Tunisian Nephroprotective Plants: A Review

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Abstract

In Tunisian folk medicine, several herbs are prescribed for reducing renal damage and to avoid kidney related complications. These can be of immense value in combating renal damage. In this review, we provide a description of the current literature on the use of indigenous herbs as alternative medicine for treating renal damage. The aim of this review was to collect information on promising active phytoconstituents such as organosulfur compounds, polyphenols, terpenes, alkaloids phenylpropanoids, and polysaccharides from Tunisian plants that have been scientifically examined for their nephroprotective capacities. Twenty-nine Tunisian medicinal plants have been reported for their significant nephroprotective activities against renal toxicities in animal models. Lamiaceae was the most commonly used Tunisian plant family used for renal protection. The leaves were maximally used for nephroprotection compared to the other plant parts. Nephroprotective agents may attenuate toxicity. Many studies have focussed on drug-caused renal failure which is one of the major problems in medical practice. Other studies focused on other important nephrotoxicity factors, including drugs and industrial chemicals. This literature review highlights the use of some medicinal plants as nephroprotective agents. To defend against this nephrotoxicity, some medicinal plants, known as nephroprotective agents, have been highlighted in this review.

Introduction

The kidneys are vital organs that have several physiological functions. Their principle role is to maintain homeostasis of body fluids by filtering and secreting metabolites and minerals from the blood and excreting the nitrogenous waste along with water, as urine. The kidneys also help to regulate blood pressure, glucose metabolism, and erythropoiesis.

The kidneys filter about 180 liters of blood daily, about four times the quantity traversing any other organ. Consequently, the kidneys are highly exposed to toxins in the blood and are susceptible to tissue damage. Kidney disease is the ninth leading cause of death, and patients with kidney disease have significant morbidity and mortality.

The number of patients presenting with kidney disorders is increasing at an alarming rate. Currently, there are approximately over one million people worldwide who require dialysis or a functioning graft. Kidney replacement has been the only therapy for end stage of renal failure, and dialysis has remained the only alternative when a kidney transplant is not possible.

Nephrotoxicity is one of the most common kidney problems induced by drugs or toxins. A number of potent therapeutic drugs, including aminoglycoside antibiotics, chemotherapeutic agents and chemical reagents (ethylene glycol, carbon tetrachloride, and sodium oxalate), and heavy metals (lead, mercury, cadmium, and arsenic), can adversely affect the kidney resulting in acute renal failure.

In addition to drugs, other factors can lead to acute renal failure, such as age, diabetes, hypertension, liver disease, and oliguria. Nephroprotective agents, such as those found in medicinal plants, have protective and curative capacities against nephrotoxicity (Fig. 1). Co-administration of various medicinal plants possessing nephroprotective activity along with different nephrotoxic agents may attenuate toxicity. Previously, Tunisian medicinal plants have been used to treat diabetes, ulcer, cancer, liver, and coronavirus illnesses. In this review, we highlighted the current literature focused on Tunisian nephroprotective plants.

We searched the PubMed, Scientific Information Database, Sco...
pus, Web of Science, Science Direct, Google and Google scholar databases for primary literature using the keywords nephroprotective effect, kidneys, nephrotoxicity, renal failure, medicinal plants, and Tunisia. A total of 175 researches was included in this work. The different experimental nephroprotective researches allowed describing 29 Tunisian medicinal plants for their significant nephroprotective activities against renal toxicities in animal models (Table 1).13–50 These toxicities were made by several toxins belonging to drugs, industrial additives and pesticides (Table 2).14,17,20–22,24,25,28,29,31,37–43,45,47,49,51

**Allium sativum**

*Allium sativum* belongs to the family of Alliaceae, popularly known as garlic. It has reported anti-atherosclerotic, cardioprotective, neuroprotective, anti-hyperlipidemic, antidiabetic, anti-hypertension, antistress, anticancer, antiviral, antibacterial, antifungal, anti-oxidant, and dermatologic properties.52 Neir et al.13 determined that the nephroprotective potential of the methanol extract from *A. sativum* cloves (20 mg/kg body weight (BW) against deltamethrin (7.2 mg/kg BW) caused oxidative damage in rat kidneys. Deltamethrin treatment increased kidney conjugated dienes and lipid peroxidase (LPO) levels. However, catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) levels were decreased. Garlic administration regulated these changes provoked by deltamethrin. Allicin is one of the major bioactive components of garlic constituted from the stable precursor alliin by the enzyme action alliinase when garlic cloves are crushed or macerated. García Trejo et al.53 determined that allicin had beneficial effects in chronic kidney disease compared to Losartan.

**Artemisia arborescens**

*Artemisia arborescens* is a perennial evergreen woody shrub belonging to the family of Asteraceae.54 *A. arborescens* is a widely used traditional medicine that possesses ethnomedical and biological benefits.55 The beneficial effects of the aqueous ethanol extract from *A. arborescens* leaves (200 mg/kg BW) was studied against oestroprogestative-induced (35 mg/kg of estradiol and 125 mg/kg of progesterone, BW) kidney damage in rats. *A. arborescens* extract was found to optimize many parameters of oestroprogestative toxicity.14 The protective effect of *A. arborescens* was mainly attributed to the presence of phenolic acids and flavonoids. *A. arborescens* is rich in catechic acid, caffeic acid, epicatechic acid, vanillic acid, naringenin, coumarin, cimic acid, quercetin, rutin, luteolin, kaempferol, and isorhamnetin. Among these phenolics,
### Table 1. Tunisian medicinal plants with nephroprotective activity

| Scientific plant name | Part used* | Extract | Bioactive compounds | Nephrotoxin used | References |
|-----------------------|------------|---------|---------------------|------------------|------------|
| *Allium sativum*      | Cloves     | Methanol| Organosulfur compound (allicin) | Deltamethrin | 13         |
| *Artemisia arborescens* | Leaves    | Aqueous ethanol | Phenolic compounds (vanillic acid, coumarin, rutin, luteolin, naringenin and quercetin) | Estradiol + progesterone | 14         |
| *Artemisia campestris* | Aerial parts | Essential oil | Terpenes (β-pinene, p-cymene and α-pinene) | Deltamethrin | 15         |
|                       |            |         |                     | Chlorpyrifos | 16         |
| *Capparis spinosa*    | Leaves    | Methanol| Phenolic compounds (rutin, resveratrol, coumarin, luteolin and epicatechin) | Cisplatin | 17         |
| *Ceratonia siliqua*   | Leaves    | Ethyl acetate | Phenolic compounds (syringic acid, myricetin glycosides and gallic acid derivatives) | CCl4 | 18         |

(continued)
| Scientific plant name | Part used  | Extract | Bioactive compounds | Nephrotoxin used     | References |
|-----------------------|------------|---------|---------------------|----------------------|------------|
| Citrus limon          | Leaves     | Essential oil | Terpene (limonene) | Aspirin               | 19         |
| Eryngium maritimum    | Seeds      | Methanol | Phenolic compounds (caffeic acid, protocatechuic acid gallic acid, luteolin and kaempferol) | Cisplatin | 20         |
| Eucalyptus globulus   | Leaves     | Aqueous | Phenolic compounds (rutin, ellagic acid, chlorogenic acid, and quercetin 3-glucuronide) | Acetaminophen | 21         |
| Euphorbia bivonae     | Leaves     | Methanol | Monosaccharides (saccharose, arabinose, inositol, glucose, pyranose, trehalose and fructose) | Hydrogen peroxide | 22         |
| Globularia alypum      | Leaves     | Methanol | Phenolic compound (globularin) | Deltamethrin | 23         |

(continued)
| Scientific plant name | Part used* | Extract | Bioactive compounds | Nephrotoxin used | References |
|-----------------------|------------|---------|---------------------|------------------|------------|
| *Hammada scoparia*    | Leaves     | Methanol| Alkaloids (carneine and N-methylisosalsoline) and flavonoids (isorhamnetin triglycerides) | Ethanol | 24 |
| *Hyparrhenia hirta*   | Aerial parts | Methanol | Flavonoid compounds (apigenin, quercetin and luteolin) | Sodium nitrate | 25 |
| *Lavandula stoechas*  | Aerial parts | Essential oil | Terpenes (tricyclene, cymene, Δ-Cadinene and Selina-3,7(11)-diene) | Malathion | 26 |
| *Lycium europaeum*    | Flowers, Leaves | Methanol | Phenolic compounds (cisplatin, caffeic acid, gallic acid, naringenin, epicatechin, vanillic acid, rutin and p-coumaric acid) Polysaccharide | CCl4, Cisplatin | 27, 28 |
| *Malva sylvestris*    | Flowers, Leaves | Aqueous | Phenolic compounds (gallic acid, p-coumaric acid, rutin, kaempferol, quercetin and luteolin) | Vanadium, Lithium carbonate | 29, 30 |
| Scientific plant name | Part used* | Extract | Bioactive compounds                                      | Nephrotoxin used   | References |
|-----------------------|------------|---------|----------------------------------------------------------|--------------------|------------|
| Mentha piperita       | Leaves     | Essential oil | Terpenes (menthol and iso-menthone)                      | CCl4               | 31         |
| Morus alba            | Leaves     | Aqueous acetone | Phenolic compounds (chlorogenic acid and its derivatives) | Glyphosate         | 32         |
| Nitraria retusa       | Fruits     | Aqueous | Phenolic compounds (chlorogenic acid, p-coumaric acid, caffeic acid, gallic acid and kaempferol) | Penconazole        | 33         |
| Olea europea          | Fruits     | Oil     | Phenolic compounds (oleuropein and hydroxytyrosol)       | Acrylamide         | 34         |
|                        | Leaves     | Aqueous |                                                    | Deltamethrin       | 35         |
|                        | Fruits     | Ethanol |                                                    | Bisphenol A        | 36         |
|                        | Cladodes   | Aqueous | Phenolic compounds quercetin, vanillic acid, gallic acid, rutin, kaempferol, catechin, epicatechin, coumarin, isorhamnetin and caffeic acid | Lithium carbonate | 38         |
|                        |            |         |                                                    | Sodium dichromate  | 39         |

(continued)
| Scientific plant name | Part used* | Extract | Bioactive compounds | Nephrotoxin used | References |
|----------------------|------------|---------|---------------------|------------------|------------|
| Periploca angustifolia | Leaves     | Monosaccharides (saccharose, trehalose, L-inositol and M-inositol) | Cadmium          | 40               |
| Phoenix dactylifera  | Fruits     | Aqueous | Phenolic acids (ferulic, caffeic and p-coumaric acids) | Dichloroacetic acid | 41        |
| Pinus halepensis     | Needles    | Essential oil | Terpenes (Z-β-caryophyllene, β-myrcene and α-pinene) | Aspirin          | 42        |
| Rhus tripartitum     | Fruits     | Methanol | Phenolic acid (betulinic acid) | Cisplatin        | 43        |
| Rosmarinus officinalis | Leaves   | Aqueous | Phenolic compounds (carnosic and rosmarinic acids) | CCl4             | 44        |

(continued)
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The potent nephroprotective effect of vanillic acid, coumarin, rutin, and luteolin was determined against cisplatin-induced nephrotoxicity in rats. Additionally, the renal protective potential of naringenin and quercetin was studied in cadmium-induced oxidative renal dysfunction in rats.

**Artemisia campestris**

*Artemisia campestris* is a perennial herb belonging to the family of Asteraceae. *A. campestris* has many medicinal actions including anthelmintic, antidiabetic, anticancer, antimicrobial, antifungal, antihypertensive, emmenagogue, and antivenom. It has been also used to treat cutaneous, genital, digestive, and respiratory disorders. Saoudi et al. investigated the protective effects of *A. campestris* essential oil against deltamethrin nephrotoxicity in rats. Deltamethrin toxicity caused a significant increase in creatinine, urea, and uric acid levels, and a decrease in LPO, SOD, CAT and GPx. However, *A. campestris* essential oil reduced the deltamethrin-induced alterations in serum levels, lipid peroxidation, and oxidative stress. The protective effect of *A. campestris* essential oil could be attributed to its antioxidant potential. Similar results were obtained by Saoudi et al. who determined the protective effect of *A. campestris* essential oil against chlorpyrifos-induced kidney injury in rats. Akrout et al. found that *A. campestris* essential oil was dominated by β-pinene, p-cymene, and α-pinene. In fact, Başar reported that pinenes in volatile oils derived from plants are used widely to treat renal stone disease.

| Scientific plant name | Part used* | Extract | Bioactive compounds | Nephrotoxin used | References |
|-----------------------|------------|---------|---------------------|------------------|------------|
| *Salvia officinalis*   | Aerial parts | Essential oil | Terpenes (β-caryophyllene, limonene and carvacrol) | Vanadium | 45 |
| *Teucrium polium*     | Aerial parts | Aqueous | phenylpropanoid glycosides (verbascoside and poliumoside), flavones (apigenin and its derivatives) and two methoxyflavones | CCl4 | 46 |
| *Trigonella foenum-graecum* | Seeds | Powder | Flavonoid glycosides (vicenin-2, isoschaftoside and isoorientin) | Aluminum chloride | 47 |
|                       | Seeds | Powder | Phenolic compounds (2,5-dihydroxybenzoic acid gallic acid, and vanillin) | Doxorubicin | 49 |
|                       | Fruits | Powder | Oxidative stress | 50 |

*Sientific plant names were followed by references

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|-----------------------|------------|---------|---------------------|------------------|------------|
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|                       | Seeds | Powder | Phenolic compounds (2,5-dihydroxybenzoic acid gallic acid, and vanillin) | Doxorubicin | 49 |
|                       | Fruits | Powder | Oxidative stress | 50 |

*Sientific plant names were followed by references
**Capparis spinosa**

*Capparis spinosa* is a spontaneous xerophyte plant belonging to Capparaceae family, widely found in the Mediterranean. *C. spinosa* is popularly used as a condiment and medicinal plant. It is used in traditional medicine to treat diseases such as gastrointestinal problems, hypertension, anemia, rheumatism, and diabetes. It is also an analgesic, anti-arthritic, antihemorrhoidal, anticancer, anti-inflammatory, depurative, diuretic, emmenagogue, and anti-oxidant. The nephroprotective action of the methanolic *C. spinosa* (200 mg/kg in olive oil) was determined against cisplatin-provoked kidney injury in rats. Pre-treatment with the methanolic extract of *C. spinosa* leaves 7 days before cisplatin exposure and daily thereafter significantly reduced plasma levels of creatinine, urea, and uric acid, reduced malondialdehyde (MDA) levels, and reduced antioxidant enzyme activity of SOD, CAT, and GPx in the kidney and reversed the kidney damage. The leaf of this plant is rich in rutin, resveratrol, coumarin, epicatechin, and luteolin, all of which have been shown to demonstrate protection against cisplatin-induced nephrotoxicity in rats, as reported by Radwan and Fattah for rutin, Valentovic *et al.* for resveratrol, Sen *et al.* for coumarin, Tanabe *et al.* for epicatechin, and Domitrović *et al.* for luteolin.

**Ceratonia siliqua**

*Ceratonia siliqua* is a slow-growth ever-green tree belonging to the Leguminosae family, cultivated for years in the Mediterranean region. *C. siliqua* fruits, brown pods 10–25 cm in length, have traditionally been used as animal and human food. The seed is mainly used for gum extraction. *C. siliqua* pods, bark, and leaves have been used in Tunisian folk medicine as a laxative, diuretic, antidiarrheal, and to treat gastroenteritis of lactating babies. Animals receiving the ethyl acetate extract of *C. siliqua* leaves (250 mg/kg BW) daily by intraperitoneal injection for 8 days followed by a single dose of CCl₄ (1 ml/kg in olive oil) using an intragastric tube after 24 hours of the last dose showed increased levels of urea, creatinine, and LPO with a concomitant decrease in SOD, CAT, and GPx in the kidney. Pretreatment with ethyl acetate extract of *C. siliqua* leaves had a potent nephroprotective effect in accordance with histopathological observations. The leaf extract of this

### Table 2. Effect of Tunisian medicinal plants on different nephrotoxins

| Neprrotoxicity factors | Model nephrotoxin used | Scientific plant name* |
|------------------------|-------------------------|------------------------|
| Pesticides            | Deltamethrin            | *Allium sativum* 13; *Artemisia campestris* 15; *Globularia alypum* 23; *Olea europea* 35 |
|                        | Chlorpyrifos            | *Artemisia campestris* 16 |
|                        | Malathion               | *Lavandula stoechas* 26 |
|                        | Glyphosate              | *Morus alba* 32 |
|                        | Penconazole             | *Nitraria retusa* 33 |
|                        | Acrylamide              | *Olea europea* 34 |
|                        | CCl₄                    | *Ceratonia siliqua* 18; *Lycium europeum* 27; *Mentha peperita* 31; *Rosmarinus officinalis* 44; *Teucrium polium* 46; *Trigonella foenum-graecum* 48 |
| Industrial additives   | Bisphenol A             | *Olea europea* 36 |
|                        | Hydrogen peroxide       | *Euphorbia bivona* 22 |
|                        | Cadmium Sodium          | *Periplaca angustifolia* 40 |
|                        | dichromate              | *Opuntia ficus-indica* 39 |
|                        | Sodium nitrate          | *Hyparrhenia hirta* 25 |
|                        | Vanadium                | *Malva sylvestris* 25; *Salvia officinalis* 45 |
| Drugs                  | Dichloroacetic acid     | *Phoenix dactylifera* 41 |
|                        | Doxorubicin             | *Vitis vinfera* 49 |
|                        | Acetomophen             | *Eucalyptus globules* 21 |
|                        | Aluminum chloride       | *Trigonella foenum-graecum* 47 |
|                        | Aspirin                 | *Citrus limon* 51; *Pinus halepensis* 42 |
|                        | Cisplatin               | *Capparis spinosa* 17; *Eryngium maritimum* 20; *Lycium europaeum* 28; *Rhus tripartitum* 43 |
|                        | Diclofenac              | *Olea europea* 37 |
|                        | Estradiol               | *Artemisia arborescens* 14 |
|                        | Ethanol                 | *Hammada scoparia* 24 |
|                        | Lithium carbonate       | *Opuntia ficus-indica* 38; *Malva sylvestris* 31 |
|                        | Progesterone            | *Artemisia arborescens* 14 |
plant mainly contains syringic acid, myricetin glycosides, and gallic acid derivatives. Sancak et al.78 noted the potential protective effect of syringic acid on kidney ischemia-reperfusion injury. The beneficial effect of myricetin on renal function was reported by Ozcan et al.79 and Asci et al.80 determined the beneficial impact of gallic acid against methotrexate-induced kidney injury in rats.

**Citrus limon**

*Citrus limon* is a medicinal plant of the family Rutaceae found in Tunisia and other Mediterranean countries (Egypt, Italy, Spain and Turkey).81 *C. limon* has been used in folk medicine to treat obesity, diabetes, high lipid, cardiovascular diseases, brain disorders, and some cancer types.82 *C. limon* leaf essential oil (1 ml/kg) was evaluated for its nephroprotective effect against a high dose of aspirin-induced acute kidney damage (600 mg/kg) in rats. *C. limon* essential oil protected against aspirin, showing a decrease in thiobarbituric acid reactive substances (TBARS) and an increase in SOD, CAT, and GPx.83 Limonene is the main component of *C. limon* essential oil fruits, leaves,84 and peels.85 Rehman et al.85 reported the protective role of limonene against doxorubicin-induced renal damage in the treatment of cancer.

**Eryngium maritimum**

*Eryngium maritimum* is a perennial herbaceous halophyte plant belonging to the Apiaceae family, which is widely distributed in dunes and sandy beaches of several Mediterranean countries and the Black Sea, Atlantic, and Baltic coasts. It has been introduced into parts of eastern North America and Australia.86 *E. maritimum* has numerous folk medicinal uses including as a diuretic, kidney stone inhibitor, aphrodisiac, expectorant, anthelmintic, and antitoxic against various infections.87 Increases in serum levels of creatinine, urea, and uric acid caused by cisplatin (13 mg/kg in corn oil) were restored by methanolic *E. maritimum* seed extract (150 mg/kg in corn oil), accompanied by an increase in CAT, SOD and GPx.88 Mejri et al.20 reported that this seed extract was rich in caffeic acid, gallic acid, protocatechuic acid, kaempferol, and luteolin. Matboli et al.89 explained the curative potential of caffeic acid against diabetic kidney disease, and Nabavi et al.89 showed that gallic acid isolated from *Peltiphyllum peltatum* had nephroprotective activity against sodium fluoride-induced kidney damage. Protocatechuic acid was found as a protective agent against cadmium-induced toxicity in the kidney and liver.89 Vijayarapakash et al.89 showed that kaempferol had significant nephroprotective potential against mercuric chloride-induced nephrotoxicity in rats. Luteolin was also found to be effective against cisplatin-induced nephrotoxicity in mice.89

**Eucalyptus globulus**

*Eucalyptus globulus* is a very common tree throughout the world belonging to the Myrtaceae family. Its leaves, bark, and fruit have been traditionally used as remedies to treat inflammation and promote wound healing.53 *E. globules* treatment has been shown to effectively protect against acetaminophen-provoked nephrotoxicity in mice by restoring SOD, CAT, and GPx levels. The nutraceutical advantage of *E. globulus* extract is attributed to its flavonoid, flavonol, and phenolic compounds.53 Ferreira et al.53 found that *E. globulus* leaves were rich in rutin, ellagic acid derivatives, quercetin 3-glucuronide, and chlorogenic acid, which have all been investigated for their nephroprotective effects.58,84–96

**Euphorbia bivonae**

*Euphorbia bivonae* is an herbaceous plant belonging to the Euphorbiaceae family and is widespread in the coastal areas of the Mediterranean basin.97 *E. bivonae* has several biological properties, including antiproliferative,98 anti-oxidant, nephroprotective,22 and hepatoprotective effects. Athmouni et al.99 evaluated the preventive action of *E. bivonae* leaf polysaccharides against hydrogen peroxide (H2O2)‐induced toxicity in human embryonic kidney (HEK293) cells. Results revealed that H2O2‐exposure induced a significant increase in intracellular reactive oxygen species and lipid peroxidation in HEK293 cells. However, *E. bivonae* polysaccharide pretreated cells (100 µg/mL) significantly enhanced the anti-oxidant status (SOD, CAT, GPx, and GSH) of HEK293 cells that was decreased after H2O2 exposure. Accordingly, the HEK293 cells pretreated with *E. bivonae* polysaccharide compounds had enhanced cell viability following H2O2 exposure. Polysaccharide analysis showed the richness of *E. bivonae* in seven monosaccharides: succharose, arabinose, inositol, glucose, pyranose, trehalose, and fructose.

**Globularia alumb**

*Globularia alumb* is a perennial shrub plant belonging to the Globulariaceae family, widely distributed in the Mediterranean area and largely used for its therapeutic virtues.100 *G. alumb* species are known for their medicinal properties.101 *G. alumb* is commonly used as a hypoglycaemic, laxative, cholagogue, stomachic, and purgative agent, as well as in the treatment of renal disease.23 The protective effect of methanol extract from *G. alumb* leaves (400 mg/kg in corn oil) against the nephrotoxicity induced by a chronic exposure to deltamethrin (4 mg/kg in corn oil) has been studied in rats. Deltamethrin administration provoked kidney damage, and treatment with *G. alumb* leaf extract restored plasma creatinine, urea, and uric acid levels and reduced the elevated MDA and PC levels. *G. alumb* leaf extract has been shown to restore renal activity in accordance with histopathological observations owing to its bioactive compounds.102 *G. alumb* leaf extract is rich mainly in globularin (60.31%). Merghache et al.103 isolated this phenolic compound and determined its antidiabetic and antilipidemic capacities in normal and streptozotocin-induced diabetic rats.

**Hammada scoparia**

*Hammada scoparia* is a small highly-branched halophytic shrub belonging to the Chenopodiaceae family. It is widely used in North African traditional medicine to prevent several diseases such as cancer, hepatitis, inflammation, and obesity. The methanol extract of *H. scoparia* leaves (200 mg/kg/day) was evaluated for its renoprotective effect against ethanol-induced (4 g/kg) renal dysfunction in rats. *H. scoparia* extract attenuated the increase of TBARS in kidneys, and enhanced the anti-oxidant status of rats by increasing the levels of SOD, CAT, and GPx. The overexpression of glycogen synthase kinase–3β and proline–rich tyrosine kinase 2 in kidneys of ethanol–treated rats was normalized after *H. scoparia* extract treatment.24 *H. scoparia* leaf extract is rich in alkaloids (carnegine and N-methylisalsolsoline) and flavonoids (isorhamnetin triglycerides), as reported by Bourouga et al.104 and Ben Salah et al.105 Qiu et al.106 determined the potential renoprotective effects of isorhamnetin in a type 2 diabetic rat model.
Hyparrhenia hirta

Hyparrhenia hirta is a perennial grass belonging to the Poaceae family. It is native to the southern Africa and Mediterranean regions. It is used in traditional medicine for its diuretic properties. Bouaziz et al. studied the nephroprotective effect of methanolic extract from H. hirta aerial parts (200 mg/kg in corn oil) against sodium nitrate-induced kidney (400 mg/kg in corn oil) dysfunction. Sodium nitrate-mediated oxidative stress in kidneys is characterized by enhanced lipid peroxidation and reduced CAT, SOD, and GPx activity. Renal damage was histologically characterized by degeneration of renal tubule cells and mononuclear cell infiltration. A reversal of anti-oxidant enzymes and peroxidative damage in kidneys by H. hirta extract has been attributed to its anti-oxidant and anti-peroxidative properties and its role as a scavenger of free radicals, which could be due to its flavonoid content, namely apigenin, quercetin, and luteolin derivatives. The potent nephroprotective effect of apigenin, quercetin, and luteolin was determined against cisplatin-induced nephrotoxicity in rats.

Lavandula stoechas

Lavandula stoechas is a medicinal plant belonging to the Lamiaceae family. Selmi et al. investigated the nephroprotective activity of L. stoechas aerial part essential oil (10, 30, and 50 mg/kg) against malathion-induced (200 mg/kg) oxidative stress in mice. Malathion treatment decreased body weight and perturbated metabolic parameters. However, L. stoechas essential oil abolished all malathion-induced body gain loss and kidney relative weight dysfunction. The essential oils also contain smaller percentages of tri-cyclene, cymene, α-cadinene, and selina-3,7(11)-diene. These molecules are the prime anti-oxidant source of this plant, and underlie its ability to scavenge free radicals, which are the major cause of lipid peroxidation.

Lycium europaeum

L. europaeum is a spiny shrub belonging to the Solonacea Family and is dispersed throughout all countries in the Mediterranean basin. It has been used in numerous traditional remedies for skin burning, rheumatic pain, constipation, hypertension, infectious ailments, and kidney and liver disorders. Cisplatin treatment has been shown to significantly augment serum levels of urea, creatinine, uric acid, and blood urea nitrogen in mice. L. europaeum leaf polysaccharide has been shown to reduce these renal biochemical parameters. Similar results were observed for the methanol extract from L. europaeum leaves on kidney injury induced by cisplatin and by CCl4. L. europaeum leaf extract is rich in caffeic acid, gallic acid, naringenin, epicatechin, vanillic acid, rutin, and coumaric acid. Its nephroprotective activity against cisplatin has been attributed to caffeic acid phenethyl ester, gallic acid, naringenin, epicatechin, vanillic acid, rutin, and p-coumaric acid.

Malva sylvestris

Malva sylvestris is a common mallow belonging to the Malvaceae family. This plant is native to Europe, Asia, and North Africa, and its medicinal applications include its use as a diuretic, laxative, spasmyloytic, lenitive, and choleretic. Malva sylvestris is also used as bronchodilator, expectorant, antitussive, and anti-diarrheal, and has been highly recommended for acne and skin care, and as an antiseptic, emollient, and demulcent. The decoction of M. sylvestris leaves and flowers was investigated for its nephroprotective action against vanadium-induced kidney damage in rats. For 90 days, rats were given 0.2 g dw/kg BW of M. sylvestris decoction and 0.24 mmol/kg BW of vanadium in drinking water. Results showed that vanadium poisoning resulted in a significant increase in the formation of free radicals and anti-oxidant enzymes (SOD, CAT, and GPX) in the kidney. However, treatment with M. sylvestris decoction restored lipid peroxidation levels, anti-oxidant enzymes activities, and histological features, which appeared normal compared to control rats. The beneficial effects of M. sylvestris leaf extract (0.2 g/kg) were also observed against lithium carbonate-induced (25 mg/kg) renal damage in rats. As reported by Ben Saad et al., the protective properties of M. sylvestris extract could be related to its rich make-up of phenolic acids (epicatechin acid, gallic acid, coumaric acid, vanillic acid, and catechic acid) and flavonoids (rutin, kaempferol, quercetin, and luteolin). In fact, potent nephroprotective effects of gallic acid, p-coumaric acid, vanillic acid, rutin, kaempferol, quercetin, and luteolin were found against several kidney toxicities in rats.

Mentha peperita

Mentha peperita is a native genus of the Mediterranean region belonging to the Lamiaceae family. It is widely used in food and in traditional medicine. Bellassoued et al. investigated M. peperita leaf essential oil for its nephroprotective action against CCl4-induced renal failure in rats. M. peperita leaf essential oil was orally administrated for 7 consecutive days (5, 15, 40 mg/kg BW) to rats prior to CCl4 (1 ml/kg BW) intraperitoneal treatment. Results showed that pretreatment with M. peperita leaf essential oil at 15 and 40 mg/kg prior to CCl4 significantly reduced stress parameters (urea and creatinine). A significant reduction in kidney lipid peroxidation (TBARS) and an increase in anti-oxidant enzymes (SOD, CAT, and GPx) were also observed after treatment with M. peperita leaf essential oil (40 mg/kg) compared to CCl4-treated rats. Furthermore, pretreatment with M. peperita leaf essential oil at 40 mg/kg markedly ameliorated the histopathological hepatic and kidney lesions induced by CCl4. M. peperita leaf essential oil contains active ingredients including menthol and iso-menthol. These two compounds exhibit a potent anti-inflammatory activity, indicating that M. peperita leaf essential oil could be a promising natural product against CCl4-induced oxidative damage in the kidney, consistent with that reported by Bellassoued et al.

Morus alba

The leaves of M. alba of the Moraceae family, commonly known as mulberry, are mainly used as food for silk worms and are sometimes used as cattle fodder in different parts of the world. The infusion and decoction of leaves have been used to prevent or treat urinary disorders. The aqueous acetonic extract of M. alba leaves (100 mg/kg) was studied against glycosphate-induced (100 mg/kg) kidney injury in mice. Renal oxidative stress induced by glycosphate was evidenced by an increase in MDA and protein carbonyl levels and a decline in SOD activity. M. alba leaf extract appeared to modulate these altered biochemical parameters by maintaining free iron and Ca2+ homeostasis, as well as regulate en-
Oleuropein (50 mg/kg BW), has been shown to protect against fruit (200 mg/kg BW) and its phenolic compound, gated acrylamide-induced nephrotoxicity. Ethanolic extract from deacetylated oleuropein and hydroxytyrosol extracted from Tunisian olive leaf caused kidney injury.\textsuperscript{33} N. retusa treatment provoked a significant decrease in the levels of MDA, H$_2$O$_2$, protein carbonyl and advanced oxidation protein products, as well as improved alkaline phosphatase (ALP) and gamma glutamyltranspeptidase activities. Polyphenol constituents of N. retusa fruit aqueous extract could enhance their anti-oxidant activities in nephroprotection. N. retusa fruit extract mainly contains hydroxycaffeic acid, epicatechin derivatives, p-coumaric acid, cyanidin derivative, 3-O-methylgallic acid, taxifoline, chlorogenic acid, and kaempferol derivative. Among these phenolics, chlorogenic acid,\textsuperscript{96} p-coumaric acid,\textsuperscript{119} caffeic acid,\textsuperscript{98} gallic acid,\textsuperscript{118} and kaempferol\textsuperscript{110} are known for their potent nephroprotection.

Olea europea

Olea europea is a known olive tree belonging to the Oleaceae family. It represents a great economic and social importance owing mainly to the great value of olive oil. This olive oil is the primary source of fat in the Mediterranean diet, which has been associated with low mortality related to cardiovascular disease.\textsuperscript{126} Ghorbel et al.\textsuperscript{34} found that extra virgin olive oil abrogated acrylamide-induced nephrotoxicity. Ethanolic extract from \textit{O. europea} fruit (200 mg/kg BW) and its phenolic compound, oleuropein (50 mg/kg BW), has been shown to protect against nephrotoxicity caused by deltamethrin (15 mg/kg bw) in rats.\textsuperscript{35} Deltamethrin administration can increase MDA levels and reduce SOD and CAT activities. \textit{O. europea} fruit and oleuropein have been used as treatments for inflammation and apoptosis. Oleuropein, verbascoside, luteolin-7-glucoside, apigenin-7-glucoside, and hydroxytyrosol are the main components of the ethanolic extract from \textit{O. europea} fruit.\textsuperscript{38} The nephroprotective effect of oleuropein and hydroxytyrosol extracted from Tunisian olive leaf extract have been investigated in rats treated with bisphenol A.\textsuperscript{36} In recent study, Soussi et al.\textsuperscript{37} found that the aqueous extract of Tunisian \textit{O. europaea} leaves protected against kidney damage induced by diethylnor in mice.

Opuntia ficus-indica

\textit{Opuntia ficus-indica} is a plant popularly known as prickly pear belonging to the Cactaceae family. It is widely distributed in the Mediterranean area, Mexico, and South Africa, and is widely known because of its nutritional and medicinal usage.\textsuperscript{127} Administration of lithium carbonate (25 mg/kg BW) has been shown to cause a significant increase in serum creatinine, uric acid, and urea levels. Additionally, a significant decrease in SOD, CAT, and GPx activities was associated with a significant increase in MDA levels. However, treatment with \textit{O. ficus indica} extract (100 mg/kg BW) prevented these alterations and maintained the anti-oxidant status in rats. Histopathological observations support this biochemical evidence of nephroprotection.\textsuperscript{38} Similar results were obtained for the aqueous extract from \textit{O. ficus-indica} cladodes on kidney injury induced by sodium dichromate.\textsuperscript{39} As reported by Saad et al.,\textsuperscript{38} the aqueous extract from \textit{O. ficus-indica} cladodes was characterized by the presence of quercetin, vanillic acid, gallic acid, rutin, kaempferol, catechin, epicatechin, coumarin,isorhamnetin, and caffeic acid. All of these phenolic compounds have been well studied for their potent nephroprotection, particularly quercetin,\textsuperscript{61} vanillic acid,\textsuperscript{56} gallic acid,\textsuperscript{118} rutin,\textsuperscript{58} kaempferol,\textsuperscript{91} catechin,\textsuperscript{128} epicatechin,\textsuperscript{45} coumarin,\textsuperscript{57} isorhamnetin,\textsuperscript{106} and caffeic acid.\textsuperscript{38}

Periploca angustifolia

\textit{Periploca angustifolia} evergreen shrub is a member of the APOYACEAE family. It is found wild in North Africa (from Morocco to Egypt), southern Spain, Sicily, Malta, Crete, Lebanon, and Syria. \textit{P. angustifolia} is used in traditional medicine for diabetes, rheumatism, hemorrhoids, and gastric ulcer.\textsuperscript{125} The preventive action of polysaccharides isolated from \textit{P. angustifolia} leaves against cadmium-caused oxidative stress in kidneys of rats has been tested. Results indicated that cadmium treatment increased the levels of urea and creatinine in the serum. The increased levels of protein oxidation and lipid peroxidation along with decreased activities of SOD, CAT and GPx were ameliorated by \textit{P. angustifolia} polysaccharides pre-treatment. Histopathological studies also supported the prevention action of \textit{P. angustifolia} polysaccharides. Saccharose is the major monosaccharide component of \textit{P. angustifolia} leaves, followed by trehalose, L-inositol, and M-inositol, as reported by Athmouni et al.\textsuperscript{50}

Phoenix dactylifera

\textit{Phoenix dactylifera} is a tree commonly known as date palm belonging to the Arecaceae family. \textit{P. dactylifera} is mostly cultivated for the consumption of its fruit, which has been utilized since ancient times as an important staple food and in ethnomedicine in different parts of the world.\textsuperscript{130} The fruit of \textit{P. dactylifera} is used as a det expressive and astringent for intestinal ailments, treatment for sore throat, colds, bronchial asthma, to relieve fever, cystitis, gonorrhea, edema, liver and abdominal ailments, and to counteract alcohol intoxication.\textsuperscript{131} Dichloroacetic acid administration (2 g/l) caused augmentation of renal MDA levels and significant diminution of GSH levels. Moreover, dichloroacetic acid altered the anti-oxidant enzyme activities and deteriorated renal function, as assessed by increased plasma urea, uric acid, and creatinine levels. Treatment with \textit{P. dactylifera} extract (4 ml/kg) significantly normalized the plasma levels of creatinine, urea, and uric acid, reduced the MDA levels, significantly normalized anti-oxidant enzyme activities and GSH levels, and restored the kidney histology in rats.\textsuperscript{41} Therefore, it has been speculated that \textit{P. dactylifera} extract protects rats from kidney damage through its anti-oxidant capacity attributed to make-up of phenolic acids, mainly ferulic, caffeic, and \textit{p-coumaric} acids.\textsuperscript{41} In fact, ferulic,\textsuperscript{132} caffeic,\textsuperscript{38} and \textit{p-coumaric} acids\textsuperscript{119} are known for their efficient nephroprotective action.

Pinus halepensis

\textit{Pinus halepensis} is a tree belonging to the Pinaceae family found around the Mediterranean basin. The resin and decoction of all \textit{Pinus} species have antiseptic, diuretic, rubefacient, vermifuge, anti-diabetic, and cicatrisant properties.\textsuperscript{133} Bouzenna et al.\textsuperscript{42} studied the protective effect of essential oil from \textit{P. halepensis} needles
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on aspirin-induced acute kidney damage in rats. Rats were orally treated with *P. halepensis* essential oil (1 ml/kg) for 56 days and then given aspirin (600 mg/kg) orally thrice a day at an interval of 4 h for 4 successive days. Results showed that aspirin induced an increase in serum biochemical parameters as well as oxidative stress in kidney. There was an increase in TBARS and a decrease in SOD, CAT, and GPx in kidney. Administration of *P. halepensis* essential oil corrected these parameters. Hamrouni et al.\textsuperscript{134} found that the essential oil of Tunisian *P. halepensis* needles was characterized by the predominance of monoterpenic hydrocarbons, mainly β-caryophyllene, β-myrcene and α-pinene. These volatile compounds could interact to protect against aspirin-induced nephrotoxicity.

**Rhus tripartitum**

*Rhus tripartitum* is a dioecious shrub belonging to the Anacardiaceae family.\textsuperscript{135} *R. tripartitum* is widely used to treat many diseases such as diarrhea and dysentery, colitis, gastrointestinal diseases, inflammatory diseases, diabetes, haemoptysis, conjunctivitis, animal bites and poisons, hemorrhoids, sexual disease, fever, pain, and various cancers. Tili et al.\textsuperscript{43} investigated the protective action of methanolic extract from *R. tripartitum* fruit (200 mg/kg in olive oil) against cisplatin-induced (13 mg/kg) nephrotoxicity in rats. The increased levels of biochemical parameters (creatinine, urea, and uric acid) were attenuated by pretreatment with *R. tripartitum* fruit extract. Histopathological observation showed that pretreatment with *R. tripartitum* fruit extract restored the pathology. These results could be due to the richness of *R. tripartitum* fruit extract in phenolics, especially betulonic acid. In fact, the efficient renoprotective effects of betulonic acid isolated from *Coronus walteri* in cisplatin-provoked renal toxicity were determined by Lee et al.\textsuperscript{136}

**Rosmarinus officinalis**

Rosmarinus officinalis, commonly known as rosemary is a perennial, aromatic medicinal plant belonging to the Lamiaceae family. It is shrub-shaped with branches full of leaves, exuding a characteristic fragrance.\textsuperscript{137} One study evaluates the effects of aqueous extract from *R. officinalis* leaves against kidney toxicity induced by CCl\textsubscript{4} in mice. Results showed that the renal damage induced by CCl\textsubscript{4} was associated with a rise in oxidative stress, an increase of TBARS, and changes the nephropathology parameters including creatinine, blood urea nitrogen, and urea. However, a decrease in GSH levels and anti-oxidant enzymes (SOD, CAT, and GPx) was observed. These findings were substantiated by histological analysis. Pretreatment with *R. officinalis* leaf extract attenuated CCl\textsubscript{4}-related toxic effects. The polyphenolic profile of Tunisian *R. officinalis* leaf extract is characterized by its richness in carnosic and rosmarinic acids.\textsuperscript{138} The potent nephroprotective effects of carnosic and rosmarinic acids were observed in cisplatin-induced nephrotoxicity in rats.

**Salvia officinalis**

*Salvia officinalis*, popularly known as sage, is a member of the Lamiaceae family. It is an aromatic plant widely distributed in the world. Since ancient times, *S. officinalis* has been an ingredient in perfumes, a flavoring in a variety of food preparations,\textsuperscript{141} and a medicinal plant used to fight fever, rheumatism, perspiration, sexual malfunction, chronic bronchitis, and various mental diseases. Koubaa et al.\textsuperscript{45} evaluated the impact of the essential oil from *S. officinalias* aerial parts (15 mg/kgBW) on renal nephrotoxicity induced by vanadium (5 mg/kg BW) in rats. A marked increase in LPO and PCO levels with a significant decrease in SOD, CAT, and GPx. However, the administration of *S. officinalis* essential oil significantly restored these biochemical markers and pathological lesions. This protective effect seems to be due to the richness of *S. officinalis* essential oil in β-caryophyllene, limonene, carvacrol, caryophyllene, borneol, α-pinene, and α-thujene, as reported by Koubaa et al.\textsuperscript{45} Horváth et al.\textsuperscript{43} found that β-caryophyllene ameliorated cisplatin-induced nephrotoxicity. Rehman et al.\textsuperscript{45} reported the protective role of limonene against renal damage induced by the anticancer drug doxorubicin. The protective effect of carvacrol on renal function in gentamicin-induced nephrotoxicity in rats was determined by Ahmadvand et al.\textsuperscript{144}

**Teucrium polium**

*Teucrium polium* is defined as golden germander belonging to the Lamiaceae family. It has been used to treat abdominal pain, indigestion, and diabetes. The aqueous extract of *T. polium* aerial parts (5 g/l) was investigated against CCl\textsubscript{4}-induced (0.5 ml/kg) nephrotoxicity in rats. CCl\textsubscript{4} treatment increase serum renal markers (urea and creatinine) and lipid peroxidation and decreased anti-oxidant enzymes (SOD, CAT and GPx). However, pretreatment with *T. polium* extract protected against oxidative damage and biochemical changes induced by CCl\textsubscript{4}, which were validated by histopathological observations.\textsuperscript{49} According to Goulas et al.\textsuperscript{145} *T. polium* aerial part extract is characterized by the presence of phenylpropanoid glycosides (verbascoside and poliomyloside), flavones (apigenin and its derivatives), and two methoxyflavones, with poliomyloside being the most abundant and active component of *T. polium* extract.

**Trigonella foenum-graecum**

*Trigonella foenum-graecum* is an annual herb popularly known as fenugreek that belongs to the Leguminosae family. It is native to an area extending from Iran to northern India and widely cultivated in China, India, Egypt, Ethiopia, Morocco, Ukraine, Greece, and Turkey.\textsuperscript{146} It is an ancient traditional medicinal plant due to its olfactory, antifever, anti-inflammatory, antimicrobial, anticancer, anti-diabetic, anti-hyperglycemic, laxative, galactagogue, and digestive effects. Belalid-Nouira et al.\textsuperscript{47} evaluated fenugreek seeds (5% in the diet) for their effects on rat nephrotoxicity caused by aluminum chloride (500 mg/kg BW for one month then 1,600 ppm via drinking water). Aluminum chloride inhibited ALP, decreased total antioxidant status, and an induced LPO in the blood and brain. Treatment with fenugreek seed powder helped to restore normal plasma values of urea, creatinine, ALP, and glucose, as well as increased the total antioxidant status, inhibited LPO, and alleviated histopathological changes in the injured kidney. Belguith-Hadrich et al.\textsuperscript{48} also determined the potent renoprotective action of fenugreek seeds on renal oxidative stress and nephropathy caused by a high cholesterol diet in rats. Mbariki et al.\textsuperscript{48} noted that fenugreek seed supplementation protected the kidney from CCl\textsubscript{4}-induced oxidative stress and toxicity in rats. According to Beláí-Nouira et al.\textsuperscript{47} Belguith-Hadrich et al.\textsuperscript{48} and Mbariki et al.\textsuperscript{48} the anti-oxidant activity of fenugreek seeds could be attributed to polyphenols, particularly flavonoids. Three flavonoid glycosides were detected in methanol extract from the fenugreek seed extract: vicenin-2, isoschaftoside, and isoorientin.\textsuperscript{149}
Vitis vinifera

Vitis vinifera is a perennial, woody climbing grapevine belonging to the Vitaceae family. It is indigenous to southern Europe and western Asia and is cultivated today in all temperature regions of the world.\(^ \text{150} \) Grape seeds contain 6–20\% oil, used for edible purposes, soaps, and as a linseed substitute. A malagma made from the seed is a folk remedy for condylomata of the joints. Leaves astringent and counteracted almost all adverse effects induced by doxorubicin. Turkı et al.\(^ \text{50} \) evaluated the protective effect of the ethanol extract from V. vinifera seeds and skin against doxorubicin-induced renal toxicity in rats. Animals were treated with the ethanol extract from V. vinifera seeds and skin for 8 days and administered doxorubicin (20 mg/kg) 4 days later. Results showed that doxorubicin induced renal toxicity by affecting the renal architecture and plasma creatinine. Doxorubicin also induced oxidative stress characterized by an increase in MDA, calcium, and H2O2 and a decrease in CAT and SOD. Unexpectedly, doxorubicin increased peroxidase and decreased carbonyl protein and plasma urea. Treatment with V. vinifera extract counteracted almost all adverse effects induced by doxorubicin. Turkı et al.\(^ \text{50} \) conducted an investigation of supplementation with grape seed extract capsules (2 g GSE/day) or placebo on chronic kidney disease patients for 6 months. Grape seed ameliorated inflammation by decreasing C-reactive protein and triglyceridemia and counteracted anemia and thrombocytopenia. Grape seed extract is a polyphenolic mixture exhibiting anti-oxidant and anti-inflammatory properties as reported by Turkı et al.\(^ \text{50} \). According to Mokni et al.\(^ \text{40} \), the main compound of grape seed and skin extracts are 2,5-dihydroxybenzoic acid, gallic acid, and vanillin. Among these phenolic compounds, gallic acid\(^ \text{118} \) and vanillin\(^ \text{152} \) have been well studied for their potent nephroprotection.

Future directions

Research on Tunisian nephroprotective plants has been mainly done in a laboratory setting with a limited number of animals. Thus, additional studies must be done with a greater number of experiments, different animal models, and human subjects. It should be mentioned that this is the first review that summarizes several reports on Tunisian nephroprotective plants. The literature demonstrates that these plants contain bioactive compounds that could be used to treat kidney disease. This review may be valuable to health professionals, scientists, and scholars working in the field of pharmacology and therapeutics to produce new safety drug formulations to treat kidney diseases.

Conclusions

In this review, 29 Tunisian medicinal plants were summarized for their significant nephroprotective activities against renal toxicities in animal models. Lamium family was the most commonly used nephroprotective Tunisian plant. Leaves were maximally used for nephroprotection compared to the other plant parts. In the case of Indian nephroprotective plants, Asif\(^ \text{153} \) also reported that the leaves were most frequently used in the treatment of nephrotoxicity, with the most dominant family being Euphorbiaceae. In this review, most studies focused on drug-induced renal failure, which is a major challenge in medical practice. Other studies focused on other important nephrotoxicity factors, including industrial chemicals, particularly CCl4, induce nephrotoxicity. In general, CCl4 enhanced levels of renal markers (urea and creatinine) in the serum of experimental animals. It also increased oxidative stress markers resulting in increased LPO with a concomitant decrease in SOD, CAT, and GPx in the kidney. To protect against this nephrotoxicity, some medicinal plants, have curative properties attributed to various complex chemical substances as organosulfur compounds, polyphenols, polysaccharides, phenylpropanoids, terpenes, and alkaloids.

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Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Conceptualization (WAW); writing (WAW); methodology (WAW); formal analysis (WAW); data curation (WAW); supervision (MST); writing, review, and editing (WAW). All authors have read and agreed to the published version of the manuscript.

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