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An overview of nephroprotective plants in the Indian traditional system of Medicine

Review Article

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Abstract

Renal diseases have emerged as a critical health problem that has a significant impact on human health. One of the most prevalent kidney issues is nephrotoxicity, which happens when the body is exposed to a medicine or toxin. As a result of the kidneys being damaged by major factors such as ischemia, hypoxia, antibiotics, chemotherapy, and NSAIDS, the condition known as acute renal failure can develop. Due to the high mortality rate associated with acute renal failure, it is a serious challenge for healthcare workers. A lack of oxygen and nutrients is a primary cause of nephrological disorders, which are exacerbated by oxidative stress and poor nephron circulation. Thus, the thought of antioxidants being used to prevent kidney disease is always an intriguing one that deserves extensive discussion. It has long been known that medicinal plants possess antioxidant properties, which may be helpful for the recovery of kidney problems. For a long time, many herbs and their formulations have been used in traditional medicine to treat kidney problems without having any side effects. The search for nephroprotective medicinal plants and their phytoconstituents was conducted using a wide range of electronic databases including PubMed, Google Scholar, etc. The primary purpose of the review article was to provide a comprehensive overview of known nephroprotective plants, as well as research-based data on mechanisms, active phytocomponents, sources, and potential applications relevant to the prevention and treatment of kidney disorders.

Key Words: Kidney diseases, Secondary metabolites, Serum creatinine, Nephrotoxicity, Antioxidant.

Introduction

In the course of their daily lives and at work, people are constantly exposed to a variety of potentially harmful surroundings and toxins. In the human body, the kidney is one of the most important organs. In general, the kidneys play a multitude of roles in the body, including acid-base balance, excretion of harmful drugs and toxins, osmolality regulation, hormone secretion, maintain the blood pressure, and production of red blood cells (1, 2). When there are abnormalities in the kidneys, there is a risk of life-threatening complications (3). It is a major public health problem that causes considerable morbidity and increases the burden on society (4). Acute renal disease is a loss of kidney function that happens in a short period of time and can typically be reversed if treated properly associated with elevation of serum creatinine and blood urea nitrogen, and a weaken the glomerular filtration rate (5). If left untreated, it can result in irreversible and leads to chronic kidney damage, which can cause end-stage renal failure. Acute kidney disease leads to the deaths of approximately 1.7 million individuals each year (6). The World Health Organization reported in 2018 that there were 1.2 million deaths related to renal disease in the year 2015, an increase of nearly 32% over 2005. In 2010, 2.62 million people worldwide underwent dialysis, and the number will reach 3.4 million by 2030 (7). Nephrological disease is estimated to cause the deaths of between 5 to 10 million people every year. The normal function of the kidneys is affected by inorganic metals such as mercury, thallium, barium, and bismuth, as well as non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen, indomethacin, and aspirin, as well as organic solvents like carbon tetra chloride and toluene, anticancer drugs, aminoglycoside antibiotics, and some antimicrobial agents (8). Nephrological problems can be attributed to a lack of oxygen and nutrients as a result of an inadequate supply of oxygen and nutrients to the kidneys and an increase in energy requirements as a result of oxidative stress (9, 10). Medicinal herbal products are becoming increasingly popular around the world as a way of treating acute and chronic kidney illness (11). In the current healthcare climate, phytochemicals and medicinal plants are becoming increasingly popular as safe and effective remedies. In contrast, secondary metabolites are derived from natural sources and have been studied for their ability to combat both infectious and non-infectious diseases (12). Several research studies have demonstrated that plant derived chemicals and medicinal plants have been used to treat a range of renal problems. The current review aims to consolidate and illustrate the most important aspects of the Indian system of medicine regarding

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medicinal plants and their application to nephrological problems. In addition, the study discusses the pharmacological effects of medicinal plant extracts and their active components that are commonly used to treat nephrological problems. This will enable us to select suitable medicinal plants or combinations of medicinal plants for future research.

Methodology

The different keywords were used to conduct the literature review, "nephroprotective" OR "nephrotoxicity" OR "kidney damage" OR "nephroprotection" OR "Indian traditional system of medicine" OR "ayurvedic formulations" OR "Indian system of medicine" OR "phytochemical" OR "active constituents" OR "phytomedicine" OR "herbal medicine" OR "medicinal herb" OR "medicinal plant extract" in the title of the article or list of keywords. The above keywords have been used to search a variety of electronic databases, books, and printed journals in search of medicinal plants. The databases include PubMed, Google Scholar, ResearchGate, Web of Science, NOPR, ScienceDirect, and others. This study reviewed articles for relevant *in vivo* and *in vitro* studies published in English between January 2000 and November 2021. From 172 publications initially screened, 106 studies were included in the study. Only primary literature and not review articles were included. Duplicated, non-relevant, and non-english language articles were excluded. In our review, we focused only on promising nephroprotective plants from Indian traditional system of medicines. We evaluated the peer-reviewed literature for several medicinal plants indigenous to the Indian system of medicines which have been reported to have a protective effect on the kidneys.

Adhatoda zeylanica

Adhatoda zeylanica (Syn. *A. vasica* Linn) (AZ), belonging to the family Acanthaceae, is one of the important drugs in the Ayurvedic system of medicine, mainly used to treat respiratory tract infections and cough symptoms. The leaves of AZ is shows the significant renal protection against gentamicin induced renal toxicity in Wistar albino rats. Gentamicin (80 mg/kg/day) treatment in rats which increases the serum creatinine and serum urea and serum protein concentrations is an indicator of earlier phase of kidney disease. The nephroprotective activity of AZ against drug induced toxicity is mainly depends on its ability to scavenge the gentamicin induced free radicals in Wistar rats (13). Ethanolic leaf extracts of AZ were used in another study to examine the effects of streptozotocin-induced diabetes mellitus and its renal complications on Wistar albino male rats. Diabetic nephropathy results from elevated levels of blood urea and serum creatinine, both indicators of glomerular damage. Biochemical and histopathological data have shown that AZ extract exerts a nephroprotective effect in animal models by inhibiting oxidative stress. The antioxidant properties of AZ may contribute to its nephroprotective effects (14). Interestingly, AZ did not cause acute toxic effects *in vitro* when exposed to HK-2 human proximal tubule cells. Even at relatively high concentrations of AZ, exposure to the extract was not toxic to HK-2 cells over the long term (15).

Aegle marmelos

Aegle marmelos (L.) (AM) is also known as bael belongs to the family Rutaceae, and all parts of the plant have therapeutic value in Ayurvedic medicine for treating various diseases. The methanolic extract of AM significantly reduces the effects of cisplatin-induced kidney damage in rats. The nephrotoxicity associated with cisplatin is due to a decrease in antioxidants and antioxidant enzymes, resulting in an increased production of ROS metabolites and lipid peroxidation (16). Antioxidants are thought to have a protective effect on the side effects. AM has strong antioxidant effects both *in vitro* and *in vivo*. The levels of GSH, SOD, and catalase were significantly increased through treatments with different doses of extracts, and malondialdehyde was significantly decreased. Moreover, the histopathology of kidney tissue (600 mg/kg) confirmed the recovery of tubular casts, glomerular damage, and epithelial desquamation. AM has a variety of phytochemicals, especially those polyphenols, responsible for nephroprotection (17). An ethyl acetate extract of AM shows a better nephroprotective effect than hydroalcholic extract against cisplatin-induced toxicity in rats. As a result of ethyl acetate extract treatment, serum creatinine and blood urea levels were reduced, antioxidant enzyme activity was restored, LPO levels were decreased, and SOD, GSH, and CAT levels were increased (18).

Aerva lanata

Aerva lanata (L.) A. L. Juss. ex Schultes (AL) is a shrub that is commonly found in India. It is known as Paashaanabheda in Ayurveda. An ethanol extract of the entire plant of AL was tested for nephroprotective activity in acute renal injury induced by cisplatin and gentamicin. A dose-dependent reduction was seen in blood urea and serum creatinine levels and normalisation of histopathological changes with the extract at 75, 150, and 300 mg/kg in the curative regimen. Similarly, the rats treated with the ethanol extract at 300 mg/kg showed good response to the gentamicin model. AL ethanol extract possesses significant nephroprotective activity with low toxicity, and it may be useful in reducing the effects of nephrotoxins like cisplatin and gentamicin on acute renal injuries (19). In the Siddha system of medicine, a decoction of the whole plant of AL is known as Sirupeelai Kudineer and is primarily used to treat renal function impairment. In a rat model, gentamicin is used to cause nephrotoxicity. During a ten-day treatment with this preparation at a dose of 500 mg/kg/body weight, blood urea and serum creatinine both decreased significantly. An examination of the kidney histopathologically proves that the powerful antioxidant properties of Sirupeelai Kudineer are responsible for renal cell repair (20). In another *in vitro* study, using cisplatin (8 µg/mL) exposed HEK 293 cell lines, the

methanol extract of *A. lanata* flowers exhibited highly positive effects on nephroprotection (97.04%) at 20 µg/mL concentrations. The dose of quercetin (8 µg/mL), considered to be the standard nephroprotective drug, was nearly equivalent (21). The nephroprotective effect of flavonoids on AL is associated with decreased expression of OCT2, increased MRP, reduced apoptosis, and decreased inflammation (22).

Andrographis paniculata

Andrographis paniculata (Burm. F.) Wall. Ex Nees, (AP) is otherwise known as Kalmegh, and belongs to the family Acanthaceae. At least twenty six ayurvedic formulae contain it as the main ingredient. Free radicals produced by gentamicin may indicate oxidative damage at the cellular level of the renal cortex. Aqueous extract of AP exhibits significant renoprotective effects in Wistar albino rats under gentamicin-induced nephrotoxicity. Serum creatinine levels were reduced by 176.92%, serum urea levels were reduced by 106.27%, and blood urea nitrogen levels were reduced by 202.90% after treatment with aqueous extract. The antioxidant and free radical-scavenging properties of AP may be responsible for its renoprotective effects (23). Oxidative stress markers such as serum creatinine and urine protein were decreased by ethanolic extracts of AP leaves (EEAP, 200 mg/kg and 400 mg/kg/orally) administered after cisplatin administration, despite the loss of antioxidant enzymes. An analysis of the kidney tissue revealed that the cisplatin-only treated rats had severe glomerular degeneration and inflammatory cell infiltration. In contrast, the EEAP-pretreated rats had mild glomerular degeneration and infiltration. The EEAP had an inhibitory effect on the Kim-1 and Nrf2 pathways in cisplatin-induced nephrotoxicity (24).

Allium sativum

Allium sativum L. (AS) an aromatic herbaceous plant of the Amaryllidaceae family, is consumed around the world as food and as a traditional medicine. Garlic prevents diabetes-induced nephropathy in diabetic rats. Streptozotocin-induced diabetic rats (45 mg/kg body weight) show significant abnormalities in urine and serum biochemistry. A thickened basement membranes, as well as thickening of the mesangium, are seen histologically. Treatment of diabetic animals with garlic extract (500 mg/kg body weight) significantly altered urine and serum biochemistry. In addition, the garlic-supplemented diabetic rats demonstrated a significant reduction in VEGF and ERK-1 expression, reducing mesangial expansion and glomerulosclerosis (25). An aqueous extract of garlic inhibits gentamicin-induced kidney damage in rats. After treatment with garlic, kidney tissue homogenates showed reduced levels of inflammatory markers like TNF-alpha, IL-6, and INF-gamma, which reversed oxidative stress and reduced the expression of Kim-1 mRNA and gentamicin-induced histological changes (26).

Azima tetracantha

Azima tetracantha Lam., (AT) is a small shrub belonging to the family Salvadoraceae. In Wistar albino rats, an ethanolic extract of AT root demonstrated increased protection against renal damage caused by glycerol. Ethanolic extracts are potent antioxidants *in vivo* and *in vitro* (250 and 500 mg/kg bw) with increased activity at higher treatment levels. As evidenced by a dose-dependent rise in antioxidant levels, AT extract protected the renal parenchyma against oxidative damage caused by glycerol. The extracts are rich in flavonoids, tannins, and terpenoids (Friedelin). Terpenoids and tannins both serve as vasodilators. GFR and urine output can be improved with renal vasodilatation, which opens up the renal artery (5). The 2, 8-dihydroxyadenine metabolite of adenine is poorly soluble. A build-up of crystals in the renal tubules results in tubular damage, inflammation, tubular blockage, and significant fibrosis. The root extract of AT protects Wistar rats' kidneys from adenine-induced injury. The treatment with ethanolic root extract (250 mg/kg bw) causes an increase in urine production, total protein, albumin, and food consumption, resulting in an increase in body weight. The serum creatinine and BUN levels are reduced. Treatment significantly reduces the size and amount of kidney oxalate crystals. An array of phytochemicals contributes to nephroprotective activity due to their antioxidant properties (27). Entering the brush-border membrane or through organic anion and cation transporters in the basolateral membrane, ferrous sulphate triggers the destruction of proximal tubule cells. The AT leaf powder can help mitigate the effects of ferrous sulphate by increasing antioxidant status, decreasing lipid peroxidation, and preserving cellular membranes (28).

Boerhavia diffusa

Boerhavia diffusa L. (BD) is known for its rejuvenating effects, particularly on the urinary system. The aqueous root extract of BD was found to prevent gentamicin-induced nephrotoxicity in rats. Treatment with separate doses of 200 and 400 mg/kg of BD root extract each day resulted in weight gain and a decrease in serum creatinine and BUN. Levels of MDA and GSH are near normal in the groups treated with BD root extract. This might be due to BD's powerful antioxidant properties. Even at lower doses of BD, treatment provides protection against acute tubular necrosis triggered by gentamicin. Para aminohippurate (PAH) clearance leads to increased renal blood flow. The PAH clearance was improved in groups that received both doses of BD (29). Standardized polyherbal combinations reduce methotrexate-induced nephrotoxicity in rats. This polyherbal combination includes four promising Ayurvedic herbs: BD, *R. emodi, N. nucifera,* and *C. nurvala*. Response surface methodology is used to optimize the extraction process. The extract contains a high concentration of polyphenols. Two combinations (ABCD and ABD) showed significantly higher DPPH scavenging potential and xanthine oxidase inhibition, IC_{50} values were 80 mg/mL and 74 mg/mL, respectively. When compared to

the toxicated group, treatment with both combinations considerably restored the high oxidative indicators such as lipid peroxidation and reactive oxygen species and also significantly decreased the elevated TNF-alpha. The nephroprotective benefit of the standardized polyherbal combination could be attributed to the combination's synergistic effect (30). Acetyl-para-aminobenzoquinoneimine, a highly reactive metabolite of acetaminophen, causes nephrotoxicity by arylating proteins in the proximal tubule. Nephrotoxicity is characterised by high BUN levels, serum creatinine levels, acute tubular necrosis, and antioxidant enzyme depletion. The nephrotoxicity caused by acetaminophen in rats can be recovered by pretreatment with an aqueous extract of BD root (200–400 mg/kg/day). The extract treatment reduced MDA levels. In the kidneys, the extract treatment appears to enhance the antioxidant defense enzymes SOD and CAT and replenish glutathione stores. The nephroprotective activity of BD is largely due to its extensive presence of secondary metabolites, which are believed to be responsible for its antioxidative properties (31). BD preventive therapy protects the kidney from the damaging effects of cisplatin. BD at doses up to 1000 mg/kg/day is safe and has no adverse effects. A higher dose of BD at 200 mg/kg prevented cisplatin-induced effects on kidney function by lowering antioxidant enzymes (SOD, GSH), suppressing the increase in MDA levels, and suppressing pro-inflammatory cytokines (IL-1beta, IL-6) and apoptotic markers (caspase-3). Due to the presence of beta-sitosterol, BD may have nephroprotective properties (32).

Camellia sinensis

A traditional beverage, green tea, has multiple health benefits. Green tea helps protect the kidneys from gentamicin-induced nephrotoxicity. Green tea extracts decrease nonenzymatic kidney marker elevations of urea (43.83±3.45mg/dL) and creatinine (0.617±0.167mg/dL). Green tea contains catechins, which scavenge free radicals produced by reactive oxygen species. Vitamins C and E also contribute to this nephroprotection. The nephroprotective effects of green tea extract can be attributed to their antioxidant properties (33). Another study found that green tea extract can protect against nicotine-induced kidney damage. The pretreatment with green tea extract reduced the levels of urea, creatinine, and uric acid in the serum, kidneys, and urine, as well as serum and renal malondialdehyde (MDA). The pretreatment also dramatically elevated vitamin E and C levels in serum and kidney tissue, as well as SOD, CAT, and GPx activity. Green tea pretreatment prior to nicotine administration demonstrated considerable nephroprotection, as evidenced by a significant decrease in oxidative damage (34). Lead acetate damages the kidneys by altering renal parameters. Inhibition of radical production and reduction of oxidative stress by CS reduces lipid peroxidation in tissues and increases antioxidant activity. CS's nephroprotective activity may be attributed to its antioxidant properties (35).

Cassia auriculata

The nephroprotective effect of *Cassia auriculata* L. (CA) root alcoholic extract was evaluated in rats with chronic renal injury induced by cisplatin and gentamicin. Two different doses of 300 and 600 mg/kg body weight of the root extract successfully decreased high blood urea and serum creatinine levels. Because of its antioxidant and nitric oxide-scavenging properties, ethanolic root extract may have nephroprotective effects against cisplatin- and gentamicin-induced kidney damage (36). Hydroalcoholic extracts of CA aerial parts have been shown to inhibit diabetic nephropathy progression. Diabetic nephropathy has been associated with an increase in glycosylated haemoglobin (above 7%). The levels of glycosylated haemoglobin were significantly reduced after treatment with the hydroalcholic extract of CA. It is possible that this is due to the presence of a variety of phytochemical groups, most notably flavonoids and tannins (37).

Cichorium intybus

Cichorium intybus L. (CI) aqueous and methanolic seed extracts protect rats from gentamicin-induced nephrotoxicity. Gentamicin damages the kidneys, increasing blood creatinine and urea levels in intoxicated animals. CI seed extracts (500mg/kg body weight/day) were found to reduce raised blood urea and creatinine levels in animals with kidney disease. Treatment with an aqueous extract of CI provides better protection than methanolic extract (38). CI roots are prescribed in Unani medicine as "Beekh Kasni" to improve urine output, protect the kidneys against toxic elements, and tonify the kidneys. In addition to restoring serum levels of urea and creatinine, methanolic and aqueous extracts also reverse renal structural abnormalities. Because these extracts contain an abundance of flavonoids known for their antioxidant properties, they may be nephroprotective. The aqueous extract of CI roots demonstrated the most significant level of protective efficacy (39). A polyherbal extract is prepared by including equal quantities and different parts of four herbs, namely roots and seeds of CI, seeds of *Cucumis melo*, stems of *Cynomorium coccineum*, and *Cynomorium songaricum*. The polyherbal extract shows better nephroprotective efficacy against diabetic models induced by streptozotocin. The administration of polyherbal extract improved glycemic control, glomerular function, and proximal reabsorptive indicators. In addition, increased levels of pro-inflammatory cytokines were recovered, as well as a disturbed redox state. A polyherbal extract's nephroprotective effect is attributed to its anti-inflammatory and antioxidant properties (40). The aerial part of CI contains significant amounts of cichoric acid. A reverse concentration-dependent manner was observed for the tincture of CI, which decreased serum creatinine, serum urea, urine creatinine, and urine urea. Creatinine clearance remained nearly unchanged. Tincture CI reduces the oxidative stress in a pretreatment animal group by lowering total oxidative status, the oxidative stress index, total nitrite, and nitrate concentrations, and enhancing the total antioxidant

capacity in a reverse concentration-dependent manner. The nephroprotective effects of tincture of CI were attributed to the presence of polyphenols, substances that may have oxidative and pro-inflammatory effects even at low concentrations (41).

Clitoria ternatea

Acetaminophen is an analgesic and antipyretic agent, but excessive consumption has adverse effects on the liver and kidneys. The rationale for acetaminophen toxicity is that CYP enzymes convert it into a highly reactive quinone imine called N-acetyl-p-benzoquinone imine. *Clitoria ternatea* L. (CT) ethanolic extracts are nephroprotective against acetaminophen-induced toxicity in rats. Two different doses of CT (250 and 500 mg/kg body weight) treatment significantly reduced blood urea and creatinine levels. Additionally, it was confirmed by histological examination that renal tissue had been restored from acetaminophen-induced necrotic damage. The nephroprotective action may result from the antioxidant activity of CT phytocompounds (42).

Commiphora mukul

Guggulsterone is the active ingredient in *Commiphora mukul* Hook. ex Stocks (CM). The active compound guggulsterone prevents kidney damage in rats caused by cyclophosphamide. Guggulsterone at a dose of 25 mg/kg for eight days was given to rats in the toxic group, resulting in lowered urea and creatinine levels. There was also a decrease in NF-kB levels at the renal level, a reduction in the kidney index, and a significant increase in the antioxidant activity of the catalase enzyme. On histopathological examination, a small zone of apoptosis and degeneration could be seen in the proximal renal tubules (43).

Crataeva nurvala

Drug-induced oxidative stress, which leads to the formation of free radicals, is a significant contributor to renal proximal tubule cell dysfunction. An oral administration of alcoholic extracts of *Crataeva nurvala* Buch. Ham. (CN) (250 and 500 mg/kg body weight) protects the damaged kidneys from nephrotoxicity caused by cisplatin. A significant contributor to the nephroprotective effect is antioxidant activity and free radical scavenging. Among the bioactive molecules present in CN are responsible for its antioxidant and nephroprotective properties (44). In another study, Triterpenoid lupeol is isolated from stem bark of CN, protecting rats against cisplatin-induced nephrotoxicity. In two different doses (40 and 80 mg/kg body weight) of lupeol reduced serum creatinine and urea levels in toxic animals. In the renal cortex, lupeol treatment increases glutathione levels and catalase activity while decreasing the levels of TBARS. Lupeol's nephroprotective effect is mediated by its antioxidant and free radical scavenging activities (45).

Cucumis sativus

Cucumis sativus L. (CS) is one of the most widely used vegetables in Indian cuisine. In a rat model, a hydroalcoholic extract of CS seeds can prevent cisplatin and gentamicin-induced nephrotoxicity. In cisplatin and gentamicin-induced toxicity in animals, two dose levels of hydroalcoholic extract were shown to alleviate the elevated levels of SC, BUN, STP, UTP, and LPO. Moreover, the hydroalcoholic extract increased creatinine clearance levels, SOD levels, CAT levels, and GSH levels in rats, and histological studies also support this finding. Seeds of CS have been found to treat drug-induced nephrotoxicity. Lead-related liver and kidney damage has been shown to be prevented with cucumber juice. Rats were given lead acetate-containing drinking water for five weeks (200 ppm). Three doses of cucumber juice were administered orally once a day for five weeks (1, 10, and 100 mg/kg). The Pb-control group showed that cucumber juice has a significantly more protective effect on body weight, food consumption, and lead concentrations in tissues, red blood cell (RBC) counts, and reticulocyte counts. Cucumber juice's biologically active components may chelate lead, resulting in a decreased amount of lead accumulating in tissue. Cucumber juice may cause sulfur-containing molecules to form ionic interactions with lead nitrate during the chelation process. Additionally, CS has anti-oxidant properties that contribute to its protective properties (46).

Curcuma longa

Turmeric is cultivated widely in India as a spice. The oral administration of aqueous extracts of *Matricaria chamomile* and *Curcuma longa* L. (CL) protects against nephrotoxicity induced by tetracyclines. Tetracycline toxicity can cause early-onset renal impairment and renal tubular damage, resulting in urinary creatinine and urea elevations. The aqueous extract-treated group significantly decreased blood urea, creatinine, sodium, and potassium levels. It greatly increased the total protein level compared to the untreated group, as evidenced by histopathology, which shows reduced collagen depositions, reduced renal tubular thickening, minor collagen depositions, and a decline in cellular infiltrates, as well as thin interstitial septa. CL may benefit the kidneys by acting as an antioxidant or free radical scavenger (47). Cadmium toxicity is mediated through various mechanisms, including apoptosis, ischemia, inflammation, oxidative stress, displacement of divalent metal ions from their binding sites, and mimicking the action of essential metal ions required for normal enzyme function and a diversity of other biological processes. An increase in urea, creatinine, and BUN levels was prevented with ginger and turmeric essential oils (50 mg/kg BW) compared to a control group. Additionally, when compared with the Cd-untreated group, treatment with ginger and turmeric essential oils decreased the inflammatory cytokine levels by preventing IL-10 depletion, reducing IL-6 and TNF-α levels, and reducing renal adenosine deaminase activity (48). The non-selective beta-blocker carvedilol has vasodilatory properties due to an alpha-1 blockade, as well as antioxidant properties. Carvedilol, aqueous and methanolic extracts of CL have more significant antinephrotoxic effects against cisplatin-induced renal

injury. Cisplatin-induced abnormalities and mortality were reduced with carvedilol and aqueous and methanolic extracts of CL. It could be due to antioxidants or the scavenging of free radicals. CL has antioxidant properties due to the presence of secondary metabolites like flavonoids, alkaloids, saponin glycosides, and the carbazole moiety in carvedilol metabolites (49). Cisplatin-induced renal tubular cell apoptosis is inhibited by curcumin in the kidneys. Histopathology results revealed that kidneys function improved significantly, indicating curcumin is capable of protecting against oxidative stress, inflammation, and tubular cell death induced by cisplatin. Curcumin is used to prevent cisplatin nephrotoxicity by inhibiting NF-Kb and pro-inflammatory cytokines. Curcumin inhibited the development of apoptosis (active caspase-3) in renal tubular cells by inhibiting and preventing the activation of the proteins (Fas, Fas-L, and p53) that cause cell death in response to cisplatin toxicity (50). Curcumin pretreatment reduces the severity of cisplatin-induced kidney damage in rats by inhibiting inflammation and apoptosis. Antioxidative status and oxidative stress were mitigated by pretreatment with curcumin administration. Cisplatin penetration and cytotoxicity are influenced by OCT-2 and CTR-1 transporters. In the kidneys, they are located primarily in the proximal tubules, which affect cisplatin accumulation. The expression of OCT-2 and Ctr1 in kidney tissue was increased after cisplatin injection and was decreased by pretreatment with curcumin. In the tubular kidney, curcumin significantly reduced cisplatin induced phosphorylation of ERK1/2 and diminished Bax/Bcl-2 elevation, suggesting diminished apoptosis. Curcumin inhibited the expression of NF-kB, a transcription factor that activates pro-inflammatory cytokines such as TNF-α and IL-6 and restores IL-10 levels in response to oxidative stress. These findings were in line with the histopathology results that demonstrated the ability of curcumin to reduce the infiltration of inflammatory cells and kidney necrosis. Curcumin inhibits the accumulation of kidney injury molecule-I (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) in kidney tissues (51).

Eclipta alba

Nephroprotection is possible through the reduction of oxidative stress. *Eclipta alba* (L.) Hassk. (EA) leaf extract contains antioxidants that protect rats against gentamicin-induced nephrotoxicity. EA has been shown to exhibit good antioxidant activity and is a rich source of flavonoids, particularly wedelolactone (52). The scavenging of free radicals and reduction of iron (III) properties of the extract may provide nephroprotection against gentamicin toxicity (53). EA ethanolic extracts (100, 200, and 400 mg/kg, oral route, body weight) suppressed gentamycin-induced renal toxicity in rats. The ethanol extract treatment resulted in a dose-dependent decrease in serum urea, serum creatinine, total protein, and uric acid. EA contains several polyphenolic compounds that reduce free radicals. The nephroprotective effects of EA might be due to these properties (54).

Glycyrrhiza glabra

Glycyrrhiza glabra L. (GG) root hydroalcoholic extract (200 mg/kg) protects renal tubular cells from gentamicin-induced inflammation in mice. GG treatment raised Gpx levels and SOD levels, resulting in Nrf2 expression and Cox-2 reduction, which counteracted inflammation and decreased IL-1β and IL-6. Moreover, GG's renoprotective properties are strongly correlated with its antioxidant properties, responsible for its phenolic content (55). The toxicity of gentamicin in male albino rats can be reversed by pretreatment with liquorice extract (150 mg/kg BW). Liquorice extract pretreatment results in a significant drop in creatinine, urea, uric acid, and K+ levels, as well as an increase in Na+ levels. In the toxic group, significant vacuolations were found in the blood vessel walls of the glomeruli as well as necrobiotictic alterations in the renal tubules, which were reversed in the liquorice treatment group. It is possible that this extract of licorice has strong antioxidant activity and a protective impact on gentamicin-induced nephrotoxicity (56). The aqueous extract of GG shows a significant renoprotective effect against CCl_4-induced nephrotoxicity in male mice. Treatment with GG (30, 90, and 270 mg/kg i.p) decreased the elevated urea and creatinine and increased the antioxidant enzymes CAT and SOD in renal tissue. Renal structural changes caused by CCl_4 treatment include enlargement of the cortex, medulla, and kidney parts. A toxin like CCl_4, which is expressed in response to cytokines, results in excessive oxygen free radicals, which causes renal hypertrophy. Treatment with GG can reduce the toxic effects of CCl_4 and positively restore the kidney's structural changes (57). Three months of treatment with the aqueous extract of GG root prevented renal failure in male rats treated with a single dose of (150 mg/kg, i.p.) thioacetamide. Three months later, oral GG root extracts (100, 200, and 300 mg/kg) significantly decreased serum levels of potassium, sodium, and creatinine when compared with the thioacetamide group, most likely due to anti-oxidant effects (58). Glycyrrhizic acid (GA), the sweet taste of liquorice root, has several therapeutic properties. GA was administered orally for seven consecutive days in mice before cisplatin administration (7 mg/kg BW, i.p). Cisplatin administration disrupted typical kidney architecture. Two varying doses of GA (75 and 150 mg/kg BW, orally) pretreatment resulted in a restored level of antioxidant enzymes, preventing oxidative stress. In a dose-dependent manner, there were significant reductions in kidney toxicity markers like BUN, creatinine, and LDH and reductions in DNA fragmentation and micronucleus formation. Kidney histology also returned to normal (59). GA and 18- β-glycyrrhetinic acid (18βGA) are active liquorice ingredients, protecting male BALB/c mice against cisplatin-induced nephrotoxicity. In the oral dose of GA or 18βGA (GA at 25, 50, or 100 mg/kg of BW or 18βGA at 10, 25, or 50 mg/kg of BW), the cisplatin-induced increases in blood urea nitrogen, creatinine, and lactate dehydrogenase were effectively decreased. The suppression of oxidative stress leads to a progressive

increase in antioxidant enzyme levels, Nrf2 up regulation, and NF-kB down regulation in the kidneys. Histopathology has shown that GA and 18βGA can slow the progression of renal injury, including tubular necrosis, tubular degeneration, and hyaline cast formation (60). Another study investigated an aqueous extract of liquorice, which was administered orally (3 mg/kg/day) for four weeks. Treatment with aqueous liquorice extract reduced thiobarbituric acid reactive substances in the kidneys, blood urea nitrogen, and creatinine in the blood. It relieved renal and ovarian histopathological lesions prompted by $CdCl_2$ toxicity in rats (61). Aqueous extracts of liquorice (50-100 mg/kg) protect against cadmium nephrotoxicity in rats since they reduce the damaged number of glomeruli while increasing Bowman's capsule thickness (62).

Homonoia riparia

The methanol extract and its various fractions from the whole plant of *Homonoia riparia* Lour. (HR) showed nephroprotective efficacy when tested *in vitro* using the HEK 293 cell line against cisplatin-induced damage. The n-butanol fractions and the aqueous fractions of HR had the most activity, with 293.09% and 345.07%, respectively, at a 200 g/mL concentration. The fractions have a rich concentration of polyphenolic compounds are responsible for their antioxidant and nephroprotective properties (63).

Momordica tuberosa

Hydroalcoholic extract derived from tubers of *Momordica tuberosa* Cogn (MT) (40 mg/kg, BW, p.o) considerably reduced kidney damage induced by cisplatin, gentamicin, and paracetamol. Phytochemical screening revealed a high saponin concentration and triterpenoids in the hydroalcoholic extract. Animals treated with hydroalcoholic extract of MT gain weight, have reduced urea and creatinine levels, and have improved nitric oxide scavenging ability. In addition, it protected against lipid peroxidation and protected tissues from glutathione (GSH) depletion. The antioxidant capabilities of MT are critical in the treatment of acute renal injury caused by different nephrotoxins (64).

Moringa oleifera

Moringa oleifera Lam. (MO) seed ethanolic extract (EEMOS) is high in essential fatty acids, mainly oleic and linoleic acid. Gentamicin's nephrotoxic impact is particularly associated with oxidative stress mediated by excessive production of reactive oxygen species. The antioxidant capacity of oleic and linoleic acids contributes to a considerable drop in plasma creatinine and urea levels. The creatinine clearance is a valuable indicator of the glomerular filtration rate. EEMOS treatment improves creatinine clearance. Creatinine clearance is a sign of a significant rise in glomerular filtration rate due to increased renal blood flow and function. Treatment with gentamicin results in an increase in relative kidney weight, which may be caused by renal edema and inflammation. The anti-inflammatory activity of EEMOS considerably decreased the relative kidney weight compared to the toxin-treated group. Due to its membrane-stabilizing effects, EEMOS seems to counteract the electrolyte imbalance caused by gentamicin. The presence of monounsaturated and polyunsaturated fatty acids, and other biologically active components, in EEMOS is directly related to a reduction in MDA and an elevation in SOD. Essential fatty acids are responsible for the antioxidant properties of EEMOS, which can protect tubular cell membranes from oxidative stress and membrane damage (65). Rabbit kidneys were protected by treatment with ethanol-water (80:20) extracts of MO leaves (150 and 300 mg/kg) after gentamicin (80 mg/kg) toxicity. An explanation for the nephroprotective activity of MO leaves in aqueous-ethanol extract is their ability to reduce elevated serum urea and creatinine in a dose-dependent manner, thereby reducing the amount of thiobarbituric acid reactive substances and restoring reduced glutathione levels in rabbit kidney cells. In addition, histopathological analysis of kidney tissues revealed improved renal tubular function after MO treatment, possibly because tubular cells could rapidly regenerate. The nephroprotective capacity of aqueous ethanol extracts of MO leaves is primarily due to their antioxidant properties (66). A methanol extract of MO leaves (400mg/kg) was administered to female rats for four weeks and resulted in a significant decrease in serum BUN and creatinine levels, as well as a decrease in body weight. Treatment has no discernible effect on the level of alanine transaminase. Methanol extract of MO administration on a long-term basis may be toxic to the liver but does not appear to be hazardous to the kidney (67). The high antioxidant capacity of methanolic extract of MO leaf raised serum albumin, globulin, and total protein concentrations with a decrease in MDA and enhancements in CAT, SOD, GSH, GPx, TNF-alpha, and IL-6 in streptozotozin-induced diabetic male Wistar rats. A bioactive secondary metabolite in MO protects diabetic kidney complications (68). Selenium nanoparticles obtained from the MO leaf reduce melamine-induced nephrotoxicity in the rat kidney by reducing oxidative stress, apoptosis, and renal function deficits. The ethanolic leaf extract of MO exhibited the same results (69). Reducing free radical generation helps prevent tissue damage from ischemia-reperfusion. The levels of malondialdehyde, protein carbonyls, and advanced oxidation protein products generated by ischemia-reperfusion were significantly decreased by treatment with two different doses of MO, reducing the serum BUN and creatinine levels. A 200 mg/kg MO dose level also reduced NO and H_2O_2 levels in the kidneys while enhancing GST and GPx activity. Histopathology examination revealed that both doses of MO significantly reduced the renal tissue injury (70).

Oxalis corniculata

Oxalis corniculata Linn (OC) is a creeping plant that contains C-glycosyl flavonoids like vitexin, isovitexin, niacin, and beta-carotene. As a traditional remedy, the leaf juice of OC is used to treat dyspepsia, anaemia, worm infestations, chronic coughs, and fever

(71). In addition to OC and other herbs like *Vitex pedungularis* and *Vitex negundo*, vitexin is an important C-glycosyl flavonoid. The methanolic extract of OC leaves and vitexin provided considerable protection against gentamicin- and cisplatin-induced nephrotoxicity in albino rats. The nephroprotective efficacy of OC depends on its ability to scavenge free radicals, particularly hydroxyl, lipid peroxide, and superoxide (72). According to another study, the antioxidant properties and the high phenolic content of OC extract produce nephroprotective effects (73).

Picrorhiza spp.

Picrorhiza is a perennial herb that is a member of the Scrophulariaceae family. The anatomy, bitterness, and known active components of *Picrorhiza kurrooa* Royle ex Benth. (PK) were found to be similar to those of *Picrorhiza scrophulariiflora* Pennell. (PS). Diabetic nephropathy is the most common cause of chronic kidney disease requiring dialysis. Inflammation plays a significant role in the pathogenesis of diabetic nephropathy, which is inhibited by the ethanol extract of PS. Streptozotocin-induced diabetic rats have been treated with an ethanol extract of PS rhizomes, resulting in reduced malondialdehyde and NADPH-oxidase-dependent superoxide production in the diabetic kidney, showing that PS inhibits redox-active inflammation in diabetic nephropathy (74). Renal nicotinamide adenine dinucleotide phosphate reduced form oxidase is a key cause of oxidative stress, with increased expression in the glomerulus and distal tubules in diabetic nephropathy. Apocynin, an anti-inflammatory phenol found in PK root extracts, has been demonstrated to suppress thromboxane production (75). PK inhibits the membrane translocation of p47phox, a selective inhibitor of NADPH oxidase, and may be a more effective treatment for diabetic nephropathy than superoxide dismutase mimics (76, 77). Treatment with iridoid glycosides enriched fraction prepared from PK rhizome ameliorates the renal damage and peripheral neuropathy in cyclophosphamide induced toxicity in rats by regulating PPAR-γ-mediated inflammatory pathways (78).

Plectranthus amboinicus

The ethanol extracts of the aerial parts of *Plectranthus amboinicus* Roxb. (PA) protects against acetaminophen-induced toxicity in rats. The administration of 250 and 500 mg/kg of extracts for seven days reduced serum urea, creatinine, MDA, SOD, CAT, and GST levels while increasing the activity of SOD, CAT, and GST. The ethanol extract mitigated the effects of the toxin-induced GSH depletion. Treatment with ethanolic extract of PA preserves the glomeruli, Bowman's capsule, and slightly swollen renal tubules. Phytochemicals in the plant possess antioxidant properties that contribute to its nephroprotective activity (79).

Rubia cordifolia

The oral administration of hydro-alcoholic root extract of *Rubia cordifolia* L. (RC) (250 and 500 mg/kg, BW) reduces the toxicity of cisplatin in Swiss albino mice. RC may stimulate the activity of antioxidant enzymes such as GPx, catalases, and SOD. The administration of the extract to mice reduced MDA production and restored GSH depletion in renal tissue. Cisplatin's nephrotoxic effects are mediated via the production of free radicals in the kidney. The nephroprotective efficacy of RC is attributed to anthraquinones, which act as antioxidants by reducing and scavenging the hydroxyl radicals (80).

Salvia officinalis

The essential oil derived from *Salvia officinalis* L. (SO) protects the renal abnormalities against ammonium metavanadate-induced toxicity in rats. In comparison to the toxin group, essential oil treatment (15mg essential oil/kg BW) reversed the raised plasma levels of urea, uric acid, creatinine, and blood urea nitrogen. The essential oil intervention replenishes SOD, CAT, and GPx levels in renal tissue. SO essential oil effectively diminished vanadium-induced histological abnormalities. As confirmed by GC-MS, SO essential oils contain β-caryophyllene, limonene, carvacrol, caryophyllene, borneol, α-pinene, and α-thujene. The phytochemicals present in this plant exhibit several biological activities, including antioxidants, anti-inflammatory, and nephroprotective properties, which could support the SO's protective effect (81). In another study, three weeks of treatment with formalin (2.4 ml/kg BW) has a detrimental effect on the renal tissue of mice, but ingestion of an aqueous extract of SO leaves (120 mg/kg BW) ameliorates formalin-induced renal cellular injury in mice. It is possible that the improvement in histopathology findings is due to the antioxidant properties of this plant, which may offer a promising strategy for minimizing kidney damage (82). Aqueous leaf extracts of SO shows protective effects against cisplatin-induced oxidative stress and renal dysfunction in rats. The aqueous extract of SO leaves (100 mg/kg BW; P.O: 7 days) protected the rats from elevated serum urea and creatinine levels and lowered MDA to normal levels, perhaps due to antioxidant properties of extract that protect kidney injury via a free radical mechanism. Reduction in the thickness of glomerular and tubular basement membranes has been seen after treatment with aqueous extract. The aqueous extract of SO is rich in flavonoids, which are antioxidants that can repair kidney tissues (83). The ethanolic extracts of SO fed to albino rats are capable of preventing chlorpyrifos- and methomyl-induced kidney damage by lowering oxidative stress and enhancing antioxidant defense mechanisms (84). Ifosfamide is an alkylating anticancer drug. The most severe adverse effect is the production of the cytotoxic metabolite chloroacetaldehyde, which may cause renal toxicity. Nanoemulsions loaded with ifosfamide and SO essential oil protect against drug-induced nephrotoxicity in mice. It is primarily due to the high antioxidant capacity of essential oils, which contain compounds like carnosol, rosmarinic acid, and caffeic acid (85).

Solanum nigrum

Gentamicin-induced nephrotoxicity is alleviated in rats by ingesting an aqueous extract of *Solanum nigrum* L. (SN) leaves, seeds, or a combination. Two doses of aqueous extract of SN leaves and seeds (250 and 500 mg/kg BW; PO) are given orally for four weeks. Pretreatment with extracts improves the gain of body weight and the normal weight of the kidney. Compared to the negative control group, aqueous extract of SN dramatically improved renal marker enzyme levels and maintained the electrolyte balance. Renin, erythropoietin, and parathyroid hormones increased due to improved renal function caused by extract treatment. Moreover, there's an increase in the activity of renal antioxidant enzymes and a partial restoration of renal deterioration. Aqueous extracts of SN leaves were more effective than aqueous seed extracts. The antioxidant properties of SN play a vital role in the nephroprotective activity (86). An *in-vitro* study found that an ethanol extract of the whole plant of SN has a cytoprotective effect on African green monkey kidney cells exposed to gentamicin. It is possible that the cytoprotective effect results from SN's ability to scavenge hydroxyl radicals (87). Aqueous SN fruit extract protects the kidneys from gentamicin-induced damage in rats. Pretreatment with aqueous extract (200 mg/kg/day; PO) results in a considerable decrease in BUN and serum creatinine levels that is remarkably similar to the standard control. In the nephrocurative model, there was no significant change in these serum markers. Antioxidant potential is mediated by a 150 kDa glycoprotein found in SN (88). Nephroprotection may be a result of their free radical scavenging and quenching properties (89). Another study showed that aqueous SN fruit extract (200 mg/kg/day; PO) treatment significantly reduced the mean weight of the kidney relative to the gentamicin-treated group, implying that the extract treatment group had less inflammation. Moreover, histological investigation demonstrated that the kidneys of the extract-treated group had less tubular damage than those of the gentamicin-treated group (90).

Solanum xanthocarpum

An alcoholic extract of *Solanum xanthocarpum* Schrad. & Wendl (SX) fruit showed nephroprotective effects against gentamicin toxicity in mice. There was a significant reduction in elevated urea and creatinine concentrations following administration of the extracts at doses of 200 and 400 mg/kg/BW and protection against an increase in kidney weight ratio. SX was also evaluated on kidney antioxidants and shown to protect the decreased activity of SOD, CAT, and GSH. The nephroprotection (400 mg/kg) is almost identical to the standard control. At 200 mg/kg, histopathological examinations revealed mild degenerative and necrotic tubular changes, whereas tubular epithelial cells were regenerated at 400 mg/kg (91).

Tinospora cordifolia

Tinospora cordifolia (Willd.) Miers ex Hook. f. & Thoms. (TC) is a commonly used herb in Ayurveda belongs to the family Menispermaceae. The ethanolic extract of TC root has been shown to be protective against Aflatoxin-B_1-induced nephrotoxicity in mice. Aflatoxin-B_1 treatment significantly increases TBARS levels in mice while decreasing SOD, CAT, GSH, GST, GPx, GR, ascorbic acid, and protein content. All of these parameters are restored to normal levels following treatment with an ethanolic extract of TC root. TC root ethanolic extract has a nephroprotective effect due to the presence of biologically active components, particularly alkaloids such as choline, tinosporin, isocolumbin, palmatine, tetrahydropalmatine, and magnoflorine (92). TC is a promising free radical scavenger (93). TC stem methanol extract protects Wistar rats from cadmium-induced nephrotoxicity and oxidative stress. Cadmium exposure results in renal dysfunction by increasing lipid peroxidation and impairing the kidney's antioxidant system. Twenty-eight days of treatment with methanolic extract of TC (100 mg/kg; BW) effectively decreased the toxin-induced biochemical changes in serum and renal tissue. Additionally, ATPase activity and glycoproteins were restored to near-normal levels (94). Another studies revealed that an alcoholic root extract of TC (200 & 400 mg/kg; BW) has a stronger protective effect against cisplatin-induced toxicity. The TC extract significantly diminished serum creatinine and urea levels when used in a nephrocurative protocol. Renal antioxidative defense systems depleted by cisplatin administration, such as superoxide dismutase, catalase, glutathione peroxide activity, and reduced glutathione level, were returned to normal following treatment with the extract (95). The alcoholic extract of TC (200 mg/kg; BW i.p.) was found to be an uroprotective agent in albino mice following cyclophosphamide toxicity. Cyclophosphamide toxicity (single chronic dose, 1.5 mmol/kg; BW., i.p.) causes inflamed and dark-colored urinary bladders in animals. Reduced levels of GSH after treatment with cyclophosphamide were dramatically elevated in the bladder and liver following treatment with TC. The bladders of the cyclophosphamide-treated group exhibited extensive necrotic damage, but the bladder architecture of the TC-treated group was restored to normal. After treatment with alcoholic extract of TC, IFN-alpha and IL-2 levels are elevated, as well as pro-inflammatory cytokine TNF-alpha levels are considerably decreased (96).

Tribulus terrestris

Mercury causes oxidative stress, which damages the kidneys by generating free radicals. *Tribulus terrestris* L (TT) possesses significant anti-inflammatory and antioxidant effects. Hydroalcoholic extract of TT at three different doses (100, 200, and 300 mg/kg; BW) decreases high BUN, serum creatinine, MDA, liver fatty acid-binding protein, and KIM-1 levels as well as increasing the level of GSH, SOD, and GPx. Higher doses of TT (300 mg/kg) are effective in nephroprotection. Treatment with TT provided considerable protection against mercuric chloride-induced kidney injury, probably due to its antioxidant and anti-inflammatory capabilities and lowering

mercury buildup in the kidney (97). The hydroalcoholic extract of TT protected Wistar albino rats against cisplatin toxicity. Nephrotoxicity emerges on the seventh day of treatment with a single dose of cisplatin (8 mg/kg, i.p.). Ten days of pretreatment with three different dosages of TT hydroalcoholic extract decreased BUN, serum creatinine, MDA, KIM-1, and L-FAB, while increasing GSH, SOD, and GPx. However, the most beneficial doses are 200 and 300 mg/kg. Additionally, extract treatment reduces platinum accumulation in renal tissues to some degree. The nephroprotective effect of the extract may be to its antioxidant and anti-inflammatory properties (98).

Vitex negundo

Ethanolic extracts of *Vitex negundo* L. (VN) leaves protect rats against nephrotoxicity mediated by thioacetamide. Thioacetamide (0.03 percent w/v in drinking water) administration for twelve weeks, two independent doses of ethanolic extracts of VN (100 and 300 mg/kg), decreased blood urea, serum creatinine, and renal MDA levels while increasing CAT and SOD activity. VN extract at a higher dose (300 mg/kg) significantly reduced renal microscopic abnormalities and nearly normalized the renal histological architecture. The VN extracts' nephroprotective effectiveness is dependent on radical scavenging activity and is most likely due to their higher flavonoids and alkaloids content (99). Vitexilactone, a diterpene of the labdane class derived from another species of *Vitex rotundifolia* (100), was found to protect rats from cisplatin-induced toxicity. Due to vitex's antioxidant, anti-inflammatory, and antiapoptotic properties, high doses of vitex (80 mg/kg/day) decreased histopathological changes in cisplatin-induced nephrotoxicity (101).

Withania somnifera

Ashwagandha, commonly known as Indian winter cherry, is an important herb in the Indian traditional system of medicine. Due to its antioxidant and free radical scavenging activities, the aqueous extract of *Withania somnifera* (L.) Dunal (WS) roots exhibits a considerable protective effect against gentamicin-induced nephrotoxicity. The mean weight of the kidney was dramatically decreased after extract treatment, indicating that the toxin-induced inflammation was reduced. Thirty days of administration with an aqueous extract of WS root indicated no tubular epithelial reorganisation or inflammatory cells, as well as a reduced amount of hyaline casts and vascular congestion (102). Aqueous root extracts of WS (250, 500, and 750 mg/kg) significantly reduced gentamicin-induced nephrotoxicity in rats. The 500 mg/kg dose was more effective than the other two doses. It is possible that a dose of 250 mg of WS is insufficient to scavenge radicals, whereas a high dose of 750 mg may interact with other molecules. Phytochemicals act as free radical scavengers by reducing cisplatin's nephrotoxicity (103). In another study, bromobenzene alone treated animal groups showed increased renal lipid peroxidation, lysosomal enzymes, and glycoproteins, along with decreased antioxidant status, mitochondrial enzymes, and aberrant kidney function markers. The presence of phytochemicals in WS (250 and 500 mg/kg) acts as free radical scavengers, allowing it to correct the metabolic changes caused by the toxin in a dose-dependent manner (104).

Zingiber officinale

The Ginger rhizome (*Zingiber officinale* Roscoe) is part of the Zingiberaceae family. Zingerone is among the active ingredients in ginger plants, which has antioxidant and anti-inflammatory properties. Because of these properties, they also provide protection against the nephrotoxicity caused by cisplatin in rats. Combining treatment with zingerone and cisplatin led to an impressive reduction in the lactate dehydrogenase enzyme activity, BUN, serum creatinine, and levels in the tissues of MDA. They also maintained the catalase-related enzymes and glutathione peroxidase when compared with those of the toxin-related group. Zingerone was not able to permit the decrease in glutathione levels within kidney tissue, and it reduced the amount of tumor necrosis factor that reduced inflammation caused by cisplatin. Histopathological changes such as vacuolation and thinning of the border of the brush were more effective when Zingerone was administered. Zingerone also made the glomerular diameters bigger, and RBCs moved more easily (105). A ginger extract rich in 6-gingerols has prevented hematotoxicity and hepatotoxicity in rats exposed to carbendazim. The 6-gingerol-rich fraction was co-administered to rats' livers and kidneys, protecting them from cabendazim-mediated hemotoxicity. It also increased antioxidant status and prevented oxidative stress injury (106).

Conclusion

Drugs made from natural sources are safer to use than drugs made from other sources. Nephrological problems are common in both developed and developing countries. There are many medicinal plants in the Indian traditional system of medicine that are used to treat nephrological problems. The conclusion of this study is that many medicinal plants and their phytoconstituents have a significant role to play in alleviating nephrological problems with fewer side effects than synthetic drugs. Our literature review gives promising evidence that *Aerva lanata, Boerhavia diffusa, Cichorium intybus, Curcuma longa, Glycerylrhiza glabra, Moringa oleifera, Salvia officinalis, Solanum nigrum, Tinospora cordifolia, Tribulus terrestris, Withania somnifera,* and *Zingiber officinale* and their active components have been shown to have nephroprotective effects against different nephrotoxic agents. There is a need to examine these plants carefully to ensure that they are safe and effective, especially for humans. Consequently, these medicinal plants could be recommended either alone or in combination with current medications for nephrological problems. Alternatively, synergistic studies can be designed to develop combinations of

botanicals and modern medications. Antioxidant activity is one of the most significant functions of medicinal plants in nephroprotection. The active components of these medicinal plants are principally responsible for their nephroprotective properties. In silico analysis of ADME, mode of action, and safety, as well as network pharmacological strategies could make a significant contribution to the development of new therapies for the treatment of kidney disease. Experimental research provides the basis for future clinical trials and helps formulation development. Consequently, medicinal plants from the Indian traditional system of medicine and their active constituents may improve the prognosis for a great number of patients with nephrological complications.

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