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ROLE OF MEDICINAL HERBS IN CISPLATIN-INDUCED TOXICITY: AN OVERVIEW

Iffat Fatma Siddiqui [1], Sony Chauhan [1], Avinash Kumar [1] and Sanjay Kumar [*2]

Department of Pharmacology [1], Hygia Institute of Pharmaceutical Education and Research, Lucknow - 226013, Uttar Pradesh, India.
Department of Pharmacology [2], Hygia Institute of Pharmacy, Lucknow - 226013, Uttar Pradesh, India.

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Correspondence to Author:
Dr. Sanjay Kumar

Professor,
Department of Pharmacology,
Hygia Institute of Pharmacy,
Lucknow - 226013, Uttar Pradesh, India.

E-mail: sanjaykumar.niec@gmail.com

ABSTRACT: Cisplatin is a widely used chemotherapeutic agent. It is highly effective against various malignancies but is often limited by its severe toxic effects, including nephrotoxicity, hepatotoxicity, neurotoxicity, and ototoxicity. Oxidative stress, inflammation, and apoptosis are key mechanisms underlying cisplatin-induced organ damage. In recent years, medicinal herbs have gained attention as potential protective agents due to their antioxidant, anti-inflammatory, and cytoprotective properties. These investigations will contribute to a deeper understanding of how these herbal treatments can effectively interact at the molecular level, potentially improving therapeutic outcomes for patients suffering from the adverse effects of cisplatin on kidney function.

INTRODUCTION: Cisplatin is a chemotherapeutic drug that is commonly used to treat various types of cancer, includes lung, bladder, testicular and ovarian cancers. Despite its effectiveness in targeting tumor cells, cisplatin is often restricted due to its potential for nephrotoxicity, which refers to its harmful effects on the kidneys. When cisplatin is administered, it can induce cellular damage and trigger an inflammatory response in renal tissues. This inflammatory cascade may lead to acute kidney injury (AKI), a serious condition characterized by a sudden decline in kidney function [1]. Cisplatin contains a platinum core surrounded by two amine ligands and two chloride ions.

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Its mechanism of action primarily involves the intercalation of cisplatin into the DNA of rapidly dividing cells. When cisplatin binds to the DNA, it creates cross-links that prevent the normal separation of the DNA strands needed for replication and transcription. These covalent interactions disrupt the cell's ability to repair DNA damage, as the lesions accumulate over time. The inability to properly separate and repair DNA results in significant genetic stress, ultimately triggering pathways that lead to programmed cell death, or apoptosis [2].

Medicinal plants hold significant promise as a vital source of antioxidants, which play a crucial role in enhancing the effectiveness of anticancer therapies. These antioxidants help to reduce the potential side effects and toxicity that chemotherapy and other cancer treatments can inadvertently inflict on essential organs and tissues in the body. The importance of exploring and utilizing medicinal plants in developing more holistic approaches to cancer care [3].

Mechanism of Action of Cisplatin: Cisplatin, a platinum-based chemotherapeutic agent, enters renal cells through both passive diffusion and facilitated transport mechanisms, which may involve specific transport proteins. Cisplatin, renal tubular cells activates a variety of intracellular signalling pathways that can promote cell death. An important pathway involved in cellular processes is the mitogen-activated protein kinase (MAPK) pathway, which mediates stress responses, the p53 pathway, known for its role in apoptosis and cell cycle regulation, and pathways activated by reactive oxygen species, which contribute to oxidative stress. Cisplatin exposure also triggers a cytoprotective response characterized by the upregulation of p21. This cyclin-dependent kinase inhibitor helps in cell cycle regulation and DNA repair processes. Cisplatin increases the level of TNF-α, tubular cells initiate a strong inflammatory response, which exacerbates tubular injury and may lead to cell death. Cisplatin not only affects the tubular cells; it can also cause damage to the renal vasculature. This vascular injury may result in reduced blood flow to the nephrons, causing ischemic conditions that lead to further tubular cell death and a decline in glomerular filtration rate (GFR). These mechanisms exemplify the complex and detrimental effects of cisplatin on renal function and health.

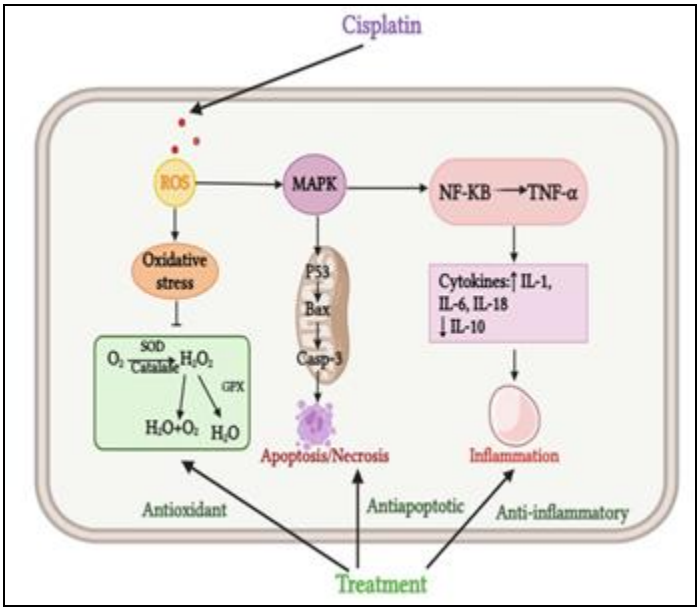

FIG. 1: PATHOPHYSIOLOGICAL MECHANISMS INVOLVED IN CISPLATIN-INDUCED NEPHROTOXICITY

TABLE 1: MEDICINAL PLANTS USED FOR THE TREATMENT OF CISPLATIN-INDUCED TOXICITY

Plant used	Extract/ Dose/ Route	Experimental animals	Outcomes/Results	References
Combretum micranthum G. Don	Hydroalcoholic extract 200,400mg/kg/day	Male albino wistar rats 200-250g	Suppressing inflammation by inhibiting NF-κB, oxidative stress, and autophagy activations.	[4]
Pomegranate Seed Oil	0.4 and 0.8 mg/kg	Male adult Wistar rats 190-220g	↓ MDA concentration in kidney tissue	[5]
Hygrophila spinose	250,500mg/kg	Male Wistar Rats150-250g	Elevate SOD, GPx, and CAT	[6]
Zingiber zerumbet (zerumbone compound)	100, 200mg/kg i.p.	Female SD rats	↑GSH,↓MDA	[7]
Cucumeropsis mannii	2000,2500,7500mg/kg for 10 days	Male albino rats100-150g & mice18-22g	↓oxidative stress	[8]
Date palm fruit	50, 100mg/kg p.o.	Male Wistar rat 180-210 g	Suppress oxidative stress and inflammation	[9]
Propolis	Ethanolic extract 200mg/kg p.o.	Female and male Wistar rats, 180g	Increase the level of antioxidants (SOD, CAT, and GPx) and ↓ the level of MDA	[10]

Cannabis sativa L.	2.5,5 and 20mg/kg i.p.	Black male mice	↓ Serum creatinine and urea level	[11]
Apium graveolens L.	500, 1000mg/kg p.o	Albino rats of Wistar strain 120-150g	↑GFR,↓serum creatinine level, and maintain the level of serum magnesium & potassium	[12]
Alhagi camelorum	400, 600mg/kg/ day p.o.	Albino wistar male rats 260-290g	↓B.W., reduce plasma creatinine and plasma & increase plasma sodium	[13]
Acacia hydaspica R.	Ethyl acetate extract 400mg/kg/BW p.o.	Male Sprague Dawley rats	↓ oxidative stress, NF-kB, and IL-6 protein	[14]
Jatropha mollissima	Hydroalcoholic extract 400, 600mg/kg	Male & female albino wistar rats	↓oxidative stress	[15]
Costus spiralis	Hydroalcoholic extract 5,15,30mg/kg p.o.	Wistar rats 180-230g	Recover renal function	[16]
Guazuma ulmifolia L.(jati belanda)	Ethanolic extract 300,600 mg/kg p.o.	White male SD160-180g	↓MDA, protects the nephrotic renal from hypertrophy	[17]
Eclipta prostrata & Daucus carota	Hydroalcoholic extract 400,600mg/kg	Albino Wistar male rats 220-270g	Improved kidney function by reducing urine creatinine &↑plasmin creatinine	[18]
Vernonia cinerea	Aqueous extract 400mg/kg p.o.	Male albino mice	Shows antioxidant activity	[19]
Phoenix dactylifera L.	Ethanolic extract 0.5, 0.25g/kg	Male wistar albino rats	↓Oxidative stress, ↑ SOD, CAT, GSH	[20]
Pistacia vera nuts (pistachio)	Hydroalcoholic extract 10, 100 mg/kg p.o.	Male mice 29-32g	Reduced cisplatin induced renal damage	[21]
Jasminum grandiflorum L. flowers	Methanolic extract 40mg/kg p.o.	Male SD rats 230-260g	↓MDA level, BUN, serum creatinine	[22]
Leonotis ocymifolia (burm.f.)	Aqueous extract 40,80 mg/kg	Male Wistar rats about 160g	Inhibition of oxidative stress, inflammation & DNA fragmentation	[23]
Thymus caramanicus	Hydroalcoholic extract 50,100,150 mg/kg	Male mice 30-33g	Reduction in kidney damage	[24]
R. vesicarius L.	Methanolic extract 25,50,100 mg/kg	Male swiss albino mice 30-32g	↓MDA, reduces oxidative stress	[25]
Zataria multiflora Boiss.	Hydroalcoholic extract 500 mg/kg p.o.	Rats180-220g	Reduced NO metabolite, inhibits lipid peroxidation	[26]
Carrichtera annua	Ethanolic extract 250 mg/kg p.o.	Adult male Wistar rats 180-200g	Reduced oxidative stress	[27]
Green coffee beans	100,200,300 mg/kg	Male swiss albino mice 34-38g	↓Plasma level of TNF-α & IL-6	[28]
Aloe vera gel	400mg/kg p.o.	Male wistar rat 180-200g	↓MDA level, ↑antioxidant enzyme activity	[29]
Allium porrum (wild leek)	Aqueous extract 500mg/kg p.o.	Adult male New Zealand white rabbit 1100-1300g	↑ SOD, CAT, and GSH	[30]
Withania somnifera root	Ethanolic extract 500mg/kg p.o.	Male albino rats	Prevent cisplatin-tubular damage in kidney	[31]
Pedalium murex fruit	Ethanolic extract 500,1000mg/kg p.o.	Wistar rats 200-250g	↓BUN, serum creatinine, and uric acid	[32]
Ophiocordyceps lanpingensis	200,800mg/kg p.o.	Male mice 6-8 weeks old	↓MDA level, ↓oxidative stress	[33]
Capparis spinose fruits	Hydroalcoholic extract 100mg/kg	Male rats 200-250g	↓ level of urea, creatinine, and total protein	[34]
Lithocarpus polystachyus (trilobatin)	50, 100mg/kg	Male ICR mice 22-25g	↓MDA,↑SOD, GSH, and CAT	[35]
Sonchus cornutus	250,500mg/kg p.o.	Male Swiss albino mice 20-30g	Inhibit NF-kβ signaling pathway	[36]

Hypericum	Hydroalcoholic extract 70mg/kg	Male Wistar rat 195-205g	↓urea, serum creatinine, and BUN	[37]
Capparis spinosa seeds	Hydroalcoholic 50,100mg/kg	Male SD rats 210-250g	↓Plasma level of TNF-α & IL-6	[38]
Gynostemma pentaphyllum leaves	0.9ml/day	Male ICR mice 3 weeks old	Diverse generation of ROS	[39]
Millettia ferruginea aerial part	Aqueous 20mg/kg	Male Wistar rat 160g	Antioxidant, antiinflammatory	[40]
Moringa oleifera seed	Hydroalcoholic extract 200mg/kg p.o.	Male wistar rats 200-250g	↓ level of cytokines (eg: TNF-α, IL-1, and IL-6)	[41]
Heracleum persicum L.	Ethanolic extract 250,500 and 750mg/kg	Wistar rats 160-200g	↓ROS	[42]
Tephrosia pupuria linn.	Alcoholic extract 100,200 and 400 mg/kg p.o.	Male albino rats	Showed significant nephroprotective action	[43]
Tinospora cordifolia & *Boerhaavia diffusa*	Aqueous extract 162.5,325mg/kg p.o.	Female wistar albino rats 208-243g	↓BUN, serum creatinine, and uric acid	[44]
Aronia melanocarpa (chokeberry)	Aqueous extract 100,200,400mg/kg	Wistar rats 200-250g	Antioxidant, anti-inflammatory	[45]
Black soybeans	Ethanolic extract 300,600mh/kg BW	Male SD rats 160-180g	Lowering the effect of cisplatin toxicity	[46]
Pomegranate peels	Methanolic extract 200mg/kg	SD rats	↓BUN, serum creatinine	[47]
Hyophorbe Lagenicaulis (leaves) &*caryota urens* (flower)	Ethanolic extract 5,50,300,2000mg/kg	Albino Wistar rat	Shows nephroprotective effect	[48]
Allium sativum (garlic)	Ethanolic extract 250mg/kg	Male rabbit 1.5-2kg	Reduced the nephrotoxicity	[49]
Rauwolfia vomitoria leaf	Ethanolic extract 100,200mg/kg	Albino Wistar rats 150-180g	↓Albuminuria, Maintain GFR	[50]
Olea europaea leaf	Ethanolic extract 150,300mg/kg	Male Wistar rats 140-180g	↓Plasma level of TNF-α & IL-6	[51]
Pleurotus columbinus	Polysaccharide extract	Wistar rats	Free radical scavenging	[52]
Hygrophilia auriculata (Schumach. Heine leaves)	Ethanolic extract 200,250mg/kg	Male wistar albino rats 200-250g	Reduced the nephrotoxicity	[53]
Hypericum perforatum	Methanolic extract 50, 100,200mg/kg p.o.	Male Swiss albino mice 20-23g	Shows anti-inflammatory and antioxidant properties	[54]
Kaempferia galangal (kaempferide)	50mg/kg	C57BL/6 male mice	↓BUN, serum creatinine, and uric acid	[55]
Ginger & garlic	200,310mg/kg	Wistar male albino rat 160-200g	↓MDA level,↑SOD, GSH	[56]
Marsdenia tenacissima	Methanolic extract 1.65,3.31k/g	Male ICR mice 20-25g	Reduced risk of nephrotoxicity	[57]
Aesulus (dried fruit peels) & *Achyranthes aspera* (leaf)	Ethanolic extract 30-40g	SD rats 150-220g	↓SGOT,SGPT, ALT,ALP,BUN and serum creatinine	[58]
Ajuga leaf	Methanolic extract 200,400,600mg/kg	Male and female Swiss albino mice 28-32g	↓SOD, GPx, and CAT	[59]
Dialium guineense (fruit)	Aqueous extract 100,250,500mg/kgi.p.	Wistar albino rats	Maintain serum creatinine, BUN	[60]
Artocarpus heterophyllus (jack	Ethanolic extract 200,400mg/kg	Rats	Shows nephroprotective effect	[61]

fruit leaves)				
Angelica keiskei	Ethanolic extract 1000,1500mg/kg	Male wistar rats 200-220g	Shows anti-inflammatory and antioxidant properties	[62]
Lichenes (pyxinol)	Methanolic extract10mg/kg	Male SD rats	↓Tunel positive cell, p21 puma bax	[63]
Alstonia scholaris linn. (leaves)	200,400mg/kg p.o.	Rat	Improves kidney health	[64]
Aloe perryi	Methanolic extract 1000mg/kg	Female albino rats 100-110g	↓MDA level,↑SOD, GSH	[65]
Tiliccora triandra	Hydroalcoholic extract 250,500 mg/kg	Male wistar rats 80-160g	Suppression of AChE, TNF-α, IL-6, IL-1β & apoptotic Bcl2/caspase-3/p53	[66]
Stachys pilifera	Hydroalcoholic extract 500 mg/kg	Wistar female rats 200-250g	↓The urea and creatinine levels	[67]
Anredera cordifolia (ten.) steenis & sonchus arvensis L.	Hydroalcoholic extract 100 mg/kg	Male wistar rats 200-300g	↓Creatinine and urea in serum	[68]
Borassus flabellifer L.(male flowers)	Ethylacetae extract and methanolic extract 1,10µg/ml & 10,50µg/ml	Rats	Shows cytoprotective effect	[69]
Benincasa hispida (thumb.) cogn.	Hydroalcoholic extract 200,400mg/kg	Albino wistar rats 200-240g	↓elevated urinary sodium, potassium, electrilytes, urinary glucose, blood urea & cretinine	[70]
Citrus sinensis (root)	Hydroalcoholic extract 50,100mg/kg	Male wistar rats 180-200g	Shows cytoprotective effect	[71]
Sargassum ilicifolium (brown seaweed)	Aqueous extract 1ml/day	Male SD rats 300-400g	↑antioxidant activity	[72]
Vaccinium macrocarpon (cranberry)	200mg/kg/BW po	Male albino mice 25-30g	Maintain GFR, ↓BUN, serum creatine	[73]
Betel nuts	Aqueous extract 2mg/ml po	Female Swiss albino mice 24.8-25.2g	Reduced serum creatinine and improve the liver health	[74]
Phoenix dactylifera (leaf)	Methanolic extract 400,1200mg/kg po	Male SD rats 245-340g	Improves liver and kidney functions	[75]
Carica papaya (leaves)	Hydroalcoholic extract 300,600mg/kg	Female Wistar rats	Repair renal tissue	[76]
Allium sativa (bulbs), *zingiber officinale*(root), *ocimum gratissium*(leaves), *carica papaya* (fruit)	Methanolic extract 400,600,800mg/kg	Male wistar rats	↑serum albumin, ↓serum urea, uric acid, creatinine	[77]
Cannabis sativa L. & *Daucus carota L.*	Ethanolic extract 2.5,5,10,20mg/kg	Male albino rats	Improves kidney health	[78]
C antaloupe, grapes & pumpkin seeds	100mg/kg	Male SD rats 180-200g	↓plasma cholesterol, triglysrides	[79]
Beetroot	Ethanolic extract 500mg/kg	Male wistar albino rats 150-180g	↓Plasma level of TNF-α & IL-6	[80]
Rhododendron luteum (leaf)	12.5,25mg/kg	Female wistar albino rats 200-250g	Suppression of oxidative stress, inflammation, and apoptosis	[81]
Phyllanthus emblica & Biocurcumin	100,300mg/kg	SD rats 200-300g	↓oxidative stress,	[82]
Triticum aestivum	Hydroalcoholic extract 200mg/kg	Male rats 200-250	↓Plasma level of TNF-α & IL-6	[83]
Achyranthes aspera	Ethanolic extract 200,400mg/kg ip	Male wistar rats 200-250	Suppress oxidative stress, antiapoptotic	[84]
Celastrus	Ethanolic extract	Female wistar rats 160-	Improve levels of antioxidants	[85]

paniculantus (seed)	400,800 mg/kg po	200g	(CAT, GPx, SOD, GR, GST, and GSH)	
Diospyros malabarica (desr.)	Ethanolic 250,500mg/kg po	Wistar rats 150-210g	Shows improvement in renal damage	[86]
Albizia julibrissin	Methanolic extract 50,100µg/ml	Male C57BL/6 mice	Maintain the level of creatinine and BUN	[87]
Zea mays L. (silk)	100,200,400mg/kg po	Male&female Wistar rats	Maintain kidney health	[88]
Phoenix dactylifera L.	Methanolic extract 600mg/kg po	Male rats 180-200g	Reduced NF-κB activity, downregulating IL-12 and COX-2.	[89]
Lactobacillus rhamnosus	125,250,500mg/kg	Male CB57BL/6 mice 20-25g	↑ cytokines TNF-α and IL-6	[90]
Diospyros lotus L.	Aqueous extract 400mg/kg po	Male SD rats 250-300g	Suppress oxidative stress	[91]
Apium graveolens (celery) & *cymbopogon flexuosus* (lemongrass)	200,400mg/kg po	Male wistar albino rats 200-300g	Maintain level of creatinine, urea	[92]
cassia occidentalis L. (kasondi root)	Hydroalcoholic extract 67mg/kg os	Albino wistar rats 150-200g	Suppress oxidative stress, antiapoptotic	[93]
Inula racemose, capsella bursa-pastoris & urtica dioica	Aqueous extract 600mg/kg	Male swiss albino mice 20-24 g	Shows nephroprotective effects	[94]
Panax ginseng	Hydroalcoholic extract 200mg/kg	Male wistar rats 200-220g	Improve renal cell injury	[95]
Vitex pseudo-negundo	Methanolic extract 400mg/kg po	Male wistar rats 120-130g	Antiapoptotic	[96]
Caenohabdtis elegans	Ethanolic extract 600mg/kg po	Wistar rats 250-300g	Shows hepatoprotective effect	[97]
Arabic gum & coconut water	100ml/kg, 7.5g/kg	Wistar rats	Improvement in serum urea and creatinine	[98]
Juglans regia (walnut tree leaves)	Hydroalcoholic extract 100,200,400mg/kg	Wistar rats 230-250g	Improve kidney health	[99]
Pumpkin seeds oil &Parsley	0.1ml/kg/bw	Male albino rats 160-200	Reduced hepatic and renal toxicity	[100]
Foeniculum vulgare (leaf)	Hydromethanolic extract100,200,400mg/kg	Mice 25-35g	↓kidney injury	[101]
Hibiscus sabdariffa	Ethanolic extract 500mg/kg	Male albino wistar rats 150-200	Antiinflammatory, antiapoptotic	[102]
Spirulina platensis	Methanolic extract 2500mg/kg	Wistar rats 165-185g	Improved spermatogenesis, ↑testosterone hormone concentration in blood	[103]

DISCUSSION: Cisplatin is a cornerstone in cancer treatment and is among the most widely utilized chemotherapeutic agents due to its remarkable effectiveness against a variety of malignancies, including ovarian, testicular, lung, and bladder cancers. This review study provides extensive evidence supporting cisplatin's pivotal role in cancer therapy, especially when utilized in combination with other agents, which can enhance its therapeutic effectiveness and mitigate the challenges posed by drug resistance. One of the significant findings of the study is the reaffirmation of cisplatin's primary mechanism of action, which involves the formation of DNA crosslinks. This process disrupts DNA replication and transcription, ultimately triggering apoptosis, or programmed cell death, in cancer cells. Nonetheless, the development of resistance to cisplatin remains a major challenge in clinical settings. This resistance often arises from several mechanisms, including an

increase in DNA repair capacity, active drug efflux by transport proteins, and alterations in apoptotic pathways that allow cancer cells to survive despite treatment. This study underscores the importance of implementing strategies such as aggressive hydration protocols, the use of nephroprotective agents to safeguard kidney function, and careful dose adjustment to enhance patient tolerance while still achieving therapeutic goals.

Future research endeavors should prioritize refining cisplatin delivery methods, such as developing and applying nanoparticle-based formulations. These innovative approaches may significantly reduce systemic toxicity and improve the specificity of drug targeting to tumour tissues. The exploration of such combination therapies could lead to synergistic effects that enhance treatment outcomes. Overall, the findings presented in this review highlight both the potential and the complexities of optimizing cisplatin therapy in cancer treatment, paving the way for future innovations in cancer care.

CONCLUSION: Herbal drugs have shown potential in protecting against cisplatin-induced toxicity by targeting oxidative stress, inflammation, and apoptosis. While preliminary studies suggest their benefits, further clinical research is necessary to confirm their effectiveness and safety for cancer patients receiving cisplatin. By combining herbal remedies with conventional chemotherapy, we may enhance treatment outcomes and reduce adverse side effects, ultimately improving patients' quality of life.

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