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# PROTECTIVE ROLE OF PLANTS AND THEIR COMPONENTS AGAINST CISPLATIN INDUCED NEPHROTOXICITY: A REVIEW

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**ABSTRACT**

Nephrotoxicity is one of the most common problems caused by various toxic compounds and chemotherapy. Cisplatin is a widely used and most potent chemotherapeutic drug for the treatment of several human malignancies. In addition to its anticancer activity, cisplatin may induce adverse effects including nephrotoxicity. Because of its superior anticancer potential, the research community is scrutinizing the renoprotective role of plant species to minimize cisplatin-induced nephrotoxicity. In this review, we have evaluated the studies made for exploring the renoprotective role of various medicinal plants and their components. Alleviating role of plant species has been considered in terms of protection/recovery of serum biochemical parameters like urea, creatinine, uric acid, blood urea nitrogen and enzymes involved in oxidative stress like LPO, GSH, SOD and CAT. Histopathological studies of kidney tissue treated with different extracts of different plant species or their components are also considered. This paper could benefit the scholars and scientists researching about nephrotoxicity or chemotherapy and for those working in therapeutics, health and pharmacology.

***Keywords - Antioxidant, Biochemical, Cisplatin, Histopathology, Nephroprotoxicity***

## 1. INTRODUCTION

Kidney is the only organ that excretes wastes such as urea and ammonium by producing urine. It acts as a natural filter of the blood by diverting the metabolic wastes to the urinary bladder. Besides metabolic wastes; they also remove drugs and various toxic industrial and environmental agents in the blood. Kidney plays an important role in

the reabsorption of water, glucose, and amino acids. It also produces hormones like calcitriol, erythropoietin, and the enzyme rennin [1].

Cisplatin is a chemotherapy medication which is used to treat a broad spectrum of malignancies including head and neck, esophagus, bladder, and metastatic testis, ovarian, breast and non-small cell lung cancer. However, side effects in normal tissues and organs including nephrotoxicity frequently hinder the use of higher doses cisplatin to maximize its antineoplastic effects [2]. Clinically, cisplatin nephrotoxicity is manifested as lower glomerular filtration rate, higher serum creatinine, and reduced serum magnesium and potassium levels. Complex signaling pathways are activated due to exposure of kidney to cisplatin, which leads to tubular cell injury and death [3].

Renal toxicity is the production and increase of free radical species, employment of antioxidant defense mechanisms, and also acute cells necrosis in renal tubules which reduces the glomerular filtration rate (GFR) and kidney dysfunction [4].

This review summarizes the research work done on medicinal plants and components for their role against cisplatin induced nephrotoxicity.

## 2. NEPHROPROTECTIVE POTENTIAL OF VARIOUS MEDICINAL PLANTS AND THEIR COMPONENTS

Antioxidant treatment with Ellagic acid on cisplatin-induced nephrotoxicity was studied using biochemical and histopatological approaches [5]. The study was done on adult male Sprague-Dawley rats with the control group receiving 0.9% saline; another group of animals received ellagic acid (10 mg/kg). Animals in the third group received only cisplatin (7 mg/kg while group fourth animals received ellagic acid for 10 days after cisplatin. Increases in plasma creatinine, urea and calcium concentrations was a mark of cisplatin induced renal failure in cisplatin treated rat group. Increased kidney tissue concentrations of malondialdehyde, and reduced activities of GSH peroxidase and catalase was an indication of cisplatin induced oxidative stress. Histopathological studies of the kidney tissue from Cisplatin treated rats showed tubular necrosis, degeneration and desquamation; luminal cast formation, karyomegaly, tubular dilatation, interstitial mononuclear cell infiltration and inter-tubular haemorrhagia. Treatment with ellagic acid counteracted the deleterious effects of cisplatin on oxidative stress and kidney biochemical markers. In the same way ellagic acid alleviated the cisplatin-induced pathological changes as compared to cisplatin group.

Aqueous and ethanolic extracts of *Portulaca oleracea* L. were investigated for the possible nephroprotective role against cisplatin-induced renal toxicity in rats [6]. Effect of both extracts on blood urea nitrogen (BUN) and serum creatinine (Scr) was studied before and after cisplatin injection (4 mg/kg). The best results in the highest dose (0.8

and 2 g/ kg), 6 and 12 hr before cisplatin injection showed reduced BUN and Scr. Histopathological studies did not revealed any tubular necrotic damage as was the case in cisplatin treated group.

*Scutellaria barbata* (*S. barbata*) administrated orally, once a day for three days (300 mg/kg body wt) reduced the levels of pro-inflammatory cytokines and tubular injury compared to cisplatin injected at 25 mg/kg body weight [7]. The study was done on mice and the results confirmed that *S. barbata* is a potent herbal medicine that reduces nephrotoxicity and renal toxic effects of cisplatin.

*Berberis aristata* (250 g) powder was added with 100 ml water, boiled on water bath for half an hour and kept overnight at room temperature (25 ± 2°C). The mixture was filtered on next day and the filtrate was concentrated to 600 ml [8]. The decoction (63 mg/ml) at doses of 500 mg/kg and 1000 mg/kg body weight was used to study the nephroprotective potential against cisplatin (6 mg/kg) induced kidney damage in Wistar rats. Decoction of root bark of *Berberis Aristata* decreased blood urea nitrogen, serum creatinine, urinary protein excretion, lipid peroxidation and increased the levels of urine to serum creatinine ratio and glutathione. Histopathological studies of cisplatin dosed rats showed congestion in glomeruli, glomerular atrophy and disappearance of nuclei in tubular cells. The plant decoction effectively protected the cisplatin induced histological damage in the kidney tissue.

Possible protective effects of stem bark ethanol and aqueous extracts of *Ficus racemosa* against cisplatin induced nephrotoxicity was evaluated in mice [9]. Cisplatin injection significantly ($P < 0.01$) elevated the serum urea, creatinine, blood urea nitrogen and lipid peroxidation levels and decreased the catalase and renal glutathione (GSH) levels compared to control group. Stem bark ethanol and aqueous extracts of *Ficus racemosa* reversed all the adverse effects of cisplatin at doses of 200 mg/kg and 400 mg/kg body weight.

Serum creatinine, urine creatinine, serum urea and blood urea nitrogen (BUN) levels were used as renal markers to investigate the possible role of aqueous extract of root of *Sida cordifolia Linn*. (SCAE) against gentamicin and cisplatin induced nephrotoxicity [10]. All these levels in wistar albino rats were significantly ($P<0.001$) normalized by the plant extract dose of 200 & 400 mg/kg body weight, as against gentamicin (100 mg/kg) and cisplatin (7 mg/kg).

Biochemical and histopathological approaches were used to evaluate the nephroprotective potential of aqueous leaf extract of *Ocimum gratissimum* against cisplatin induced kidney damage [11]. A group of male albino wistar rats were injected with 5 mg/kg B.W of cisplatin, which caused a significant increase in serum urea, creatinine, uric acid, urine volume and urinary protein. It also decreased the urinary creatinine levels and body weight of rats. *Ocimum gratissimum* (5% and 10%). leaf extract ameliorated most of these changes in a dose and timely dependent manner. This was also evident from the reduced histopathological alterations of kidney tissues treated with plant extract.

*Rheum ribes* extract decreased ($P < 0.001$) the serum BUN and blood cholesterol levels compared to cisplatin group. It did not have any significant effect on blood creatinine level but the serum glucose level was increased

significantly ($P < 0.001$) compared to cisplatin [12]. This study was done on albino male rats and cisplatin dose of 3 mg/kg was injected against 150 mg/kg body weight of *Rheum ribes*. Histopathological studies of kidney revealed renal injuries induced by cisplatin, but *Rheum ribes* had no effect on the architecture of kidney tissue.

The ability of *Thespesia populnea* extract to alleviate the harmful effects of cisplatin was tested on male Sprague Dawley rats [13]. Animals were divided into 3 groups of Normal, cisplatin (6 mg/kg/b.wt.) and combined treatment of cisplatin and *Thespesia populnea* (5 mg/kg/b.wt). Administration of *Thespesia populnea* extract significantly ($P < 0.05$) reduced the levels of serum urea (112 ± 2.16), creatinine (0.54 ± 0.004), ALT (76.4 ± 1.45), AST (58.80 ± 1.6) and bilirubin (3.96 ± 0.85) as compared to serum urea (137 ± 1.6), creatinine (1.69 ± 0.14), ALT (96.18 ± 3.44), AST (80.84 ± 3.34) and bilirubin (4.57 ± 0.08) of cisplatin dosed group. This was concluded that the plant extract protected the kidney and liver damage induced by cisplatin.

Mice were used as a model to evaluate the potential role of *Cactus cladode* extract against Cis-Platinum (II) (cis-diammine dichloroplatinum; CDDP)-induced oxidative stress and genotoxicity [14]. Malondialdehyde (MDA), catalase activity, superoxide dismutase (SOD) activity, chromosome aberrations (CA) test, SOS Chromotest, expressions of p53, bax and bcl2 in kidney were also analyzed along with serum biochemical analysis for renal function. Adult, healthy balb/c (20–25 g) male mice were pre-treated with intraperitonial administration of CCE (50 mg/kg.b.w) for 2 weeks. Another two groups of animals received both CDDP and CCE, in one group CCE was given before CDDP and the other received CCE after CDDP treatment. The results showed that CDDP induced kidney dysfunction as was evident by oxidative stress markers, chromosomal aberrations and kidney biochemical parameters. However, CCE treatment before or after CDDP showed reduction of CDDP induced oxidative stress, prevention of chromosomal aberrations, restriction of the effect of CDDP by differential modulation of the expression of p53 which is decreased as well as its associated genes such as bax and bcl2 and also resuming the values of serum creatinine, urea, albumin and total protein levels to near normal.

Nephrotoxicity was induced in rats by intraperitonial dose of cisplatin (12.5 mg/kg) to study the protective role of aqueous extract of *Cuminum cyminum* [15]. The plant extract was dosed at 100 and 200 mg/kg body weight for 10 days. Blood sample was collected for serum creatinine and urea analysis, kidney tissue was homogenized for the estimation of lipid peroxidation, reduced glutathione, superoxide dismutase (SOD) and catalase. Marked elevation of serum urea, creatinine and lipid peroxidation levels was the evidence of cisplatin induced nephrotoxicity along with decreased levels of glutathione, SOD and catalase. Treatment with aqueous extract of *Cuminum cyminum* altered the kidney marker levels and oxidative enzymes near to normal, which was the indication that the plant extract has significant nephroprotective potential.

Cisplatin at a dose of 7.5 mg/kg body weight induced acute renal failure in male wistar rats [16]. Oral dose of methanolic extract of *Hygrophila spinosa* (250 mg/kg and 500 mg/kg body weight) declined the blood urea and serum creatinine levels and weakened the increase in MDA and decrease in reduced GSH, and CAT and SOD and

GSH peroxidase activities due to cisplatin. Amelioration of tubular necrosis induced by cisplatin was done the methanolic extract of aerial parts of *Hygrophila spinosa*.

Male albino rats were used to evaluate the renoprotective and antioxidant activities of methanolic extract of leaves of *Vitex negundo* against cisplatin induced nephrotoxicity [17]. They were divided into four groups of control, cisplatin group, silymarin group and *Vitex negundo* group. At the end of experimental period (15 days) the kidney of each rat was excised and homogenized for the analysis of antioxidant enzymes. *Vitex negundo* treated group showed significant reduction in MDA level and increased GPx, CAT and SOD activities. Histopathological observations showed amelioration of cisplatin influenced toxicity on kidney structure by the plant extract.

Petroleum ether and ethanol extracts of grape, coriander, roselle and fennel were mixed in the same ratio of their occurrence in the parent plant [18]. The extract mixture was investigated for the protective role against cisplatin induced kidney dysfunction. Phytochemical evaluation of these plants revealed that roselle ethanol extract has highest phenolic content (15.584 g GAE/100 g extract) while Coriander oil contained highest content of unsaturated fatty acids (85%). Grape oil showed the highest content of phytosterol (15.9%). Significant biochemical and histopathological changes were induced by cisplatin as compared to control group. Treatment with extract mixture reduced the plasma urea, creatinine malondialdehyde and increased the plasma albumin, total protein, catalase activity, total antioxidant level and creatinine clearance. Cisplatin also induced chromosomal aberration, sperm-shape abnormalities and kidney dysfunction was observed by histopathological studies of cisplatin treated rat group. Rat groups treated with extract mixtures showed improvements in biochemical, histopathological and cytogenetic parameters.

Nephrotoxicity was induced in Wistar rats by intraperitoneal injection of Cisplatin (5 mg/kg) [19]. The ethanolic extract of *Morinda citrifolia (EEMC)* fruits was investigated for its nephroprotective potential at doses of 100 and 200 mg/kg b.w. Significant decrease in serum creatinine, urea and protein was shown by the treated groups as compared to cisplatin group. Cisplatin induced glomerular atropy, infiltration of cells and tubular congestion as was evident by the histopathological studies of the kidney tissue. However, these changes were reduced in the groups treated with EEMC.

Investigation of the effect of pomegranate seed oil against cisplatin induced nephrotoxicity was carried out in adult rats [20]. They divided the animals into four groups, corn oil (1 ml/kg) was given to Group I animals and cisplatin (8 mg/kg) was given to Group II rats. Animals in the Group III and IV were treated with pomegranate seed oil (PSO) 0.4 ml/kg and 0.8 ml/kg one hour before cisplatin injection for 3 days, respectively. Blood collected by cardiac puncture was used to measure urea, creatinine, protein and glucose concentration. They fixed the part of kidney in formalin for hispathoplogical studies and another part was homogenized for the measurement of malondialdehyde and total sulfhydryl. Cisplatin group displayed significant increase in serum creatinine, urea, urinary glucose, protein concentrations, and non-significant decrease in total thiol content and increase in MDA level in kidney

homogenates. Histopathological studies revealed tubular cell necrosis, hyaline casts, and vascular congestion in kidney tissue of cisplatin treated rats. Treatment with pomegranate seed oil significantly decreased the urinary protein, glucose, and serum creatinine concentration. It also reduced the serum urea and renal MDA non-significantly, and increased the thiol content as well.

*In vitro* and *in vivo* protective activity of methanolic extract of *Dendropanax morbifera* (DP) against cisplatin-induced acute kidney injury was investigated on renal tubular cells (NRK-52E) and rat models respectively [21]. The extract of DP was separated into n-hexane, CHCl3, EtOAc, n-BuOH, and $H_2O$ fractions through successive liquid extraction. The cisplatin-induced increase in blood urea nitrogen and serum creatinine and histopathologic damage was ameliorated by DPCF treatment in *In vivo* rat models. It also attenuated the level of anti-oxidant enzymes, and inhibited renal apoptosis.

Incidence of nephrotoxicity in cisplatin given along with ethanol extract of *Curcuma comosa* decreased significantly compared to cisplatin given alone [22]. Microscopic observations of kidney tissue showed decreased number of swollen, necrotic and apoptotic cells compared to cisplatin group. It also displayed less renal tubular damages and COX-2 expression. This study was done on mice which were divided into 4 groups of control, cisplatin control *C. comosa* (200 mg/kg) + cisplatin and *C. comosa* control groups. The results proved the benefits of *C. comosa* in aspect of renal protection against cisplatin induced nephrotoxicity.

Protective potential of ethanolic extract of *Annona reticulate* against gentamicin and cisplatin induced nephrotoxicity was investigated in rats [23]. Cisplatin (5 mg/kg) and gentamicin (40 mg/kg) treated group of animals showed considerable increase in the concentration of serum urea, creatinine, Uric acid, Total protein and Urine Urea, uric acid, creatinine than the normal group of animals. However, treatment with aerial parts of plant extract (500 mg/kg) ameliorated the above mentioned parameters which confirm the nephroprotective effect of *Annona reticulate*.

Cisplatin dose of 5 mg/kg body weight was used to induce nephrotoxicity in albino rats [24]. The nephroprotector activity of ethanolic extract of *Catunaregam Uliginosa* was assessed at dosed at 200 mg/kg and 400 mg/kg body weight. They determined the blood urea nitrogen, serum creatinine, urinary total protein (UTP) and creatinine clearance (Clcr) levels and found that increased serum marker levels and reduced creatinine clearance (Clcr) due to cisplatin were ameliorated by the plant extract. They observed that antioxidant enzymes like super oxide dismutase (SOD), catalase (CAT), glutathione reduced (GSH) activities were increased and lipid peroxidation (LPO) decreased in rats injected with cisplatin. *Catunaregam Uliginosa* treatment reversed these effects at both doses. Histopathological studies also supported their biochemical results, as *Catunaregam Uliginosa* extract caused regenerative changes in kidney tissue and reduced the renal damage.

The preliminary phytochemical screening of methanolic (70%v/v) extract of *Caralluma umbellata* Roxb. stem showed the presence of steroids, triterpenes, alkaloids, glycosides and flavonoids [25]. Its *in vitro* antioxidant activity was tested on superoxide, hydroxyl and DPPH free radicals and nephroprotective activity was carried out using cisplatin and gentamicin induced renal injury. The results showed that the mean $IC_{50}$ values for ascorbic acid to superoxide anion, hydroxyl radical and DPPH radical to be 54.4 µg, 68 µg and 22 µg. Kidney biochemical parameters such as blood urea, serum creatinine, serum total protein and serum albumin were ameliorated by the methanolic stem extract of *Caralluma umbellata* at doses of 250 mg/kg and 500 mg/kg body weight.

Protective potential of aqueous-ethanolic extract of *Nigella sativa* (100 and 200 mg/kg, BW) and vitamin E (100 mg/kg, BW) against cisplatin induced blood and urine biochemical alterations and kidney function was studied in rats [26]. Serum urea and creatinine concentration in preventive and preventive + vitamin E treated and preventive + N. sativa (200 mg/kg, BW) treated groups and also serum creatinine concentration in preventive + N. sativa (100 mg/kg, BW) treated group significantly decreased as compared to 6 mg/kg group of cisplatin. Urine glucose concentration also decreased in preventive and preventive + N. sativa treated groups while as urine output in preventive and preventive + N. sativa (200 mg/kg, BW) treated group was significantly reduced as compared to cisplatin group. It was concluded that vitamin E improved the kidney biochemical markers in a dose dependent manner; however, investigation needs to be done on the mechanism of nephroprotection by N. sativa.

The modulatory effect β-sitosterol (BT) on cisplatin (CP) induced nephrotoxicity was studied by targeting oxidative stress and biochemical parameters for kidney function markers in rats [27]. An intraperitoneal dose of cisplatin (7.5 mg/kg BW) was given at one time. β-sitosterol (BT) 5 ml/kg was administered for 10 days. Blood sample was collected for the measurement of serum creatinine and BUN. Kidney was removed for the determination of xanthine oxidase, lipid peroxidation, ($H_2O_2$) generation and antioxidant enzymes, like, catalase, glutathione reductase and glutathione peroxidase Histopathological studies of kidney tissue were also done. Animal groups administered with cisplatin increased the glutathione depletion, xanthine oxidase and lipid peroxidation activity and decrease in (glutathione reductase, catalase and glutathione peroxidase) and phase-II detoxifying (quinine reductase and glutathione-S- transferase) enzyme activities. Histopathological studies showed that cisplatin causes severe interstitial edema, glomerular and peritubular necrosis. β-sitosterol (BT) treatment alleviated the cisplatin induced oxidative damage and histological changes through its antioxidant actions.

Free radical scavenging activity of Fermented black ginseng (FBG) was measured using 1,1-diphenyl-2-picrylhydrazyl (DPPH) and its protective effect against cisplatin-induced renal damage was tested in rats [28]. Oral dose of FBG (150 mg/kg) was given for 10 days and a single dose of cisplatin was administered intraperitoneally (7.5 mg/kg body weight) with 0.9% saline on the 4th day. FBG showed stronger DPPH radical-scavenging activity (IC50¼ 384 mg/ml) than that of raw ginseng. This was mediated by the generation phenolic compounds. The altered creatinine clearance levels due to cisplatin treatment were reduced to the normal level after the administration of

FBG. Inhibition of NF-kB/p65, COX-2, and caspase-3 activation due to FBG dosage protected the cisplatin induced oxidative renal damage in rats. It was concluded that FBG ameliorates the cisplatin induced nephrotoxicity by regulating oxidative stress, inflammation, and apoptosis.

The possible Reno-protective effects of n-BuOH extract of *Centaurea choulettiana Pomel* leaves (BECC) against cisplatin-induced nephropathy in mice [29]. Single dose of Cisplatin (8 mg/kg) increased the blood urea nitrogen (BUN), creatinine level and oxidative stress in kidney tissue. Histopathological studies showed extensive vacuolization of epithelial cell, swelling, desquamation and necrosis. Pretreatment with BECC (150 mg/kg; 10 days) ameliorated the creatinine (80.15 %) and BUN (57.58%) level and suppressed malondialdehyde (MDA) (54.90 %), restored GSH level (63.29%) and reversed the antioxidant enzymes, CAT (67.61%), SOD (68.16%), GPX (66.38 %) and GST (70.18 %). These results were comparable with those of vitamin E.

Nephroprotective potential of dietary containing *Ocimum sanctum* against cisplatin-induced nephrotoxicity was investigated in rats [30]. Adult male rats were divided into four groups of six rats each. Group 1 and 2 were fed basal diet (50% skimmed milk, 36% corn starch, 10% groundnut oil, and 4% mineral and vitamin premix) for 6 weeks. Group 3 and 4 were fed basal diet supplemented with 2% and 4% *O. sanctum* leaves, respectively, for 6 weeks. Groups 2-4 received a single intraperitoneal dose of cisplatin (7.5 mg/kg BW) after the 5th week of the experiment. Administration of basal diet supplemented with 2% and 4% *O. sanctum* to rats significantly reduced the creatinine, urea, uric acid, urine pH, BUN, and total protein compared to cisplatin control group. It also reduced the cisplatin induced histopathological changes in kidney tissue.

## 3. CONCLUSION

Cisplatin is one of the most widely used chemotherapeutic drugs for the treatment of several human cancers. Despite its various adverse effects, it remains to be a preferred modality for the treatment of large number of cancers. Cisplatin causes accumulation of platinum within the kidney which disturbs renal tubular tissue and function. Nephrotoxicty is one of the most studied side effects of cisplatin and various approaches, including use of medicinal plants and components against cisplatin induced renal injury have been evaluated.

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