REVIEW
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The natural sources, extraction, and nephroprotective function of oleanolic acid and ursolic acid: a review

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Competing interests
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Abbreviations
8-iso-PGF2α, 8-epi-prostaglandin F2α; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; AA, aristolochic acid; AAN, aristolochic acid nephropathy; Aco2, aconitase 2; AKI, acute kidney injury; AKT, protein kinase B; APAP, acetaminophen; AR, aldose reductase; ARAP1, angiotensin II type 1 receptor-associated protein; ASC, apoptosis-associated speck-like protein 4 containing CARD; ASE, accelerated solvent extraction; α-SMA, α-smooth muscle actin; AT1R, angiotensin II type 1 receptor; ATF4, activating transcription factor 4; Atg, autophagy-related protein; Bax, Bcl-2-associated X protein; Bcl-2, B cell leukaemia/lymphoma 2; BUN, blood urea nitrogen; BW, body weight; CAT, catalase; CCl_4, carbon tetrachloride; CHOP, CCAAT/enhancer-binding protein (C/EBP) homologous protein; CKD, chronic kidney diseases; COM, calcium oxalate monohydrate; COX-2, cyclooxygenase-2; CP, cisplatin; CsA, cyclosporine; CTGF, connective tissue growth factor; CypD, Cyclophilin D; Cyt-C, cytochrome C; DN, diabetic nephropathy; EMT, Epithelial-mesenchymal transdifferentiation; ER, endoplasmic reticulum; ERK, extracellular-regulated kinase; ERS, endoplasmic reticulum stress; FBG, fasting blood glucose; FN, fibronectin; GCLc, γ-glutamylcysteine ligase; GLI, glyoxalase I; GMCs, glomerular mesangial cells; GPX, glutathione peroxidase; GRP78, 78 kDa glucose-regulated protein; GSH, glutathione; HEK293T, human embryonic kidney 293T; HK-2, human proximal tubule epithelial-originated kidney-2; HO-1, heme oxygenase-1; HRE, heat reflux extraction; IL-1β, interleukin 1β; ILK, integrin-linked protein kinase; I/R, Ischemia/reperfusion; IRE1α, inositol-requiring enzyme-1α; Keap1, Kelch-like ECH-associated protein 1; KI, kidney index; KIM-1, kidney injury molecule 1; KW, kidney weight; LC3B, microtubule-associated protein 1A/1B-light chain 3B; Lonp1, LN, lupus nephritis; Lon protease 1; LPS, lipopolysaccharide; MAE, microwave-assisted extraction; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemotactic protein 1; MDA, malondialdehyde; ME, maceration; MMP-9, matrix metalloproteinase-9; mTOR, mammalian target of rapamycin; MyD88, myeloid differentiation primary response protein 88; NF-κB, nuclear factor-kappa B; NGAL, neutrophil gelatinase-associated lipocalin; NLRP3, NOD-like receptor thermal protein domain associated protein 3; NOX2, NADPH oxidase 2; Nrf2, nuclear factor erythroid 2-related factor 2; OA, oleanolic acid; OTA, ochratoxin A; p-AMPK, phosphorylated AMP-activated protein kinase; p-eIF2α, phosphorylated α subunit of eukaryotic translation initiation factor 2; PGC-1α, peroxisome proliferators-activated receptor γ coactivator 1-α; PI3K, phosphatidylinositol 3-kinase; p-PERK, phosphorylated protein kinase R-like ER kinase; p-Smad, phosphorylated mothers against decapentaplegic homologue; PTEN, phosphatase and tensin homolog; ROS, reactive oxygen species; SCr, serum creatinine; SE, Soxhlet extraction; SFE, supercritical fluid extraction; Sig-1R, Sigma 1-type opioid receptor; SOD, superoxide dismutase; STAT3, signal transducer and activator of transcription 3; SUMO1, small ubiquitin like modifier 1; TAC, total antioxidant capacity; TGF-β1, transforming growth factor β1; TIMP-1, tissue inhibitor of metalloproteinases 1; TLR4, toll-like receptor 4; TNF-α, tumour necrosis factor-α; TRAP1, tumor necrosis factor receptor-associated protein 1; UA, Ursolic acid; UAE, ultrasonic-assisted extraction; UMA, urinary microalbumin; UUO, unilateral ureteral obstruction.

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Abstract
Oleanolic acid (OA) and ursolic acid (UA) are commonly present in the cuticular wax of many edible fruits and medicinal herbs. OA and UA belong to the group of bioactive pentacyclic triterpenoids, exhibiting a wide range of beneficial effects including protection for the kidneys, liver, heart, gastrointestinal tract, and spinal cord. Additionally, OA and UA exhibit antioxidant, anti-ferroptotic, anti-apoptotic, anti-inflammatory, anti-tumor, anti-viral, anti-diabetic, anti-microbial, anti-parasitic, analgesic, wound-healing, hypolipidemic, and hypoglycemic properties, often without notable side effects. Due to the extensive array of their positive functions, it is not feasible to thoroughly cover all aspects in this review. Therefore, the primary focus lies on reviewing the natural sources, extraction, and nephroprotective properties of OA and UA. To summarize, current literatures highlight the nephroprotective mechanisms of OA and UA, primarily involving inhibiting oxidative stress, endoplasmic reticulum stress, glycative stress, dyslipidemia, inflammation, apoptosis, pyroptosis, and renal fibrosis, promoting diuresis, as well as fine-tuning autophagy.

Keywords: oleanolic acid; ursolic acid; natural sources; nephroprotective; nephrotoxicity

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Background

Oleanolic acid (OA), chemically known as 3β-hydroxy-olea-12-en-28-oic acid (Figure 1), is a bioactive pentacyclic triterpenoid that has been extracted from over 1600 plant species, with the majority being edible plants and medicinal herbs [1]. Among triterpenes, pentacyclic OA stands out due to its unique biological activities, including nephro-, hepato-, cardio-, gastro-, and spinal cord-protective effects [2]. Additionally, it exhibits antioxidant properties, prevents ferroptosis [3], suppresses apoptosis [4], mitigates inflammation [5], and demonstrates anti-cancer, anti-viral, anti-diabetic, anti-microbial, anti-parasitic, analgesic, wound-healing [1], hypolipidemic, and hypoglycemic effects [6], often without observable side effects [7]. In addition, it is considered highly safe, with an oral LD_{50} value in mice greater than 2 g/kg [8]. Moreover, in rats treated daily with 60 mg/kg intraperitoneally for 6 weeks, no adverse effects on animal health were reported [8].

Ursolic acid (UA), also known as 3β-hydroxyl-urs-12-en-28-oic acid (Figure 1), belongs to the ursane-type pentacyclic triterpenoids and is a structural isomer of OA, differing only in the position of one methyl group [9]. UA is commonly found in the cuticular wax of various highly edible fruits, particularly those within the Rosaceae family such as apple, loquat, pear, peach and quince [10], as well as in holy basil [11]. UA exhibits numerous beneficial effects [11], and in animal models of specific diseases, its administration has been shown to protect and maintain the functionality of various organs including the liver, kidneys, pancreas, skeletal muscle, and brain [9]. UA has demonstrated beneficial effects in rodent models of hypertension, obesity, diabetes, and diabetic complications such as atherosclerosis [9]. Furthermore, UA boasts a high safety profile, with LD_{50} values exceeding 637 mg/kg and 8330 mg/kg for intraperitoneal and oral routes in mice, respectively, in mice [11]. Injection of UA at a dose of 3500 mg/kg hypodermically did not result in any mortality within 72 hours in mice [11]. Similarly, hypodermic injection of UA at a dose of 500 mg/kg for 30 days in rats did not elicit any discernible effects on body weight, blood parameters, cardiogram, liver, or kidney functions compared to control rats, with no observable pathological changes in vital organs [11].

Considering the extensive range of beneficial functions associated with OA and UA, it is not feasible to thoroughly cover all aspects in this review. Therefore, this article primarily focuses on reviewing the natural sources of these compounds and their nephroprotective functions, which have not been comprehensively reviewed in existing literature.

Natural sources of OA and UA

Natural sources of OA

OA is abundantly present in various fruit skins, including olive, cranberry, strawberry, blueberry, cherry, persimmon, grape, prune, fig, apricot, orange, and lemon, as well as in food sources such as argan, papaya, and date [1,4]. Additionally, it is found in various medicinal herbs such as *Ligustrum lucidum* Ait [12, 13], *Eriobotrya japonica* (Thunb.) Lindl. [13], *Salvia officinalis* L. [14], *Chaenomeles* [15], *Flos campsis*, *Folium photiniae* [16], *Arctostaphylos uva ursi* Leaves [17], *Swertia angustifolia* Leaves & Stems [18], and *Rosmarinus officinalis* L. [19, 20]). Tabulated partial reports on the natural sources of OA are provided in Table 1.

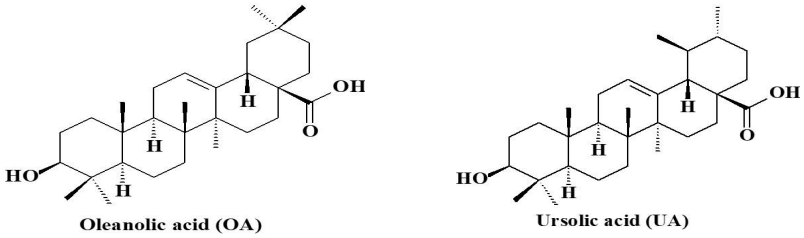

Figure 1 Chemical structure of OA and UA

Table 1 The natural sources and contents of oleanolic acid

Cultivars	Contents (mg/g dry weight)	References	Cultivars	Contents (mg/g dry weight)	References
Ziziphus jujuba	0.0285~0.6272	[21]	table olives	0.170~0. 841	[22]
Eriobotrya japonica Lindl. flowers	0.38~0.51	[23]	*Cornus officinalis* Sieb. et Zucc.	0.812~0.853	[12]
Eriobotrya japonica Lindl. leaves	1.4	[24]	*Fructu Ligustrum lucidum* Ait	5.963~6.261	[12]
green raisins	0.79	[25]	*Plantago asiatica* Linn.	1.142~1.199	[12]
Sultana raisins	0.659	[25]	*Prunus mume* Sieb. et Zucc.	0.547~0.574	[12]
Kyoho raisins	0.385	[25]	*Hedyotis diffusa Willd*	0.129~0.135	[12]
cranberries	0.178	[25]	*Eriobotrya japonica* leaf	0.699~0.734	[12]
blueberries	0.139	[25]	*Crataegus pinnatifida* Bge.	0.932~0.983	[12]
cherries	0.017	[25]	*Gardenia jasminoides* Ellis	0.124~0.13	[12]
Argania spinosa leaves	1.605~1.931	[26]	*Achyranthes bidentata* Bl.	0.004	[12]
Argania spinosa fruits	0.4~0.492	[26]	*Hedyotis diffusa*	0.917	[27]
Plantago major L. leaves	0.7	[28]	*Cornus officinalis* Sieb. Et Zucc.	0.101	[29]
Plantago major L. Seeds	0.05	[28]	*Rabdosia rubescens*	0.245~0.542	[30]
Eriobotrya japonica	2.19	[13]	*Sambuci* fructus	1.2~1.8	[31]

(Thunb.) Lindl.					
Prunella vulgaris L.	1.12	[13]	*Chaenomeles sinensis* fruits	0.05~0.3	[32]
Chaenomeles speciosa (Sweet) Nakai	4.88	[13]	*Chaenomeles cathayensis*	6.22	[15]
Ligustrum lucidum Ait.	16.87	[13]	*Chaenmoeles lagenaria*	4.82	[15]
Cornus officinalis Sieb. et Zucc.	0.63	[13]	*Chaenomeles thibetica*	5.26	[15]
Folium Ilicis Purpureae	1.36~2.03	[33]	*Chaenomeles sieneis*	14.4	[15]
Mentha spp.	0.12~2.41	[34]	*Chaenomeles japonica*	8.22	[15]
Chaenomeles speciosa peels	0.311	[35]	apples peels	3.6	[36]
Chaenomeles speciosa flesh	0.471	[35]	*Rosa Multiflora* Thunb. roots	0.387	[37]
Chaenomeles speciosa endocarps	0.918	[35]	*Rosa Multiflora* Thunb. stems	0.154	[37]
Chaenomeles sinensis peels	0.09	[35]	*Rosa Multiflora* Thunb. fruits	0.272~0.867	[37]
Chaenomeles sinensis flesh	0.102	[35]	*Pyrola calliantha*	0.98~1.15	[38]
Chaenomeles sinensis endocarps	0.193	[35]	*Ligustrum lucidum* Ait	78.3	[16]
Mesona chinensis Benth.	0.88~1.42	[39]	*Folium photiniae*	27.9	[16]
Sambucus chinensis Lindl	0.26~0.41	[40]	*Flos campsis*	65.5	[16]
Sambucus adnata Wall	2.1	[41]	*Sambucus nigra* L.	4.7	[42]
Nepeta bracteate	0.425~1.033	[43]	*Viscum album* L.	6.28	[42]
Ziziphora clinopodioides	0.76	[44]	*Lycopi Herba*	1.32	[45]
Rubus suavissimus S. Lee	0.0562~0. 273	[46]	*Pterocephalus hookeri*	0.21~1.12	[47]
Damnacanthus indicus	0.064~0.095	[48]	*Hyssopus officinalis* L.	1.43	[14]
almonds green husk extracts	1.01	[49]	*Marrubium vulgare* L.	0.16	[14]
Macrocarpium officinalis (Sieb. et Zucc.) Nakai	0.5~0.82	[50]	*Melissa officinalis* L.	1.7	[14]
Chaenomeles sinensis Koehne	0.378	[51]	*Salvia officinalis* L.	6.53	[14]
Perilla frutescens Leaves	1.1~1.61	[52]	*Satureja montana* L.	1.38	[14]
Perilla frutescens Aerial parts	0.66~1.01	[52]	*Rosmarinus officinalis* L.	9.09	[19]
Perilla frutescens Stems	0.22~0.36	[52]	*Salvia officinalis* L.	7.56	[19]
Perilla frutescens Roots	0.19~0.30	[52]	*Salvia sclarea* L.	0.95	[19]
Celastrus orbiculatus Thunb. Roots	0.256	[53]	*Salvia glutinosa* L.	0.90	[19]
Celastrus orbiculatus Thunb. Stems	0.675	[53]	*Satureja montana* L.	5.36	[19]
Celastrus orbiculatus Thunb. Barks	0.519	[53]	*Arctostaphylos uva ursi* Leaves	4.47	[17]
Celastrus orbiculatus Thunb. Leaves	0.183	[53]	*Gaultheria procumbens* Leaves	1.58	[17]
Swertia angustifolia Leaves & Stems	6.77~28.47	[18]	*Vaccinium myrtillus* Leaves	1.78	[17]

Swertia mussotii Leaves & Stems	6.30~39.59	[18]	*Vaccinium vitis idaea* Leaves	0.74	[17]
Swertia racemosa Leaves & Stems	11.00~16.50	[18]	apple pomace	4.70	[54]
Swertia graciliescens Leaves & Stems	12.86~26.98	[18]	apple (*Malus domestica*) peels	0.96	[10]
Swertia nervosa Leaves & Stems	3.56~7.02	[18]	peach (*Prunus persica*) peels	1.49	[10]
Swertia franchetiana Leaves & Stems	6.31~27.76	[18]	pear (*Pyrus communis*) peels	1.25	[10]
rosemary	6.6~15.5	[20]	quince (*Chaenomeles japonica*) peels	0.25	[10]
Sambuci flos Flowers	2.06	[55]	loquat (*Eriobotrya japonica*) peels	1.46	[10]

Table 2 The natural sources and contents of ursolic acid

Cultivars	Contents (mg/g dry weight)	References	Cultivars	Contents (mg/g dry weight)	References
Ziziphus jujuba	0.0616~1.5124	[21]	*Cornus officinalis* Sieb. et Zucc.	1.868~1.993	[12]
Eriobotrya japonica Lindl. flowers	2.15~2.68	[23]	*Fructu Ligustrum lucidum* Ait	1.423~1.566	[12]
Eriobotrya japonica Lindl. leaves	5.6	[24]	*Plantago asiatica* Linn.	2.133~2.222	[12]
cranberries	0.659	[25]	*Prunus mume* Sieb. et Zucc.	2.900~3.021	[12]
blueberries	0.118	[25]	*Hedyotis diffusa Willd*	0.227~0.236	[12]
cherries	0.097	[25]	*Eriobotrya japonica* leaf	1.423~1.666	[12]
persimmon	0.01	[25]	*Crataegus pinnatifida* Bge.	6.679~6.957	[12]
Argania spinosa leaves	1.997~4.541	[26]	*Gardenia jasminoides* Ellis	0.310~0.358	[12]
Argania spinosa fruits	0.465~1.08	[26]	*Achyranthes bidentata* Bl.	0.007	[12]
Plantago major L. leaves	2.2	[28]	*Hedyotis diffusa*	3.54	[27]
Plantago major L. Seeds	0.07	[28]	*Cornus officinalis* Sieb. Et Zucc.	0.282	[29]
Eriobotrya japonica (Thunb.) Lindl.	10.15	[13]	*Rabdosia rubescens*	1.058~2.298	[30]
Prunella vulgaris L.	5.47	[13]	*Sambuci* fructus	3.0~5.7	[31]
Chaenomeles speciosa (Sweet) Nakai	6.26	[13]	*Chaenomeles sinensis* fruits	0.4~2.0	[32]
Ligustrum lucidum Ait.	4.29	[13]	*Chaenomeles cathayensis*	4.21	[15]
Cornus officinalis Sieb. et Zucc.	2.74	[13]	*Chaenmoeles lagenaria*	2.60	[15]
Folium Ilicis Purpureae	0.63~1.98	[33]	*Chaenomeles thibetica*	4.28	[15]
Mentha spp.	0.39~5.72	[34]	*Chaenomeles sieneis*	6.24	[15]
Chaenomeles speciosa peels	0.239	[35]	*Chaenomeles japonica*	5.62	[15]
Chaenomeles speciosa flesh	0.376	[35]	apples peels	14.9	[36]
Chaenomeles speciosa endocarps	0.688	[35]	golden-red apple peels	0.108	[56]
Chaenomeles sinensis peels	0.08	[35]	golden-red apple flesh	0.006	[56]
Chaenomeles sinensis flesh	0.052	[35]	golden-red apple pomaces	0.0498	[56]
Chaenomeles sinensis endocarps	0.177	[35]	*Rosa Multiflora* Thunb. roots	0.384	[37]
Pyrola calliantha	4.62~6.15	[38]	*Rosa Multiflora* Thunb. stems	0.115	[37]

Ligustrum lucidum Ait	20.7	[16]	*Rosa Multiflora* Thunb. fruits	0.160~0.641	[37]
Folium photiniae	79.8	[16]	*Ziziphora clinopodioides*	1.176	[44]
Flos campsis	60.4	[16]	*Rubus suavissimus* S. Lee	0.411~1.12	[46]
Sambucus adnata Wall	4.2	[41]	*Hyssopus officinalis* L.	4.07	[14]
Nepeta bracteate	0.733~2.217	[43]	*Marrubium vulgare* L.	0.32	[14]
Lycopi Herba	1.59	[45]	*Melissa officinalis* L.	6.12	[14]
Pterocephalus hookeri	0.43~0.53	[47]	*Salvia officinalis* L.	18.61	[14]
Damnacanthus indicus	0.134~0.187	[48]	*Satureja montana* L.	5.07	[14]
almonds green husk extracts	0.68	[49]	*Rosmarinus officinalis* L.	15.8	[19]
Macrocarpium officinalis (Sieb. et Zucc.) Nakai	1.07~1.7	[50]	*Salvia officinalis* L.	15.16	[19]
Chaenomeles sinensis Koehne	0.626	[51]	*Salvia sclarea* L.	0.91	[19]
Perilla frutescens Leaves	3.12~4.11	[52]	*Salvia glutinosa* L.	1.91	[19]
Perilla frutescens Aerial parts	2.02~2.86	[52]	*Satureja montana* L.	0.94	[19]
Perilla frutescens Stems	0.78~0.95	[52]	*Arctostaphylos uva ursi* Leaves	18.61	[17]
Perilla frutescens Roots	0.42~0.58	[52]	*Gaultheria procumbens* Leaves	5.76	[17]
Swertia angustifolia Leaves & Stems	0.48~1.83	[18]	*Vaccinium myrtillus* Leaves	1.30	[17]
Swertia mussotii Leaves & Stems	0.41~0.42	[18]	*Vaccinium vitis idaea* Leaves	2.50	[17]
Swertia racemosa Leaves & Stems	0.61~0.77	[18]	*Celastrus orbiculatus Thunb.* Roots	0.372	[53]
Swertia graciliescens Leaves & Stems	0.92~0.95	[18]	*Celastrus orbiculatus Thunb.* Stems	0.156	[53]
Swertia nervosa Leaves & Stems	0.33~0.50	[18]	*Celastrus orbiculatus Thunb.* Barks	0.110	[53]
Swertia franchetiana Leaves & Stems	0.48~1.60	[18]	*Celastrus orbiculatus Thunb.* Leaves	0.0677	[53]
apple pomace	7.06	[54]	apple (*Malus domestica*) peels	9.38	[10]
rosemary	10.2~27.5	[20]	peach (*Prunus persica*) peels	2.97	[10]
Sambuci flos Flowers	11.56	[55]	pear (*Pyrus communis*) peels	7.25	[10]
Mesona chinensis Benth.	2.53~4.02	[39]	quince (*Chaenomeles japonica*) peels	5.69	[10]
Sambucus chinensis Lindl	2.46~3.45	[40]	loquat (*Eriobotrya japonica*) peels	8.01	[10]
Sambucus nigra L.	8.9	[42]			

Natural sources of UA

UA serves as the predominant waxy component naturally found in apple peels [10, 36]. Additionally, it is present in various edible plants, including *Eriobotrya japonica* Lindl. Leaves [24], *Crataegus pinnatifida* Bge., *Plantago asiatica* Linn., *Prunus mume* Sieb. et Zucc. [12], *Eriobotrya japonica* (Thunb.) Lindl., *Chaenomeles speciosa* (Sweet) Nakai, *Prunella vulgaris* L., *Ligustrum lucidum* Ait. [13], *Chaenomeles* [15], *Flos campsis* [16], *Salvia officinalis* L. [14], *Arctostaphylos uva ursi* Leaves [17], and *Rosmarinus officinalis* L. [19, 20]. Partial reports detailing the natural sources of UA are provided in Table 2

Extraction of OA and UA

Traditional extraction techniques, such as maceration (ME), Soxhlet extraction (SE), and heat reflux extraction (HRE), had primarily been used to extract OA and UA from fruits and medicinal plants [57]. The choice of method and/or solvents depended on the raw material [58]. Conventional solvents used for extracting OA and UA include water, lower alcohols and their mixtures with water, chloroform, acetone, hexane, diethyl ether, and ethyl acetate [58].

Modern techniques such as assisted extraction methods and supercritical fluid extraction (SFE) offered significant advantages over conventional methods, including enhanced mass transfer rates, reduced solvent volume, prevention of thermo-sensitive compounds degradation, and shortened processing times [58]. These improvements resulted in lower energy consumption and higher yields [58]. For example, ultrasonic-assisted extraction (UAE), microwave-assisted extraction (MAE), and accelerated solvent extraction (ASE) had been employed to enhance extraction selectivity and minimize extraction times, achieving efficient extraction and recovery [58]. UAE had successfully extracted OA and UA from various plants such as *Hedyotis diffusa* [59], *H. corymbosa* [60], *Rosmarinus officinalis* leaves [61], *Ligustrum lucidum* Ait [62], and *Punica granatum* L. flowers [63]. MAE reduced solvent usage, enhanced efficiency, and improved extraction rates [58]. It had effectively extracted OA and UA from red jujubes, gardenia, loquat leaves, cinquefoil herb [58], *Ligustrum lucidum* Ait [64], *Lamii albi flos* [57], and *Swertia* [65]. ASE had also been successful in extracting OA and UA from *Lamii albi flos* [57]. SFE offered superior selectivity and specificity in OA and UA extraction [58]. It had been effectively applied to extract these compounds from eriobotrya leaves and *Hedyotis diffusa* [58].

Moreover, the adoption of integrated technologies reduced extraction times [58]. For instance, a combined approach involving supercritical CO_2 extraction at room temperature, molecular distillation, and UAE was proposed for simultaneous extraction of essential oil and UA from wild *Ledum palustre* [58].

Nephroprotective function of OA and UA

Protective effects of OA or UA on diabetic nephropathy (DN)

Diabetes stands as one of the principal culprits behind chronic kidney diseases (CKD), encompassing DN [66]. However, recent investigation unveiled that complications pertaining to kidney function in diabetes commence during the prediabetic phase [66]. Gamede et al. [66] documented that OA administration (80 mg/kg orally for 12 weeks) could mitigate oxidative stress while reinstating plasma aldosterone and kidney injury molecule 1 (KIM-1) levels, alongside regulating urine electrolytes in the kidneys of male Sprague Dawley prediabetic rats induced by a high-fat high-carbohydrate diet. In another study, Lee et al. [67] observed that Otsuka Long-Evans Tokushima Fatty rats treated with OA (100 mg/kg) via oral gavage for 20 weeks exhibited increased blood insulin secretion and superoxide dismutase (SOD) levels, alongside reduced triglyceride levels and urinary albumin/creatinine ratios. Moreover, OA treatment facilitated renal structural recovery by upregulating nephrin and endothelial selective adhesion molecules and downregulating endoplasmic reticulum (ER) stress (ERS) and renal fibrosis, evidenced by decreased expressions of transforming growth factor β1 (TGF-β1)/phosphorylated mothers against decapentaplegic homologue (p-Smad)2/3 [67]. In summary, OA exhibited therapeutic potential against DN by exerting antioxidant effects, reducing ERS, and mitigating renal fibrosis [67].

Additionally, dyslipidemia and inflammation play pivotal roles in DN development [7]. Liu et al. [7] demonstrated that administering 50 mg OA/kg or 100 mg OA/kg orally for 18 weeks notably lowered fasting blood glucose (FBG), kidney index (KI), serum lipid, 24-hour urinary microalbumin (UMA), serum creatinine (SCr), and uric acid levels in diabetic rats. OA treatment also obviously attenuated renal structure abnormalities and lipid accumulation in diabetic rats [7]. Furthermore, OA upregulated protein expression levels of nephrin, phosphorylated AMP-activated protein kinase (p-AMPK), and peroxisome proliferators-activated receptor γ coactivator 1-α (PGC-1α), while downregulating expressions of macrophage marker CD68, Collagen-IV, toll-like receptor 4 (TLR4), nuclear factor-kappa B (NF-κB), and TGF-β1 in renal tissues of OA-treated diabetic rats [7]. In brief, OA could ameliorate renal injury in diabetic rats by improving lipid metabolism and mitigating inflammation through the AMPK/PGC-1α and TLR4/NF-κB signaling pathways [7].

Ling et al. [68] documented that streptozotocin-induced diabetic rats treated with 0.2% UA for 16 weeks exhibited notable reductions in urine albumin excretion, oxidative stress, NF-κB activity, and P-selectin expression, thereby preventing histopathologic and biochemical changes associated with diabetes in the kidneys. Furthermore, Wu et al. [69] reported that UA (50 mg/kg, orally) and empagliflozin (10 mg/kg, orally), either alone or in combination for 8 weeks, could alleviate increases in blood glucose, glycosylated haemoglobin, blood lipid levels, inflammatory factors (tumour necrosis factor-α (TNF-α), interleukin 1β (IL-1β), IL-6), oxidation factors (SOD, malondialdehyde (MDA), glutathione (GSH), catalase (CAT), nitric oxide), renal fibrosis and pro-fibrosis factors (fibronectin (FN), E-cadherin, matrix metalloproteinase-9 (MMP-9), tissue inhibitor of metalloproteinases 1 (TIMP-1), α-smooth muscle actin (α-SMA), TGF-β1, Smad, mitogen-activated protein kinase (MAPK)) in a diabetic rat model. These treatments also ameliorated DN by preventing abnormal proliferation of glomerular mesangial cells under high-glucose conditions, aberrant apoptosis, and excessive generation of reactive oxygen species (ROS) [69]. Moreover, Xu et al. [70] demonstrated that UA administration (35 mg/kg, intragastrically) for 8 weeks notably decreased levels of FBG, kidney weight (KW)/body weight (BW), blood urea nitrogen (BUN), SCr, and MDA, while increasing SOD activity in diabetic rats. Additionally, UA treatment effectively mitigated renal structural abnormalities and the upregulation of TNF-α, monocyte chemotactic protein 1 (MCP-1), and IL-1β expression levels [70]. In summary, UA exhibited nephroprotective effects through its antioxidant and anti-inflammatory properties [70]. Ma et al. [71] reported that feeding 0.3% UA for 10 weeks effectively reduced BW, the urinary albumin/creatinine ratio, and blood glucose levels, and improved glomerulosclerosis index and renal tissue lesions in db/db mice. Compared with Group DN, UA-induced reductions in renal protein levels of angiotensin II type 1 receptor-associated protein (ARAP1), angiotensin II type 1 receptor (AT1R), NADPH oxidase 2 (NOX2), NOX4, FN, TGF-β1, collagen IV, IL-1β, and IL-18 were observed *in vivo* and/or *in vitro* [71]. In summary, UA mitigated renal injury in type 2 diabetic db/db mice by downregulating proteins in the ARAP1/AT1R signaling pathway, thereby inhibiting oxidative stress, extracellular matrix accumulation, inflammation, and fibrosis [71].

Wang et al. [72] observed that treatments with OA or UA at concentrations of 0.1% and 0.2% for 10 weeks obviously reduced renal aldose reductase (AR) activity and dose-dependently downregulated renal AR mRNA expression in diabetic mice. Furthermore, OA or UA at 0.2% notably decreased renal sorbitol dehydrogenase activity [72]. OA treatments at doses of 0.1% or 0.2% dose-dependently elevated renal glyoxalase I (GLI) activity, upregulated renal GLI mRNA expression and reduced renal methylglyoxal level [72]. These notable anti-glycative stress effects suggest that supplementation with OA or UA could be beneficial for preventing or alleviating renal diseases associated with glycation [72].

In conclusion, OA or UA could attenuate DN by mitigating oxidative stress, ERS, glycative stress, dyslipidemia, inflammation, and renal fibrosis.

Protective effects of OA or UA on drug-induced renal injury

Potočnjak et al. [5] explored the therapeutic potential of OA (administered at doses of 10 and 40 mg/kg for 2 days) in cisplatin (CP, at a dose of 13 mg/kg)-induced nephrotoxicity. CP administration resulted in elevated serum markers, histological signs of kidney injury, increased renal expression of antioxidant and anti-inflammatory markers, and elevated protein levels of activation of extracellular-regulated kinase (ERK) 1/2, signal transducer and activator of transcription 3 (STAT3), NF-κB, microtubule-associated protein 1A/1B-light chain 3B (LC3B)-II, and autophagy-related protein (Atg) 5 [5]. However, treatment with OA attenuated these effects, suggesting its potential in ameliorating CP-induced nephrotoxicity by suppressing oxidative stress, apoptosis, autophagy, and inflammatory response [5].

Abdel-Zaher et al. [73] demonstrated that pretreatment of rats with OA (at a dose of 25 mg/kg intramuscularly) provided marked protection against nephrotoxicity and hepatotoxicity triggered by an acute oral toxic dose of acetaminophen (APAP) (at 2.5 g/kg). Likewise, daily administration of a lower dose of OA (5 mg/kg) to rats, along with a reduced toxic dose of APAP (750 mg/kg), for one week also conferred protection against APAP-induced nephrotoxicity and hepatotoxicity [73]. Pretreatment with OA mitigated moderate cloudy swelling of proximal convoluted tubules, severe vacuolar degeneration of distal tubules, elevation in SCr and urea nitrogen levels, and depletion of renal and hepatic intracellular GSH induced by APAP [73]. The prevention of excessive nitric oxide production and the subsequent maintenance of intracellular GSH levels might play a crucial role in the protective effect of OA against APAP-induced renal and hepatic damages [73].

Hong et al. [74] observed that treatment with cyclosporine (CsA) led to reduced kidney function and urine osmolality, accompanied by elevated urine volume and urinary albumin levels. However, these CsA-induced alterations were ameliorated by OA treatment (at a dose of 25 mg/kg via intraperitoneal injection for 1 week) in male ICR mice [74]. Notably, OA administration reduced tubulointerstitial fibrosis and inflammation scores, as well as urinary levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG) and 8-epi-prostaglandin F2α (8-iso-PGF2α) that were elevated in CsA-treated mice [74]. The beneficial effects of OA were attributed to an elevated ratio of nuclear to total nuclear factor erythroid 2-related factor 2 (Nrf2), leading to enhanced expression of heme oxygenase-1 (HO-1), along with a stable expression level of Kelch-like ECH-associated protein 1 (Keap1), suggesting enhanced nuclear translocation of Nrf2 [74]. Additionally, OA treatment significantly mitigated increased apoptotic cell death and a high ratio of B cell leukaemia/lymphoma 2 (Bcl-2)-associated X protein (Bax) to Bcl-2 observed in CsA-treated mice [74]. In summary, OA alleviated chronic CsA nephropathy by repressing oxidative stress, inflammation, and apoptosis [74].

Chen et al. [75] found that pretreatment with *Cynomorium songaricum* extracts, which contain UA as a major ingredient, offered protection against gentamicin-induced nephrotoxicity. This protection was evidenced by decreased levels of SCr and BUN [75]. The observed nephroprotection was linked to enhancements in mitochondrial functional ability, characterized by improved ATP generation [75]. Moreover, there was an improvement in the GSH redox status, possibly facilitated by mitochondrial uncoupling induction in rat kidney tissues [75].

Aristolochic acid (AA) is primarily found in herbal extracts and is known to induce clinical nephropathy [76]. Epidemiological studies have linked aristolochic acid nephropathy (AAN) with a high long-term risk for renal failure and urothelial cancer [76]. Ding et al. [76] demonstrated that treatment with UA (at concentrations of 1, 10, and 20 ppm) could mitigate the AA-induced inflammatory response associated with blood circulation and kidney malformations progression in zebrafish embryos.

In summary, OA or UA could ameliorate drug-induced renal injury by enhancing mitochondrial function and inhibiting oxidative stress, inflammation, apoptosis, and autophagy.

Protective effects of OA or UA on chemical reagents-induced nephrotoxicity

Carbon tetrachloride (CCl_4) is a haloalkane utilized in various industrial and chemical applications [77]. It has been widely employed as a grain fumigant, refrigerant, anthelmintic, fire extinguisher, rodenticide, cleaning agent, and intermediate in the synthesis of chlorofluorocarbons [77]. Ma et al. [77] demonstrated that UA (administered at 50 mg/kg intragastrically once daily for six weeks) significantly mitigated CCl_4-induced nephrotoxicity in a dose-dependent manner in male ICR mice, as indicated by both histopathological examination and diagnostic indicators of kidney damage. Furthermore, UA treatment inhibited the profound elevation of ROS and oxidative stress induced by CCl_4, as evidenced by elevated levels of lipid peroxidation and 8-hydroxy-2-deoxyguanosine (a product of oxidative DNA damage), along with depletion of total antioxidant capacity (TAC) levels in the kidney [77]. UA also enhanced the phosphorylation of STAT3, subsequently activating NF- κ B and reducing the levels of pro-inflammatory cytokines (TNF-α, IL-6, IL-17, and cyclooxygenase-2 (COX-2)) in CCl_4-treated mouse kidneys [77]. In summary, UA's inhibition of CCl_4-induced inflammation could be attributed, at least in part, to its antioxidant activity and its capacity to regulate the STAT3/NF-κB signaling pathways [77].

In summary, UA could alleviate CCl_4-induced nephrotoxicity by inhibiting oxidative stress and inflammation.

Protective effects of OA or UA on mycotoxins-induced nephrotoxicity

Ochratoxin A (OTA), found ubiquitously in a variety of animal feeds and foods [78–80], is a nephrotoxic secondary metabolite [81–85] produced by mycotoxigenic filamentous fungi such as *Aspergillus* and *Penicillium* [86, 87]. Zhang et al. [4] demonstrated that pretreatment with 2 μM OA for 2 hours prominently alleviated OTA-induced mitochondrial-mediated and ERS-mediated apoptosis in human proximal tubule epithelial-originated kidney-2 (HK-2) cells. The protective effect of OA on OTA-induced nephrotoxicity was attributed to the activation of tumor necrosis factor receptor-associated protein 1 (TRAP1), leading to inhibition of 78 kDa glucose-regulated protein (GRP78), phosphorylated protein kinase R (PKR)-like ER kinase (p-PERK), phosphorylated α subunit of eukaryotic translation initiation factor 2 (p-eIF2α), activating transcription factor 4 (ATF4), and CCAAT/enhancer-binding protein (C/EBP) homologous protein (CHOP), Cyclophilin D (CypD), Bax, cytochrome C (Cyt-C), Cleaved Caspase-9, and Cleaved Caspase-3, while promoting Bcl-2 [4].

Li et al. [88] observed that a 24-hour treatment with 8 μM OTA repressed the expression of Lon protease 1 (Lonp1), leading to inhibition of aconitase 2 (Aco2) and TRAP1, consequently elevating ROS and triggering cell death in human embryonic kidney 293T (HEK293T) cells, which could be alleviated by a 2-hour pretreatment with 1 μM UA. Similarly, Zhang et al. [89] found that a 24-hour treatment with 5 μM OTA conspicuously induced mitochondrial-mediated apoptosis by suppressing Lonp1 and Sigma 1-type opioid receptor (Sig-1R), thereby upregulating the protein expressions of GRP78, p-PERK, p-eIF2α, CHOP, inositol-requiring enzyme-1α (IRE1α), and Bax, while suppressing the protein expression of Bcl-2 in HK-2 cells. This effect was significantly alleviated by a 2-hour pretreatment with 4 μM UA [89]. In brief, through mutual facilitation between Lonp1 and Sig-1R, UA effectively mitigated OTA-induced apoptosis *in vitro* and disrupted the vicious cycle between oxidative stress and ERS, thereby suppressing the activation of the mitochondrial-mediated apoptosis [89].

In summary, OA or UA could mitigate OTA-induced nephrotoxicity by inhibiting oxidative stress, ERS- and mitochondrial-mediated apoptosis.

Protective effects of OA or UA on renal fibrosis

Renal interstitial fibrosis is a prevalent pathological characteristic in various kidney diseases that can advance to end-stage renal disease [90]. Epithelial-mesenchymal transdifferentiation (EMT) plays a pivotal role in the progression of renal interstitial fibrosis, ultimately culminating in renal failure [91]. He et al. [91] investigated the impact of OA on EMT in a rat renal proximal tubular epithelial cell line (NRK-52E) induced by TGF-β1. Treatment of NRK-52E cells with TGF-β1 induced EMT, characterized by a transition to a spindle-like morphology, downregulation of E-cadherin expression, and upregulation of α-SMA and FN expression [91]. However, OA treatment reversed all EMT markers in a dose-dependent manner [91]. OA also restored the expression of Nrf2 and klotho, reduced the phosphorylation of Smad2/3, Integrin-linked protein kinase (ILK), and Snail (an EMT initiator) in cells triggered by TGF-β1 [91]. Briefly, OA alleviated renal fibrosis by counteracting TGF-β1-mediated EMT in NRK-52E cells [91]. Chen et al. [92] further demonstrated that OA mitigated diabetic renal fibrosis by enhancing autophagy through the regulation of the miR-142-5p/phosphatase and tensin homolog (PTEN) axis via the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway in NRK-52E cells.

Chung et al. [93] noted that administration of 0.2% OA prominently mitigated unilateral ureteral obstruction (UUO)-induced collagen deposition and fibrosis in the obstructed kidneys of UUO mice on day 7. Moreover, OA-treated mice exhibited notably reduced inflammatory cell infiltration, a decreased ratio of Bax to Bcl-2 expression, and fewer apoptotic cells in the obstructed kidneys [93]. OA promoted nuclear translocation of Nrf2, upregulated the expression of HO-1, heat shock protein 70, and NAD(P)H:quinone oxidoreductase 1, and reduced lipid peroxidation in the obstructed kidney of UUO mice [93]. In summary, OA demonstrated beneficial effects on renal fibrosis by enhancing nuclear translocation of Nrf2, consequently alleviating renal oxidative stress, inflammation, and apoptosis [93]. Additionally, Zhao and Luan [94] discovered that male Sprague-Dawley rats orally administered with OA (6 mg/kg) for 21 days following UUO surgery exhibited evident reductions in KI, levels of SCr and BUN, as well as urinary levels of microalbumin, α1-microglobulin, and *N*-acetyl-β-glucosaminidase, along with collagen deposition. OA treatment also downregulated the mRNA expressions of collagen I, collagen III, FN, and α-SMA, along with the protein expressions of TGF-β, TGF-β receptor I, TGF-β receptor II, and p-Smad2 [94]. In summary, OA could relieve renal fibrosis by targeting the TGF-β/Smad pathway [94].

Pei et al. [90] established a UUO model by surgically ligating the right ureter of rats and administered UA preparation (40 mg/kg) via oral gavage post-operation, once daily for 7 days. UA treatment drastically ameliorated the increased renal dysfunction, pathological damage, renal interstitial fibrosis, apoptosis, oxidative stress damage, and decreased antioxidant levels induced by UUO [90]. Specifically, UA exhibited renal protective effects against interstitial fibrosis by notably activating the Nrf2/HO-1 signaling pathway in kidney tissue post-UUO [90].

Mao et al. [95] established a mouse model of kidney fibrosis through UUO and administered various doses of UA (50, 100, 200 mg/kg) via continuous intragastric administration for 7 days post-operation. In comparison to the model group, the UA-treated groups exhibited significant reductions in creatinine and urea nitrogen levels, decreased collagen deposition, ameliorated inflammatory cell infiltration, elevated expression of E-cadherin, and reduced expression of α-SMA, TGF-β1, and p-Smad2/3 [95]. In essence, UA attenuated renal fibrosis and renal tubular EMT by suppressing the TGF-β1/Smads signaling pathway [95].

Thakur et al. [11] induced a CKD model in adult male albino Wistar rats by feeding them adenine at a concentration of 0.75% for 28 days. Adenine feeding resulted in an increased KW/BW index, impaired kidney function indicated by elevated markers such as serum urea, uric acid, cystatin C, creatinine, and neutrophil gelatinase-associated lipocalin, and triggered a fibrotic response in the kidney by upregulating profibrotic proteins including TGF-β1, FN, connective tissue growth factor (CTGF), and collagen [11]. However, simultaneous administration of UA (30 mg/kg) with adenine feeding for 28 days reversed the damage induced by adenine, as evidenced by the reduction in kidney injury and fibrosis markers [11].

In summary, OA or UA exhibited protective effects against renal fibrosis by promoting autophagy while mitigating oxidative stress, inflammation, apoptosis, and fibrosis markers.

Protective effects of OA or UA on lupus nephritis (LN)

Chen et al. [96] demonstrated that UA prominently ameliorated LN in MRL/lpr lupus-prone mice, leading to notable reductions in proteinuria generation, immune cell infiltration, and renal tissue damage. Moreover, UA inhibited IL-1β, IL-18, apoptosis-associated speck-like protein 4 containing CARD (ASC) speck formation, caspase-1, and pyroptosis in primary mouse glomerular mesangial cells (GMCs) and mouse glomerular mesangial cell line (SV40-MES-13) cells [96]. Furthermore, UA promoted the degradation of NOD-like receptor thermal protein domain associated protein 3 (NLRP3) by repressing small ubiquitin like modifier 1 (SUMO1)-mediated SUMOylation of NLRP3 [96].

In summary, UA could attenuate LN by inhibiting pyroptosis.

Protective effects of OA or UA on acute kidney injury (AKI)

Ischemia/reperfusion (I/R)-associated AKI poses a significant clinical challenge in both native and transplanted kidneys [97]. Long et al. [97] investigated the administration of OA (12.5, 25, and 50 mg/kg) to rats for 15 consecutive days before inducing bilateral renal I/R. OA prominently and dose-dependently mitigated I/R-induced renal damage, evidenced by reduced levels of creatinine, BUN, lactate dehydrogenase, and KIM-1 [97]. Additionally, OA exhibited protective effects against oxidative stress, as indicated by diminished levels of MDA, enhanced activities of SOD, CAT, and glutathione peroxidase (GPX), as well as elevated GSH levels [97]. OA also reduced levels of pro-inflammatory cytokines, such as interferon-γ, IL-6, and myeloperoxidase, while increasing the anti-inflammatory cytokine IL-10 [97]. Furthermore, OA prevented I/R-induced increases in caspase-3 levels and apoptosis, accompanied by a decrease in mRNA expression levels of Nrf2 and γ-glutamylcysteine ligase (GCLc) [97]. The stabilization of Nrf2/GCLc signaling and subsequent maintenance of the GSH pool were deemed vital for the protective effects of OA against renal I/R injury [97]. In summary, pretreatment with OA prevented renal damage induced by I/R through its antioxidant, anti-apoptotic, and anti-inflammatory activities [97].

Additionally, Zhao et al. [98] demonstrated that pretreating mice with UA noticeably protected against lipopolysaccharide (LPS)-induced AKI. This protection was attributed to the reduction of inflammatory factors such as TNF-α, IL-6, and IL-1β secretion in macrophages upon LPS stimulation, and the blockade of the LPS-induced TLR4/myeloid differentiation primary response protein 88 (MyD88) pathway [98]. UA was found to enhance autophagy in macrophages by upregulating the expression of both Beclin-1 and LC3B, thereby altering macrophage function [98]. In short, UA could mitigate AKI by suppressing inflammation and enhancing autophagy [98].

To summarize, OA or UA exhibited protective effects against AKI by enhancing autophagy and suppressing oxidative stress, inflammation, and apoptosis.

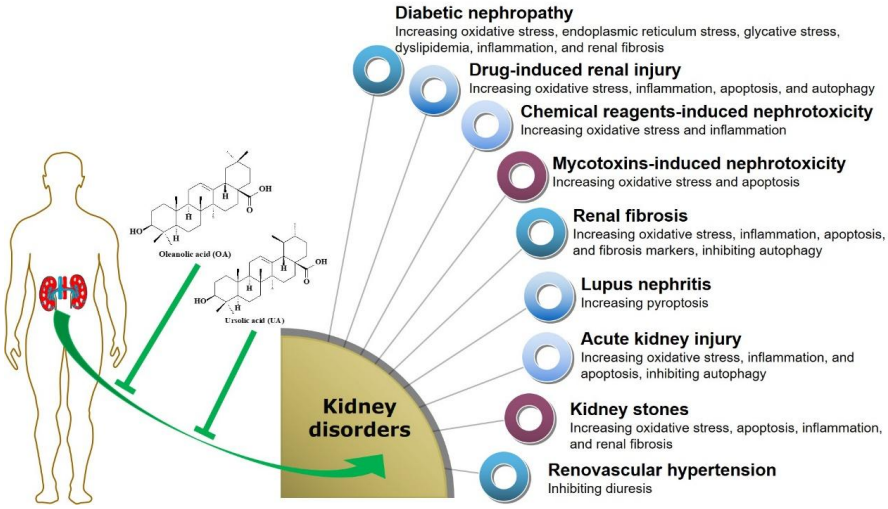

Figure 2 The mechanisms underlying the nephroprotective functions of OA and UA. The symbol ⊥ represents inhibition

Protective effects of OA or UA on kidney stones

Jia et al. [99] investigated the effects of UA (20 mg/kg and 40 mg/kg, administered via gavage) on kidney damage induced by calcium oxalate monohydrate (COM) crystals, a significant component of kidney stones. UA administration led to a reduction in COM crystals in the kidneys of rats with COM-induced nephropathy [99]. Moreover, UA treatment resulted in decreased levels of urea, creatinine, and neutrophil gelatinase-associated lipocalin (NGAL) in rat plasma [99]. UA also mitigated kidney tissue and renal tubular epithelium cell apoptosis, evidenced by the downregulation of Bax expression and the upregulation of Bcl-2 expression [99]. Furthermore, UA attenuated renal fibrosis in COM rats by suppressing α-SMA and collagen I protein expressions in the kidney and renal tubular epithelium cells [99]. Additionally, UA mitigated COM-induced oxidative damage both *in vitro* and *in vivo* by upregulating the Nrf2/HO-1 pathway, leading to increased levels of SOD and reduced levels of MDA [99]. Moreover, UA decreased levels of pro-inflammatory cytokines TNF-α, IL-1β, and IL-6 both *in vitro* and *in vivo* by inhibiting the activation of the TLR4/NF-κB pathway [99].

In summary, UA exhibited a protective effect against kidney stones by mitigating oxidative stress, apoptosis, inflammation, and renal fibrosis.

Protective effects of OA or UA on renovascular hypertension

Ahn et al. [100] reported that OA (at doses of 20 mg/kg or 30 mg/kg administered via oral gavage for 1 or 3 weeks) increased urinary volume, electrolyte excretion (Na^+, K^+, Cl^-), and glomerular filtration rate in normotensive rats, while also reducing arterial blood pressure in hypertensive rats. The cardiorenal benefits of OA are closely linked to its modulation of the cardiac natriuretic hormone system and renin-angiotensin system [100]. Furthermore, Bachhav et al. [101] administered OA (at a dose of 60 mg/kg) to hypertensive rats for 4 weeks and observed improvements in renal tubular cystic dilation and epithelial atrophy. Additionally, OA treatment resulted in decreased SCr levels, increased urinary sodium and potassium excretion, and enhanced urine volume, indicating a diuretic and nephroprotective role for OA.

In summary, OA exhibited beneficial effects in alleviating renovascular hypertension primarily through its diuretic action.

Finally, the mechanisms underlying the nephroprotective functions of OA and UA are summarized in Figure 2.

Perspectives

OA and UA, widely distributed throughout the plant kingdom, exhibit a plethora of biological activities and are considered safe, holding significant research potential for human health. In the realm of kidney protection, numerous researchers have delved into understanding the mechanisms underlying the nephroprotective functions of OA and UA, yielding substantial breakthroughs. Presently, the nephroprotective mechanisms of OA and UA primarily involve the inhibition of oxidative stress, ERS, glycative stress, dyslipidemia, inflammation, apoptosis, pyroptosis, and renal fibrosis, while also promoting diuresis and fine-tuning autophagy. However, the intricacies of kidney protection are manifold and warrant further exploration. For example, are recently discovered regulatory cell death modes, such as ferroptosis and cuproptosis, involved in kidney protection? Do different regulatory cell death modes exhibit synergistic or antagonistic effects in kidney protection? For another example, the regulation of autophagy by OA and UA presents a paradox, as they have been reported to both promote and inhibit autophagy, highlighting the complexity of their mechanisms. Understanding how OA and UA regulate moderate autophagy to achieve optimal kidney protection is an intriguing area for future investigation. Additionally, exploring the roles of different types of selective autophagy in kidney protection may shed light on novel therapeutic avenues for renal health. Furthermore, it is worth exploring in the future whether derivatives of OA and UA can enhance their nephroprotective effects.

Conclusions

To sum up, current literature highlights the nephroprotective mechanisms of OA and UA, which primarily encompassed inhibiting oxidative stress, ERS, glycative stress, dyslipidemia, inflammation, apoptosis, pyroptosis, and renal fibrosis, promoting diuresis, as well as fine-tuning autophagy.

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