Journal of Exploratory Research in Pharmacology **2023** vol. 8(1) | 74–91
DOI: 10.14218/JERP.2022.00031

Review Article

Tunisian Nephroprotective Plants: A Review

Wissem Aidi Wannes* and Moufida Saidani Tounsi

Laboratory of Aromatic and Medicinal Plants, Biotechnologic Center Borj-Cedria Technopark, Hammam-Lif, Tunisia

Received: April 03, 2022 | **Revised:** May 31, 2022 | **Accepted:** July 25, 2022 | **Published online:** September 21, 2022

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. Nephrotoxicity is commonly the result of several nephrotoxins. 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.[1]

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.[2] Kidney disease is the ninth leading cause of death,[3] and patients with kidney disease have significant morbidity and mortality.[4]

The number of patients presenting with kidney disorders is increasing at an alarming rate.[5] 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.[3]

Nephrotoxicity is one of the most common kidney problems induced by drugs or toxins.[6] 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.[3] In addition to drugs, other factors can lead to acute renal failure, such as age, diabetes, hypertension, liver disease, and oliguria.[5] 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.[7] Previously, Tunisian medicinal plants have been used to treat diabetes,[8] ulcer,[9] cancer[10], liver,[11] and coronavirus[12] illnesses. In this review, we highlighted the current literature focused on Tunisian nephroprotective plants.

We searched the PubMed, Scientific Information Database, Sco-

Keywords: Nephroprotective effect; Kidney; Renal failure; Toxicity; Medicinal plants; Tunisia.

Abbreviations: ALP, alkaline phosphatase; CAT, catalase; CCl_4, carbon tetrachloride; GPx, glutathione peroxidase; GSH, reduced glutathione; H_2O_2, hydrogen peroxide; LPO, lipid peroxidase; MDA, malondialdehyde; PCO, protein carbonyl; ROS, reactive oxygen species; SOD, superoxide dismutase.

***Correspondence to:** Wissem Aidi Wannes, Laboratory of Aromatic and Medicinal Plants, Biotechnologic Center Borj-Cedria Technopark, BP 901, 2050, Hammam-lif, Tunisia. ORCID: https://orcid.org/0000-0003-3134-0457. Tel: +21679325738, Fax: 2167941263, E-mail: aidiwissem@yahoo.fr

How to cite this article: Wannes WA, Tounsi MS. Tunisian Nephroprotective Plants: A Review. *J Explor Res Pharmacol* 2023;8(1):74–91. doi: 10.14218/JERP.2022.00031.

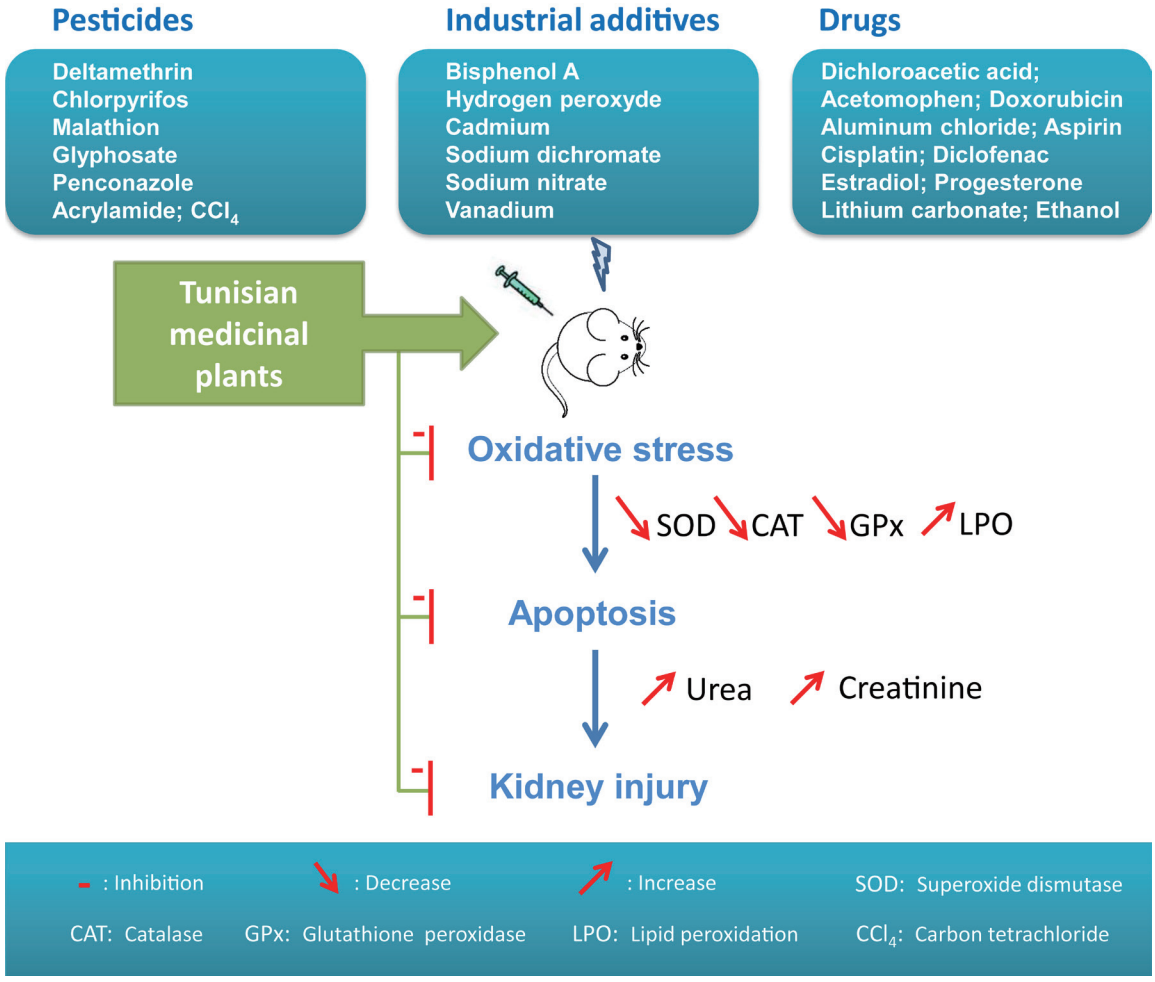


Fig. 1. A diagram illustrating the proposed nephroprotective mechanism of Tunisian medicinal plants against nephrotoxins.

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 nephroprotectve 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, antihyperlipidemic, antidiabetic, antihypertension, antistress, anticancer, antiviral, antibacterial, antifungal, anti-oxidant, and dermatologic properties.[52] Ncir *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 allicin 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

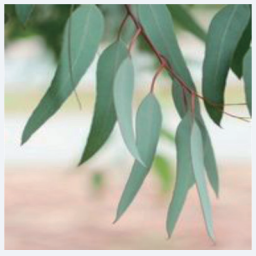
Artemisia arborescens is a perennial evergreen woody shrub belonging to the family of Asteraceae.[54] *A. arborescens* is a widely used traditional medicine that possesses ethnomedical and biological benefits.[55] The beneficial effects of the aqueous ethanol extract from *A. arborscens* leaves (200 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, cinamic 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 Chlorpyrifos	15 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)

Table 1. *(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		Monosaccharides (saccharose, arabinose, inositol, glucose, pyranose, trehalose and fructose)	Hydrogen peroxide	22
 *Globularia alypum*	Leaves	Methanol	Phenolic compound (globularin)	Deltamethrin	23

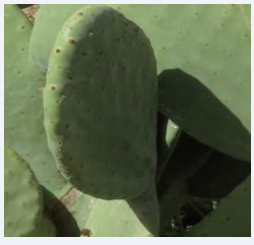
(continued)

Table 1. *(continued)*

Scientific plant name	Part used*	Extract	Bioactive compounds	Nephrotoxin used	References
 *Hammada scoparia*	Leaves	Methanol	Alkaloids (carnegine 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*	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 Methanol	Phenolic compounds (gallic acid, p-coumaric acid, vanillic acid, rutin, kaempferol, quercetin and luteolin)	Vanadium Lithium carbonate	29 30

(continued)

Table 1. *(continued)*

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 Leaves Fruits	Oil Aqueous Ethanol	Phenolic compounds (oleuropein and hydroxytyrosol)	Acrylamide Deltamethrin Bisphenol A Diclofenac	34 35 36 37
 *Opuntia ficus-indica*	Cladodes	Aqueous	Phenolic compounds quercetin, vanillic acid, gallic acid, rutin, kaempferol, catechin, epicatechin, coumarin, isorhamnetin and caffeic acid)	Lithium carbonate Sodium dichromate	38 39

(continued)

Table 1. *(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)

Table 1. *(continued)*

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 CCl4	47 48
 *Vitis vinifera*	Seeds/Skin Fruits	Ethanol Powder	Phenolic compounds (2,5-dihydroxybenzoïc acid gallic acid, and vanillin)	Doxorubicin Oxidative stress	49 50

*Sientific plant names were followed by references

the potent nephroprotective effect of vanillic acid,[56] coumarin,[57] rutin,[58] and luteolin[59] was determined against cisplatin-induced nephrotoxicity in rats. Additionally, the renal protective potential of naringeninn[60] and quercetin[61] 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.[62] Saoudi *et al*.[15] 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 anti-oxidant potential. Similar results were obtained by Saoudi *et al*.[16] who determined the protective effect of *A. campestris* essential oil against chlorpyrifos-induced kidney injury in rats. Akrout *et al*.[63] found that *A. campestris* essential oil was dominated by β-pinene, *p*-cymene, and α-pinene. In fact, Başar[64] reported that pinenes in volatile oils derived from plants are used widely to treat renal stone disease.

Table 2. Effect of Tunisian medicinal plants on different nephrotoxins

Nephrotoxicity 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]
	CCl_4	*Ceratonia siliqua* [18]; *Lycium europaeum* [27]; *Mentha peperita* [31]; *Rosmarinus officinalis* [44]; *Teucrium polium* [46]; *Trigonella foenum-graecum* [48]
Industrial additives	Bisphenol A	*Olea europea* [36]
	Hydrogen peroxyde	*Euphorbia bivonae* [22]
	Cadmium Sodium	*Periploca angustifolia* [40]
	dichromate	*Opuntia ficus-indica* [39]
	Sodium nitrate	*Hyparrhenia hirta* [25]
	Vanadium	*Malva sylvestris* [29]; *Salvia officinalis* [45]
Drugs	Dichloroacetic acid	*Phoenix dactylifera* [41]
	Doxorubicin	*Vitis vinifera* [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]

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[65] and medicinal plant.[66] It is used in traditional medicine to treat diseases such as gastrointestinal problems, hypertension, anemia,[67] rheumatism,[68] and diabetes.[69] It is also an analgesic, anti-arthritic,[70] antihemorrhoidal, anticancer,[71] anti-inflammatory,[72] depurative, diuretic,[73] emmenagogue, and anti-oxidant.[74] The nephroprotective action of the methanolic *C. spinosa* (200 mg/kg in olive oil) was determined against cisplatin-provoked (13 mg/kg in olive oil) 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.[17] The leaf of this plant is rich in rutin, resveratrol, coumarin, epicatechin, and luteolin,[73] all of which have been shown to demonstrate protection against cisplatin-induced nephrotoxicity in rats, as reported by Radwan and Fattah[58] for rutin, Valentovic *et al*.[75] for resveratrol, Sen *et al*.[57] for coumarin, Tanabe *et al*.[76] for epicatechin, and Domitrović *et al*.[59] 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.[77] 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 CCl_4 (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

plant mainly contains syringic acid, myricetin glycosides, and gallic acid derivatives.[18] Sancak *et al*.[78] noted the potent 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.[51] *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.[82] Limonene is the main component of *C. limon* essential oil fruits,[82] leaves,[83] and peels.[84] 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 antitoxin 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.[20] Mejri *et al*.[20] reported that this seed extract was rich in caffeic acid, gallic acid, protocatechuic acid, kaempferol, and luteolin. Matboli *et al*.[88] 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.[90] Vijayaprakash *et al*.[91] 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 .[59]

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.[92] *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.[21] Ferreira *et al*.[93] 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.[58,94–96]

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[99] effects. Athmouni *et al*.[22] evaluated the preventive action of *E. bivonae* leaf polysaccharides against hydrogen peroxide (H_2O_2)-induced toxicity in human embryonic kidney (HEK293) cells. Results revealed that H_2O_2-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 H_2O_2 exposure. Accordingly, the HEK293 cells pretreated with *E. bivonae* polysaccharide compounds had enhanced cell viability following H_2O_2 exposure. Polysaccharide analysis showed the richness of *E. bivonae* in seven monosaccharides: saccharose, arabinose, inositol, glucose, pyranose, trehalose, and fructose.

Globularia alubum

Globularia alubum 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. alubum* species are known for their medicinal properties.[101] *G. alypum* 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. alypum* 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 kideney damage, and treatment with *G. alypum* leaf extract restored plasma creatinine, urea, and uric acid levels and reduced the elevated MDA and PC levels. *G. alypum* leaf extract has been shown to restore renal activity in accordance with histopathological observations owing to its bioactive compounds.[102] *G. alypum* 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 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-methylisosalsoline) and flavonoids (isorhamnetin triglycerides), as reported by Bourogaa *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.[107] *H. hirta* is used in traditional medicine for its diuretic properties.[108] Bouaziz *et al*.[25] 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 antiperoxidative properties and its role as a scavenger of free radicals, which could be due to its flavonoid content, namely apigenin, quercetin, and luteolin derivatives.[109] The potent nephroprotective effect of apigenin,[110] quercetin,[111] and luteolin[59] was determined against cisplatin-induced nephrotoxicity in rats.

Lavandula stoechas

Lavandula stoechas is a medicinal plant belonging to the Lamiaceae family.[112] Selmi *et al*.[26] 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 increase, hemodynamic, and metabolic disorders, as well as renal oxidative stress.[26] The chemical composition of *L. stoechas* essential oil is characterized by the presence of d-fenchone, α-pinene, camphor, camphene, Eucapur, limonene, linalool, and endobornyl acetate. The essential oils also contain smaller percentages of tricyclene, cymene, Δ-cadinene, and selina-3,7(11)-diene.[113] 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.[114]

Lycium europaeum

L. europaeum is a spiny shrub belonging to the Solonaceae Family and is dispersed throughout all countries in the Mediterranean basin.[115] It has been used in numerous traditional remedies for skin burning, rheumatic pain, constipation, hypertension, infectious ailments, and kidney and liver disorders.[116] 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[27] and by CCl_4.[28] *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,[117] gallic acid,[118] naringenin,[60] epicatechin,[76] vanillic acid,[56] rutin,[58] and *p*-coumaric acid.[119]

Malva sylvestris

*Malva sylvestri*s 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, spasmolytic, lenitive, and choleretic. Malva sylvestris is also used as bronchodilator, expectorant, antitussive, and antidiarrheal, and has been highly recommended for acne and skin care, and as an antiseptic, emollient, and demulcent.[120] The decoction of *M. sylvestris* leaves and flowers was investigated for its nephroprotective action against vanadium-induced kidney damage in rats.[29] 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 enzyme 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.[30] As reported by Ben Saad *et al*.[30] the protective properties of *M. sylvestris* extract could be related to its rich make-up of phenolic acids (epicatechic 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,[118] *p*-coumaric acid,[119] vanillic acid,[56] rutin,[58] kaempferol,[91] quercetin,[61] and luteolin[59] 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.[121] Bellassoued *et al*.[31] investigated *M. peperita* leaf essential oil for its nephroprotective action against CCl_4-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 CCl_4 (1 ml/kg BW) intraperitoneal treatment. Results showed that pretreatment with *M. peperita* leaf essential oil at 15 and 40 mg/kg prior to CCl_4 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 CCl_4-treated rats. Furthermore, pretreatment with *M. peperita* leaf essential oil at 40 mg/kg markedly ameliorated the histopathological hepatic and kidney lesions induced by CCl_4. *M. peperita* leaf essential oil contains active ingredients including menthol and iso-menthone. These two compounds exhibit a potent anti-inflammatory activity,[121] indicating that *M. peperita* leaf essential oil could be a promising natural product against CCl_4-induced oxidative damage in the kidney, consistent with that reported by Bellassoued *et al*.[31]

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.[122] The infusion and decoction of leaves have been used to prevent or treat urinary disorders.[123] The aqueous acetonic extract of *M. alba* leaves (100 mg/kg) was studied against glyphosate-induced (100 mg/kg) kidney injury in mice.[32] Renal oxidative stress induced by glyphosate 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 parametres by maintaining free iron and Ca^{2+} homeostasis, as well as regulate en-

dogenous anti-oxidant enzymes. The aqueous acetonic fraction of *M. alba* leaves is rich in chlorogenic acid and its isomers,[32] which can protect kidneys from glyphosate-induced nephrotoxicity.[96]

Nitraria retusa

Nitraria retusa belongs to the Nitrariaceae family and is used for its anti-inflammatory properties[124] and to facilitate healing.[125] In this study, the nephroprotective effect of aqueous extract from *N. retusa* fruit (300 mg/kg BW) against penconazole (67 mg/kg BW) caused kidney injury.[33] *N. retusa* treatment provoked a significant decrease in the levels of MDA, H_2O_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,[96] *p*-coumaric acid,[119] caffeic acid,[88] gallic acid,[118] and kaempferol[91] 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.[126] Ghorbel *et al*.[34] found that extra vierge olive oil abrogated acrylamide-induced nephrotoxicity. Ethanolic extract from *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.[35] Deltamethrin administration can increase MDA levels and reduce SOD and CAT activities. *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 *O. europea* fruit.[35] The nephroprotective effect of oleuropein and hydroxytyrosol extracted from Tunisian olive leaf extract have been investigated in rats treated with bisphenol A.[36] In recent study, Soussi *et al*.[37] found that the aqueous extract of Tunisian *O. europaea* leaves protected against kidney damage induced by diclofenac in mice.

Opuntia ficus-indica

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.[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 *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.[38] Similar results were obtained for the aqueous extract from *O. ficus-indica* cladodes on kidney injury induced by sodium dichromate.[39] As reported by Saad *et al*.,[38] the aqueous extract from *O. ficus-indica* cladodes was characterized by the presence of quercetin, vanillic acid, gallic acid, rutin, kampferol, catechin, epicatechin, coumarin, isorhamnetin, and caffeic acid. All of these phenolic compounds have been well studied for their potent nephroprotection, particularly quercetin,[61] vanillic acid,[56] gallic acid,[118] rutin,[58] kaempferol,[91] catechin,[128] epicatechin,[65] coumarin,[57] isorhamnetin,[106] and caffeic acid.[88]

Periploca angustifolia

Periploca angustifolia evergreen shrub is a member of the Apocynaceae family. It is found wild in North Africa (from Morocco to Egypt), southern Spain, Sicily, Malta, Crete, Lebanon, and Syria. *P. angustifolia* is used in traditional medicine for diabetes, rheumatism, hemorrhoids, and gastric ulcer.[129] The preventitive action of polysaccharides isolated from *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 *P. angustifolia* polysaccharides pre-treatment. Histopathological studies also supported the prevention action of *P. angustifolia* polysaccharides. Saccharose is the major monosaccharide component of *P. angustifolia* leaves, followed by trehalose, L-inositol, and M-inositol, as reported by Athmouni *et al*.[40]

Phoenix dactylifera

Phoenix dactylifera is a tree commonly known as date palm belonging to the Arecaceae family. *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.[130] The fruit of *P. dactylifera* is used as a detersive and astringent for intestinal ailments, treatment for sore throat, colds, bronchial asthma, to relieve fever, cystisis, gonorrhea, edema, liver and abdominal ailments, and to counteract alcohol intoxication.[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 *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.[41] Therefore, it has been speculated that *P. dactylifera* extract protects rats from kidney damage through its anti-oxidant capacity attributed to make-up of phenolic acids, mainly ferulic, caffeic, and *p*-coumaric acids.[41] In fact, ferulic,[132] caffeic,[88] and *p*-coumaric[119] acids are known for their efficient nephroprotective action.

Pinus halepensis

Pinus halepensis is a tree belonging to the Pinaceae family found around the Mediterranean basin. The resin and decoction of all Pinus species have antiseptic, diuretic, rubefacient, vermifuge, antidiabetic, and cicatrisant properties.[133] Bouzenna *et al*.[42] studied the protective effect of essential oil from *P. halepensis* needles

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*.[134] found that the essential oil of Tunisian *P. halepensis* needles was characterized by the predominance of monoterpene 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.[135] *R. tripartitum* is widely used to treat many diseases such as diarrhea and dysentery, colitis, gastointestinal diseases, inflammatory diseases, diabetes, haemoptysis, conjunctivitis, animal bites and poisons, hemorrhoids, sexual disease, fever, pain, and various cancers. Tlili *et al*.[43] investigated the protective action of methanolic extract from *R. tripartitum* fruit (200 mg/kg in olive oil) against cisplatin-induced (13 mg/kg) nephrotoxicty in rats. The increased levels of biochemical parameters (creatinine, urea, and uric acid) were attenuated by pretreatment with *R. tripartitum* fruit extract. Histopathologic 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 betulinic acid. In fact, the efficient renoprotective effects of betulinic acid isolated from *Cornus walteri* in cisplatin-provoked renal toxicity were determined by Lee *et al*.[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.[137] One study evaluates the effects of aqueous extract from *R. officinalis* leaves against kidney toxicity induced by CCl_4 in mice. Results showed that the renal damage induced by CCl_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_4-related toxic effects.[44] The polyphenolic profile of Tunisian *R. officinalis* leaf extract is characterized by its richness in carnosic and rosmarinic acids.[138] The potent nephroprotective effects of carnosic[139] and rosmarinic[140] 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,[141] and a medicinal plant used to fight fever, rheumatism, perspiration, sexual malfunction, chronic bronchitis, and various mental diseases.[142] Koubaa *et al*.[45] evaluated the impact of the essential oil from *S. officinalis* 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*.[45] Horváth *et al*.[143] found that β-caryophyllene ameliorated cisplatin-induced nephrotoxicity. Rehman *et al*.[85] 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*.[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_4-induced (0.5 ml/kg) nephrotoxicity in rats. CCl_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_4, which were validated by histopathological observations.[46] According to Goulas *et al*.,[145] *T. polium* aerial part extract is characterized by the presence of phenylpropanoid glycosides (verbascoside and poliumoside), flavones (apigenin and its derivatives), and two methoxyflavones, with poliumoside 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.[146] It is an ancient traditional medicinal plant[147] due to its olfactory, antifever, anti-inflammatory, antimicrobial, anticancer, antidiabetic, antihyperglycemic, laxative, galactogogue, and digestive effects. Belaïd-Nouira *et al*.[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*.[148] also determined the potent renoprotective action of fenugreek seeds on renal oxidative stress and nephropathy caused by a high cholesterol diet in rats. Mbarki *et al*.[48] noted that fenugreek seed supplementation protected the kidney from CCl_4-induced oxidative stress and toxicity in rats. According to Belaïd-Nouira *et al*,[47] Belguith-Hadrich *et al*,[148] and Mbarki *et al*,[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.[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.[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 has been used in diarrhoea. The juice of unripe fruit astringent has been used to treat throat affections. Dried fruit as demulcent, cooling, sweet, laxative, stomachic, has been used in thirst, body heat, coughs, hoarseness, consumption, and wasting diseases. The fruit, prepared in various manners, is said to be a remedy for mola, uterine tumors, and hardness of the liver, tumors, and cancer.[151] Mokni *et al*.[49] 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 H_2O_2 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. Turki *et al*.[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 Turki *et al*.[50] According to Mokni *et al*.,[49] the main compound of grape seed and skin extracts are 2,5-dihydroxybenzoïc acid, gallic acid, and vanillin. Among these phenolic compounds, gallic acid[118] and vanillin[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. Lamiaceae 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[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 CCl_4-induce nephrotoxicity. In general, CCl_4 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.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare no conflicts of interest.

Author contributions

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

References

[1] Javaid R, Aslam M, Nizami Q, Javaid R. Role of antioxidant herbal drugs in renal disorders: An overview. Free Rad Antiox 2012;2(1):1–5. doi:10.5530/ax.2012.2.2.
[2] Janakiraman M, Jeyaprakash K. Nephroprotective potential of medicinal plants: A Review. Biochem 2015;4(9):543–547.
[3] Sundararajan R, Bharampuram A, Ravindranadh Koduru R. A review on phytoconstituents for nephroprotective activity. Pharmacoph 2014; 5(1):160–182.
[4] Satlin LM, Bockenhauer D. Physiology of the developing kidney: potassium homeostasis and its disorder. Pediatr Nephrol 2016;17:219–246. doi:10.1007/978-3-662-43596-0_7.
[5] Ali Noorani A, Gupta K, Bhadada K, Kale MK. Protective effect of methanolic leaf extract of *Caesalpinia bonduc* (L) on gentamicin-induced hepatotoxicity and nephrotoxicity in rats. Iranian J Pharmacol and Ther 2011;10(1):21–25.
[6] Porter GA, Bennett WM. Nephrotoxic acute renal failure due to common drugs. Am J Physiol 1981;241(1):F1–F8. doi:10.1152/ajprenal.1981.241.1.F1, PMID:7018267.
[7] Gaikwad K, Dagle P, Choughule P, Joshi YM, Kadam V. A review on some nephroprotective medicinal plants. Int J Pharm Sci Res 2012;3(8):2451–2454.
[8] Aidi Wannes W, Marzouk B. Research progress of Tunisian medicinal plants used for acute diabetes. J Acute Dis 2016;5(5):357–363. doi:10.1016/j.joad.2016.08.001.
[9] Aidi Wannes W, Saidani Tounsi M, Marzouk B. A review of Tunisian medicinal plants with anticancer activity. J Complement Integr Med

2017;15(1):20170052. doi:10.1515/jcim-2017-0052, PMID:28915116.
[10] Aidi Wannes W, Saidani Tounsi M. Research advances in ulcer treatment using Tunisian medicinal plants. Biointerface Res Appl Chem 2017;7(3):2035–2039.
[11] Aidi Wannes W, Saidani Tounsi M, Marzouk B. Tunisian hepatoprotective plants. Chem Res J 2018;3(3):148–167.
[12] Aidi Wannes W, Saidani Tounsi M. Can medicinal plants contribute to the cure of Tunisian COVID-19 patients? J Med Plants Stud 2020;8(5):218–226. doi:10.22271/plants.2020.v8.i5c.1218.
[13] Ncir M, Saoudi M, Sellami H, Rahmouni F, Lahyani A, Makni Ayadi F, *et al*. In vitro and in vivo studies of Allium sativum extract against deltamethrin-induced oxidative stress in rats brain and kidney. Arch Physiol Biochem 2018;124(3):207–217. doi:10.1080/13813455.2017.1376335, PMID:28920707.
[14] Dhibi S, Bouzenna H, Samout N, Tlili Z, Elfeki A, Hfaiedh N. Nephroprotective and antioxidant properties of Artemisia arborescens hydroalcoholic extract against oestroprogestative-induced kidney damages in rats. Biomed Pharmacother 2016;82:520–527. doi:10.1016/j.biopha.2016.05.020, PMID:27470392.
[15] Saoudi M, Badraoui R, Bouhajja H, Ncir M, Rahmouni F, Grati M, *et al*. Deltamethrin induced oxidative stress in kidney and brain of rats: Protective effect of Artemisia campestris essential oil. Biomed Pharmacother 2017;94:955–963. doi:10.1016/j.biopha.2017.08.030, PMID:28810533.
[16] Saoudi M, Badraoui R, Rahmouni F, Jamoussi K, El Feki A. Antioxidant and protective effects of *Artemisia campestris* essential oil against chlorpyrifos-induced kidney and liver injuries in rats. Front Physiol 2021;12:618582. doi:10.3389/fphys.2021.618582, PMID:33716767.
[17] Tlili N, Feriani A, Saadoui E, Nasri N, Khaldi A. Capparis spinosa leaves extract: Source of bioantioxidants with nephroprotective and hepatoprotective effects. Biomed Pharmacother 2017;87:171–179. doi:10.1016/j.biopha.2016.12.052, PMID:28056421.
[18] Hsouna AB, Saoudi M, Trigui M, Jamoussi K, Boudawara T, Jaoua S, *et al*. Characterization of bioactive compounds and ameliorative effects of Ceratonia siliqua leaf extract against CCl_4 induced hepatic oxidative damage and renal failure in rats. Food Chem Toxicol 2011;49(12):3183–3191. doi:10.1016/j.fct.2011.09.034, PMID:21996303.
[19] Bouzenna H, Dhibi S, Samout N, Rjeibi I, Talarmin H, Elfeki A, *et al*. The protective effect of Citrus limon essential oil on hepatotoxicity and nephrotoxicity induced by aspirin in rats. Biomed Pharmacother 2016;83:1327–1334. doi:10.1016/j.biopha.2016.08.037, PMID:27571876.
[20] Mejri H, Tir M, Feriani A, Ghazouani L, Allagui MS, Saidani-Tounsi M. Does *Eryngium maritimum* seeds extract protect against CCl4 and cisplatin induced toxicity in rats: Preliminary phytochemical screening and assessment of its in vitro and in vivo antioxidant activity and antifibrotic effect. J Funct Food 2017;37:363–372. doi:10.1016/j.jff.2017.07.054.
[21] Dhibi S, Mbarki S, Elfeki A, Hfaiedh N. Eucalyptus globulus extract protects upon acetaminophen-induced kidney damages in male rat. Bosn J Basic Med Sci 2014;14(2):99–104. doi:10.17305/bjbms.2014.2272, PMID:24856382.
[22] Athmouni K, Belhaj D, El Feki A, Ayadi H. Optimization, antioxidant potential, modulatory effect and anti-apoptotic action in of Euphorbia bivonae polysaccharides on hydrogen peroxide-induced toxicity in human embryonic kidney cells HEK293. Int J Biol Macromol 2018;116:482–491. doi:10.1016/j.ijbiomac.2018.04.172, PMID:29727642.
[23] Bellakhdar J, Claisse R, Fleurentin J, Younos C. Repertory of standard herbal drugs in the Moroccan pharmacopoeia. J Ethnopharmacol 1991;35(2):123–143. doi:10.1016/0378-8741(91)90064-k.
[24] Bourogaa E, Jarraya R, Jarraya, Damak M, El Feki A. Therapeutic efficacy of Hammada scoparia extract against ethanol induced renal dysfunction in Wistar rats. J Food Biochem 2017;41(2):e12307. doi:10.1111/jfbc.12307.
[25] Bouaziz H, Rafrafi M, Ben Salah G, Marrekchi R, Kammoun H, Jamoussi K, *et al*. Nitrate provoked kidney toxicity and DNA impairment in adult rats: Alleviation by *Hyparrhenia hirta*. Pak Vet J 2015;35(4):397–402.
[26] Selmi S, Jallouli M, Gharbi N, Marzouki L. Hepatoprotective and renoprotective effects of Lavender (Lavandula stoechas L.) essential oils against malathion-induced oxidative stress in young male mice. J Med Food 2015;18(10):1103–1111. doi:10.1089/jmf.2014.0130, PMID:25835641.
[27] Rjeibi I, Feriani A, Ben Saad A, Ncib S, Sdayria J, Hfaiedh N, *et al*. *Lycium europaeum* Linn as a source of polysaccharide with *in vitro* antioxidant activities and in vivo anti-inflammatory and hepato-nephroprotective potentials. Journal of Ethnopharmacol 2018;225:116–127. doi:10.1016/j.jep.2018.06.036.
[28] Rjeibi I, Feriani A, Ben Saad A, Ncib S, Sdayria J, Saidi I, *et al*. Phytochemical characterization and bioactivity of Lycium europaeum: A focus on antioxidant, antinociceptive, hepatoprotective and nephroprotective effects. Biomed Pharmacother 2017;95:1441–1450. doi:10.1016/j.biopha.2017.09.035, PMID:28946192.
[29] Marouane W, Soussi A, Murat JC, Bezzine S, El Feki A. The protective effect of Malva sylvestris on rat kidney damaged by vanadium. Lipids Health Dis 2011;10:65. doi:10.1186/1476-511X-10-65, PMID:21513564.
[30] Ben Saad A, Rjeibi I, Brahmi D, Smida A, Ncib S, Zouari N, *et al*. Malva sylvestris extract protects upon lithium carbonate-induced kidney damages in male rat. Biomed Pharmacother 2016;84:1099–1107. doi:10.1016/j.biopha.2016.10.026, PMID:27780138.
[31] Bellassoued K, Ben Hsouna A, Athmouni K, Pelt JV, Makni Ayadi F, Rebai T, *et al*. Protective effects of *Mentha piperita* L. leaf essential oil against CCl_4 induced hepatic oxidative damage and renal failure in rats. Lipids Heal dis 2018;17:1–14. doi:10.1186/s12944-017-0645-9.
[32] Rebai O, Fattouch S, Amri M. Nephroprotective effect of aqueous acetonic extract of *Morus alba* and its underlying mechanisms against glyphosate-induced toxicity - *in vivo* model. Pestic Phytomed 2021;36(1):45–59. doi:10.2298/PIF2101045R.
[33] Chaâbane M, Koubaa M, Soudani N, Elwej A, Grati M, Jamoussi K, *et al*. Nitraria retusa fruit prevents penconazole-induced kidney injury in adult rats through modulation of oxidative stress and histopathological changes. Pharm Biol 2017;55(1):1061–1073. doi:10.1080/13880209.2016.1278455, PMID:28198206.
[34] Ghorbel I, Elwej A, Fendri N, Mnif H, Jamoussi K, Boudawara T, *et al*. Olive oil abrogates acrylamide induced nephrotoxicity by modulating biochemical and histological changes in rats. Ren Fail 2017;39(1):236–245. doi:10.1080/0886022X.2016.1256320, PMID:27846768.
[35] Maalej A, Mahmoudi A, Bouallagui Z, Fki I, Marrekchi R, Sayadi S. Olive phenolic compounds attenuate deltamethrin-induced liver and kidney toxicity through regulating oxidative stress, inflammation and apoptosis. Food Chem Toxicol 2017;106(Pt A):455–465. doi:10.1016/j.fct.2017.06.010, PMID:28595958.
[36] Mahmoudi A, Ghorbel H, Bouallegui Z, Marrekchi R, Isoda H, Sayadi S. Oleuropein and hydroxytyrosol protect from bisphenol A effects in livers and kidneys of lactating mother rats and their pups'. Exp Toxicol Pathol 2015;67(7-8):413–425. doi:10.1016/j.etp.2015.04.007, PMID:25963946.
[37] Soussi R, Hfaiedh N, Saklya M, Ben Rhouma K. The aqueous extract of *Olea europaea* leaves protects from haematotoxicity and kidney damage induced by diclofenac in Swiss albino mice. Royal Soci Chem 2019;9(40):23352–23361. doi:10.1039/C9RA01670H.
[38] Saad AB, Rjeibi I, Ncib S, Zouari N, Zourgui L. Ameliorative effect of cactus *(Opuntia ficus indica)* extract on lithium-induced nephrocardiotoxicity: a biochemical and histopathological study. Biomed Res Int 2017;2017:8215392. doi:10.1155/2017/8215392, PMID:29376078.
[39] Hfaiedh M, Brahmi D, Zourgui MN, Zourgui L. Phytochemical analysis and nephroprotective effect of cactus (Opuntia ficus-indica) cladodes on sodium dichromate-induced kidney injury in rats. Appl Physiol Nutr Metab 2019;44(3):239–247. doi:10.1139/apnm-2018-0184, PMID:30086244.
[40] Athmouni K, Belhaj D, El Feki A, Ayadi H. Optimization, antioxidant properties and GC-MS analysis of Periploca angustifolia polysaccharides and chelation therapy on cadmium-induced toxicity in human HepG2 cells line and rat liver. Int J Biol Macromol 2018;108:853–862. doi:10.1016/j.ijbiomac.2017.10.175, PMID:29101047.
[41] El Arem A, Thouri A, Zekri M, Saafi EB, Ghrairi F, Zakhama A, *et al*. Nephroprotective effect of date fruit extract against dichloroacetic acid exposure in adult rats. Food Chem Toxicol 2014;65:177–184. doi:10.1016/j.fct.2013.12.023, PMID:24394489.
[42] Bouzenna H, Samout N, Amani E, Mbarki S, Tlili Z, Rjeibi I, *et al*. Protective Effects of Pinus halepensis L. Essential Oil on Aspirin-induced Acute Liver and Kidney Damage in Female Wistar Albino Rats. J Oleo

Sci 2016;65(8):701–712. doi:10.5650/jos.ess15287, PMID:27430382.
[43] Tlili N, Feriani A, Allagui MS, Saadoui E, Khaldi A, Nasri N. Effects of Rhus tripartitum fruit extract on CCl4-induced hepatotoxicity and cisplatin-induced nephrotoxicity in rats. Can J Physiol Pharmacol 2016; 94(8):801–807. doi:10.1139/cjpp-2016-0029, PMID:27351070.
[44] Hamed H, Boulila S, Ghrab F, Kallel R, Boudawara T, El Feki A. The preventive effect of aqueous extract of Rosemary (*Rosmarinus officinalis*) leaves against the nephrotoxicity of carbon tetrachloride in mice. Arch Physiol Biochem 2020;126(3):201–208. doi:10.1080/13813455.2018.1508236, PMID:30501137.
[45] Koubaa FG, Abdennabi R, Salah ASB, El Feki A. Microwave extraction of *Salvia officinalis* essential oil and assessment of its GC-MS identification and protective effects versus vanadium-induced nephrotoxicity in Wistar rats models. Arch Physiol Biochem 2019;125(5):404–413. doi:10.1080/13813455.2018.1478427, PMID:29884068.
[46] Rahmouni F, Badraoui R, Amri N, Elleuch A, El-Feki A, Rebai T, *et al*. Hepatotoxicity and nephrotoxicity in rats induced by carbon tetrachloride and the protective effects of Teucrium polium and vitamin C. Toxicol Mech Methods 2019;29(5):313–321. doi:10.1080/15376516.2018.1519864, PMID:30676168.
[47] Belaïd-Nouira Y, Bakhta H, Haouas Z, Flehi-Slim I, Ben Cheikh H. Fenugreek seeds reduce aluminum toxicity associated with renal failure in rats. Nutr Res Pract 2013;7(6):466–474. doi:10.4162/nrp.2013.7.6.466, PMID:24353832.
[48] Mbarki S, Alimi H, Bouzenna H, Elfeki A, Hfaiedh N. Phytochemical study and protective effect of Trigonella foenum graecum (Fenugreek seeds) against carbon tetrachloride-induced toxicity in liver and kidney of male rat. Biomed Pharmacother 2017;88:19–26. doi:10.1016/j.biopha.2016.12.078, PMID:28092841.
[49] Mokni M, Hamlaoui S, Kadri S, Limam F, Amri M, Marzouki L, *et al*. Grape seed and skin extract protects kidney from doxorubicin-induced oxidative injury. Pak J Pharm Sci 2016;29(3):961–968. PMID:27166540.
[50] Turki K, Charradi K, Boukhalfa H, Belhaj M, Limam F, Aouani E. Grape seed powder improves renal failure of chronic kidney disease patients. EXCLI J 2016;15:424–433. doi:10.17179/excli2016-363, PMID:27822171.
[51] Campêlo LM, de Almeida AA, de Freitas RL, Cerqueira GS, de Sousa GF, Saldanha GB, *et al*. Antioxidant and antinociceptive effects of Citrus limon essential oil in mice. J Biomed Biotechnol 2011;2011:678673. doi:10.1155/2011/678673, PMID:21660140.
[52] Bongiorno PB, Fratellone PM, LoGiudice P. Potential health benefits of garlic (*Allium sativum*): A narrative review. J Complement Integr Med 2008;5(1):1–24. doi:10.3390/antiox9070619.
[53] García Trejo EMÁ, Arellano Buendía AS, Sánchez Reyes O, García Arroyo FE, Arguello García R, Loredo Mendoza ML, *et al*. The beneficial effects of allicin in chronic kidney disease are comparable to losartan. Int J Mol Sci 2017;18(9):E1980. doi:10.3390/ijms18091980, PMID:28926934.
[54] Gonzalez J, Cruz Freire JM, Domınguez H, Parajo JC. Production of antioxidants from *Artemisia arborescens* wood by solvent extraction of hemicellulose hydrolysates. Food Chem 2004;84:243–251. doi:10.1016/S0308-8146(03)00208-5.
[55] Mulyaningsih S, Sporer F, Zimmermann S, Reichling J, Wink M. Synergistic properties of the terpenoids aromadendrene and 1,8-cineole from the essential oil of Eucalyptus globulus against antibiotic-susceptible and antibiotic-resistant pathogens. Phytomedicine 2010;17(13):1061–1066. doi:10.1016/j.phymed.2010.06.018, PMID:20727725.
[56] Sindhu G, Nishanthi E, Sharmila R. Nephroprotective effect of vanillic acid against cisplatin induced nephrotoxicity in wistar rats: a biochemical and molecular study. Environ Toxicol Pharmacol 2015;39(1):392–404. doi:10.1016/j.etap.
[57] Sen Z, Jie M, Jingzhi Y, Dongjie W, Dongming Z, Xiaoguang C. Total Coumarins from *Hydrangea paniculata* Protect against Cisplatin-Induced Acute Kidney Damage in Mice by Suppressing Renal Inflammation and Apoptosis. Evid Based Complement Alternat Med 2017;2017:5350161. doi:10.1155/2017/5350161, PMID:28367225.
[58] Radwan RR, Abdel Fattah SM. Mechanisms involved in the possible nephroprotective effect of rutin and low dose γ irradiation against cisplatin-induced nephropathy in rats. J Photochem Photobiol B 2017;169:56–62. doi:10.1016/j.jphotobiol.2017.02.022, PMID:28282556.
[59] Domitrović R, Cvijanović O, Pugel EP, Zagorac GB, Mahmutefendić H, Škoda M. Luteolin ameliorates cisplatin-induced nephrotoxicity in mice through inhibition of platinum accumulation, inflammation and apoptosis in the kidney. Toxicology 2013;310:115–123. doi:10.1016/j.tox.2013.05.015, PMID:23770416.
[60] Renugadevi J, Prabu SM. Naringenin protects against cadmium-induced oxidative renal dysfunction in rats. Toxicology 2009;256(1-2):128–134. doi:10.1016/j.tox.2008.11.012, PMID:19063931.
[61] Wang J, Pan Y, Hong Y, Zhang QY, Wang XN, Kong LD. Quercetin protects against cadmium-induced renal uric acid transport system alteration and lipid metabolism disorder in rats. Evid Based Complement Alternat Med 2012;2012:548430. doi:10.1155/2012/548430, PMID:22690247.
[62] Dib I, Angenot L, Mihamou A, Ziyyat A, Tits M. Artemisia campestris L. Ethnomedicinal, phytochemical and pharmacological review. J Herb Med 2017;7:1–10. doi:10.1016/j.hermed.2016.10.005.
[63] Akrout A, Chemli R, Chreïf I, Hammami M. Analysis of the essential oil of *Artemisia campestris* L. Flav Fragr J 2001;16(5):337–339. doi:10.1002/ffj.1006.
[64] Başar A. The dissolving effect of α- and β pinenes in pine resin to kidney stone. Acad J Med Pl 2014;2(6):85–87. doi:10.15413/ajmp.2014.0106.
[65] Rivera D, Inocencio C, Obon C, Alcaraz F. Review of food and medicinal uses of *Capparis* L. *subgenus Capparis* (Capparidaceae). J Econ Bot 2003;57:515–534. doi:10.1663/0013-0001(2003)057[0515:ROFAMU]2.0.CO;2.
[66] Jiang HE, Li X, Ferguson DK, Wang YF, Liu CJ, Li CS. The discovery of Capparis spinosa L. (Capparidaceae) in the Yanghai Tombs (2800 years b.p.), NW China, and its medicinal implications. J Ethnopharmacol 2007; 113(3):409–420. doi:10.1016/j.jep.2007.06.020, PMID:17693045.
[67] Eddouks M, Lemhadri A, Michel JB. Hypolipidemic activity of aqueous extract of Capparis spinosa L. in normal and diabetic rats. J Ethnopharmacol 2005;98(3):345–350. doi:10.1016/j.jep.2005.01.053, PMID:15814271.
[68] El-Hilaly J, Hmammouchi M, Lyoussi B. Ethnobotanical studies andeconomic evaluation of medicinal plants in Taounate Province (Northern Morocco). J Ethnopharmacol 2003;86:149–158. doi:10.1016/s0378-8741(03)00012-6.
[69] Lemhadri A, Mohamed E, Thierry S, Remy B. Antihyperglycaemic andanti-obesity effects of *Capparis spinosa* and *Chamaemelum nobile* aqueous extracts in HFD mice. Am J Pharmacol Toxicol 2007;2(3):106–110. doi:10.3844/ajptsp.2007.106.110.
[70] Feng X, Lu J, Xin H, Zhang L, Wang Y, Tang K. Anti-arthritic active fraction of Capparis spinosa L. fruits and its chemical constituents. Yakugaku Zasshi 2011;131(3):423–429. doi:10.1248/yakushi.131.423, PMID:21372539.
[71] Matsuyama K, Villareal MO, El Omri A, Han J, Kchouk ME, Isoda H. Effect of Tunisian Capparis spinosa L. extract on melanogenesis in B16 murine melanoma cells. J Nat Med 2009;63(4):468–472. doi:10.1007/s11418-009-0355-3, PMID:19685105.
[72] Rajesh P, Selvamani P, Latha S, Saraswathy A, Rajesh Kannan V. A review on chemical and medicobiological applications of capparidaceae family. Pharmacogn Rev 2009;3(6):378–387.
[73] Sher H, Al-Yemeni MN, Sher H. Forest Resource utilization assessment for economic development of rural community, Northern parts of Pakistan. J Med Plants Res 2010;4(12):1197–1208. doi:10.5897/JMPR10.206.
[74] Allaith AAA. Assessment of the antioxidant properties of the caper fruit (*Capparis spinosa* L.) from Bahrain. J Assoc Arab Univ Basic Appl Sci 2014 2016;19:1–7. doi:10.1016/j.jaubas.2014.07.001.
[75] Valentovic MA, Ball JG, Brown JM, Terneus MV, McQuade E, Van Meter S, *et al*. Resveratrol attenuates cisplatin renal cortical cytotoxicity by modifying oxidative stress. Toxicol In Vitro 2014;28(2):248–257. doi:10.1016/j.tiv.2013.11.001, PMID:24239945.
[76] Tanabe K, Tamura Y, Lanaspa MA, Miyazaki M, Suzuki N, Sato W, *et al*. Epicatechin limits renal injury by mitochondrial protection in cisplatin nephropathy. Am J Physiol Renal Physiol 2012;303(9):F1264–F1274. doi:10.1152/ajprenal.00227.2012, PMID:22933302.
[77] Kivçak B, Mert T, Ozturk HT. Antimicrobial and cytotoxic activity of *Ceratonia siliqua* L. Extracts. Turk J Biol 2002;26:197–200.
[78] Sancak EB, Akbas A, Silan C, Cakir DU, Turkon H, Ozkanli SS. Protective effect of syringic acid on kidney ischemia-reperfusion injury. Ren Fail 2016;38(4):629–635. doi:10.3109/0886022X.2016.
[79] Ozcan F, Ozmen A, Akkaya B, Aliciguzel Y, Aslan M. Beneficial effect of myricetin on renal functions in streptozotocin-induced diabetes.

Clin Exp Med 2012;12(4):265–272. doi:10.1007/s10238-011-0167-0, PMID:22083509.
[80] Asci H, Ozmen O, Ellidag HY, Aydin B, Bas E, Yilmaz N. The impact of gallic acid on the methotrexate-induced kidney damage in rats. J Food Drug Anal 2017;25(4):890–897. doi:10.1016/j.jfda.2017.05.001, PMID:28987366.
[81] Di Vaio C, Grazianib G, Gasparib A, Scaglione G, Nocerino S, Ritieni A. Essential oils content and antioxidant properties of peel ethanol extract in 18 lemon cultivars. Sci Hortic 2010;126:50–55. doi:10.1016/j.scienta.2010.06.010.
[82] AL-Jabri NN, Hossain MA. Comparative chemical composition and antimicrobial activity study of essential oils from two imported lemon fruits samples against pathogenic bacteria. Beni-Suef Univ J Basic Appl Sci 2014;3(4):247–253. doi:10.1016/j.bjbas.2014.10.011.
[83] Kirbaslar G, Kirbaslar I. Composition of Turkish bitter orange and lemon leaf oils. J Essent Oil Res 2004;16(2):105–108. doi:10.1080/10412905.2004.9698663.
[84] Lota ML, de Rocca Serra D, Tomi F, Jacquemond C, Casanova J. Volatile components of peel and leaf oils of lemon and lime species. J Agric Food Chem 2002;50(4):796–805. doi:10.1021/jf010924l, PMID:11829647.
[85] Rehman MU, Tahir M, Khan AQ, Khan R, Oday-O-Hamiza, Lateef A, *et al*. D-limonene suppresses doxorubicin-induced oxidative stress and inflammation via repression of COX-2, iNOS, and NFκB in kidneys of Wistar rats. Exp Biol Med (Maywood) 2014;239(4):465–476. doi:10.1177/1535370213520112, PMID:24586096.
[86] Isermann M, Rooney P. Biological Flora of the British Isles: *Eryngium maritimum*. J Ecol 2014;102(3):789–821. doi:10.1111/1365-2745.12243.
[87] Erdem SA, Nabavi SF, Orhan IE, Daglia M, Izadi M, Nabavi SM. Blessings in disguise: a review of phytochemical composition and antimicrobial activity of plants belonging to the genus Eryngium. Daru 2015;23:53. doi:10.1186/s40199-015-0136-3, PMID:26667677.
[88] Matboli M, Eissa S, Ibrahim D, Hegazy MGA, Imam SS, Habib EK. Caffeic Acid attenuates diabetic kidney disease via modulation of autophagy in a high-fat diet/streptozotocin- induced diabetic rat. Sci Rep 2017;7(1):2263. doi:10.1038/s41598-017-02320-z, PMID:28536471.
[89] Nabavi SM, Habtemariam S, Nabavi SF, Sureda A, Daglia M, Moghaddam AH, *et al*. Protective effect of gallic acid isolated from Peltiphyllum peltatum against sodium fluoride-induced oxidative stress in rat's kidney. Mol Cell Biochem 2013;372(1-2):233–239. doi:10.1007/s11010-012-1464-y, PMID:23014933.
[90] Adefegha SA, Omojokun OS, Oboh G. Modulatory effect of protocatechuic acid on cadmium induced nephrotoxicity and hepatoxicity in rats in vivo. Springerplus 2015;4:619. doi:10.1186/s40064-015-1408-6, PMID:26543754.
[91] Vijayaprakash S, Langeswaran K, Kumar SG, Revathy R, Balasubramanian MP. Nephro-protective significance of kaempferol on mercuric chloride induced toxicity in Wistar albino rats. Biomed Aging Pathol 2013;3:119–124. doi:10.1016/J.BIOMAG.2013.05.004.
[92] Sugimoto K, Nakagawa K, Hayashi S, Amakura Y, Yoshimura M, Yoshida T, *et al*. Hydrolyzable tannins as antioxidants in the leaf extract of *Eucalyptus globulus* possessing tyrosinase and hyaluronidase inhibitory activities. Food Sci Technol Res 2009;15:331–336. doi:10.3136/fstr.15.331.
[93] Santos Ferreira C, Pereyra A, Patriarca A, Mazzobre MF, Polak T, Abram V, *et al*. Phenolic compounds in extracts from *Eucalyptus globulus* leaves and Calendula officinalis flowers. J Nat Res Prod 2016;2(1):53–57.
[94] Ayhanci A, Cengiz M, Mehtap Kutlu H, Vejselova D. Protective effects of ellagic acid in D-galactosamine-induced kidney damage in rats. Cytotechnology 2016;68(5):1763–1770. doi:10.1007/s10616-015-9928-z, PMID:26660314.
[95] Wong CC, Botting NP, Orfila C, Al-Maharik N, Williamson G. Flavonoid conjugates interact with organic anion transporters (OATs) and attenuate cytotoxicity of adefovir mediated by organic anion transporter 1 (OAT1/SLC22A6). Biochem Pharmacol 2011;81(7):942–949. doi:10.1016/j.bcp.2011.01.004, PMID:21244849.
[96] Domitrović R, Cvijanović O, Šušnić V, Katalinić N. Renoprotective mechanisms of chlorogenic acid in cisplatin-induced kidney injury. Toxicology 2014;324:98–107. doi:10.1016/j.tox.2014.07.004, PMID:25043994.
[97] Frederick C. Guide illustré de la flore Zingaro, Palerme. L'Epos Publishing Company; 1999:100.
[98] Di Stefano V, Pitonzo R, Schillaci D. Chemica constituents and anti-proliferative activity of *Euphorbia bivonae*. Chem Nat Comp 2011;47(4):630–663. doi:10.1007/s10600-011-0026-y.
[99] Athmouni K, El Feki A, Ayadi H. Hepatotoxic effects of Euphol-rich fractions from Euphorbia bivonae-Relevance to cytotoxic and anti-tumor activities. Pathophysiology 2019;26(1):69–76. doi:10.1016/j.pathophys.2018.10.003, PMID:30401578.
[100] Jrah Harzallah H, Neffati A, Skandrani I, Maaloul E, Chekir Ghedira L, Mahjoub T. Antioxidant and antigenotoxic activities of *Globularia alypum* leaves extracts. J Med P Res 2010;4(19):2048–2053. doi:10.5897/JMPR10.385.
[101] Le Floch E. Boulos Loufty. —Medicinal Plants of North Africa Reference Publication, Inc. 218 St. Clair River Drive, Box 344. Algonac, Michigan 48001, 1983. Journ d'Agric Trad et de Bota Appl 1984;XXXI:127.
[102] Feriani A, Del Mar Contreras M, Talhaoui N, Gómez-Caravaca AM, Taamalli A, Segura-Carretero A, *et al*. Protective effect of *Globularia alypum* leaves against deltamethrin induced nephrotoxicity in rats and determination of its bioactive compounds using high-performance liquid chromatography coupled with electrospray ionization tandem quadrupole–time-of-flight mass spectrometry. J Funct Food 2017;32:139–148. doi:10.1016/j.jff.2017.02.015.
[103] Merghache S, Zerriouh M, Merghache D, Tabti B, Djaziri R, Ghalem S. Evaluation of hypoglycaemic and hypolipidemic activities of Globularin isolated from *Globularia alypum* L. in normal and streptozotocin-induced diabetic rats. J Appl Pharmaceut Sci 2013;3(4):1–7. doi:10.7324/JAPS.2013.3401.
[104] Bourogaa E, Nciri R, Mezghani-Jarraya R, Racaud-Sultan C, Damak M, El Feki A. Antioxidant activity and hepatoprotective potential of Hammada scoparia against ethanol-induced liver injury in rats. J Physiol Biochem 2013;69(2):227–237. doi:10.1007/s13105-012-0206-7, PMID:22893526.
[105] Ben Salah H, Jarraya R, Martin MT, Veitch NC, Grayer RJ, Simmonds MS, *et al*. Flavonol triglycosides from the leaves of Hammada scoparia (POMEL) ILJIN. Chem Pharm Bull (Tokyo) 2002;50(9):1268–1270. doi:10.1248/cpb.50.1268, PMID:12237550.
[106] Qiu S, Sun G, Zhang Y, Li X, Wang R. Involvement of the NF-κB signaling pathway in the renoprotective effects of isorhamnetin in a type 2 diabetic rat model. Biomed Rep 2016;4(5):628–634. doi:10.3892/br.2016.636, PMID:27123259.
[107] Clayton WD. A revision of the genus Hyparrhenia. Kew Bulletin, Addit. Ser. 2. London: HMSO 1969;2:1–96.
[108] Boukef MK. Medecine traditionnelle et pharmacopee: Les Plantes dans la médecine traditionnelle tunisienne. Paris: Agence De Cooperation Culturelle Et Technique; 1986:350.
[109] Bouaziz-Ketata H, Ben Salah G, Ben Salah H, Marrekchi R, Jamoussi K, Boudawara T, *et al*. Nitrate-induced biochemical and histopathological changes in the liver of rats: Ameliorative effect of *Hyparrhenia hirta*. Biomed Environ Sci 2014;27(9):695–706. doi:10.3967/bes2014.105.
[110] Hassan SM, Khalaf MM, Sadek SA, Abo-Youssef AM. Protective effects of apigenin and myricetin against cisplatin-induced nephrotoxicity in mice. Pharm Biol 2017;55(1):766–774. doi:10.1080/13880209.2016.1275704, PMID:28064632.
[111] Chaudhary S, Ganjoo P, Raiusddin S, Parvez S. Nephroprotective activities of quercetin with potential relevance to oxidative stress induced by valproic acid. Protoplasma 2015;252(1):209–217. doi:10.1007/s00709-014-0670-8, PMID:25000991.
[112] Benabdelkader T, Zitouni A, Guitton Y, Jullien F, Maitre D, Casabianca H, *et al*. Essential oils from wild populations of Algerian Lavandula stoechas L.: composition, chemical variability, and in vitro biological properties. Chem Biodivers 2011;8(5):937–953. doi:10.1002/cbdv.201000301, PMID:21560242.
[113] Sebai H, Selmi S, Rtibi K, Souli A, Gharbi N, Sakly M. Lavender (Lavandula stoechas L.) essential oils attenuate hyperglycemia and protect against oxidative stress in alloxan-induced diabetic rats. Lipids Health Dis 2013;12:189. doi:10.1186/1476-511X-12-189, PMID:24373672.
[114] Kogiannou DA, Kalogeropoulos N, Kefalas P, Polissiou MG, Kaliora AC. Herbal infusions; their phenolic profile, antioxidant and anti-inflammatory effects in HT29 and PC3 cells. Food Chem Toxicol 2013;61:152–159. doi:10.1016/j.fct.2013.05.027, PMID:23712099.

[115] Polunin O, Smythies BE. . Flowers of south-west Europe a field guide. Oxford: Oxford University Press; 1973:544.
[116] Said O, Khalil K, Fulder S, Azaizeh H. Ethnopharmacological survey of medicinal herbs in Israel, the Gollan Heights and the West Bank region. J Ethnopharmacol 2002;83(3):251–265. doi:10.1016/s0378-8741(02)00253-2.
[117] Ozen S, Akyol O, Iraz M, Söğüt S, Ozuğurlu F, Ozyurt H, *et al*. Role of caffeic acid phenethyl ester, an active component of propolis, against cisplatin-induced nephrotoxicity in rats. J Appl Toxicol 2004;24(1):27–35. doi:10.1002/jat.941, PMID:14745844.
[118] Akomolafe SF, Akinyemi AJ, Anadozie SO. Phenolic acids (gallic and tannic acids) modulate antioxidant status and cisplatin induced nephrotoxicity in rats. Int Sch Res Notices 2014;2014:984709. doi:10.1155/2014/984709, PMID:27382634.
[119] Ekinci Akdemir FN, Albayrak M, Çalik M, Bayir Y, Gülçin İ. The protective effects of p-coumaric acid on acute liver and kidney damages induced by cisplatin. Biomedicines 2017;5(2):E18. doi:10.3390/biomedicines5020018, PMID:28536361.
[120] Leporatti ML, Ghedira K. Comparative analysis of medicinal plants used in traditional medicine in Italy and Tunisia. J Ethnobiol Ethnomed 2009;5:31. doi:10.1186/1746-4269-5-31, PMID:19857257.
[121] Cowan MM. Plant products as antimicrobial agents. Clin Microbiol Rev 1999;12(4):564–582. doi:10.1128/CMR.12.4.564, PMID:10515903.
[122] Singh R, Bagachi A, Semwal A, Kaur S, Bharadwaj A. Traditional uses, phytochemistry and pharmacology of *Morus alba* Linn.: A review. J Med Plant Res 2013;7(9):461–469. doi:10.5897/JMPR012.1079.
[123] Yang Y, Gong T, Liu C, Chen RY. Four new 2-arylbenzofuran derivatives from leaves of Morus alba L. Chem Pharm Bull (Tokyo) 2010;58(2):257–260. doi:10.1248/cpb.58.257, PMID:20118592.
[124] Iida A, Usui T, Zar Kalai F, Han J, Isoda H, Nagumo Y. Protective effects of Nitraria retusa extract and its constituent isorhamnetin against amyloid β-induced cytotoxicity and amyloid β aggregation. Biosci Biotechnol Biochem 2015;79(9):1548–1551. doi:10.1080/09168451.2015.1027655, PMID:25965116.
[125] Shaltout KH, Sheded MG, El-Kady HF, Al-Sodany YM. Phytosociology and size structure of *Nitraria retusa* along the Egyptian Red Sea coast. J Arid Environ 2003;53:331–345. doi:10.1006/jare.2002.1054.
[126] Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, *et al*. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med 2013;368(14):1279–1290. doi:10.1056/NEJMoa1200303, PMID:23432189.
[127] Alimi H, Hfaiedh N, Bouoni Z, Hfaiedh M, Sakly M, Zourgui L, *et al*. Antioxidant and antiulcerogenic activities of Opuntia ficus indica f. inermis root extract in rats. Phytomedicine 2010;17(14):1120–1126. doi:10.1016/j.phymed.2010.05.001, PMID:20638261.
[128] Sardana A, Kalra S, Khanna D, Balakumar P. Nephroprotective effect of catechin on gentamicin-induced experimental nephrotoxicity. Clin Exp Nephrol 2015;19(2):178–184. doi:10.1007/s10157-014-0980-3, PMID:24825545.
[129] Ghrabi Z. A guide to medicinal plants in North Africa. Gland: IUCN Centre for Mediterranean Cooperation; 2005.
[130] Abu-Reidah IM, Gil-Izquierdo Á, Medina S, Ferreres F. Phenolic composition profiling of different edible parts and by-products of date palm (Phoenix dactylifera L.) by using HPLC-DAD-ESI/MS^n. Food Res Int 2017;100(Pt 3):494–500. doi:10.1016/j.foodres.2016.10.018, PMID:28964373.
[131] Barh D, Mazumdar BC. Comparative nutritive values of palm saps before and after their partial fermentation and effective use of wild date (*Phoenix sylvestris* Roxb.) sap in treatment of anemia. Res J Med Med Sci 2008;3(2):173–176.
[132] Bunel V, Antoine MH, Nortier J, Duez P, Stévigny C. Nephroprotective effects of ferulic acid, Z-ligustilide and E-ligustilide isolated from Angelica sinensis against cisplatin toxicity in vitro. Toxicol In Vitro 2015;29(3):458–467. doi:10.1016/j.tiv.2014.12.017, PMID:25561245.
[133] Uncini Manganelli RE, Camangi F, Tomei PE. Curing animals with plants: traditional usage in Tuscany (Italy). J Ethnopharmacol 2001;78(2-3):171–191. doi:10.1016/s0378-8741(01)00341-5.
[134] Hamrouni L, Hanana M, Amri I, Romane AE, Gargouri S, Jamoussi B. Allelopathic effects of essential oils of *Pinus halepensis* Miller: chemical composition and study of their antifungal and herbicidal activities. Arch Phytopathol Plant Protect 2015;48:145–158. doi:10.1080/03235408.2014.884667.
[135] Mahjoub MA, Ammar S, Mighri Z. A new biflavonoid and an isobiflavonoid from Rhus tripartitum. Nat Prod Res 2005;19(8):723–729. doi :10.1080/14786410412331272068, PMID:16317819.
[136] Lee S, Jung K, Lee D, Lee SR, Lee KR, Kang KS, *et al*. Protective effect and mechanism of action of lupane triterpenes from Cornus walteri in cisplatin-induced nephrotoxicity. Bioorg Med Chem Lett 2015;25(23):5613–5618. doi:10.1016/j.bmcl.2015.10.035, PMID:26592171.
[137] De Oliveira JR, Camargo SEA, De Oliveir LD. *Rosmarinus officinalis* L. (rosemary) as therapeutic and prophylactic agent. J Biomed Sci 2019;26:1–22. doi:10.1186/s12929-019-0499-8.
[138] Bahri S, Ben Ali R, Gasmi K, Mlika M, Fazaa S, Ksouri R, *et al*. Prophylactic and curative effect of rosemary leaves extract in a bleomycin model of pulmonary fibrosis. Pharm Biol 2017;55(1):462–471. doi:10 .1080/13880209.2016.1247881, PMID:28093019.
[139] Sahu BD, Rentam KK, Putcha UK, Kuncha M, Vegi GM, Sistla R. Carnosic acid attenuates renal injury in an experimental model of rat cisplatin-induced nephrotoxicity. Food Chem Toxicol 2011;49(12):3090–3097. doi:10.1371/journal.pone.0171612.
[140] Domitrović R, Potočnjak I, Crnčević-Orlić Z, Škoda M. Nephroprotective activities of rosmarinic acid against cisplatin-induced kidney injury in mice. Food Chem Toxicol 2014;66:321–328. doi:10.1016/j.fct.2014.02.002, PMID:24518541.
[141] Kozłowska M, Laudy AE, Przybył J, Ziarno M, Majewska E. Chemical composition and antibacterial activity of some medicinal plants from Lamiaceae family. Acta Pol Pharm 2015;72(4):757–767. PMID:26647633.
[142] Alinezhad H, Baharfar R, Zare M, Azimi R, Nabavi SF, Nabavi SM. Biochemical activities of acetone extracts of Hyssopus angustifolius. Acta Pol Pharm 2012;69(4):617–622. PMID:22876603.
[143] Horváth B, Mukhopadhyay P, Kechrid M, Patel V, Tanchian G, Wink DA, *et al*. β-Caryophyllene ameliorates cisplatin-induced nephrotoxicity in a cannabinoid 2 receptor-dependent manner. Free Radic Biol Med 2012;52(8):1325–1333. doi:10.1016/j.freeradbiomed.2012.01.014, PMID:22326488.
[144] Ahmadvand H, Tavafi M, Asadollahi V, Jafaripour L, Hadipour-Moradi F, Mohammadrezaei-Khoramabadi R, *et al*. Protective effect of carvacrol on renal functional and histopathological changes in gentamicin-induced-nephrotoxicity in rats. Zahedan Res Med Sci 2016;18(4):e6446. doi:10.17795/zjrms-6446.
[145] Goulas V, Gomez-Caravaca AM, Exarchou V, Gerothanassis I. P, Segura-Carretero A, Gutiérrez AF. Exploring the antioxidant potential of *Teucrium polium* extracts by HPLC–SPE–NMR and on-line radical-scavenging activity detection. LWT - Food Sci Technol 2012;46(1):104–109. doi:10.1016/j.lwt.2011.10.019.
[146] Petropoulos GA. Fenugreek-the genus Trigonella. 1st ed. London: CRC Press; 2002:120–127.
[147] Basu A, Basu SK, Ashwani K, Sharma M, Chalghoumi R, Hedi A, *et al*. Fenugreek (*Trigonella foenum-graecum* L.), a potential new crop for Latin America. Am J Soc Issues Humanit 2014;4:145–162.
[148] Belguith-Hadriche O, Bouaziz M, Jamoussi K, El Feki A, Makni-Ayedi F. Renoprotective effects of fenugreek seeds against oxidative stress in hypercholesterolemic fed rats. Herald J Agric Food Sci Res 2014;3(1):7–13.
[149] Keskes H, Belhadj S, Jlail L, El Feki A, Sayadi S, Allouche N. LC-MS-MS and GC-MS analyses of biologically active extracts of Tunisian Fenugreek (*Trigonella foenum-graecum* L.) Seeds. J Food Meas Charact 2018;12(1):209–220. doi:10.1007/s11694-017-9632-0.
[150] Nassiri-Asl M, Hosseinzadeh H. Review of the pharmacological effects of Vitis vinifera (Grape) and its bioactive compounds. Phytother Res 2009;23(9):1197–1204. doi:10.1002/ptr.2761, PMID:19140172.
[151] Valli Kanagarla NSSA, Kuppast IJ, Veerashekar T, Laxman Reddy C. A review on benefits and uses of *Vitis vinifera* (Grape). Res Rev BioSci 2013;7(5):175–180.
[152] Zabad IEM, Amin MN, El-Shishtawy MM. Protective effect of vanillin on diabetic nephropathy by decreasing advanced glycation end products in rats. Life Sci 2019;239:117088. doi:10.1016/j.lfs.2019.117088, PMID:31759039.
[153] Asif M. A review on various medicinal plants with for nephroptotective activity. Int J Recent Adv Biotech Nanotech 2017;1(1):1–29.