative markers have been proposed as non-invasive detection methods for early prognosis of renal damage associated to cisplatin administration. [21] Reported a preliminary observation in 8 patients with cancer who presented an increase in urinary MDA excretion, 24 h after cisplatin treatment

The mechanisms of cisplatin-induced kidney damage involve various pathways, such as inflammatory mediators, oxidative stress, necrosis and apoptosis, and autophagy. To date, researchers have not found that these mechanisms are involved in cisplatin-

induced nephrotoxicity, starting with excess ROS generation, which leads to oxidative stress, triggering inflammatory and autophagy pathways that damage DNA and induce apoptosis in the kidney. It is still unclear how the various pathways integrate and ultimately lead to kidney damage. [22]

#### HERBS THEIR PHYTOCONSTITUENTS AND PART USED IN CISPLATIN NEPHROTOXICITY

Herbs	Extract used	Part used	Phytochemical substances	Refernce
Rubia cordifolia	Hydro-alcoholic	Roots	Anthra quinones	[23]
Aerva lanata	Ethanolic	Whole plant	Flavonoids, Lupeol	[24]
Morchella esculenta	Aqueous-ethanolic	Dried Mushroom mycelia	polysaccharides, terpenoids	[18]
C. auriculata	Ethanolic	Roots	Flavonoids	[25]
Apocynum cannabinum	aqueous	Roots	Apocynin [26]	
Vigna angularis	aqueous	seeds	Proanthocyanidins, Polyphenols,	[26]
Green tea	aqueous	leaves	Terpenoids, Flavonoids	[27]
Luteolin	aqueous	leaves	flavonoids	[27]

#### CONCLUSION

There is no specific treatment for cisplatin-induced renal dysfunction or injury. Anticancer drugs cause nephrotoxicity through activating pathways of oxidative stress, damage-associated molecular patterns production, inflammatory processes, and cell apoptosis, while medicinal plants and their derivatives can cause reduction in nephrotoxicity and anticancer drugs side effects via their antioxidant and anti-inflammatory properties.

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