Review Article

A Review on Medicinal Plants Possessing Nephroprotector Activity

Smitha jose[1]* and Adikay Sreedevi[2]

[1]Department of Pharmaceutical chemistry, Visveswarapura Institute of Pharmaceutical Sciences, Banashankiri, Bangalore-560 080, Karnataka, India.
[2]Department of Pharmaceutical Techonology, Sri Padmavathy Mahila Visvavidyalayam University, Tirupati-517 502, Andra Pradesh, India.

ABSTRACT

Nephrotoxicity is the most common adverse effect when the body is exposed to a drug or a toxin. Therapeutic agents of natural , synthetic and semisynthetic can adversely affect the kidney resulting in acute renal failure, chronic interstitial nephritis, and nephritic syndrome.[1] The main therapeutic agents which causes nephrotoxcity are aminoglycoside antibiotics, chemotherapeutic agents and NSAIDs. Exposure to chemical agents like ethylene glycol, carbon tetra chloride, sodium oxalate and heavy meals like lead ,mercury, arsenic and cadmium also induces nephrotoxicity. Dietary factors such as carbohydrate, lipid, and protein intake alter renal function and the presence of contaminants and natural toxicants may add to the toxic burden of the kidney.

Kidney is a complex and dynamic organ. Excretion of wastes and maintaining homeostasis is the primary function of kidney. Regulation of extracellular volume ,control of electrolyte and acid balance are also important functions of kidney. Any toxicological insult to kidney will be reflected as failure of the excretory function of the kidney. This results in the retention of the nitrogeneous waste of metabolism in the blood. In addition to these, there is failure of regulation of fluid and electrolyte balance along endocrine dysfunction.

INTRODUCTION

Chemicals, therapeutic agents and diagnostic agents are known to be nephrotoxic[1]. The following are the well known therapeutic agents which are nephrotoxic.[2]

A) Analgesics and non-steriodal anti-inflammatory drugs (NSAIDs)

B) Antineoplastic agents.

Alkylating agents: Cisplatin, Cyclophosphamide.

Nitrosoureas: Streptozotocin,Carmustine.

Antimetabolites: High dose Methotrexate, 5-flurouracil.

C) Antibiotics: Gentamicin, Amikacin, Kanamycin, Cephalosporins,Tetracyclines, Pencillamine.

D) Antimicrobial Agents: Acyclovir.

E) Heavy metals: Mercury, Arsenic, Lead, Bismuth, Gold etc.

F) Chemicals: Ethylene glycol, Volatile Hydrocarbons, Chloroform, Halogenated alkenes.

Nephropathies Caused Due To Different Mechanisms

Cisplatin Toxicity

Cisplatin is a water soluble anticancer drug, organic complex formed by an atom of platinum surrounded by chloride and ammonium atoms. Cisplatin is a potent antitumor drug, but its clinical use is limited due to its renal toxicity. The mechanism of action include after entering the cell, the chloride ions dissociates leaving a reactive complex. This complex reacts with water and then interacts with DNA resolving in denaturation of DNA chain. Cisplatin also damages cell mitochondria, arrests cell cycle in G_2 phase inhibits ATPs activity, alters the cellular transport system and eventually causing apoptosis, inflammation, necrosis and death in the cells. [3]. It is predominantly localized in S_3 segments of proximal tubules in the corticomedullary region.[4] Thus cisplatin decreases the antioxidants and antioxidant enzymes resulting in generation of reactive oxygen metabolites and lipid peroxidation due to renal toxicity.

Gentamicin Toxicity

Gentamicin, an effective widely used antibiotic but the risk of nephrotoxicity and oxidative damage limits its long term use. Gentamicin has a relatively shorter half life in the plasma but the half life in the kidney is considerably longer, suggesting that the material is tightly bound to renal tissue. Recent evidences suggest that gentamicin is filtered and a small fraction is taken up by cells of the proximal tubule, presumably by a pinocytotic process where it accumulates to toxic concentration in lysomes. Subsequent release of hydrolytic lysomes then produces cell damage.[5]

Acetaminophen Toxicity

Acetaminophen, known as paracetamol is a widely used NSAID for wide range of treatments. Overdose of acetaminophen causes hepatic and renal damage in humans. The different pathways of acetaminophen metabolism involves conjugation with sulphate, glucuronide and through cytochrome p450 oxidase enzyme system.[6] Metabolism of paracetamol involves an initial N-hydroxylation to form N-hydroxyacetaminophen and spontaneous dehydration of this N-hydroxyamide produces an N-acetyl imidoquine which is a very reactive electrophilic metabolite and is excreted by kidney. In therapeutic doses, glutathione present in the liver combines with this metabolite forming corresponding glutathione conjugate. In acetaminophen overdose, glucuronidation and sulfation pathways becomes saturated. The amount and rate of formation of reactive metabolite is greatly increased, the covalent binding of the reactive intermediate occurs with macromolecules leading to cellular necrosis and kidney dysfunction.[7]

General Methods of Evaluation of Nephrotoxicity

Due to complex nature and multiple functions of the kidney, no single test can detect nephrotoxicity. The nephrotoxicity assessment involves *invitro and invivo* studies. Invitro methods provide information on the mechanism of primary insult and the effect on cell viability. The invitro techniques can be divided into those where the anatomical relationship between cells is maintained. (perfusion, micropuncture,and slices),those where glomerulai and tubular fragments are isolated and those where cells are isolated. Invivo experimental studies include evaluation of glomerular function and tubular functions, Protenuria, urinary excretion of single plasma proteins, enzymuria, immunoreactive tissue constituents, urinary excretion of prostaglandins.[2]

Nephroprotective agents are the substances which possess protective activity against nephrotoxicity.Previous literatures have prescribed various medicinal herbs for the cure of renal disorders .Medicinal plants possess curative and protective proporties due to presence of various complexes like terpenoids, flavanoids, tannins ,glycosides, alkaloids etc present in the plants. Coadministration of various medicinal plants possessing nephroprotective activity along with different nephrotoxic agents had helped in reversing the nephrotoxicity.[8] The present review is aimed to collect the history of medicinal plants , which are proved in treating renal disorders in different animal models. The following are the review of some medicinal plants which possess nephrotoxicity.

S.No	Botanical Name	Family	Parts used	Chemical Constituents
1	*Aegle marmelos*	Rutaceae	Leaves	Aegeline, Aegelinine, Rutin,Lupeol, Sterol,Tannins,Flavanoids,Quercetin β-sitostersol, β-D-glucoside.[9]
2	*Aerva lanata*	Amaranathaceae	Whole	Botulin, β-sitostersol, Amyrin,Campesterol, Kaempferol,Propionic acid, Aervoside, Aervolanine.[10]
3.	*Acorus calamus*	Araceae	Aerial parts	Monoterpene, Sesquiterpene, Phenylpropanoid, Flavanoid, Quinone ,Basarone[11.]
4	*Bauhinia variegatea linn*	Caesalpiniaceae	stems	Stigmasterol,Flavone glycosides,Lupeol, Kaempferol-3-glucoside, β-setosterol.[12]
5	*Boehaavia diffusa*	Nyctaginaceae	Roots	Flavanoids, Alkaloids,Triterpenoids, Proteins, Carbohydrates, Glycosides, Lipids,Lignins,Glycoprotiens.[13]
6	*Carica papaya*	Caricaceae	Seeds	Seed Flavanoids, Phenols Alkaloids,Terpenoids, Protein, Sterols, Carbohydrates, Tannins, Glycosides, Saponins.[14]
7	*Crataeva nurvula*	Capparidaceae	Fruits	Kaemferol-3-O-A-D-Glycoside, Flavanoids, Glucosinolates, Steroids, Lupeol ,Tannins.[12]
8	*Cassia auriculata*	Fabaceae	Roots	Tannins, Di-(2 ethyl)hexyl phthalate, Alkaloids, Resins, Ca^{2+} and phosphorous[15].

9	*Caranarium scheinfurthii*	Burseraceae	Stem bark	Octylacetate, Nerolidol, Protien, Starch, Cellulose,K Ca,Oleic acid,Stearic acid[16].
10	*Cucurbita pepo*	Cucurbitaceae	Seeds	Flavanoids , Phenols, Alkaloids,Protein, Sterols, Terpenoids, Steriods ,Carbohydrates, Tannins, Glycosides, Saponins.[12]
11	*Curcuma longa*	Zingeberaceae	Rhizome	Curcumin, Termeric oil, Terpenoids,Curcumen,Starch, Albumnoids.[17]
12	*Dichrostachys cinera*	Mimosaceae	Roots	Fixed oils, steroids,Flavanoids,n-octacosanol, , β-sitostersol, β-amyrin acetate, Friedelan 3-one,Friedelan 3-ol,Friedlen, α-amyrin.[18]
13	*Emblica officinalis*	Euphorbiaceae	Fruits	Vitamin C, Carotene, Nicotinic acid, Riboflavin, D-Glucose, D-fructose, Tannins,Ellagic acid,Lupeol Oleanolic acid, Fatty acids etc.[12]
14	*Euphorbia nerifolia*	Euphorbiaceae	leaves	Flavanoids, Tannins, Saponins.[19]
15	*Ficus religiosa L*	Moraceae	Latex	Aminoacids and Tannins.[20]
16	*Ginkgo biloba*	Ginkgoceae	Whole plant	Flavanoids, Bilobalide, Gingkolide A, Gingkolide B , Gingkolide C Biflanoide.[21]
17	*Glycyrrhiza glabra*	Fabaceae	Rhizome	Glycyrrhizin, Glyclyrrhizic acid, Glycosides, Steriods, Glucose ,Sucrose, Resin, Starch, and essential oil[12].
18	*Hygrophila spinosa*	Acanthaceae	Whole plant	β-sitostersol,Lupeol,Minerals like Na, K,Ca, P and Polyphenols.[22]
19	*Indegoferabarberi L*	Fabaceae	Whole plant	Flavaoids,Phenolic acids, and Sterols.[23]
20	*Kigelia Africana*	Bignoniaceae	Matured fruits	Naphthoquinones , Flavanoids, Terpenes, Tannins, Steriods, Saponins, Caffeic acid.[24]
21	*LepidiumsativumL*	Brassicaceae	Seed	Volatile essential aromatic oils, Fatty oils, Carbohydrate, Protien, Fatty acid,Vitamin B Carotene, Riboflavin, Niacin, Ascorbic acid, Flavanoids, Gytcosides, Isothiocynates.[25]
22	*Morinda citrifolia*	Rubiaceae	Fruit	Americanol A, 3-31-bis dimethyl pinoresinol, AmericaninA, Americanoic acid A, Isoprincepin[26].
23	*Moringa oleifera*	Moringaceae	Seeds	Vitamin A, Nicotinic acid, Ascorbic acid, Vitamin B, Fatty acid, Glucose, ,Sucrose, Fumaric acid, Oxalic acid.Citric acid, Malic acid, Succinic acid .[27]
24	*Nigelle sativa*	Ranunulaceae	Whole plant	Alanine, L-Spinasterol, Arabic acid,Arginine ,Aminoacid, Aspargine. Aspartic acid, Carvone, Cystine, Cholesterol, Glutamic acid,Linoleic acid,Melanthin, Myristic acid, Oleic acid, Tannins.[12]
25	*Ocimum sanctum*	Lamiaceae	leaves	Eugenol,Eugenol methyl ether, Carvacrol, Caryophyllene, Ursolic acid, Apigenin, Luteolin, Ascorbic acid, Carotene, Alkaloids, Gycosides Saponins Tannins.[12]
26	*Orthosiphon stamineus*	Laminaceae	Whole plant	Flavanoids, Phenols, Carbohydrates, Steroids, Glycosides,Saponins ,Tannins.[28]
27	*Panax ginseng*	Araliacae	Root	Glycosides,Saponins Ginsenosides,Panaxosides.[12]
28	*Peladium murex Linn*	Pedaliaceae	Dried fruits	Flavanoids, Flavones, Alkaloids,Titerpenoids,Carbohydrates,Glycosides, Saponins.[29]
29	*Pimpinella tirupatiensis*	Apiaceae	Whole plant	Flavanoids, Flavones, Alkaloids,Volatile oils, Cis – Carveol, Enemol, Methylgeranate, Δ –Carveol, Δ-3-Carene.[30]
30	*Pongamia pinnata*	Papilionaceae	Flowers	Pongamol,Protien, Alkaloids, Tannins, Sugar, Resin, Fatty oil.[12]
31	*PunicagranatumL*	Puniaceae	Fruit peel	Ellagic acid, Ellagitannins, Gallic acid.[31]
32	*RubiacordifoliaLinn*	Rubiaceae	Roots	Purpurin, Manjistin, Garancin, Purpuroxanthin, Resin, Glucose, Sucrose, Triterpenes, Lucidine,Anthroquinone, Fattyacids Gum.[32]
33	*Rhazya stricta*	Apocynaceae	Leaves	I-cabomehoxy – β-carboline, Condyloacarpine, Vincanicine.[12]
34	*Salviae radix*	Lamiaceae	Whole plant	Salvianolic acid –G, Rosmarinic acid, Lithospermic acid, Isoferulic acid, Tanshinone I, IIA,IIB.[12]
35	*Solanum nigrum*	Solanaceae	Whole plant	Alkaloids, Reducing sugars, Steroids, Glycosides,Saponins ,Leutein, Lycopene, Vitamin C,Glucose, Fructose, Caffeicsolasodine, Tamatidenol,Solamargine, Solasomine,Trigogenine, Potassium,Sulphur, Calcium, Phosphorous.[12]
36	*Strychnos potatorum*	Loganiaceae	Seed	Flavanoids, Phenols, Steroids, Tannins, Glycosides,Saponins ,Alkaloids,Lignins.[33]
37	*Tamarindus indica*	Caesalpinaceae	Fruit pulp	Polysaccaharides, Balsamine, Catechin, Nasturtium, Tamarin, Phoshpatidic acid, Phosphatidic choline, Ethanollamine, Serine, Inositol,Alkaloid,Citic acid,

				Tartaric acid, Potasiumbitartarate.[12]
38	*Tectona grandis*	Verbanaceae	Bark	Lapachol, Dehydro-α- Lapachone, Methyl quinizarin, Squalene.[34]
39	*Tribulus sativus*	Zygophyllaceae	Fruits	Alkaloids, Harmine, Harman,Saponins, Steriodal Sapogenins, Flavanoids, Kaemferol,Fixed oil, Resin, Essential oil, Nitrates.[12]
40	*Vernonia cinerea*	Compositae	Aerial parts	α-amyrin, β -amyrin, lupeol.Triterpenoids ,Fatty acids, Steriods.[35]
41	*Vitisvenefera*	Vitaceae	Seed	7
42	*Withania somnifera*	Solanaceae	Root	Alkaloids, Withaminon, Wasamin, Sugars, Glycosides, Aminoacids, Essential oils, Withaniol, Phytosterol, Oils.[12]
43	*ZingiberzerumbelSmith*	Zingiberaceae	Rhizome	Zerumbone, Afzelin, Diacetylafzelin, derivatives of kaemferol and 3-flavanol.[36]

CONCLUSION

The literature collected clearly shows that the medicinal plants play a prominent role against nephrotoxicity. The nephroprotective proterties of plants are due to the presence of their different biologically active chemicals like flavanoids, terpenoids, glycosides etc. These biologically active chemicals of plant contribute to their antioxidant properties which acts as a nephroprotective agent. Though the above plants vary in their chemical ingredients, they showed a good potential against kidney damage. The information of the above medicinal plants serves as valuable resource for plant based drug development programs and for designing a novel drug.

REFERENCES

1. Druet P. Contribution of immunological reactions to nephrotoxicity; Toxicol Let. 1989;46:55-64.
2. Kleinknecht D, Kanfer A, Morel-Maroger L and Mery JP. Immunologically mediated drug induced acute renal failure. Contrib Nephrol. 1978;10:42-52.
3. Lieberthal W, Tricaca V and Levine J. Mechanism of death induced by cisplatin in proximal tubular epithelial cells:apoptosis vs necrosis. Am J Physiol. 1996;270:F700-8.
4. Kroning R, Lichtenstein AK and Nagami GT. Sulphur containing aminoacids decrease cisplatin cytotoxicity and uptake in renal tubule epithelial cell lines. Cancer Chemother Pharmacol. 2000;45:43-9.
5. Appel GB and Neu HC. N Engl J Med. 1977;269,663-670,722-728,784-787.
6. Presscott L. Oral or Intravenous N-aceyylcysteine for Acetaminphen poisoning. Ann Emerg Med. 2005;45:409-413.
7. Mugford CA and Tarloff JB. The contribution of oxidation and deacetylation to acetaminophen Nephrotoxicity in female Sprague-Dawley rats. Toxicol Lett. 1997;93:15-22.
8. Paller MS. Drug induced nephropathies. Med Clin North Am. 1990;74(4):909-917.
9. Kore KJ, Shete RV and Jadhav PJ. Nephroprotective role of A Marmelos extract. International Journal of Research in Pharmacy and Chemistry. 2011;1(3):617-623
10. Annie Shirwaikar, Deepti Issac and Malini S. Effect of Aerva lanata on cisplatin and Gentamicin models of acute renal failure. Journal of -Ethanopharmacology. 2004;4:81-86.
11. Palani S, Raja S, Praveen Kumar R, Paramaswaran P and Senthil Kumar B. Therapeutic efficacy of Acorus calamus on acetaminophen induced nephrotoxicity and oxidative stress in male albino rats. Acta Pharmaceutica Sciencia. 2010;52:89-100.
12. http://farmacists.blogspot.com.
13. Surendra K Pareta, Kartik, Patra C, Ranjeet Harwansh, Manoj Kumar, Kedar Prasad and Meena. Protective effects of Boerhaavia Diffusa against Acetaminophen –Induced Nephrotoxicity in Rats. Pharmacology online. 2011;2:698-706.
14. Subal Debnath, Nilesh Babre, Manjunath YS, Mallareddy, Pabba Paramashwar and Hariprasath K. Nephroprotective evaluation of ethanolic extract of the seeds of papaya and pumpkin fruit in cisplatin induced nephrotoxicity. Journal of Pharmaceutical Science and Technoogy. 2010;2(6):246.
15. Annie S, Rajagopal PL and Malini S. Effect of Cassia auriculata Linn Root extract on cisplatin and gentamicin induced renal injury Phytomedicine. 2005;12:555-560.
16. Okwuosa CN, AchukwuAchukwu PU, Eze AA and Azubuike NC.

Nephroprotective activity of stem bark extracts of Canariumschweinfurthiion acetaminophen –induced renal injuries in rats Journal of College of Medicine. 2009;14(1).
17. Eduardo Molina-Jijon, Edilia Tapia, Cecilia Zazueta, Mohammed El Hafidi, Zyanya Lucia Zatarain-Barron and Rogelio Hernandez-Pando. Curcmin prevents Cr(VI)-induced renal oxidant damage by a mitochondrial pathway. Food and Chemical Toxicology. 2011;FRB-10747:(1-15).
18. Sreedevi Adikay, Bharathi Konganti and Prasad KVSRG. Effect of alcoholic extract of root of Dichrostachyscinera Wight & Arn. Against cisplatin induced nephrotoxicity in rats. Natural Product Radiance. 2009;8(1):12-18.
19. Pracheta P and Veena Sharma. Chemopreventive effect of hydroethanolic extract Euphorbia neriifolia leaves against DENA – Induced renal carcinogenisis in mice. Asian Pacific J Cancer Prev. 2011;12:677-683.
20. Yogesh Chand Yadav, Srivastava DN, Vipin Saini, Sarita Singhal, Seth AK, Sharad Kumar, Tejas K, Ghelani and Anujmalik. Nephroprotective and curative Activity of methanolic extract of Ficus religiosal. Latex in Albino Rats Using Cisplatin Induced Nephrotoxiciy. Pharmacology onoline. 2011;1:132-139.
21. Welta K, Weissa J, Martinb R, Hermsdorfc T, Drewsa S and Fitzla G. Ginkgo bilba extract protects rat kidney from diabetic and hypoxic damage. Phytomedicine. 2007;14:196-203.
22. Bibu KJ, Joy AD and Mercy AK. Therapeutic effect of ethanolic extract of HygrophilaspinosaT.Anders on gentamicin induced nephrotoxicity in rats. Indian Journal of Experimental Biology. 2010;48(9):911-917.
23. Palani S,Senthil Kumar B, Praveen Kumar R, Venkatesan D and Raja Sathendra E. Effect of the ethanolic extract of Indigoferabarberi(L) in acute acetaminophen –induced Nephrotoxic rats. Advanced Bioteh. 2008;9:28-31.
24. Onyemaechi O Azu, Francis IO Duru, Abraham A Osinubi, Crescie C Noronha, Stephen O Elesha and Abayomi O Okanlawon. 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):84-88.
25. Yogesh Chandyadav, Srivastav DN, Seth AK, Vipin Saini Kuldeep S and Yadav. Nephropharmacological activity of ethanolic extract of Lepidium sativuml seeds in albino rats using cisplatin induced acute renal failure.International Journal of Pharmaceutical sciences Review and Research. 2010;4(3):64-68.
26. Jnaneshwar P Shenoy, Preethi G Pai, AhsanShoeb, Gokul P, AvdhootKulkarni and Kotian Ms. An evaluation of diuretic activity of Morinda Citrifolia (Linn) (Noni) fruit juice in normal rats. International Journal of Pharmacy and Pharmaceutical Sciences. 2011;3(2):119-121.
27. Ranjan R, Swarup D, Patra RC, Chandra and Vikas. Tamarindusindica L and Moringaoleifera M extract administration ameliorates fluoride toxicity in rabbits. Indian Journal of Experimental Biology. 2009;47(11):910-920.
28. Kannappan N, Madhukar, Mariyammal, Uma sindhura and Mannavalan R. Evaluation of nephroprotective activity of OrthosiphonstamineusBenth extract using rat models. International Journal of PharmTech Resarch. 2(3):209-215.
29. Shelke T, Kothai TR, Adkar PP, Bhaskar VH, Juvale KC, Kamble BB and Oswal RJ. Nephroprotective activity of ethanolic extract of dried fruits of Pedalium murex Linn. Journal of Cell and Tissue Research. 2009;9(1):1687-1690.
30. Palani S, Raja S, Praveen Kumar R, Soumya Jaya kumar and Senthil Kumar. Therapeutic efficacy of Pimpinellatirupatiensis (Apiaceae) on acetaminophen induced nephrotoxicity and oxidative stress in male albino rats. International Journal of Pharm Tech Research. 2009;1(30):925-934.
31. Mahgoub Mohammed Ahamed and Safaa Eid Ali. Protective effect of pomegranate peel ethanol extract against ferric nitriloacetate induced renal oxidative damage in rats." Journal of Cell and Molecular Biology. 2010;8(1):35-43.
32. Kalyani Divakar, Pawar AT, Chandrasekhar SB, Dighe SB and Goli Divakar. Protective effect of the

hydro-alcoholic extract of Rubiacordifolia roots against ethylene glycol induced urolithiasis in rats. Food and Chemical Toxicology. 2010;48:1013-1018.
33. Ruby Varghese, Mohammed Moideen, Mohammed Suhail MJ and Dhanapal CK. Nephroprotective effect of ethanolic extract of Strychnospotatorm seeds in rat models. Resarch Journal of Pharmaceutical Biological and Chemical Sciences ais.
34. Ghaisas MM, Navghare VV, Takawale AR, Zope VS and Phanse MA. Antidiabetic and Nephroprotective effect of Tectonagrandis L in alloxan induced diabetes. Arspharmaceutica. 2010;51:195-206.
35. Sreedevi A, Bharathi K and Praasd KVSRG. Effect of Veronicacinera ariel parts against Cisplatin induced nephrotoxicity in rats. Pharmacologyonline. 2011;2:548-555.
36. Ajith TA, Aswathy MS and Hema U. Protective effect of Zingiber officinaleroscoe against anticancer drug doxorubicin induced acute nephrotoxicity, Food and Chemical Toxicology. 2008;46:3178-3181.