Review

# Drug-induced Nephrotoxicity and Medicinal Plants

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Drug-induced nephrotoxicity is one of the most common causes of acute kidney injury. There are various agents that exert nephrotoxic effects through different pathogenic mechanisms. Aminoglycoside antibiotics, chemotherapeutic agents, radiocontrast media, and nonsteroidal anti-inflammatory drugs are among common nephrotoxic agents. In recent years, natural compounds are being increasingly used in the treatment of kidney diseases. Given many reports available on the curative effects of a variety of medicinal plants against drug-associated nephrotoxicity, we aimed to review the protective effects of medicinal plants on certain nephrotoxic drugs.

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## INTRODUCTION

Acute kidney injury (AKI) is a sudden loss of kidney function resulting in the accumulation of waste materials such as creatinine and urea in the body. Water and sodium retention, decrease in glomerular filtration rate, hyperkalemia, and metabolic acidosis are other features of AKI.[1] Drug-induced nephrotoxicity is a common condition and the cause of around 8% to 60% of all AKI cases in the intensive care unit.[2] Various therapeutic drugs, including aminoglycoside antibiotics, chemotherapeutic agents, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, radiocontrast media, and nonsteroidal anti-inflammatory drugs (NSAIDs), exert nephrotoxic effects via different pathogenic mechanisms.[3] For example, NSAIDs perturb kidney function through interstitial nephritis and inhibition of vasodilatory prostaglandin production in the renal cortex and medulla.[4] Angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors reduce glomerular hydrostatic pressure and may cause kidney dysfunction.[5] Moreover, anticancer drugs, aminoglycoside antibiotics, and radiocontrast media may injure renal tubular epithelial cells, leading to acute tubular necrosis.[5]

In spite of the innumerable preventive strategies used to limit drug-induced renal injury, this condition still remains a big health challenge in hospitalized patients. On the other hand, medicinal plants possess protective activity against nephrotoxicity through their various pharmacological actions. Several studies have shown that the co-administration of different medicinal plants along with various nephrotoxic drugs may reduce the incidence of kidney injury.[6-8] However, there are studies indicating the limitation of herbal administration against drug-induced kidney injury. The following is a review of some nephrotoxic drugs beside the effects of various medicinal plants.

## ANTIBIOTICS AND NEPHROTOXICITY

Antibiotics are a wide-spread class of drugs and the principal cause of drug-associated nephropathy.[9] Aminoglycosides are one of the most important classes of antibiotics exerting toxic effects on the kidney function. In patients receiving gentamicin for 3 to 5 days, nephrotoxicity occurs in 10% to 25% of the cases.[10] Gentamicin is filtered from the glomeruli into the renal tubules, where it binds with phospholipids in the apical membrane of proximal epithelial cells.[11] The main cause of aminoglycoside-induced nephrotoxicity is tubular toxicity caused by apoptosis and necrosis of tubular epithelial cells as well as dysfunction of the cellular components

involved in the transport of water and solutes. In mild degrees of gentamicin-induced kidney injury, glomerular filtration rate is reduced, which is a result of mesangial and vascular contraction, whereas in severe cases, the major cause of glomerular filtration rate reduction is tubular obstruction.[12,13] Furthermore, it has been shown that in the presence of gentamicin, the production of reactive oxygen species is increased besides a reduction in renal antioxidant enzymes activity.[14] The co-administration of different medicinal plants along with gentamicin has revealed to reduce its nephrotoxic effects to some extent. Some of these medicinal plants are presented in Table 1.[7,15-42]

**Table 1.** Plants With Protective Effects Against Gentamicin-induced Nephrotoxicity*

| Plant | Part of Plant | Animal Study | Gentamicin | Herb | Time Protocol | Outcome |
|---|---|---|---|---|---|---|
| *Ginkgo biloba* | Leaves | Rat[15] | 80 mg/kg, IP | 300 mg/kg, oral | Gentamicin was injected for 8 days and extract was administrated 2 days before and 8 days concurrently with Gentamicin. | • Improvement of serum biochemical parameters and glomerular filtration<br>• Reduction in serum and tissue lipid peroxidation products<br>• Improvement of renal histology |
| *Nigella sativa* | Seeds | Rat[16] | 100 mg/kg, SC | 5 ml/kg, oral | Gentamicin was injected for 7 days and extract was administered as pre-, post- and concomitant treatment for 7 days in the nephrotoxic rats. | Improvement in biochemical parameters and renal cortical histology which were more evident in the post-treatment group than the pretreatment and the concomitantly-treated group |
| *Kalanchoe pinnata* | Leaves | Rat[17] | 100 mg/kg, IP | 125 mg/kg, IP | Gentamicin and extract were injected concurrently for 8 days. | • Improvement of serum and urine biochemical parameters<br>• Amelioration in oxidative stress<br>• Improvement of renal histology |
| *Trianthema portulacastrum* | Leaves | Rat[18] | 100 mg/kg, IP | 200 mg/kg, IP | Gentamicin and extract were injected concurrently for 14 days. | • Improvement of serum and urine biochemical parameters<br>• Amelioration in oxidative stress<br>• Improvement of renal histology |
| *Nigella sativa* | Oil | Rat[19] | 100 mg/kg, IP | 0.2,0.4 ml/kg, IP | Gentamicin and Nigella sativa oil were injected concurrently for 6 days. | • Decrease in plasma malondialdehyde and nitric oxide<br>• Increase in erythrocyte superoxide dismutase and glutathione peroxidase activities<br>• Improvement of renal histology |
| *Zingiber officinale* | Rhizomes | Rat[20] | 100 mg/kg, IP | 200 mg/kg, oral | Gentamicin and extract were administrated concurrently for 8 days | • Improvement of serum biochemical parameters<br>• Improvement of renal histology |
| *Ficus carica* | Fruits | Rat[21] | 100 mg/kg, IP | 250, 500, 750 mg/kg, IP | Extract was administrated for 8 days and then Gentamicin concomitant with extract were administrated for 8 days. | • Improvement of serum biochemical parameters<br>• Amelioration in oxidative stress |

*IP indicates intraperitoneal; SC, subcutaneous; and IM, intramuscular.

**Table 1.** (Continued)

| Plant | Part of Plant | Animal Study | Gentamicin | Herb | Time Protocol | Outcome |
|---|---|---|---|---|---|---|
| *Enicostemma littorale* | Whole plant | Rat[22] | 80 mg/kg, IP | 2.5 g/kg, Gavage | Gentamicin was injected for 8 days and extract treatment was started three days prior to the gentamicin treatment and continued till the end of gentamicin treatment. | • Improvement of serum biochemical parameters<br>• Increase in antioxidant parameters<br>• Improvement of renal histology |
| *Caesalpinia bonduc* | Leaves | Rat[23] | 80 mg/kg, IP | 250,500 mg/kg, oral | Gentamicin and extract were administrated concurrently for 7 days. | • Improvement of serum biochemical parameters<br>• Improvement of renal histology |
| *Cassia occidentalis* | Leaves | Rat[24] | 80 mg/kg, IP | 200,400 mg/kg, oral | Gentamicin was injected for 8 days, extract administration was started three days prior to the Gentamicin injections and continued with eight days Gentamicin treatment. | • Improvement of serum and urine biochemical parameters<br>• Amelioration in oxidative stress<br>• Improvement of renal histology |
| *Phaseolus radiates* | Seeds | Rat[25] | 40 mg/kg, IP | 100,200 mg/kg, oral | Gentamicin and extract were administrated concurrently for 14 days. | Improvement of serum biochemical parameters |
| *Punica granatum* | Fruits | Rat[26] | 100 mg/kg, IP | 100 mg/kg, oral | Gentamicin and extract were administrated concurrently for 8 days.<br>Gentamicin was injected for 8 days and a single dose of extract was administrated on day 8 of the experiment. | • Improvement of serum biochemical parameters and renal histology which were better when the extract co-administered with gentamicin than when given after gentamicin-induced nephrotoxicity |
| *Khaya senegalensis* | Stem bark | Rat[27] | 100 mg/kg, IM | 250, 500 mg/kg, oral | Extract was administrated for 8 days and Gentamicin was injected for last 5 days. | • Improvement of serum biochemical parameters<br>• Improvement of hematological parameters<br>• Improvement of renal histology |
| *Olea europaea* | Leaves | Rat[28] | 100 mg/kg, IP | 25,50,100 mg/kg, oral | Gentamicin and extract were administrated concurrently for 12 days. | • Improvement of serum biochemical parameters<br>• Amelioration in oxidative stress<br>• Improvement of renal histology |
| *Moringa oleifera* | Leaves | Rabbit[29] | 40 mg/kg, IP | 150,300 mg/kg, IP | Gentamicin and extract were administrated concurrently for 10 days. | • Improvement of serum biochemical parameters<br>• Reduction in renal lipid peroxidation<br>• Improvement of renal histology |
| *Tephrosia purpurea* | Leaves | Rat[30] | 40 mg/kg, SC | 200 mg/kg, oral | In preventive group extract was administrated 30 minutes before Gentamicin injection.<br>In curative group extract was administrated 7 days after Gentamicin injection. | Improvement of serum biochemical parameters, amelioration in oxidative stress and improvement of renal histology in both preventive and curative groups |

**Table 1.** (Continued)

| Plant | Part of Plant | Animal Study | Gentamicin | Herb | Time Protocol | Outcome |
|---|---|---|---|---|---|---|
| *Cissampelos pareira* | Whole plant | Rat[31] | 80 mg/kg, IP | 200,400 mg/kg, oral | Gentamicin was injected for 8 days and extract was administrated 3 days before and 8 days concurrently with Gentamicin. | • Improvement of serum and urine biochemical parameters<br>• Amelioration in oxidative stress |
| *Costus afer* | Leaves | Rat[32] | 90 mg/kg, IP | 375,750,1125 mg/kg | Gentamicin and extract were administrated concurrently for 7 days. | • Improvement of serum biochemical parameters<br>• Improvement of renal histology |
| *Elaeocarpus ganitrus* | Seeds | Rat[33] | 100 mg/kg, IP | 100,200,400, oral | Gentamicin and extract were administrated concurrently for 6 days. | • Improvement of serum and urine biochemical parameters<br>• Amelioration in oxidative stress<br>• Improvement of renal histology |
| *Myristica fragrans* | Fruits | Rat[34] | 80 mg/kg, IP | 150, 300 mg/kg | Gentamicin and extract were administrated concurrently for 15 days. | • Improvement of serum biochemical parameters<br>• Amelioration in oxidative stress |
| *Pistacia khinjuk* | Fruits | Rat[35] | 80 mg/kg, IP | 150, 300, 600 mg/kg, oral | Gentamicin and extract were administrated concurrently for 14 days. | • Improvement of serum biochemical parameters<br>• Amelioration in oxidative stress |
| *Tamarindus indica* | Fruits | Rabbit[36] | 80 mg/kg, IM | 200 mg/kg, oral | Gentamicin and extract were administrated concurrently for 3 weeks. | • Improvement of serum and urine biochemical parameters<br>• Improvement of renal histology |
| *Citrus medica* | Fruits | Rat[37] | 80 mg/kg, IP | 250,500 mk/kg, oral | Gentamicin was injected for 8 days and extract was administrated 14 days before and 8 days concurrently with Gentamicin. | • Improvement of serum biochemical parameters<br>• Amelioration in oxidative stress<br>• Improvement of renal histology |
| *Nigella sativa* | Thymoquinone | Rat[38] | 80 mg/kg, IP | 10 mg/kg, oral | Gentamicin and thymoquinone were administrated concurrently for 10 days. | • Improvement of serum biochemical parameters<br>• Amelioration in oxidative stress<br>• Improvement of renal histology |
| *Mangifera indica* | Commercial extract (vimang) and fruits | Rat[7] | 80 mg/kg, IP | Vimang: 50, 100 mg/kg Extract: 200,400 mg/kg | Preventive groups received vimang or extract for 18 days and Gentamicin was used for the last 8 days of the experiment.<br>Treatment groups received vimang or extract and Gentamicin concurrently for the last 8 days of experiment. | • Improvement of serum biochemical parameters that was more evident in preventive groups especially by extract (200 mg/kg)<br>• Improvement of renal tissue damage that was more evident in preventive groups especially by extract (400 mg/kg) and vimang |
| *Nigella sativa* | Thymoquinone | Rat[39] | 80 mg/kg, IP | 10 mg/kg, IP | Gentamicin and thymoquinone were administrated concurrently for 10 days. | • Improvement of serum biochemical parameters<br>• Amelioration in oxidative stress |

**Table 1.** (Continued)

| Plant | Part of Plant | Animal Study | Gentamicin | Herb | Time Protocol | Outcome |
|---|---|---|---|---|---|---|
| *Crocus sativus* | Saffron | Rat[40] | 80 mg/kg, IP | 40,80 mg/kg, oral | Saffron was given for 10 days and Gentamicin was injected for five days starting from day 6. | • Improvement of serum biochemical parameters<br>• Amelioration in oxidative stress<br>• Improvement of renal histology |
| *Viscum articulatum* | Oleanolic acid | Rat[41] | 100 mg/kg, IP | 40, 60, 80 mg/kg, oral | Gentamicin and oleanolic acid were administrated concurrently for 8 days. | • Improvement of serum and urine biochemical parameters and glomerular filtration<br>• Improvement of renal histology |
| *Crocus sativus* | Safranal | Rat[42] | 80 mg/kg, IP | 0.5 ml/kg, IP | Gentamicin and safranal were administrated concurrently for 6 days. | Improvement of serum and urine biochemical parameters |

Vancomycin is another nephrotoxic antibiotic that causes nephrotoxicity in 10% to 20% of patients receiving its conventional doses. The exact mechanism by which vancomycin exerts its nephrotoxic effects has not yet been fully understood; however, oxidative stress has been reported as the most possible mechanism.[43] For this reason, the use of natural antioxidants has recently been taken under consideration. Curcumin is the active ingredient of *Curcuma longa*, the renoprotective effects of 200 mg/kg of which were demonstrated in rats for 2 weeks before and 1 week after vancomycin-induced renal toxicity.[44]

## ANTICANCER DRUGS AND NEPHROTOXICITY

Renal toxicity is an inherent side effect of some anticancer drugs.[45] Cisplatin and doxorubicin are among the most important nephrotoxic agents. Cisplatin is freely filtered at the glomerulus and taken up into renal tubular cells, dominantly through a transport-mediated process.[46] Cisplatin has multiple cellular effects including mitochondrial dysfunction, activation of mitogen-activated protein kinases signaling pathways, and production of reactive oxygen species. These factors can induce apoptosis and necrosis and result in tubular damage and dysfunction.[47] Understanding the mechanisms of cisplatin-induced kidney injury has led to multiple approaches in the prevention or treatment of renal adverse manifestations. Therefore, the application of medicinal plants with various pharmacologic properties can be useful against cisplatin-induced renal toxicity (Table 2).[6,48-66] In addition, doxorubicin

**Table 2.** Plants With Protective Effects Against Cisplatin-induced Nephrotoxicity*

| Plant | Part of Plant | Animal Study | Cisplatin | Herb | Time Protocol | Outcome |
|---|---|---|---|---|---|---|
| *Brassica rapa* | Root | Rat[48] | 7 mg/kg, IP | 50,100, 200 mg/kg, oral | Extract was administrated 14 days before single dose injection of cisplatin. | • Improvement of serum and urine biochemical parameters<br>• Amelioration in oxidative stress |
| *Phyllanthus maderaspatensis* | Whole plant | Mouse[49] | 5 mg/kg, IP | 200,400,600 mg/kg, oral | Extract was administrated 7 days and cisplatin was injected 2 hours after the last dose of extracts. | • Improvement of serum biochemical parameters.<br>• Improvement of renal histology |
| *Ficus hispida* | Whole plant | Rat[50] | 5 mg/kg, IP | 250, 500 mg/kg, oral | In curative groups, extract was administrated 6 days after cisplatin injection.<br>In prophylactic groups, extract was administrated 10 days before cisplatin injection. | Improvement of serum and urine biochemical parameters, amelioration in oxidative stress and improvement of renal histology in both curative and prophylactic groups |

*IP indicates intraperitoneal.

**Table 2.** (Continued)

| Plant | Part of Plant | Animal Study | Cisplatin | Herb | Time Protocol | Outcome |
|---|---|---|---|---|---|---|
| *Nigella sativa* | Seeds and oil | Rat[51] | 5 mg/kg, IP | Extract: 50 mg/kg, IP<br>Oil: 400 mg/kg, oral | Cisplatin injection repeated 4 times, with 5 days free interval in between.<br>Supportive treatments were started 5 days before the experiment and continued daily till the 15th day of the experiment. | • Normalization of the kidney function<br>• Amelioration in oxidative stress<br>• Improvement of apoptotic markers<br>• Improvement of renal histology |
| *Matricaria chamomilla* | Leaves andflowers | Rat[51] | 5 mg/kg, IP | 50 mg/kg, IP | Cisplatin injection repeated 4 times, with 5 days free interval in between.<br>Supportive treatments were started 5 days before the experiment and continued daily till the 15th day of the experiment. | • Normalization of the kidney function<br>• Amelioration in oxidative stress<br>• Improvement of apoptotic markers<br>• Improvement of renal histology |
| *Nigella sativa* | Seeds | Rat[52] | 3 mg/kg, IP | 100 mg/kg, oral | Cisplatin was injected for 3 alternative days and after 2 weeks, extract was administrated for 42 days. | • Increase in serum levels of urea, creatinine and triglycerides and decrease in urine glucose concentration<br>• Amelioration in renal histology |
| *Ginkgo biloba* | Leaves | Rat[53] | 10 mg/kg, IP | 150 mg/kg, IP | Extract was administrated for 5 days and cisplatin was injected on 2th day of experiment. | • Improvement of serum biochemical parameters<br>• Amelioration in oxidative stress<br>• Improvement of renal histology |
| *Heliotropium eichwaldi* | Root | Mouse[54] | 16 mg/kg, IP | 200, 400 mg/kg, oral | Extract was administrated for 7 days and cisplatin was injected on the 4th day of experiment. | • Improvement of serum biochemical parameters<br>• Amelioration in oxidative stress<br>• Improvement of renal histology |
| *Vaccinium myrtillus* | Whole plant | Rat[55] | 7.5 mg/kg, IP | 200 mg/kg, oral | Extract was administrated for 10 days and cisplatin was injected on the 2th day of experiment. | • Amelioration in oxidative stress<br>• Improvement of renal histology |
| *Punica granatum* | Flowers | Rat[56] | 2.5 mg/kg, IP | 25,50 mg/kg, oral | Extract was administrated for 9 days and from day 3 cisplatin was added to the treatment. | • Improvement of serum biochemical parameters<br>• Amelioration in oxidative stress<br>• Improvement of renal histology |
| *Nigella sativa* | Seeds | Rat[6] | 6 mg/kg, IP | 100,200 mg/kg, IP | In preventive groups, extract was administrated 5 days before cisplatin injection.<br>In preventive-treatment groups, extract was administrated 5 days before and 5 days after cisplatin injection. | Improvement of serum and urine biochemical parameters which were more evident in preventive-treatment groups |
| *Crocus sativus* | Stigma | Rat[57] | 3 mg/kg, IP | 50 mg/kg, IP | Extract was injected 30 min before cisplatin injection, for 5 alternate days. | • Improvement of serum biochemical parameters.<br>• Amelioration in oxidative stress. |

**Table 2.** (Continued)

| Plant | Part of Plant | Animal Study | Cisplatin | Herb | Time Protocol | Outcome |
|---|---|---|---|---|---|---|
| *Capsicum solanaceae* | Capsaicin | Rat[58] | 5 mg/kg, IP | 10 mg/kg, oral | Capsaicin was given for 6 consecutive days after cisplatin injection. | • Improvement of serum biochemical parameters.<br>• Amelioration in oxidative stress. |
| *Curcuma longa* | Curcumin | Rat[59] | 5 mg/kg, IP | 8 mg/kg, gavage | Curcumin was given at two doses: one dose 24 h and the second 10 min before cisplatin injection. | Without any protection against cisplatin-induced nephrotoxicity |
| *Crocus sativus* | Crocin | Rat[60] | 5 mg/kg, IP | 100, 200, 400 mg/kg, IP | Extract was injected for four consecutive days followed by a single dose of cisplatin only at first day. | • Improvement of serum biochemical parameters<br>• Amelioration in oxidative stress<br>• Improvement of renal histology |
| *Curcuma longa* | Curcumin | Mouse[61] | 20 mg/kg, IP | 100 mg/kg, IP | Curcumin was injected immediately after cisplatin injection. | • Improvement of kidney function<br>• Decrease in renal tumor necrosis factor-α, monocyte chemoattractant protein-1, and intercellular adhesion molecule-1<br>• Improvement of renal histology |
| *Curcuma longa* | Curcumin | Rat[62] | 20 mg/kg, IP | 200 mg/kg, IP | Curcumin was injected 24 h prior to cisplatin injection. | • Improvement of serum biochemical parameters<br>• Amelioration in oxidative stress<br>• Improvement of renal histology |
| *Nigella sativa* | Thymoquinone | Rat & Mouse[63] | 5 mg/kg, IP | 50 mg/L, oral | Thymoquinone was administrated 5 days before and 5 days after cisplatin injection. | Improvement of serum biochemical parameters and glomerular filtration rate |
| *Plantago major* | Whole plant | Rat[64] | 7 mg/kg, IP | 300, 600, 1200 mg/kg, oral | Extract was administrated for 20 consecutive days and cisplatin on the 6$^{th}$ day of experiment. | • Decrease of serum creatinine, urea and potassium in all extract-treated animals<br>• Elevation in serum sodium levels in the extract 600 mg/kg group<br>• Decrease of renal malondialdehyde concentration and increase of superoxide dismutase activity in extract 1200 mg/kg group<br>• Increase of catalase activity in all extract-treated animals |
| *Silybum marianum* | Silymarin | Human[65] | | 280 mg, oral | Silymarin tablet was administrated 7 days before cisplatin administration. | Decrease of serum creatinine and urea 2 weeks after cisplatin administration. |
| *Silybum marianum* | Silymarin | Human[66] | | 1260 mg, oral | Silymarin administration started 24 to 48 hours before the initiation of cisplatin infusion and continued consecutively to the end of the three 21-day cisplatin-containing chemotherapy courses. | Oral silymarin administration could not prevent cisplatin associated nephrotoxicity and tubular dysfunction in clinical setting. |

is another anticancer nephrotoxic drug attracting attention towards the nephroprotective effects of some medicinal plants. Doxorubicin disturbs the balance between free radicals and antioxidants and thereby injures the renal tissue. It is believed that the mechanisms of renal toxicity induced by doxorubicin are mediated through free radical generation, iron-dependent oxidative damage of biological molecules, membrane lipids peroxidation, and protein oxidation. These effects can increase glomerular capillaries permeability and tubular atrophy.[67,68] Pharmacological actions of medicinal herbs including antioxidant effects are able to improve kidney function against doxorubicin-induced nephrotoxicity (Table 3).[8,69-72] In contrast to other studies Antunes and colleagues showed that curcumin was not able to ameliorate the cisplatin-induced renal injury in the rat (Table 2).[59]

## OTHER DRUGS AND NEPHROTOXICITY

Although, the use of NSAIDs is associated with relatively prevalent adverse renal effects, the incidence of such adverse events is approximately 1% to 5% among all patients using NSAIDs.[73] Different forms of renal injury including acute interstitial nephritis, papillary necrosis, and changes in renal hemodynamics may occur following NSAID consumption. In healthy individuals, these disorders are rare, but might be considered as serious in patients whom their kidney function is prostaglandin dependent.[74] Acetaminophen is one of the most popular antipyretic and analgesic drugs that unlike NSAIDs has no anti-inflammatory activity and does not produce gastrointestinal damage. Renal toxicity occurs in 1% to 2% of patients with acetaminophen overdose. The possible mechanisms of acetaminophen-induced nephrotoxicity are activation of cytochrome P450 pathway mainly in the cortex, binding the prostaglandin endoperoxidase synthase to acetaminophen, formation of toxic metabolites mainly in the medulla, deacetylation of acetaminophen by N-deacetylase enzymes, and generation of free radicals.[75] It has been demonstrated that medicinal herbs exert beneficial properties against the deleterious effects of acetaminophen in kidneys. Some of these protective actions of medicinal herbs are presented in Table 3.

**Table 3.** Plants With Protective Effects Against Other Drug-induced Nephrotoxicity*

| Plant | Part of Plant | Animal Study | Name of Drug | Dosage | Time Protocol | Outcome |
|---|---|---|---|---|---|---|
| *Curcuma longa* | Whole plant | Mouse[8] | Acetaminophen | Extract: 400, 800,1000 mg/kg, oral<br>Acetaminophen: 500 mg/kg<br>oral | Acetaminophen and extract were administrated at a same time. | • Improvement of serum biochemical parameters<br>• Improvement of renal histology |
| *Pimpinella tirupatiensis* | Whole plant | Rat[70] | Acetaminophen | Extract: 500, 750 mg/kg, oral<br>Acetaminophen: 750 mg/kg, oral | Extract was administrated for 14 days and acetaminophen was given on the 14th day of the study. | • Improvement of serum biochemical parameters.<br>• Amelioration in oxidative stress<br>• Improvement of renal histology |
| *Allium sativum* | Oil | Rat[71] | Acetaminophen | *Allium sativum* oil: 100 mg/kg, oral<br>Acetaminophen: 1000 mg/kg, IP | *Allium sativum* oil was given one week prior to acetaminophen given on the 7th day of experiment. | • Improvement of serum biochemical parameters.<br>• Improvement of renal histology |
| *Curcuma longa* | Curcumin | Rat[69] | Doxorubicin | Curcumin: 200 mg/kg, oral<br>Doxorubicin: 7.5 mg/kg, IV | Curcumin was given 7 days before and 30 days after doxorubicin. | • Improvement in kidney function tests<br>• Amelioration in oxidative stress |
| *Nigella sativa and Curcuma longa* | *Nigella sativa*: seeds<br>*Curcuma longa*: rhizome | Rat[72] | Doxorubicin | Doxorubicin: 5 mg/kg, IV<br>*Nigella sativa*: 200 mg/kg, oral<br>*Curcuma longa*: 1000 mg/kg, oral | *Nigella sativa* and *Curcuma longa* were administrated 6 days before and 28 days after doxorubicin injection. | • Amelioration in oxidative stress |

*IP indicates intraperitoneal and IV, intravenous.

## DISCUSSION

In recent years, there is an increasing number of hospitalized patients with drug-induced kidney problems; drug-induced nephrotoxicity is accounted for about 60% of hospital-acquired acute kidney injuries.[76] In spite of different good supportive strategies including hydration and electrolytes replacement, dose adjustment based on kidney function and avoidance of nephrotoxic drugs, about 10% to 30% of treated patients experience nephrotoxicity.[65] The medicinal plants, due to the presence of chemical components, play an outstanding role against different kidney diseases. Numerous investigations have reported the significant nephroprotective activity of a variety of medicinal plants and their extracts in animal models as well as in vitro studies. However, some of these effects are not seen when they are applied in human in clinical setting.[65] Also, there are some possible limitations that restrict the clinical use of the herbal remedies in real life including concerns about the administration of high animal dose in human and likely interaction of medicinal plant with nephrotoxic drugs.

It has also been shown that herbal remedies are more efficacious when they are administered prior to the nephrotoxic drug. In clinical setting, the administration of some nephrotoxic agents especially antibiotics are unpredictable. However, there are enough studies indicating nephroprotctive effects of medicinal plants when they administered concomitantly or after nephrotoxic drugs. Likewise, based on the results of different investigations, the medicinal herbs show renoprotection against experimentally induced nephrotoxicity in different animal models. However, in some cases, the administration of medicinal plant showed no significant or even reverse effects against nephrotoxicity associated with drugs.[52,59] However, these adverse effects of medicinal herbs could be markedly reduced if the plants are prescribed based on the recommendation of the pharmacopoeia with attention to its dose, origin, duration of administration, and way of preparation.

## CONCLUSIONS

Drugs are a common cause of acute kidney injury. In recent years, the use of natural remedies has developed to reduce the adverse effects of nephrotoxic drugs. Although herbal medicines have promising renoprotective actions in animal models, their effects on human remain to be investigated. Therefore, it is essential for healthcare professionals to furnish with adequate information when prescribing these herbal remedies against drug-induced kidney injury in humans. In this article, major studies that focused on the use of different medicinal plants as nephroprotective agents have been reviewed. Most of these studies have been accomplished in animals, which help to develop the future clinical trials. Also, the active components of these herbs should be identified and tolerable levels of toxicity must be determined.

## CONFLICT OF INTEREST

None declared.

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