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A Review on Bioactive Compounds from Plants Available in South India with Uroprotective and Nephroprotective Activity

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Abstract

Nephrotoxicity and urotoxicity are two menacing entities that can wreak havoc on renal function and patient wellbeing, making them a pressing concern in the realms of clinical medicine and drug research. The review examines the underlying causes and mechanisms of these conditions, including drug-induced nephrotoxicity and the effects of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), antibiotics, and chemotherapeutic agents. In vivo and in vitro methods for studying these outcomes are also explored. The advantages and limitations of different experimental models for studying nephrotoxicity are discussed, such as rodents, zebrafish, and organ-on-a-chip technologies. Additionally, botanical extracts such as Punica granatum and Curcuma longa are considered for their potential therapeutic benefits in managing nephrotoxicity. These extracts have shown antioxidative, anti-inflammatory, and immunomodulatory properties that make them promising candidates for future research. This review aims to encourage and inspire further research and innovation in the field of nephrotoxicity and urotoxicity management, by highlighting the potential of botanical extracts and the importance of utilizing experimental models for studying these conditions.

Keywords: Nephrotoxicity; Urotoxicity; Herbal extract; Drug induced nephrotoxicity

Introduction

Nephron is the most fundamental unit of kidney, both structurally and functionally at microscopic level. The constitution is comprised of a renal corpuscle and a renal tubule. The renal corpuscle is comprised of a glomerulus, which has a bundle of capillaries, and Bowman's capsule, shaped like a cup. The renal tubule originates from the renal capsule. The capsule and tubule exhibit interconnectivity and are comprised of epithelial cells featuring a central cavity. An individual with good health possesses approximately 1 to 1.5 million nephrons in each of their kidneys [1].

As the fluid from the capsule descends into the tubule, it undergoes processing by the epithelial cells that lines the tubule. This processing involves reabsorption of water and the exchange of substances, being added, and removed. The exchange occurs initially with the interstitial fluid outside the tubules and subsequently with the plasma in the adjacent peritubular capillaries through the endothelial cells lining that capillary. This physiological mechanism maintains homeostasis of body fluids and various biochemical's. Upon reaching the terminus of the tubule, the residual liquid, known as urine, is expelled. This substance is comprised of water, metabolic byproducts, and harmful substances, as documented by Stevens, et al. [2].

The four mechanisms employed for the generation and manipulation of the filtrate (which leads to the conversion of blood into urine) are filtration, reabsorption, secretion, and excretion [1,3]. Filtration or ultrafiltration takes place within the glomerulus and is primarily a passive process that relies on the intra-capillary blood pressure. Approximately 20% of the plasma undergoes filtration during its transit through the glomerular capillaries, while the remaining 80% proceeds into the peritubular capillaries. Typically, the sole constituents of the blood that do not undergo filtration into Bowman's capsule are blood proteins, erythrocytes, leukocytes, and thrombocytes. Daily, the glomeruli of an adult individual receive a volume of fluid exceeding 150 litres, out of which 99% of the water content is subjected to reabsorption. Reabsorption takes place within the renal tubules and can be passive, resulting from diffusion, or active resulting from pumping against a concentration gradient. The process of secretion is also observed in the tubules and collecting duct and it is an active phenomenon. The substances that are subjected to reabsorption comprises of water, sodium chloride, glucose, amino acids, lactate, magnesium, calcium phosphate, uric acid, and bicarbonate. The excretory process involves the secretion of various substances such as urea, creatinine, potassium, hydrogen, and uric acid. Several hormones regulate the reabsorption or secretion rate in the tubules to maintain homeostasis. These hormones include antidiuretic hormone (water), aldosterone (sodium, potassium), parathyroid hormone (calcium, phosphate), atrial natriuretic

peptide (sodium), and brain natriuretic peptide (sodium). The renal medulla employs a counter current system to produce a hypertonic interstitium, facilitating the retrieval of solute-free water from the nephron and its subsequent return to the venous vasculature as needed.

In this context, we have conducted a review on nephro/ urotoxicity and the effect of plants that exhibit nephroprotective properties against pre-renal, intrinsic, and post-renal diseases. The utilization of nephroprotective plants as a supplementary pharmacological intervention was supported by scientific evidence that demonstrated their effectiveness in mitigating the pathophysiology's that result in kidney injuries (Figure 1).



Literature Review

Nephro/urotoxicity

Nephro/urotoxicity is characterized by the swift decline in renal function resulting from the toxic influence of pharmaceuticals and chemicals. There exist diverse manifestations, and certain pharmaceuticals might impact the renal system through multiple mechanisms. Nephrotoxic substances exhibit nephrotoxicity. It is important to differentiate nephrotoxicity from medications that are primarily excreted through the kidneys and require dosage adjustment in the presence of renal impairment, such as heparin. The renal toxicity of the majority of medications is more pronounced in individuals who are already experiencing renal dysfunction. Several prevalent clinical manifestations of anticancer drugs on the kidneys are Acute Kidney Disease (AKI) glomerulopathy-induced caused by tubular necrosis, proteinuria, hypertension, electrolyte disturbance-induced tubulopathies, and Chronic Kidney Disease (CKD) (Figure 2) [4].



Approximately 20% of instances of nephrotoxicity are druginduced. This proportion is amplified in geriatric populations due to prolonged lifespans and the use of multiple medications. Frequent risk factors associated with drug-induced nephrotoxicity in patients include underlying renal insufficiency (GFR<60 mL per minute per 1.73 m²), age over 60 years, hypertension, congestive heart failure, diabetes, and volume depletion [5].

Sex and genetic variability are frequently implicated in the predisposition to drug-induced nephrotoxicity, with males exhibiting greater susceptibility than females due to hormonal disparities. In addition, it has been observed that dehydration, heart failure, and hepatic insufficiency are among the contributing factors that elevate the susceptibility to druginduced renal damage [6].

There exist various mechanisms of nephrotoxicity, such as renal tubular toxicity, inflammation, glomerular damage, crystal nephropathy, and thrombotic microangiopathy, as reported by Al-Kuraishy, et al. [7].

Moreover, impairment of the kidneys leads to postponed elimination and processing of drugs and widespread toxicity. Consequently, numerous medications may necessitate dosage modification in the setting of renal insufficiency [5].

Drug induced nephro-uro toxicity

The selective endocytosis and accumulation of aminoglycosides *via* the multi-ligand receptor megalin causes nephrotoxicity, which specifically affects the proximal tubule epithelial cells. The induction of oxidative stress by toxic agents and drugs can potentially damage the tubular transport system, resulting in tubular mitochondrial damage. Aminoglycoside, amphotericin B, and antivirals like adefovir and foscarnet are known to cause tubular damage, as per the research conducted by Vormann, et al., which has been tabulated in Table 1 [8].

Table 1: Drugs involved	n nephrotoxic	mechanism.
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Nephrotoxic mechanism	Drugs involved	References
Selective endocytosis and accumulation	Aminoglycosides	Vormann, et al.
Tubular damage	Aminoglycoside, Amphotericin B, Adefovir, Foscarnet	Vormann, et al.
Tubular damage	Antiretroviral drugs, Cisplatin	Qu, et al.
Decrease in intra-glomerular pressure and glomerular filtration rate	Diclofenac, Valsartan, Captopril	Sudjarwo, et al.
Vasoconstriction of the afferent arteriole	Cyclosporine, Tacrolimus	Sudjarwo, et al.
Interstitial nephritis	Allopurinol, Rifampicin, Sulfonamide, Lansoprazole, Quinolones, Cyclosporine, Chinese Herbal Medicine, NSAID's (over 1 gram/day for 2 years)	Suzuki, et al.
Glomerulonephritis	Gold, Interferon, NSAIDs, Lithium, Hydralazine, Pamidronate	Frazier, et al.
Crystal formation in renal tubules	Sulfonamides, Ampicillin, Acyclovir, Ciprofloxacin, Methotrexate, Triamterene	Pawar, et al.
Drug-induced microangiopathy	Ticlopidine, Cyclosporine, Quinine	Brocklebank, et al.

The compact nature of renal drug transporters plays a significant role in the heightened susceptibility of proximal renal tubules to toxic substances like antiretroviral drugs and cisplatin, as per the findings of Qu, et al. [9].

Nonsteroidal anti-inflammatory drugs such as diclofenac, angiotensin receptor blockers like valsartan, and angiotensinconverting enzyme inhibitors like captopril have been observed to cause significant decline in intraglomerular pressure and glomerular filtration rate. Furthermore, it has been observed that cyclosporine and tacrolimus induce vasoconstriction of the afferent arteriole in a dose-dependent manner, as reported by Sudjarwo, et al. [10].

An allergic reaction to certain medications such as allopurinol, rifampicin, sulfonamide, lansoprazole, and quinolones may result in interstitial nephritis. Several pharmaceutical agents have been identified to potentially induce chronic interstitial nephritis, such as cyclosporine, Chinese herbal medicine, and nonsteroidal anti-inflammatory drugs administered at a dosage exceeding one gram per day for a duration of 2 years. The timely identification and acknowledgement of this ailment's onset and preliminary stages is imperative, as it has the potential to advance into a state of renal failure [11].

Glomerulonephritis is an inflammatory condition of the glomeruli that can be triggered by various nephrotoxic agents such as gold, interferon, NSAIDs, lithium, hydralazine, and pamidronate [12].

Numerous pharmaceutical agents generate crystals that exhibit poor solubility in urine and subsequently deposit within the distal renal tubules, thereby eliciting an interstitial response and obstructing the tubular lumen. The crystal formation is frequently observed in sulfonamides, ampicillin, acyclovir, ciprofloxacin, methotrexate, and triamterene drugs, as reported by Pawar, et al. [13]. Microangiopathy induced by drugs is a result of an immune response triggered by drugs that causes thrombotic thrombocytopenic purpura and platelet activations. This eventually leads to endothelial cytotoxicity, as observed in various medications like ticlopidine, cyclosporine, and quinine [14].

Treatment

The renal dysfunctions caused by nephrotoxic agents are mostly reversible. Therefore, the primary approach in this condition is to cease and desist the causative agents. Several nephrotoxic agents have been observed to elevate blood urea and serum creatinine levels. However, it has been noted that trimethoprim and cimetidine may cause an increase in serum creatinine levels prior to the onset of nephrotoxic effects. This could be attributed to their competition with creatinine during renal tubular secretion, as suggested by Elsby, et al. [15].

The assessment of renal function is better accomplished by utilizing serum creatinine as a marker, as it remains unaffected by dietary factors, unlike blood urea. Therefore, an increase of 50% or greater in baseline creatinine levels by 2 mg/dL is considered an early indication of acute kidney failure. Additionally, it is necessary to perform a thorough assessment of the patient's medications in order to determine the nephrotoxic agent responsible for the adverse effects [16].

Intravenous administration of normal saline or hypertonic saline, with or without mannitol supplementation, is employed to mitigate the toxic effects of the drug through induced diuresis. Magnesium supplementation is administered to alleviate the condition of hypomagnesemia. Amifostine, a glutathione analog and free radical scavenger, is known to

prevent nephrotoxicity by being taken up by healthy cells and mitigating the effects of cisplatin.

It is noteworthy that the irreversible nephrotoxic consequences of ifosfamide in children have been associated with the concurrent usage of ifosfamide and cisplatin. Supplementation of vitamin D is imperative in the paediatric population that is affected [17].

Mesna is utilized as a prophylactic measure against the development of cyclophosphamide-induced nephrotoxicity owing to its capacity to bind toxic metabolites with sulfhydryl groups. While mesna has been found effective in preventing haemorrhagic cystitis and bladder cancer resulting from cyclophosphamide, its efficacy is limited in cases of renal injury caused by ifosfamide. As ifosfamide is transported into proximal tubular cells *via* OCT2, we are currently exploring the potential of cimetidine as a preventative measure by acting as a competitive inhibitor to OCT2, as suggested by Ciarimboli, et al. [18].

The efficacy of glucocorticoid therapy, such as prednisone, in treating interstitial nephritis caused by bortezomib is still uncertain. However, some studies have indicated that kidney function may improve with this treatment [19].

Hypomagnesemia is the primary nephrotoxic effect observed in association with cetuximab. The observed phenomenon can be attributed to the reliance of magnesium on EGF signalling at the basolateral membrane to facilitate absorption in the distal convoluted tubule. The administration of intravenous magnesium, in addition to calcium and potassium, is typically necessary for the management of hypomagnesemia, as stated by Schrag, et al. [20]. The discontinuation of vemurafenib leads to reversible renal damage, as reported by Hurabielle [21]. The renal toxicity linked with IL-2 is ascribed to pre-renal azotaemia due to hypoperfusion and hypotension, as reported by Webb [22]. The cessation of IL-2 administration resulted in the manifestation of typical levels of urinary protein and serum creatinine. The reversible nephrotoxicity caused by IL-2 can be effectively managed by promptly administering fluid boluses upon the onset of oliguria, as reported by Guleria, et al. [23].

Drug interactions

The significance of meticulous medication management in clinical practice is exemplified by the drug-drug interactions that occur between antibiotics such as aminoglycosides, vancomycin, and quinolones, and nonsteroidal anti-inflammatory agents. The interactions may result in escalated nephrotoxicity or elevated susceptibility to seizures, thereby requiring meticulous observation and dosage modifications to mitigate unfavourable outcomes. Scientists must maintain an elevated level of vigilance, especially when dealing with susceptible groups like premature neonates or individuals with a past medical history of kidney impairment or neurological conditions. By keeping abreast of possible drug interactions and implementing suitable measures to handle them, scientists can enhance patient outcomes and guarantee the safety and effectiveness of their therapies and these were tabulated in Table 2.

Table 2: Class of drugs with adverse effects leading to nephrotoxicity.

Drug or drug class	Potential renal adverse effects	Proposed measures
Aminoglycosides (when combined with NSAID's)	Increased nephrotoxicity	Monitor patients for signs of increased nephrotoxicity
Aminoglycosides and vancomycin	Increased nephrotoxicity	Monitor aminoglycoside serum levels and adjust dosage accordingly
NSAID's and quinolones	Increased risk of seizures	Consider increased risk of seizures when co-prescribing, especially in those with impaired renal function, history of seizures, or high dosages/serum levels
NSAID's	Chronic renal dysfunction, acute interstitial nephritis	Monitor renal function, limit duration of use
Opioids	Albuminuria, alterations in renal parameters	Use caution with prolonged use, consider alternative pain management
Statins	Acute kidney injury	Monitor renal function, consider alternative therapies if necessary
Fibrates	Transient elevation in serum creatinine levels	Monitor renal function, adjust dosage as needed

Proton Pump Inhibitors (PPIs)	Allergic interstitial nephritis, acute and chronic renal failure, end-stage renal disease	Use caution when prescribing, consider alternative therapies in those with renal dysfunction
Metformin	Accumulation in those with renal dysfunction	Monitor renal function, adjust dosage as needed, consider alternative antidiabetic therapies if necessary
Aminoglycosides	Renal toxicity	Monitor renal function and drug administration
Fluoroquinolones	Allergic interstitial nephritis	Use caution when prescribing, monitor renal function
Tetracyclines (specifically doxycycline)	Potential role in reducing proteinuria in diabetic nephropathy	Monitor renal function, adjust dosage as needed
Vancomycin	Nephrotoxicity	Monitor vancomycin levels and renal function

The administration of NSAID's has been observed to decrease the excretion of aminoglycosides, a class of antibiotics utilized in the treatment of gram-negative bacterial infections. This interaction could potentially elevate the likelihood of nephrotoxic consequences linked with aminoglycosides. It is recommended that healthcare professionals observe patients for indications of heightened nephrotoxicity upon commencing or elevating the dosage of a nonsteroidal anti-inflammatory drug while the patient is undergoing aminoglycoside treatment. This holds significant importance for premature neonates as per Zarfin, et al., study conducted in 1985 [24].

The co-administration of aminoglycosides with vancomycin, a potent antibiotic utilized to treat severe bacterial infections, may exacerbate the nephrotoxic impact. The co-administration of these pharmaceuticals may result in heightened nephrotoxicity. It is imperative for healthcare professionals to diligently observe aminoglycoside serum levels and modify the dosage accordingly when co-administered with vancomycin. It is advisable to monitor for indications of elevated nephrotoxicity as per the findings of Farber, et al. [25].

Nonsteroidal Anti-Inflammatory Drugs (NSAID's) have the potential to augment the neuroexcitatory and/or seizurepotentiating properties of quinolones, a group of antibiotics utilized for the management of diverse bacterial infections. Furthermore, Nonsteroidal Anti-Inflammatory Drugs (NSAID's) have the potential to elevate the serum levels of quinolone antibiotics. The concomitant use of NSAID's and quinolone antibiotics is associated with an elevated likelihood of experiencing seizures. It is recommended that scientists consider the increased likelihood of seizures when co-prescribing NSAID's and quinolones. Other variables that could potentially elevate the likelihood of this interaction encompass impaired renal function, a past medical history of seizures or other neurological maladies, and elevated dosages/serum levels of either compound [26].

Comprehending the potential renal adverse effects of diverse drug categories, such as analgesics, lipid-lowering agents, proton

pump inhibitors, hypoglycaemic agents, and antimicrobial agents, is of utmost importance for healthcare professionals. Through meticulous observation and diligent surveillance of renal function throughout the course of therapy, scientific practitioners can mitigate the potential for renal impairment and guarantee the safety and effectiveness of their interventions. The optimal management of patients involves weighing the therapeutic advantages of medication against the possible negative consequences, while also considering alternative treatment options when appropriate. In the end, raising awareness about the renal complications caused by drugs aids in enhancing patient outcomes and encourages the use of safe and efficient pharmacotherapy.

Nonsteroidal Anti-Inflammatory Drugs (NSAID's) are a commonly prescribed group of analgesics that have the potential to induce chronic renal dysfunction with prolonged use. Acute interstitial nephritis represents a plausible unfavourable outcome in acute scenarios. It is imperative for scientists to observe renal function and restrict the duration of NSAID administration to mitigate the likelihood of renal impairment.

The precise mechanisms underlying the various impacts of opioids on renal function are yet to be fully elucidated. Prolonged utilization of opioids has been correlated with the manifestation of albuminuria and alterations in renal parameters. As scientists, we should exercise prudence while prescribing opioids for prolonged durations and explore alternative pain management techniques whenever feasible. Statins belong to a pharmacological category utilized for the purpose of reducing cholesterol levels. However, it has been observed that they can pose a potential threat to the occurrence of acute kidney injury, especially in the elderly population. It is recommended that scientists closely monitor the renal function of individuals who are taking statins and explore alternative therapies for reducing lipid levels if needed. Fibrates belong to a distinct category of drugs that are effective in reducing lipid levels and have the potential to induce a transient elevation in serum creatinine levels. The monitoring of renal function and

appropriate adjustment of fibrate dosing is crucial in order to mitigate the potential for renal damage. Proton Pump Inhibitors (PPI's) are frequently recommended by medical professionals to decrease the secretion of gastric acid. Nevertheless, these have been linked to drug-triggered allergic interstitial nephritis, acute renal failure, chronic renal failure, and end-stage renal disease. Medical professionals ought to exercise prudence while recommending PPIs and contemplate substitutive therapies for patients with documented renal dysfunction.

Metformin is a commonly prescribed medication for diabetes management that has the potential to accumulate in individuals with renal dysfunction. In these instances, it is imperative to modify metformin dosages to mitigate additional renal impairment. It is recommended that scientists closely monitor the renal function of individuals who are taking metformin and explore alternative antidiabetic therapies if deemed necessary. Aminoglycosides belong to a category of antimicrobial agents that are recognized for their capability to cause renal toxicity. Renal toxicity may manifest even following a solitary administration; however, renal performance typically recuperates within a period of 20 days post cessation. Prudent surveillance of renal function and aminoglycoside administration is imperative to mitigate the possibility of renal impairment. Fluoroquinolones belong to the class of antibiotics that have the potential to induce allergic interstitial nephritis, which is a type III hypersensitivity reaction. The majority of instances are resolved within a time limit of one week to two months following cessation. It is advisable for scientists to exercise prudence while recommending fluoroquinolones and closely observe renal function. Tetracyclines function as inhibitors of protein synthesis, and certain types, such as doxycycline, may have a potential role in mitigating proteinuria among individuals with diabetic nephropathy. It is imperative to observe the renal function of individuals undergoing tetracycline treatment and make necessary dosage modifications. Vancomycin is a compound that inhibits the synthesis of cell walls and has been linked to the occurrence of nephrotoxicity. This matter presents various quandaries for scientists who must consider the advantages of administering vancomycin therapy versus the likelihood of renal impairment. The surveillance of vancomycin

levels and renal function is of utmost importance in these instances [27].

Models to investigate nephro/urotoxicity

In-vivo: The utilization of animal models has been broadly employed to comprehend pathogenesis and fundamental mechanisms of renal disease. Mice and rats are frequently utilized in research to investigate nephrotoxicity and therapeutic targets, as well as to discover novel biomarkers. This is primarily due to their ease of breeding and relatively low cost of housing and maintenance. However, limited progress has been made in comprehending the mechanisms of nephrotoxicity or in discovering novel biomarkers or a set of biomarkers. Based on our investigation, primates have also been utilized in the study. Nevertheless, irrespective of the dimensions and species of the creatures, the findings did not exhibit a reliable ability to detect unfavourable impacts in Homo sapiens [28]. The scientific inquiry has encompassed models such as ischemia-reperfusion, druginduced nephrotoxicity (cisplatin, gentamicin, aristolochic acid, folic acid), glycerol-induced nephrotoxicity, and warfarin-related nephrotoxicity.

The ischemia-reperfusion model is a widely used experimental techs model is cantered on the proximal tubule and endothelium, emulating the pathophysiology of acute nephrotoxicity in humans. The methodology entails the occlusion of the renal artery for a period of 30-45 minutes, succeeded by a reperfusion duration of 24-48 hours. The primary benefit of this model lies in its ability to mimic the pathology akin to the human ailment, rendering it a valuable tool for investigating the fundamental mechanisms and potential therapeutic targets. Nevertheless, a noteworthy constraint is the necessity for surgical intervention, which may give rise to inconsistencies and intricacies [29].

Models of nephrotoxicity induced by drugs

Mechanism of nephrotoxicity induced by drugs has been tabulated in Table 3.

Model	Inducing agent/method	Animal	Key features
Cisplatin	Cisplatin	Rodents	Proximal tubule-specific; mimics human pathology and drug doses
Gentamicin	Gentamicin	Rodents	Affects proximal tubule and glomerulus; induces chronic kidney disease
Aristolochic acid	Aristolochic acid	Rodents	Proximal tubule-specific; induces rapidly progressing chronic kidney disease
Folate	Folic acid	Rodents	Proximal tubule-specific; mimics acute nephrotoxicity induced by

Table 3: Inducing models with targets.

			elevated folate intake
Glycerol-induced nephrotoxicity	Glycerol	Rodents	Proximal tubule-specific; mimics acute nephrotoxicity associated with rhabdomyolysis
Warfarin-induced nephrotoxicity	Warfarin	Rodents	Proximal tubule and glomerulus-specific; mimics sudden nephrotoxicity induced by anticoagulant agents
5/6 Nephrectomy	Surgical procedure	Rodents	Induces chronic kidney disease; resembles human condition
Streptozotocin-induced diabetic nephropathy	Streptozotocin	Rodents	Replicates diabetic nephropathy; various genetically modified models available
Hypertensive nephropathy	Uninephrectomy, Ang II	Rodents	Mimics hypertensive nephropathy; angiotensin II infusion model also available
Adriamycin or puromycin- induced glomerular injury	Adriamycin, Puromycin	Rodents	Replicates acquired glomerular injury; valuable for studying focal segmental glomerulosclerosis
IgA nephropathy	IgA deposits	Rodents	Models available but with limitations in replicating human disease progression
Polycystic Kidney Disease (PKD)	Genetically modified	Rodents	Various genetically modified models available; mimic certain aspects of PKD
Chronic tubulointerstitial nephritis	Dose-dependent	Rodents	Model for chronic tubulointerstitial nephritis; replicates CKD-associated changes
Inherited glomerular injury	Genetically modified	Rodents	Models available for studying hereditary glomerular diseases
Calcium oxalate stone formation	Naturally occurring	Canines, felines	Utilizes naturally occurring animal models; pathophysiology not fully understood

Cisplatin: Cisplatin, a chemotherapeutic agent that is extensively used and has been found to cause nephrotoxicity. This experimental design specifically focuses on the proximal tubule and entails administering a solitary Intraperitoneal (IP) injection of cisplatin at a dosage ranging from 6-20 mg/kg, succeeded by a 72-hour monitoring phase. The model exhibits advantageous features such as similarity to the pathology, timing, and drug doses observed in human diseases. Nevertheless, there is no immediate clinical correlation as the observed nephrotoxicity is a result of drug-induced factors rather than an inherent renal process [30].

Gentamicin: The aminoglycoside antibiotic known as Gentamicin has been observed to induce nephrotoxicity by affecting both the proximal tubule and glomerulus. This experimental design entails administering gentamicin through intraperitoneal injections in a sequential manner, with varying dosages of 40-200 mg per kg per day over a period of 4-10 days. The primary benefit of this model is its ability to induce Chronic Kidney Disease (CKD) at a rapid pace. However, it does not completely replicate clinical diseases observed in humans, thereby restricting its utility in investigating human nephrotoxicity [31].

Aristolochic acid: The naturally occurring compound Aristolochic acid, which is present in specific plants, has been associated with nephrotoxicity. This experimental design specifically focuses on the proximal tubule and entails administering aristolochic acid *via* intraperitoneal injections at a dosage of 5 mg per kg per day over the course of five consecutive days. Analogous to the gentamicin model, this particular model has the potential to elicit swiftly advancing chronic kidney disease. Nevertheless, it exhibits a deficiency in clinical correlation, thereby constraining its pertinence to human pathology.

Folate: At elevated levels of folate intake, acute nephrotoxicity may occur. This experimental design specifically focuses on the proximal tubule and entails administering a solitary intraperitoneal injection of folic acid at a concentration of 250 mg/kg, followed by a monitoring period of 24-48 hours. The benefit of this model lies in the resemblance of the pathology findings to acute nephrotoxicity in humans induced by other factors. Nevertheless, it lacks a straightforward clinical correlation, since the observed nephrotoxicity is a result of the elevated dosage of folic acid rather than an inherent renal mechanism [32].

The glycerol-induced nephrotoxicity model is designed to target the proximal tubule. It requires a single I.M injection of 8 mL/kg of 50% glycerol, followed by a 24–48 hours observation period. The principal benefit of this model lies in its clinical significance, as it bears resemblance to acute nephrotoxicity associated with rhabdomyolysis in humans. Nevertheless, this model exhibits certain constraints. The research emphasizes the manifestation of symptoms and the general process of nephrotoxicity, rather than delving into the specific underlying mechanisms. Furthermore, it is noteworthy that the extent of nephrotoxicity induced by glycerol may exhibit variations from the human condition, thereby affecting the translational potential of the results [28].

The proposed model aims to study the nephrotoxic effects of warfarin. The model specifically focuses on the proximal tubule and glomerulus. It involves performing a 5/6 nephrectomy procedure and administering warfarin for eight consecutive days. This particular model proves to be beneficial in the examination of sudden nephrotoxicity instigated by anticoagulant agents such as warfarin. Nevertheless, it cannot be ensured that the observed nephrotoxicity will adhere to the identical mechanism as human cases, and the surgical procedure of 5/6 nephrectomy brings in supplementary variables and complexities [33].

It is imperative to acknowledge that a solitary model cannot encompass all facets of acute nephrotoxicity or chronic kidney disease in humans. Rather than relying on a single model or approach, it is advisable for scientists to utilize multiple models or complementary methods to corroborate their discoveries and guarantee the applicability of their outcomes to human subjects.

Chronic Kidney Disease (CKD) is a situation characterized by a gradual and permanent decline in kidney function. Various animal models have been established to investigate the progression from Acute Kidney Injury (AKI) to Chronic Kidney

Disease (CKD), such as the 5/6 nephrectomy model in rodents. This experimental design entails the excision of 66.67% of the renal tissue, resulting in a decline in renal capacity and the emergence of Chronic Kidney Disease (CKD) at the right time. This model is deemed analogous to the human condition; however, it has certain constraints such as the elevated mortality rate of the second surgery, particularly in mice, and necessitates technical proficiency. In addition, it has been observed that various strains of mice exhibit varying degrees of responsiveness to renal mass reduction in terms of chronic kidney disease progression. Moreover, the quantity of kidney tissue available for analysis following the surgical procedure is limited and may be subject to distortion, as per the findings of Ortiz, et al. [27].

Diabetic nephropathy is a type of kidney disease that occurs in people with diabetes. It is caused by damage to the small blood vessels in the kidneys, which can lead to kidney failure if left untreated. Symptoms of diabetic nephropathy include protein in the urine, high blood pressure, and swelling in the legs and feet. Treatment options include controlling blood sugar levels, managing blood pressure, and taking medications to protect the kidneys.

Diabetes-induced kidney disease, well known as diabetic nephropathy, a prevalent complication of diabetes and a primary contributor to Chronic Kidney Disease (CKD) on a global scale. Numerous animal models have been established for the investigation of diabetic nephropathy, such as streptozotocininduced diabetic rats and mice, NOD mice, BB-DP rats, ob/ob mice, db/db mice, STZ-eNOS-/-mice, and db/db-eNOS/mice. These genetically modified models are readily available for commercial use, and they offer a valuable tool for investigating the underlying mechanisms of diabetic nephropathy. However, none of the numerous animal models flawlessly imitate the human ailment. Furthermore, certain strains exhibit infertility, and the models induce slight albuminuria without any reduction in GFR, as reported by Kitada, et al. [34].

Hypertensive nephropathy is a renal disorder that arises as a result of chronic high blood pressure. Hypertensive nephropathy is a prevalent etiology of Chronic Kidney Disease (CKD). Various animal models have been established to investigate hypertensive nephropathy, such as the model involving uninephrectomy in Spontaneously Hypertensive Rats (SHR) and models involving infusion of angiotensin II. These models exhibit high relevance to hypertensive nephropathy and serve as valuable tools for investigating the impact of angiotensin II on renal function. The SHR rodents exhibit higher resistance towards streptozotocin-induced diabetes. Additionally, inducing significant kidney injury necessitates uninephrectomy. Moreover, there is no gradual decline in glomerular filtration rate, and elevated dosages or extended durations of exposure result in heightened serum creatinine levels. These models can be costly and have the potential to induce prolonged stress in animals, as noted by Ruiz-Ortega, et al. [35].

Acquired glomerular injury is a pathological condition affecting the glomeruli, which are the tiny filters in the kidneys responsible for removing waste products from the blood. The etiology of Chronic Kidney Disease (CKD) often involves acquired glomerular injury, which encompasses Focal Segmental

Glomerulosclerosis (FSGS) as a frequent pathology. The Adriamycin or puromycin models are frequently employed in scientific research to investigate acquired glomerular injury, particularly in rats and mice. These models replicate acute glomerular injury and are valuable for investigating the mechanisms of FSGS. Typically, these models exhibit insufficient replication of the gradual advancement of the human ailment, and there exists no clinical application of efficacious NOD.

IgA nephropathy is a renal disorder characterized by the deposition of Immunoglobulin A (IgA) in the glomerular mycangium, leading to inflammation and damage to the kidneys. IgA nephropathy is the prevailing primary glomerulonephritis globally. Various animal models have been established for the investigation of IgA nephropathy, such as the ddY mouse, HIGA mice, and Uteroblobin-deficient mice. The models utilized successfully replicate human pathology; however, the progression of the disease is mild and does not advance towards end-stage renal disease, nor does it result in a gradual decline of the glomerular filtration rate. Furthermore, the efficacious models presented by Ortiz, et al., have yet to be translated into clinical practice [27].

Polycystic Kidney Disease (PKD) is a genetic disorder characterized by the formation of multiple cysts in the kidneys. Polycystic Kidney Disease (PKD) is an inherited condition that manifests as the formation of numerous cysts filled with fluid in the kidney. The utilization of genetically modified mouse models is a prevalent approach in the investigation of PKD. These models serve as valuable tools for investigating the underlying mechanisms of PKD and identifying potential therapeutic targets. The outcomes have also led to the attainment of regulatory authorization for Tolvaptan in Japan concerning autosomal dominant polycystic kidney disease in humans. However, these murine models typically exhibit a limited range of human phenotypes, and ARPKD murine models often exhibit a limited range of human phenotypes. Furthermore, the exorbitant expense poses a constraint as per the findings of Ortiz, et al. [27].

Chronic tubulointerstitial nephritis is a medical condition characterized by inflammation and damage to the tubules and interstitial tissue of the kidneys. Chronic tubulointerstitial nephritis is a prevalent etiology of chronic kidney disease. The utilization of a dose-dependent reduction in glomerular filtration rate serves as a common model for chronic tubulointerstitial nephritis in scientific research. The model exhibits potential reversibility in rats and effectively replicates extrarenal complications, function, and molecular changes associated with CKD. Nevertheless, male rats with adenine-induced kidney disease exhibited a more pronounced deterioration, and the animal model lacks human specificity [36].

Inherited glomerular injury encompasses a range of conditions such as PKD, Alport syndrome, and other hereditary glomerular diseases. Various genetically modified mouse models are frequently utilized to investigate hereditary glomerular damage. These models include the *Pkd1* or *Pkd2* geneengineered mouse model, Col4a43 gene knockout mouse, and Alport syndrome mouse model. These models successfully replicate characteristics of the human ailment, such as gradual

decline in glomerular filtration rate, presence of protein in urine, and eventual renal malfunction. Nonetheless, the translation of genetic discoveries into enhanced patient outcomes poses a challenge, and the exorbitant expenses involved serve as a constraint. These models have led to clinical recommendations.

In addition to the species, canines and felines have also been proposed as potential subjects for investigating calcium oxalate stone formation, given the potential advantages of utilizing a naturally occurring animal model. Although this approach may serve as a promising model, the pathophysiological and etiological mechanisms underlying calcium oxalate nephrolithiasis remain incomplete, as per the findings of O'Kell, et al. [37].

The primary focus of these models should be on molecular mechanisms. This is because comprehending these mechanisms can aid in the development of therapeutic interventions and clinical diagnoses, and also facilitate the identification of novel biomarkers for nephrotoxicity. Therefore, it is also our scientific belief that novel approaches are crucial for progress in this field. Furthermore, alternative methodologies, as discussed in this analysis, are significant instruments that can alter the nephropathy paradigm and revolutionize the process of designing novel, potent, and less hazardous compounds.

In-vitro models

Our search results indicate that the quantity of *in vivo* investigations has increased commensurately with that of *in vitro* studies. However, these models have exhibited constraints in producing insights into nephrotoxic mechanisms in human beings. In contrast, there is a growing need for novel techniques that enhance, minimize, and substitute the utilization of animals. The utilization of cell culture methodologies is highly pertinent in conducting *in vitro* investigations on nephrotoxicity. The quantity of investigations utilizing animal models and *in vitro* assessments to evaluate renal toxicity has increased over the past two decades. Despite the heightened employment of both methodologies, no documented findings have yielded a more comprehensive comprehension of the mechanisms underlying nephrotoxicity.

Through the creation of human induced Pluripotent Stem Cells (hiPSCs) derived from individuals afflicted with a specific genetic ailment, such as degenerative conditions and malignancies, it is conceivable to investigate personalized disease mechanisms and conduct drug screening *in vitro*, obviating the need for animal models. Significantly, recent developments in genome editing have presented novel methodologies for simulating genetic kidney disorders through the utilization of human Pluripotent Stem Cells (hPSCs) *in vitro*, as reported by Dakhore, et al. [38].

The screening of nephrotoxicity *in vitro* models typically involves the utilization of primary human renal proximal tubule cells, which are commonly obtained from cadaveric specimens and cultured in a two-dimensional format. Nevertheless, primary cells exhibit substantial interdonor variability, possess restricted expansion potential, and are susceptible to dedifferentiation and transporter expression loss [39].

The challenge of preserving transporter and metabolic activity in primary cells and cell lines, as well as achieving transporter function levels that match those observed *in vivo*, is due to the utilization of static 2D culture configurations. The *in vitro* assays for renal transport or toxicity typically involve the utilization of primary proximal tubule cells or cell lines that are cultured in a monolayer on a permeable support system, such as a Transwell insert. This system is coated with an extracellular matrix, as described by Wilmer, et al. [40].

Renal cells derived from pluripotent stem cells and reprogrammed cells have garnered significant attention due to their capacity to differentiate into fully functional renal cells. These pluripotent cells possess the ability to differentiate into any cell lineage within the human anatomy and can be conveniently amplified [41].

By utilizing a combination of growth factors and small molecules that simulate the natural progression of embryonic kidney development, renal cells have been successfully generated *in vitro* from both embryonic stem cells and human induced Pluripotent Stem Cells (hiPSCs) [42].

The cell lines utilized in this study were obtained from various origins including human foreskin, human dermal fibroblasts, human pluripotent stem cells, and human female fibroblasts. The cell lines were differentiated using various inducing factors such as activin A, BMP7, CHIR, FGF2, RA, and FGF9.

The cellular lineage originates from human foreskin and human dermal fibroblasts (α), and the differentiation methodology employed is IMa, which incorporates CHIR, FGF2, and RA. The cellular mechanism in response to nephrotoxicity for this particular cell line remains undescribed as per the findings of Lam, et al. [40].

Likewise, the cellular lineage obtained from a human pluripotent stem cell. The differentiation protocol is IMa, which employs activin A, BMP7, and CHIR. The response of this cell line to nephrotoxicity is characterized as AQP1c and LTLc, as reported by Mae, et al. [43]. The cell line specified has been obtained from human pluripotent stem cells. The differentiation process employed includes the utilization of BMP4 and bFGF in the IM protocol, and RA, activin A, and BMP2 in the UB protocol, as documented by Xia, et al. [44]. The human dermal fibroblasts utilized in the experiment were obtained from the RIKEN bioresource centre. The differentiation process employed was IM, which necessitated the application of activin A, BMP4, CHIR, RA, and bFGF. The cellular response to nephrotoxicity is explicated as being modulated by SALL1 and Cadherin 6, according to Taguchi, et al's findings [45].

The cell line mentioned is obtained from human BJ foreskin fibroblasts, human HDF α dermal fibroblasts, human LR5-iPSCs, and human fibroblast hfib2-iPS4 and hfib2-iPS5 iPSCs. The employed differentiation protocol is IMa, which entails the utilization of CHIR, and MM and nephrogenesis, which necessitate the use of B27 supplement. The cellular response to nephrotoxicity is elucidated by the organoids that exhibit KIM1 expression upon exposure to cisplatin and gentamycin treatment, along with Megalin and Cubilin, as reported by Freedman, et al. [46].

The human female fibroblasts were utilized to derive the cell line, and the differentiation process employed the IM protocol. This protocol entails the utilization of CHIR, FGF9, and heparin. Additionally, the MM and nephrogenesis stages were incorporated, which involved using CHIR pulse and FGF9 for the initial five days, followed by FGF9 for the subsequent 12-25 days. The cellular response to nephrotoxicity involves the activation of caspase 3 in LTL+ECAD+PTECs within organoids following exposure to cisplatin and Cubilin, as reported by Takasato, et al. [47].

The human foreskin fibroblasts utilized in this study were obtained from the WiCell Research Institute. The differentiation process involved the utilization of BMP2, BMP7, and B27 supplement, and the IMa and MM protocols were employed to generate HPTC-like cells. The cellular response to nephrotoxicity is characterized by the expression of NF- κ B, γ H2AX, and 4-HNE in 2D cells upon exposure to cisplatin and aristolochic acid. Additionally, the cell line exhibits the presence of various transporters including GLUT1c, SGLTc, AQP1c, OAT3c, PEPT1c, and ATPasec [48].

The human dermal fibroblasts utilized in this study were obtained from Invitrogen C-013-5C. The differentiation process employed the IM protocol, which entails the administration of CHIR, Noggin, and activin A. Additionally, the MM and nephrogenesis stages involved the application of FGF9 and CHIR for the initial 14 days, followed by a growth factor-free period for the subsequent 14 days. The cellular response to nephrotoxicity was observed in organoids that expressed KIM1 upon treatment with cisplatin and gentamycin, and γH2AX expression was observed upon treatment with cisplatin, as reported by Morizane, et al. [49].

Organoids

The nephrons exhibit intricate three-dimensional architecture. Therefore, in summary, in order to reconstruct these anatomical features outside of the organism, it is necessary to establish three-dimensional cultivation methodologies. Organoids are three-dimensional tissue structures that closely resemble the structural and functional characteristics of in vivo organs when cultured in laboratory plates. Organoids derived from human Pluripotent Stem Cells (hPSCs) present a promising avenue for investigating the underlying mechanisms of inherited kidney disorders in humans. This approach could potentially be extended to more prevalent diseases and aid in the development of novel drug therapies utilizing human tissue. Such methodology may enhance the translatability of research findings to human subjects. To optimize this methodology, it is imperative to thoroughly consider differentiation protocols, genetic background, and epigenetic variation when examining disease phenotypes in kidney organoids.

The objective of human Pluripotent Stem Cell (hPSC) research is to restore renal function. The kidneys are intricate organs that facilitate blood filtration, and the unit responsible for reabsorbing urine is crucial for maintaining their function and overall balance within the body. The utilization of organoids to produce operational bioengineered kidney tissues poses several challenges. The induction of vascularization in kidney organoids

must be conducted in a systematic manner to ensure proper arterial blood flow and venous drainage. This phenomenon poses as one of the significant obstacles concerning vascularization, as stated by Morizane, et al. [50].

expression in comparison to the cells cultured in 2D, even in the

Kidney-on-a-chip

Renal cells are seeded in a microfluidic device that enables the flow of media across the cell surface and/or cell surfaces, thereby creating kidneys-on-a-chip. In a pioneering investigation of this technology, primary human proximal tubule cells were cultivated on 2D chips featuring apical and basolateral media compartments. The study revealed that the flow of fluid across the apical surface triggered MDR1 expression and function and led to the development of tight junctions and columnar morphology [51].

Biofunctionalized hollow fibers

In 2015, a study was conducted which demonstrated that proximal tubule epithelial cells with conditional immortality could be utilized to seed the exterior surface of hollow fibres coated with an extracellular matrix. This resulted in the creation of biofunctionalized hollow fibres that possessed a monolayer of cells. The fibres on which the proximal tubule cells were grown exhibited enhanced formation of tight junctions and OAT1

Table 4: Herbs and extracts used to treat nephron/urotoxicity.

absence of flow through the fibres. This indicates that the 3D culture alone led to an improvement in the expression of these markers, as per the findings of Jansen, et al. [52].

Herbs as nephroprotective

Renal disorders can be tackled at various stages based on the physiological pathway of the underlying etiology. Pharmacological interventions are available for both pre-renal and post-renal diseases. However, it is noteworthy that most of the drugs utilized in the treatment of these conditions are associated with unfavourable outcomes and may even result in intrinsic renal impairment. Included in the list are Non-Steroidal Anti-Inflammatory Agents (NSAIDs), proton pump inhibitors, antibiotics, as well as chemotherapeutic agents. The potential nephrotoxicity of drugs used to treat pre-renal and post-renal diseases, as well as other medical conditions, is now recognized as a significant risk factor for both acute and chronic kidney disorders has been tabulated in Table 4. To mitigate the negative impacts of medication, various alternatives have been explored for the treatment of these pathologies, as noted by Petejova, et al. [53].

S. no	Plant (part used- family)	Type of extract	Dose	Mechanism	References
1	Descurainia sophia (seed-Brassicaceae)	Ethyl alcohol extract	50, 100, 200, and 300 mg/kg	Reduce inflammation, swelling and necrosis	Moshaie-Nezhad P, et al.
2	<i>Eurycoma longifolia</i> (root- Simaroubaceae)	Standardized aqueous extract	100, 200, and 400 mg/kg	Improves biomarkers of kidney function, and histopathology changes	Chinnappan SM, et al.
3	<i>Theobroma cacao</i> (fruit-Malvaceae)	Hydroalcoholic extract of natural Forastero cocoa	10% of diet	Decrease glucose levels	Alvarez-Cilleros, et al.
4	<i>Caffea arabica</i> (fruit-Rubiaceae)	Aqueous extract	1000 mg/kg	Raise catalase levels	Boonphang O, et al.
5	<i>Eysenhardtia polystachya</i> (bark-Fabaceae)	Methanolic extract (flavonoids)	20 mg/kg	Decrease oxidative stress	Perez-Gutierrez RM, et al.
6	Anchomanes difformis (leaf-Araceae)	Aqueous extract	200 mg and 400 mg/ kg	Induce dissociation of Nrf2/keap, activating Nrf2, reduced oxidative stress	Alabi TD, et al.
7	<i>Hibiscus sabdariffa</i> (flower-Malvaceae)	Aqueous extract	2% in drinking water	Increase the antioxidant systems	Rodriguez-Fierros FL, et al.

				including non- enzymatic and enzymatic effect	
8	Passiflora spp. (peel-Passifloraceae)	Methanolic extract	250, 500 mg/kg	Keep urea and creatinine at normal levels	Nerdy N, et al.
9	<i>Euphorbia paralias</i> (Aerial parts- Euphorbiaceae)	Methanolic extract	100, 200 mg/kg	Reduce levels of urea and creatinine	Al-Yousef HM, et al.
10	<i>Pistacia atlantica</i> (leaf-Anacardiaceae)	Hydroethanolic extract	200, 400, and 800 mg/kg	Decrease levels of urea, creatinine, and uric acid	Heidarian E, et al.
11	Costusafer (leaf-Costaceae)	Aqueous leaf extract	375, 750 and 1125 mg/kg	Decrease serum potassium and BUN levels	Ezejiofor AN, et al.

Discussion

Throughout history, plants have been utilized as remedies for a multitude of illnesses, including those related to pre, intra, and post-renal factors. The secondary metabolites of plants are responsible for their medicinal properties, as they can provide protection against pathogens and offer significant physiological advantages that aid in the prevention of certain illnesses [54].

Moreover, botanical nephroprotective agents alleviate phenomena such as interstitial nephritis, modified intraglomerular hemodynamic, tubular necrosis, or glomerulonephritis [55]. Prior research has extensively examined the utilization of plants and phytochemicals as nephroprotective agents, yielding valuable insights into the mechanisms by which extracts or individual compounds modulate molecular pathways to ameliorate kidney ailments [56].

The limited utilization of medicinal plants worldwide, particularly in countries where modern medicines are prevalent, can be attributed to the insufficient comprehension of their mechanism of actions. The utilization of botanicals as a fundamental element of harmonizing and alternative medicine has garnered renewed concentration. As a noteworthy achievement, the conventional Chinese medicine, which primarily relies on botanical sources, has gained worldwide recognition, and is extensively employed across all tiers of the healthcare system in China. The administration and academic establishments have already put in place protocols for endorsing and utilizing plant-based remedies. Likewise, Ayurveda and other traditional medicines of India have demonstrated their efficacy in treating various ailments and hold significant value in the Indian healthcare industry's economy [57].

Combined approach to treat urotoxicity

In the field of renal pathophysiology, it has been demonstrated by Moorthi, et al. [58]. That a plant based diet can be advantageous, particularly for patients with mild proteinuria and diabetic nephropathy. Similarly, herbal formulations have been found to decrease the need for dialysis by addressing the underlying causes and modifying symptoms of renal failure. Additionally, they can aid in alleviating the adverse effects of dialysis [59]. Hence, the contemporary methodology of utilizing flora as an adjunctive therapy confers a dual advantage; they aid in combating the ailment and simultaneously function as agents that protect the kidneys. The synergistic integration of Western and Indigenous medicinal practices presents novel inquiries regarding the therapeutic applications of botanicals and natural substances. The efficacy of Indian and Chinese medicines is widely acknowledged, as they have been found to have fewer adverse effects when compared to contemporary medical systems. Moreover, the utilization of plants in disease management is being advocated as a viable and economical substitute [60].

The Table 5 presents an analysis of the nephroprotective properties of diverse botanical extracts, with a particular emphasis on their potential to safeguard and enhance renal function. The observed nephroprotective effects of these extracts can be ascribed to their anti-oxidative, antiinflammatory, and Reno protective mechanisms. The subsequent sections will offer a comprehensive examination of every plant extract, specifying the plant component employed the extract type, the dosage, and the mechanism by which it applies its nephroprotective properties.

Table 5: Herbal isolated molecules used to treat nephro/urotoxicity.

S. no	Plant	Mechanism	Bioactive	Model of study	References
1	Tinospora crispa	Increase SOD activity	Genkwanin	Albino Wistar rats+CCl₄	Rakib A, et al.
2	Suaeda vermiculata	Decrease AST and ALT	Quercetin, quercetin-3-O- rutinoside	Male Sprague Dawley rats+CCl ₄	Mohammed SA, et al.
3	Arbutus pavarii	Exert bacteriostatic and bactericidal effect, against different methicillin-resistant <i>Staphylococcus</i> <i>aureus</i> strains	Proanthocyanins, quercetin	Disc diffusion assay	Buzgaia N, et al.
4	Punica granatum	Improve kidney function biomarkers.	Dulcitol, loganin, bergenin, guercitrin,	Wistar rats +gentamicin	Mestry SN, et al.
		exerted antioxidant activity	cosmosin, folic acid, khayanthone	g	
5	Cichorium intybus	Improve the systolic function and increase the levels of LVEF and LVFS	1,4- naphthalenedione, oleic acid, β-asarone, naphtho furanone	Wistar albino rats +ISO-induced myocardial ischemia model	Epure A, et al.
6	Gardenia jasminoides	Exert antioxidant activity and decreased CK-MB, AST, ALT, and MDA levels.	Geniposide	Wistar SHR, and Wistar Kyoto rats	Hou Y, et al.
7 Curc	Curcuma longa	Reduce ROS, inflammation, and histopathology changes	Curcumin	C57BL/6J mice	Guerrero - Hue M, et al.
		Increase enzymatic antioxidant activity		Wistar rats +doxorubicin	Benzer F, et al.
8	Passiflora spp.	Keep urea and creatinine at normal levels	Ellagic acid, Kaempferol and Quercetin glycosides	Albino rats +paracetamol	Alabi TD, et al.
9	Cynanchum wilfordii	<i>via</i> down regulation of androgen receptor 5α gene expression	4-hydroxyacetopheno ne	Male Sprague- Dawley rats +testosterone	Lee G, et al.

The seeds of *Descurainia sophia* exhibit anti-inflammatory, anti-swelling, and anti-necrotic properties. The administration of ethyl alcohol extract at varying doses of 50, 100, 200, and 300 mg/kg has exhibited properties that protect the kidneys. The anti-inflammatory and anti-necrotic properties of this extract play a role in maintaining renal function, mitigating the likelihood of complications associated with the kidneys.

Eurycoma longifolia is a plant species belonging to the family Simaroubaceae. It is commonly known as Tongkat Ali and is native to Southeast Asia. The plant has been traditionally used for its medicinal properties, particularly as an aphrodisiac and to treat various ailments such as fever, malaria, and high blood

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pressure. Scientific studies have also shown that *Eurycoma longifolia* contains compounds that may have potential benefits for improving athletic performance, reducing stress, and enhancing male fertility. Further research is needed to fully understand the mechanisms of action and potential therapeutic applications of this plant. standardized aqueous extract of the root.

Eurycoma longifolia, an indigenous plant to Southeast Asia, possesses a prolonged chronicle of utilization in customary medicine. The standardized aqueous extract of the root has demonstrated a significant improvement in kidney function biomarkers and a reduction in histopathological alterations in

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the kidney at doses of 100, 200, and 400 mg/kg. The observed nephroprotective effects may be ascribed to the extract's capacity to augment renal function and regenerate impaired renal tissue.

The hydroalcoholic extract obtained from the fruit of Theobroma cacao, commonly known as natural *Forastero cocoa*, has exhibited hypoglycemic effects upon being incorporated into the diet at a concentration of 10%. The decrease in glucose levels can aid in preserving renal function by hindering the onset of diabetic nephropathy, a prevalent cause of renal failure among diabetic patients.

The aqueous extract of *Coffea arabica*, a well-known beverage commonly referred to as coffee, has been observed to elevate catalase levels at a dosage of 1000 mg/kg. Catalase is an enzyme with antioxidant properties that counteracts the deleterious effects of reactive oxygen species. These species are known to induce oxidative stress and inflict harm upon renal cells. Through upregulating catalase expression, the aforementioned extract confers nephroprotection by mitigating renal oxidative stress.

The bark methanolic extract of *Eysenhardtia polystachya*, a plant indigenous to Mexico, is abundant in flavonoids. This particular extract, when administered at a dosage of 20 mg/kg, has demonstrated a reduction in oxidative stress within the renal system. Through the reduction of oxidative stress, the extract facilitates the preservation of renal cells and sustains the general renal function.

The aqueous leaf extract of *Anchomanes difformis*, a plant species found in tropical regions, has been observed to trigger the dissociation of Nrf2/keap, leading to the activation of Nrf2 and a subsequent decrease in oxidative stress. This effect has been observed at doses of 200 mg and 400 mg/kg. The activation of Nrf2, a transcription factor responsible for regulating the expression of antioxidant enzymes, plays a crucial role in bolstering the kidneys' defence against oxidative stress, safeguarding kidney function.

The aqueous extract of *Hibiscus sabdariffa*, commonly referred to as roselle, has been found to enhance non-enzymatic and enzymatic antioxidant systems. This effect was observed when the extract was administered at a concentration of 2% in drinking water. The improved antioxidant mechanisms aid in shielding the kidneys against oxidative stress-induced harm, thereby conserving renal function.

The methanolic extract obtained from the aerial parts of *Euphorbia paralias*, a plant species found in coastal areas, has demonstrated the ability to decrease urea and creatinine levels in subjects administered with doses of 100 and 200 mg/kg. The observed decrease in waste products suggests an enhancement in renal performance, highlighting the potential nephroprotective properties of the aforementioned botanical extract.

The hydroethanolic extract of *Pistacia atlantica* leaves has been found to exhibit potential in reducing levels of urea, creatinine, and uric acid. The tree is indigenous to the Mediterranean and Middle East regions. The administration of doses of 200, 400, and 800 mg/kg has been observed to be effective. The observed decrease in waste products indicates a positive impact on renal function, underscoring the nephroprotective properties of the aforementioned extract.

The aqueous leaf extract of *Costus afer*, an indigenous African medicinal plant, has been observed to exhibit hypokalaemia and hypoureaemic effects at varying doses of 375, 750, and 1125 mg/kg. A reduction in serum potassium and BUN levels is indicative of enhanced renal function, as the kidneys exhibit greater proficiency in eliminating these metabolic by-products from the bloodstream.

The observed effects of *Tinospora crispa* indicate that it enhances the activity of Superoxide Dismutase (SOD), thereby exhibiting nephroprotective properties. The bioactivity observed can be attributed to the presence of genkwanin, a compound that is naturally occurring in the plant. The study investigated the nephroprotective properties of *Tinospora crispa* in albino Wistar rats that were exposed to Carbon Tetrachloride (CCl₄).

Suaedavermiculata demonstrates nephroprotective characteristics through the reduction of AST and ALT levels. The bioactive compounds accountable for this phenomenon comprise of quercetin and quercetin-3-O-rutinoside. The observed nephroprotective activity was noted in male Sprague Dawley rats that were subjected to CCl₄ treatment.

While not possessing direct nephroprotective properties, Arbutus pavarii exhibits bactericidal and bacteriostatic effects against various strains of Methicillin-Resistant *Staphylococcus aureus* (MRSA), which may have the potential to safeguard the kidneys against damage caused by infections. The effect can be attributed to the bioactive compounds namely proanthocyanidins and quercetin. The investigation of Arbutus pavarii's activity was conducted through the utilization of a disc diffusion assay.

Punica granatum is a deciduous shrub or small tree belonging to the family Lythraceae. It is widely cultivated for its edible fruit, which is commonly known as pomegranate. The fruit is a complex structure consisting of numerous seeds surrounded by juicy arils, enclosed in a tough, leathery skin. Pomegranate has been used for medicinal purposes for centuries and is believed to have various health benefits due to its high content of antioxidants and other bioactive compounds. Its phytochemical composition and biological activities have been extensively studied, and it is considered a promising source of natural products for the development of new drugs and functional foods. Punica granatum, scientifically referred to as such, exhibits a positive impact on biomarkers associated with kidney function and demonstrates antioxidant properties. The bioactive constituents of the substance comprise dulcitol, loganin, bergenin, quercetin, cosmosin, folic acid, and khayanthone. The study investigated the potential nephroprotective properties of Punica granatum in Wistar rats that were administered with gentamicin, a known nephrotoxic antibiotic.

Cichorium intybus, scientifically referred to as chicory, enhances systolic function and elevates the levels of Left Ventricular Ejection Fraction (LVEF) and Left Ventricular Fractional Shortening (LVFS). The effect observed can be

attributed to the bioactive compounds namely 1,4naphthalenedione, oleic acid, β -asarone, and naphtho furanone. The study investigated the effects of *Cichorium intybus* on myocardial ischemia in Wistar albino rats induced by Isoproterenol (ISO).

The antioxidant activity of *Gardenia jasminoides* is evidenced by its ability to reduce the levels of Creatine Kinase-MB (CK-MB), AST, ALT, and Malondialdehyde (MDA). The effects observed are attributed to geniposide, a bioactive constituent present in the plant. The study investigated the nephroprotective potential of *Gardenia jasminoides* in Wistar Spontaneously Hypertensive Rats (SHR) and Wistar Kyoto rats.

Curcuma longa is a perennial plant belonging to the ginger family, Zingiberaceae. It is commonly known as turmeric and is widely used as a spice in many cuisines. Its active ingredient, curcumin, has been extensively studied for its potential health benefits. Turmeric, scientifically referred to as Curcuma longa, has been found to possess the ability to decrease the levels of (ROS), inflammation, Reactive Oxygen Species and histopathological alterations in the kidneys. The bioactive compound curcumin is renowned for its robust antioxidant and anti-inflammatory properties. The study investigated the nephroprotective properties of Curcuma longa in C57BL/6J mice.

Passiflora spp., also referred to as passion fruit, aids in the regulation of urea and creatinine levels, which are crucial markers of renal function. The effect can be attributed to the bioactive compounds such as ellagic acid, kaempferol, and quercetin glycosides. The study investigated the nephroprotective potential of Passiflora spp. in albino rats subjected to paracetamol-induced renal toxicity, a well-known adverse effect of the drug at high dosages. The administration of 250 and 500 mg/kg doses of the extract can aid in this regard. Urea and creatinine are nitrogenous waste products that undergo renal filtration, and their concentrations in the bloodstream are reliable markers of renal performance. By maintaining these levels within the normal range, the extract demonstrates nephroprotective characteristics.

The nephroprotective effects of *Cynanchum wilfordii* are observed through the downregulation of the androgen receptor 5α gene expression. The bioactive compound that is accountable for this particular activity is 4-hydroxyacetophenone. The study investigated the potential nephroprotective properties of *Cynanchum wilfordii* in male Sprague-Dawley rats subjected to testosterone-induced renal damage.

Conclusion

In summary, the botanical extracts expounded upon in this manuscript demonstrate renal safeguarding characteristics via diverse pathways, encompassing antioxidative, antiinflammatory, and nephroprotective effects. The bioactive compounds that exhibit these effects exhibit potential therapeutic significance in the prevention and management of renal complications. Nevertheless, it is imperative to carry out additional investigations to determine the most effective dosages, safety profiles, and probable interactions with

medications or other supplements. It is imperative to seek advice from a medical expert prior to integrating these botanical extracts into an individual's dietary or supplementary routine. The induction of nephrotoxicity is a major concern in drug development, environmental exposure, and disease management. As the scientific community's comprehension of the molecular pathways involved in nephrotoxicity deepens, there is an increasing demand for the identification of innovative pharmacological compounds capable of safeguarding and revitalizing renal function. The botanical extracts and biologically active molecules mentioned in this manuscript present a valuable reservoir of promising nephroprotective agents that require additional scrutiny. The forthcoming outlooks in this domain ought to concentrate on thorough investigation of the mechanisms of action, safety profiles, and ideal dosages for the botanical extracts and bioactive molecules possessing nephroprotective characteristics. Moreover, it is imperative to carry out meticulously planned clinical trials to authenticate the therapeutic effectiveness of these extracts in human cohorts. Further investigations should also examine probable interactions with pharmaceuticals or other nutraceuticals, along with any potential adverse reactions or contraindications. The integration of plant extracts and their bioactive compounds into evidence based, integrative strategies for kidney health holds promise for enhancing patient outcomes and overall renal health. Sustained investigation in this domain is imperative for unleashing the complete potential of these auspicious therapeutic agents and broadening our array of instruments to counteract renal disorders and their correlated complications.

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