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Review On Nephroprotective Activity of Medicinal Plants On Drug-Induced Nephrotoxicity

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ABSTRACT

The excess use of drugs for various ailments is resulting in increasing cases of drug-induced nephrotoxicity. Acute kidney injury is the most common type of drug-induced nephrotoxicity, which accounts for 85% of cases of nephrotoxicity. Herbal medications, due to the presence of various phytoconstituents, possess nephroprotective activity and are used in the treatment of kidney disorders like acute kidney injury, nephrotic syndrome, chronic interstitial nephritis, etc. The present review aimed to elucidate the list of medicinal plants which are scientifically proven to have nephroprotective activity against drug-induced nephrotoxicity.

Keywords: Nephrotoxicity, Nephroprotective activity, Gentamicin-induced nephrotoxicity, Medicinal plants.

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INTRODUCTION

Nephrotoxicity is one of the most common kidney disorders and occurs when the body is exposed to a drug or toxin. A number of therapeutic drugs can adversely affect the kidney and results in acute renal failure, chronic interstitial nephritis, and nephrotic syndrome as there is an increase in the number of potent therapeutic agents like aminoglycoside antibiotics, NSAID's and chemotherapeutic agents have been added to the therapeutic magazine in recent years[1]. Exposure to chemical substances like ethylene glycol, carbon tetrachloride, sodium oxalate and heavy metals like lead, mercury, cadmium and arsenic also causes nephrotoxicity. Timely recognition of the disease and stopping of responsible drugs is usually the only necessary treatment. Nephroprotective agents are the substances which possess defensive activity against nephrotoxicity. Medicinal plants aid in the treatment of acute and chronic kidney injury due to the presence of a variety of complex chemical constituents. Early literatures established various herbs for the cure of renal disorders. Concurrent use of various herbal medicines possessing nephroprotective activity along with different nephrotoxic agents may reduce nephrotoxicity.

The term renal failure primarily refers to the failure of the excretory function of the kidney, which leads to the retention of nitrogenous waste products of metabolism in the blood [2]. In addition to this, along with endocrine dysfunction, there is a failure of regulation of fluid and electrolyte balance. Renal failure is categorized as acute and chronic renal failure [3].

Acute renal failure (ARF) or acute kidney injury (AKI):

ARF or AKI is defined as the sudden, reversible loss of renal function which develops over a period of days or weeks. The main cause of AKI includes acute tubular necrosis which occurs due to ischemia or exposure to toxins and commonly accounts for 85% of incidence. The toxins may be exogenous or endogenous. The exogenous agents are radiocontrast agents, cyclosporine, antibiotics, chemotherapeutic agents, organic solvents, paracetamol and illegal abortifacients [3], while the endogenous compounds include myoglobin and heamoglobin [4].

Chronic renal failure (CRF):

CRF is an irreversible retrogradation in the renal function which develops over a period of years and results in loss of excretory metabolic and endocrine functions. Various causes of chronic renal failure are disorders like hypertension, diabetes mellitus, etc., and antineoplastic agents like cyclophosphamide, vincristine and cisplatin, etc.[2].

EPIDEMIOLOGY

The epidemiology of drug-induced nephrotoxicity is based on literature targeting acute kidney failure. It is mostly seen in hospitalized patients, especially the ICU patients. AKF is reported in

55-60% of patients taking drugs like gentamicin and cisplatin. It is common in adults compared to paediatrics. Acute tubular necrosis has 85% of incidence compared to other disorders of nephrotoxicity.

ETIOLOGY

Acute kidney failure is mainly caused by the following conditions:

- Impaired blood flow to the kidneys
- Direct damage to the kidneys
- Urine Blockage in the kidneys
- Presence of nephrotoxic agents[5]

The well-known nephrotoxic agents are drugs, diagnostic agents and chemicals. The important nephrotoxic agents are as follows [6]

Table 1: Nephrotoxicity agents

S. No	Class	Examples
1	Heavy metals	Mercury, Arsenic, Lead, Bismuth, etc.,
2	Anticancer drugs	**Alkylating agents :** Cisplatin, Cyclophosphamide **Nitro sources:** Streptozotocin, Carmustine, Lomustine, and Semustine **Anti-metabolites:** Methotrexate, Cytosine Arabinose, 6-thioguanine, 5-fluorouracil **Anticancer antibiotics:** Mitomycin, Mithramycin, doxorubicin **Biological agents :** Recombinant leucocyte and interferons
3	Antimicrobial agents	Tetracycline, Acyclovir, Pentamidine, Sulphadiazine, Trimethoprim, Rifampicin, amphotericin B
4	Aminoglycosides	Gentamicin, Amikacin, Kanamycin, Streptomycin
5	Angiotensin II receptor blockers	Valsartan
6	Angiotensin converting enzyme inhibitors	Trandolapril [7]
7	Non-steroidal anti-inflammatory drugs(NSAID's)	Paracetamol, Ibuprofen, Indomethacin and Aspirin
8	Radio contrast agents	Iodinated contrast media, Contrast CT's, Angiography, Venography, etc.,

PATHOPHYSIOLOGY

Gentamicin-induced nephrotoxicity:

Aminoglycosides are the most common antibiotics used to treat Gram-ve bacterial infections. Also their toxic effects on kidneys and ears are the major drawbacks in clinical use. Among the various aminoglycoside antibiotics, gentamicin has greater nephrotoxicity than tobramycin and lesser than neomycin.

In gentamicin-induced nephrotoxicity, the appearance of cellular necrosis and renal failure is very well related to an increase in calcium concentration in renal cortex and mitochondria. The

intracellular metabolism of gentamicin results in the formation of reactive oxygen species(ROS) like free radicals, which are toxic for the cell. The formation of superoxide ion during oxidation generates hydroxyl ions, thereby resulting in lipid peroxidation. This causes oxidative degeneration of polyunsaturated lipids of membranes which leads to marked modification of structure and function of the cell. Gentamicin decreases the levels of antioxidants like superoxide dismutase, glutathione, catalase, vitamin E, ascorbic acid, etc., which are the protective compounds that inhibit oxidative mechanisms and thus get rid of ROS[8]. Gentamicin-induced nephrotoxicity causes modifications in tubular cell integrity which may be sub-lethal or lethal. Those pre-lethal modifications are the development of abnormally enlarged lysosomes and myeloid bodies, loss of brush border membrane, vacuolization and dilation of the endoplasmic reticulum. Enzymuria is used as a biomarker to determine the occurrence renal tubular cell injury [6].

Cisplatin-induced nephrotoxicity:

Cisplatin is an effective anticancer drug, but its clinical use has been restricted because of its serious adverse effects on kidneys. It reduces the activity antioxidants and antioxidant enzymes resulting in increased generation of reactive oxygen species(ROS) and lipid peroxidation[9]. Reports showed that kidney injury might occur in 50 to 75% of patients receiving cisplatin, and is dose limiting.

Paracetamol induced:

Paracetamol (acetaminophen) is a Non-steroidal anti-inflammatory drug (NSAID), which is extensively and safely used in the treatment of spasm and pyrexia [10]. Paracetamol overdose is common in humans and is frequently related to liver and kidney injury [11, 12]. Even though kidney damage does not occur more frequently than liver damage in paracetamol overdose, but renal tubular damage and acute renal failure is found without liver damage [13, 14]. Investigations are going on around the world to explore agents which have defense activity against hepatic and nephrotoxicity with very little or no adverse effects [15, 16].

SIGNS AND SYMPTOMS

The signs and symptoms of acute kidney failure may include:

- Reduced urine output
- Fluid retention, which leads to swelling in legs, ankles or feet
- Shortness of breath
- Irregular heartbeat
- Chest pain
- Fatigue

- Nausea
- Weakness
- Confusion
- Seizures or coma in severe cases[5]

MANAGEMENT

- Volume homeostasis should be maintained
- Biochemical abnormalities should be detected and corrected
- Fluid overload can be treated with furosemide
- Severe acidosis should be treated by administering alkalis which also helps in dialysis
- Hyperkalemia should be treated
- Hematologic abnormalities such as anaemia, uremic platelet dysfunction, etc., should be corrected with RBC or platelet transfusions or administration of desmopressin or estrogens
- Dietary changes are an important solution for treating AKI. Salt and fluid restriction is vital in treating oliguric renal failure [7].

PRE-CLINICAL STUDIES

Pre-clinical studies were done on many drugs and natural products for their protective activity against nephrotoxicity. Most of the pre-clinical studies evaluated the nephroprotective activity of substances against drug-induced nephrotoxicity like aminoglycoside- and cisplatin-induced nephrotoxicity. Studies up to December 2018 were identified and studied. The studies were grouped based on the nephroprotective mechanisms and route of administration of the test drug.

Rats and mice of different strains like Albino Wistar, Sprague Dawley, Swiss Albino were mostly used for these studies. Parameters like plasma creatinine, blood urea nitrogen (BUN), etc., were evaluated. Many test drugs showed effective nephroprotective activity against aminoglycoside-induced nephrotoxicity based on creatinine results. It was also studied that they showed a dose-dependent protective activity(both in creatinine and BUN).

Orally administered test drugs were more effective than i.p administered drugs. Most of the test drugs used have anti-oxidant activity and these proved statistically significant nephroprotective activity. The mean difference with 95% confidence interval was calculated for each study and group [17].

MEDICINAL PLANTS WITH NEPHROPROTECTIVE ACTIVITY

Nephroprotective activity refers to the defensive action of a drug or herb against acute and chronic kidney injury. Medicinal herbs aid in treating nephrotoxicity due to the presence of various phytoconstituents like flavonoids, phenolic compounds, triterpenoids, tannins, saponins,

glycosides, sterols, etc., The various medicinal plants showing nephroprotective activity against drug-induced nephrotoxicity are listed in Table-1.

Table 2: Medicinal plants showing Nephroprotective active against drug-induced nephrotoxicity

Sr n	Plant	Family	Part Used	Extract	Chemical Constituents	Animal Model	Screening Method	Dose	Ref.
1.	*Aerva lanata*	Rutaceae	Whole plant	Ethanol	Botulin, β-sitisterol, aervoside, amyrin, Aervolanine, hentriacontane, campesterol, stigmasterol, propionic acid and β-carboline-1	Albino rats	Mercuric chloride-induced	200 and 400mg/kg	[18]
2.	*Aerva javanica*	Amaranthaceae	Fresh roots	Aqueous	Isoquercetin,5-methylmellein, 2-hydroxy-3-o-β-primeveroside,naphthalene-1,4-dione, kaempferol, aspigenin7-oglucoronide	Albino wistar rats	Cisplatin induced	200 and 400mg/kg	[19]
3.	*Anethum graveolens*	Umbelliferae	Seeds	Aqueous	Flavonoids,alkaloids,saponins,tannins ,cardiac glycosides,terpenoids,and anthocyanins	Wistar albino rats	Gentamicin induced	500,100 and 2000/kg	[20]
4.	*Amomum subulatum*	Zingiberaceae	Seeds	Aqueous	Protocatechualdehyde,protocatechuic acid,1,7-bis(3,4 dihydroxyphenyl)hepta-4E,6E-dien-3-one and 2,3,7-trihydroxy-5-(3,4-dihydroxy-E-styryl)-6,7,8,9-teterahydro	Albino rats	Cypermethrin induced	200 and 400mg/kg	[21]
5.	*Aconitum heterophyllum*	Ranunculaceae	Roots	Ethanol	Flavonoids, freidelin(terpenoid), stanina, phenolic compounds and saponins	Wistar albino rats	Glycerol induced	250 and 500mg/kg	[22]
6.	*Azima tetracantha*	Salvadoraceae	Roots	Ethanol	Flavonoids, terpenoids, alkaloids, tannins, saponins and glucosinolates.	Albino wistar rats	Glycerol induced	250 and 500mg/kg	[23]
7.	*Annona reticulata*	Annonaceae	Aerial parts	Ethanol	Flavonoids, saponins, tannins, phytosterols, glycosides, alkaloids, fixed oils and fats.	Wistar rats	Cisplatin induced	250 and 500mg/kg	[24]
8.	*Aloe barbadensis*	Aloeaceae	Leaves	Aqueous	Flavonoids, polyphenols,indole alkaloids and phytosterols	Albino rats	Gentamicin induced	150 and 300mg/kg	[25]
9.	*Allium cepa*	Liliaceae	Leaves	Ethanol	Quercetin, quercetin-3-glucoside, flavonoids, flavenols, xylose,galactose, sulfyr,selenium,	Sprague dawley rats	Gentamicin induced	200 and 400 mg/kg	[26]

					seleno compounds,thiosulfinatex				
10.	*Andrographis paniculata*	Acanthaceae	Leaves	Aqueous,ethanol and acetone	Flavonoids,polyphenolic compounds	Albino wistar rats	Gentamicin induced	300mg/kg	[27]
11.	*Acorus calamus*	Araceae	Aerial parts	Ethanol	Monoterpenes, sesquiterpenes, phenylpropanoids, flavonoids, quinone and basarone.	Albino rats	Paracetamol induced	250 and 500mg/kg	[28]
12.	*Aegle marmelos*	Rutaceae	Leaves	Hydro-alcoholic and ethyl acetate	Flavonoids, carbohydrates and phenolic compounds	Wistar rats	Cisplatin induced	200 and 400 mg/kg	[29]
13.	*Bauhinia purpurea*	Nyctaginaceae	Bark and unripe pods	Ethanol	Flavonoids, glycosides, steroids, tannins, alkaloids and phlobotannins.	Wistar albino rats	Gentamicin induced	400mg/kg	[30]
14.	*Boerhaavia diffusa*	Nyctaginaceae	Whole plant	Hydroalcoholic	Flavonoids, alkaloids, steroids, triterpenoids,lipids,lignins,carbohydrates,proteinsand glycoproteins	Wistar rats	Cisplatin induced	200 and 400	[31]
15.	*Bauhinia variegatea*	Caesalpinaceae	Leaves	Methanol	Stigmasterol, flavones, glycosides, lupeol, kaempferol-3-glucosides, and β-sitosterol.	Swiss albino rats	Gentamycin induced	400mg/kg	[32]
16.	*Brassica rapa*	Brassicaceae	Roots	Ethanol	flavonoids (isorhamnetin, kaempferol, and quercetin), glycosides, phenylpropanoid derivatives, indole alkaloids and sterol glucosides	Sprague-dawley rats	Cisplatin	50, 100 and 200mg/kg	[33]
17.	*Benincasa hispidia*	Cucurbitaceae	Fruit	Hydro-alcoholic	β-sitosterol, asparagines, manitol, proline, arginine, aspartic acid, glucose and vitamin B1	Albino wistar rats	Paracetamol	200 and 400mg/kg	[34]
18.	*Carissa carandas*	Apocyanaceae	Fruit	Methanoli	Flavonoids, phenolic compounds, triterpenoids, saponins, carbohydrates, alkaloids, and tannins	Sprague-dawley rats	Gentamicin	100, 200 and 400mg/kg	[35]
19.	*Carica papaya*	Caricaceae	Seed	Aqueous	Flavonoids, saponins, alkaloids and carbohydrates	Wistar rats	Carbon tetrachloride	100 and 400mg/kg	[36]
20	*Crataeva nurvula*	Capparaceae	Stem bark	Ethanol	Triterpenoids, glycosides, alkaloids, flavonoids, proteins, tannins and	Wistar rats	Cisplatin	200, 400 and	[37]

					saponins			600mg/kg	
21.	*Cichorium intybus*	Asteraceae	Roots	Aqueous	Carbohydrates, flavonoids, terpenoids, tannins and saponins	Abino rabbits	Gentamicin	250 and 500mg/kg	[38]
22.	*Dendropanax morbifera*	Araliaceae	Leaves	Successive extraction	Flavonoids and phenolic compounds	Sprague-dawley rats	Cisplatin	25mg/kg	[39]
23.	*Eclipta prostata*	Asteraceae	Leaves	Hydro-alcoholic	Terpenoids, glycosides, alkaloids, sterol, flavonoids, volatile oils and saponins	Albino wistar rats	Gentamicin	250 and 500mg/kg	[40]
24.	*Ficus hispida*	Moraceae	Fruit	Methanol	Fixed oils, fats, steroids, flavonoids, triterpenoids and alkaloids	Albino wistar rats	Cisplatin	500mg/kg	[41]
25.	*Ficus racemosa*	Moraceae	Stem bark	Aqueous	Glycosides, phenols, flavonoids, tannins and carbohydrates	Albino wistar rats	Gentamicin	200 and 400mg/kg	[42]
26.	*Ficus religiosa*	Moraceae	Latex	Methanol	Glycosides, alkaloids, tannins, phenolic compounds, saponin gluanol acetate and amino acids	Albino wistar rats	Cisplatin	200mg/kg	[43]
27.	*Graptophyllum pictum*	Acanthaceae	Whole plant	Ethanol	Flavonoids , carbohydrates and phenolic compounds	Albino wistar rats	Gentamicin	75,150 and 300mg/kg	[44]
28.	*Hygrophila spinosa*	Acanthaceae	Whole plant	Methanol	Phenolic compounds, steroids, alkaloids, flavonoids and triterpenoids	Albino wistar rats	Cisplatin	250 and 500mg/kg	[45]
29.	*Indigofera tinctoria*	Fabaceae	Roots and leaves	Decoction	Glycoside indican, indigotine, indirubin, and flavonoids	Albino wistar rats	Cisplatin	500 and 1000mg/kg	[46]
30.	*Juniperus sabina*	Cupressaceae	Aerial parts	Ethanol	Carbohydrates, Diterpene acids, sesquiterpene alcohols, naphthalene derivatives, lignans, flavonoids, and coumarins	Wistar rats	Carbon-tetrachloride	200 and 400mg/kg	[47]
31.	*Lantana camara*	Verbanaceae	Leaves	Methanol	Flavonoids , carbohydrates, terpenoids, tannins and phenolic compounds	Albino wistar rats	Cisplatin	100-400mg/kg	[48]
32.	*Morinda citrifolia L.*	Rubiaceae	Fruit	Juice	Carbohydrates, fibres, vitamins, flavonoids, alkaloids, and fatty acids	Albino wistar rats	Gentamicin	5 and 10mg/kg	[49]
33.	*Mentha arvensis*	Lamiaceae	Leaves	Hydro-alcoholic	Glycosides, flavanoids, triterpene, steroids, tannin, and phenolic	Sprague-dawley rats	Cisplatin-induced	200 and 400mg/kg	[50]

					compounds.				
34.	*Moringa pterigosperma*	Moringaceae	Leaves	Ethanol	Deic, palmitic and stearic acid, saponins, glycoside, gum, protein Vitamins: A, B1, B2, B3, C Minerals: calcium, iron, phosphorus, magnesium	Sprague-dawley rats	Paracetamol	100 and 200mg/kg	[51]
35.	*Murraya koenigii*	Rutaceae	Leaves	Methanol and aqueous	Carbohydrates, flavonoids, tannin, alkaloids, glycosides, protein and steroids	Albino wistar rats	Cyclophosphamide	100 and 200 mg/kg	[52]
36.	*Morus alba*	Moraceae	Leaves	Hydro-alcoholic	Carbohydrates, proteins, fats, vitamins, fibers and minerals	Albino rabbits	Isoniazid	400 and 800mg/kg	[53]
37.	*Nelumbo nucifera*	Nymphaceae	Roots, leaves and flowers	Ethanol	Flavonoids, glycosides, alkaloids and carbohydrates	Albino rats	Gentamicin	100mg/kg	[54]
38.	*Ocimum basilicum*	Lamiaceae	Whole plant	Hydro-alcoholic	Flavonoids, vitamin C, vitamin E, Carbohydrates and glycosides	Albino rats	Cisplatin	100, 300 and 500mg/kg	[55]
39.	*Ocimum gratissimum*	Lamiaceae	Leaves	Aqueous	Flavonoids and carbohydrates	Albino rats	Paracetamol	200, 300 and 500mg/kg	[56]
40.	*Orthosiphon stamineus*	Lamiaceae	Leaves	Ethanol	Flavonoids, polyphenolic compounds, carbohydrates, volatile oils and β-sitosterol	Albino rats	Ethylene glycol	200mg/kg	[57]
41.	*Pimpinella anisum*	Umbelliferae	Seeds	Aqueous	flavonoids, tannins, and phenolic acids	Albino wistar rats	Gentamicin	1000, 2000 and 4000mg/kg	[58]
42.	*Polygonum glabrum*	Polygonaceae	Whole plant	Methanol	Flavonoids, glycosides, phenols and tannins	Albino wistar rats	Cisplatin and gentamicin	200 and 400mg/kg	[59]
43.	*Pongamia pinnata*	Fabaceae	Flowers	Ethanol	Carbohydrates, alkaloids, saponins, tannins, flavonoids and phenolic compounds	Albino wistar rats	Cisplatin and gentamicin	300 and 600mg/kg	[60]
44.	*Rosa damascena*	Rosaceae	Flowers	Aqueous	Terpenoids, saponins, alkaloids, flavonoids, glycosides and tannins	Albino rabbits	Gentamicin	250 and 500mg/kg	[38]

45.	*Rubus ellipticus*	Rosaceae	Fruit	Successive	Carbohydrates, alkaloids, saponins, tannins, flavonoids and phenolic compounds	Albino rats	Paracetamol	200mg/kg	[61]
46.	*Salviae radix*	Lamiaceae	Leaves	Methanol	Carbohydrates, flavonoids, tannins, alkaloids, saponins, triterpenoids, cardiac glycosides and anthraquinones	Rabbits	Cisplatin	250 and 500mg/kg	[62]
47.	*Solanum xanthocarpum*	Solanaceae	Fruit	Petroleum ether and ethanol	Steroidal alkaloids, coumarins, carbohydrates, flavonoids and tannins	Albino wistar rats	Gentamicin	200 and 400mg/kg	[63]
48.	*Tephrosia purpurea*	Fabaceae	Stem bark	Ethanol	Carbohydrates, flavonoids, alkaloids, glycosides, amino acids, fats and oils, proteins, lipids, triterpenoids, saponins, and steroids	Albino wistar rats	Gentamicin and cisplatin	200 and 400mg/kg	[64]
49.	*Terminalia arjuna*	Combretaceae	Bark	Methanol	Phenols, flavonoids, triterpenoids, tannins and carbohydrates	Albino rats	Paracetamol	500mg/kg	[65]
50.	*Tinospora cordifolia*	Menispermeaceae	Roots	Hydro-alcoholic	Alkaloids, amino acids, flavonoids, glycosides, saponins, steroids, tannins and triterpenoids	Albino rats	Cisplatin	200 and 400mg/kg	[66]
51.	*Tribulus terrestris*	Zygophyllacea e	Whole plant	Ethanol	Steroidal saponins, alkaloids, and protodioscin,	Albino wistar rats	Carbontetrachloride	200 and 400mg/kg	[67]
52.	*Tricosanthes dioica*	Cucurbitaceae	Fruit	Methanol	Flavonoids, saponins, tannins, carbohydrates, alkaloids and terpenoids	Albino wistar rats	Gentamicin	100, 200 and 400mg/kg	[68]
53.	*Vernonia cinereaa*	Compositae	Aerial parts	Successive	Flavonoids, triterpenoids, phenolic compounds, tannins and steroids	Albino rats	Cisplatin	500mg/kg	[69]
54.	*Vitex negundo*	Lamiaceae	Leaves	Ethanol	Alkaloids, flavonoids, iridoid glycosides, vitamin C, carotene, benzoic acid, β-sitosterol and C-glycoside	Sprague-dawley rats	Thiacetamide-induced	100 and 300mg/kg	[70]
55.	*Withania somnifera*	Solanaceae	Roots	Aqueous	Alkaloids, withanolides, and few flavonoids. In particular, glycowithnolide substances sitoindosides VII-X and withaferin A	Albino-wistar rats	Gentamicin	250, 500 and 750mg/kg	[71]

CONCLUSION

It is clear that many plants were proven to have potent curative properties against various disorders. Many plants have been investigated for their significant nephroprotective activity in various animal models. The nephroprotective activity the nephroprotective activity is probably due to the presence of phytochemicals like flavonoids and phenolic compounds in all the few medicinal plants. The present review study gives evidential mechanism of action of medicinal plants against drug-induced acute kidney failure.

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