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Review

A review on causes of nephrotoxicity and herbal treatment



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|  | Abstract |
| Published on: 2 Sep 2024 | <p>Nephrotoxicity is one of the most common kidney problems and occurs when body is exposed to a drug or toxin. There are various numbers of therapeutic agents responsible for the occurrence of nephrotoxicity like anticancer drugs, antibiotics, some NSAIDs, etc. Many medicinal herbs, natural compounds, and dietary components have been studied as possible nephroprotective agents. Medicinal plants may serve as a vital source of potentially useful new compounds for the development of effective therapy to combat a variety of kidney problems. Medicinal plants have curative properties due to the presence of various complex chemical substances. Many kinds of literature searches have been done and proved that; many medicinal plants have nephroprotective activity. The present review is about the some of the medicinal plants possessing nephroprotective activity on Cisplatin and Gentamicin induced nephrotoxicity.</p> |
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| | Keywords: Nephrotoxicity, Herbal medicine, Medicinal plants, Gentamycin. |

INTRODUCTION

The kidney is the main organ required by the human body to achieve and perform different important functions including detoxification, regulation of extracellular fluids, homeostasis, and excretion of toxic metabolites [1].

Nephrotoxicity is defining as rapid deterioration in the kidney function due to toxic effect of medications and chemicals. There are various forms, and some drugs may affect renal function in more than one way. It refers to side effects that damage kidney function associated with filtration, reabsorption, and excretion. Nephrotoxicity occurs when kidney-specific detoxification and excretion do not work properly due to the damage or destruction of kidney function by exogenous or endogenous toxicants. Nephrotoxicity is a kidney-specific feature in which excretion does not go smoothly owing to toxic chemicals or drugs.

Approximately 20% of nephrotoxicity is induced by drugs, but medication of the elderly increases the incidence of nephrotoxicity up to 66% as the average life span increases. Chemotherapy or anticancer medicine has been of limited use due to nephrotoxicity.

Nephrotoxicity can be diagnosed through a simple blood test. Evaluation of nephrotoxicity through blood tests includes the measurements of blood urea nitrogen (BUN), concentration of serum creatinine, glomerular filtration rate and creatinine clearance. However, these assessments of nephrotoxicity are only possible when a majority of kidney function is damaged [2].

Etiology

Nephrotoxicity refers to kidney damage caused by exposure to toxic substances. The etiology, or causes, of nephrotoxicity can be varied and often involve both exogenous (external) and endogenous (internal) factors.

Medications are a relatively common cause of kidney injury. The general population is exposed to a large number of prescribed and over-the-counter drugs as well as a variety of substances available at health food stores (natural products, supplements, herbal remedies). Various imaging agents used for diagnostic purposes are also associated with nephrotoxicity.

Nephrotoxicity, or kidney damage caused by exposure to harmful substances, can arise from a variety of sources. Common medications like NSAIDs, certain antibiotics, chemotherapy agents, antiviral drugs, and diuretics are known to cause kidney damage, especially with prolonged or high-dose use. Environmental toxins such as heavy metals and organic solvents also pose significant risks. Radiographic contrast media used in imaging procedures can induce nephrotoxicity, as can certain herbal supplements like those containing aristolochic acid or traditional Chinese medicines. Medical conditions such as acute kidney injury (AKI), chronic kidney disease (CKD), poorly controlled diabetes, and hypertension increase susceptibility to nephrotoxicity. Infections like hepatitis B, hepatitis C, HIV, and severe bacterial infections contribute to kidney damage as well. Additionally, substances like myoglobin from rhabdomyolysis and high levels of uric acid in conditions like gout or tumor lysis syndrome can lead to nephrotoxicity. Preventative measures include careful monitoring of kidney function, maintaining hydration, and avoiding unnecessary use of nephrotoxic substances [3].

Many drugs can cause nephrotoxicity, including

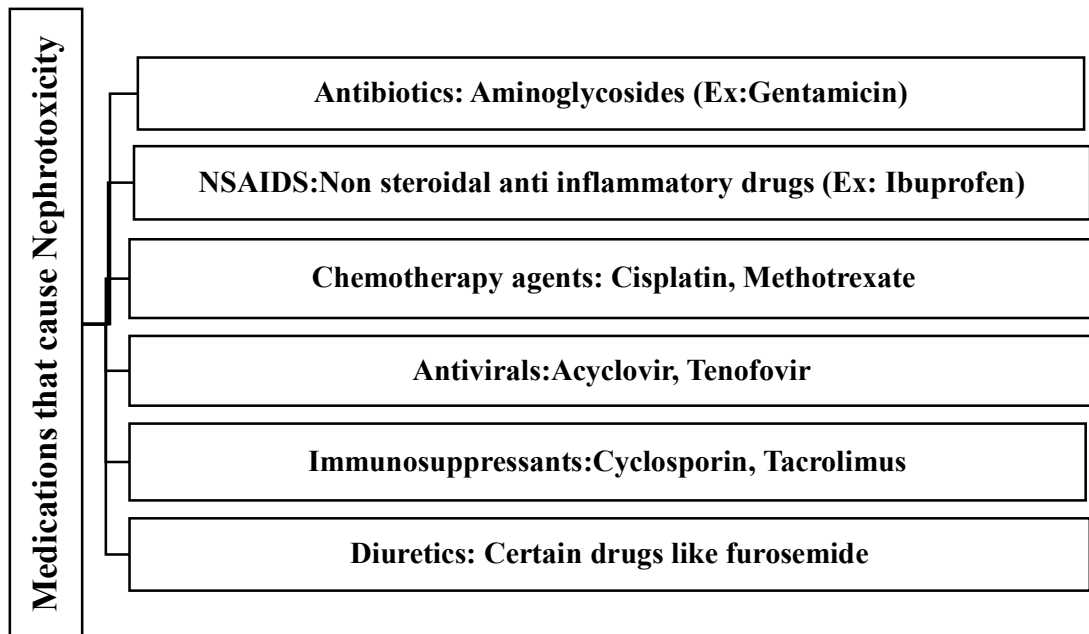


Fig 1: Medications that cause nephrotoxicity

Other causes that included in causing Nephrotoxicity are:

Toxins

- ❖ **Heavy metals:** Lead, mercury, arsenic.
- ❖ **Organic solvents:** Ethylene glycol (antifreeze), methanol.
- ❖ **Herbal and dietary supplements:** Certain herbs like aristolochic acid.

Infections

- ❖ **Bacterial infections:** Sepsis, pyelonephritis.

- ❖ **Viral infections:** Hantavirus, HIV.

Metabolic Disorders

Genetic Factors

- ❖ **Inherited kidney diseases:** Polycystic kidney disease, Alport syndrome.

Environmental Exposures

- ❖ **Industrial chemicals:** Pesticides, solvents.
- ❖ **Air pollutants:** Particulate matter, ozone.

High blood pressure

High blood pressure can damage blood vessels in the kidneys so they don't work as well. If the blood vessels in your kidneys are damaged, your kidneys may not work as well to remove wastes and extra fluid from your body. Extra fluid in the blood vessels may then raise blood pressure even more, creating a dangerous cycle [4].

Diabetes

Too much glucose, also called sugar, in your blood damages your kidneys' filters. Over time, your kidneys can become so damaged that they no longer do a good job filtering wastes and extra fluid from your blood.

Pathophysiology

Drugs in our systems are broken down via the kidneys, gastrointestinal system, and liver. There are two possible routes for the excretion of medicines and their metabolites: extra renal and renal. Focusing on renal excretion, medications can be removed through tubular secretion or glomerular filtration. The tubules and the surrounding interstitium are exposed to potentially hazardous chemicals along each excretion pathway. The substances produced into the tubular lumen can expose the (mostly proximal) tubules through apical contact, uptake by the tubular epithelial cells, or apical efflux from the peritubular circulation (the basolateral regions of the tubular cells) into the tubular lumen. The substances that are eliminated from the body through tubular secretion and glomerular filtration travel from the proximal tubule (PT) to the loop of Henle and ultimately to the distal tubule. Drugs may precipitate, crystallize, or form casts in the more distal portions of the tubules, resulting in tubular blockage. A further pathway involves the emergence of interstitial nephritis, which is caused by tubule interstitial inflammation.

To summarize, there are three mechanisms through which drug-induced nephrotoxicity arises:

1. A dose-dependent mechanism involving proximal tubular injury and acute tubular necrosis (ATN) through apical contact with drugs or their metabolites, drug transport from the apical surface, and drug secretion from the basolateral surface into the tubular lumen;
2. A dose-dependent mechanism involving tubular obstruction by crystals or casts containing drugs and their metabolites; and
3. A dose-independent mechanism involving interstitial nephritis brought on by drugs and their metabolites.

GM causes oxidative stress and generates reactive oxygen species and activates different types of cytokines via NF-κB. This results in insult of nephron as tubular necrosis, fibrosis, inflammation and damage of glomerulus (renal dysfunction).

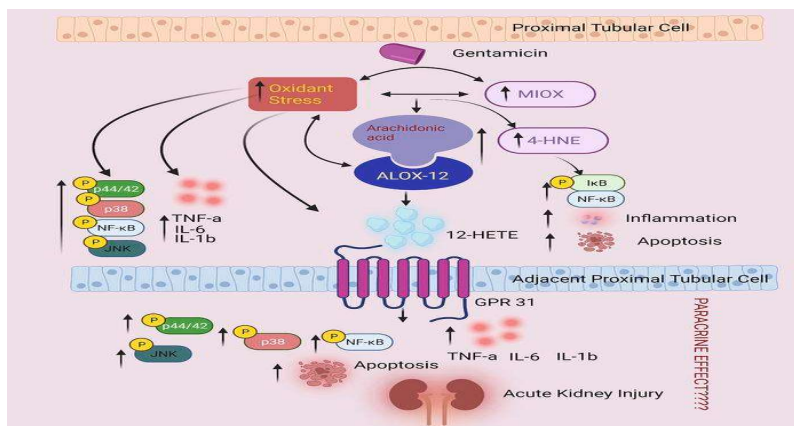


Fig 2: Gentamicin induced nephrotoxicity.

Herbal treatment

Herbal medicine (HM) has been widely used to treat diseases for thousands of years and has greatly contributed to the health of human beings. With the extensive use and deepening pharmacological research on HM, the adverse effects of HMs have also been determined. HM differs from western medicine, its side effects are considered slight, and it can be taken for a long time or at a large dose. Herbal medicine involves the use of natural compounds, which have relatively complex active ingredients with varying degrees of side effects [5].

According to the World Health Organization, traditional medicine is either the mainstay of medical treatment or serves as a complement to it in up to 75%–80% of the world population, mostly in the developing world. Demand for medicinal plants is increasing in both developing and developed countries.

Research on medicinal plants is one of the leading areas of research globally. A medicinal plant is any plant which, in one or more of its organs, contains substances that can be used for therapeutic purposes or which are precursors for the synthesis of useful drugs. Number of plants have been used in traditional medicine for many years. For thousands of years, medicinal plants have been used to treat human diseases. The value of medicinal plants and traditional health systems in resolving global health issues is becoming more widely recognized. The use of medicinal plants has had a mysterious strict significance and diverse viewpoints in relation to the concepts of health and infection that occurred within each culture during the evolution of human culture [6].

Plant-based drugs are becoming more common throughout the world. There have been significant advancements in the neuroprotective assessment of different plants used in traditional systems of medicine as a result of modern studies on medicinal plants or medicine. Medicinal plants have already played an important role in human health security, both in ancient and contemporary cultures. World Health Organization (WHO) reported that 80% of the earth's population rely on traditional medicine for their primary health care needs, and most of this therapy involves the use of plant extracts and their active components. The plant derived drugs in modern medicine has been connected to the uses of plant derivative materials as an indigenous cure in traditional system of medicine [7].

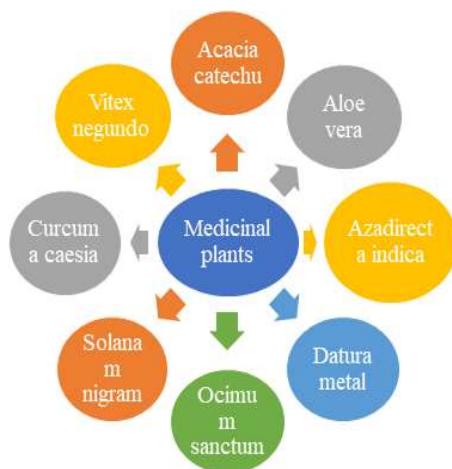


Fig 3: Some medicinal plants which are most commonly used in herbal drugs.

Nephroprotective agents are the substances which possess protective activity against nephrotoxicity. Medicinal plants have curative properties due to the presence of various complex chemical substances. Ancient literature has prescribed various herbs for the cure of kidney disease. Co-administration of various medicinal plants possessing nephroprotective activity along with different nephrotoxic agents may attenuate its toxicity [8]. The following are some of the medicinal plants reviewed possessing nephroprotective activity are:

Plants containing protective activity against gentamicin induced nephrotoxicity

Aegle marmelos

Aegeline, Aegelinine, Rutin, Sterol, β -sitosterol, β -D-glucoside, Mamesinine, Lupeol, Tannins, Phlobatannins, Flavonoids, Umbelliferone, Quercetin and Volatile oils.



Fig 4: *Aegle marmelos*

Nigella sativa

Alanine, L-Spinasterol, Arabic acid, Arginine, Amino acid, Asparagine, Aspartic acid, Carvone, Cystine, Cholesterol, Glutamic acid, Linoleic acid, Linolenic acid, Melanthin, Myristic acid, Oleic acid and Tannins [9, 10].



Fig 5: *Nigella sativa*

Solanum nigrum

Alkaloids, Reducing sugars, Glycosides, saponins, Steroids, Leutein, Lycopene, Vitamin-c, Glucose, Fructose, Caffeicolasodine, Tamatidenol, Solamargine, Solasomine, Trigogenine, Pottasium, Sulphur, Calcium and Phosphorous [11, 12].

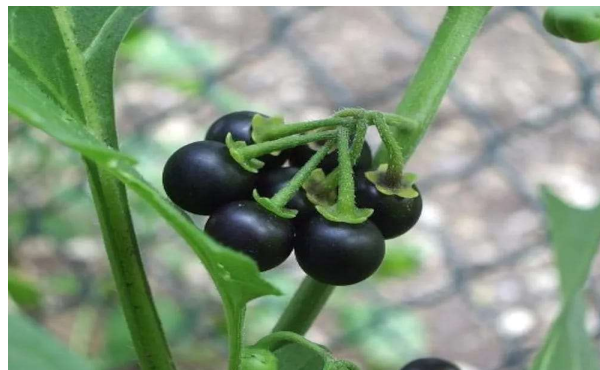


Fig 6: *Solanum nigrum*

Rhazya stricta

1-carbomethoxy- β -carboline, Condyloacarpine and Vincanicine.



Fig 7: *Rhazya stricta*

Nephroprotective Phyto constituents from Different Medicinal Plants

Aerva lanata

The ethanolic extract of *Aerva lanata* possesses marked nephroprotective activity with stripped toxicity because of the flavonol glycoside like kaempferol-3-rhamnoside & kaempferol-3-rhamnogalactoside which supplied a promising role within the treatment of acute nephritic injury caused by nephrotoxins like cisplatin and antibiotics [13, 14].



Fig 8: *Aerva lanata*

Andrographis paniculata

The nephroprotective effect of ethanol extract is due to the terpenoids like artemisia ketone, α -pinene, 1,8-cineole of *Artemisia annua* L [15, 16].

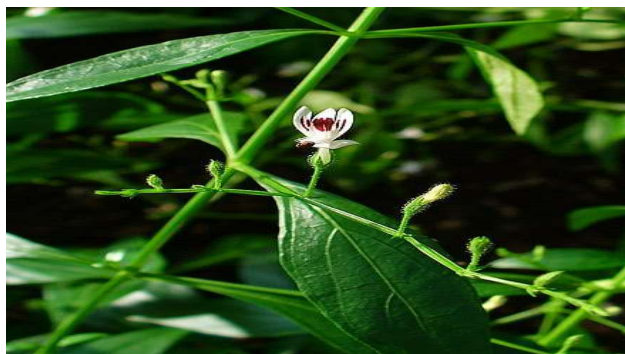


Fig 9: *Andrographis paniculata*

Berberis vulgaris

Berberine, an alkaloid is one of the active principles in *Berberis vulgaris* possessing the nephroprotective activity [17, 18].



Fig 10: *Berberis vulgaris*

Capsaicin

Once a chemical irritant capsaicin cream or ointment is employed on the skin (topical use), it helps relieve pain. It also strengthens respiratory organ tissues and facilitates to treat respiratory disorder. Modern research showed that capsaicin is also proven to have nephroprotective activity [19].



Fig 11: *Capsaicin*

Zingiber officinale

Ginger (*Zingiber officinale* Roscoe, *Zingiberaceae*) is one amongst the vital medicinal plant that naturally occurs in several country like Asian country, China, South East Asia, West Indies, Mexico and other parts of the planet. Aqueous and ethanolic extracts of *Zingiber officinale* contains Gingerols, which showed protective effect against anticancer drug doxorubicin-induced acute nephrotoxicity [20].



Fig 12: *Zingiber officinale*

Ramulus mori

Ethanollic extract of *Ramulus mori* showed nephroprotective effect because of active constituents like Rutin, Quercetin, Morin and mulberroside [21].



Fig 13: *Ramulus mori*

CONCLUSION

From this study, it is clear that many medicinal plants process significant Nephroprotective activity. Medicinal plants have shown significant potential in mitigating nephrotoxicity, a serious condition often induced by drugs, toxins, or disease. These plants, rich in bioactive compounds such as flavonoids, saponins, and alkaloids, offer protective effects through various mechanisms, including antioxidant activity, anti-inflammatory effects, and enhancement of renal function. The use of medicinal plants as an alternative or complementary approach to conventional treatments is promising, especially given their lower side effects. Medicinal plants may play an increasingly important role in the prevention and treatment of nephrotoxicity, potentially improving patient outcomes and reducing the burden of kidney-related diseases.

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