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REVIEW ARTICLE

NEPHROTOXICITY: AN OVERVIEW

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ABSTRACT

Nephrotoxicity is one of the most common situations faced by people due to easy availability of over the counter medication like NSAIDs, antibiotics and angiotensin converting enzyme inhibitors etc. There are various types of nephrotoxicities caused by various drugs like aminoglycosides nephrotoxicity, amphotericin B nephrotoxicity, cisplatin nephrotoxicity and herbal nephrotoxicity etc. So, experiments to discover nephroprotective agents are going on worldwide employing various animal models. Every year so many herbal drugs are experimentally proved to be possed nephroprotective activity. This present review is aimed to enlist various animal models employed in searching nephroprotective agents and some of the medicinal plants, which are scientifically proven in treating harmful effects of nephrotoxicity.

Keywords: Nephrotoxicity, Nephroprotective activity, Medicinal plants

INTRODUCTION:

Nephrotoxicity can be defined as renal disease or dysfunction that arises as a direct or indirect result of exposure to medicines, and environmental or industrial chemicals.[1] A number of therapeutic drugs can adversely affect the kidney resulting in acute renal failure, nephritic syndrome and chronic interstitial nephritis because there is an increasing number of potent therapeutic agents like aminoglycoside antibiotics, NSAID's, chemotherapeutic agents have been added to the therapeutic arsenal in recent years. [2]

The incidence of drug-induced nephrotoxicity has been increasing with the ever increasing number of drugs and with easy availability of over-the-counter medication *i.e.* non steroidal anti-inflammatory drugs (NSAIDs). Antibiotics, angiotensin converting enzyme inhibitors (ACEI) and contrast agents are the major culprit drugs contributory to kidney damage.[3]

About 6% of all hospital admissions can be attributed to adverse drug reactions, with nephrotoxicity accounting for 7% of all medication-related toxicities. The kidneys are routinely exposed to high concentrations of medications or their metabolites because their intrinsic function is to metabolize, concentrate, and excrete compounds. Therefore, it is not surprising that, as with prescribed medications, many dietary supplements have been associated with nephrotoxicity, either as a direct toxic effect, or secondary to liver dysfunction, rhabdomyolysis, or nephrolithiasis.[4]

Types of nephrotoxicities:

Aminoglycoside nephrotoxicity:

Aminoglycosides preferentially affect the proximal tubular cells. These agents are freely filtered and quickly taken up by the epithelial cells of proximal tubule, where they are incorporated into lysosomes after first interacting with phospholipids on the brush border membranes. They exert their main toxic effect within the tubular cell by altering phospholipid metabolism. In addition to their direct effect on cells, aminoglycosides cause renal vasoconstriction.[5]

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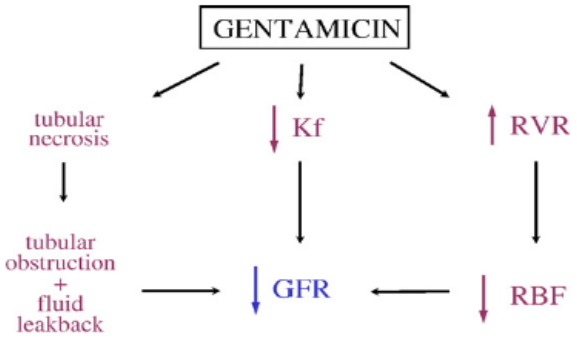

Figure 1: Schematic diagram showing the major mechanisms leading to glomerular filtration rate reduction by gentamicin. GFR: Glomerular filtration rate; Kf: Ultrafiltration coefficient; RBF: Renal blood flow; RVR: Renal vascular resistance.

Amphotericin-B nephrotoxicity:

Amphotericin B tends to bind to sterols in cell membranes, thereby creating pores that compromise membrane integrity and elevate membrane permeability. It binds not only to ergosterol in fungal cell walls but also to cholesterol in human cell membranes; this is what accounts for its nephrotoxicity.

Intratubular cast formation- Heme proteins are believed to be involved in the multiple segments of the renal tubule- namely, the proximal tubule, the medullary ascending limb of the loop of Henle, and the collecting duct. Characteristic electrolyte abnormalities include wasting of magnesium and potassium. The back-leak of hydrogen ions in the collecting duct leads to distal renal tubular acidosis (dRTA).[6, 7]

- **Calcineurin inhibitors nephrotoxicity**:

Cyclosporine and tacrolimus cause acute renal failure (ARF) by inducing afferent arteriolar vasoconstriction. These drugs cause ARF by inducing afferent arteriolar vasoconstriction. Persistent injury can lead to interstitial fibrosis. Tacrolimus has been shown to cause thrombotic microangiopathy as a result of endothelial injury.[8, 9]

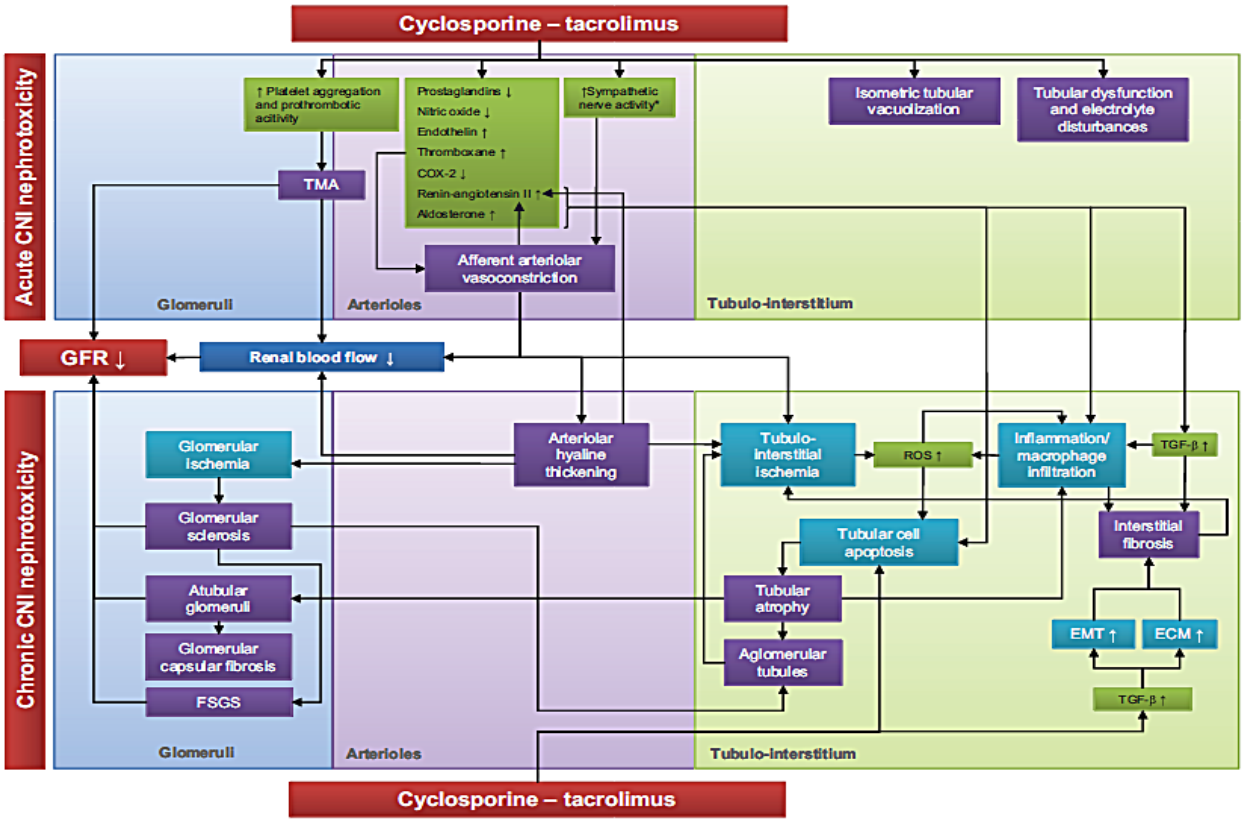

Figure 2: Schematic representation of the etiology of calcineurin inhibitor nephrotoxicity. CNI-Calcineurin inhibitor; TMA-Thrombotic microangiopathy; EMT-Epithelial mesenchymal transition; ECM- Extracellular matrix; GFR- Glomerular filtration rate; FSFS- Focal segmental glomerulosclerosis; ROS- Reactive oxygen species. *Only in native kidneys.

- **Cisplatin nephrotoxicity** –

Cisplatin usually affects the proximal and distal tubules. It causes the release of toxic hydroxyl radicals when chloride ions in the cis position are replaced by water. Characteristically, it is associated with urinary wasting of magnesium.[10]

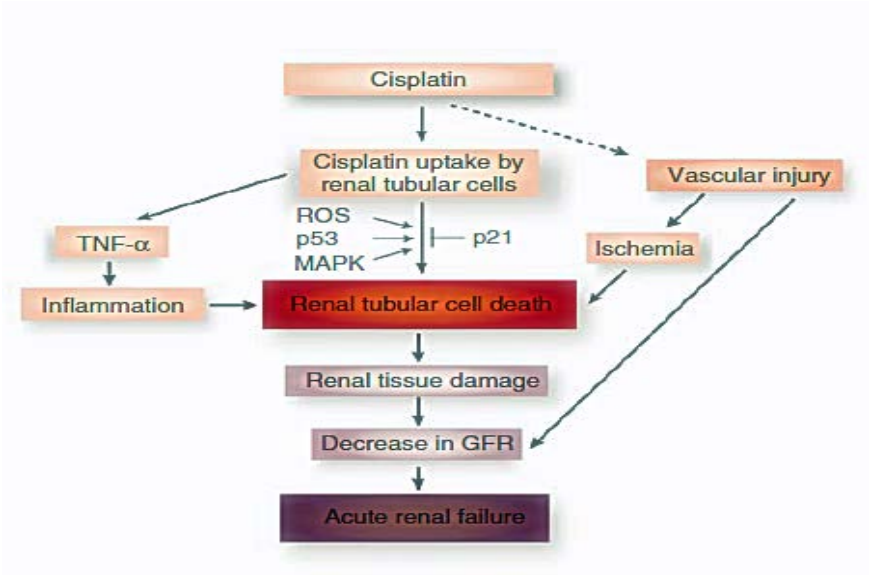

Figure 3: Overview of the pathophysiological events in cisplatin nephrotoxicity

- **Ifosfamide nephrotoxicity**- Ifosfamide is a known analog of cyclophosphamide. Although cyclophosphamide is not nephrotoxic, ifosfamide, by virtue of its metabolite chloroacetaldehyde, is nephrotoxic, with preferential involvement of the proximal tubule. [11,12]
- **Foscarnet nephrotoxicity**- Foscarnet, which is used to treat resistant cytomegalovirus (CMV) infections, causes intratubular crystal obstruction and acute interstitial nephritis. It is notable for inhibiting proximal tubular reabsorption of phosphate (leading to hypophosphatemia) by virtue of its being a phosphate analog. Chelation of calcium by foscarnet leads to hypocalcemia.[13]
- **Rhabdomyolysis**-

Rhabdomyolysis refers to the breakdown of skeletal muscle fibers, which leads to the release of potentially nephrotoxic intracellular contents into the circulation. ARF develops in this setting via the following 3 mechanisms-

- Renal vasoconstriction
- Heme-mediated proximal tubular epithelial cell toxicity
- Generation of reactive oxygen species (ROSs and intracellular enzymes) which are known to cause tubular injury through peroxidation of membrane lipid.[14]

- **Herbal nephrotoxicity**

Nephrotoxicity due to herbal medicines has been described. *Rhizoma rhei* extracts (contain anthraquiones), *Aristolochia manshuriensis* (contains aristolochic acid), cape aloes, and *Ajuga nipponensis* Maniko are known nephrotoxins. Herbal-induced renal toxicity may manifest by acute renal failure, metabolic acidosis, acute interstitial nephritis, rhabdomyolysis, and tubular dysfunction. Herbal medicines contaminated with heavy metals or adulterated with non-steroidal anti-inflammatory drugs (NSAIDs) and tubular dysfunction. Herbal medicines contaminated with heavy metals or adulterated with non-steroidal anti-inflammatory drugs (NSAIDs) also may induce acute renal failure.[15]

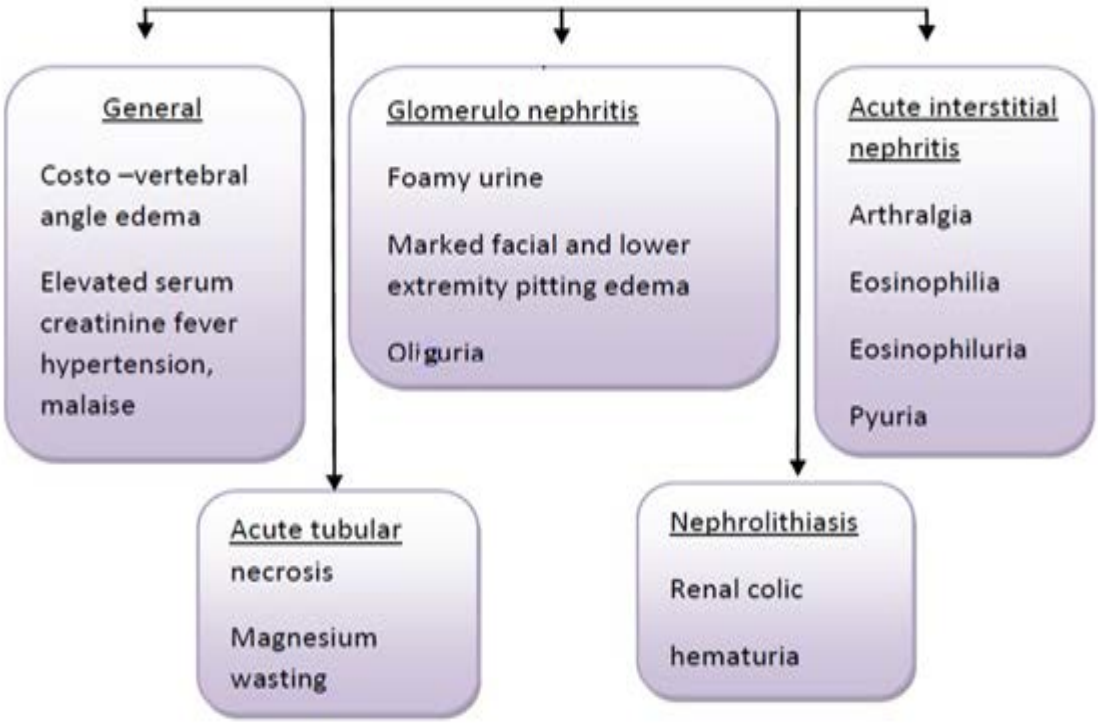

Figure 4: Clinical features of drug induced nephrotoxicity

Acute Renal Failure:

Acute renal failure (ARF) is characterized by a rapid, potentially reversible, decline in renal function including rapid reduction in glomerular filtration rate (GFR) and retention of nitrogenous waste products over a period of hours or days. The mortality rate of patient with ARF has remained 25-70% despite the use of various pharmacologic agents. Therefore, it continues to be a frequent threatening complication following trauma, complex surgical procedures, and in patients hospitalized in intensive care units (ICU). Acute renal failure can be induced in experimental animal by administration of various drug and chemicals, following are the extensively employed methods by which ARF can be induced in experimental animals-

1. **Glycerol**

Single dose of 8-10 ml/kg, i.m. used for induction of ARF

2. **Gentamicin**

Dose range 40–200 mg/kg for 4–10 days

Dose 100 mg/kg, i.p. for 5 days is more commonly used for the induction of ARF.

3. **Cisplatin**

Dose range 5–40 mg/kg, i.p. single dose

4. **NSAIDs**

Acetaminophen

Dose range 375–3000 mg/kg, i.p. single dose.

Dose 750 mg/kg, per oral and 600 mg/kg, i.p. single dose is more commonly used for the induction of ARF.

5. **Ifosfamide**

Dose range 50–1100 mg/kg, i.p. 1–5 days

Dose 550 mg/kg, i.p. single dose is more commonly used for the induction of ARF.

6. **Potassium dichromate**

Single dose 15 mg/kg, s.c. is used for the induction of ARF.

7. **Radiocontrast media**

Diatrizoate

Single dose range 2–10 ml/kg, i.v.

Dose 7 and 10 ml/kg, i.v. is more commonly used for the induction of ARF.[16]

Chronic renal failure (CRF) is an irreversible deterioration in the renal function which classically develops over a period of years, leading to loss of excretory metabolic and endocrine functions. Various causes of renal failure has been recognized like diabetes mellitus, hypertension, antineoplastic agents like cyclophosphamide, vincristin and cisplatin etc. Nephroprotective agents are the substances which possess protective activity against nephrotoxicity. Medicinal plants have curative properties due to the presence of various phytoconstituents.[2]

The following are some of the medicinal plants having nephroprotective activity, were already documented, employing various animal models of acute renal failure. These plants are very useful to cure and prevent the various types of nephrotoxicities.

Table 1: List of plants having nephroprotective property[17-32]

Sr. No.	Botanical Name	Common name	Part used	Extract/Preparation used	Screening model used
1.	*Boerhaevia difffusa*	Rakta Punarnava	Roots	Kwath	Gentamicin
2.	*Citrus aurantium*	Bitter orange	Fruit peel	Ethanolic extract	Gentamicin
3.	*Clitoria ternatea*	Butterfly pea	Aerial parts	Ethanolic extract	Acetaminophen
4.	*Curcuma longa*	Haldi	Rhizome	-	Cisplatin
5.	*Cymbopagon citrate*	Lemon grass	Leaf	Aqueous extract	Cisplatin
6.	*Houttuynia cordata*	E-Sung-Cho	Whole plant	Methanolic extract	Gentamicin
7.	*Indegofora tinctoria* (*Avuri kudineer*)	Indigo plant	Leaf	Decoction	Cisplatin
8.	*Merremia emarginata*	Aakhu parni	Leaf	Ethanolic extract	Cisplatin
9.	*Moringa oleifera*	Moringa, drumstick tree	Leaf	Ethanolic extract	Streptozotocin
10.	*Moringa pterygosperma*	Drumstick tree, Sahjan	Leaf	Ethanolic extract	Paracetamol
11.	*Ocimum basilicum*	Damaro	Herb	Hydroalcoholic extract	Cisplatin
12.	*Pedalium murex*	Gokhru	Dry fruits	Ethanolic extract	Cisplatin
13.	*Peucedanum grande*	Wild carrot	Seed and fruits	Methanolic extract	Potassium dichromate
14.	*Pseudocedrela kotschyi*	Emi-gbegi, Tuna	Roots	Ethanolic extract	Alloxan
15.	*Tribulus terrestris*	Gokshur	Fruits	Kwath	Gentamicin
16.	*Vernonia amygdalina*	Bitter leaf	Leaf	Ethanolic extract	Streptozotocin
17.	*Vitex nugundo*	Five leaved chaste tree	Bark	Methanolic extract	paracetamol
18.	*Zingiber zerumbet*	lempoyang or wild ginger	Rhizome	Methanolic extract	Paracetamol

Guidelines to preventing drug-induced nephrotoxicity:

In brief, prevention is the best clinical approach to drug-induced nephrotoxicity, which starts with the recognition that drug-induced renal injury occurs and is seen predominantly in patients at risk. The following steps are necessary-

✓ Anticipate. Be aware of nephrotoxic potential of specific drugs.

✓ Identify patients at risk (those with renal insufficiency, salt-retaining states, dehydration, diabetes, and multiple myeloma).

✓ Avoid dehydration mandatorily in high-risk patients. Pretreatment hydration is very important.

✓ Be aware of increased risk in elderly patients.

✓ Carefully assess the benefits of prescribed drugs against potential risk.

✓ Whenever possible, select diagnostic procedures or therapeutic measures without nephrotoxic potential.
✓ Avoid a combination of potentially nephrotoxic drugs.
✓ Limit total daily dosage and duration of treatment with certain drugs.
✓ Adjust the daily dosage to ongoing changes in the GFR.
✓ Urinary alkalinization to prevent renal failure from methotrexate, sulphonamides, triamterene, etc.[1]

CONCLUSION:

Nephrotoxicity is the most common problem for the mankind. The aim of this review is to provide information regarding nephrotoxicity and its treatment. The herbal treatment is safer because no side effect is induced by this. The study will be fruitful for the researcher who wants to search new herbal treatment for nephrotoxicity.

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