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NEPHROPROTECTIVE POTENTIAL OF MEDICINAL PLANTS: A SYSTEMATIC REVIEW

***Raj Vikram Singh, Satkar Prasad**

RKDF School of Pharmaceutical Sciences, Bhabha University, Bhopal (M.P.)

*Corresponding Author's Email id: rajvikram123321@gmail.com

Abstract

Nephrotoxicity is a major clinical concern characterized by deterioration of renal function resulting from exposure to therapeutic drugs, environmental toxins, and chemical agents. The increasing use of nephrotoxic medications such as aminoglycoside antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), chemotherapeutic agents, and radiographic contrast media has significantly contributed to the prevalence of acute and chronic kidney disorders. Drug-induced nephrotoxicity is mediated through multiple mechanisms including oxidative stress, inflammation, apoptosis, mitochondrial dysfunction, and alterations in renal hemodynamics. Among the nephrotoxic agents, gentamicin, cisplatin, and paracetamol are widely used experimental models for evaluating nephroprotective interventions. Medicinal plants have gained considerable attention as potential nephroprotective agents owing to their rich content of bioactive phytoconstituents such as flavonoids, phenolics, alkaloids, tannins, and saponins, which exhibit antioxidant, anti-inflammatory, and cytoprotective activities. Numerous preclinical studies have demonstrated the efficacy of various medicinal plants in preventing or attenuating renal damage induced by nephrotoxic agents. This review summarizes the etiology, pathophysiology, epidemiology, clinical manifestations, and management of nephrotoxicity, with particular emphasis on drug-induced renal injury. Furthermore, the review highlights the nephroprotective potential of medicinal plants, their mechanisms of action, and experimental evidence supporting their use in renal disorders. The findings suggest that plant-derived therapeutics may serve as promising alternatives or adjuncts in the prevention and management of nephrotoxicity, although further clinical investigations are required to establish their safety and efficacy in humans.

Keywords: Nephrotoxicity; Nephroprotective Activity; Acute Kidney Injury; Chronic Renal Failure; Medicinal Plants; Gentamicin; Cisplatin; Paracetamol; Oxidative Stress; Drug-Induced Nephrotoxicity; Antioxidants; Phytoconstituents; Renal Protection; Herbal Medicine; Kidney Disorders.

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. 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 (Hoitsma *et al*., 1991).

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. In addition to this, along with endocrine dysfunction, there is a failure of regulation of fluid and electrolyte balance (Helms and Quan, 2006).

Renal failure is categorized as acute and chronic renal failure:

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 (Vaya *et al*., 2017). The exogenous agents are radiocontrast agents, cyclosporine, antibiotics, chemotherapeutic agents, organic solvents, paracetamol and illegal abortifacients, while the endogenous compounds include myoglobin and heamoglobin (Evenepoel, 2004).

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 (Helms and Quan, 2006).

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 (Yadav *et al*., 2007).

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 (Mayo, 2018)

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 amino glycoside antibiotics, gentamicin has greater nephrotoxicity than tobramycin and lesser than neomycin (Vaya *et al*., 2017).

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 (Medscape, 2019). 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 (Purohit *et al*., 2009).

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. Reports showed that kidney injury might occur in 50 to 75% of patients receiving cisplatin, and is dose limiting (Yasuyuki *et al*., 1992).

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 (Nelson, 1995; Boelsterli, 1993; Holtzman, 1995). Paracetamol overdose is common in humans and is frequently related to liver and kidney injury. 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. 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 (Jones and Vale, 1993; Eguia and Materson, 1997; Montilla *et al*., 2005).

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 (Yasuyuki *et al*., 1992)

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 (MEDSCAPE, 2019).

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 (Mansour *et al*., 2006).

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 amino glycoside induced nephrotoxicity based on creatinine results. It was also studied that they showed a dose dependent protective activity (both in creatinine and BUN) (Vicente *et al*., 2017).

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 (Soumya *et al*., 2011).

Agents Which Inducing Nephrotoxicity:

Number of chemical agents, therapeutic drugs and diagnosing agents are responsible for clinically inducing significant nephrotoxicity. Hence, agents which causes nephrotoxicity are well known to be nephrotoxic in nature.

Table 1: drugs which causes nephrotoxicity

Drugs	Example
Analgesic	Acetaminophen, Aspirin
Anti-depressant	Amitriptyline, Fluoxetine, Doxepin
Anti-microbial	Amphotericin-B, Acyclovir, Foscarnet, Ganciclovir, Trimethoprim, Rifampicin
Anti-retroviral	Adefovir, Tenofovir, Indinavir
Chemotherapeutic	Carmustine, Cisplatin, Cyclophosphamide
Proton pump inhibitor	Omeprazole, Pantoprazole
Aminoglycosides	Gentamycin, Amikacin, Kanamycin, Streptomycin
Biological agents	Recombinant leucocyte and Interferon

Mechanism of Some Important Drug Induced Nephrotoxicity

Cisplatin Induced Nephrotoxicity:

Cisplatin is chemotherapeutic agent responsible for high prevalence of nephrotoxicity. Clinically cisplatin nephrotoxicity was seen after 10 days of drug administration, which causes decrease in the GFR rate, elevation of serum creatinine level and decrease serum Mg and K ions (Pabla and Dong, 2008).

When cisplatin diffuses into kidney cells via passive or facilitated transport mechanism, renal tubular cells get exposed to cisplatin results in the activation of some important signalling pathways, such as MAPK, p^{53}, ROS and SO or p^{21} which are involved in renal cell death. Mainly cisplatin induces TNF-α production in renal tubular cell, which intern triggers the tissue inflammatory response and further contributes to cell injury and renal cell death. Or cisplatin also cause injury to renal vasculature leads to ischemia of tubular cells cause decrease GFR (Jamshidzadeh *et al*., 2015). Together of these cascade pathway leads to acute renal failure (ARF).

Gentamicin Induced Nephrotoxicity:

Gentamicin belongs to the category aminoglycosides antibiotic, widely used in the treatment of Gram Negative bacterial infection. Despite of this nephroprotective is a deleterious adverse effect of aminoglycoside therapy (Adil *et al*., 2016).

Patient with gentamicin therapy having renal impairment but exact mechanism involved in gentamicin induced nephrotoxicity till now not yet cleared. Renal proximal tubule cells are primary target for aminoglycosides antibiotic where accumulation and cause nephrotoxicity via specific transporter, other mechanism may also contribute for gentamicin induced nephrotoxicity like excess production of ROS, hydroxyl radical, superoxide anions and RNS, also inhibition of Na K^+ ATPase inhibition and also mitochondrial oxidative phosphorylation. Accumulation of gentamicin also suggest that cell apoptosis, necrosis and oxidative stress (Reshi *et al*., 2020).

Acetaminophen Induced Nephrotoxicity:

Acetaminophen is commonly used analgesic or anti-pyretic, overdosing of this drug might cause potentially inducing hepatorenal damage in experimental animals and human. Nephrotoxicity of acetaminophen depends on its metabolic profile, at therapeutic dose acetaminophen get conjugated in liver with Glucuronide or sulphate results in formation of water soluble, non-toxic compound that is easily excreted via bile. Small amount of acetaminophen metabolised into highly reactive and toxic metabolite called N-acetyl-p-benzoquinone-imine (NAPQI) by microsomal enzyme P-450. Intracellular GSH conjugate with NAPQI, result in the formation of mercapturic acid, which eliminate via kidney.

Hence its plays crucial role in detoxification of acetaminophen. So overdose of acetaminophen, the active amount of NAPQI exceeds binding capacity of GSH result in the accumulation of NAPQI, active NAPQI binds with intracellular macromolecule lead to tissue damage. Then consequent activation of lysosomal enzyme induce tissue necrosis and organ dysfunction. Proximal renal tubules are primary target for acetaminophen toxicity (Haritha *et al*., 2019).

Table 2: Medicinal plants showing Nephroprotective active

Sr. no.	Plant	Part used	Animal model	Reference
1.	*Aerva lanata*	Whole plant	Albino rats	Soumya *et al*., (2011)
2.	*Aerva javanica*	Fresh roots	Albino wistar rats	Movaliya *et al*., (2011)
3.	*Anethum graveolens*	Seeds	Albino wistar rats	Rao, (2018)
4.	*Amomum subulatum*	Seeds	Albino rats	Puttanna *et al*., (2016)
5.	*Aconitum heterophyllum*	Roots	Wistar albino rats	Konda *et al*., (2016)
6.	*Azima tetracantha*	Roots	Albino wistar rats	Konda *et al*., (2016)
7.	*Annona reticulata*	Aerial parts	Wistar rats	Devi *et al*., (2016)
8.	*Aloe barbadensis*	Leaves	Albino rats	Shamim *et al*., (2018)
9.	*Allium cepa*	Leaves	Sprague dawley rats	Chinnala *et al*., (2017)
10.	*Andrographis paniculata*	Leaves	Albino wistar rats	Padmalochana and Rajan, (2015)
11.	*Acorus calamus*	Aerial parts	Albino rats	Palani *et al*., (2010)
12.	*Aegle marmelos*	Leaves	Wistar rats	Dwivedi *et al*., (2017)
13.	*Bauhinia purpurea*	Bark and unripe pods	Wistar albino rats	Rana *et al*., (2014)
14.	*Boerhaavia diffusa*	Whole plant	Wistar rats	Nalini *et al*., (2015)
15.	*Bauhinia variegatea*	Leaves	Swiss albino rats	Harish *et al*., (2012)
16.	*Brassica rapa*	Roots	Spraguedawley rats	Kim *et al*., (2006)
17.	*Benincasa hispidia*	Fruit	Albino wistar rats	Varghese *et al*., (2013)

18.	*Carissa carandas*	Fruit	Spraguedawley rats	Dhodi *et al.*, (2015)
19.	*Carica papaya*	Seed	Wistar rats	Olagunju *et al.*, (2009)
20.	*Crataeva nurvula*	Stem bark	Wistar rats	Shelkea *et al.*, (2011)
21.	*Cichorium intybus*	Roots	Abino rabbits	Khaliq *et al.*, (2015)
22.	*Dendropan axmorbifera*	Leaves	Spraguedawley rats	Kim *et al.*, (2015)
23.	*Eclipta prostata*	Leaves	Albino wistar rats	Ahmad *et al.*, (2018)
24.	*Ficus hispida*	Fruit	Albino wistar rats	Swathi *et al.*, (2011)
25.	*Ficus racemosa*	Stem bark	Albino wistar rats	Swamy, (2008)
26.	*Ficus religiosa*	Latex	Albino wistar rats	Yadav *et al.*, (2006)
27.	*Graptophyll um pictum*	Whole plant	Albino wistar rats	Srinivasan *et al.*, (2015)
28.	*Hygrophila spinosa*	Whole plant	Albino wistar rats	Ingale *et al.*, (2013)
29.	*Indigofera tinctoria*	Roots and leaves	Albino wistar rats	Priyadarsini *et al.*, (2012)
30.	*Juniperus sabina*	Aerial parts	Wistar rats	Abdel *et al.*, (2018)
31.	*Lantana camara*	Leaves	Albino wistar rats	Abdel *et al.*, (2017)
32.	*Morinda citrifolia L*	Fruit	Albino rabbits	Pai *et al.*, (2013)
33.	*Mentha arvensis*	Leaves	Spraguedawley rats	Singh *et al.*, (2014)
34.	*Moringa pterigosperma*	Leaves	Spraguedawley rats	Lakshmana *et al.*, (2013)
35.	*Murraya koenigii*	Leaves	Albino rabbits	Mahipal and Pawar, (2017)
36.	*Morus alba*	Leaves	Albino rabbits	Muhammad *et al.*, (2014)
37.	*Nelumbo nucifera*	Roots, leaves and flowers	Albino rats	Dubey *et al.*, (2014)

38.	*Ocimum basilicum*	Whole plant	Albino rats	Zaveri *et al.*, (2011)
39.	*Ocimum gratissimum*	Leaves	Albino rats	Ezeonwu and Dahiru, (2013)
40.	*Orthosiphon stamineus*	Leaves	Albino rats	Gaikwad *et al.*, (2012)

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 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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