# Nephroprotective Activity of Medicinal Plants report

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# Nephroprotective Activity of Medicinal Plants, Herbal Preparations, and Phytocompounds: A Comprehensive Review


## Abstract

Among the most prevalent illnesses, nephrotoxicity is one of the most dangerous problems as a result of its high fatality rate, which occurs when the body is exposed to a drug or toxicants. Antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), chemotherapeutic medicines, and other chemical compounds are all create renal damage. Many traditional plants and herbs are being used for renal disorders. There are thousands of plant extracts, herbal preparations, and phytocompounds that have been reported that have the nephroprotective ability. The present review discusses and highlighted the prospective medicinal plant extracts, herbal preparations, and phytocompounds based on scientific reports as useful materials to assist individuals with renal disease and also help the scientists for further investigations and to consider these materials in the process of discovery of novel therapeutics for the treatment of renal diseases.



**Keywords:** nephrotoxicity, traditional plants, renal disease, phytocompounds, chemical compounds, illnesses.


## Introduction

The human kidneys are considered one of the vital organs, and it is responsible for the filtering and eliminating nitrogenous and other byproducts, maintaining fluid homeostasis, controlling blood pressure, erythrocyte formation, and bone density, regulating hormonal balance, and maintaining the fluid equilibrium of healthy functioning of the human body (Sujana et al, 2021; Tienda-Vázquez et al, 2022). A large number of nephrons together give the shape of a kidney which is also known as the anatomical and functional unit of the kidney (Negi and Mirza, 2020). When any alteration in the normal functional status of the kidney occurs, it hampers all the regulatory activities that might be deadly incidence (Sujana et al, 2021).

Acute and Chronic Kidney disease are the two forms of renal impairments and both the conditions are developed into the serious stages if they are untreated (Tienda-Vázquez et al, 2022; Jager et al, 2019). Every day humans are getting exposed to different hazards and chemicals that initiate the progression of renal damage (Negi and Mirza, 2020). A variety of powerful therapeutic drugs, such

as aminoglycoside antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), chemotherapeutic agents, and chemical reagents such as ethylene glycol, carbon tetrachloride, sodium oxalate, and heavy metals such as lead, mercury, cadmium, and arsenic, can negatively affect the kidney, resulting in acute renal failure, chronic interstitial nephritis, and other kidney complications (Sundararajan et al, 2014; Gaikwad et al, 2012). Nephrotoxin-induced pathways for renal cell death include oxidative stress, proximal tubule necrosis, loss of brush border membrane and polarity, reduced glomerular filtration rate (GFR), and renal blood flow (Negi and Mirza, 2020).

Traditionally, several plants have been used for the ailments of different diseases and disorders (Lawson et al, 2021). Plants' therapeutic properties have been linked to secondary metabolites, which can defend against infections or provide significant physiological advantages in the prevention of certain illnesses (Isah, 2019). Plants include a myriad of phytochemical compounds that have antioxidant, anti-inflammatory, diuretic, anticancer, and antibacterial properties (Das et al, 2019). In modern society, the frequent use of medicinal plants which act as a significant component of complementary and alternative medicine is gaining popularity (Tienda-Vázquez et al, 2022). In this review article, we gathered and presented scientific information about the nephroprotective capabilities of various possible medicinal plants on *in vitro & in vivo* models to establish their ethnobotanical usage among the general public.

## Nephrotoxic agents and their toxic mechanism of actions

Renal damage is caused by a variety of chemical agents, therapeutic medications, and diagnostic agents which are called nephrotoxic agents (Naveen et al, 2022). Agents responsible for the nephrotoxicity are given below with their mechanism of nephrotoxicity. Modifications in glomerular hemodynamics, tubular cell toxicity, inflammation, crystal nephropathy, rhabdomyolysis, and thrombotic microangiopathy are a few common pathways that contribute to nephrotoxicity (kim and Moon, 2012).

### Changes in glomerular hemodynamics

Glomerular filtration rate (GFR) for young adults in good health is 120 ml/min. By controlling blood flow in the afferent and efferent arteries for managing intraglomerular pressure, kidneys may maintain a consistent filtration rate and also the relocation of urine. Prostaglandin circulation is performed to enlarge afferent arteries. It has been demonstrated that anti-prostaglandin medications, such as NSAIDs (nonsteroidal anti-inflammatory drugs) or medications with anti-angiotensin activity for the avoidance of hypertension, such as ACE inhibitors and angiotensin receptor blockers (ARBs), can affect nephrotoxicity in the glomerulus (kim and Moon, 2012).

**Tubular cell toxicity**

Drug toxicity has a significant impact on renal tubules because they are introduced to medicines during the concentration and reabsorption procedure through the glomerulus, particularly the proximal tubule cells. Cytotoxicity is led on by injured mitochondria in tubules, an inadequate tubular transport system, and an elevation in oxidative stress caused on by the production of free radicals. Aminoglycoside antibiotics, antifungal treatments like amphotericin B, antiviral medicines like adefovir, and anticancer medicines like cisplatin and foscarnet are some of the medications, that generate cytotoxicity (kim and Moon, 2012).

**Inflammation**

Medicines may create inflammatory alterations that result in fibrosis and renal scarring in the glomerulus, renal tubular cells, and the interstitium around it (Naughton, 2008). Glomerulonephritis, acute and chronic interstitial nephritis, and also other immune-mediated conditions interrupt the normal kidney mechanics and cause adverse effects. It has been established that proteinuria and glomerulonephritis are directly associated. NSAIDs and antibacterial medications like rifampicin can trigger an immunological reaction identified as acute interstitial nephritis. Generally, long-term use of calcineurin inhibitors, lithium, certain anticancer medications, or analgesics results in chronic interstitial nephritis (Kim and Moon, 2012).

**Crystal nephropathy**

Medicines those produce insoluble crystal in human urine also affects renal function. The development of insoluble crystals relies on the acidity of urine and medication concentration. Antibiotics, such as ampicillin, and antiviral medicines, such as acyclovir, can both result in crystal Nephropathy (Kim and Moon, 2012).

**Rhabdomyolysis**

While skeletal muscle is damaged owing to an injury, rhabdomyolysis occurs, that causes the release of muscle fibers into the circulation. Due to muscle tissue injury, myoglobin and serum creatine kinase are released into the blood when renal muscle cells break down. Myoglobin weakens and inhibits kidney filtering activity, leading to acute tubular necrosis or renal failure. Addiction to heroin, methadone, methamphetamine, and statin drugs, as well as alcoholics, are biggest factors of rhabdomyolysis (Kim and Moon, 2012).

**Thrombotic microangiopathy**

Drug-induced thrombotic microangiopathy is caused by renal epithelial cells that are directly or indirectly toxic, causing organ damage. It has been demonstrated that antiplatelet medications such as cyclosporin, mitomycin-C, and quinine can result in thrombotic microangiopathy (Kim and Moon, 2012).

**Agents responsible for the nephrotoxicity are given below with their mechanism of nephrotoxicity**

**Acetaminophen:** Overdosing of acetaminophen, a frequently used painkiller has been linked to renal damage in both animal models and humans. Acetaminophen's nephrotoxicity is determined by its metabolic profile. Acetaminophen combines with glucuronide or sulfate in the liver and creates a water-soluble, non-toxic molecule. The biotransformation of acetaminophen results in N-acetyl-p-benzoquinone-imine (NAPQI) by microsomal enzyme P-450, which is considered a poisonous metabolite. Intracellular GSH adducts with NAPQI to create mercapturic acid, which is excreted by the kidneys. This process is essential in the detoxification of acetaminophen. As a result of the acetaminophen overdose, the active concentration of NAPQI surpasses the binding ability of GSH, resulting in NAPQI aggregation. Active NAPQI combines with intracellular macromolecules, triggering tissue damage. Following that, lysosomal enzyme activation causes tissue necrosis and organ malfunction. Acetaminophen poisoning mostly affects the proximal renal tubules (Reshi et al, 2020).

**Cisplatin:** Cisplatin is an anticancer drug that causes a lot of neurotoxic effects. Once cisplatin propagates into kidney cells through a passive or facilitated transportation system, it activates crucial signaling pathways implicated in renal cell death, including MAPK, p53, ROS, and SO, or p21. Cisplatin primarily stimulates the synthesis of TNF- in renal tubular cells, which in turn activates the tissue inflammatory response and leads to cell damage and death. Cisplatin, on the other hand, causes harm to the renal vasculature, resulting in ischemia of tubular cells and a reduction in GFR. Acute renal failure is caused by the combination of these cascade pathways (ARF) (Pabla and Dong, 2008).

**ACE inhibitors:** ACE inhibitors are the mostly used cardiovascular drugs, nevertheless, these drugs produce moderate renal insufficiency by reducing the GFR concentration (Muneer & Nair, 2017). Such abnormalities develop because angiotensin II-dependent efferent arteriole vasoconstriction is required to sustain intraglomerular capillary pressure (Rolland et al, 2021). GFR

drops dramatically when the angiotensin–renin pathway is blocked. Furthermore, for patients who use beta-blockers, NSAIDs, or potassium-sparing diuretics, the medicine might induce severe hyperkalemia (Caires et al, 2019).

**Gentamicin:** Gentamicin is considered an aminoglycoside class antibiotic, and it is most commonly used for the ailment of Gram-Negative bacterial infection (Jamshidzadeh et al, 2014). Aminoglycoside antibiotics cause nephrotoxicity at the side of renal proximal tubule cells. Excess generation of ROS, hydroxyl radical, superoxide anions, and RNS, as well as inhibition of Na K+ ATPase and mitochondrial oxidative phosphorylation, may all promote gentamicin-induced nephrotoxicity. Apoptosis, necrosis, and oxidative stress are all possible causes of gentamicin deposition (Adil et al, 2016).

**Cadmium:** Cadmium is a toxic metal that harms the environment (Järup &Åkesson, 2009). Cadmium mainly affects the kidney via its chronic exposure to the kidney. The kidney typically uptake cadmium through receptor-mediated endocytosis. In that site, it attaches to metallothionein and builds up. Cadmium is transferred into the cytosol when lysosomal enzymes disintegrate the cadmium–metallothionein interaction, resulting in the generation of reactive oxygen species (ROS), cellular damage, and death in renal tissue (Panel, E. C, 2009).

**Lead:** When the kidney gets exposed to lead, it accumulates in the proximal renal tubular lining cells of the kidney. Acute nephrotoxicity is characterized by proximal tubular impairment, which can be treated with chelating drugs. Interstitial fibrosis, increasing nephron loss, azotaemia, and renal failure are all symptoms of chronic lead nephrotoxicity. Gout and hypertension are two possible side effects of lead nephropathy (Goyer, 1989).

**Mercury:** Mercury is a useful heavy metal for industry and agriculture. Mercury, both in its elemental and organic forms, is a hazard that primarily affects the central nervous system, liver, and kidneys (Bernhoft, 2012). The inhibition of Sirt1/PGC-1 signaling has been proposed as one mechanism for mercury-induced renal failure. The Sirt1 deacetylation function was blocked by mercury, which closed the PGC-1 and Nrf2 axis and increased oxidative stress. The consequence was a mitochondrial malfunction accompanied by an increase in dynamin-related protein 1 and a reduction in mitofusin 2. The renal cells were susceptible to apoptosis due to mitochondrial abnormalities (Li et al, 2019).

**Antineoplastic Agents:** The medications used to treat cancer malignancy can cause a range of renal impairment and electrolyte abnormalities. Many antineoplastic agents and their derivatives are excreted by the kidneys. These agents are usually removed from the kidney either by glomerular filtration or tubular secretion. When it comes to non-protein-bound small molecules, glomerular filtration is an important system. If such compounds are protein-bound in the circulation, they cannot be eliminated; however, if they are removed through the renal root, they can hamper the glomerulus, and proximal tubule, and finally leads to renal damage via glomerulopathies or interstitial nephritis (Małyszko et al, 2017).

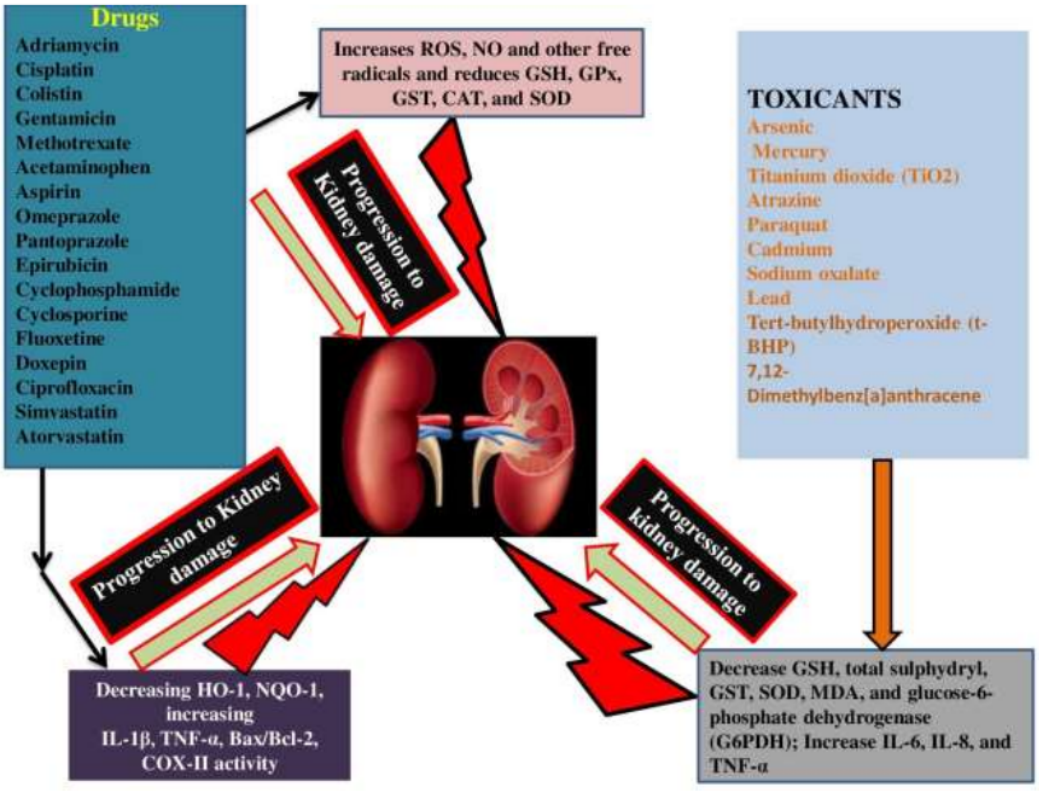


Figure 1: Nephrotoxicity inducing agents

## BIOMARKERS OF NEPHROTOXICITY

Blood urea and serum creatinine, which are conventional indicators of nephrotoxicity and renal dysfunction, are specific but have limited sensitivity in detecting early renal impairment. As a result, novel biomarkers that are more sensitive and selective to the site of fundamental renal damage were necessary for the detection of the first renal injury (Al‐Naimi et al, 2019).

A urinary protein is thought to be a possible measure of acute and chronic renal impairment. The glomeruli normally prevent high molecular-weight proteins from migrating from the circulation into the nephron lumen, however, due to nephron malfunction, high molecular-weight proteins can be recognized and discovered in the urine during pathological situations (Al-Kuraishy et al, 2013). Albumin, transferrin, and immunoglobulin G are high-molecular-weight proteins that are more susceptible to the early diagnosis of glomerular filtration failure, glomerular injury, and morphological glomerular injury (Kim and Moon, 2012). Low molecular weight proteins are normally recycled back mostly by the renal proximal tubules, but when low molecular weight protein levels are abundant, this causes nephron overload, which surpasses the reabsorbing ability of the proximal renal tubules. As a result of the loss of the reabsorption efficiency, proximal renal tubule injury causes low molecular weight proteinuria (Al-Kuraishy et al, 2018). Low-molecular-weight proteins including 1microglobulin, 2microglobulin, Cystatin C (Cys C), retinol-binding protein, and kidney injury molecule 1 (KIM1) are recognized as the primary proteins that represent the underlying renal glomerular and/or tubular dysfunction in nephrotoxicity (Hao et al, 2016). Due to ischemia-reperfusion damage, nephrotoxic drugs such as cisplatin, NSAIDs, and aminoglycosides cause overexpression of KIM-1. Thus, the response of the immune system to renal proximal tubule injury during nephrotoxicity is connected with the blood level of KIM-1. Furthermore, granulocytes are coupled to neutrophil gelatinase-associated lipocalin (NGAL), a 25 kDa protein that has been linked to nephrotoxicity because it is involved with inflammation during renal ischemia and acute renal damage (Al-Kuraishy et al, 2019). Different cytokines, such as interleukin (IL), interferon, and colony-stimulating factors, play a vital and fundamental role in renal tubular destruction and recovery, and as a result, they are used as biomarkers of renal damage in drug-induced nephrotoxicity. IL18 was first identified and described as an interferon-gamma inducing factor that is triggered by caspase 1 during apoptosis. IL-18 binds to particular receptors on cells such as mast cells, dendritic cells, T cells, and basophils. Obesity, inflammatory bowel disease, and chronic renal disease all have IL-18 implicated in their pathophysiology. Furthermore, high levels of IL-18 in the blood have been related to renal tubular atrophy and interstitial fibrosis. Also, a high level of IL-18 in the urine is linked to acute kidney damage and drug-induced nephrotoxicity. In acute kidney injury, increased amounts of IL-18 may operate as a biomarker for

renal damage or as a protective factor that slows the disease's development. Integrin (ITN) is a transmembrane receptor that helps in extracellular matrix binding. It is made up of two subunits: α and β. ITN's anti-fibrotic impact regulates essential cell processes and homeostasis during glomerular damage, resulting in considerable glomerular protection. ITN α2β1, on the other hand, may cause glomerular impairment by stimulating collagen production; hence, ITN α2β inhibitors might be very beneficial in controlling nephrotoxicity (Al‐Naimi et al, 2019).

## NUCLEAR FACTOR-κB (NF- κB) SIGNALING PATHWAY AND ACCUTE KIDNEY DAMAGE

Nuclear factor κB (NF-κB) was first identified as a B cell nuclear protein targeting the immunoglobulin κlight chain gene of the κ enhancer (Zhang and Sun, 2015). NF-B induction affects two types of signaling pathways: canonical and noncanonical. The multisubunit inhibitors (IκBs) kinase (IKK) is a conventional pathway that consists of two catalytic subunits, IKKα and IKKβ with a controlling subunit, NF-κB key regulator or IKKγ. The p50/NF-κB1, p65/RelA, and c-Rel with their usual dimers p50/NF-κB1-p65/RelA, and p50/NF-κB1-c-Rel are the canonical signaling members of NF-κB. NF-κB is localized in the cytoplasm in a combination with NF-κB IκBs in the normal physiologic conditions. In the presence of certain stimuli, the NF-κB IκBs complex leads to relocate the free NF-κB to the nucleus via the phosphorylation, production of ubiquitination, and destruction of the IκB. NF-κB binds to a particular region in the promoter area that results in the pro-inflammatory impact or encoding gene, and also the IκB protein, to reestablish a steady state. Several factors associated with kidney injuries, such as cytokines and growth factors, pathogen-related damage, and metabolic stress, activate the heterodimer p65–p50 (NF-κB). Ischemia-reperfusion, which places the kidneys in a hypoxic condition with poor RBF, stimulates NF-κB in kidney damage. AKI-induced inflammation is a key element that worsens renal dysfunction and reducing inflammation is a good way to reduce kidney injury and quick healing. Inflammation begins with the initiation of signaling pathways in tissue cells and leukocytes that control the production of pro and anti-inflammatory mediators. The signaling starts by the members of the IL-1 and TNF receptor families, as well as Toll-like microbial pattern recognition receptors related to the IL-1R, IL-1, and TNF families, and are produced shortly after tissue damage or infection (Sujana et al, 2021).

## NFR2 SIGNALING PATHWAY ACTIVATION AND THE ANTIOXIDANTS

### Oxidative Stress in Kidney

Renal tubular epithelial cells create adenosine triphosphate continuously to retain water and solutes from pre-urine, while the numerous mitochondria use oxygen. Reactive oxygen species (ROS) are produced by mitochondrial respiration and are chemically toxic to biomolecules, including genomic DNA. Low-level reactive oxygen species (ROS) are required for intra- and intercellular signaling to maintain kidney homeostasis and function, such as vascular reactivity, renal hemodynamics, glomerular filtration, tubular reabsorption, and hormonal secretion, whereas excessive ROS can cause oxidative stress in renal cells. The kidneys receive roughly 20–25 percent of the cardiac output to transport oxygen via blood flow, which is a large amount given the size of the kidneys in comparison to other organs. Nevertheless, uneven blood flow and IR are frequently caused by the features of the renal vasculature, which produce multiple arterial-to-venous shunts. The mitochondrial respiration chain and/or nicotinamide adenine dinucleotide phosphate (NADPH) oxidases create ROS during the reperfusion phase of renal IRI. Oxidative stress is triggered by the buildup of electrophilic molecules in addition to ROS. Convoluted blood flow with shear stress produces an electrophilic molecule, 15-deoxy-D12, 14)-prostaglandin J2, which triggers Nrf2 in endothelial cells. Excessive ROS and electrophiles disrupt cellular balance and cause oxidative stress, which results in inflammation, tissue damage, and fibrosis. ROS are generated by inflammatory cells that are stimulated locally in the renal microenvironment or emigrate from hematopoietic organs. As a result, oxidative stress is thought to be a critical exacerbating factor for the onset and development of AKI and CKD, including diabetic nephropathy, hypertension-associated kidney disease, and toxin-induced nephropathy, just like inflammation. Electrophiles build as a result of inadequate detoxification and aberrant metabolism in several forms of kidney disease, aggravating oxidative stress and exacerbating the problem. As a result, oxidative stress defense is seen as a critical therapeutic target for avoiding renal disease development (Nezu and Suzuki, 2020).

### Role of the Keap1-Nrf2 System against Oxidative Stress

The nephroprotective action of medicinal plants has been linked to a number of processes. The antioxidant defense system is the most prevalent mechanism among them. Antioxidants are substances that counteract oxidative stress, which is caused by an inconsistency in the rate of oxidant generation and elimination (Amarasiri et al, 2020). The transcription factor Nrf2 acts an integrative role in protecting cells from damaging oxidative stress by stimulating the expression of

genes encoding enzymes involved in antioxidant (e.g., glutathione and NADPH) synthesis and pro-oxidant reduction (e.g., heme and quinonoid). Nrf2 is constitutively generated in unstressed cells, but it is destroyed by the Nrf2-specific ubiquitin ligase complex, which is directly targeted by the stress-sensor protein Keap1. To detect cellular oxidative stress, a Keap1 molecule includes reactive cysteines that are adducted by oxidants and electrophiles. Nrf2 escapes destruction and promotes the expression of its target genes under oxidative stress conditions because cysteine-modified Keap1 no longer binds to it. Several proteins that directly connect to Nrf2 in nuclei have been recognized as key transcriptional cofactors. Nrf2 binding to CsMBE (CNC and small Maf binding element, 50-(A/G)TGA(G/C)nnnGC) found in promoters of Nrf2-target genes requires the creation of a heterodimer with one of the small Maf (musculoaponeurotic fibrosarcoma) proteins (MafF, MafG, and MafK). CREB-binding protein (CBP), brahma-related gene 1 (BRG1), and chromodomain helicase DNA binding protein 6 (CHD6), in addition to DNA-binding factors like small Maf proteins, are associated with transcriptional activation of genes linked to cytoprotection against oxidative stress by directly binding to Nrf2. Furthermore, the transcriptional mediator complex influences antioxidant gene expression through direct communication between Nrf2 and MED16, a mediator component (Nezu and Suzuki, 2020).

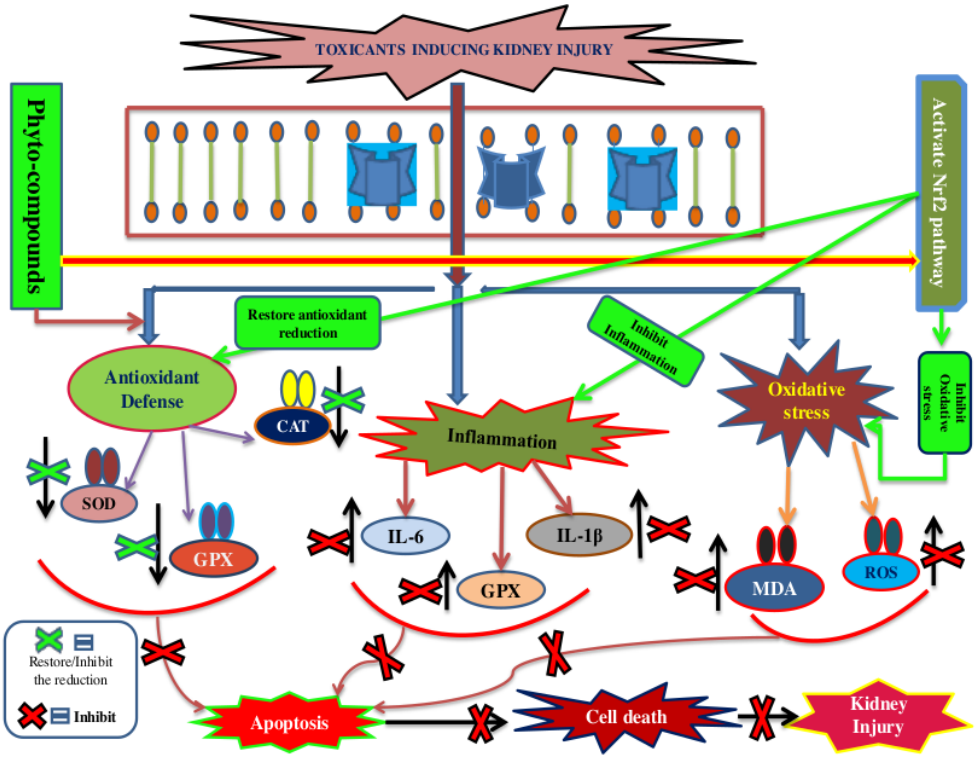


Figure 2: Nephroprotective Mechanism by Phytochemicals

## SIGNIFICANCE OF NATURAL PRODUCTS IN NEPHROPROTECTIVE ACTIVITY

Herbs are the most prevalent type of complementary and alternative medicine (CAM) utilized by CKD patients. Traditional medicinal plant-based treatment explores the causes as well as the results of renal illness in order to avoid the need for hemodialysis and lessen the negative effects of dialysis treatments. Herbs can also help with cutaneous itching, weariness, sadness, muscular cramps, and uremic bruises, which are all common CKD comorbidities. These herbs may also help to reduce the number of times of dialysis. As a result, there has been a significant growth in the use of medicinal plant-derived herbal remedies by hemodialysis patients during the last decade. These herbal drugs' diuretic characteristics are beneficial not only to hemodialysis patients, but also to pre-dialysis patients by boosting their deteriorating kidney function and therefore postponing the need for dialysis. Herbal medicines have been used for thousands of years and are widespread among all the general populace. Furthermore, medicinal plants employed in conventional medicine have aided in the development of a lot of modern allopathic drugs. Aspirin, atropine, ephedrine, digoxin, morphine, quinine, reserpine, and tubocurarine are examples of drugs produced based on traditional medicine findings. Medicinal plants are thought to be the source of almost one-third of all newly authorized chemicals in modern pharmacology. As a result, the World Health Organization has advised that herbal medicine be emphasized in order to meet the needs for illness treatment that are not fulfilled by current allopathic medicine (Amarasiri et al, 2020).

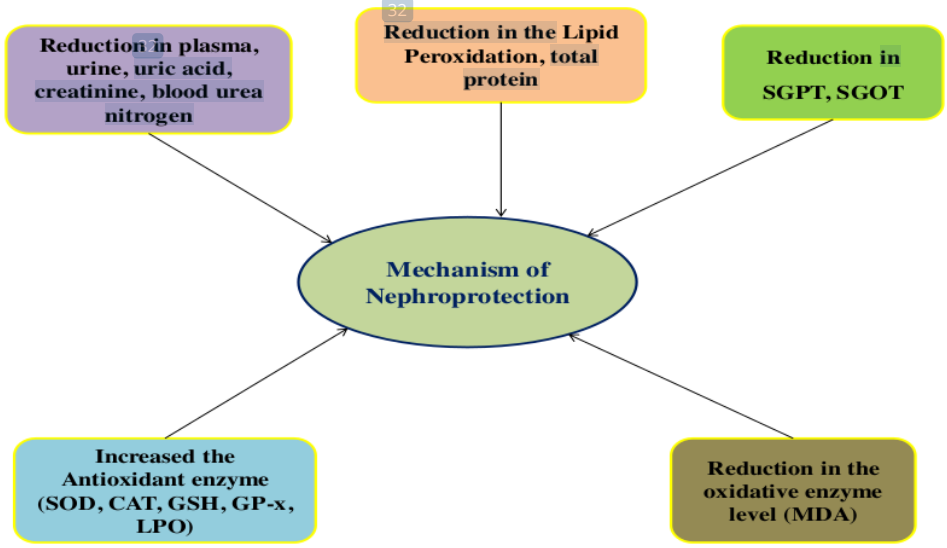


Figure 3: General overview on different enzyme's activity that produces nephroprotection

## Article search strategy and keywords:

The articles were extensively searched from the following databases: PubMed, Web of Science, Scopus, Wiley Online Library, ScienceDirect, Research Gate, Google Scholar, and Google. The search of articles was focused on *in-vivo* animal studies although any kind of articles containing scientific reports of nephroprotective activity of natural products, herbal medicine and nutraceuticals were considered. The keywords used for searching the articles in the search bar include – "Plant extract", "Herbal formulation", "Ethanol extract", "Aqueous extract", "Hydroalcoholic extract", "Medicinal plants", "*In-vivo*", "*In-vitro*", "Animal model" combined with "Nephroprotective activity''.

## Some medicinal plants having Nephroprotective effects

### *Solanum xanthocarpum* Schrad. & Wendl

*Solanum xanthocarpum* Schrad. & Wendl. belongs to the family Solanaceae. Commonly this plant is known as Yellow Berried Nightshade which is a thorny spreading bright green perennial herb. The fruits of this plant have several medicinal properties such as anthelmintic, antipyretic, laxative, anti-inflammatory, anti-inflammatory. The fruits have been shown to contain a various steroidal alkaloids as solanacarpine, solanacarpidine, solancarpine, solasonine and also other compopunds as caffeic acid, coumarins like aesculetin, aesculin, steroidscarpesterol, and triterpenes as cycloartanol and cycloartenol and other compounds were isolated. The nephroprotective activity of this plant is so impressive. When the experimental animals were administered GM as a toxicant, an increased level was observed in the plasma and urine urea, creatinine, kidney weight, blood urea nitrogen, renal lipid peroxidation and significant reduction in the level of urine output, renal enzymatic and non-enzymatic antioxidants. The fruit extract of *Solanum xanthocarpum* reduced the elevated level of plasma and urine urea, creatinine, kidney weight, blood urea nitrogen, renal lipid peroxidation and also elevated the urine output, renal enzymatic and non-enzymatic antioxidants level at the dose of 200 mg/kg, and 400 mg/kg (Hussain et al, 2012).

### *Tanacetum parthenium* L.

*Tanacetum parthenium* L. comes from the family Asteraceae. This plant originates from Eurasia and is extensively grown all over the world. It's a medicinal plant which has been used to treat things like fever, asthma, and inflammatory diseases. It has also been used in the treatment of migraines. Even though the phytochemistry of *T. parthenium* has not been well investigated, sesquiterpene lactones, parthenolide, 3b-hydroxy parthenolide, canin, and artecanin, all of which contain a α-methylene butyrolactone moiety, are the plant's most active chemicals. In the

investigation of nephroprotective activity, this plant showed potential effects. An elevated level was seen in urea, creatinine, uric acid and albumin (C/A) ratio level in serum when $CCl_4$ was induced to the animals. The toxicant also reduced the total antioxidant enzymes (SOD and GPx). But the methanolic extract of *T. parthenium* significantly reduced the urea, creatinine, uric acid and albumin (C/A) ratio level and increased the antioxidant enzymes at the dose of 120mg/kg (Mazani et al, 2018).

***Macrothelypteris oligophlebia* (Bak.)**

Macrothelypteris oligophlebia (Bak.) Ching is a plant of the family Thelypteridaceae. This plant is widespread in southwestern China. Its rhizomes are used as a traditional medicine to cure edema, boils, burns, and roundworms, among other ailments. Numerous flavonoids, including kaempferol, rutin, and kaempferol-3-O-β-rutinoside, were identified from a prior study of the chemical contents of this species. This plant produced significant nephroprotective activity in experimental animals. In the administration of gentamicin in experimental animals, the BUN, Cr, MDA, NO levels were increased and the SOD and CAT concentrations were decreased. However, the ethanolic extract of this plant significantly reduced the BUN, Cr, MDA, NO levels and increased the SOD and CAT levels (Wu et al, 2012).

***Abelmoschus esculentus* L**

The vegetable crop *Abelmoschus esculentus*, popularly known as Orka Pods, is a member of the family Malvaceae. This herb's different components are used to cure dysentery, diarrhoea, demulcent, spermatorrhoea, and laxative. This plant exerted valuable nephroprotective activity. Sodium nitrate, a toxicant increased the level of BUN and creatinine and also decreased the SOD and CAT level. Sodium nitrate produces kidney tubule necrosis as well, although the kidney necrosis in the okra pods-treated animal is significantly reduced. *Abelmoschus esculentus* preparation reduces the BUN and creatinine levels while increasing SOD and CAT activities. As a result, the medication exhibits effective nephroprotective properties in an animal model (Naveen et al, 2022).

***Descurania sophia***

*Descurania sophia* is a dicot perennial weed that comes from the family Brassicaceae. Commonly it is called “flixweed” or “Khak-e-sheer. This plant is widespread in different geographic location such as Asia, North Africa, North America, and Europe. In Iranian, Chinese, and Indian conventional medicine, this plant has been used to treat asthma, cough, heart malfunction, and edema. At least 26 physiologically active elements have been discovered from this plant. This plant

showed great activity in the nephroprotective activity. Gentamicin treatment increased the *BUN, creatinin,* urinary Na+ concentration and fractional excretion of sodium (FeNa+), cholesterol, triglycerides levels. All the parameters were decreased by the methanol extract of *Descurania sophia* at the dose of 1600 mg/kg & 2400 mg/kg (Askari et al, 2021).

***Biophytum sensitivum* Linn**

*Biophytum sensitivum* L. is a perennial herb in the family Oxalidaceae. It is usually called lajjalu. This herb is used to treat diabetes mellitus. Typically, this medicine was used to treat tonics, stimulants, stomachaches, asthma, sleeplessness, and cramps, among other things (Manisha and Kumar, 2018). In wistar albino rats, an ethanol extract of the entire plant Biophytum sensitivum (linn) has nephroprotective effects against cisplatin-induced nephrotoxicity. Urine level, total protein, sodium, potassium, calcium and magnesium were increased when toxicant cisplatin was administered. The ethanol extract of *Biophytum sensitivum* L effectively attenuated the Urine level, total protein, sodium, potassium, calcium and magnesium, also the BUN, creatinine concentration and significant increase in the body weight, urine pH, and serum level of protein, calcium and sodium levels (Abhirama et al, 2017).

Several plant extracts, herbal preparations, phytochemicals having potential nephrooprotective effects in both in-vivo and in-vitro models are presented in Table 1, 2, 3 and 4.

## Table 1: Effect of Extracts/Phytochemicals/Herbal Preparations for Nephroprotective Activity

| Sl. No | Name of Plant(s) | Family | Plant part(s) used | Type of Extract(s) | Study animal(s) | Nephrotoxicity Inducer | Results | References |
|---|---|---|---|---|---|---|---|---|
| 01 | *Solanum xanthocarpum* Schrad. & Wendl | Solanaceae | Fruits | Ethanol extract | Wister rats | Gentamicin | Significantly reduced (P<0.001) in plasma, urine urea, creatinine, renal lipid Peroxidation, and increased the enzymatic and non-enzymatic antioxidants at the dose of 200 mg/kg, and 400 mg/kg. | Hussain et al, 2012 |
| 02 | *Annona reticulate* | Annonaceae | Aerial parts | Ethanolic extract | wistar rats | Gentamicin and Cisplatin | Significantly reduced (P<0.001) in serum, urea, creatinine, uric acid, total protein and urine urea SGPT, SGOT, MDA level, and elevation in SOD levels at the dose of 500 mg/kg in both toxicant groups. | Devi et al, 2016. |
| 03 | *Combretummicranthum* G.Don | Combretaceae | Fresh leaves of Combretum | Hydroalcoholic extract | Male Albino Wistar rats | Cisplatin | Significantly reduced (P<0.001) in serum, urea, creatinine, uric acid, MDA and increased in GSH levels at the dose of 400mg/kg. | Kpemissi, et al, 2019. |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 04 | *Tanacetumparthenium* L | Asteraceae | Aerial parts | Methanolic extract | Male wistar rats | Carbon tetracholride | Significantly increased (P<0.001) in total protein, serum, creatinine, urea, and reduced total antioxidant and antioxidant enzymes (SOD and GPX) levels at the dose of 120mg/kg. | Mazani et al, 2018 |
| 05 | *Macrothelypteris Oligophlebia* (Bak.) | Thelypteridaceae | Rhizomes | Ethanol extract | Male wister rat. | Gentamycin | Significantly reduced (P<0.01) in creatinine and blood urea nitrogen, MDA levels, and increased in SOD, CAT, NO, GSH-PX levels at the dose of 500mg/kg. | Wu et al, 2012. |
| *06* | *Crataeva nurvula* Buch Hum | Capparaceae | Stem barks | Ethanolic extract | Male Wistar rats | Cisplatin | Significantly reduced (P<0.5) in serum urea, uric acid, and creatinine levels at the dose of 600mg/kg. | Shelkea et al , 2011 |
| 07 | *Ficus Hispida* | Moraceae | Fruit | Methanolic extract | Wister albino rats | Cisplatin | Significantly reduced (P<0.001) in serum creatinine, urine creatinine, blood urea nitrogen, urinary total protein, and MDA levels at the dose of 500 mg/kg. | Swathi, et al, 2011. |
| 08 | *Carica papaya* Linn | Caricaceae | Unripe fruits | Aqueous seed extract | Wistar rats | Carbon tetrachloride | Significantly reduced (P<0.001) in serum levels of uric acid, urea and creatinine, and increased the enzymatic and non-enzymatic antioxidants at the dose of 400mg/kg. | Olagunjua et al, 2009. |
| 09 | *Biophytum* | Oxalidacea | Whole | Methanol, | Wistar albino | Gentamicin | Significantly reduced | Chandavarkar et al, |

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|---|---|---|---|---|---|---|---|---|
| | *sensitivum* (Linn.) | e | plant | chloroform and aqueous extracts | rats. | | (P<0.01) in serum urea, serum creatinine, blood urea nitrogen, uric acid ,SOD, CAT levels, and increased in LPO, GSH levels at the dose of 200 mg/kg. Methanol extract is more effective than aqueous extract. | 2017. |
| 10 | *Jatropha curcas* Linn | Euphorbia ceae | Fruit | Methanol, and aqueous extracts | Wister rats | Carbon Tetrachloride | Significantly reduced (P<0.001) in creatinine, blood urea, albumin, and total protein levels at the dose of 250mg/kg. Aqueous extract is more effective than methanol extract. | Komail et al, 2017. |
| 11 | *Thaumatococcus danielli* (Benth.) | Marantace ae | Fresh leaves | Ethanolic leaf extract | Wistar albino female Rats | Streptozotocin | Significantly increased (P<0.05) in serum, total protein levels and reduced in urea and creatinine levels. | Olorunnisola et al, 2017. |
| 12 | *Trema guineensis* | Ulmaceae | Leaves | Aqueous and hydroethanolic extract | Wistar albino rats | Gentamicin | Significantly reduced (P<0.001, P<0.01) in serum biochemical parameter at the dose of 200mg/kg. Aqueous extract is more effective than hydroethanolic extract. | Cyril et al., 2017. |
| 13 | *Orthosiphon Stamineus* | Lamiaceae | Leaves | Ethanolic extract | Rats | Ethylene glycol | Reduced in the serum parameters like Creatinine, Uric Acid, Urea, total protein and the serum marker enzymes SGOT, SGPT and ALP levels. | Rajeshkumar et al, 2014. |

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| 14 | *Pedalium Murex* Linn | Pedaliaceae | Dried fruits | Ethanolic extract | Swiss Albino mice | Cisplatin | Significantly reduced (P<0.01) in serum creatinine and, blood urea levels at the dose of 250 mg/kg. | Shelke et al, 2009. |
| 15 | *Barleria longiflora* L. | Acanthaceae | Leaf | Ethanol extract | Male albino Wistar rats | Gentamicin | Reduced in serum creatinine, blood urea, uric acid, and increased in SOD, LPO, CAT levels at the dose of 400 mg/kg. | Manjula and Ganthi, 2018. |
| 16 | *Leea asiatica* (L.) | Leeaceae | Leaves | Methanol, ethyl acetate and petroleum ether extracts | Albino mice | Cisplatin | Significantly reduced (p<0.05, P<0.01) in serum creatinine, blood urea nitrogen, uric acid ,MDA levels, increased in total proteins, albumin at the dose of 300mg/kg. Methanol extract showed better effective than other extract. | Sen et al, 2013 |
| 17 | *Prosthechea michuacana* (Lex.) | Orchidaceae | Bulbs | Methanol, hexane, and chloroform extracts | Rats | Cisplatin | Significantly reduced in blood urea, serum creatinine levels and increased in LPO, GSP, GSH levels. | Gutierrez et al, 2010. |
| 18 | *Momordica tuberosa* Cogn. | Cucurbitaceae | Tuber | Hydroalcoholic extract (70% ethanol extract) | Albino rats | Gentamicin, cisplatin and paracetamol | Significantly reduced (P<0.05, P<0001) in blood urea, serum creatinine levels and increased in GSH levels at the dose of 40mg/kg in these toxicant groups. | Kumar et al, 2011. |

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| 19 | *Caesalpinia bonduc* and *Momordica dioica* | Fabaceae And Cucurbitaceae | Rhizome | Hexane , ethyl acetate and methanol extract | Wister rats | Cisplatin | Significantly reduced (P<0.05) in creatinine, urea, uric acid, blood urea nitrogen, SGPT levels at the dose of 100mg/kg and 200mg/kg. | Talukdar et al, 2018. |
| 20 | *Pimpinella anisum* L. | Apiaceae | Seeds | Aqueous extract | Wistar Rats | Gentamicin | Significantly reduced (P<0.05) in serum urea, serum creatinine, serum uric acid and blood urea nitrogen levels at the dose of 2g/kg. | Aiswarya et al, 2017. |
| 21 | *Sonchus oleraceus* | Asteraceae | Aerial part | Ethanol extract | Wistar Rats | Ischemia-Reperfusion | Significantly reduced (P<0.001) in blood urea nitrogen, creatinine, MDA levels and increased in SOD levels. | Torres-González et al, 2017. |
| 22 | *Bauhinia variegate* (Linn.) | Fabaceae | Whole stem | Ethanolic extract | Albino male rats | Cisplatin | Significantly reduced (P<0.01) in serum creatinine, serum albumin, serum urea, urine creatinine, urine albumin levels at the dose of 400mg/kg. | Pani et al, 2010. |
| 23 | *Hybanthus Enneaspermus* (L) F.Muell. | Violaceae | whole plant | Alcoholic and aqueous extract | Male albino rats of Wistar strain | Cisplatin | Significantly reduced (P<0.01,P<0.05) in serum creatinine , blood urea, blood proteins levels and increased in LPO,SOD,GST,GSH levels at the dose of 500mg/kg. Aqueous extract is more effective than alcoholic extract. | Setty et al, 2005. |

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| 24 | *Indigofera tinctoria* Linn | Fabaceae | Leaves | Decoction of *Indigofera tinctoria* | Male Wistar rats | Cisplatin | Significantly reduced (P<0.01) in serum creatinine, urea levels at the dose of 1000mg/kg. | Priyadarsini et al, 2012. |
| 25 | *Lens culinaris* | Fabaceae | Seed | Hydroalcoholic extract | Wistar strain albino rats | Cisplatin | Significantly reduced (P<0.05) in blood urea nitrogen, serum creatinine, urine total protein ,LPO levels, and increased in SOD, GSH, CAT levels at the dose of 400mg/kg. | Sreedevi, 2018. |
| 26 | *Lantana camara* L. and *Cucurbita pepo* (Squash) | Verbenaceae | Leaves | Methanolic Extract | Male Wister albino rats | Cisplatin | Significantly reduced (P<0.05) in creatinine, urea, MDA levels, and increased in SOD, GPX, CAT levels at the dose of 400mg/kg. | Abdel-Hady et al, 2018. |
| 27 | *Aegle Marmelos* | Rutaceae | Leaves | Hydro-alcoholic (HAEAM) and ethyl acetate (EAEAM) extracts | Animal(unknown) | Cisplatin | Significantly reduced (P<0.001) in creatinine, blood urea nitrogen levels and increased in SOD, GSH, CAT at the dose of 400mg/kg. Ethyl acetate extract is more effective than hydro-alcoholic extract. | Dwivedi et al, 2017. |
| 28 | *Eclipta prostrate* (L.) | Asteraceae | Leaves | Ethanol extract | Wistar rats | Gentamicin | Significantly reduced (P<0.01) in serum creatinine, serum urea, serum uric acid and blood urea nitrogen levels at the dose of 500 mg/kg. | Ahmad et al, 2018. |

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| 29 | *Eurycoma longifolia* | Simaroubaceae | Roots | Ethanol extract | Wistar rats | Paracetamol | Significantly reduced (P<0.05) in serum creatinine and blood urea levels at the dose of 400mg/kg. | Chinnappan et al, 2019. |
| 30 | *Phyllanthus niruri* L. | Euphorbiaceae | Whole plant | Methanolic Extract | Albino rats of Wistar strain | Gentamicin | Significantly reduced (p<0.05, P<0.01, P<0.001) in serum creatinine, serum urine, serum protein, MDA levels, and increased in GSH levels at the dose of 400mg/kg. | Reddy et al, 2015. |
| 31 | *CostusAfer Ker gawl* | Costaceae | Leaf | Aqueous leaf extract | Wistar albino rats | Cyclosporin | Significantly reduced (P<0.05) in plasma creatinine, blood urea nitrogen, MDA levels and increased in GSH, SOD, CAT, GST, GPA levels at the dose of 1125 mg/kg. | Ezejiofor et al, 2016. |
| 32 | *Ipomoea staphylina* | Convolvulaceae | Leaves | hydroalcoholic extract | Rats | Gentamicin | Significantly reduced (P<0.001) in serum creatinine, blood urea, blood urea nitrogen, AST, ALP levels at the dose of 200mg/kg. | Bag and Mumtaz, 2013. |
| 33 | *Clitoria ternatea* Linn | Papilionaceae | Aerial part | Ethanol extract | Wister Aibino male rats | Acetaminophen | Significantly reduced(P<0.01,P<0.05) in uric acid, MDA levels and increased in SOD,CAT,GSH and GPX levels at the dose of 500mg/kg. | Sarumathy et al, 2011. |

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| 34 | *Elephantophus Scaber* Linn | Asteraceae | Leaves | Ethanolic extract | Wister rats | Gentamicin | Significantly reduced (P<0.01) in serum creatinine, total protein, serum urea levels at the dose of 600mg/kg. | Bhusan et al, 2012. |
| 35 | *Juglans mollis* | Juglandaceae | Bark | Methanolic extract | Wister rats | Ischemia – reperfusion | Significantly reduced (P<0.05) in blood urea nitrogen, creatinine, ALT, MDA and increased in SOD levels at the dose of 300mg/kg. | Perez-Meseguer et al, 2019. |
| 36 | *Kalanchoe Pinnata* (Lam.) Pers. | Crassulaceae | Leaves | Aqueous extract | Male albino wister rat | Gentamicin | Significantly reduced (P<0.05) in plasma creatinine, blood urea nitrogen levels. | Harlalka et al, 2007. |
| 37 | *Ginkgo biloba* L. | Ginkgoaceae | Leaves | Ethnolic extract | Wistar albino rats | Gentamicin | Significantly reduced (P<0.01) in blood urea nitrogen, serum creatinine, serum uric acid, serum urea levels | Mansoor et al, 2015. |
| 38 | *Trianthema Portulacastrum* Linn. | Aizoaceae | Fresh plant sample | Powder | Male albino rats | Drug | Significantly reduced in creatinine, urea, uric acid, AST, ALT levels and increased in LPO, SOD, GPX levels at the dose of 100mg/kg. | Vallabi and Elango, 2015. |
| 39 | *Salacia fruticose Heyne ex Lawson* | Hippocrateacea | Fresh of *Salacia fruticosa* Heyne ex Lawson | Ethanol extract | Wister albino male rats | Acetaminophen | Significantly reduced (P<0.001,P<0.01) in creatinine, uric acid, blood urea ,MDA levels and increased in SOD, CAT,GPX,GSH levels at the dose of 500mg/kg. | Rajalingam and Palani, 2017. |

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| 40 | *Cynodon dactylon* | Poaceae | Whole plant | Aqueous extract | Male albino wistar rat | Streptozotocin | Significantly reduced (P<0.001) in serum total protein, serum creatinine, blood urea levels and increased in LPO levels. | Madhan et al, 2016. |
| 41 | *Bauhinia purpurea* | Fabaceae | Unripe pods and bark | Ethanolic Extract | Albino rats | Cisplatin | Significantly reduced (P<0.01) in serum creatinine, blood urea, creatinine clearance , MDA levels, and increased in GSH,CAT levels at the dose of 400mg/kg. | Rana et al, 2016. |
| 42 | *Morus Alba* Linn | Moraceae | *M. alba* L. leaves | Hydroalcoholic extract | Albino rabbits | Isoniazid | Significantly reduced (P<0.05) in serum creatinine, blood urea nitrogen levels at the dose of 800mg/kg. | Muhammad et al, 2014. |
| 43 | *Pterocarpus marsupium* Roxb. | Fabaceae | Heartwood of *P. marsupium* | Alcoholic extract | Male Sprague Dawley rats | Streptozotocin | Significantly reduced (P<0.05) in creatinine, blood urea nitrogen, uric acid, albumin levels and increased in LPO, CAT,GSH levels at the dose of 400mg/kg. | Gupta et al, 2016. |
| 44 | *Ziziphus Jujube* (L) | Rhamnaceae | The fruits of *Ziziphus jujube* | Methanol extract | Sprague-Dawely rats | Cisplatin | Significantly reduced (P>0.001) in creatinine, urea, MDA levels and increased (P<0.005) in CAT, GST levels at the dose of 500m/kg. | Tenaiji and Zoubi, 2019. |
| 45 | *Ficus religiosa Linn* | Moraceae | Stem Bark | Ethanolic and hydroalcoholic extract | Albino rabbits | Isoniazid and Rifampicin | Significantly reduced (P<0.05) in creatinine, blood urea nitrogen levels. Ethanolic extract is more effective than hydroalcoholic extract. | Hashmi et al, 2013. |

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| 46 | *Feijoa Sellowiana* | Myrtaceae | Leaves | Aquesous or methanol extract | Male albino mice | Acute dose of ecstasy (MDMA) | Significantly reduced (P<0.001, P>0.05) in serum creatinine, serum urea levels at the dose of 40mg/kg. Aqueous extract is more effective than methanol extract. | Karami et al, 2013. |
| 47 | *Croton zambesicus* Muell Arg. | Euphorbiaceae | Root | Ethanol extract | Both male and female animals (mice and rats | Gentamicin | Significantly reduced (P<0.01) in serum creatinine, urea at the dose of 54mg/kg. | Okokon et al, 2011. |
| 48 | *Ceratonia siliqua* L. | Fabaceae | Pods and leaves | Ethanol extract | Albino male mice | Cisplatin | Significantly reduced (P<0.05) in creatinine , urea, MDA levels and increased in SOD, CAT,GPX,GSH,GST levels at the dose of 200 mg/kg. | Ahmed, 2010. |
| 49 | *Dioscoreaalata* and *Moriengaolifera* | Dioscoreaceae and Moringaceae | Tuber (parts of *Dioscoreaalata* )and Seed (pods of *Moringaoleifera)* | Methanolic extract | Swiss albino rat | Cisplatin | Restored renal antioxidant defense system. | Rahman et al, 2018. |
| 50 | *Amomum subulatum* | Zingiberaceae | Seeds | Ethanolic extract | Male Wistar albino rats | Cypermethrin | Significantly reduced (P<0.01, P<0.05) in creatinine, serum urea, LPOMDA, CAT, GPX levels at the dose of 400mg/kg. | Puttanna et al, 2016. |

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| 51. | *Abelmoschus esculentus* L | Malvaceae | Okra pods | Methanol extract | Mice | Sodium nitrate | Significant reduction in kidney necrosis, level of BUN, creatinine and increase activity of SOD, CAT levels. | Wahyuningsih et al, 2020. |
| 52. | *Corallocarpus epigaea* | Cucurbitaceae | Rhizomes | Hydroalcoholic extract | Wistar rats | Cisplatin | Increased in SOD, decrease in malondialdehyde level. | Amruta et al, 2020. |
| 53. | *Biophytum sensitivum* Linn | Oxalidaceae | Leaves | Ethanol extract | Wistar albino rats | Cisplatin | Reduced in urine excretion of total protein, calcium, low level of serum BUN. | Abhirama et al, 2017. |
| 54. | *Descurainia sophia* (L.) | Cruciferae | Seeds | Hydroalcoholic extract | Male Wistar rats | Gentamicin | Reduced in serum level of BUN, creatinine, cholesterol, triglycerides, Na excretion and cell death rate. | Askari et al, 2021. |
| 55. | *Sphaeranthus amaranthoides* burm f. | Asteraseae | Whole plant | Aqueous extract | Wistar albino rat | Gentamicin | Normal level of LDH, GGT, creatinine, BUN and electrolyte in both serum and urine. | Rethinam et al, 2021. |
| 56. | *Morinda pubescens* J.E.Sm | Rubiaceae | The bark of *Morinda pubescens* J.E.Sm. | Aqueous extract | Male Wistar rats | Gentamicin | Significantly increased ($P<0.05$) in Urea, Uric acid,Blood urea nitrogen level and reduced in Albumin and protein level at the dose of 200mg/kg, p.o. | Jedage and Manjunath, 2016. |
| 57. | Plectranthus amboinicus Benth | Lamiaceae | Leaves and stem. | Aqueous extract | Wistar albino rats | Adriamycin | Significantly reduced in the serum creatinine level. | Kumar et al, 2020. |
| 58. | *Withania somnifera* | Solanceae | Root | Aqueous extract | Adult male albino Wistar rats | Gentamicin | Significantly increased ($P<0.05$) in urea, creatinine, urinary protein levels at the dose of 500mg/kg. | Jeyanthi and Subramanian, 2009. |

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| 59. | *Cassia auriculata* Linn. | Caesalpiniaceae | Root | Ethanol extract | Male albino rats. | Cisplatin and gentamicin | Reduced in blood urea and serum creatinine levels. | Annie et al, 2005. |
| 60. | *Viscum articulatum* Burm. f. | Viscaceae | Plant | Chloroform extract | Male albino Wistar rats | Gentamicin | Significantly reduced in serum albumin, serum urea, serum creatinine, urine creatinine, urine urea, urine albumin levels at the dose of 80mg/kg. | Patil et al, 2009. |

## Table 2: Nephroprotective effects of some phytocompounds

| Sl No. | Class of compounds/Specific compound | Source | Possible Mechanism of Nephroprotection | References |
|---|---|---|---|---|
| 1 | Azadirachtin, nimbolide | *Azadirachta indica* A. Juss. | Reduction of Oxidative damage | Alzohairy, 2016 |
| 2 | Flavonoids, phenol | *Cassia auriculata* L. | Antioxidant and free-radical-scavenging property | Annie, et al, 2005 |
| 3 | Alkaloids, Phenols, Flavonoids | *Foeniculum vulgare* Mill, *Solanum Nigrum* Linn | Free radical scavenging and antioxidant activity | Shaheen et al, 2014 |
| 4 | C-glycosyl flavones, proanthocynidin | *Biophytum sensitivum* (Linn.) DC | Antioxidant activity | Chandavarkar et al, 2017 |
| 5 | Emodin, monomethyl, ether, tannin, aloe emodinrhein | *Rheum emodi* Wall.exMeiss | Antioxidant activity | Malik et al, 2016 |
| 6 | Phenols, steroids | *Curculigo orchioides* Gaertn | Antioxidant activity | Murali, 2015 |
| 7 | Aloin | *Aloe barbadensis* Burm.f | Normalized oxidative stress | Iftikhar et al, 2015 |
| 8 | Pentosan, vitamin A, vitamin C, phytosterols | *Dolichos biflorus* sensu auct non L. | Antioxidant activity | Saha and Verma, 2015 |
| 9 | Crocin | *Crocus sativus* L. | Reduction of oxidative stress | Naghizadeh et al, 2010 |
| 10 | Curcumin | *Curcuma longa* | Suppression of oxidative stress | Venkatesan et al, 2000 |
| 11 | Quercetin | *Phoenix dactylifera* L. | Antioxidant and free radicals scavenging activity | Abdel-Raheem et al, 2009 |
| 12 | Solasodine | *Solanum xanthocarpum* Schrad. & Wendl. | Inhibition of CaOx crystal formation | Patel et al, 2012 |
| 13 | Gingerols | *Zingiber officinale* Roscoe | Prevent the decline of Antioxidant activity | Ajith et al, 2008 |
| 14 | Rutin | | Modulation of oxidative stress | Radwan and Fattah, 2017 |
| 15 | Apigenin and myricetin | Tea, berries, fruits and vegetables | Antioxidant and anti-inflammatory effects | Hassan et al, 2017 |
| 16 | Luteolin | | Normalizing oxidative/nitrosative stress | Domitrović et al, 2013 |

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| 17 | Kaempferol | | Free radical scavenger, antioxidant property | Vijayaprakash et al, 2013 |
| 18 | Catechin | | Antioxidant activity | Sardana et al, 2014 |
| 19 | ferulic acid, Z-ligustilide and E-ligustilide, | Angelica sinensis (Oliv.) | Enhancing cell regeneration capacities, limiting the oxidative stress. | Bunel et al, 2015 |
| 20 | vanillic acid | | Antioxidant activity | Sindhu et al, 2015 |
| 21 | Gallic acid, catechin and caffeic acid | *Sida cordata* | Antioxidant activity | Shah et al, 2017 |
| 22 | Flavonoids, tannins (gallic acid) and phenol | *Morinda pubescens* J.E.Sm. | Antioxidant activity | Jedage and Manjunath, 2016 |
| 23 | 2,3,5,4′-Tetrahydroxystilbene-2-O-β-d-glucoside | *Polygonum multiflorum* Thunb. | Antioxidant activity | Bayarsengee, et al, 2017 |
| 24 | Thymoquinone | *Nigella sativa oil* | Attenuate the oxidative stress, ameliorating inflammatory tissue damage. | Elsherbiny & El-Sherbiny, 2014 |
| 25 | Embelin | | Reduce oxidative stress and inflammation | Qin et al, 2019 |
| 26 | Farrerol | | Normalize oxidative stress and inflammation | Ma et al, 2019 |
| 27 | 6-hydroxy-1-methylindole-3-acetonitrile | *Brassica rapa* | Reducing oxidative stress | Moon et al, 2013 |
| 28 | Isoorientin | *Phyllostachys pubescens* | Decrease oxidative stress inflammation and apoptosis | Fan et al, 2020 |
| 29 | Kaempferol | | Activate RK and NF-κB pathway. | Wang et al, 2020 |
| 30 | Mangiferin | Mango tree | Antioxidant and anti-inflammatory properties | Sadhukhan et al, 2018 |
| 31 | Piceatannol | | Inhibit the inflammatory and apoptotic pathways | Wahdan et al, 2019 |
| 32 | S-allylcysteine | garlic | Reduce oxidative stress | Gómez-Sierra et al, 2014 |
| 33 | Sinapic acid | | Reduces oxidative stress, inflammation, and apoptosis | Ansari, 2017 |
| 34 | Lycopene | | Antioxidant activity | Dai et al, 2014 |
| 35 | Pinocembrin | honeybee propolis, *Boesenbergia pandurata* | Antioxidant and anti-apoptotic effects | Promsan et al, 2015 |
| 36 | Berberine | *Coptis sp, Berberis sp* | Antioxidant and anti-inflammatory activity. | Hassanein et al, 2019 |

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| 37 | Chicoric acid | | Activation of Nrf2/ARE/HO-1 signaling pathway | Abd El-Twab et al, 2019 |
| 38 | 18b-glycyrrhetinic acid | *Glycyrrhiza glabra* L. | Attenuating oxidative stress and inflammation | Abd El-Twab et al, 2016 |
| 39 | Formononetin | *Trifolium pretense, Astragalus membranaceus* | Attenuate oxidative damage and inflammation. | Aladaileh et al, 2019 |
| 40 | Vincamine | | Suppressing oxidative stress | Shalaby et al, 2019 |
| 41 | Sulforaphane | Broccoli, brussels sprouts, and cabbage | Antioxidant activity | Thangapandiyan et al, 2019 |
| 42 | Tannic acid | | Inhibition of oxidative stress | Jin et al, 2020 |
| 43 | Carnosic Acid | *Rosmarinus officinalis* L., *Salvia officinalis* L. | Attenuating renal oxidative stress, inhibiting ROS | Das et al, 2019 |
| 44 | Proanthocyanidins | Grapes | Reduce the oxidative stress | Bashir et al, 2015 |
| 45 | Tangeretin | | Reduce oxidative stress | Lakshmi & Subramania, 2014 |
| 46 | Luteolin | | Antioxidant activity | Albarakati et al, 2020 |

## Table 3: Nephroprotective effect of Herbal Formulation

| No. | Name of the Formulation | Component of the Formulation | Renal disease model | Observation/Result | Reference |
|---|---|---|---|---|---|
| 1. | HUF | *Revand Chini* (*Rheum emodi* wall), *Khar-e-Khasak-Khurd* (*Tribulus terrestris* L.) *Filfil Siyah* (*Piper nigrum* L.) *Zanjabeel* (*Zingiber officinale* Rosc.) | Human | Significant effect in the biochemical and clinical parameters. | Azhar, 2018. |
| 2. | AJMAL06 | *Vitex nigundu, Piper nigrum*, *Itrifal Kishnizi Jawarish Zarooni Sada* | Human | Significant improvement and relief of symptoms. | Siddiqui et al, 2016. |
| 3. | \VI-28 | *Radix ginseng*, *Cornu cervi, Cordyceps, Radix salviae, Semen allii, Fructus cnidii, Fructus evodiae* and *Rhizoma kaempferiae* | Animal (Rats) | Significantly increased in GSH, Mn-SOD, GPX and GST levels at the dose of 240 mg/kg. | Poon et al, 2007. |
| 4. | PAE(polyherbal alcoholic extract) | *Withania somnifera* (root), *Aegle marmelos* (leaves), *Tribulus terrestris* (fruit) | Wistar rats | Significantly increased in BUN, creatinine, AST, ALT, ALP, total protein, albumin and globulin levels. | Aswar et al, 2022. |
| 5. | Eefooton | *Astragalus membranaceus*, *Codonopsis pilosula, Ligustrum lucidum*, *Panax quinquefolius*, and *Rhodiola sacra*. | Human | Significantly decreased in serum creatinine levels. | Yao and Lin, 2019. |
| 6. | Neeri (NS-RF) | Lead acetate | Wistat rats | Significantly increased in serum creatinine, serum urea, and urinary protein and reduced in serum albumin, serum total proteins, and urinary creatinine at the dose of 3280 mg/kg. | Barwal et al, 2015. |

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| 7. | Chinese herbal medicines | *Astragalus membranaceus* (*Fisch*), Astragalus or Astragalus in combination with Angelica (*Angelica sinesis)* Ligusticum *(Ligusticum wallichii)*, Triptolide (*Tripterygium wilfordii Hook F*), Rhubarb (*Rheum officinale*). | Human | Showed the progressive levels of chronic kidney disease (CKD) and kidney-related injuries. | A peng et al, 2005. |
| 8. | HAF(Hydroalcoholic polyherbal formulation) | *Bergenia ciliata*, *Pedalium murex*, *Tribulus terrestris*, *Tinospora cordifolia*, *Sphaeranthus indicus*, and *Piper longum*. | Wister albino rats | Significantly increased (P<0.001) in serum urea levels and reduced in serum creatinine and blood urea nitrogen levels at the dose of 400mg/kg. | Srivastava et al, 2018. |
| 9. | Triphala | *Terminalia belerica* Roxb. | Wistar albino rats | Significantly reduced (P<0.05) in serum total protein and albumin levels and increased in serum creatinine, urea and uric acid levels. | Baskaran et al, 2015. |
| 10. | Neeri-KFT | *Boerhaavia diffusa*, *Tinospora cordifolia*, *Nelumbo nucifera*, *Butea monosperma*, *Tribulus terrestris*, *Moringa oleifera*, *Veteveria zizanioides*, *Crataeva nurvala*, *Amaranthus spinosus*. | Wistar rats | Significantly reduced in serum creatinine, serum urea, urea creatinine and urea protein levels and increased in albumin, total protein levels. | Tiwari et al, 2016. |
| 11. | MEWS(Methanol Extract *Withania somnifera*) | *Withania somnifera* (*WS*) (Aswagandha) | Wister rats | It is shown that the protection of renal failure. | Das et al, 2009. |
| 12. | Novel polyherbal formulation | Whole plant of Punarnava (*Boerrhavia Diffusa*), Fruit of Gokshura (*Tribulus terrestris*), Whole plant of Pashanabheda (*Aerva lanata*), Rhizome of Shunti (*Zingiber officinale*), Seeds of Jeeraka (*Cuminum cyminum*). | Wister albino rats | It is shown that the protection of chronic kidney diseases. | Kamaraj et al, 2022. |
| 13. | *Arişţa* (coded as DB-07) | *Āmalakī (Emblica officinalis* Gaertn), *Methikā* (*Trigonella foenum-graecum* L.), *Aśvagandhā* (*Withania somnifera* (L.) Dunal), *Tvak* (*Cinnamomum zeylanicum* Blume), *haridrā* (*Curcuma longa* L.), *Kāravellaka* (*Momordica* | Wistar rats | Significantly reduced in creatinine, urea, blood urea nitrogen and uric acid levels at the dose of 3.5 ml/kg. | Dey et al, 2022. |

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| | | *charantia* L.), *Guḍūcī* (*Tinospora cordifolia* (Willd.) Miers), *Jambu* (*Syzygium cumini* (L.) Skeels), *Nimba* (*Azadirachta indica* A. Juss.), *Meṣaśṛngi* (*Gymnema sylvestre* (Retz.) R.Br. ex Sm.), *Raktapunarnavā* (*Boerhavia diffusa* L), *Kālamegha* (*Andrographis paniculata* (Burm. f.) Nees), *Gokṣura* (*Tribulus terrestris* L.), *Tvakpatra* (*Cinnamomum tamala* (Buch.-Ham.) T. Nees and Eberm), *Lavaṅga* (*Syzygium aromaticum* (L.) Merr.and L.M. Perry), *śuṇṭhī* (*Zingiber officinale* Roscoe), *Marica* (*Piper nigrum* L.), *Yavānī* (*Trachyspermum ammi* (L.) Sprague), *Drākṣā* (*Vitis vinifera* L.), *Madhūka* (*Madhuca indica* J.F. Gmel.), (*Aloe barbadensis* Mill.) | | | |
| 14. | Novel formulation | Unopened inflorescence of coconut trees (*Cocos nucifera*). | Wistar rats | Significantly ($p<0.05$) reduced the levels of antioxidant enzymes (SOD, CAT, GPx) and GSH and increased ($p<0.05$) the levels of creatinine, uric acid, urea levels. | Jose et al, 2016. |
| 15. | Bi-Herbal Formulation | *Ocimum gratissimum* and *Gongronema latifolium* | Albino rats | Significantly ($p < 0.05$) increase in the levels of ALT, AST, ALP, creatinine and urea levels at the dose of 500 mg/kg. | Ezeonwu and Dahiru, 2013. |
| 16. | DHC-1 | *Bacopa monniera*, *Emblica officinalis*, *Glycyrrhiza glabra*, *Mangifera indica* and *Syzygium aromaticum*. | Albino rats | Significantly reduced in the serum markers of kidney damage and the increased of lipid peroxidation with a concomitant increase in the enzymatic (SOD and CAT). | Bafna and Balaraman, 2005. |
| 17. | Jawarish Zarooni Sada(JZS) | Maghz-Tukhm-Kharpazah (*Cucumis melo* Linn.), Maghz-Tukhm-Kheyar (*Cumis cusativus* Linn.), Tukhm-e-Karafs (*Apium graveolens* Linn.), Post-Beekh-e-Karafs ( *Apium graveolens* Linn.), Tukhm-e-Gazar (*Daucus carota* Linn.), | Wistar albino rats | Significantly ($P<0.001$) increased in the serum creatinine and serum urea levels. | Afzal et al, 2004. |

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| | | Nankhah (*Trachyspermum ami* Sprague.), Badiyan (*Feniculum vulgare* Mill.), Qaranfal (*Syzygium aromaticum* Merr and Perry), Filfi siyah (*Piper nigrum* Linn.), Aqarqarha (*Anacyclus pyrethrum* D.C.), Darchini (*Cinnamomum zeylanicum* Blume.), Mastagi (*Pistacia lentiscus* Linn.), Zafran (*Crocus sativus* Linn.), Ood Hindi (Agar) (*Aquilaria agallocha* Roxb.), Bisbasa (*Myristica fragrans* Hout). | | | |

## Discussion

Kidney disease has been affected people in greater numbers in recent years. Because of the presence of chemical constituents, medicinal plants are highly effective against many renal illnesses (Rad et al, 2017). People in underdeveloped nations frequently employ herbal remedies not only because they are thought to be safe but also because many cannot afford the prices of contemporary medications. Despite the West's inability to develop effective medications to treat many complicated metabolic renal illnesses, medicinal plants can still be used. These phytochemicals connected to medicinal plants provide a broad perspective of nephroprotection that takes place via several modes of action (Negi and Mirza, 2020). Extensive researches have shown that several medicinal herbs and their extracts have intense nephroprotective action in animal models and in vitro experiments. However, when they are used on human models, some of these effects are not noticeable. Additionally, there may be certain restrictions on the therapeutic use of herbal treatments in regular life, such as worries about the delivery of large animal doses to humans and a potential interaction between medicinal plants and nephrotoxic medications. It has also been observed that herbal remedies are more efficacious when they are administered prior to the nephrotoxic drug (Rad et al, 2017). Phytochemicals such as flavonoids, phenols, phenolic acid, glycoproteins, sterols, kaempferols, alkaloids, terpenoids, tannins, glycosides, saponins, catechins, terpins, and others are extracted from different plants and herbs showed significant antioxidant, free radical scavenging, and nephroprotective activities. So it would be a great effort for the globe to domore research using plants, herbs, or other sources (Negi and Mirza, 2020).

## CONCLUSION

Plants and plant-derived medications that exhibit significant nephroprotective effect in in-vivo and in-vitro test paradigms have been summarized in this review paper. Natural plant remedies,in addition to current allopathic treatment system, are widely utilized to cure renal disease, and their usage has expanded internationally. Researchers are attempting to investigate the topic of natural medicine, both with and without the use of contemporary allopathic drugs, as a means of treating such issues. In animal trials, this study found that many plants have the capacity to heal renal injury. These plants can be useful in determining the potential lead compounds for usage in renal issues or any other major health condition.

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