Review Article

Potential of Pure Phytoconstituents and Herbs in Protection of Drug Induced Nephrotoxicity

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ABSTRACT

Global trend is setting towards improved 'quality of life', for that there is considerable evidence of an increase in demand for medicinal plants. According to the WHO report, between 65% and 80% of the populations of developing countries use medicinal plants as remedy nowadays. Kidney is one of the vital organs of body and Nephrotoxicity is one of the most common problems and it occurs as a result when body is exposed to a drug or toxin. This review article aims to report and to introduce the effect of most important medicinal herbs, herbal formulations and some of the specific phytoconstituents that are used to prevent and treat anticancer, aminoglycoside, non-steroidal anti-inflammatory and few other classes of drug-induced nephrotoxicity. Particularly anti-cancer drugs among all other classes of drugs, cause high toxicity leading kidney damage and irreparable kidney injury. So, attention has recently been paid to seek out alternatives such as natural drugs that are effective and also less toxic. According to the studies carried out on different animals and cell line, many medicinal plants, herbal formulations and a few plant-based constituents by their antioxidant, free-radical and anti-inflammatory properties are found to be helpful in preventing drug-induced nephrotoxicity.

Key words: Nephrotoxicity, Cisplatin, Gentamicin, Natural compounds, Medicinal plants.

INTRODUCTION

The tribal and rural populations all over world very largely depend on medicinal plants for their health care and for their livestock too. This attracted the interest of many botanists which lead to an array of reports on ethno-medicine.[1] Plant species have a major role to play as about many others are the synthetic analogues made on prototype compounds which are isolated from these plant species.[2] According to the report of World Health Organization (WHO, 2005), about 80% of the total world's population directly or indirectly depends upon Traditional Medicine to fulfil their healthcare needs. As a source of raw material, medicinal plants have great importance in alternative system of medicine (Ayurveda, Unani, Siddha and Homoeopathy) and it marks them as an influential therapeutic agent. However, increasing demand at global level leads to create a need for usage of herbal medicine due to its worldwide acceptance in treating a number of diseases. Various chemical constituents of the Medicinal plants belonging to different families have curative effect against diseases.[3]

Reno-toxicity is a poisonous result of the substances both like toxic chemicals and medications, on kidney function and Nephroprotective agents are the drugs which are having protective effect against nephrotoxicity. Chronic kidney disease, with its high frequency, morbidity and mortality, has become an important public health problem. Even, chronic kidney disease and other non-communicable diseases have often been neglected in the face of persistent challenges from and competition for resources for communicable diseases and

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high infant and maternal mortality.[4] With about <3% of land mass, India hosts about 17% of the Earth's population. Very large number of patients below the poverty line, low gross domestic product and low monetary allocations for health care have led to sub-optimal results.

Anticancer drugs are related to nephrotoxicity, i.e. one of the most common anticancer drug-induced side effects of the anticancer drugs is nephrotoxicity, that is, it causes either causes temporary or permanent kidney damage. Moreover, it can endanger the lives of cancer patients and therefore intensify their conditions. In about 60% of all the clinical cases, Studies have shown that nephrotoxicity is the cause of acute renal injuries and is induced mainly by anticancer drugs.[5-9] Nephrotoxicity can be diagnosed through simple blood tests or assessment of nephrotoxicity through blood parameters such as measurement of blood urea nitrogen (BUN), glomerular filtration rate (GFR), concentration of serum creatinine and creatinine clearance. Also, Body is unable to get rid of excess urine and wastes from the body and blood electrolytes such as potassium and magnesium will result in their elevation when kidney damage occurs. A number of potent therapeutic drugs like aminoglycoside antibiotics, chemotherapeutic agents and NSAIDS have been added to the therapeutic arsenal in recent years and a number of therapeutic agents can adversely affect the kidney resulting in acute renal failure, chronic interstitial nephritis and nephritic syndrome.

Prompt recognition of disease and preventing the use of responsible drug are the only necessary therapy. Chemical constituents of the Medicinal plants belonging to different families have curative effect and ancient literature has proposed a number of herbs for the treatment of kidney disease. Administration of medicinal plants having nephroprotective effect along with the nephrotoxic agents (drugs) may reduce its toxicity.[3,10,11]

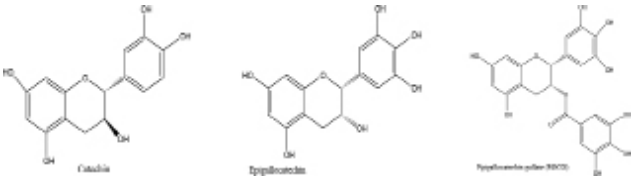
Herbs and some of their phytoconstituents for treating drug-induced nephrotoxicity

Phytoconstituents having nephroprotective effects against cisplatin-induced nephrotoxicity

Catechin, epigallocatechin and epigallocatechin gallate

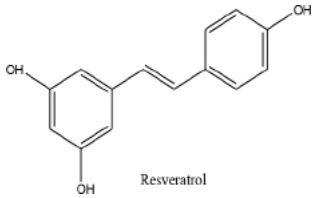
The compounds such as catechin, epigallocatechin and epigallocatechin gallate (EGCG) found in green tea have been reported to be effective against nephrotoxicity.[12] A study carried out on mice with cisplatin-treatment showed that pre-treatment with polyphenols (EGCG and epigallocatechin) led to decline the toxic changes, cisplatin-induced side effects and improved renal function in mice[13] thus, it was also found that administration of 20-40 mg/kg of catechin and EGCG led to decline in tumour necrosis factor alpha (TNF-α) and MDA (malondialdehyde) and enhanced glutathione level.

In another study carried out on rats, EGCG was found preventing the oxidative stress, suppressing systemic inflammation and leucocytosis and, polyphenol is reported preventing chances of side effects and mortality due to cisplatin-induced nephrotoxicity and thus proved nephroprotective in nature.[14]



Resveratrol

Resveratrol a polyphenolic compound found in white hellebore (*Veratrum grandiflorum* O Loes) root, apple, grape and, also in other medicinal plants. A study was carried out on mice and was checked for nephroprotective action of Resveratrol using cisplatin-induced nephrotoxicity model. And, it gave indications of renal injury and toxicity as elevated serum creatinine level and urine proteins in resveratrol and found to be lower than those taken in controls. Also, administration of resveratrol led to decrease in glutathione depletion and lipids peroxidation.[15,16] Resveratrol also shows anti-inflammatory properties and suppresses oxygen species activity and its antioxidant property is linked with declined 4-HNE (4-hydroxynonenal) and carbonyl-adduction,[15] thus it is concluded that its nephroprotective action is due to its reported anti-oxidant potential. Another study reported, was carried out on rats which demonstrated an increase in levels of serum creatinine, urine protein and volume, lipids peroxidation and glutathione depletion in cisplatin-treated rats. And, changes and nephritis were found to be alleviated in resveratrol treated rats.[17]

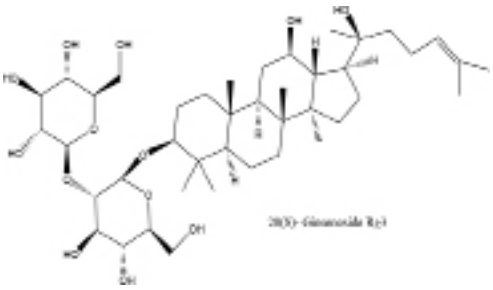


Resveratrol

Ginsenosides

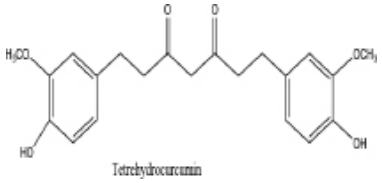
20(S)- Ginsenoside Rg3 having antioxidant potential is an active compound present in plants like *Panax ginseng*, is used in the treatment of renal disorders in various regions of the world. A study was carried out for

Cisplatin-induced apoptosis in porcine proximal tubular in pig kidney cells (LLC-PK1) through inhibiting c-Jun N-terminal kinase (JNK)-p53-caspase-3 signalling cascade can be prevented by the use of this plant-based compound 20(S)- Ginsenoside Rg3.[18] Also use of ginsenosides Rg3, Rg5 and Rk1 and processed ginseng can prevent damage to the LLC-PK1 cells. And also, expressions of *p*53 and c-Jun N-terminal kinase (JNK) proteins that are depressed by cisplatin are restored. Antitoxic activity of this compound is due to its anti-inflammatory and anti-apoptotic properties.[19] Even, more compounds of ginseng like Rh4 and Rk3 can lead to decrease, the induced nephrotoxicity in the LLC-PK1cells.[20]



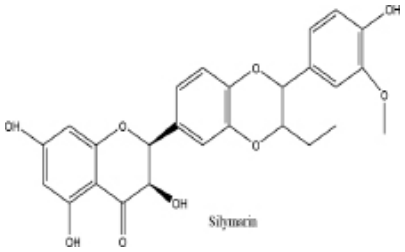
Tetrahydro-curcumin

Tetrahydro-curcumin is an important compound found in curcuminoids of root of turmeric plant. A study was carried out to check for the nephroprotective action of Tetrahydro-curcumin and it was reported showing anti-inflammatory properties and preventing cisplatin-induced nephrotoxicity in addition with preventing the activities of certain enzymes such as caspase-3 and cyclooxygenase-2.[21] Most probably, due to its antioxidant potential it was found nephroprotective in nature.



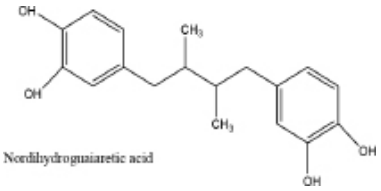
Silymarin

Is a plant-based flavonoid compound from *Silybum marianum*. Silymarin tend to show anti-inflammatory effect by decreasing TNF-α and also found reducing acute nephrotoxicity through protecting lysis of red blood cells. Silymarin is found to reduce BUN and serum creatinine levels and thus protecting cisplatin-induced nephrotoxicity in patients, which is found credited to its immunomodulatory, antioxidant and anti-inflammatory properties.[22]



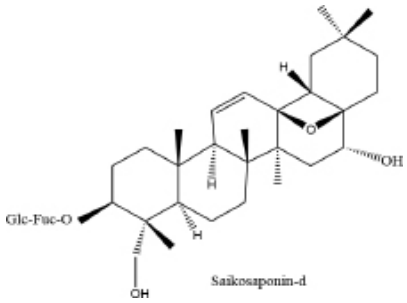
Nor-dihydroguaiaretic acid (NDGA)

Nordihydroguaiaretic acid (NDGA) is a phenolic lignan is a natural compound found to be present in the evergreen shrubs like *Larrea divaricata* and *Guaiacum officinale*.[23] And it is reported to have anti-inflammatory, anti-cancer and anti-oxidant activity, is also reported to treat cisplatin-induced renal toxicity when carried out on Female Sprague–Dawley rats.[24] And assessment of parameters creatinine (Cr) and BUN in the serum samples by using auto blood analyser (Siemens, Dimension Xp and Plus) was done after 5 days of cisplatin administration and body weight decrease and kidney/body weight ratios were calculated as to get rates of kidney injury. The amelioration was detected clearly by significant deduction in serum BUN as 86.51 g/dl and creatinine as 5.30 g/dl levels and significant improvement in body weight change as −10.34 g and kidney weight as 728 mg/kg and also, restored antioxidant enzymes activity like SOD (superoxidase dismutase) as 86.28% inhibition, inflammatory markers like TNF-α as 34.6 pg./ml) and also histopathological examination.[25]



Saikosaponin-d (SSd)

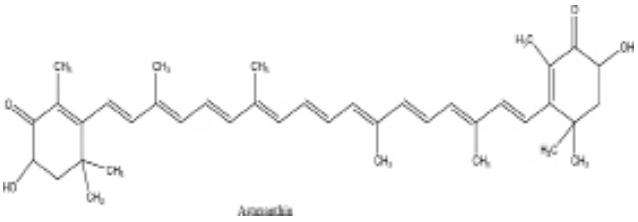
Saikosaponin-d is a triterpenoid saponin, known to have various pharmacological properties and is reported to observe, how SSd protected against cisplatin-induced nephrotoxicity. SSd led to decline the level of reactive oxygen species (ROS) accumulation and that the specific ROS scavenger N-acetylcysteine (NAC) and markedly stopped the cisplatin-induced activation. It has an ability to reduce the activity of ROS, hence proven nephroprotective in nature.[26]



Phytoconstituents having nephroprotective effect against Colistin sodium methane sulfonate (CMS)-induced nephrotoxicity

Astaxanthin

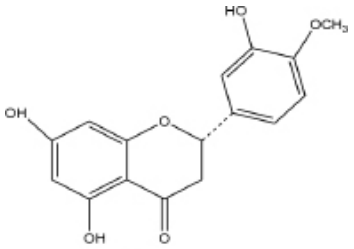
In a study on Male Wistar rats weighing 250 ± 20 g Astaxanthin (ASX) is a carotenoid red-orange in colour naturally found in a large variety of aquatic organisms, such as microalgae, fishes and crustaceans such as shrimps, it is known for its antioxidant and anti-inflammatory properties.[27,28] The levels of urine creatinine (Cr), urine -glutamyl-transferase (GGT) and renal tissue activities in malondialdehyde (MDA), SOD, catalase (CAT), glutathione peroxidase (GPx) and reductase (GSH), as well as renal histology were observed. And the results obtained were showed that ASX has an action of changing the level of the antioxidant enzyme in an assay, plasma and renal enzyme markers and thus, CMS was reported to induce renal injury. And, CMS was observed to decrease the level of the antioxidant enzyme assay. Astaxanthin of 20 mg /kg b.w. and vitamin E of 100 mg/ kg b.w. was reported to prevent declined effect caused by CMS.[29]



Phytoconstituents having nephroprotective effect against Ferric nitrilotriacetate (Fe-NTA) induced -nephrotoxicity

Hesperidin

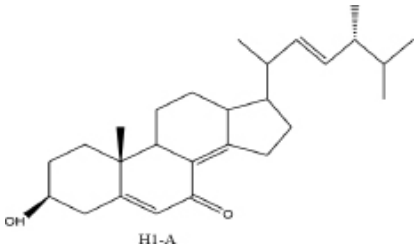
Hesperidin (HS) is a flavone glycoside commonly found in citrus fruits. A study on Male wistar rats (150–200 g), 6–8 weeks old was carried out to check for nephroprotective effect of Hs against Fe-NTA induced -nephrotoxicity and Fe-NTA in 9 mg/kg i.p. was reported to induce inflammation in kidney. Kidney toxicity was observed by the changes in kidney antioxidant enzyme and its kidney morphology. Nitrilotriacetate was known to prevent antioxidant property of the kidney tissues and hence leading to nephrotoxicity. And, the treatment with hesperidin was observed to prevent the abnormalities in the kidney function.[30]



Phytoconstituents having nephroprotective effect against IgA nephropathy model

H1-A

H1-A is a pure compound from *Cordyceps sinensis* (Cs), which is a blade-shaped fungus derives its nutrient from larvae of Lepidoptera.[31,32] In an IgA nephropathy model, a fractionated crude methanolic extract of the fruiting bodies of Cs significantly led to decrease haematuria and proteinuria and improved kidney histology. Purified compound of Cs by silica gel column chromatography and high-performance liquid chromatography also showed positive results towards renal protective action against IgA nephropathy. Cs and its component H1-A led to reduce haematuria and protein urea in a murine model of IgA nephropathy model.[33]

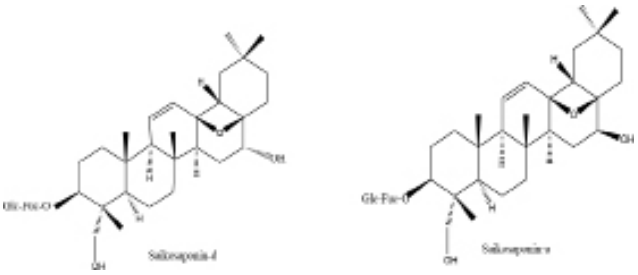


Phytoconstituents having nephroprotective effect against Gentamicin-induced nephrotoxicity

Saikosaponin a and d

Major triterpenoid saponin derivatized from of *R. bupleuri* are Saikosaponin a (SSa) and its epimer saikosaponin d (SSd), which have been used as an anti-inflammatory agent.[34] Studies separately on Cellular mechanisms, Animal (rat, mice) and Human were carried out and it has a potential of an Anti-inflammatory, immuno-modulatory. It resulted in deduction of the urinary protein excretion and kidney injury in the nephrectomy model, in rat model of gentamicin nephrotoxicity, etc. Also, SSd reduces proteinuria and

extracellular matrix deposition and moderate level of evidence in patients with IgA nephropathy, likely by inhibiting mesangial cell proliferation.[33]



Herbs having nephroprotective effect against methotrexate -induced nephrotoxicity

(*Allium sativum*) Garlic

A study was carried out on Forty Wistar Albino male rats (100–120 g), to investigate the protective effect of aqueous extract of garlic on methotrexate-induced nephrotoxicity which exhibited that aqueous *A. sativum* extract led to enhanced filtration rate, improved renal function and activities of antioxidant enzymes. Also, garlic extract led to decrease oxidative stress and prevented morphological changes in the kidney.[35] And when observed for parameters results were, Garlic lead to decrease in MDA level and improved kidney function because of exerting antioxidant, antiapoptotic and anti-inflammatory effects. Also, the extract leads to somehow protect cisplatin-induced side effects including histo-morphological, ultrastructural and biochemical changes.[36]

Herbs and Herbal extracts having nephroprotective effect against cisplatin-induced nephrotoxicity

Grape

Grapes are found to mainly consist of antioxidant phytochemicals polyphenols, flavonoids, proanthocyanidins and resveratrol. A study was carried out on 4-week-old with weight 125-140 on about twenty-one male Wistar rats for renal protective effects of antioxidant properties of whole grape juice (with skin and seeds) on cisplatin-induced acute nephrotoxicity in rats. And, it showed no significant changes in oxidative stress and antioxidant status in the kidneys of cisplatin-treated rats. Rather, after pre-treatment with whole grape juice tubular cell vacuolization, tubular dilatation and cast formation in kidney tubules were observed to be slightly improved.[37]

Green tea

Green tea commonly known as *Camellia sinensis* is a very frequently used plant in traditional system of medicine. A Study in male rat for the protective effects against cisplatin induced nephrotoxicity, was carried out to show that green tea is effective on increased Pi transport activity along with reducing cisplatin induced destructive changes. Administration of green tea and royal jelly when compared with that of chemotherapy, a decrease in BUN and serum creatinine was observed followed by increased MDA production and creatinine level in rats. Thus, green tea showed protective effect against cisplatin-induced nephrotoxicity.[38]

Rubia cordifolia

R. cordifolia belonging to family Rubiacea, a commonly used herb in Indian traditional medicine, was found to have antioxidant properties. A study was carried out on 4-6-week-old male Swiss Albino mice (20-25 gm) to check for the protective action of hydro-alcoholic extract of *R. cordifolia* extract and the effect in cisplatin-treated mice showed that this extract led to reduce urea levels and serum creatinine and Lipid peroxidation in the kidney tissues was also found decreased in *R. cordifolia* extract treated animals. And, finally Hydro-alcoholic extracts of *R. cordifolia* was found effective in reducing the cisplatin induced-renal damage.[39]

Phyllanthus fraternus

P. fraternus belonging to family Euphorbiaceae have attracted pharmacologist's attention for its pharmaceutical uses. A study on wistar rats (100 g) was carried out to check protective effect shown by extract of *P. fraternus* on cisplatin and cyclophosphamide induced nephrotoxicity in rats when they both given in combination to each other. And the results led to show that administration of cisplatin (12 mg/kg, i.p) and cyclophosphamide (150 mg/kg, oral) together to wistar rats (100 g) significantly altered mitochondrial structure and hence function. Aqueous extract of P. *fraternus* was found to reduce nephrotoxicity in this co-administration of cisplatin and cyclophosphamide-induced model. This plant can also attune lipids peroxidation and mitochondrial respiratory disorders.[40]

Sphaeranthus indicus

Only a few of the researches have been conducted on *S. indicus*, commonly known as East Indian globe thistle, which is used in treatment of various diseases. A study was carried out on mice and ethanolic extract of *S. indicus* was used for about 10 days after administration of cisplatin and it was found effective in reducing the nephrotoxicity, as reduction in the indices like BUN level and serum creatinine level were observed. And also, it led to enhance antioxidant indices like superoxide dismutase, catalase and glutathione peroxidase in kidney

and regulated glutathione level in mice and was found nephroprotective in nature.[41]

Urtica dioica L.

U. dioica, is known as common nettle and is being used in traditional system of medicine. A study on kidney of mice for the antitoxic effects of common nettle was performed followed by administration of cisplatin. And it was found to observe that methanolic extract of *U. dioica* exerted preventive effect by decreasing BUN level, lipids peroxidation, myeloperoxidase and proteins oxidation due to its antioxidant properties. Also, it led to decrease the activities of certain enzymes such as superoxide dismutase, glutathione S-transferase, catalase and glutathione peroxidase as well as glutathione content and found potent antioxidant and thud nephroprotective in nature.[42]

Glycyrrhiza glabra

Licorice extract from the dried root of *G. glabra* is found being commonly used in Chinese traditional medicine. It possesses antioxidant potential so it was observed to have nephrotoxic effects. A study was carried out in mice where the administration of licorice extract where it was found preventing all the side effects due to cisplatin-induced nephrotoxicity including elevated BUN and serum creatinine as well as raised oxidative stress in mice. However, when licorice extract was given in combination with cisplatin, the therapeutic efficacy (destruction of tumour cells) was tend to reduce. So, it is recommended to use this extract alone rather than in combination with cisplatin for exerting anticancer effect. Thus, it could be concluded that it possesses antioxidant potential and so nephroprotective in nature.[43]

Panax ginseng

A study was carried out on pig kidney cells to check for nephroprotective effect of fermented then lyophilised black ginseng extract against cisplatin-induced nephrotoxicity. The impaired renal function was observed by increases in the total protein level and renal enzyme markers. *Panax ginseng* extract was analysed to restore the level of alteration caused by cisplatin and in repair in kidney damage. And it was observed that cisplatin-induced cell viability was significantly recovered with this ginseng extract.[18]

Sphagnum palustre

A study was carried out on LLC-PK1 (pig kidney epithelium, CL-101) cells, to check for nephroprotective action of ethanolic (EtOH) extract of *Sphagnum palustre* and its active ingredients. And the increased percentage of apoptotic cells by cisplatin was significantly decreased after cotreatment with the EtOH extract of *S. palustre* and ergosterol peroxide, (3β,22E,24S)-3-hydroxyergosta-5,22-dien-7-one and betulinic acid and also, the protective potential effect of *S. palustre* was by its ability in inhibiting the mitogen-activated protein kinase response.[44]

Pulsatilla dahurica (PD), *Centipeda minima* (CM), *(Loranthus parasiticus)* LP, *Sinapis alba* (SA), *Curcuma longa* (CL), *(Scutellaria barbata)* SB and *Paeonia suffruticosa* (PS)

A study was carried out on Six-week-old BLAB/c male mice (weighing 20–25 g) and the spray-dried extracts of 239 products produced by 7 medicinal plants ((PD), (CM), LP, (SA), (CL), SB and (PS)) and they were screened to quantitatively determine the recovery effects of herbal medicines (HM) on the cisplatin-induced nephrotoxicity using cytotoxicity assays of cisplatin-treated HEK 293 cells. And the results suggested that SB, CL, PS and SA are the best herbal medicines for the recovery of cisplatin-induced nephrotoxicity.[45]

Pueraria tuberosa D.C.

A study was carried out on the albino rats of Charles foster strain (both sexes, 150–200 g) was performed to check the nephroprotective effect of an herbal preparation PTY from methanolic extract of tubers of *Pueraria tuberosa* D.C., in cisplatin induced nephrotoxicity model. Rats were administered orally PTY in different doses for seven consecutive days, along with cisplatin (8 mg/kg B.W., i.p.) on 4th day. And it was found to observe that PTY prevented the elevation in serum creatinine level, BUN. It led to prevent the decline in glutathione content, activities of superoxide dismutase and catalase and also prevented DNA damage, tubular swelling, cellular necrosis and protein cast deposition as compared with the experimental control group in kidney.[46]

Nigella sativa

A study on rats was carried out to check for the nephroprotective action of seeds of plant *Nigella sativa* against cisplatin induced nephrotoxicity in rats. Dose administration of *N. sativa* seed extract (50 mg/kg) 30 min prior to the administration of the drug cisplatin was effective in making the better biochemical and physiological indices of nephrotoxicity.[47] And, thymoquinone is reported reducing the nephrotoxicity of cisplatin and enhances its antitumor activity, may be due to the prior reported antioxidant action of the extract.[48,49]

Other Medicinal Plants with their specific part and chemical constituents used in treating Cisplatin Induced Nephrotoxicity

Plant Name	Part used	Family	Chemical constituents
Bauhinia variegatea linn	Stems	Caesalpiniaceae	stigmasterol, flavone glycosides, lupeol, kaempferol-3-glucoside, β-sitosterol.[50]
Cassia auriculate	Roots	Fabaceae	Tannins, Di-(2-ethyl) hexyl phthalate, Alkaloids, Resins, Ca2+ and Phosphorous.[51]
Ceratonia Silique	Pods and Leaves	Fabaceae	Flavanoids.[52]
Ficus religiosa	Latex	Moraceae	Amino acids and Tannins.[53]
Kigelia Africana	Matured fruits	Bignoniaceae	Iridoids, Naphthoquinones, Flavonoids, Terpenes, Tannins, Steroids, Saponins and Caffeic acid.[54]
Lepidium sativum	Seeds	Brassicaceae	Volatile aromatic oils, Fatty oils, Carbohydrate, Protein, Fatty acid, Vitamin B-carotene, Riboflavin, Niacin, Ascorbic acid, Flavonoids, Glycosides and Isothiocynates.[55]
Panax ginseng	Roots	Araliacae	Saponin, glycosides, Ginsenosides (Dammarol), Panaxosides (Oleanolic acid) and Chikusetsu saponin.[56]
Picrorhiza kurroa Royle	Rhizome	Scrophulariaceae	Tannins.[57]
Pongamia pinnata	Flowers	Papilionaceae	Flowers Pongamol, Protien, Alkaloids, Tannins, Sugar, Resin and Fatty oil (Karanjin).[56]
Vernonia cinereal	Aerial parts	Compositae	Triterpenoids like α-amyrin, β-amyrin and lupeol.[58]

Herbal extracts having nephroprotective effect against cyclophosphamide-induced nephrotoxicity

Curcuma caesia Roxb.

For treating various ailments and metabolic disorders *C. caesia* Roxb is considered to be very commonly used herb in traditional system of medicine. A study on *C. caesia* Roxb. was carried out on mice against chemotherapeutic drug cyclophosphamide to check for its nephroprotective effect. And it was observed that use of methanolic extract of *C. caesia* Roxb reduced serum levels of aspartate aminotransferase (AST) and alanine transaminase (ALT) and kidney peroxidation in the treatment group cyclophosphamide and it exerted toxicity on the kidney in mice. The study suggested that the methanolic extract of *C. caesia* Roxb has reduced the genotoxicity caused by cyclophosphamide and showed the protective effects against kidney.[59]

Phyllanthus fraternus

P. fraternus belonging to family Euphorbiaceae have attracted pharmacologist's attention for its pharmaceutical uses. A study on wistar rats (100 g) was carried out to check protective effect shown by extract of P. *fraternus* on cisplatin and cyclophosphamide induced nephrotoxicity in rats when they both given in combination to each other. And the results led to show that administration of cisplatin (12 mg/kg, i.p.) and cyclophosphamide (150 mg/kg, oral) together to wistar rats (100 g) significantly altered mitochondrial structure and hence function. Aqueous extract of P. *fraternus* was found to reduce nephrotoxicity in this co-administration of cisplatin and cyclophosphamide-induced model. This plant can also attune lipids peroxidation and mitochondrial respiratory disorders.[60]

Herbal extracts having nephroprotective effect against gentamicin-induced nephrotoxicity

Eclipta prostrate

E. prostrate is a natural product, which was reported to have a beneficial effect upon gentamicin-induced renal toxicity in rats. And, this experiment was evaluated on Sprague–Dawley rats, which was observed to show an increase in the level of renal enzyme markers and renal antioxidant assay on the administration of 80 mg/ kg b.w. gentamicin. The study was carried out for 7 days to find the beneficial effect of *E. prostrate*. And the results showed the elevated level of renal enzyme markers and minimised renal antioxidant assay, by the potential activity of *E. prostrate*. This beneficial activity is probably be due to the radical scavenging and ferrous ion elimination properties of the *E. prostrate*.[61]

Moringa oleifera

A study on rabbits to check for protective effect of *Moringa oleifera* leaves extract at the dose 300 mg/kg b.w. was carried out and it reported to improve complications caused by gentamicin-induced renal injury in rabbits. Gentamicin at the dosage 80 mg/ kg b.w. showed a significant elevation in the renal enzyme markers and Kidney morphology was observed to have complicated renal damage. *M. oleifera*-treated rabbits were found to normalize the alteration made by

gentamicin on kidney and hence found to be nephroprotective effect of *M. oleifera* extract.[62]

Euclea divinorum

A study on rats was carried out and was checked for nephroprotective effect of extract of plant *Euclea divinorum* against gentamicin-induced renal toxicity in rats. Gentamicin led to cause alteration in renal enzyme markers and antioxidant enzyme assay. And, *E. divinorum* extract was observed normalising the alteration caused in renal enzyme markers and antioxidant enzyme assay and thus, *E. divinorum* extract was found to be nephroprotective in nature.[63]

Pimpinella anisum

Plant *Pimpinella anisum* commonly known for its different medicinal properties is also a natural antioxidant and a free radical scavenger. A study was carried on Wistar albino rats of either sex, weighing 150–200 g into different groups and administered as normal saline, gentamicin 80mg/kg, intraperitoneally for about 8 days, aqueous extract of *Pimpinella anisum* seeds at 1, 2 and 4g/kg, administration of extract 3 days before and continuously with gentamycin for 5 days. And blood collected at last and was observed as, increase in serum urea, serum uric acid, serum creatinine and blood urea nitrogen as (107.5±16.92mg/dl, 0.8±0.09 mg/dl, 3.05±0.29 mg/dl, 47.8±9.07 mg/dl) respectively when compared with the saline treated groups. Also, Co-administration of *Pimpinella anisum* extract with gentamicin led to decrease the raised levels in a dose dependent manner. Also, Histopathological analysis was carried out and showing epithelial loss with intense granular degeneration, whereas aqueous extract of *Pimpinella anisum* led to show serious the effect of gentamicin-induced renal damage.[64]

Turmeric

Turmeric is known to have efficacy against gram negative bacteria, resistant bacteria, nosocomial infections and cost effectiveness. Also, Turmeric has various different medicinal properties including potent antioxidant activity. So, a study was carried out on animals in different groups with varying number, simultaneously were administered with extract of turmeric and gentamycin, on last day animals were sacrificed and results observed were, Severe renal dysfunction (146 ± 9.2, 2.03 ± 0.26), highest renal injury grading (3.66 ± 0.24) was observed in only gentamicin treated groups followed by spontaneous recovery after withdrawal of drug but with higher levels of oxidative stress (0.04 ± 0.01). Gentamicin and Turmeric treated groups maintained renal function and had lower level of renal damage grades and oxidative stress. Turmeric pre-treated group was having lowest oxidative stress (0.12 ± 0.03), histopathology grade (0.60 ± 0.06) with normal renal functions. And, hence turmeric was found to be nephroprotective in nature.[65]

Anethum graveolens

Anethum graveolens is a major source of bioactive compounds that are having varying pharmacological activities including antioxidant. A study on Wistar albino rats of either sex, weighing 150-200g for Nephroprotective effect of *Anethum graveolens* against gentamycin-induced nephrotoxicity was performed. And, Serum urea, creatinine, uric acid, BUN parameters and histopathological examination of kidney were observed. As a result, Gentamicin treatment led to nephrotoxicity, as seen marked increase in Serum urea, creatinine, uric acid and BUN as 107.5±16.92 mg/dl, 0.88±0.09 mg/dl, 3.05±0.29 mg/dl and 47.80±9.07 mg/dl respectively and is compared to saline treated animals. Then, Administration of aqueous extract of *Anethum graveolens* at doses 0.5, 1 and 2g/kg/ body wt. led to decline the rise in these parameters in a dose dependent manner. However, 1 and 2g/kg body wt. doses showed statistical significance, when compared to the gentamicin treated group. Also, histopathological analysis led to epithelial loss with intense granular degeneration and, led to show serious effect of gentamicin-induced renal damage. Hence, extract of *Anethum graveolens* was found to be nephroprotective in nature.[50]

Petroselinium Sativum, Eruca Sativa, Curcuma Longa

A study was carried out on forty-two male Sprague dawley rats to check for the action of *Petroselinium Sativum, Eruca Sativa* and *Curcuma Longa* alone and in combination, against gentamycin induced nephrotoxicity. First group was administered with 0.2ml/rat normal saline and second group injected with gentamicin 80mg/kg bw i.p. for consecutive 8 days and rest four groups were give aqueous extract of these three alone and in combination 1ml/rat, 150mg/kg bw along with gentamicin. After 24 h, biochemical analysis was done of blood and urine and kidney specimen for histopathology. *Petroselinium Sativum, Eruca Sativa, Curcuma Longa* caused nephroprotective effect with decreased in levels of serum and urea and ALP activity and normalised Na^+ and K^+ electrolytes. Enhanced output of urine and concentration of Na^+ and K^+, giving diuretic activity. The nephroprotective effect could be due to its antioxidant effect as observed from previous studies as evident by increasing activity of antioxidant enzymes. Results conclude that combination of all

these herbs are effective in gentamicin induced nephrotoxicity.[66]

Hemidesmus indicus L.

A study using albino Swiss mice, for nephroprotective effect of *Hemidesmus indicus* was carried out and Efficacy was evaluated against gentamicin-induced nephrotoxicity, on rats in different groups. Mice were killed on day 13 of the study but from gentamicin treated group mice were killed on the seventh day. And, determination of the drug efficacy was observed by using haematological and histological examination. The toxicity study using albino Swiss mice, gave a a result that the drug was relatively safe up to the dose 7 g/kg bw. Results showed that the treatment with *H. indicus* helped preventing the gentamicin induced renal damage, in mice and, the histological examination of kidneys also supported the findings from haematological evaluations.[67]

Nephroprotective effect against Gentamicin Induced Nephrotoxicity.

Plant name	Part used	Family	Chemical constituents
Withania somnifera	Roots	Solanaceae	Alkaloids (Somniferon), Withaminon, Wasamin, Sugars, Glycosides, Amino acids, Essential Oils, Withaniol, Hexatriacontane, Phyto sterol and oils.[56]
Solanum nigrum	Whole plant	Solanacea	Alkaloids, Reducing sugars, Glycosides, saponins, Steroids, Leutein, Lycopene, Vitamin-c, Glucose, Fructose, Caffeicsolasodine, Tamatidenol, Solamargine, Solasomine, Trigogenine, Pottasium, Calcium and Phosphorous.[56]
Rhazya stricta	Leaves	Apocynaceae	1-carbomethoxy-β-carboline, Condyloacarpine and Vincanicine.[56]
Nigella sativa	Whole plant	Ranunculaceae	Alanine, L-Spinasterol, Arabic acid, Arginine, Amino acid, Aspargine, Aspartic acid, Carvone, Cystine, Cholesterol, Glutamic acid, Linoleic acid, Linolenic acid, Melanthin, Myristic acid, Oleic acid and Tannins.[56]
Glycyrrhiza glabra	Rhizomes	Fabaceae	Glycyrrhizin, Glyciyrrhizic acid, Glycosides, Steroids, Glucose, Sucrose, Resin, Starch and Essential oil.[56]
Emblica officinalis	Fruits	Euphorbiaceae	Vitamin-C, Carotene, Nicotinic acid, Riboflavin, D-glucose, D-fructose, Myoinositol, Darabinosyl, D-xylosyl, Lrhamnosyl, G-glycosyl, D-manosyl, D-galactosyl, Embicol, Mucic and Phyllambic acid, Phellembin, Fatty acid, Leucodelphinidine, Procyanidin, 3-O-gallated Prodelphindin, Tannins, Ellagic acid, Lupeol and Oleanolic acid.[56]
Aerva lanata	Whole plant	Amaranthaceae	Botulin, β-sitosterol, Amyrin, Plant Hentriacontane, Campesterol, Stigmasterol, Kaempferol, Propionic acid, β-carboline-I, Aervoside and Aervolanine.[68]
Cassia auriculate	Roots	Fabaceae	Tannins, Di-(2-ethyl) hexyl phthalate, Alkaloids, Resins, Ca2+ and Phosphorous.[51]

Herbal extracts and herbal formulation having nephroprotective effect against acetaminophen-induced nephrotoxicity

Ledebouriella divaricata, Sparganium simplex, Panax ginseng, Aster tataricus, Citrus aurantium, Sanguisorba officianlis, Arisaema consanguineum and Polygonum aviculare: A study was carried out on HEK 293(transformed primary embryonal kidney) cell line by having been used the centrifuged extract of about 251 herb medicines and a damage was found to be observed by acetaminophen when evaluated for MTS assay. It was found that from the total of 251, 8 herbs as *Ledebouriella divaricata, Sparganium simplex, Panax ginseng, Aster tataricus, Citrus aurantium, Sanguisorba officianlis, Arisaema consanguineum* and *Polygonum aviculare* were found showing a remarkable effective change on acetaminophen-induced damage in HEK 293 cell line. And, non-linear regression analysis of Dose response demonstrated that *P. aviculare* was found reflecting the best recovery rate (98%) with the smallest EC50 value of 0.1 ng/mL out of the screened herbal medicine candidates.[69] Also, on the basis of results obtained it was analysed that, acetaminophen is a painkiller drug used worldwide but causes severe kidney damage[69]

Bi-herbal formulation of *Ocimum gratissimum* and *Gongronema latifolium* aqueous leaf extracts

A study was carried out on forty albino rats (100-110g) to check for the protective effect of aqueous leaves extract of *Ocimum gratissimum* and *Gongronema latifolium* on acetaminophen-induced nephrotoxicity model. The extracts were orally administered with dose each as 200, 300 and 500 mg/kg body weight (bw), 500 mg/kg bw separately and 100 mg/kg bw silymarin (reference drug)

was administered to rats for 10 days. Also, a suspension of acetaminophen with dose 750 mg/kg bw was administered once every 72 h to induce Nephrotoxicity in rats. Results reflected an increase in the levels of creatinine, urea level with a reduction in total protein (TP) levels of rats administered acetaminophen only. And, a dose dependent reversal change was seen in rats pre-treated with 200, 300 and 500 mg/kg bw of the bi-herbal extract was found to observe that the aqueous bi-herbal extract of *Ocimum gratissium* and *Gonglonema latifolium* possessed better protective activity as against the mono extracts in acetaminophen-induced toxicity.[70]

Herb having nephroprotective effect against diclofenac-induced acute kidney injury (AKI)

Vinpocetine

A study was carried out on 1-month-old Swiss mice of about 20-25g and vinpocetine was investigated for its effect and mechanisms on diclofenac-induced AKI. Mice was administered a stimulus with diclofenac in 200 mg/kg, p.o. dose and after 30 min. treated with 0.3, 1, or 3 mg/kg, p.o of vinpocetine. Blood and urine sample were collected 24 h post diclofenac administration and it was observed elevation in levels of protein and blood urea, creatinine and oxidative stress levels. Diclofenac led to enhanced oxidative stress and it caused morphological changes leading to renal damage. Also, diclofenac resulted in kidney cells apoptosis, up-regulated pro-inflammatory cytokines and led to the activation of NF- $\varkappa$B (necrosis factor-kappa B) in kidney tissues. On the other hand, vinpocetine inhibited diclofenac-induced oxidative stress, morphological changes, apoptosis, cytokine production and NF-$\varkappa$B activation and resulted in reducing diclofenac-induced blood urea and creatinine. Hence, vinpocetine at dose 3 mg/kg was chosen effective for the experiment.[71]

Herbal extract having nephroprotective effect against Tramadol-induced nephrotoxicity

Moringa oleifera

A study was carried out on 20 adult albino mice, divided into different groups. Control group 1 was given by i.p. injection of normal saline only, group 2 received oral dose of *Moringa oleifera* leaves extract (20 mg/kg/bw) for three weeks, group 3 received daily i.p. dose of tramadol (0.3 mg/kg/bw) for the same period, group 4, was administered daily oral dose of *Moringa oleifera* leaves extract, (20 mg/kg/bw) three h before injecting i.p. dose of tramadol (0.3 mg/kg/bw), for that period. Tramadol + *Moringa oleifera* group reflected significant difference in the mean values of urea and creatinine when compared with tramadol-treated group. So, *Moringa oleifera* leaves extract have been shown to reduce effect and renal dysfunction, improve the renal architecture, with nearly normalization of serum urea and creatinine levels which indicate improvement of renal function. Co-administration of *Moringa oleifera* leaves led to show the negative effects of tramadol-induced nephrotoxicity; due to its antioxidant action.[72]

Herbal extracts having nephroprotective effect against Streptozotocin (STZ)-induced nephrotoxicity

Erycibe obtusifolia

Extract of plant *Erycibe obtusifolia* which is generally used in place of *Tripterygium wilfordii* to treat auto immune disorders was used to carry out a study on ICR-strain male mice 6–7 weeks old. After the extract administration, BUN in the serum were observed and results obtained were increased blood urea nitrogen at doses of 20 and 30 mg/kg of the extract. And, thus how extract of *Erycibe obtusifolia* was found to be nephroprotective in nature.[73]

Mentha spicata

Extract of the herb *Mentha spicata* which is related to *M. piperita* (peppermint) was studied for its nephroprotective effect in STZ-induced nephrotoxicity model in rats. About, forty-eight male Wistar albino rats weighing 200/250 g were used for the study. Control group (group I); 20 g/L *M. piperita* tea (group II); 20 g/L M. spicata tea (group III); 40 g/L M. spicata tea (group IV) were the following groups with different number of rats in a group. Results showed that at doses of 2.2 and 4.4 g/kg per day but as a carminative tea for humans, this would be consumed at a dose of 5 g/cup. Results observed were, no toxicity observed with *M. piperita* and hence in *Mentha spicata.*[74]

Opuntia megacantha

Is a commonly used herb for diabetes in many developing countries onto which a study was carried out using rats for STZ induced- nephrotoxicity in diabetic rats with the dose 200 mg/kg per day administered orally of leaves extract of *O. megacantha* and control rats were administered with normal saline 0.1 ml/100 mg body weight. *O. megacantha* leaf extracts led to show an increase in plasma creatinine and urea concentrations in non-diabetic and STZ-diabetic rats both and increased GFR (glomerular filtration rate) in STZ-diabetic rats. Elevation in plasma urea and creatinine concentrations and the decline in the level of plasma Na^+ concentration, thus is proved nephrotoxic in nature.[75]

Herbs having nephroprotective effect against Galactosamine -induced nephrotoxicity

Cajanus indicus

A study using shrub *Cajanus indicus* belonging to family Leguminosae and subfamily papilionacea was carried out on Swiss albino mice (male, body weight 20 ± 2 g). And, a protein was purified from the leaves of *Cajanus indicus*, then both the preventive as well as curative effects of the protein were observed in the given study. Galactosamine administered at a dose of 800 mg/kg body weight intraperitoneally for 3 days before and after the protein treatment at an intraperitoneal dose of 2 mg/kg body weight for 4 days. To determine the status of the antioxidative Defence system, the activities of antioxidant enzymes like SOD, catalase, glutathione reductase (GR) and glutathione-S-transferase (GST), levels of cellular metabolites, reduced GSH, total thiols, oxidized glutathione (GSSG) and lipid peroxidation end products were performed. And, serum creatinine and urea nitrogen (UN) levels were measured to check nephrotoxicity. And it was found that galactosamine caused a severe oxidative damage in kidney and Protein treatment both before and after the galactosamine intoxication could protect the kidney tissue against galactosamine-induced oxidative stress.[76]

Herbal extract having nephroprotective effect against Nitrobenzene-induced nephrotoxicity

Euphorbia hirta L. extract

A study was carried out on albino rats (1000 mg/kg body weight) to check nephroprotective activity of ethanolic extract of *Euphorbia hirta* (400 mg/kg body weight) in nitrobenzene-induced model. The levels of antioxidant enzymes SOD, catalase, GPx, GST and the levels of reduced GSH), total thiols and vitamin C in the kidney tissues and histopathology were determined. And, it was analysed that Nitrobenzene administration significantly ($P < 0.01$) increased the lipid peroxidation and significantly ($P < 0.05$) decreased the levels of SOD, CAT, GPx, GST, GSH, total thiols and vitamin C and treatment with extract normalised antioxidant level and *Euphorbia hirta* extract was proven effective protector against nitrobenzene-induced nephrotoxicity, through its antioxidant capacity.[77]

Herbs having nephroprotective effect against Bromobenzene-induced nephrotoxicity

Triphala

A study on female Wistar albino rats was carried out to check for nephroprotective action of triphala powder on Bromobenzene-induced nephrotoxicity. Mice were divided into groups and treated with no treatment, bromobenzene (10 mmol/kg), bromobenzene and Triphala (250 and 500 mg/kg, respectively), Triphala alone (500 mg/kg) and bromobenzene and silymarin (100 mg/kg). Antioxidant effect and serum kidney functional parameters were analysed. And the results obtained was significant ($P < 0.05$) decreases in the antioxidant enzymes like catalase, superoxide dismutase, glutathione-S-transferase and glutathione peroxidase as well as total reduced glutathione. Also, a significant ($P < 0.05$) decrease in serum total protein and albumin as well as significant ($P < 0.05$) increases in serum creatinine, urea and uric acid levels. Also, histopathological examinations of kidney sections of the experimental rats supported the biochemical observations.[78]

Phytoconstituents having nephroprotective effect against Dichlorvos induced nephrotoxicity

Nigella sativa oil (NSO)

A study was carried out on twenty-four Wistar rats were randomly divided into groups. And, rats were administered with phosphate buffer solution as controls, Dichlorvos **(**DDVP), DDVP+NSO and NSO alone. Post 2 weeks treatment with this, blood samples were collected and haematological parameters like red blood cells count (RBC), haemoglobin (Hb), erythrocyte indices mean cell volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC) and Platelets, renal function parameters (albumin, urea, total protein, chloride, sodium and potassium ions) and nonspecific immune response white blood cells count (WBC) were observed. And it was observed that NSO maintained optimal levels of RBC count, Hb, packed cell volume, albumin, WBC count and urea, indicative of its protective effect against haemo-, immuno- and nephrotoxicity of Dichlorvos.[79]

CONCLUSION

It can be concluded from above mentioned studies that pure phytoconstituents, herbal extracts and few of their formulations have got enough potential to be used as Nephroprotective agent with least toxicity as the above-mentioned drugs are being traditionally used by different systems of medicine over 3000 years. Although, to substantiate the claims further studies are needed with more relevant, reliable and advanced parameters.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest with publication of this manuscript.

ABBREVIATIONS

WHO: World Health Organisation; **BUN:** Blood urea nitrogen; **GFR:** Glomerular filtration rate; **N N-AIDS:** Non-steroidal anti-inflammatory drugs; **EGCG:** Epigallocatechin gallate; **TNF- α:**Ttumour necrosis factor- α; **MDA:** Malondialdehyde; **4-HNE:** 4-hydroxynonenal; **LLC-PK1:** Lilly laboratories cell-porcine kidney1; **JNK-P53:** c-Jun N-terminal kinase; **NDGA:** Nordihydroguaiaretic acid; **SOD:** Superoxidase dismutase; **ROS:** Reactive oxygen species; **NAC:** N-acetylcysteine; **CMS:** Colistin sodium methane sulfonate; **GGT:** Glutamyl-transferase; **MDA:** Malondialdehyde; **GPx:** Glutathione peroxidase; **Fe-NTA:** Ferric nitriloacetate; **SSa:** saikosaponin-a; **SSd:** Saikosaponin-d; **Cr:** Creatinine; **AST:** Aspartate amino transferase; **ALT:** Alanine transaminase; **HEK-293:** Transformed primary embryonal kidney; **TP:** Total protein; **NF-KB:** Necrosis factor-kappa B; **AKI:** Acute kidney injury; **STZ:** Streptozocin; **GST:** Glutathione-S-transferase; **GSH:** Glutathione; **GSSG:** Total thiols oxidised glutathione; **UN:** Urea nitrogen; **RBC:** Red blood cells; **Hb:** Haemoglobin; **MCH:** Mean corpuscular Hb; **MCV:** Mean cell volume; **MCHC:** Mean corpuscular Hb concentration; **WBC:** White blood cells.

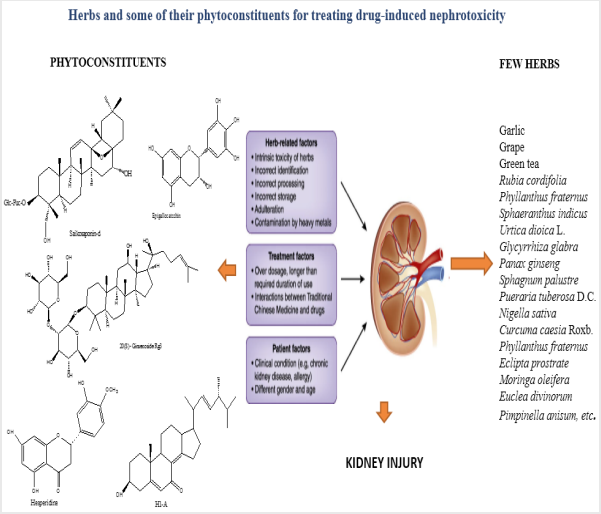
REFERENCES

1. Sevugaperumal G, Venkateshan G, Banumathy N. Medicinal plants used by ethnic group thottianaickens of semmalai hills (reserved forest), Tiruchirappalli district, Tamil Nadu. Indian Journal of Traditional Knowledge. 2006;5(2):245-52.
2. Rao MR, Palada MC, Becker BN. Medicinal and aromatic plants in agro-forestry systems. Agroforestry Systems. 2004;61(1):107-22.
3. Porter GA, Bennett WM. Nephrotoxic acute renal failure due to common drugs. American Journal of Physiology. 1981;241(7):F1-8.
4. Abraham G, Varughese S, Thandavan T, Iyengar A, Fernando E, Naqvi SA, *et al.* RK*:* chronic kidney disease hotspots in developing countries in South Asia*.* Clin Kidney J. 2016;9(1)*:*135-41.
5. Yao X, Panichpisal K, Kurtzman N, Nugent K. Cisplatin nephrotoxicity: a review. Am J Med Sci. 2007;334(2):115-24. doi: 10.1097/MAJ.0b013e31812dfe1e.
6. Basile DP, Anderson MD, Sutton TA. Pathophysiology of acute kidney injury. Comprehen Physiol. 2012;2(2):1303-53. doi: 10.1002/cphy.c110041.
7. Oh GS, Kim HJ, Shen A, Lee SB, Khadka D, Pandit A, *et al.* Cisplatin-induced kidney dysfunction and perspectives on improving treatment strategies. Electrolyte Blood Press. 2014;12(2):55-65. doi: 10.5049/EBP.2014.12.2.55.
8. Yao X, Panichpisal K, Kurtzman N, Nugent K. Cisplatin nephrotoxicity: a review. Am J Med Sci. 2007;334(2):115-24. doi: 10.1097/MAJ.0b013e31812dfe1e.
9. Ahmed W, Zaki A, Nabil T. Prevention of methotrexate-induced nephrotoxicity by concomitant administration of garlic aqueous extract in rat. Turk J Med Sci. 2015;45(3):507-16.
10. Hoitsma AJ, Wetzels JF, Koene RA. Drug induced nephrotoxicity: aetiology, clinical features and management. Drug Saf. 1991;6(2):131-47.
11. Paller MS. Drug induced nephropathies. Med Clin North Am. 1990;74(4):909-17.
12. Hisamura F, Kojima-Yuasa A, Kennedy DO, Matsui-Yuasa I. Protective effect of green tea extract and tea polyphenols against FK506-induced cytotoxicity in renal cells. Basic Clin Pharm Toxicol. 2006;98(2):192-6. doi: 10.1111/j.1742-7843.2006.pto_284. x.
13. Ahn TG, Kim HK, Park SW, Kim SA, Lee BR, Han SJ. Protective effects of green tea polyphenol against cisplatin-induced nephrotoxicity in rats. Obstet Gynecol Sci. 2014;57(6):464-70. doi: 10.5468/ogs.2014.57.6.464.
14. El-Mowafy AM, Al-Gayyar MM, Salem HA, El-Mesery ME, Darweish MM. Novel chemotherapeutic and renal protective effects for the green tea (EGCG): role of oxidative stress and inflammatory-cytokine signaling. Phytomedicine. 2010;17(14):1067-75. doi: 10.1016/j.phymed.2010.08.004.
15. Valentovic MA, Ball JG, Brown JM, Terneus MV, McQuade E, Meter SV, *et al.* Resveratrol attenuates cisplatin renal cortical cytotoxicity by modifying oxidativestress. Toxicol *in vitro.* 2014;28(2):248-57. doi: 10.1016/j.tiv.2013.11.001.
16. DoAmaral CL, Francescato HD, Coimbra TM, Costa RS, Darin JD, Antunes LM, *et al.* Resveratrol attenuates cisplatin-induced nephrotoxicity in rats. Arch Toxicol. 2008;82(6):363-70. doi: 10.1007/s00204-007-0262-x.
17. El-Ghiaty MA, Ibrahim OM, Abdou SM, Hussein FZ. Evaluation of the protective effect of Cystone against cisplatin-induced nephrotoxicity in cancer patients and its influence on cisplatin antitumor activity. Int Urol nephrol. 2014;46(7):1367-73. doi:10.1007/s11255-014-0644-y.
18. Han MS, Han IH, Lee D, An JM, Kim SN, Shin MS, *et al.* Beneficial effects of fermented black ginseng and its ginsenoside 20(S)-Rg3 against cisplatin-induced nephrotoxicity in LLC-PK1 cells. J Ginseng Res. 2016;40(2):135-40. doi: 10.1016/j.jgr.2015.06.006.
19. Park JY, Choi P, Kim T, Ko H, Kim HK, Kang KS, *et al.* Protective effects of processed ginseng and its active ginsenosides on cisplatin-induced nephrotoxicity: *in vitro* and *in vivo* studies. J Agric Food Chem. 2015;63(25):5964-9. doi: 10.1021/acs.jafc.5b00782.
20. Baek SH, Piao XL, Lee UJ, Kim HY, Park JH. Reduction of Cisplatin-induced nephrotoxicity by ginsenosides isolated from processed ginseng in cultured renal tubular cells. Biol Pharm Bul. 2006;29(10):2051-5.
21. Song KI, Park JY, Lee S, Lee D, Jang HJ, Kim SN, *et al.* Protective effect of tetrahydrocurcumin against cisplatin-induced renal damage: *in vitro* and *in vivo* studies. Planta Med. 2015;81(4):286-91. doi: 10.1055/s-0035-1545696.
22. Momeni A, Hajigholami A, Geshnizjani S, Kheiri S. Effect of silymarin in the prevention of cisplatin nephrotoxicity, a clinical trial study. J Clin Diagn Res. 2015;9(4):OC11-3. doi: 10.7860/JCDR/2015/12776.5789.
23. Guerra BA, Bolin AP, Otton R. Carbonyl stress and a combination of astaxanthin/vitamin C induce biochemical changes in human neutrophils. Toxicol *in vitro.* 2012;26(7):1181-90.
24. Mundhe NA, Kumar P, Ahmed S, Jamdade V, Mundhe S, Lahkar M. Nordihydroguaiaretic acid ameliorates cisplatin induced nephrotoxicity and potentiates its anti-tumor activity in DMBA induced breast cancer in female Sprague–Dawley rats. Int Immunopharmacol. 2015;28(1):634-42
25. Pashkow FJ, Watumull DG, CampbelL CL. Astaxanthin: a novel potential treatment for oxidative stress and inflammation in cardiovascular disease. Am J Cardiol. 2008;101(10):58-68.
26. Ma X, Dang C, Kang H, Dai Z, Lin S, Guan H, *et al.* Saikosaponin-D reduces cisplatin-induced nephrotoxicity by repressing ROS-mediated activation of MAPK and NF-κB signalling pathways. Int Immunopharmacol. 2015;28(1):399-408.
27. Ali BH, Blunden G. Pharmacological and Toxicological Properties of *Nigella sativa*. Phytother Res. 2003;17(4):299-305.
28. Baskaran UL, Martin SJ, Mahaboobkhan R, Prince SE. Protective role of Triphala, an Indian traditional herbal formulation, against the nephrotoxic effects of bromobenzene in Wistar albino rats. J Integr Med. 2015;13(2):115-21.
29. Ghlissi Z, Hakim A, Sila A, Mnif H, Zeghal K, Rebai T, *et al.* Evaluation of efficacy of natural astaxanthin and vitamin-E in prevention of colistin-induced nephrotoxicity in the rat model. Environ Toxicol Pharmacol. 2014;37(3):960-6.
30. Siddiqi A, Hasan SK, Nafees S, Rashid S, Saidullah B, Sultana S. Chemo-preventive efficacy of hesperidin against chemically induced nephrotoxicity and renal carcinogenesis via amelioration of oxidative stress and modulation of multiple molecular pathways. Exp Mol Pathol. 2015;99(3):641-53.
31. Zhu JS, Halpern GM, Jones K. The scientific rediscovery of a precious ancient Chinese herbal regimen: *Cordyceps sinensis* Part II. J Altern Complement Med. 1998;4(4):429-57.

32. Paterson RR. Cordyceps: a traditional Chinese medicine and another fungal therapeutic biofactory?. Phytochemistry. 2008;69(7):1469-95.
33. Zhong Y, Deng Y, Chen Y, Chuang PY, He JC. Therapeutic use of traditional Chinese herbal medications for chronic kidney diseases. Kidney International. 2013;84(6):1108-18.
34. Ashour ML, Wink M. Genus Bupleurum: a review of its phytochemistry, pharmacology and modes of action. J Pharm Pharmacol. 2011;63(3):305-21.
35. Ahmed W, Zaki A, Nabil T. Prevention of methotrexate-induced nephrotoxicity by concomitant administration of garlic aqueous extract in rat. Turk J Med Sci. 2015;45(3):507-16.
36. Perazella MA. Onco-nephrology: renal toxicities of chemotherapeutic agents. Clin J Am Soc Nephrol. 2012;7(10):1713-21. doi: 10.2215/CJN.02780312.
37. Ko JL, Tsai CH, Liu TC, Lin MY, Lin HL, Ou CC. Differential effects of grape juice on gastric emptying and renal function from cisplatin-induced acute adverse toxicity. Hum Exp Toxicol. 2016;35(8):808-17. doi:10.1177/0960327115607079.
38. Yapar K, Cavusoglu K, Oruc E, Yalcin E. Protective effect of royal jelly and green tea extracts effect against cisplatin-induced nephrotoxicity in mice: a comparative study. Med Food. 2009;12(5):1136-42. doi:10.1089/jmf.2009.0036.
39. Joy J, Nair CK. Amelioration of cisplatin induced nephrotoxicity in Swiss albino mice by *Rubia cordifolia* extract. J Cancer Res Ther. 2008;4(3):111-5.
40. Kumari KK, Setty OH. Protective effect of *Phyllanthus fraternus* against mitochondrial dysfunction induced by co-administration of cisplatin and cyclophosphamide. J Bioenerg Biomembr. 2012;44(1):179-88. doi:10.1007/s10863-012-9423-6.
41. Mathew JE, Joseph A, Srinivasan K, Dinakaran SV, Mantri A, Movaliya V. Effect of ethanol extract of *Sphaeranthus indicus* on cisplatin-induced nephrotoxicity in rats. Nat Prod Res. 2012;26(10):933-8. doi:10.1080/14786419.2010.534999.
42. Ozkol H, Musa D, Tuluce Y, Koyuncu I. Ameliorative influence of *Urtica dioica* L against cisplatin-induced toxicity in mice bearing Ehrlich ascites carcinoma. Drug Chem Toxicol. 2012;35(3):251-7. doi:10.3109/01480545.2011.598531.
43. Lee CK, Park KK, Lim SS, Park JH, Chung WY. Effects of the licorice extract against tumour growth and cisplatin-induced toxicity in a mouse xenograft model of colon cancer. Biol Pharm Bull. 2007;30(11):2191-5.
44. Kang HR, Lee D, Eom HJ, Lee SR, Lee KR, Kang KS, *et al*. Identification and mechanism of action of renoprotective constituents from peat moss *Sphagnum palustre* in cisplatin-induced nephrotoxicity. J Funct Foods. 2016;20:358-68.
45. Sohn SH, Lee H, Nama JY, Kim SH, Jung HJ, Kima Y*, et al*. Screening of herbal medicines for the recovery of cisplatin-induced nephrotoxicity. Environmental Toxicology and Pharmacology. 2009;28(2):206-12.
46. Nagwani S, Tripathi YB. Amelioration of cisplatin induced nephrotoxicity by PTY: A herbal preparation. Food and Chemical Toxicology. 2010;48(8-9)2253-8.
47. ElDaly ES. Protective effect of cysteine and vitamin E, Crocus sativus and *Nigella sativa* extracts on cisplatin induced toxicity in rats. J Pharm Bel. 1998;53(2):87-95.
48. Badary OA, Nagi MN, Al-Shabanah OA, Al-Shawaf HA, Al-Sohaibani MO, Al-Bekairi AM. Thymoquinone ameliorates the nephrotoxicity induced by cisplatin in rodents and potentiates its antitumor activity. Can J Physiol Pharmacol. 1997;75(12):1356-61.
49. Ali BH, Blunden G. Pharmacological and Toxicological Properties of *Nigella sativa*. Phytother Res. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives. 2003;17(4):299-305.
50. Pani SR, Mishra S, Sahoo S, Panda PK. Protective effect of herbal drug in cisplatin induced nephrotoxicity. Indian Journal of Pharmacology. 2011;43(2):200-2.
51. Annie S, Rajagopal PL, Malini S. Effect of *Cassia auriculata* Linn. Root extract on cisplatin and gentamicin-induced renal injury. Phytomedicine. 2005;12(8):555-60.
52. Ahmed AA. Biochemical Studies on Nephroprotective Effect of Carob (*Ceratonia siliqua L*.) Growing in Egypt. Nature and Science. 2010;8(3):41-7.
53. Yadav YC, Srivastava DN, Saini V, Singhal S, Seth AK, Sharadkumar, *et al.* Nephroprotective and curative Activity of methanolic extract of *Ficus religiosal*. Latex in Albino Rats Using Cisplatin Induced Nephrotoxicity. Pharmacologyonline. 2011;1:132-9.
54. Azu OO, Duru FIO, Osinubi AA, Noronha CC, Elesha SO, Okanlawon AO. Protective agent, *Kigelia africana* fruit extract against cisplatin induced kidney oxidant injury in Sprague dawley rats. Asian Journal of Pharmaceutical and Clinical Research. 2010;3(2):84-8.
55. Chandyadav Y, Srivastav DN, Seth AK, Saini V, Kuldeep S, Yadav KS. Nephropharmacological activity of ethanolic extract *lepidium sativum L*. seeds in albino rats using cisplatin induced acute renal failure. International Journal of Pharmaceutical Sciences Review and Research. 2010;4(3):64-8.
56. http://farmacists.blogspot.com
57. Yamgar S, Sali L, Salkar R, Jain NK, Chhaya GH. Studies on nephroprotective and nephrocurative activity of ethanolic extract of *Picrorhiza kurroa Royle* and *Arogya wardhinibati* in rats. International Journal of Pharmacy and Technology. 2010;2(3):472-89.
58. Sreedevi A, Bharathi K, Prasad KVSRG. Effect of *Vernonia cinerea* aerial parts against Cisplatin-induced nephrotoxicity in rats. Pharmacologyonline. 2011;2:548-55.
59. Devi HP, Mazumder PB. Methanolic extract of *Curcuma caesia Roxb* prevents the toxicity caused by cyclophosphamide to bone marrow cells, liver and kidney of mice. Pharmacogn Res. 2016;8(1):43-9. doi: 10.4103/0974-8490.171106.
60. Kumari KK, Setty OH. Protective effect of *Phyllanthus fraternus* against mitochondrial dysfunction induced by co-administration of cisplatin and cyclophosphamide. J Bioenerg Biomembr. 2012;44(1):179-88. doi:10.1007/s10863-012-9423-6.
61. Dungca NTP. Protective effect of the methanolic leaf extract of *Eclipta alba* (L.) Hassk. (Asteraceae) against gentamicin-induced nephrotoxicity in Sprague Dawley rats. J Ethnopharmacol. 2016;184:18-21.
62. Ouédraogo M, Lamien-Sanou A, Ramdé N, Ouédraogo AS, Ouédraogo M, Zongo SP, *et al.* Protective effect of *Moringa oleifera* leaves against gentamicin-induced nephrotoxicity in rabbits. Exp Toxicol Pathol. 2013;65(3):335-9.
63. Feyissa T, Asres K, Engidawork E. Renoprotective effects of the crude extract and solvent fractions of the leaves of *Euclea divinorum Hierns* against gentamicin-induced nephrotoxicity in rats. J Ethnopharmacol. 2013;145(3):758-66.
64. Aiswarya N, Rashmi R, Preethi S, Chandran V, Teerthanath S, Sunil P, *et al.* Nephroprotective Effect of Aqueous Extract of *Pimpinella anisum* in Gentamicin Induced Nephrotoxicity in Wistar Rats. Pharmacogn J. 2018;10(3):403-7.
65. Jogdand SD, Shinde R, Sinha V, Chandrakar N. Nephroprotective effect of turmeric on oxidative stress, renal histopathology and toxicity induced by gentamicin. IJBCP. 2017;6:2279-780.
66. Elgazar AF, Abo RAO. Nephroprotective and Diuretic Effects of Three Medicinal Herbs against Gentamicin-Induced Nephrotoxicity in Male Rats. Pakistan Journal of Nutrition. 2013;12(8):715-22.
67. Kotnis MS, Patel P, Menon SN, Sane RT. Reno protective effect of *Hemidesmus indicus*, A herbal drug used in gentamicin-induced renal toxicity. Nephrology. 2004;9(3):142-52.
68. Movaliyaa V, Khamarb D, Setty MM. Nephroprotective activity of aqueous extract of *Aerva Javanica* roots in cisplatin induced renal toxicity in rats. Pharmacology Online. 2011;1:68-74.
69. Sohn SH, Lee EY, Lee JH, Kim Y, Shin M, Hong M, *et al.* Screening of herbal medicines for recovery of acetaminophen-induced nephrotoxicity. Environ Toxicol Pharmacol. 2009;27(2):225-30.
70. Ezeonwu VU, Dahiru D. Protective Effect of Bi-Herbal Formulation of *Ocimum gratissimum* and *Gongronema latifolium* Aqueous Leaf Extracts on Acetaminophen-induced Hepato-Nephrotoxicity in Rats. American Journal of Biochemistry. 2013;3(1):18-23.
71. Fattoria V, Borghia SM, Guazellia CF, Giroldoa AC, Crespigiob J*, et al.* Vinpocetine reduces diclofenac-induced acute kidney injury through inhibition of oxidative stress, apoptosis, cytokine production and NF-κB activation in mice. J PHRS. 2017;120:10-22.
72. Al-brakati A. Protective Effect of *Moringa Oleifera* Leaves Against Tramadol-Induced Nephrotoxicity in Mice. IJTPR. 2017;9(2):156-62.

73. Hsu HY, Lin CC, Chen JY, Yang JJ, Zhang R. Toxic effects of *Erycibe obtusifolia*, a Chinese medicinal herb, in mice. J Ethnopharmacol. 1998;62(2):101-5.
74. Akdogan M, Kilinc I, Oncu M, Karaoz E, Delibas N. Investigation of biochemical and histopathological effects of *Mentha piperita* L. and *Mentha spicata* L. on kidney tissue in rats. Hum Exp Toxicol. 2003;22(4):213-9.
75. Bwititi P, Musabayane CT, Nhachi CF. Effects of *Opuntia megacantha* on blood glucose and kidney function in streptozotocin diabetic rats. J Ethnopharmacol. 2000;69(3):247-52.
76. Sinha M, Manna P, Sil PC. Amelioration of galactosamine-induced nephrotoxicity by a protein isolated from the leaves of the herb, *Cajanus indicus* L. ISCMR. 2007;7(1):11.
77. Suganya S, Sophia D, Raj CA, Rathi MA, Thirumoorthi L, Meenakshi P, *et al.* Amelioration of nitrobenzene-induced nephrotoxicity by the ethanol extract of the herb *Euphorbia hirta*. Pharmacognosy Res. 2011;3(3):201-7.
78. Baskaran UL, Martin SJ, Khan RM, Prince SE. Protective role of Triphala, an Indian traditional herbal formulation, against the nephrotoxic effects of bromobenzene in Wistar albino rats. J Integr Med. 2015;13(2):115-21.
79. Ajao MS, Sansa AB, Imam A, Ibrahim A, Adana MY, Oluwafuyi AA, *et al.* Protective Effect of *Nigella Sativa* (Black Caraway) Oil on Oral Dichlorvos Induced Hematological, Renal and Nonspecific Immune System Toxicity in Wistar Rats. IJT. 2017;11(6):1-5.

PICTORIAL ABSTRACT



SUMMARY

According to the WHO report, between 65% and 80% of the populations of developing countries use medicinal plants as remedy nowadays. Kidney is one of the vital organs of body and Nephrotoxicity is one of the most common problems and it occurs as a result when body is exposed to a drug or toxin. This review article aims to report and to introduce the effect of most important medicinal herbs, herbal formulations and some of the specific phytoconstituents that are used to prevent and treat anticancer, aminoglycoside, non-steroidal anti-inflammatory and few other classes of drug-induced nephrotoxicity. Particularly anti-cancer drugs among all other classes of drugs, cause high toxicity leading kidney damage and irreparable kidney injury. So, attention has recently been paid to seek out alternatives such as natural drugs that are effective and also less toxic. According to the studies carried out on different animals and cell line, many medicinal plants, herbal formulations and a few plant-based constituents by their antioxidant, free-radical and anti-inflammatory properties are found to be helpful in preventing drug-induced nephrotoxicity

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