REVIEW ARTICLE

Nephroprotective and Therapeutic Potential of Traditional Medicinal Plants in Renal Diseases

Kavita Negi[1], Asma Mirza[2]

Abstract

Aim and objective: The present review enlists some medicinal plants possessing nephroprotective and nephrocurative activity against drug-induced nephrotoxicity.

Background: Nephrotoxicity, one of the most common kidney problems, occurs when the body is exposed to a drug or toxin. A number of therapeutic drugs such as antibiotics, chemotherapeutic agents, and NSAIDs can weaken the kidney function resulting in acute renal failure, chronic interstitial nephritis, and nephritic syndrome. Many herbs possess nephroprotective properties due to presence of several potent phytoconstituents and other chemical compounds. Many herbs and their formulations have been used in traditional system of medicine to cure kidney disorders since millennia without any side effects. This review presents classical examples of some medicinal plants and nephroprotective compounds present in them.

Review results: Based on the plethora of evidences presented for the plant-derived nephroprotective agents, the plants reviewed belonged to 12 different families (dicotyledons). The seeds and leaves have been largely reported to treat renal disorders Phenols and flavonoids were observed as the common bioactive compounds along with terpenes (mon-, di- and sesq-) of different classes.

Conclusion: The phytochemical review of different plants reveals the presence of many bioactive compounds such as sesquiterpenoids, flavonoids, phenols, steroids, and alkaloids with different biological activities. These compounds possess potent nephroprotective properties.

Clinical significance: The extracts of the plants reviewed exhibited significant dose-dependent nephroprotective and nephrocurative activity (5–600 mg/body weight).

Keywords: Nephroprotective activity, Nephroprotective agents, Renal diseases, Traditional medicine.

Journal of Drug Research in Ayurvedic Sciences (2020): 10.5005/jdras-10059-0079

Introduction

Humans have always been exposed to several potentially toxic conditions and toxic agents in their natural and occupational environments. The kidneys are the most vital organs of the human body which are involved in the excretion of metabolic substances and toxic waste from the body.[1] Certain physiological features of the kidneys such as high-metabolizing activity, largest endothelial surface by weight, highest concentration of filtered chemicals in tubular fluid, and extensive blood flow (20–25% of the total cardiac output) to the organ also contribute to its high vulnerability toward toxins.[2]

Most nephrotoxicities can lead to acute or chronic tubular injury, although the majorly recognized syndromes of toxic renal injury include acute renal failure (ARF), chronic renal failure (CRF), chronic interstitial nephritis, and nephritic syndrome.[3] Acute renal failure (ARF) is the sudden severe reduction in the glomerular filtration rate which can be reversed if treated. The widely recognized cause of ARF is tubular necrosis, occurring chiefly due to ischemia or toxins.[4] Chronic renal failure (CRF) is the major cause of death in India with a prevalence of 7,852 per million.[5] CRF develops over a period of years, instituting a permanent loss of endocrine and metabolic functions.[6] Renal cell death is crucial to nephrotoxicity, involving changes in the nephrons. A typical kidney is composed of millions of nephrons, which form the structural and functional unit of the organ. These nephrons work in tandem to ensure the vital functions of the kidney.[7] Renal cell death along any part of the nephron induces changes in the tubules, glomeruli, interstitium, and intra-renal blood vessels, thereby impairing the kidney function.

[1]Division Botany, Central Council for Research in Unani Medicine, Ministry of AYUSH, New Delhi, India

[2]Drug Standardization Research Unit, Central Council for Research in Unani Medicine, Ministry of AYUSH, New Delhi, India

Corresponding Author: Kavita Negi, Division Botany, Central Council for Research in Unani Medicine, Ministry of AYUSH, New Delhi, India, Phone: +91 7579473610, e-mail: negikavita123@gmail.com

How to cite this article: Negi K, Mirza A. Nephroprotective and Therapeutic Potential of Traditional Medicinal Plants in Renal Diseases. J Drug Res Ayurvedic Sci 2020;5(3):175–183.

Source of support: Nil

Conflict of interest: None

Nephrotoxin-induced mechanism for renal cell death includes oxidative stress, proximal tubule necrosis, loss of brush border membrane and polarity, altered glomerular filtration rate (GFR), and renal blood flow.[8]

Nephrotoxic Agents and Nephropathies Associated with Them

Nephrotoxicity is one of the most common kidney problems and can be defined as a renal disease or dysfunction occurring when our body indirectly or directly gets exposed to harmful drugs and industrial or environmental chemicals.[9] Due to the concentrating ability and excretory function, kidneys become highly susceptible to the effects of environmental toxins.[10] These toxins damage the kidneys, elevate the blood electrolytes (potassium and magnesium),

and render them unable to rid the body of excess urine and wastes.[11,12] Several exogenous and endogenous toxic agents such as illegal abortifacients, antineoplastic agents, antibiotics, and long-term exposure to heavy metals are responsible for the manifestation of these diseases.[13] The following are the important well-known nephrotoxic agents which can be divided under the following groups:

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.[14]

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

The major nephropathies due to NSAIDs such as ibuprofen, indomethacin, aspirin cause interstitial nephritis, pre-renal/renal ARF, K+ retention, and hypertension.[4,15]

Solvents

Major solvents include carbon tetrachloride (CCl_4), tetrachloroethylene, and toluene. CCl_4 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.[16]

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.[17]

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.[19]

Aminoglycosides

Gentamicin, amikacin, kanamycin, and streptomycin have been widely used for treating gram-negative bacterial infections. However, their nephrotoxicity and ototoxicity are the major limitations in clinical use. Gentamicin-mediated nephrotoxicity causes tubular necrosis, generation of ROS, non-oliguric renal failure, with slow yet significant rise in serum creatinine and hypo-osmolar urinary output.[18,19]

Antimicrobial Agents

Tetracycline, acyclovir, pentamidine, sulfadiazine, trimethoprim, and rifampicin.[16]

Biochemical Mechanism for Drug-induced Nephrotoxicity

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

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 membrane-associated membrane processes.[20]

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 Ca^{2+} concentration and ATP depletion. This induces cellular blebbing and alterations in cytoskeleton and integral membrane proteins.[21]

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.[20,21]

Factors Associated with Renal Injury

Factors associated with kidney injury are primarily dependent on exposure to the potential nephrotoxic drug, underlying patient characteristics, and interaction of kidneys with such harmful substances. Some combinations of these risk factors explain the variability and heterogeneity observed with drug-induced nephrotoxicity.[22]

Drug

Exposure to a potential toxic agent forms the initial step in the development of renal injury. Many drug characteristics and medications cause renal injury through various mechanisms. Innate direct cell toxicity occurs in conditions of high doses and prolonged courses of drugs (such as aminoglycosides, colistin and amphotericin B) causing excessive exposure to nephrotoxicants, even in patients with minimal or no risk.[23] Crystalline nephropathy is associated with drug and metabolite insolubility in urine (such as methotrexate, acyclovir, and sulfadiazine). The precipitated crystals cause interstitial inflammation in addition to obstructing urinary flow. Intracellular accumulation of certain drugs (such as, sucrose, dextran, and hydroxyethyl starch) due to lack of metabolizing enzymes induce osmotic nephropathy. Such drugs accumulate within the tubular cells causing lysosomal dysfunction and cell swelling.[24]

Patient

There are several patient-specific underlying factors that increase the risk of drug-induced nephrotoxicity. Older age and female sex are the nonmodifiable risk factors leading to excess drug dosing. Females are associated with decreased lean body mass and reduced total body water subjecting them at greater risk of nephrotoxicity. Similarly, the elderly individuals are at an increased propensity to vasoconstriction.[25] A patient's underlying genetic composition can also enhance the vulnerability of kidneys to potential nephrotoxins. This is because the metabolism, drug transporters, elimination, and repair pathways vary between patient populations due to different genetic makeup. Genetic alterations in immune system may produce inflammatory injury and thereby augment the risk to medication-induced nephrotoxicity. Comorbid conditions, such as liver diseases, heart diseases, and acutely developed metabolic perturbations, like hypokalemia, hypocalcemia, and hypomagnesemia, are also important risk factors for drug-induced nephrotoxicity in the form of acidosis, alkalosis, nephrolithiasis, and intratubular crystal deposition.[26]

Kidney

The metabolic and excretory pathways of kidney to remove toxins are the important factors that enhance risk for drug-induced nephrotoxicity. High rate of renal blood flow and excessive cellular activity within a hypoxic environment make the organ more susceptible to renal injury. High concentration of medications, metabolites, and reactive oxygen species (ROS) affect local antioxidants and induce tubular injury. Extensive cellular uptake of potential nephrotoxins via apical and basolateral transportation routes also increases renal toxicity.[26,27]

According to WHO, over 80% of the world population relies on traditional medicine for their primary healthcare needs.[28] Traditional medicine continues to provide health coverage for over 80% of the world's population, especially in the developing world.[29] To overcome the problem of increased resistance and side effects of pharmaceutical drugs, the demand for safer and cheaper plant-based therapeutics has been increased.

Medicinal plants possess abundant phytochemicals, such as alkaloids, carotenoids, and several phenolic compounds, which exhibit antioxidative effect. Due to their therapeutic properties, these plants are considered as a healthy alternative for treating oxidative stress–related conditions and therefore can be used for treating various kidney disorders.[27,28] The antioxidants found in plants have been reported to ameliorate oxidative-induced kidney damage by enhancing the free radical scavenging mechanism and reducing lipid peroxidation in the body.

Angiosperms, since ancient times, have been used for the management of kidney disorders in the conventional system of medicine all over the world.[30] It has been reported that 61 plant families and 143 species are nephroprotective and effective in renal diseases. In all, 85% of plants are diuretic in nature, 10% are used to treat burning micturition, and 6.3% aid against stone formation.[31]

Materials and Methods

A comprehensive literature search was done, and information on the present review article has been extracted from different online databases, namely, PubMed, BioMed Central, Science Open, SCOPUS, Google scholar, etc. The data collected are arranged in the table regarding different plant's scientific names, local names, and their bioactive constituents. The pharmacological reports focus on the dose of the different plant extracts against nephrotoxicity caused by various chemical agents in the animal system.

Pharmacological Reports

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.[30]

Senna auriculata (L.) Roxb. syn. *Cassia auriculata*

The ethanolic extract of *C. auriculata* roots exhibited nephroprotective activity against cisplatin- and gentamicin-induced 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.[31]

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.[32]

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 lead-induced 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*.[33]

Annona reticulata L.

Nephroprotective activity of ethanolic extract of aerial parts of *Annona reticulata* was evaluated against gentamicin and cisplatin-induced 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. Acetogenins and alkaloids are known to provide nephroprotective activity and cytotoxic effects. Hence, the collective presence of acetogenins and alkaloids in the ethanol extract could be attributed to the observed significant nephroprotection against these toxicants.[34]

Biophytum Sensitivum (L.) DC

Aqueous and methanolic extract of *B. sensitivum* where evaluated for where antinephrotoxicity in Wistar albino rats at a dose of 200 mg/kg. Nephrotoxicity, induced by gentamicin which, is characterized by elevated levels of urea and creatinine in plasma as well as urine. Oral administration of the extract brought down the elevations of serum urea and creatinine produced by Gentamicin and reverted histopathological changes in the kidneys to normal. Nephroprotective activity of *B. sensitivum* extract may be attributed mainly due to the presence of saponins, as it possesses anticrystallization and anti-urolihiatic properties. Significant antioxidant property of the extract is due to the presence of bioactive phytoconstituents such as amentoflavone, a bioflavonoid with trace amounts of cupressoflavone, luteolin, isoorientin, and isovitexin. Hence, these combined effects of *B. sensitivum* extract protects against gentamicin-induced renal injury.[35]

Cichorium intybus L.

The nephroprotective effects of *C. intybus* (aqueous and ethanolic extract) were evaluated against gentamicin-induced nephrotoxicity. Both aqueous and ethanolic extracts of *C. intybus* were administered at 3.4 mg/kg orally. Important kidney markers such as serum urea and urea creatinine were found to decrease significantly with the administration of test drug. Histopathological examination depicted normal glomerular and tubular histology with reduced tissue necrosis and slight blood vessel congestion. The effect of aqueous extract of plant was reported to be better than methanolic extracts. The plant root has been reported to be a storehouse of kaempferol, quercetin-3 galactoside, and bioflavonoids. These phytoconstituents possess antioxidant property, the likely mechanism of nephroprotection from oxidative stress. Hence *C. intybus* extract demonstrates significant nephroprotective activity by decreasing the level of two important kidney function markers and reverting the structural integrity of kidney to near normal.[36]

Foeniculum vulgare Mill

Aqueous seed extract of *F. vulgare* was evaluated for its nephroprotective and nephrocurative properties against gentamicin (GM)-induced toxicity in male Albino rats the rate of 200 mg/kg/oral. Gentamicin caused structural change in the kidney and alters the renal circulation leading to reduced glomerular filtration rate (GFR). Administration of *F. vulgare* seed extract abolished nephrotoxic effects of GM-induced toxicity. Possible mechanism for renal protection is attributed to the free radical scavenging and antioxidant activity of the phenolics and flavonoids components found in the seed extract.[37]

Solanum nigrum L.

Aqueous extract of the fruits *of S. nigrum* were evaluated for their nephroprotective and nephrocurative properties against gentamicin-induced toxicity in male albino rats the rate of 200 mg/kg/oral. Gentamicin-induced oxidative stress caused kidney hypertrophy in treated animals. The administration of aqueous extract significantly prevented renal damage by normalizing increased levels of renal markers. Amelioration of the histopathological changes induced by gentamicin was observed along with reduction in oxidative stress biomarkers. Hence, it is suggested that ameliorative effect of aqueous extract Solanum nigrum may be attributed to their antioxidant anti-inflammatory properties. The presence of alkaloids have been reported to inhibit lipid peroxidation and renal damage.[37]

Lantana camara L.

Nephroprotective activity of methanolic extract of *L. camara* was evaluated against cisplatin-induced nephrotoxicity in male Wistar albino rats. Methanolic extract of *L. camara* exhibited potential nephroprotective effects at doses of 100 to 400 mg/kg.b.wt by reducing the levels of renal parameters to near normal. Histopathological examination depicted the effect of the extract on renal antioxidant enzymes. HPLC-ESI-MS analysis of *L. camara* extracts exhibited bioactive phenolic compounds including phenyl ethanoid, flavonoids and phenolic acids. These phyto-constituents show a positive correlation with the plant's nephroprotective activity.[38]

Musa sapientum L. Syn. *M. paradisiaca* L.

The nephroprotective activity of methanolic extract of different parts of *M. paradisiaca* viz., bract, flower, trachea and tracheal fluid against gentamicin-induced nephrotoxicity in mice was reported.[39] The methanolic extract of bract (100 and 250 mg/kg, body weight) and flowering stalk (trachea) (250 and 500 mg/kg, body weight) significantly prevented biochemical and histological changes produced by gentamicin toxicity.[40]

Pimpinella anisum L.

Nephroprotective activity of aqueous extract of seeds of *P. anisum was* evaluated in Wistar rats against gentamicin-induced nephrotoxicity. Different concentrations of seed extract (1, 2 and 4 g/kg body weight) were administered orally to different animal groups. The aqueous extract of test drug exhibited protective effects at all doses by reducing the levels of serum urea, creatinine, uric acid, and blood urea nitrogen when compared to gentamicin-treated group. This significant reduction in biochemical parameters is supported by histopathological evaluation. Concurrent administration of *P. anisum* extract appeared to preserve the tubular histology and mitigate the severity of the gentamicin-induced renal necrosis. Phytochemical screening revealed the presence of polyphenolic compounds, such as flavonoids, tannins, and phenolic acids as major components. These compounds act as hydrogen donors and thus neutralize the free radicals arising as a product of lipid peroxidation. This free radical scavenging activity and antioxidant property are responsible for its preventive and therapeutic effects on renal injury.[39]

Rheum emodi Wall.ex Meissn

The renal effects of water-soluble and water-insoluble fractions of the alcoholic extract of *R. emodi* were determined on cadmium chloride, mercuric chloride, potassium dichromate, and gentamicin-induced nephrotoxicity in rats by monitoring the levels of urea nitrogen and creatinine in serum. Water-insoluble fraction has nephroprotective effect on all the proximal tubule segments

possibly through antioxidant action of the tannins present in the fraction.[41]

Tamarindus indica L.

The methanolic extracts of various parts, the fruit pulp, stem bark, fruit bark, and seeds, showed the most effective nephroprotective potential against CCl_4-induced nephrotoxicity in albino rats at 10 mg/kg body weight (intraperitoneal pretreatment). This study exhibited significant (p value = 0.05) decrease in urea and creatinine levels in the extracts treated groups when compared to control groups. The organ protective and therapeutic effects exhibited by different parts of *T. indica* may be ascribed to the phytoconstituents groups present in them. Methanolic extracts of plant parts have been reported to have polyphenols with a profile dominated by proanthocyanidins, epicatechins, catechins, and procyanidins.[42]

Tribulus terrestris L.

Evaluation of the nephroprotective activities of the ethanolic plant extract, petroleum ether, dichloromethane, aqueous, and methanol extracts of *T. terrestris* against CCl–-induced nephrotoxicity was done in adult Wistar rats. The best effect was observed with 95% ethanol extract at 400 mg/kg on the urea and creatinine levels. Both malondialdehyde and non-protein sulfhydryl groups in kidney tissues were improved to levels comparable to those obtained by silymarin.[43]

Curculigo orchioides Gaertn

The role of *C. orchoides* against cyclophosphamide (CPA)-induced urotoxicity and nephrotoxicity was evaluated in Swiss albino mice at doses of 20 mg/kg of body wt. The plant extract was able to significantly reduce the serum level in the kidneys by the production of antioxidants and pro-inflammatory cytokines.[44]

Hemidesmus indicus (L.) R. Br. ex Schult.

The extracts of *H. indicus* and *Acorus calamus* protected the renal tissue effectively from cisplatin-induced toxicity. The combination of plant drugs used for the treatment of cisplatin-administered animals from oxidative damage in the renal tissue as evidenced from the decreased levels of lipid peroxidation and enhanced activities of the antioxidants in the renal tissue.[45]

Aloe vera (L.) Burm.f

Administration of *A. vera* at different doses (200–600 mg/kg) to albino rabbits decreased diclofenac sodium and silymarin-induced nephrotoxicity. Extracts of *A. vera* exhibited ameliorative effects on BUN and serum creatinine levels (p value <0.05 significance) and produced significant positive results at different graded doses. Histopathalogical studies also showed normal renal parenchyma in treated groups. These results showed that *A. vera* can normalize the effects of oxidative stress and can be used as an effective nephroprotective agent against drug-induced nephrotoxicity.[46]

Elephantopus scaber L.

Ethanolic extract of *E. scaber* leaves was evaluated for its nephroprotective activity against gentamicin-induced nephrotoxicty. The extract was administered in male albino Wistar rats at a dose of 200–600 mg/kg/day for 7 days. Biochemical assays of renal parameters and histopathological examination of kidney cells were evaluated. The extract significantly (p value < 0.01) decreases the levels of serum creatinine, total protein, and serum urea but shows slightly increase on the electrolyte levels in a dose dependent manner. The nephroprotective effects of *E. scaber* are possibly due to flavonoid content and the inherent antioxidant moieties found in the extract.[47]

Acorus calamus L.

Details given above (attached with *Hemidesmus indicus*).[45]

Dolichos biflorus L.

Hydro-alcoholic extract of *D. biflorus* seeds was tested for its antinephrolithiatic and antioxidant efficacy against ethylene glycol–induced nephrolithiasis. The extract was administered in adult female Wistar rats for 28 days at a concentration of 150 and 300 mg/kg body weight. Ethylene glycol also caused a significant increase in lipid peroxidation and decrease in antioxidant enzyme activity in kidney (p value < 0.001). Biochemical parameters of urine as well as of kidney were increased, whereas a decrease in calcium, sodium, and magnesium in serum was observed (p value < 0.001). The administration of seed extract caused a significant restoration of all these parameters (p value < 0.001). These results indicated that the *D. biflorus* seed extract has significant prophylactic effect in preventing nephrolithiasis. *D. biflorus* has been reported to contain a number of flavonoids, which are highly effective scavengers of singlet oxygen and free radicals implicated in renal diseases. These flavonoids effectively combat with oxidative stress imposed by hyperoxaluria, possibly mediated through antioxidant activity.[48]

Cucurbita pepo L.

Nephroprotective activity of methanolic extract of *C. pepo* was evaluated against cisplatin-induced nephrotoxicity in male Wistar albino rats at doses of 100 to 400 mg/kg.b.wt. C. pepo led to significant reduction in the levels of serum urea and creatinine as well as Mg ions values, whereas Na and K significantly increased compared to the toxic group. Histopathological examination depicted protective effect against degenerative kidney injury caused by cisplatin. HPLC-ESI-MS analysis of *C. pepo* extracts exhibited bioactive phenolic compounds, namely, phenolic acid derivatives, favonoids, phenylethanoids, and iridoids. These phyto-constituents show a positive correlation with the plant's nephroprotective activity.[39]

Combretum micranthum G. Don

Antioxidant and nephroprotective activities of *C. micranthum* were evaluated *ex vivo* in male Wistar albino rats against glucose induced toxicity in kidney cells. Exposure of kidney cells to high glucose (100 mM) for 72 hours significantly reduced the cell viability resulting in morphological changes, such as cell shrinkage, rounded cell shape, and cytoplasmic vacuolation. Treatment with the extract at 10 and 25 µg/ mL resulted in significant improvement in cell viability from 10–23% compared to the high glucose control. Hydroalcoholic extract of *C. micranthum* exhibited strong antioxidant activity by scavenging AAPH, DPPH, nitric oxide, hydrogen peroxide, and chelating metal ions. Considerable lipid peroxidation inhibiting activity in kidney tissue homogenate was also observed. Phytochemical investigation reconfirmed the presence of flavonoids, terpenoids, steroids, and alkaloids with many biological activities.[49]

Discussion

People in developing countries rely on herbal medicines not only because they are considered safe but also because the costs associated with modern medicines fall beyond the reach of many people. Medicinal plants could still be exploited as the Western world fails to provide drugs of cure to many complex metabolic renal diseases. These phytocompounds associated with medicinal plants give an overview of nephroprotection occurring through diverse mechanisms of actions.

The intracellular metabolism of drugs leads to the formation of toxic free radicals. Lipid peroxidation occurs as a result of normally produced superoxide ion forming hydroxyl radicals. This in turn causes oxidative deterioration of polyunsaturated lipids of membranes and modification of kidney structure and function.[50] The interlinking mechanisms of oxidative stress and inflammation in renal diseases have been shown to play key role in processes leading to renal cell death. These toxic agents reduce the concentration of antioxidants which protect the organ and remove reactive oxygen species.[51] The results of renal function tests, antioxidant assays, and histopathological examinations together exposited suggests that rats treated with plant extracts were significantly protected from drug-induced acute nephrotoxicity.[52] For instance, attenuation of renal parameters, reduction in renal LPO, elevation in renal antioxidant enzyme markers, and restoration of normal histological features supports the antioxidant-mediated defense against renal oxidative stress and free radical assaults (Table 1).[52,53]

Table 1: List of nephroprotective plants and their bioactive compounds used in traditional system of medicine

S. no.	*Common name*	*Botanical name*	*Family*	*Part used*	*Bioactive compound*	*References*
Antinephrotoxicity activity						
1	Neem (E), Limba (L)	*Azadirachta indica* A. Juss.	Meliaceae	Stem, bark, leaves	Azadirachtin, nimbolide	30
2	Tanner's Cassia, Avaram (E) Tarwad (L)	*Senna auriculata* (L.) Roxb.syn. *Cassia auriculata*	Fabaceae	Flower, buds	Flavonoids, phenol	31
3	Spreading hog weed (E), Punarnava (L)	*Boerhaavia diffusa* L.	Nyctaginaceae	Whole plant	Alkaloid trianthemine, nicotinic, ascorbic acid	32
4	Chirchira (L), SafedAghedo(E)	*Achyranthes aspera* L.	Amaranthaceae	Whole plant	Achyranthine, betaine, tannins, Glycosides	33
5	Custard apple(E), Bullock's-heart(L)	*Annona reticulata* L.	Annonaceae	Leaf	Phenols, steroids, tannins, alkaloids	34
6	Little tree plant(E), Lajalu (L)	*Biophytum sensitivum* (Linn.) DC	Oxalidaceae	Whole plant	C-glycosyl flavones, proanthocynidin	35
7	Kasmi(E), Chicory (L)	*Cichorium intybus* L.	Asteraceae	Seeds, roots	Inulin, coumarins(chicoriin,esculetin,esculin,umbel-iferon,scopoletin).	36
8	Fennel (E), Saunf (L)	*Foeniculum vulgare* Mill.	Apiaceae	Seeds	Volatile oil, fenchone and methylchavicol, flavonoid	37
9	black nightshade(E), Mokoi (L)	*Solanum nigrum* L.	Solanaceae	Leaf	Solanine, solamargine, Spirostanol glycoside – uttrosides A, B	37
10	wild-sage (E), Kuri(L)	*Lantana camara* L.	Verbenaceae	Leaf	Lantanine, phellandrene, diterpene, eugenol	38
11	Banana (E), Kela (L)	*Musa sapientum* L. Syn. *M. paradisiacal*	Musaceae	Rhizome, pulp of fruit	Vitamin C, Vitamin B, starch, fructose	40
12	Anise (E), (L)	*Pimpinella anisum* L.	Apiaceae	Root	Estragol, γ-himachalene and trans-anethole	39
13	Himalayan Rhubarb (E), Rewanchini (L)	*Rheum emodi* Wall. exMeissn	Zygophyllaceae	Root	Emodin, monomethyl, ether, tannin, aloe emodinrhein	41
14	Tamarind Tree (E), Imli (L)	*Tamarindus indica* L.	Fabaceae	Seeds	Flavone C-glycosides-orientin, vitexin, lauric acid and stearic acid,	42
15	Small Caltrops (E), Chota-gokhru (L)	*Tribulus terrestris* L.	Zygophyllaceae	Fruit	Diosgenin, gitogenin,chlorogenin, ruscogenin, kaempferol, rutin	43

Contd…

Contd…

S. no.	*Common name*	*Botanical name*	*Family*	*Part used*	*Bioactive compound*	*References*
Chronic renal failure (CRF) or chronic kidney disease (CKD)						
16	Black musale (E), Kali musli (L)	*Curculigo orchioides* Gaertn.	Hypoxidaceae	Root	Phenols, steroids	44
17	Indian sarsaparilla (E), Anantmool (L)	*Hemidesmus indicus* (L.) R. Br. ex Schult.	Periplocaceae	Root	Essential oil, starch, coumarin, tannic acid, triterpenoidsaponins	45
18	Aloe (E), Chinna-kata (L)	*Aloe vera* (L.)Burm.f	Xanthorrhoeaceae	Pulp of plant	Aloin	46
19	Prickly Leaved Elephant's wood (E) Cahndeasr (L)	*Elephantopus scaber* L.	Asteraceae	Whole plant root	Elephantopin	47
20	Kinkeliba (E), Senegal (L)	*Combretum micranthum* G.Don	Combertaceae	Leaves	Flavonoids, tannins, phenols	49
Kidney stone						
21	Sweet flag (E), Bach (L)	*Acorus calamus* L.	Araceae	Rhizome	α-and β-asarones	48
22	Horse gram (E), kulthi (L)	*Dolichosbiflorus* L.	Fabaceae	Seeds	Pentosan, vitamin A, vitamin C, phytosterols	36 and 48
23	Pumpkin (E), kaddu (L)	*Cucurbita pepo* L.	Cucurbitaceae	Seeds	Triterpenoids, ent-kauranetype diterpene, and cucurbitaglycosides	40

E = English; L = Latin

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.[54,55] It is well documented that these compounds exhibit significant antioxidant, free radical scavenging, and nephroprotective activities Therefore, the study of plants as a source of medicine has become more significant.

Conclusion

There are several nephrotoxic agents (heavy metals, solvents, pesticides, and NSAIDs) 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 substantiate 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.

References

1. Newman T, Biggers A, What do the kidneys do? Medical News Today. 2018; https://www.medicalnewstoday.com/articles/305488.php.
2. Soderland P, Lovekar S, Weiner DE. Chronic kidney disease associated with environmental toxins and exposures. Adv Chronic Dis 2010;17(3):254–264. DOI: 10.1053/j.ackd.2010.03.011.
3. Hoitsma AJ, Wetzels JF, Koene RA. Drug-induced nephrotoxicity. Aetiology, clinical features and management. Drug Saf 1991;6(2):131–147. DOI: 10.2165/00002018-199106020-00004.
4. Misurac JM, Knoderer CA, Leiser JD, et al. Nonsteroidalanti-inflammatory drugs are an important cause of acute kidney injury in children. J Pediatr 2013;162(6):1153–1159. DOI: 10.1016/j.jpeds.2012.11.069.
5. Siddiqi A, Alam SS, Begum S, et al. Evaluation of therapeutic potential of *Picrorhiza kurroa* glycosidal extract against nimesulide nephrotoxicity: a pilot study. J Ayub Med Coll 2015;27(2):312–313.
6. Cooksey C. Health concerns of heavy metals and metalloids. Sci Prog 2012;95(1):73–88. DOI: 10.3184/003685012X13286247093244.
7. Arany I, Kaushal GP, Portilla D, et al. Cellular mechanisms of nephrotoxicity. Clinical Nephrotoxins. Boston: Springer; 2008. pp. 155–170.
8. Barnett LMA, Cummings BS. Nephrotoxicity and renal pathophysiology: a contemporary perspective. Toxicol Sci 2018;164(2):379–390. DOI: 10.1093/toxsci/kfy159.
9. World Health Organization, Principles and methods for the assessment of nephrotoxicity associated with exposure to chemicals, United Nations Environment Programme International Labour Organisation, and the World Health Organization, Geneva. 1991.
10. Yang CS, Su T, Li XM. Aristolochic acid nephropathy: variation in presentation and prognosis,. Nephro Dial Transplant 2012;27(1):292–298. DOI: 10.1093/ndt/gfr291.
11. Sebastian S. Handbook of toxicology of chemical and warfare agents 2009. pp. 268–270.
12. Salgado MC, López HFJ, López-Novoa JM. Glomerular nephrotoxicity of aminoglycosides. Toxicol. Appl Pharmacol 2007;223(1):86–98. DOI: 10.1016/j.taap.2007.05.004.
13. Benjamin AV, D'Haese PC, Verhulst A. Environmental toxin induced acute kidney injury. Clin Kidney J 2017;10(6):747–758. DOI: 10.1093/ckj/sfx062.
14. Gheshlaghi F. Toxic renal injury at a glance. J Renal Inj Prev 2012;1(1):15–16. DOI: 10.12861/jrip.2012.07.
15. Zimmerman JL. Cocaine intoxication. CritCareClin 2012;28(4):517–526. DOI: 10.1016/j.ccc.2012.07.003.

16. Prakash J, Sen D, Kumar NS, et al. Acute renal failure due to intrinsic renal diseases: review of 1122 cases. Ren Fail 2003;25(2):225–233. DOI: 10.1081/JDI-120018723.
17. Vaya KR, Sharma A, Singhvi IJ, et al. Nephroprotective plants: a review. J Biosci Tech 2017;8(1):801–812.
18. Lakshmi MS, Reddy U, Sandhya, et al. A review on medicinal plants for nephroprotective activity. Asian J Pharm Clin Res 2012;5(4):14.
19. Commandeur J, Vermeulen PN. Molecular and biochemical mechanisms of chemically induced nephrotoxicity: a review. Chem Res Toxicol 1990;3(3):171–194. DOI: 10.1021/tx00015a001.
20. Niemann CU, Serkova NJ. Biochemical mechanisms of nephrotoxicity: application for metabolomics. Expert Opin Drug Metab Toxicol 2007;3(4):527–544. DOI: 10.1517/17425255.3.4.527.
21. Volarevic V, Djokovic B, Jankovic GM, et al. Molecular mechanisms of cisplatin-induced nephrotoxicity: a balance on the knife edge between renoprotection and tumor toxicity. J Biomed Sci 2019;26(1):25. DOI: 10.1186/s12929-019-0518-9.
22. Kandasamy K, Su R, Huang P, et al. Prediction of drug-induced nephrotoxicity and injury mechanisms with human induced pluripotent stem cell-derived cells and machine learningmethods. Sci Rep 2015;5(1):12337. DOI: 10.1038%2Fsrep12337.
23. Ashour M, Teresa F, Pisani A, et al. Molecular mechanisms of renal cellular nephrotoxicity due to radiocontrast media. Biomed Res Int 2014;2014:10. DOI: 10.1155/2014/249810.
24. Perazella AM. Renal vulnerability to drug toxicity. CJASN 2009;4(7):1275–1283. DOI: https://doi.org/10.2215/CJN.02050309.
25. Droz S, Laughlin MK. Use of xenopus frogs to study renal development/repair. Kidney Dev Dis 2017;60:70–107.
26. Fahamiya N, Shiffa MSM, Farzana MUZN, Renal tonics (Muqawwi-e-Gurda) mentioned in traditional medicine with recent advancements-a review. 2018. file:///C:/Users/Acer/AppData/Local/Packages/Microsoft.MicrosoftEdge_8wekyb3d8bbwe/TempState/Downloads/Renaltonics.pdf.
27. Naggayi M, Mukiibi N, Iliya E. The protective effects of aqueous extract of *Carica papaya* seeds in paracetamol induced nephrotoxicity in male Wistar rats. Afr Health Sci 2015;15(2):598–605. DOI: 10.4314/ahs.v15i2.37.
28. Bharti D, Raghunath T, Kumar MZ, et al. Plants: A review. Int J Pharm Pharm 2012;4:8–16.
29. Srinivasan KK, Mathew JE, D'Silva KJ, et al. Nephroprotective potential of *Graptophyllum pictum* against renal injury induced by gentamicin. Iran J Basic Med Sci 2015;18(4):412–416.
30. Mohammad AA. Therapeutics role of *Azadirachta indica* (neem) and their active constituents in diseases prevention and treatment. J Evid Based Compl Altern Med 2016. 1–11.
31. Annie S, Rajagopal PL, Malini S. Effect of *Cassia auriculata* root extract on cisplatin and gentamicin-induced renal injury. Phytoemdicine 2005;12(8):550–560. DOI: 10.1016/j.phymed.2003.11.010.
32. Indhumathi T, Shilpa K, Mohandass S. Evaluation of nephroprotective role of *Boerhaavia diffusa* leaves against mercuric chloride induced toxicity in experimental rats. J Pharm Res 2011;4(6):1848–1850.
33. Jayakumar T, Sridhar MP, Bharathprasad TR, et al. Experimental studies of *Achyranthes aspera* (L) preventing nephrotoxicity induced by lead in albino rats. J Health Sci 2009;55(5):701–708. DOI: 10.1248/jhs.55.701.
34. Devi MARL, Deepika MY, Nagaraju B, et al. Evaluation of nephroprotective activity of ethanolic extracts of *Annona reticulata* in gentamicin and cisplatin induced nephrotoxicity in rats. Int J Pharm Sci Res 2016;8(9):995.
35. Chandavarkar S, Desai SM, Gautam G. Nephroprotective activity of different extracts of *Biophytum sensitivum* (Linn.) DC. Int J Herb Med 2017;5(1):31–34.
36. Zaman R, Alam A, Jafri MA, et al. Nephroprotective effect of Beekh Kasni (roots of *Cichorium intybus*) in the form of methanolic and aqueous extract in gentamycin induced rat models. J Pharmacogn Phytochem 2017;6(3):337–341.
37. Shaheen U, Manzoor Z, Khaliq T, et al. Evaluation of nephroprotective effects of *Foeniculum vulgare* Mill, *Solanum nigrum* Linn. and their mixture against gentamicin-induced nephrotoxicity in albino rats. Int J Pharm Sci Rev Res 2014;25(1):1–9.
38. Abdel-Hady H, El-Sayed MM, Abdel-Hady AA, et al. Nephroprotective activity of methanolic extract of *Lantana camara* and squash (*Cucurbita pepo*) on cisplatin-induced nephrotoxicity in rats and identification of certain chemical constituents of *Lantana camara* by HPLC-ESI-MS. Pharmacognosy Journal 2018;10(1):136–147. DOI: 10.5530/pj.2018.1.24.
39. Abbas K, Rizwani GH, Zahid H, et al. Evaluation of nephroprotective activity of *Musa paradisiaca* L. in gentamicin-induced nephrotoxicity. Pak J Pharm Sci 2017;30(3):881–890.
40. Aiswarya N, Chandran V, TeerthanathS, et al. Nephroprotective effect of aqueous extract of *Pimpinella anisum* in gentamicin induced nephrotoxicity in Wistar rats. Pharmacogn J 2018;10(3):403–407. DOI: 10.5530/pj.2018.3.66.
41. Malik MA, Bhat SA, Fatima B, et al. *Rheum emodi* as a valuable medicinal plant. Int J Gen Med Pharm 2016;5:35–44.
42. Liman ML, Sunday EA. Hepatoprotective and nephroprotective effects of methanolic extract of different parts of *Tamarindus indica* Linn in rats following acute and chronic carbon tetrachloride intoxication. Annu Res Rev Biol 2015(2):109–123. DOI: 10.9734/ARRB/2015/8838.
43. Zaman R, Alam A, Choudhry SS, et al. Nephroprotective agents used in Unani medicine-an evidence based approach. J Nephrol Therapeut 2017(03):15–16. DOI: 10.4172/2161-0959.1000296.
44. Murali VP, Kuttan G. *Curculigo orchioides* Gaertn effectively ameliorates the uro- and nephrotoxicities induced by cyclophosphamide administration in experimental animals. Integr Cancer Ther 2016;15(2):205–215. DOI: 10.1177/1534735415607319.
45. Chakrabortty S, Choudhary R. *Hemidesmus indicus* (Anantmool): rare herb of Chhattisgarh. Indian J Sci Res 2014;4(1):89–93.
46. Iftikhar A, Hasan IJ, Sarfraz M, et al. Nephroprotective effect of the leaves of *Aloe barbadensis (Aloe vera*) against toxicity induced by diclofenac sodium in albino rabbits. West Indian Med J 2015;64(5):462.
47. Ho WY, Ky H, Yeap SK, et al. Traditional practice, bioactivities and commercialization potential of *Elephantopus scaber* Linn. J Med Plants Res 2009;3:1212–1221.
48. Saha S, Verma RJ. Antinephrolithiatic and antioxidative efficacy of *Dolichos biflorus* seeds in a lithiasic rat model. Pharma Biol 2015;53(1):16–30. DOI: 10.3109/13880209.2014.909501.
49. Kpemissi M, Eklu-Gadegbeku K, Veerapur VP, et al. Antioxidant and nephroprotection activities of *Combretum micranthum*: a phytochemical, in-vitro and ex-vivo studies. Heliyon 2019;5(3):1365. DOI: 10.1016/j.heliyon.2019.e01365.
50. Nasri H, Rafieian-Kopaei M. Kidney tubular cell protection; recent findings. Iran J Pediatr 2014;24(6):781–783.
51. Sadeghian MM, Mortazaienezhad F. Investigation of compounds from *Azadirachta indica* (neem). Asian J Plant Sci 2007;6(2):444–445. DOI: 10.3923/ajps.2007.444.445.
52. Ketkarand YC, Ketkar M. Various uses of neem products Schmutterer H, ed. The Neem Tree. Weinheim, Germany: John Wiley & Sons; 2004. pp. 518–525.
53. Hossain MA, Toubi-Al W, Weli AMR QA, et al. Identification and characterization of chemical compounds in different crude extracts from leaves of omani neem. J TaibahUnivSci 2013;7(4):181–188. DOI: 10.1016/j.jtusci.2013.05.003.
54. Huang A, Vita JA, Venema RC, et al. Ascorbic acid enhances endothelial nitric-oxide synthase activity by increasing intracellular tetrahydrobiopterin. J Biol Chem 2000;275(23):17399–17406. DOI: 10.1074/jbc.M002248200.
55. Nagaraj M, Sunitha S, Varalakshmi P. Effect of lupeol, a pentacyclictriterpene, on the lipid peroxidation and antioxidant status in rat kidney after chronic cadmium exposure. J Appl Toxicol 2000;20(5):413–417. DOI: 10.1002/1099-1263(200009/10)20:5<413::AID-JAT706>3.0.CO;2-Y.

हिंदी सारांश

रीनल रोगों में पारंपरिक औषधीय पादपों का नेफ्रोप्रोटेक्टिव और चिकित्सीय प्रभाव

उद्देश्य: वर्तमान समीक्षा ड्रग-इण्ड्यूज्ड नेफ्रोविषाक्तता के विरुद्ध नेफ्रोप्रोटेक्टिव और नेफ्रोक्यूरेटिव गतिविधि दर्शाने वाले कुछ औषधीय पादपों की सूची दर्शाती है।

पृष्ठभूमि: नेफ्रोविषाक्तता, एक बहुत ही सामान्य किडनी समस्या है, जो औषध या विषाक्त पदार्थ के संपर्क में आने से होती है। कुछ चिकित्सीय औषधियां यथा एंटीबायोटिक्स, कीमोथेराप्यूटिक एजेंट्स और नॉनस्टेरोइडल एंटीइन्फ्लेमेटरी औषधियां (एनएसएआईडी) किडनी की कार्यक्षमता को कमजोर कर सकती हैं, जिसके कारण एक्यूट रीनल फेल्यूर (एआरएफ), क्रोनिक इंटर्स्टीशियल नेफ्राईटिस और नेफ्राईटिक सिंड्रोम होता है। बहुत सी जड़ीबूटियां विभिन्न प्रभावकारी फाइटोकोंस्टीट्यूएंट्स और अन्य रासायनिक औषधयोगों की उपस्थिति के कारण नेफ्रोप्रोटेक्टिव गुणकर्म दर्शाती हैं। सदियों से, बिना किसी दुष्प्रभाव के पारंपरिक चिकित्सा पद्धति में प्रयोग की जाने वाली बहुत सी जड़ीबूटियों और औषधयोगों का प्रयोग किडनी विकारों को ठीक करने में किया जाता है। यह समीक्षा इनमें उपस्थित कुछ औषधीय पादपों और नेफ्रोप्रोटेक्टिव औषधयोगों के शास्त्रीय उदाहरणों को दिखाती है।

समीक्षा परिणाम: पादप से लिए गए नेफ्रोप्रोटेक्टिव एजेंट्स से प्राप्त बहुत से साक्ष्यों के आधार पर, समीक्षा वाले पादप 12 विभिन्न परिवारों (दिवबीजपत्री) से संबंधित हैं। रीनल विकारों के उपचार में बीजों और पत्तियों का व्यापक प्रयोग किया गया है। विभिन्न श्रेणियों के टरपींस (mon-, dii- और sesq-) के साथ सामान्य बायोएक्टिव औषधयोग के रूप में फिनोल्स और फ्लेवोनोइड्स को देखा गया।

निष्कर्ष: विभिन्न पादपों की फाइटोकेमिकल समीक्षा विभिन्न जैविक गतिविधियों के साथ सेस्क्युटरपेनोइड्स, फ्लेवेनोइड्स, फिनोल्स, स्टेरोइड्स और एल्केलोइड्स जैसे बहुत से बायोएक्टिव औषधयोगों की उपस्थिति दिखाती है। इन औषधयोगों में प्रभावकारी नेफ्रोप्रोटेक्टिव गुणकर्म हैं।

नैदानिक प्रासंगिकता: समीक्षय पादपों के एक्सट्रेक्ट (5-600 मिलिग्राम/ शरीर भार), सार्थक मात्रा-आधारित नेफ्रोप्रोटेक्टिव गतिविधि को दर्शाते हैं।

मुख्य शब्द: नेफ्रोप्रोटेक्टिव गतिविधि, नेफ्रोप्रोटेक्टिव एजेंट्स, रीनल रोग, पारंपरिक औषधियां।