

REVIEW

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Drug-induced nephrotoxicity and its reversal using botanicals of traditional Indian medicine in different animal models: way forward

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Abstract

Background Acute kidney injury (AKI) and chronic kidney disease (CKD) pose significant global health challenges, often worsened by the use of certain therapeutic agents and exposure to environmental toxins. This review aims to explore the nephroprotective role of botanicals, specifically focusing on the damage to kidneys caused by prolonged use of modern medicines and environmental toxicants.

Main body of the abstract This review provides a detailed overview of Traditional Indian Medicinal Plants (TIMP), highlighting their botanical components and the potential mechanisms through which they offer nephroprotection in cases of chronic kidney disease. The analysis includes existing research studies on the nephroprotective effects of these plants, particularly in the context of both acute and chronic kidney diseases. Findings suggest that botanicals derived from TIMP hold promising potential for developing nephroprotective therapies.

Short conclusion Research has shown that TIMP can effectively reduce kidney damage induced by various nephrotoxic agents, as evidenced by studies on animal models. Some of the TIMP with notable potential for treating chronic kidney disease include *Camelia sinensis* (L.), *Nigella sativa* (L.), *Andrographis paniculata* (Burm.f.), *Daucus carota* (L.), *Foeniculum vulgare* (L.), *Glycyrrhiza glabra* (L.), and *Cucumis sativus* (L.).

Keywords Kidney diseases, Nephrotoxic agents, Nephroprotection, Traditional Indian medicinal plants (TIMP), Animal models

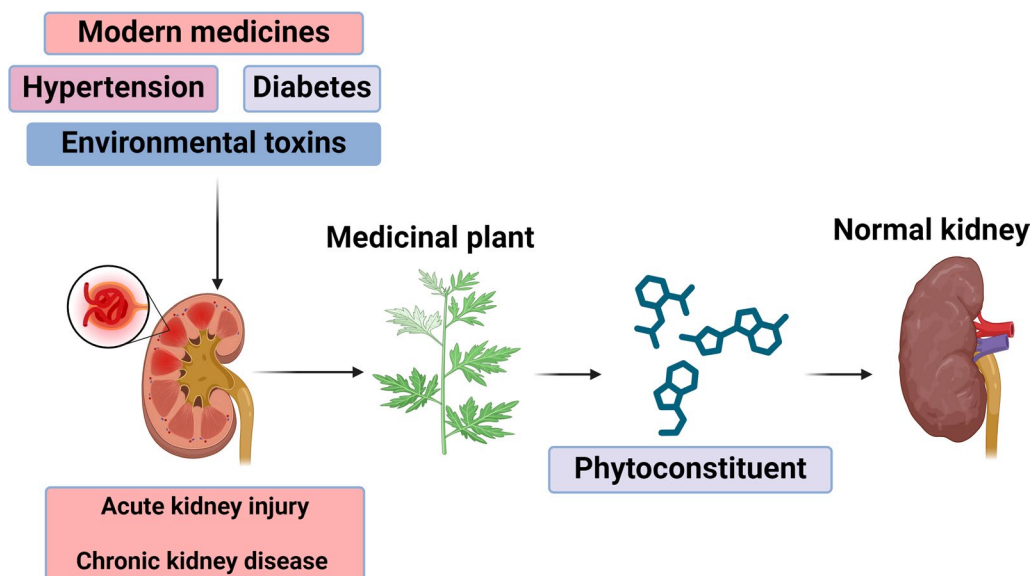
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Graphical abstract



Background

A global public health concern, kidney injury is marked by rising incidence and prevalence, high expenditures, and adverse results [1]. Due to the significant exposure to numerous therapeutic as well as environmental toxicants, kidneys are overwhelmed by several major or minor disorders like acute kidney injury (AKI) and chronic kidney disease (CKD). AKI is a sudden loss of kidney function accompanied by the accumulation of waste materials including creatinine and urea in the body. Other characteristics of AKI include retention of water and sodium, a decline in glomerular filtration rate (GFR), hyperkalaemia, and metabolic acidosis [2]. Studies on the Global Burden of Disease (GBD) have revealed that CKD has become a major global cause of death. A kidney's anatomical or functional abnormalities, with or without a reduction in the GFR, are considered CKD. That is to say, pathological abnormalities such as variations in blood or urine composition or abnormalities in imaging tests are signs of kidney injury. Additionally, CKD can develop into end-stage kidney disease (ESKD), which necessitates renal replacement therapy in addition to dialysis and/or kidney transplantation for patients. Other than these two major kidney diseases, many others have been reported [3], such as acute renal failure (ARF), vascular disease of the kidney, nephritic syndrome, tubulointerstitial disease, nephrotic syndrome, and papillary necrosis.

One of the leading causes of death and suffering in the 21st is CKD. The frequency of CKD differed significantly

among the laboratory-based definitions; utilizing a single eGFR value resulted in 8327 cases per 100,000 population, whereas a time-limited repeated eGFR-based definition resulted in 4637 cases per 100,000 population [4].

Moreover, when employing a definition based on International Classification of Diseases (ICD) diagnostic codes, the prevalence of CKD was significantly reduced, with 775 cases per 100,000 population [5]. In addition, the epidemiology of CKD provides statistics on the death rate as a percentage of the population (pmp) in 1990, 2006, and 2010—that is, 15.7% and 16.3%, respectively [6].

Finding the variables that are linked to a prominent risk of getting CKD is crucial, including hypertension, diabetes mellitus, metabolic syndrome, glomerulonephritis, genetic diseases, urological disorders (obstruction, recurrent urinary infections), infections, vasoconstriction, (NSAIDs, antibiotics, light chains), dyslipidaemia, tubular cell toxicity, interstitial nephritis, crystal deposition, and proteinuria as nephrotoxins that affect intra-glomerular hemodynamics. The major risk factors of CKD along with their prevalence mentioned in (Fig. 1) based on research looking at the prevalence of CKD globally, an estimated 843.6 million people (stages 1–4) are afflicted with CKD worldwide.

Also, prevalence among men & women in stages 1–3 and stages 2–5 is depicted in (Fig. 1).

To overcome nephrotoxicity, it may be valuable to exploit the traditional benefit of herbal medicines.

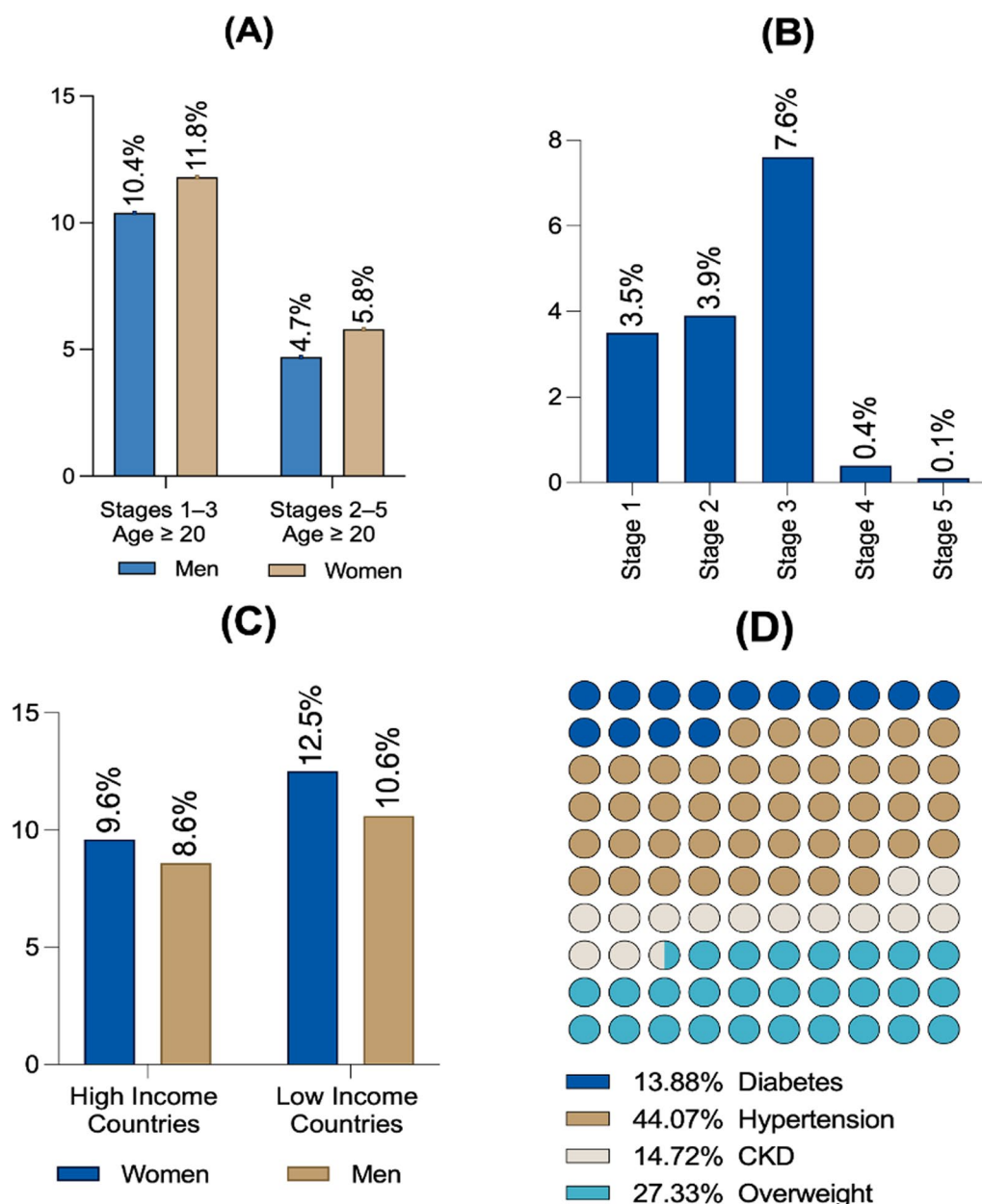


Fig. 1 **A** Gender-specific global prevalence of (CKD) in stages 1–3 and stages 2–5, **B** percentage distribution of the global prevalence of various stages of (CKD) among individuals worldwide, **C** gender-specific global prevalence of (CKD) in both high and low-income countries, **D** prevalence of the Global Burden of Disease (GBD) in India

Botanicals found in medicinal plants (and their counterparts) have produced a large number of therapeutically beneficial medications for the treatment of acute and/or chronic illness, and they continue to be a vital part of the quest for novel therapeutics. Therefore, it is possible to efficiently examine these historically utilized plants to discover new medicinal aspects, or phytopharmaceuticals, for the treatment of both acute and chronic illnesses.

For this purpose, this review discusses the possibility of medicinal plants as nephroprotective agents in treating chronic and acute diseases. It highlights the earnest need of evaluating scientific claims against nephrotoxics, such as modern medicines and environmental pollutants, in terms of nephroprotection. Traditional medicinal plants play a significant role in this process, and their employment requires evaluation through in vivo animal models. The review also provides exhaustive data on

phytoconstituent class and their potential as nephroprotective in kidney disease models in animals.

Materials and methods

After a thorough search of the literature, data for the current review article were collated from a variety of internet sources, including PubMed, SCOPUS, Google Scholar, and others. The information is grouped together in the table according to in vivo animal models, medicinal herbs, nephrotoxins, and nephroprotection. The dosage of the various plant extracts against nephrotoxicity brought on by different chemical agents in the animal system is the main topic of the pharmacological reports. Moreover, the table provides a summary of number of animal models.

Main text

Drug-induced nephrotoxicity

Nephrotoxicity occurs when kidney function is damaged or destroyed by exogenous or endogenous toxicants, or as a result of using medications or toxic substances, impairing the ability of the kidneys to properly detoxify and excrete waste products. There are acute and chronic phases to the dose-dependent condition known as nephrotoxicity [7]. Renal dysfunction usually occurs through the utilization of certain medications or exposure to poisons (Fig. 2). Numerous modern medications can induce interstitial nephritis, which is often how AKI and CKD are brought on. Penicillin, non-steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors, diuretics, and antiretrovirals are medications associated with acute interstitial nephritis. Moreover, nephrogenic diabetes insipidus and interstitial nephritis may result with long-term lithium therapy. Seldom, medications like penicillamine and gold can also result in glomerulonephritis. The most common class of medications and the main contributor to drug-associated nephropathy are antibiotics. One of the most significant groups of antibiotics that adversely impacts kidney function is aminoglycoside. 10–25% of patients who receive gentamicin for 3–5 days experience nephrotoxicity [8]. Within days of starting anti-hypertensive medication therapy, kidney damage can also happen from Angiotensin converting enzyme (ACE) inhibitors, β -blockers, NSAIDs/selective cyclooxygenase II (COX-2) inhibitors, cocaine, and occupational toxins¹¹. Nephrotoxins differ in terms of their chemical makeup, cellular targets, and methods of cellular harm in the kidney. They also cause variable degrees of kidney damage. AKI, tubulointerstitial disease, and renal scarring can result from these medications due to their variable degrees of damage, alteration in intra-glomerular hemodynamic, and inflammatory alterations in renal tubular cells [9]. The kidneys are susceptible to

a variety of injuries since they serve as the body's main organ for eliminating foreign substances like medications and poisons [10]. Due to its high blood flow and excretory function, the kidney is also thought to be a particularly sensitive target for water pollutants; nonetheless, exposure to environmental toxins has received little attention as a cause of AKI and CKD. Through both inhalational and cutaneous exposure, heavy metals like lead and cadmium have long been known to be the primary cause of kidney illness associated to the workplace [11]. Nephrotoxicity may also be induced by commonly used modern drugs. For instance, interstitial nephritis and the suppression of vasodilatory prostaglandin synthesis in the renal cortex and medulla are two ways that NSAIDs impair kidney function. Renal impairment may result with ACE inhibitors and angiotensin II receptor blockers, which lower glomerular hydrostatic pressure. Furthermore, renal tubular epithelial cells may be harmed by anticancer medications, aminoglycoside antibiotics, and radiocontrast medium, which could result in acute tubular necrosis. Previous reports have revealed that the prevalence of drug-induced nephrotoxicity is about (66%) higher in senescent adults as compared to infant or adolescent age [12]. Numerous nephrotoxins have been listed in (Table 1). With their mechanism of action, therapeutic activities and toxic effects. Moreover, several herbs that cause nephrotoxicity are commonly used to treat a variety of illnesses, such as *Achillea millefolium* (Brinjasif) [13], *Capparis spinosa* (Beekh Kiber) [14], *Polypodium vulgare* (Bisfaij) [15], *Allium ascalonicum* (Tukhm Gandana) [16], *Draceana cinnabari* (Dammul Akhwain) [17], *Ferula persica* (Sakbeenaj) [18], *Nardostachys jatamansi* (Sumbul teeb) [19], *Cinnamomum cassia* (Saleekha) [20], *Portulaca oleraceae* (Tukm Khurfa) [21], *Rumex vesicarius* (Tukhm Hammaz) [22] and *Aristolochia indica* (Zaravand Taveel) [23]. Therefore, it is necessary to mitigate the effect of toxicity of herbal drugs too at its minimal level, so that it can be useful for therapeutic efficacy [24]. The following pathogenic pathways, including thrombotic microangiopathy [25], inflammation, tubular cell toxicity [26], altered intra-glomerular hemodynamic [27], crystal nephropathy [28], and rhabdomyolysis [29], can be used to indicate drug-induced nephrotoxicity. While the most important one is oxidative stress which leads to renal destruction, followed by nuclear factor kappa B (NF- κ B) activation and enhanced synthesis of inflammatory cytokines, including nitric oxide (NO), interleukin-1 β (IL-1 β), IL-6, tumor necrosis factor- α (TNF- α), and cyclooxygenase- II (COX- II). These modifications may cause an imbalance in the cell's antioxidant defense system and these inflammatory factors' homeostasis, which ultimately results in a pathophysiological malfunction and apoptosis [30].

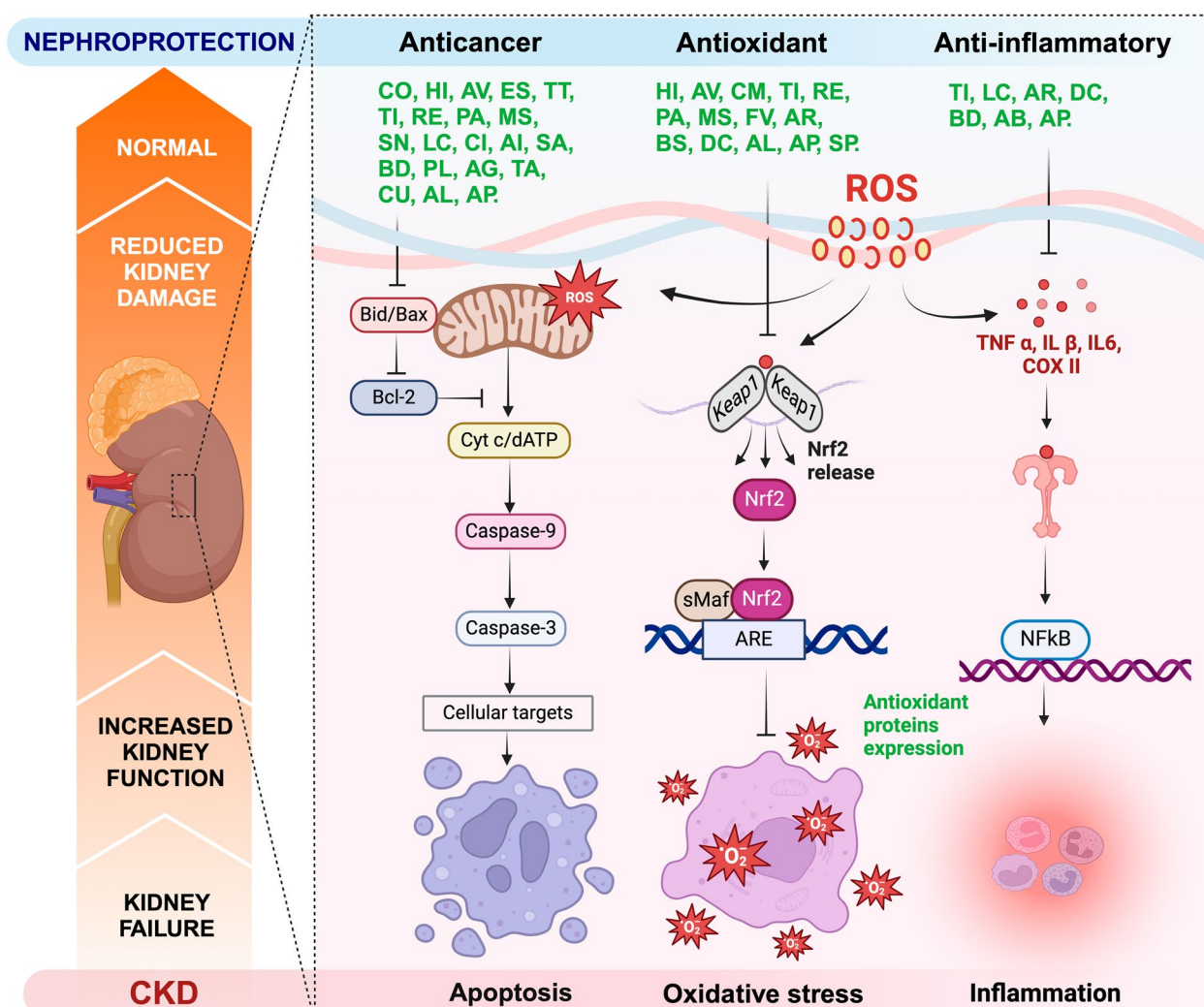


Fig. 2 Mechanism of action of Natural compounds (NCs) through antioxidant properties has beneficial effects in the mitigation of nephrotoxicity. Activation of nuclear factor erythroid 2 (NFE2)-related factor 2 (Nrf2) has been suggested to play a significant role in the protective effect of many of these antioxidant agents. The figure includes a range of medicinal plants with their respective two-letter abbreviations, highlighting their diverse therapeutic effects. The list includes *Curculigo orchioides* (CO), *Hemidesmus indicus* (HI), *Aloe vera* (AV), *Elephantopus scaber* (ES), *Combretum micranthum* (CM), *Tribulus terrestris* (TT), *Tamarindus indica* (TI), *Rheum emodi* (RE), *Pimpinella anisum* (PA), *Musa sapientum* (MS), *Solanum nigrum* (SN), *Lantana camara* (LC), *Foeniculum vulgare* (FV), *Annona reticulata* (AR), *Biophytum sensitivum* (BS), *Cichorium intybus* (CI), *Azadirachta indica* (AI), *Senna auriculata* (SA), *Boerhaavia diffusa* (BD), *Plectranthus amboinicus* (PL), *Anethum graveolens* (AG), *Daucus carota* (DC), *Trachyspermum ammi* (TA), *Cucumis melo* (CU), *Aerva lanata* (AL), *Apium graveolens* (AP), *Abutilon indicum* (AB), *Morus alba* (MA), *Embelia ribes* (ER), and *Salvadora persica* (SP)

Angiotensin receptor blockers (ARBs) and ACE inhibitors are the two main medications utilized in modern medicine to produce reno-protection [31]. Nevertheless, these treatments or managements are mostly useful in treating nephropathies connected with blood pressure, diabetes, etc. They are neither the preferred medications for this purpose nor can be used entirely to create reno-protective effects. These agents' concomitant toxicities also severely limited their utilization. While ACE inhibitors are more

dangerous than ARBs, both medications can have similar adverse effects, including proteinuria, angioneurotic oedema, hyperkalaemia, and neutropenia, particularly in patients with renal impairment (Fig. 3) which call into question these agents' ability to treat patients. For individuals experiencing renal dysfunction or failure, a medication that is classified as specifically effective as a nephroprotective agent and does not carry the risk of producing any major adverse effects is the apparent choice [32].

Table 1 A comprehensive list of modern drugs classified by pharmacological class, accompanied by their indications, mechanisms of action, and associated toxic effects on the kidney

Pharmacological class	Indication	Mechanism of action	Drugs	Toxic effects on kidney	References
Antidepressant	Premenstrual dysphoric disorder, smoking cessation & urinary stress incontinence	The on-norepinephrine transporter is not significantly impacted by highly selective SERT blockade (NET)			
	Amitriptyline, Imipramine & Doxepin	Acute tubular necrosis, rhabdomyolysis & Acute kidney injury	[80]		
Antifungal	Candidiasis, aspergillosis, cryptococcosis, blastomycosis, histoplasmosis, mucormycosis & sporotrichosis	Forms pores in the membranes of fungi that contain ergosterol, but not in the membranes of mammals that possess cholesterol			
	Amphotericin B	Renal tubular acidosis, nephrogenic diabetic insipidus, irreversible renal failure, reduced renal blood flow and glomerular filtration rate	[81]		
Thrombolytic	Thrombosis & reperfusion injury	Acts indirectly by converting plasminogen into active plasmin through the formation of the "active complex" of plasminogen-streptokinase	Tissue-plasminogen activator and streptokinase	Ischemia and necrosis of the renal tissue Infarction	[82] [12]
Antihistamine	IgE immediate allergies, antiemetic & anti-motion sickness	Competitive antagonism/inverse agonism at H1 receptors	Diphenhydramine & doxylamine	Rhabdomyolysis, muscarinic blockade symptoms & orthostatic hypotension	[83]
Antihypertensive	Hypertension, angina & arrhythmia	Block vascular calcium channels > cardiac calcium channels, nonselective blockade of L-type calcium channels	Angiotensin-converting enzyme inhibitors, such as hydralazine and minoxidil, as well as angiotensin II receptor blockers	Prerenal azotemia due to volume depletion and RAS	
Antimicrobial	[84]				
	Ocular, pulmonary & intestinal infections	Results in defective proteins that insert into and damage the cytoplasmic membrane by causing mismatches between codons and anticodons	Aminoglycosides	Renal nephrotoxicity & Acute interstitial nephritis	[85]
	Catheter-related infections, Bacterial meningitis & Peritonitis	Large molecules inhibit peptidoglycan chain interactions, blocking transglycosylation and transpeptidation	Vancomycin	Acute tubular necrosis, tubular damage & nephrotoxicity	[86]
	Anthrax & meningococcal infection	Kills the cell by preventing DNA replication and inhibiting the function of DNA gyrase	Ciprofloxacin	Acute tubular necrosis, acute renal failure, and allergic interstitial nephritis	[87]
	Pneumococemia	Directly interacts with PBPs, preventing transpeptidase action	Penicillin	Acute interstitial nephritis & glomerulonephritis	[88]
	Moraxella (Branhamella) catarrhalis, <i>E. coli</i> , Klebsiella, Proteus infection	Interacts directly with PBPs and inhibit transpeptidase activity	Cephalosporin	Acute interstitial nephritis	[89]

Table 1 (continued)

Pharmacological class	Indication	Mechanism of action	Drugs	Toxic effects on kidney	References
Antiretroviral	Cytomegalovirus retinitis treatment, adenovirus, human papillomavirus, BK polyomavirus, vaccinia, and poxvirus infections	By being incorporated into the viral DNA chain, a potent inhibitor serves as a substitute substrate for viral DNA polymerase and competitively inhibits DNA synthesis	Cidofovir & adefovir	Proximal tubular nephrotoxicity	[90] [89]
	Human immunodeficiency virus & hepatitis B virus	Induces chain termination after insertion into DNA and inhibits HIV reverse transcriptase	Tenofovir	Tubular cell toxicity & Acute renal failure	[91]
Antiviral	HIV & HBV	Inhibitor of CYP3A4	Indinavir	Nephrolithiasis tubular crystallization	[92]
	HIS & Varicella zoster infections	Viral DNA chain termination and irreversible suppression of herpes virus DNA polymerase	Valacyclovir	Nephrolithiasis & Acute renal failure	[93]
	Herpes simplex virus & Varicella zoster	It blocks the viral DNA polymerase and functions as a terminator of viral DNA chains	Acyclovir	Acute kidney injury	[94]
Calcineurin inhibitor	Breast cancers, encephalomyelitis, adjuvant arthritis & the humoral immune response	Blocking the protein kinase known as the mammalian target of rapamycin	Rapamycin	Acute renal failure, chronic renal disease & crystal nephropathy	[95]
Chemotherapeutic	Cancers affecting the head and neck, ovaries, breasts, bladder, non-small cell and small cell lung, as well as germ cells	Creates interstrand and intrastrand DNA crosslinks and binds to cytoplasmic and nuclear proteins		Tubular collapse & vacuolization nephrocalcinosis	
	Cisplatin	Chronic interstitial nephritis, tubular cell toxicity & Nephrotoxicity	[96] [97]		
[101]	Breast cancer, stomach (gastric) cancer, non-small cell lung cancer, and superficial bladder cancer	Cross-links DNA and functions as an alkylating agent; it also produces oxygen free radicals, which attack DNA	Mitomycin C	Nephrotoxicity & renal failure	[98] [99]
	Acute lymphoblastic leukemia & non-oncologic diseases including rheumatoid arthritis & psoriasis	Inhibits thymidylate synthase, dihydrofolate reductase, and de novo purine nucleotide synthesis	Methotrexate	Nephrotoxicity & renal dysfunction	[100]
Diuretics	Nephrolithiasis, nephrogenic diabetes insipidus, hypertension, and moderate heart failure	Na/Cl transporter inhibition in the distal convoluted tubule	Thiazides	Acute interstitial nephritis	[102] [103]
	Pulmonary edema, peripheral edema, heart failure, hypertension, acute hypercalcemia, and electrolyte imbalances	Inhibition of the Na/K/2Cl transporter in the ascending limb of Henle's loop	Loop diuretics	Acute interstitial nephritis	[103]
	Liddle's syndrome and lithium-induced polyuria are lessened by hypokalemia from other diuretics	Blocks epithelial sodium channels in collecting tubules	Potassium-sparing diuretics	Acute interstitial nephritis	[104]

Table 1 (continued)

Pharmacological class	Indication	Mechanism of action	Drugs	Toxic effects on kidney	References
Immunosuppressive	Antifungal & antiparasitic	Suppression of several lymphokines' production, including interleukin-2, which is produced in reaction to antigen stimulation	Cyclosporine	Reduction in glomerular filtration & increased Proximal tubular nephrotoxicity	[105] [106]
Anticonvulsant	Focal & tonic-clonic Blockage of sodium channel Phenytoin	Acute interstitial nephritis & diabetes insipidus	[107]		
Non-narcotic analgesic	Antipyretics Fever, pain & inflammation in diseases such as rheumatoid arthritis and osteoarthritis Non-steroidal anti-inflammatory medications	Inhibit the enzymatic production of prostaglandins Both COX-1 and COX-2 inhibition	Aspirin & acetaminophen	Chronic interstitial nephritis & Acute tubular necrosis	[108] [109]
Osmotic	Glaucoma & intracranial hypertension	Through the blood arteries in the retina and uveal tract, this osmotic gradient pulls water from the intraocular space into the circulation	[107] [110] Dextran and Mannitol	Isometric proximal tubule vacuolization and swelling	
Bisphosphonates	[111] [112] Paget's disease, hypercalcaemia, Block the physicochemical processes that cause bone calcification in vivo	Bisphosphonate & zoledronate	Renal failure & inhibition of renal tubular reabsorption	[113]	
Narcotic analgesic	Graft-versus-host, uveitis, rheumatoid arthritis, psoriasis & Asthma	Cyclosporine inhibits calcineurin via binding to immunophilin; moreover, cyclophilin inhibits the cytochrome P450 system [114]	Cyclosporine		
Antiplatelet	Acute nephrotoxicity & chronic nephrotoxicity				
Anticoagulants	Antithrombotic & atrial fibrillation Atrial fibrillation & venous thromboembolism	P2Y12 receptor blockade Blocking the vitamin K-epoxide reductase	Ticlopidine & clopidogrel Warfarin & heparin	Thrombotic microangiopathy Acute kidney injury	[115] [116] [117]

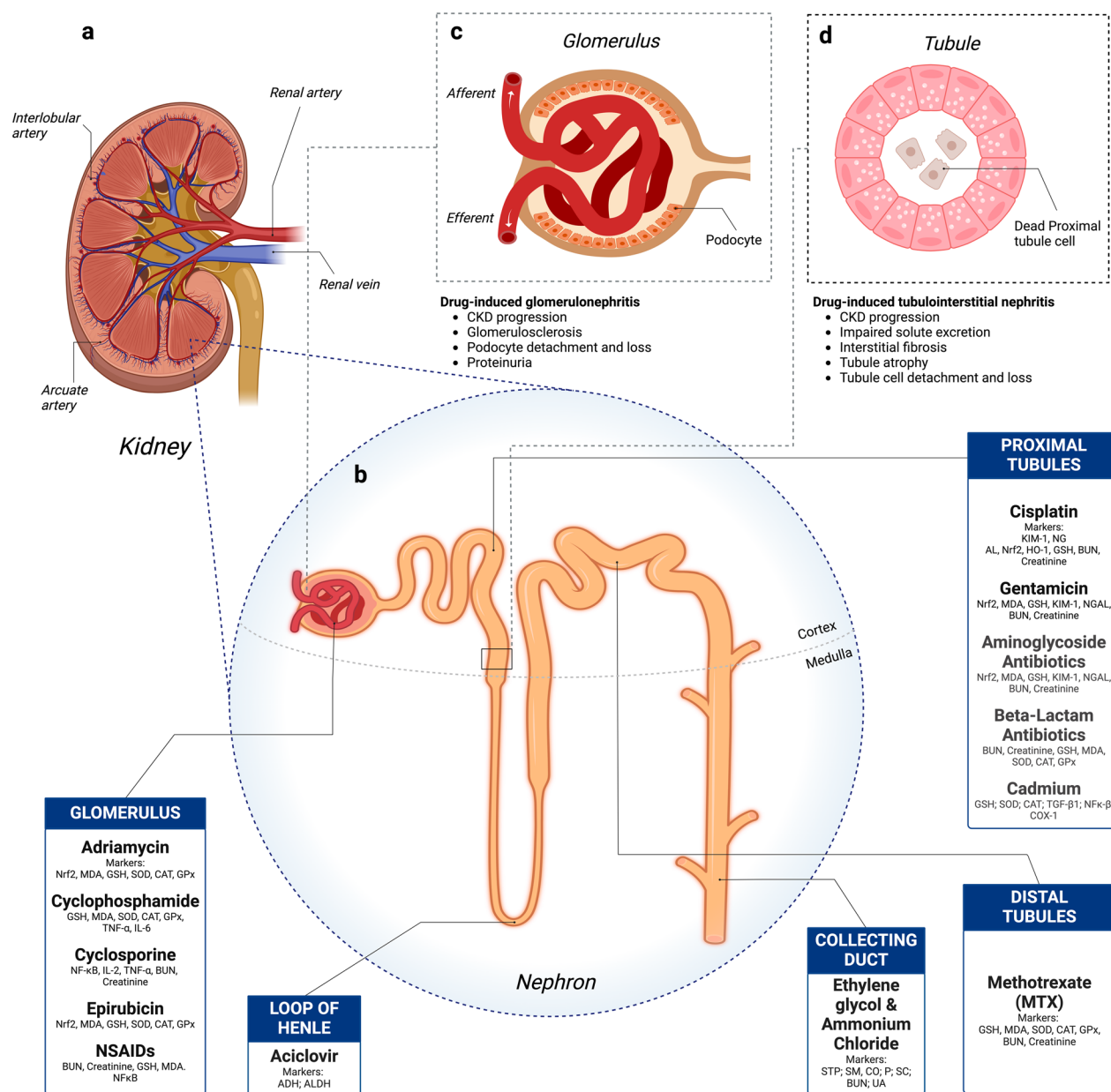


Fig. 3 Comprehensive view of kidney structure and nephron function, representing the impact of various drugs. **A** Illustrates the kidney's vascular anatomy; **B** details the nephron's structure and segments; **C** focuses on the glomerulus and associated drug-induced damage; and **D** Highlights the tubular segment of the nephron, with emphasis on cellular damage from specific medications

In vivo animal models for CKD

Numerous scientific findings on the physiology of humans have come from research on animals, particularly rodents like mice and rats [33]. Animal models of CKD are similar to human circumstances and can be used to better understand the disease's pathophysiology and devise effective treatment plans [34]. Their contributions to comprehending disease processes and creating potent treatments like insulin, antibiotics, and vaccinations have

been significant. Animal models are live experimental setups created by one species to investigate phenomena that happen in another species [35]. Apart from nephrectomy and unilateral ureteral blockage models, CKD is induced by nephrotoxic drugs such as adenine, adriamycin, cisplatin, folic acid, aristolochic acid, and oxalate. Pharmacology, toxicology, immunology, and other disciplines have undergone a paradigm change as a result of the use of animal models to study human anatomy and

physiology. Many animal models have been effectively created up to this point using various techniques to mimic human diseases, such as CKD. These models have been crucial in the development of therapeutic agents derived from natural products for the benefit of renal disease [36]. Interstitial, tubule, glomerular, and/or vascular damage that occur periodically or gradually cause CKD. As a result of the degenerative process that causes CKD, patients experience difficulties that impact many organs and bodily processes [37]. It is therefore challenging to research the illness with human participants. Therefore, creating rodent models for animal research is crucial to overcoming this, because in vivo animal models serve as a useful experimental tool for investigating the physiological, biochemical, and histological processes of CKD. The spontaneously hypertensive rat (SHR) is widely employed as a primary model for studying hypertension and cardiovascular disease. The SHR strain was developed through the process of selectively breeding Wistar–Kyoto (WKY) rats with elevated blood pressure. The 5/6 nephrectomy model involves reducing the overall kidney mass by 5/6th. The commonly used technique comprises a two-step procedure. Initially, a complete unilateral nephrectomy (UNX) is conducted on one kidney. Subsequently, two-thirds of the remaining kidney mass is removed through either anterior or posterior ligation of renal artery branches or through resection of the kidney pole. In this review, we have mentioned the key information related to in vivo models of CKD developed through spontaneous, acquired, and genetic methods. Some of the imperative in vivo models are listed in (Table 2).

Mitigation of nephrotoxicity by traditional Indian medicinal plants

Throughout history, medicinal plants have been used extensively to treat, manage and cure illnesses or disorder all over the world [38]. Over 80% of people worldwide get their main healthcare from conventional medicine, according to the World Health Organization. Herbs, vitamins, minerals, trace elements, and nutritional supplements are just a few examples of the natural products found in traditional and complementary medicine, which have been extensively utilized in both developed and developing nations [39]. Medicinal plants are utilized worldwide to heal medical conditions and are the source of different types of natural antioxidants [40]. However, they are exploited for nephroprotective activities. The current state of global trade, where oxidative stress is identified as one of the major causes of health concerns, has made the pharmacognostic study of plants, minerals, and animals as sources of medicine even more important [41]. According to reports, there are 61 plant families, with euphorbiaceae being the most prominent.

Among the 143 species of medicinal plants, 85% are used as diuretics, 10% are used to burn urine, and 6.3% are used to prevent the formation of stones. The percentage of the plant that has favourable effects on renal disorders is as follows: leaves (30%), roots (22%), seeds (18%), fruit (15%), pods (10%), bark 8%, gum 5%, and the entire plant 2% [42]. A growing number of people have been consuming standardized extracts and other forms of herbal medicine in the past few decades because of the various adverse effects and expensive nature of chemically patented medications. Uncertainty surrounded the potential benefits of these old herbs, even as rejuvenators for various forms of degenerative kidney disease [43].

It is common practice to treat renal function and postpone the development of kidney disorders into end stage renal disease (ESRD) by using the metabolites of ancient medical systems. The management of renal illnesses is quite difficult and hard due to their complex nature and development to both acute and chronic renal failure and ESRD. Because there aren't many new biomarkers for renal disorders in their early stages, most instances go unreported until they get to a more advanced or severe state, at which point standard treatment measures are typically insufficient to fully eliminate the disease (Table 3). However, the main issue with kidney disease is that it progresses to a point where almost no treatment is effective save for renal replacement therapy (RRT). The startling rise in CKD prevalence, which leads to ESRD and necessitates RRT, necessitates significant financial commitment [44]. 1.783 million individuals worldwide were getting treatment for ESRD; of these, 23% received functional kidney transplants and 77% were on dialysis. This number is rapidly rising at a pace of 7% per year. Researching conditions like ARF, nephritic syndrome, and chronic interstitial nephritis methodically is necessary to develop a potential herbal remedy for renal problems [45].

Since a few decades, although technology and modern medicine have developed extensively throughout the world. Most countries made it obligatory to utilize natural resources for pharmaceuticals and a variety of other uses, including the treatment of illnesses [46]. Due to the confined therapeutic effect and a broader spectrum of adverse effects of modern medicines, they are not secure and liable for prolonged use; to overcome this discrepancy one may rely upon the alternative or Indian systems of medicine (ISM) like, Ayurvedic & Unani. Some drugs cited in Ayurvedic and Unani texts, utilized by physicians, have shown significant therapeutic benefits as diuretics, anti-inflammatory agents, antioxidants, and nephroprotective agents against various toxins. Recently, some important drugs and formulations of Unani system of medicine such as *Aerva lanata*, Juss. [47], *Rheum*

Table 2 Compilation of animal models utilized in CKD research, categorizing them by model type

Model	Types	Method	ROA/Strains	Parameters/Endpoint	Duration	References
Spontaneous	Glomerular & interstitial injury models (Lupus nephritis)	Immune complex mediated glomerulonephritis	MRL/lpr, BXSB & NZB/W	Interstitial inflammation & late-stage fibrosis/ Renal failure	10–12 months	[37] [34] [118]
	Ageing	Progression of renal impairment & scarring	Sprague–Dawley rats & C57BL/6	Severe scarring, GS & tubulointerstitial	3 months	[119]
	Spontaneously hypertensive rats	Augmented vasoconstrictor ability	Hypertensive rats	GS & interstitial fibrosis/ 180–200 mmHg	5–6 weeks	[119]
	Buffalo/mna rat	Podocyte alterations	Buffalo/mna rat	Focal & segmental GS/ nephrotic syndrome	6 months	[120]
	CKD as a consequence of acute kidney injury	Ischemic acute kidney	Rats & mice	Long-term interstitial fibrosis, PRI & Renal fibrosis	-	[121]
	Congenital deficiency of nephrons (5/6 Nephrectomy)	Ligation & ablation model	Munich Wistar Frömter rat	Proteinuria/significant GS/ SBP (140 to 150 mm Hg)	10 weeks	[119]
	Thy-1 nephritis	IgA nephropathy & Henoch–Schönlein purpura nephritis	C57BL/6 strain mice	Progressive GS & TIF/reduction in renal mass	1–2 weeks	[122] [123]
			Monoclonal antibody against Thy 1 in mice or serum against Thymocytes in rabbits	Proliferative lesions accompanied by interstitial fibrosis and progressive chronic sclerosis	2 days	[124]
	Unilateral ureteral obstruction	Tubulointerstitial fibrosis	Rats and mice	Obstructed kidney/reduction in RBF & GFR	Within 24 h	[125] [126]
	Adenine induced CKD	Intra-peritoneal adenine	Rats & mice	Renal failure	-	[122]
Acquired models		Degenerative alterations in the renal tubules and the interstitial space	Rats	Blockage of the renal tubules	-	[127]
	Adriamycin-induced CKD	Renal injury	Male rats	Acute tubular necrosis & renal injury	-	[128]
	Diabetic nephropathy	Pancreatic (β-cell) toxin streptozotocin	Akita mice Zucker rats	Pancreatic β-cell failure & renal fibrosis	-	[121]
	Anti-glomerular basement membrane diseases model	Complete Freund's adjuvant	Rats & mice/ Wistar Kyoto	Glomerulonephritis/ tubulointerstitial	Within 2–3 weeks	[129]
	Type-2 diabetes	Focal interstitial fibrosis	Zucker rats	Albuminuria & glomerular injury	-	[130]

Table 2 (continued)

Model	Types	Method	ROA/Strains	Parameters /Endpoint	Duration	References
Other models (Environmental toxins, heavy metals and alternative medicines)	Folic acid & aristolochic acid	AKI & interstitial fibrosis	Male mice	Progressive fibrosis and kidney failure	1 – 14 days	[121]
	Cyclosporine A	Renal fibrosis	-	Tubular necrosis, preglomerular ischemia & RIF	28 days	[130]
	Cisplatin	Renal impairment	-	Renal blood flow decreases within 3 h and GFR falls	-	[131]
	Radiation nephropathy	Total-body irradiation	CBA/C57/BL6 mice	Acute endothelial damage, proportionate tubulointerstitial fibrosis, and chronic, progressive secondary sclerosis	6–8 weeks	[132]
	Genetically engineered models	The genetic deletion of the alpha-3 chains encoding gene of collagen IV	NEP25, chimeric mice & Rats/ Mice (Tg26) mice	Podocyte-depletion and CRI/ podocytopathies	-	[133]
	HIV-associated nephropathy	Replication-deficient version of HIV	Moribund mice, (Tg26) mice	Proteinuria/damaged podocytes leading to GS	24 days	[134]
	Alport syndrome	GBM that is irregularly thickening and separating	Alport mice	Glomerulosclerosis	4 weeks	[135] [136]
	Deoxycorticosterone acetate-salt nephropathy	Unilateral nephrectomy	-	Renal injury, LRI/proteinuria, GS & impaired endothelium-dependent relaxation	-	[137] [138]

Table 3 Delineates nephrotoxicants, their indications, and the protective attributes of herbal drugs, adhering to scientific conventions with referenced details

Therapeutic class	Nephro-toxicants	Indication	Molecular Biomarkers	Nephroprotective Plant	Extract/ Part Used	Dose	Duration/ ROA	Active metabolites/ Class	Therapeutic Activities of NP Plant	References
Anthracycline & antitumor antibiotic	Adriamycin (Doxorubicin)	Kaposi's sarcoma, lymphoma & ALL	CAT; GPx; Nrf2; HO-1, GST α1, SOD1, SOD2, and SOD3	<i>Camelia Sinensis</i> (L.) Kuntze	Aqueous/ leaf extract	15 or 45 mg/kg/day	Orally 12 months	Vitamins C & E/PC	Antioxidant, cardiovascular disorders & NSI	[62] [139] [140]
			COL1A1; COL4A1; COL4A2; Podocin; HO-1; NQO-1; Nrf2; FN	<i>Polygonum multiflorum</i> Thunb	Ethanollic	10 mg/kg/day	Orally (24 days)	2,3,5,4-Tetrahydroxystilbene- 2-O-β-D glucoside / hydroxystilbene	Anti-inflam-matory, antioxidant & nephropathy	[141] [142] [143] [144]
			FN; Nrf2; HO-1, NQO-1, COL1A1, COL4A1; COL4A2; Podocin	<i>Nigella sativa</i> (L.)	Aqueous	50 mg/kg/day	Orally (3 weeks)	Thymoqui-none	Antioxidant, anti-inflam-matory, urolithiasis & anticancer	[145, 146] [147] [148]
	Cisplatin	Cancers	Urine; AOPP, MDA, NO, MPO, PT, XO, TP, PC, SOD, GSH, GPx, GST, NPT	<i>Andrographis paniculata</i> (Burm.f.) Nees	Ethanollic/ leaf extract	200 & 400 mg/kg/day	Orally (7 days)	Lactones, flavonoids & di-terpenoids,	Liver disorders, & renoprotective	[149] [75] [59]
				<i>Aerva lanata</i> (L.)	Ethanollic Extract	300 mg/kg		Flavonoids (kaempferol 3-rhamnoside & kaempferol 3-rhamnoga-lactoside)	Antioxidant & nephropro- tective	[150] [47]
			SOD; CAT; GPx; GSH; MDA	<i>Biophytum sensitivum</i> (L.)	Ethanollic extract	250 mg/kg/day	P.O (9 days)	Flavonoids & phenolic compounds	Urolithiasis, antioxidant, anti-tumour & anti-inflam-matory	[60] [151] [152] [153]
			SAA; A; SA; GGT; AP; TB; C; UA & U	<i>Azadiracta indica</i> (L.)	Ethanollic & methanollic extract	500 mg/kgBW	I.P (5 days)	Azadiradione	Antiulcer activity, anti-inflammatory, hepatoprotective & nephro-protective	[154] [155]

Table 3 (continued)

Therapeutic class	Nephro-toxicants	Indication	Molecular Biomarkers	Nephroprotective Plant	Extract/ Part Used	Dose	Duration/ ROA	Active metabolites/ Class	Therapeutic Activities of NP Plant	References
			BU; SC; UA; BUN;	<i>Withania somnifera</i> (Dunal)	Powder	700 & 1400 mg/kg/B.W	Orally (Per day0	Alkaloids (withaferin A, withanolides A-Y, cuscohygrine, anahygrine), steroidal chemicals (ergostane type)	Diuretics, adoptogenic, anti-inflam-matory & antitumor	[156] [157]
			NFB; SOD; CAT; GR; GPx; TNF- α ; IL-6; MRP-1; KIM-1; Akt; Nrf2; HO-1; Caspase-3;	<i>Curcuma longa</i> (L.)	Aqueous & Methanolic	100 mg/kg	Orally (5 days)	Carvedilol & curcumin/PC	Anti-inflam-matory, antioxidant, anti-carcino-genic & hepatoprotec-tive	[158] [159]
			p-NF- κ Bp65; MDA; IL-1 β ; TNF- α ; HO-1; NF κ Bp65; p-I κ B α ; I κ B α ; ROS, Nrf2	<i>Daphne odora</i> Thunb	-	2.5, 5, 10 mg/kg/for 3 days/	IP (3 days)	Daphnetin (Derivative of coumarin)	Anti-inflam-matory & anti-oxida-tive	[159] [160] [161] [162]
			-	<i>Boerhaavia diffusa</i> (L.)	Polyherbal combination	100, 200 & 400 mg/kg	Orally	Polyphenols, flavonoids & tannins	Hepatopro- tective, Anti-inflam-matory & anti-cancer	[61], [163]
			HO-1, GCLC, GCLM, AP-1, COX-II, I κ B- α , NF- κ B, IL-1 β , IL-6, TNF- α , Sirt1, Keap1, MDA, SOD, GSH, GSH-Px, Nrf2	<i>Dioscorea nipponica</i> <i>Dioscorea zingiber-ensis Makino Wright, C.H</i>		10, 20 & 40 / mg kg/ day	Orally (12 days)	Dioscin (Steroid sapo-nins)	Anti-inflam-matory, anti-tumor, anti-thrombotic, anti-viral & anti-fungal activity	[164] [165] [166] [167]
			SU; SC; Na; K; MDA; CAT; GPx; SOD CAT; GPx; H ₂ O ₂	<i>Lantana camara</i> (L.)	Methanolic Extract	100–400 mg/kg	Orally (15 days)	Phenolic acid derivatives, flavonoids & phenyletha-noids	Anti-inflam-matory & antioxidant	[168] [169] [170] [171]

Table 3 (continued)

Therapeutic class	Nephro-toxicants	Indication	Molecular Biomarkers	Nephroprotective Plant	Extract/ Part Used	Dose	Duration/ ROA	Active metabolites/ Class	Therapeutic Activities of NP Plant	References
			HO-1; GSH; GR; GST; CAT; SOD; MDA; NF-κB; IL-1β; IL-6; TNFα; Nrf2;	<i>Embelia ribes</i> Burm.f	Fruit	25 & 50 mg / kg/ day	Orally (2 weeks)	Embelin (Hydroxy benzoquinone)	Anti-inflam-matory, anti-tumorigenic & antioxidant	[172] [173]
			Nrf2, NQO-1, Keap1, NOX4, p-JNK, T-JNK, p-ERK, T-ERK, T-p38, p-NF-κB, p-p65, NLRP3, p53, Bcl-2, HO-1, Bax, Caspase-3, and cell viability	<i>Rhododendron dauricum</i> (L.)	Leaves	20 mg/kg	I.P	Farrerol (flavanone)	Anti-inflam-matory, anti-oxidant, anti-bacterial & anti-cancer	[174] [175] [176]
			H ₂ O ₂ , MDA, GSH, CAT, Nrf2, HO-1, SOD, CAT, GR, and creatinine	<i>Brassica rapa</i> (L.)	Ethanollic extract/roots	25, 50, or 100 μM	Orally (3 h)	6-Hydroxy-1-methylin-dole-3-Acetonitrile (6-HMA)	Antitumor, antioxidant, anti-inflam-matory, hepatoprotec-tive & nephro-protective	[177] [178] [179]
			p-JNK; T-JNK; p-ERK; T-ERK; pp38; T-p38; p-NF-κB; pp65; NLRP3; pp53; p53; Bax; Cas-pase-3; MPO; MDA; SOD; GSH; Sirt1; Sirt6; Nrf2; HO-1; NQO-1; Keap1; NOX4;	<i>Phyllostachys pubescens</i> (L.) <i>Gentiana patrinia</i> (L.) & <i>Pueraria tuberosa</i> (Roxb. ex Willd.) DC	Tubers	50 mg/kg	I.P (3 days)	Isoorientin (flavone) 3',4',5,7-tetrahydroxy-6-C-glucopyranosyl	Anti-inflam-matory, anticancer & antioxidant	[63] [180] [64]

Table 3 (continued)

Therapeutic class	Nephro-toxicants	Indication	Molecular Biomarkers	Nephroprotective Plant	Extract/ Part Used	Dose	Duration/ ROA	Active metabolites/ Class	Therapeutic Activities of NP Plant	References
			TP53, PARP, IL-12, TNF- α , MPOp38; ERK1/2; Nrf2, HO-1, TBARS, iNOS, GSH, SOD, CAT, GR, GST, NQO1; Caspase-3, Caspase-9; Bax; Bcl-2; TP53,	<i>Spinacia oleracea</i> (L.) <i>Brassica oleracea</i> var <i>Phaseolus vulgaris</i> (L.) <i>Camellia sinensis</i> (L.)	Vegetables	50, 100, 150 & 200 mg/kg	Orally (2 weeks)	Kaempferol (flavonoid)	ROS, anticancer, antioxidant, hepatoprotective & anti-inflammatory	[165] [181]
			HO-1, β -Actin, Nrf2, CAT, GPx, SOD, and NF- κ B	<i>Carica papaya</i> (L.) <i>Daucus carota</i> (L.) <i>Solanum Lycopersicum</i> (L.)	Fruits	6 mg /kg/ day	Orally (10 days)	Lycopene (carotenoid)	Antioxidant activity & anti-inflammatory	[182] [183] [184] [185]
			Caspase-3, Calpain, Caspase-12, Nrf2, HO-1, SOD-2, Bax, Bcl-2, IL-6, IL-10, TNF α , NDH, SDH, IL-1 β , NF- κ B, and so on	<i>Mangifera indica</i> (L.)	Fruit	5–30 μ M	Orally	Mangiferin (nonsteroidal polyhydroxy polyphenolic)	Hepatoprotective, anti-cancer & renoprotective	[186] [187] [188] [189]
			GST, HO-1, KIM-1, NGAL, Nrf2, NF- κ B, OC, GCLC, GCLM, and	<i>Cassia garretiana</i> (L.) & <i>Rheum undulatum</i> Pall		10 mg /kg/ day	I.P (7 days)	Piceatannol (stilbene hydroxylated analogue of resveratrol)	Anticancer & anti-inflammatory	[190] [62] [191] [192] [193]
			MDA; Oxidized proteins; GSH; Nrf2; PKC β 2; p47phox; gp91phox; CAT; GPx; GR	<i>Allium sativum</i> (L.)	Rhizome	6.25, 12.5, 15, 20, 25, 50, 100, 150 & 200 mg/kg	I.P. two dosages on days one and two Days 3 and 4: One dosage	S-allyl Cysteine (Organosulfur compound)	Antioxidant, anti-viral & anti-apoptotic	[194] [195] [196]
			NQO-1, HO-1, GCLC, GSH, MDA, Nrf2, and SOD	<i>Schisandra sphenanthera</i> (Rehder & E.H. Wilson)	Ethanolic extract	500 mg/ kg/ day	I.P (10 days)	Schisandrol	Anticancer, anti-oxidation, anti-inflammatory & hypoglycaemic	[197] [62] [198] [199]

Table 3 (continued)

Therapeutic class	Nephro-toxicants	Indication	Molecular Biomarkers	Nephroprotective Plant	Extract/ Part Used	Dose	Duration/ ROA	Active metabolites/ Class	Therapeutic Activities of NP Plant	References
			SOD; CA; GSH; NO; Lipid peroxidation: MDA, total protein, IL-6, TNF- α , MPO, NF- κ B [p65], Bax 3, Bcl2, NRF2, HO-1, etc	<i>Fragaria ananassa</i> (Duchesne Weston) <i>Oxyccoccus</i> <i>Macrocarpus</i> (L.) <i>Anethum graveolens</i> (L.)		20 mg/kg	Orally (10 days)	Sinapic acid (phenylpropenoid)	Anti-inflammatory, antioxidant, anticancer & anti-anxiety	[200] [201] [202] [203] [204] [205]
			Bax; Bcl-2; HMGB-1; PPAR- γ ; KIM-1; TLR4; Caspase-3; Nrf2; HO-1; NQO-1; TNF- α ; IL-1 β ; ATP	<i>Ligusticum wallichii</i> Franch		50 & 100 mg/kg/day	I.P (2 weeks)	Tetramethylpyrazine & ligustrazine	Reno protective, antioxidant, anti-inflammatory & anti-fibrosis	[206] [207] [208] [209]
			SOD, GSH, DCFH-DA, DCF, Nrf2, HO-1, MDA, TNF- α , IL-1 β , IL-6, TLR4, NF- κ B, and I κ B α	<i>Humulus lupulus</i> (hops.)	Inflorescences	12.5, 25, 50 mg/kg/day	I.P (3 days)	Xanthohumol	Anti-inflammatory, antimicrobial & anti-apoptotic	[210] [211]

Table 3 (continued)

Therapeutic class	Nephro-toxicants	Indication	Molecular Biomarkers	Nephroprotective Plant	Extract/ Part Used	Dose	Duration/ ROA	Active metabolites/ Class	Therapeutic Activities of NP Plant	References
Antineoplastic	Cyclophosphamide	Acute inflammation of the urinary bladder & renal damage	NFB, NRF2, HMOX1, NQO-1, Actb, MDA, NO, GSH, SOD, CAT, GPx, TNF- α , IL-1 β , Bax, Bcl-2, Caspase-3, NFB, RRF2	<i>Boesenbergia rotunda</i>		20 mg/kg		(Alpinetin, cardamonin, pinostrombin, panduratin & pinocembrin)	Anti-inflammatory, nephroprotective & anticancer	[212]
				<i>Aerva lanata</i> (L.)	Ethanollic extract	75, 150 & 300 mg/kg	PO (10 days)	Flavonoids (kaempferol & kaempferol 3-rhamnoside)	Anti-oxidant & nephroprotective	[47] [213]
				<i>Annona reticulata</i> (L.)	Ethanollic extract	500 mg/kg	PO (15 days)	Alkaloids, glycosides, saponins & flavonoids	Antioxidant	[214]
				<i>Combretum micranthum</i> (G. Don)	Hydro-alcoholic extract	200 & 400 mg/kg	PO	Polyphenols	Anti-oxidant, anti-inflammatory & nephroprotective	[215] [216] [217]
				<i>Foeniculum vulgare</i> (L.)	Aqueous extract	(150 mg/kg B.W)	(10 days)	Cardiovascular glycosides, coumarins, sterols, triterpenes, flavonoids, and volatile oils	Anti-inflammatory, hepatoprotective, nephroprotective & analgesic	[218] [66] [219]
				<i>Senna auriculata</i> (L.) Roxb	Ethanollic extract	300 & 600 mg/kg B.W	PO (10 days)	Flavonoids, polysaccharides, tannins & saponins	Nephroprotective & antioxidant	[67] [220]
				<i>Olea europaea</i> (L.)	Aqueous leaf extract	100 or 200 mg/kg	(15 days)	Luteolin, rutin, Oleuropein & apigenin,	Anti-oxidant, nephritis & Nephroprotective	[221] [222] [223] [224]

Table 3 (continued)

Therapeutic class	Nephro-toxicants	Indication	Molecular Biomarkers	Nephroprotective Plant	Extract/ Part Used	Dose	Duration/ ROA	Active metabolites/ Class	Therapeutic Activities of NP Plant	References
Immunosuppressant	Cyclosporine (Beauveria <i>nivea</i>)	Anti-fungal, anti-rheumatic, immunosuppressive	SOD1; SOD2; CAT; MDA; 8-iso-PGF2a8-OHdG; Bax; Bcl-2; β -Actin; α -SMA; Nrf2; Keap1; HO-1; NQO-1;	<i>Olea europaea</i> (L.)	Ethanollic	25 mg /kg/ day	I.P (7 days)	Oleanolic acid (Pentacyclic triterpene carboxylic acid)	Antioxidant, antihypertensive & hypoglycaemic	[225] [226] [227] [228]
			MDA, CAT, GSH-Px, BUN, P-gp, Nrf2, HO-1, GAPDH, and Creatinine	<i>Schisandra chinensis</i> (Turcz.) Baill	Ethanollic Extract	54,108 & 216 mg/kg	Orally	Schizanthrin A, schizanthrin B deoxyschizanthrin, Schizandrin & schizanthrol	Anti-cancer, antioxidant, neuro-protective, hepatoprotective & anti-inflammatory	[228] [229] [72] [230] [231]
Anthracycline	Epirubicin	Breast cancer	GR, SCR, TNF- α , IL-6, CAT, SOD, NO, iNOS, Caspase-9, Caspase-3, Bax, Bcl-2, Nrf2, HO-1, p-NF- κ B, p-IKK α / β , and I κ B α	<i>Paeonia suffruticosa</i> (Andr)	Root, bark	30 mg kg/ day	I.G (4 days)	Paeonol (2'-Hydroxy 4'-methoxy acetophenone)	Anti-inflammatory, diabetic encephalopathy & anti-tumour	[232] [233] [234] [235] [236]
Aminoglycoside antibiotic	Gentamicin	Pneumonia, urinary tract infections & sepsis	Nrf2; NF- κ B; Na ⁺ ; K ⁺	<i>Actinidia deliciosa</i> (L.)	Fruit	37 g/kg	Orally (8 days)	Polyphenols, carotenoids & flavonoids	Anti-inflammatory, anti-carcinogenic & antioxidant	[237] [238] [239]
			-	<i>Aerva lanata</i> (L.)	Ethanollic Extract	300 mg/kg		Flavonoids (kaempferol & 3-rhamnoglucoside) 3-rhamnoglactoside	Antioxidant & nephroprotective	[47] [213]
			LD; OS; Cl; ROS; SOD; CGP;	<i>Abutilon indicum</i> (L.) <i>Boerhaavia diffusa</i> (L.)	Extracts	200 mg/kg	(21 days)	Phenolic glycoside -punarnavoside, c-methyl flavone-borhaavone	Diuretic, nephrotic, syndrome, anti-inflammatory & antioxidant	[46] [240] [241]

Table 3 (continued)

Therapeutic class	Nephro-toxicants	Indication	Molecular Biomarkers	Nephroprotective Plant	Extract/ Part Used	Dose	Duration/ ROA	Active metabolites/ Class	Therapeutic Activities of NP Plant	References
			SC; TP; SU	<i>Elephantopus scaber</i> (L.)	Ethanolic leaf extract	200–600 mg/kg/day	(7 days)	Epifriedelinol, lupeol & stigmastero	Hepato-protective, antimicrobial & anti-inflam-matory	[242] [243]
			BU; SC	<i>Cassia auriculata</i> (L.)	Ethanol extract	300 & 600 mg/kg/BW	(10 days)	Flavonoids, tannins & saponins	Nephropro- tective & antioxidant	[220]
			HO-1, NQO-1, Bax, Bcl-xl, Caspase-3, Nrf2, PKCa, NOX4, MDA, SOD, Oat3, [3H] ES adop- tion	<i>Boesenbergia pandu- rata</i> (L.) <i>Boesenbergia rotunda</i> (L.) <i>Baccharis dracuncu- lifolia</i> (L.)	Rhizomes	50 & 75 mg kg/day	I.P (10 days)	Pinocembrin (5,7dihydroxy- flavonone)	Antioxidant, anti-inflam- matory, neuro-protec- tive, cardio- protective & anticancer	[244] [245] [246] [247]
			Caspase activ- ity, LDH, PARP, Bax, Bcl-2, Nrf2, HO-1, NQO-1, ROS, SO, and cell viability	<i>Oryza sativa</i> (L.)	Extract	100 mg/kg	Orally (15 consecu- tive days)	Rice berry bran vitamin E complex (tocopherols, tocotrienols) & β -carotene	Antioxidant	[248] [249]
			AOE; SOD, CAT, GPx, GR; GST; SOD; CAT; caspase-3; Bcl-2; p53; (Bcl-2) (SU; SC)	<i>Citrus x paradise</i> (L.)		50 and 100 mg/kg	Orally (7 days)	Naringin Flavonoids & polyphenolic compounds	-	[250] [251] [252]
				<i>Cichorium intybus</i> (L.)	Aqueous & methanolic extracts	3.4 mg/kg	Orally once daily (12 days)	Chicoric acid (phenylpropa- noid)	Diuretic, nephropro- tective & tonic for kidneys	[253]
			OS; MDA; GSH; SOD; CAT	<i>Musa Sapientum</i> (L.)	Ethanolic extract	250 & 500 mg/kg	P.O (7 days)	Flavonoids, phenolic compounds, alkaloids & glycosides	Antioxidant, nephritis & anti-inflam- matory	[254]
				<i>Foeniculum vulgare</i> (Mill.) <i>Solanum nigrum</i> (L.)	Aqueous extract	250 & 500 mg/kg	Orally (21 days)	Fenchone, limonene, sterols, piperidone & piperitone oxide	Nephropro- tective & antioxidant	[255]

Table 3 (continued)

Therapeutic class	Nephro-toxicants	Indication	Molecular Biomarkers	Nephroprotective Plant	Extract/ Part Used	Dose	Duration/ ROA	Active metabolites/ Class	Therapeutic Activities of NP Plant	References
Anti-apoptotic	Methotrexate	Cutaneous T cell lymphoma, breast cancer, leukaemia & lung cancer	BU; SC; UA; BUN	<i>Pimpinella anisum</i> (L.)	Aqueous extract	1, 2 & 4 g/kg, per	Orally (8 days)	Polyphenolics	Antiviral, antioxidant & anticonvulsant	[256] [257]
			BU; SC; UA; BUN	<i>Tamarindus indica</i> (L.)	Aqueous-ethanol	200 mg/kg	3 (weeks)	Flavonoids & phenolic	Nephroprotective & antioxidant	[258] [259]
			Keap1, Nrf2, P38, MAPK, β -actin, NF- κ B, TBPS, GSH, SOD, NO, Bax, Bcl-xl, Caspase-3, Caspase-2, HepG2, MCF-7	<i>Berberis vulgaris</i> (L.)	Methanolic extract	50 mg/kg/day	Orally (10 days)	Berberine	Neuro-protective effects, anti-oxidative, anti-apoptotic & anti-ischemic	[260] [261]
			Bax; Bcl-2; β -actin; KIM-1/ROS; MDA; NO; TNF- α ; GSH; SOD; CAT; GPx; NF- κ B; NF- κ Bp65; NLRP3; Caspase-1p20; IL-1 β	<i>Ocimum basilicum</i> (L.) <i>Cichorium intybus</i> (L.)	-	25 & 50 mg / kg/ day	Orally (15 days)	Chicoric acid (phenylpropanoid)	Antioxidant and immune-stimulating, anti-inflammatory & anti-ageing properties	[262] [263] [264]
			NF- κ B; TNF- α ; IL-1 β ; Nrf2, HO-1, SOD, CAT, GPx, Bax, Bcl-2, GSH	<i>Commiphora molle</i> (Engl.)	Ethanollic	125 & 250 / mg kg/ day	Orally (15 days)	Myrrh	Anti-inflammatory, neuro-protective, anti-diabetic & antioxidant	[265] [266] [267]
			TNF- α , GSH, SOD, GPx, CST, Bax, Bcl-2, β -actin, KIM-1, Nrf2	<i>Glycyrrhiza glabra</i> (L.)		50 & 100 mg/ kg/ day	Orally (7 days)	Enoxolone (18 b-Glycyrrhetic acid) glycyrrhizin	Antioxidant, anti-cancer & anti-inflammatory	[268] [62]

Table 3 (continued)

Therapeutic class	Nephro-toxicants	Indication	Molecular Biomarkers	Nephroprotective Plant	Extract/ Part Used	Dose	Duration/ ROA	Active metabolites/ Class	Therapeutic Activities of NP Plant	References
Ethylene glycol and ammonium Chloride			PPAR γ ; Bax; Bcl-2; ROS; MDA; SOD; CAT; GPx; Caspase-3; NLRP3; 1p20; IL-1 β ; NF- κ Bp65; Cytochrome c	Zea mays (L.) Solanum Lycopersicon (L.)		25 & 50 mg/kg/day	Orally (15 days)	Ferulic acid (Hydroxycinnamic acid)	Antioxidant; cardiovascular diseases, diabetes, neurodegenerative diseases & cancer	[269] [270]
			COX-II, Nrf2, HO-1, NF- κ B, IL-1 β , IL-6, TNF- α , MDA, LPO, TBARS, NO, ATP, GSH, GR, GST, CAT, SOD, MDA, AND GST	Trifolium Pratense (L.), Glycine max (L.) Merr. Sophora flavescens Aiton		10, 20, & 40 mg/kg/day	Orally (10 days)	Formononetin	Anti-inflammatory, anticancer & antioxidant	[237] [271] [272] [273]
			Caspase-3, Nrf2, HO-1, MDA, SOD, CAT, NF- κ B, IL-1 β , IL-10, TNF- α , MPO, COX-II	<i>Vinca minor</i> (L.)	Ethanollic extract	10, 20 & 40 mg/kg	Orally	Vincamine (Indole alkaloid)	Diuretic, antioxidant & anti-cancer	[274] [275] [276]
Analgesic	Acetaminophen		STP; SM	<i>Vigna unguiculata</i> (L.) <i>Hordeum vulgare</i> (L.)	Aqueous, alcoholic	200 mg/kg & 300 mg/kg	Orally (28 days)	-	Diuretic & nephroprotective	[277]
			CO $_2$; P; SC; BUN; UA	<i>Cucumis sativus</i> (L.)	Hydro-alcoholic	100, 200 & 400 mg/kg/BW	Orally (1st day till 28th)	-	Antiolithiatic	[278]
Cadmium			GSH; LP	<i>Lantana camara</i> (L.)	Methanolic extract	200 & 400 mg/kg	Orally (14 days)	Flavonoids,	Anti-inflammatory & matory	[279] [280]
			GSH; SOD; CAT; TGF- β 1; NF- κ B; COX-1	<i>Musa.paradisica</i> (L.)	Hydro-alcoholic	(300 mg/kg B.W	I.P (10 days)	Phenolics & flavonoids	Antilucer, anti-inflammatory & antioxidant	[281] [282]

officinalis [48], *Terminalia chebula* [49], *Zingiber officinale* [50], *Withania somnifera* [51], *Tribulus terrestris* [52], and Jawarish Zarooni Sada (a poly herbal formulation) [53], have shown noteworthy nephroprotective effects.

Reversal of nephrotoxic effects of Adriamycin by medicinal plants

Anthracycline drugs, such as adriamycin (doxorubicin), are used to treat cancer. Nevertheless, there are many adverse effects associated with its treatment [54]. Renal toxicity induced by adriamycin may arise from multi-organ damage primarily caused by the buildup of free radicals, which in turn induces membrane lipid peroxidation [55]. It is harmful to renal tissue because it builds up in the kidney and causes tubular degeneration [56] and increased glomerular capillary permeability. Herbal medications have been shown to be beneficial in reducing the effects of renal impairment. Herbal medications in the form of alcoholic *P. multiflorum* extract, aqueous extracts of *C. sinensis* and *N. sativa*, and other extracts have demonstrated encouraging nephroprotection through the production of antioxidant and anti-inflammatory properties.

Reversal of nephrotoxic effect of Cisplatin by medicinal plants

Cisplatin is a drug for cancer treatment; due to its limited clinical application, frequent adverse effects in the form of acute kidney injury, glomerular capillary endothelial injury, tubulointerstitial disease, and renal electrolyte disorders, which constitute the major reasons of morbidity and mortality among cancer patients [57]. This adverse effect has been employed in developing animal models for kidney disorders and for screening and identifying of several herbal drugs in mitigating the said damage. The defatted methanolic extract of *Lantana camara* is discovered to have a nephroprotective effect on rats given oral doses ranging from 100 to 400 mg/Kg for fifteen days, thereby preventing cisplatin-induced nephrotoxicity. The phytochemical ingredient profile of the plant, which is rich in phenolic and flavonoids, was found to positively correlate with the results [58]. The majority of plant drugs reviewed presently in cisplatin-induced nephrotoxicity were found to be rich in flavones and flavonoids including *Andrographis paniculata* [59], *Aerva lanata*, *Biophytum sensitivum* [60], *Boerhaavia diffusa* [61], *Rhododendron dauricum* [62], *Phyllostachys pubescens* [63], *Gentiana patrinia* [62], *Pueraria tuberosa* [64], *Brassica oleracea* [65], *Foeniculum vulgare* [66], *Senna auriculata* [67], and *Cassia garretiana* [68].

Reversal of nephrotoxic effect of cyclophosphamide by medicinal plants

Cyclophosphamide is a wide-spectrum anticancer drug with multiple complications, including nephrotoxicity. Cyclophosphamide is highly reabsorbed through the tubules, with only a small portion is eliminated by the kidneys. Numerous investigators have documented that oxidative stress is a significant factor in renal impairment caused by cyclophosphamide. Reactive oxygen species mostly affect the cells of kidney's proximal tubules, resulting in nephrotoxicity [69]. An aqueous extract of *Olea europaea* leaves at doses of 100 and 200 mg/Kg body weight for fifteen days, restored the nephrotoxic effects of cyclophosphamide. It was demonstrated to upregulate the expression of bcl2, Nrf2/ARE/HO-1 signalling, and Bax while downregulating the expression of cytochrome c, caspase-3, and Bax, thereby increasing the antioxidant activity and reducing the inflammatory and apoptotic responses [70]. The Modulation of oxidative stress, inflammatory cytokines, and apoptosis in rats to prevent cyclophosphamide-induced nephrotoxicity and its Ppoteffective effect [71].

Reversal of nephrotoxic effect of cyclosporine by medicinal plants

Cyclosporine A is an immunosuppressive administered following solid organ transplantation to prevent rejection and treat autoimmune diseases. Nevertheless, its use is linked to elevated blood levels of creatinine and uric acid, as well as the eventual development of renal failure, which restricts its application. Cyclosporine-induced renal injury is believed to be mediated via vasculopathy, which reduces blood supply to the kidney. Low concentrations of cyclosporine have also been demonstrated to interact with cell membranes, inducing oxidative stress, endoplasmic reticulum stress, and autophagy to cause proximal tubule damage [72]. Ethanolic extract of *Schisandra chinensis* was found to reverse the cyclosporine-induced nephrotoxicity in rats by suppressing the decrease in the histopathological alterations and the increase in blood urea nitrogen (BUN) and serum creatinine levels [73]. Similar results were also revealed by ethanolic extracts of *Olea europaea* [74].

Reversal of nephrotoxic effect of gentamicin by medicinal plants

Gentamicin is a typical broad-spectrum aminoglycoside used to treat potentially lethal infections brought on by Gram (+ve) and Gram (–ve) bacteria is gentamicin (GM). However, 15–30% of treated participants have nephrotoxicity. The scientific community is investigating the renoprotective role of plant species to minimize

gentamicin-induced nephrotoxicity [75]. Administration of aqueous and ethanolic extracts of *Gomphrena celosioides*, *Cola nitida*, and *Entendrophragma angolense* mitigate the effect of nephrotoxicity in the serum biochemical parameters deciphering kidney functions (urea, creatinine, uric acid, blood urea nitrogen) and oxidative stress (MDA/LPO, GSH/GPX, CAT, SOD) [76].

Reversal of nephrotoxic effect of methotrexate by medicinal plants

The primary uses of methotrexate (MTX) are the treatment of autoimmune diseases and specific types of malignancies. High dose of methotrexate (HD-MTX), defined as doses of 500 mg/m² or more, can lead to toxicities like pulmonary toxicity, bone marrow suppression, nephrotoxicity, hematological toxicity, and many infectious diseases [77]. The hepato-renal toxicity of HD-MTX and extended intake at lower dosages can be explained by the concentration- and time-dependent toxicity generated by MTX. MTX-induced hepato-renal damage was assessed by serum toxicity biomarkers (AST, ALT, BUN, and creatinine), oxidative stress estimation (MDA, GSH, SOD, CAT, peroxidase, and glutathione reductase), interleukins profiling (TNF- α , IL-1 β , IL-6, and IL-12), tissue histopathology and immunohistochemical (caspase-3 and NFkB) examination. *Glycyrrhiza glabra* is a traditional medicinal herb with demonstrated anti-inflammatory, anti-oxidant, hepato-protective and nephro-protective properties [78]. Proposed the possibility that GGE might shield organs against MTX-induced harm. In fact, studies showed that MTX caused significant hepato-renal damage, which may be reversed by taking *Glycyrrhiza glabra* extract concurrently. Additionally, the study reveals targets for lowering MTX-induced tissue harm, including oxidative stress, inflammation, and apoptosis [79].

Conclusion and way forward

In conclusion, kidney damage, including CKD and AKI, is a significant global health concern with rising incidence and poor outcomes; notably CKD is a leading cause of mortality worldwide. Risk factors such as hypertension, diabetes, genetic predispositions, and exposure to nephrotoxic agents contribute to its multifactorial etiology. Traditional medicinal plants offer a promising avenue for nephroprotection and kidney disease treatment, potentially yielding therapies with fewer side effects than conventional medications. Pharmacognostic studies have unveiled the nephroprotective potential of medicinal plants, with various botanicals demonstrating efficacy in mitigating nephrotoxicity and renal damage. Animal models, particularly rodents, are crucial for understanding kidney disease pathogenesis and developing therapeutic strategies. By simulating human conditions, these

models aid in studying disease mechanisms and testing potential treatments. Their use has facilitated the discovery of nephroprotective agents from natural products, highlighting the importance of traditional medicine in kidney disease management. However, further research is needed to validate the efficacy, safety, and mechanisms of action of medicinal plants. Rigorous scientific evaluation through preclinical and clinical studies is essential to establish their role as adjuncts or alternatives to conventional therapies. Moving forward, collaborative efforts among researchers, healthcare professionals, and policy-makers are essential to advance nephroprotection using traditional medicinal plants. Key areas for exploration include conducting additional preclinical studies to elucidate botanicals' mechanisms of action, undertaking clinical trials to evaluate herbal formulations' safety, efficacy, and dosage regimens, exploring synergistic effects of combining medicinal plants with conventional therapies, developing standardized cultivation, extraction, and formulation protocols, and raising awareness among healthcare providers and patients about integrating traditional medicine into kidney disease management. By fostering interdisciplinary collaboration and prioritizing research in this field, we can harness the therapeutic potential of medicinal plants to mitigate the global burden of kidney disease and enhance patient outcomes. In future these traditional Indian medicinal plants *Camellia sinensis* (L.) Kuntze, *Nigella sativa* (L.), *Andrographis paniculata* (Burm.f.) Nees, *Daucus carota* (L.), *Foeniculum vulgare* (L.), *Glycyrrhiza glabra* (L.) and *Cucumis sativus* (L.) and their botanicals could be the hope for the prevention and management of CKD.

Abbreviations

AKI	Acute kidney injury
ALL	Acute lymphocytic leukemia
ALT	Alanine aminotransferase
AM	Animal models
AP	Alkaline phosphatase
AP-1	Activator protein-1
ARE	Antioxidant response element
AST	Aspartate aminotransferase
BCCs	Basal cell carcinomas
BUN	Blood urea nitrogen
CAT	Catalase
CIN	Chronic interstitial nephritis
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
Cr	Creatinine
CVD	Cardiovascular disease
DIN	Drug-induced nephrotoxicity
DNA	Deoxyribonucleic acid
E. coli	Escherichia coli
ESKD	End-stage kidney disease
GBD	Global Burden of disease
GBM	Glomerulus basement membrane
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transpeptidase
GS	Glomerulosclerosis
GSH	Glutathione

GSH-Px	Glutathione peroxidase
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
HO	Heme oxygenase-1
HRP	Horseradish peroxidase
HSV	Herpes simplex virus
ICAM-1	Intercellular adhesion molecule 1
IFN- γ	Interferon- γ
IgA	Immunoglobulin A
IKK	I κ B (inhibitor of NF- κ B) kinase
IL-1 β	Interleukin-1 β
IL-2	Interleukin-2
IL-6	Interleukin-6
IRF	Irreversible renal failure
LPO	Lipid peroxidation
MAPK	Mitogen-activated protein kinase
MDA	Malondialdehyde
NMSC	Non-melanoma skin cancer
NF- κ B	Nuclear factor kappa B
NO	Nitric oxide
NP _s	Natural products
Nrf2	Nuclear factor erythroid-2-related factor-2
NSAIDs	Non-steroidal anti-inflammatory drugs
NT	Nephrotoxicity
OS	Oxidative stress
PBPs	Penicillin-binding proteins
PC	Polyphenolic compounds
PMP	Per million population
RBC	Red blood cell
RBF	Renal blood flow
RAS	Renal artery stenosis
RIF	Renal interstitial fibrosis
RNA	Ribonucleic acid
ROS	Reactive oxygen species
SAA	Serum alanine aminotransferase
SCCs	Squamous cell carcinomas
SERT	Serotonin transporter
SOD	Superoxide dismutase
TB	Total bilirubin
TIF	Tubulointerstitial fibrosis
TLR4	Toll-like receptor 4
TNF- α	Tumor necrosis factor- α
TRAF6	Tumor necrosis factor receptor-associated factor 6
U	Urea
UA	Uric acid

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Author contributions

AR & RP contributed to conceptualization, data curation, and investigation. AR & Sageer Abass contributed to writing and original draft. Sageer Abass & NRP contributed to visualization, methodology, resources, and formal analysis; BP & SA contributed to supervision, project administration, validation, software, and verification. RP, BP & NRP contributed to supervision, methodology, validation, resources, software, and visualization; SA & RP contributed to supervision, project administration, validation, and visualization. All authors read and approved the final manuscript.

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