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"Nurturing the Kidneys: Exploring the Therapeutic Power of Traditional Medicinal Plants in Renal Health"

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Abstract : The following review highlights various medicinal plants known for their nephroprotective and nephrocurative properties against drug-induced nephrotoxicity, a prevalent kidney issue triggered by exposure to certain medications or toxins. Common therapeutic drugs like antibiotics, chemotherapeutic agents, and NSAIDs can impair kidney function, leading to conditions such as acute renal failure, chronic interstitial nephritis, and nephritic syndrome. Throughout history, traditional medicine has utilized numerous herbs with nephroprotective effects, owing to their rich phytoconstituents and bioactive compounds. This review presents examples of medicinal plants and their nephroprotective compounds, primarily belonging to 12 different dicotyledonous families. Seeds and leaves are frequently utilized parts of these plants for treating renal disorders. Phenols, flavonoids, and various terpenes (mono-, di-, and sesqui-) are identified as common bioactive compounds present in these plants. The phytochemical analysis of these plants underscores the presence of sesquiterpenoids, flavonoids, phenols, steroids, and alkaloids, which exhibit diverse biological activities, including potent nephroprotective effects. Extracts from these plants have demonstrated significant dose-dependent nephroprotective and nephrocurative activities within the range of 5–600 mg/body weight.

IndexTerms - nephroprotective effect, phytoconstituents, nephrocurative, phytochemical analysis, cardiac output, nephrotoxin

I. INTRODUCTION:

Throughout history, humans have encountered various potentially harmful conditions and substances in both natural and occupational settings. Among the organs, the kidneys hold paramount importance in the elimination of metabolic byproducts and toxins from the body. Several physiological characteristics make the kidneys particularly susceptible to damage, including their high metabolic activity, significant endothelial surface area relative to weight, concentration of filtered chemicals in tubular fluid, and substantial blood flow, accounting for approximately 20–25% of total cardiac output.

Nephrotoxicities commonly manifest as acute or chronic tubular injuries, with recognized syndromes such as acute renal failure (ARF), chronic renal failure (CRF), chronic interstitial nephritis, and nephritic syndrome. ARF signifies a sudden and severe reduction in glomerular filtration rate, often reversible with prompt treatment. Tubular necrosis, primarily caused by ischemia or toxins, is a well-recognized trigger of ARF. CRF, a leading cause of mortality in India, develops gradually over years, resulting in irreversible loss of endocrine and metabolic functions.

Renal cell death plays a pivotal role in nephrotoxicity, impacting various components of the nephron—the fundamental structural and functional unit of the kidney. Consisting of millions of nephrons, each nephron collaborates to maintain vital kidney functions. Any form of renal cell death along the nephron can lead to alterations in tubules, glomeruli, interstitium, and intra-renal blood vessels, ultimately impairing kidney function Mechanisms underlying nephrotoxin-induced renal cell death involve oxidative stress, proximal tubule necrosis, disruption of brush border membrane and polarity, altered glomerular filtration rate (GFR), and changes in renal blood flow.

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II. NEPHROTOXIC AGENTS AND NPHROPATHIES :

Nephrotoxicity stands as a prevalent kidney ailment characterized by renal disease or dysfunction resulting from direct or indirect exposure to harmful drugs, industrial, or environmental chemicals. The kidneys, owing to their concentration and excretory functions, are particularly vulnerable to the impact of environmental toxins. These toxins inflict damage upon the kidneys, disrupt electrolyte balance (notably potassium and magnesium levels), and impede their ability to eliminate excess urine and waste from the body. A multitude of exogenous and endogenous toxic agents, including illegal abortifacients, antineoplastic agents, antibiotics, and prolonged exposure to heavy metals, contribute to the onset of these conditions. The following categorizes some significant nephrotoxic agents.

2.1 Metals :

Mercury and the elemental mercury vapor, both are nephrotoxic causing necrosis of the proximal tubular cells and ARF. Bismuth causes oliguric ARF along with tubular dysfunction and necrosis. Lithium commonly causes polyuria along with distal renal tubular acidosis. Lead slowly gives rise to tubular injury causing chronic interstitial nephritis with fibrosis. Gold may cause nephrotic syndrome often with hematuria. Membranous immune complex nephropathy can be expected. Thallium is associated with albuminuria, ARF, tubular necrosis, and interstitial inflammation. Barium inhibits potassium exit from the cells causing severe hypokalemia.

2.2 Nonsteroidal Anti-inflammatory Agents (NSAIDs) :

The major nephropathies due to NSAIDs such as ibuprofen, indomethacin, aspirine cause interstitial nephritis, pre-renal/renal ARF, K+ retention, and hypertension.

2.3 Solvents :

Major solvents include carbon tetrachloride (CCl 4), tetrachloroethylene, and toluene. CCl4 within the proximal tubules of the kidney is converted to trichloromethyl and trichloromethylperoxyl free radicals. These free radicals cause direct renal tubular injury and cellular necrosis hypertension.6 Toluene causes hippuric acidosis, high anion gap acidosis, distal renal tubular acidosis, and severe hypokalemia. Tetrachloroethylene poisoning causes ARF from tubular necrosis.

2.4 Glycols :

Ethylene glycol when metabolized to glycolic acid and oxalic acid results in the deposition of calcium oxalate crystals within renal tubules. This causes obstruction and acute renal failure. Crystals also produce severe interstitial inflammation evoking hematuria, proteinuria, followed by oliguria or anuria.

2.5 Antineoplastic Agents

These include alkylating agents, antimetabolites, nitrosoureas, radiocontrast agents, and antitumor antibiotics.18 Cisplatin is a potent antitumor alkylating drug, but its clinical use is limited due to renal toxicity. Cisplatin has been reported to decrease antioxidants and antioxidant enzymes, causing enhanced production ROS metabolites and lipid peroxidation.

III. BIOCHEMICAL MECHANISM FOR DRUG-INDUCED NEPHROTOXICITY :

Nephrotoxicity, based on biochemical and molecular events, can be categorized into three major stages.

I. **Initiation Phase** The toxins interact with the critical biological molecules, such as proteins, lipids, RNA, and DNA causing functional inactivation of these molecules. The toxicant may have reversible (charge–charge interactions) or irreversible (covalent binding) interaction with the biomolecules resulting in different types of propagation. Lipid peroxidation, generation of ROS, and free radicals is initiated as a consequence of such interactions. This produces a strong effect on membrane permeability, fluidity, integrity, and other membraneassociated membrane processes.

II. **Propagation Phase** The toxicant–biomolecular interaction disrupts several biomolecular pathways that may or may not be reversible. A recovery can occur if the injury stimulus is removed. Pathogenesis of renal cytotoxicity includes increase in cytosolic free Ca2+ concentration and ATP depletion. This induces cellular blebbing and alterations in cytoskeleton and integral membrane proteins.

III. **Termination Phase** The primary insult by a toxin ultimately leads to cell necrosis. The toxins impair cell organelles and disrupt plasma membrane causing leakage of cellular contents. Oxidative stress creates a hypoxic cellular state due to vasoconstriction, ultimately causing damage to the kidney at cellular level and renal cell death.

Pharmacological Reports

1. ***Azadirachta indica A. Juss.*** An experiment was made to investigate the effects of leaves of methanolic extract of A. indica on cisplatin-induced nephrotoxicity in rats. The results confirmed that the organic extract effectively rescues the kidney from cisplatin-induced mediated oxidative damage. Further, the polymerase chain reaction results for caspase-3 and caspase-9 and Bax genes showed downregulation in methanolic leaves extract of A. indica–treated groups. The leaf extracts were also capable of normalizing the levels of malondialdehyde (MDA), nitric oxide (NO) production, and enzymatic and nonenzymatic antioxidants.

2. ***Senna auriculata (L.) Roxb. syn. Cassia auriculata*** The ethanolic extract of C. auriculata roots exhibited nephroprotective activity against cisplatin- and gentamicininduced renal injury in male albino rats at doses of 300 and 600 mg/ kg body weight, respectively. The free-radical scavenging property attributed to nitric oxide and abundant reserve of antioxidants account for the plants nephroprotection activity.

3. ***Boerhaavia diffusa L***. 10% aqueous extract of B. diffusa leaves was tested against mercuric chloride–induced toxicity in male Wistar albino rats at a dose of 200 mg/kg body weight. Administration of B. diffusa leaves extract to mercuric chloride treated rats reverted the biochemical losses to near normal and caused a significant increase in the level of renal marker enzymes. This observed nephroprotective activity exhibited by B. diffusa leaves extract is accredited to the presence of antioxidant defense system and phytochemicals such as alkaloids, phenols, tannins, flavonoids, glycosides, and thiols.

4. ***Achyranthus aspera L.*** Methanolic extract of A. aspera was administered to male albino Wistar rats to evaluate its nephroprotective property against lead acetate-induced nephrotoxicity at a dose of 200 mg/kg body weight. The methanolic extract mitigated major signs of leadinduced nephrotoxicity (hypertrophy of total kidney mass, tubular damage, and enzyme losses), improved thiol status, and reduced oxidative stress in blood and kidney tissues. This reversal of renal damage is due to non-alkaloid fractions, immunostimulatory compounds found in root extract, and antioxidant property of A. aspera.

5. ***Annona reticulata L***. Nephroprotective activity of ethanolic extract of aerial parts of Annona reticulata was evaluated against gentamicin and cisplatininduced renal toxicity in male Wistar rats at the concentration of 250 mg/kg p.o. and 500 mg/kg p.o, respectively. On evaluating biochemical parameters, it was found that animal groups treated with ethanolic extract of A.reticulata showed significant decrease (p value < 0.001) in concentration of serum urea, creatinine, uric acid, total protein and urine urea, uric acid, and creatinine compared to both gentamicin- and cisplatin-treated groups. Physiological parameters of body weight, kidney weight urine volume, and pH also improved in treatment groups. Histopathological results reveal that plant extract at dose of 500 mg/kg (curative) have protective effect on gentamicin-induced nephrotoxicity. Phytochemical investigation reported the major chemical constituents of the ethanol extract to be acetogenins, alkaloids, flavonoids, proteins, carbohydrates, etc.

IV. DISCUSSION

In developing countries, reliance on herbal medicines persists not only due to their perceived safety but also because the expenses associated with modern pharmaceuticals often exceed the means of many individuals. As the Western medical system struggles to provide effective treatments for numerous complex metabolic renal diseases, medicinal plants continue to offer a promising avenue. These plants harbor phytocompounds that confer nephroprotection through various mechanisms of action. The metabolic breakdown of drugs within cells generates harmful free radicals, leading to lipid peroxidation initiated by superoxide ions, ultimately causing oxidative damage to membrane lipids and altering kidney structure and function.

The intricate interplay between oxidative stress and inflammation in renal diseases plays a pivotal role in processes culminating in renal cell death. These toxic agents diminish the levels of antioxidants crucial for organ protection and the removal of reactive oxygen species. Cumulative evidence from renal function tests, antioxidant assays, and histopathological examinations indicates that rats treated with plant extracts experience significant protection against drug-induced acute nephrotoxicity. Notably, observed outcomes such as improved renal parameters, reduced renal lipid peroxidation, elevated levels of renal antioxidant enzyme markers, and restoration of normal histological features underscore the antioxidant-mediated defense against renal oxidative stress and the onslaught of free radicals.

S. no.	Common name	Botanical name	Family	Part used	Bioactive compound
Antinephrotoxicity activity					
1	Neem (E), Limba (L)	*Azadirachta indica* A. Juss.	Meliaceae	Stem, bark, leaves	Azadirachtin, nimbolide
2	Tanner's Cassia, Avaram (E) Tarwad (L)	Senna auriculata (L.) Roxb.syn. *Cassia auriculata*	Fabaceae	Flower, buds	Flavonoids, phenol
3	Spreading hog weed (E), Punarnava (L)	*Boerhaavia diffusa* L.	Nyctaginaceae	Whole plant	Alkaloid trianthemine, nicotinic, ascorbic acid
4	Chirchira (L), SafedAghedo(E)	*Achyranthes aspera* L.	Amaranthaceae	Whole plant	Achyranthine, betaine, tannins, Glycosides
5	Custard apple(E), Bullock's-heart(L)	*Annona reticulata* L.	Annonaceae	Leaf	Phenols, steroids, tannins, alkaloids

Table 1.1

Phytochemical investigations of all the reviewed plants demonstrated presence of flavanoids, phenols, phenolic acid, glycoproteins, sterols, kaempferols, alkaloids, terpenoids, tannins, glycosides, saponins, catechins, terpins (monoterpene, sesquiterpene, and triterpene) and phenyl propanoid as chief phytoconstituents.

V. CONCLUSION

There are several nephrotoxic agents (heavy metals, solvents, pesticides, and NSAID's) that cause nephrotoxicity (renal damage and necrosis). In this review, a sincere attempt has been made to enlist various plants with nephroprotective properties mentioned in traditional system of medicine. All the plants studied were found potent to prevent the nephrotoxicity and other nephropathies associated with them. The study subatantiate and confirms the ethno medical usefulness of the reviewed plants as nephroprotective and antioxidant agents. The review also provides an insight into the multitude prospects and perspectives of traditional system of medicine in the management of renal diseases. Further research on details of efficacy and safety studies especially on human subjects is recommended.

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