Small Molecule Natural Products Targeting Nrf2-HO-1 Signaling

Subjects: Urology & Nephrology

Contributor: Md Jamal Uddin , Hunjoo Ha , Eehyun Kim , Md Abdul Hannan

The global burden of chronic kidney disease (CKD) intertwined with cardiovascular disease has become a major health problem. Oxidative stress (OS) plays an important role in the pathophysiology of CKD. The nuclear factor erythroid 2-related factor 2 (Nrf2)-antioxidant responsive element (ARE) antioxidant system plays a critical role in kidney protection by regulating antioxidants during OS. Heme oxygenase-1 (HO-1), one of the targets of Nrf2-ARE, plays an important role in regulating OS and is protective in a variety of human and animal models of kidney disease. Thus, activation of Nrf2-HO-1 signaling may offer a potential approach to the design of novel therapeutic agents for kidney diseases.

chronic kidney diseases oxidative stress Nrf2 HO-1 small molecule natural products

1. Introduction

The incidence and prevalence of chronic kidney disease (CKD) patients is increasing worldwide. The prevalence of CKD between male and female patients is not constant between countries, however, kidney functions decline faster in males than females [1]. Importantly, CKD is not only a risk factor for increasing global mortality but it is also a critical factor involved in cardiovascular disease (CVD) [2]. The close link between CKD and CVD has been known for a long time [3][4][5]. Not only traditional risk factors such as hypertension, dyslipidemia, and diabetes, but also non-traditional risk factors such as disturbed minerals and vitamins in CKD may play important roles in the progression of CVD. The current treatment options for CKD are controlling blood pressure, serum glucose, and serum lipid profile [6], as well as a modification of lifestyle [7][8]. Since the efficacy of the current therapeutic strategy is still limited [9], there is a need to develop a more effective therapeutic option for treating CKD. Although the exact mechanism involved in the development of CKD is elusive, many lines of evidence strongly suggest that oxidative stress (OS) plays a critical role in the progression of CKD [10][11][12][13].

OS is an imbalance between cellular reactive oxygen species (ROS) levels and antioxidant enzymes, leading to a pathological condition. ROS regulates various signaling pathways, including the growth and differentiation of cells, mitogenesis, production, and breakdown of the extracellular matrix (ECM), inflammation, and apoptosis [14]. OS-mediated damaging effects of cells are controlled by activating the antioxidant defense system. OS has also been noticed to be affected by sex hormones in ischemic kidney injury [15]. Unfortunately, there is an impairment of antioxidative defense and a reduced activity of antioxidant enzymes in CKD [16]. Hence, promoting the endogenous antioxidants defense system may become an important strategy in inhibiting OS-mediated cellular damage in CKD.

Phytochemicals and other natural products are cytoprotective against OS by scavenging oxygen-free radicals and enhancing the level of antioxidants [17]. The literature on protective effects of antioxidant natural products against CKD has been reported [18][19][20]. Nuclear factor erythroid 2-related factor 2 (Nrf2) is the master regulator of the cellular antioxidant defense system [17]. Studies review that augmentation of Nrf2 activity prevents the progression of acute kidney injury (AKI) to CKD transition [21][22]. Natural bioactive compounds and their sources have been demonstrated to have kidney protective potential by activating Nrf2 in experimental CKD models [23][24]. In a recent review on clinical studies, bardoxolone methyl (CDDO-me), a semi-synthetic triterpenoid activating the Nrf2 pathway, has been reported as an effective therapeutic for diabetic kidney disease (DKD), although it has limitations in that it increases the risk of heart failure [25]. Heme oxygenase-1 (HO-1), one of the target molecules of Nrf2, attenuates the overall production of ROS through its ability to degrade heme and to produce carbon monoxide (CO), biliverdin/bilirubin, and the release of free iron. Induction of HO-1 mediates many beneficial effects in the cardiovascular system and kidney [26]. Also, the modulatory role of HO-1 has been reported in various kidney injury models including CKD [27][28][29][30][31][32][33][34]. Several natural HO-1 inducers and their therapeutic applications in various diseases, including CKD, have been reported [35].

2. Small Molecule Natural Products Activating Nrf2-HO-1 Signaling

A substantial quantity of natural products has been reported to confer renoprotection and improve disease outcomes of the various types of CKD, primarily through activating the Nrf2/HO-1 antioxidant defense systems and attenuating the proinflammatory signaling pathways. Here, researchers reviewed the existing literature over the past decade to compile comprehensive information on the kidney protective potential of naturally occurring compounds. Experimental and disease models, the pathobiology involved, the research outcomes, and the molecular markers altered by these compounds are summarized in **Table 1** and **Table 2** and **Figure 1**. To facilitate the discussion, researchers have categorized the kidney protective effects of these natural compounds into two distinct chemical groups: phenolic and non-phenolics. This categorization also highlights common bioactive compounds, belonging to phenolic group which represents the largest chemical class showing enormous bioactivity with the potential to be future drug candidates.

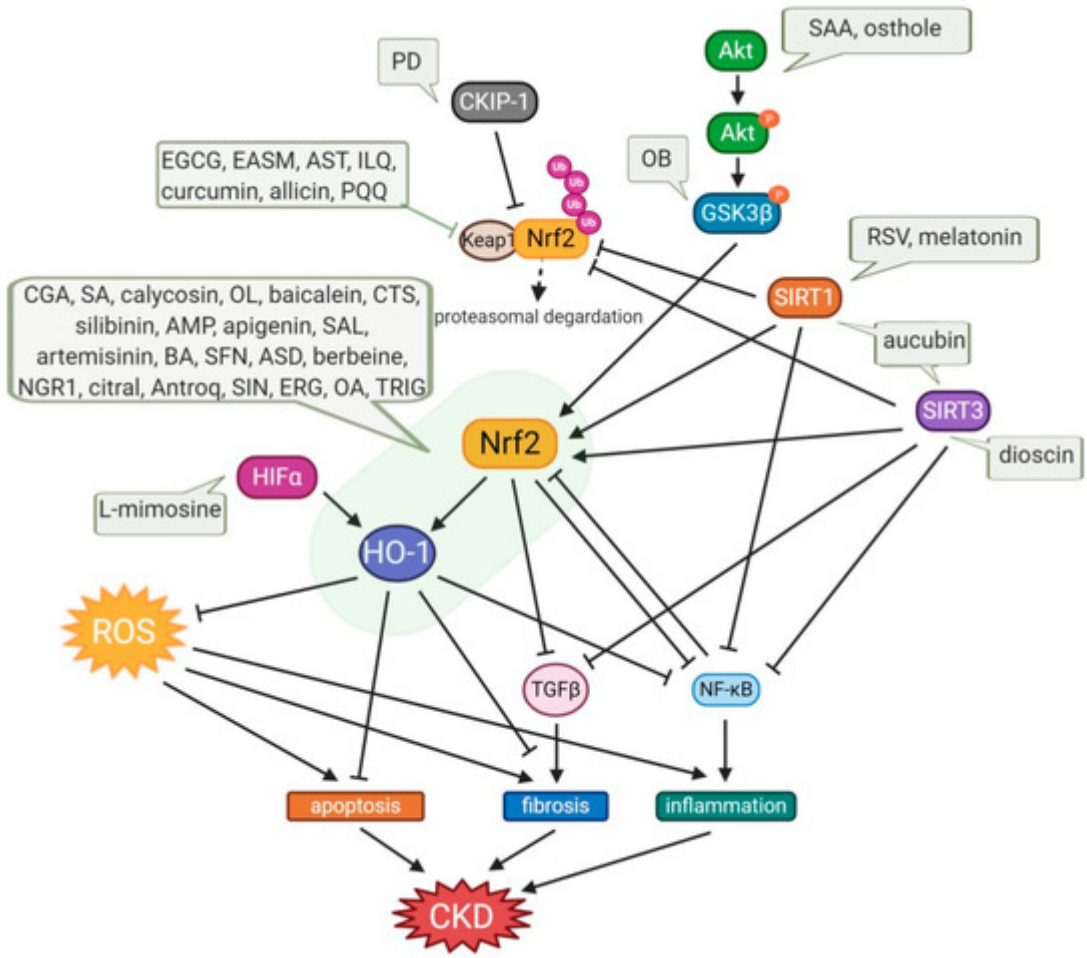

Figure 1. Protective effects of small-molecule natural products on OS in CKD. Osthole and SAA enhance the activation of the Akt/Nrf2/HO-1 signaling pathway with suppression of NF-kB and TGFβ1, consequently attenuating OS, inflammation, and fibrosis. OB induces the phosphorylation of GSK3β, which inhibits Fyn-mediated Nrf2 nuclear export, and activates the transcription of Nrf2-driven antioxidant genes. Expression of SIRT1, which inhibits NF-kB activity, and the activation of Nrf2 are enhanced by aucubin, melatonin, and RSV, which also upregulates SIRT3, resulting in amelioration of kidney injury. Dioscin upregulates SIRT3 level, promotes Nrf2, and suppresses Keap1 expression, resulting in inhibition of inflammation, lipid metabolism, OS, and kidney fibrosis. PD increases the CKIP-1 expression level and promotes the interaction of CKIP-1 with Nrf2, consequently activating the Nrf2-ARE antioxidative pathway. Allicin, AST, curcumin, EASM, EGCG, ILQ, and PQQ attenuate OS via the Nrf2/HO-1 signaling pathway with inhibition of Keap1, and they also reduce TGFβ-mediated fibrosis and NF-kB-induced inflammation. In the cases of an anti-fibrotic effect of apigenin, ASD, baicalein, BA, CGA, CTS, ERG, OL, and SFN, AMP, antroq, artemisinin, berbeine, calycosin, SA, SIN, and TRIG, they are mediated not only by upregulation of the Nrf2/HO-1 antioxidant signaling pathway and downregulation of NF-kB-induced inflammation, but also via TGFβ suppression. Treatments with citral, NGR1, OA, SAL, and silibinin have potency for anti-apoptotic effects with regulation of Bcl2/Bax and caspase3. The decrease in the NLRP3 inflammasome was also observed in treatments with baicalein, EGCG, and OL. L-mimosine activates HIF1α, which upregulates renoprotective HIF target genes, such as VEGF, HO-1, and GLUT1, and decreases fibrosis markers. AMP, ampelopsin; Antroq, antroquinonol; ASD, akebia saponin D; AST, astaxanthin; BA, betulinic acid; CGA, chlorogenic acid; CTS,

cryptotanshinone; EASM, ethyl acetate extract of Salvia miltiorrhiza; EGCG, Epigallocatechin gallate; ERG, ergone; GSK3β, glycogen synthase kinase 3β; HIFα, hypoxia-inducible factor α; ILQ, isoliquiritin; NGR1, notoginsenoside R1; OA, oleanolic acid; OB, obacunone; OL, oleuropein; PD, polydatin; PQQ, pyrroloquinoline quinone; RSV, resveratrol; SA, sinapic acid; SAA, salvianolic acid A; SAL, salidroside; SFN, sulforaphane; SIN, sinomenine; TRIG, trigonelline.

Table 1. Kidney protective effects provided by phenolic compounds of phytochemicals targeting the Nrf2-HO-1 signaling pathway.

No.	Modulator	Chemical Class and Natural Sources	Experimental Model	Disease Model	Pathobiology Involved	Major Research Outcomes	Molecular Markers	Ref.
Phenolic compounds								
1	Ampelopsin	Flavonoid; *Ampelopsis grossedentata*	HG-stimulated hGMCs	OS	OS, ECM accumulation	Amelioration of OS and ECM accumulation	↓ROS, ↓MDA, ↑SOD, ↓Nox2, ↓Nox4, ↓NADPH, ↓FN, ↓Col IV, ↑n-Nrf2, ↑HO-1,	[36]
2	Apigenin	Flavonoid; common fruits and vegetables	HG-treated HK-2 cells	Oxidative damage	Oxidative damage	Decrease in apoptosis, inhibition of OS, and inflammatory response	↓LDH, ↓MDA, ↑SOD, ↑CAT, ↓TNFα, ↓IL-1β, ↓IL-6, ↑Nrf2, ↑HO-1	[37]
3	Astaxanthin	Xanthophyll carotenoid; algae, shrimp, lobster, crab, salmon, and other organisms	STZ-injected rat	DKD	ECM accumulation	Amelioration of kidney injury	↓FN, ↓TGFβ1, ↓ICAM-1	[38]
			HG-treated GMCs	Kidney fibrosis	OS	Increase in antioxidative capacity	↓FN, ↓TGFβ1, ↓ICAM-1, ↑SOD, ↓MDA, ↓ROS, ↓DHE, ↑n-Nrf2, ↓keap1, ↓SOD-1, ↓Nqo1, ↓HO-1	[38]
			Adriamycin-treated BALB/c mice	FSGS	OS, inflammation	Anti-inflammation, antioxidation	↓TGFβ1, ↓collagen1, ↓α-SMA, ↓MDA, ↑GSH, ↑SOD, ↑CAT, (serum: ↓IL-1 β, IL-18), ↑Nrf2, ↓NLRP3	[39]
4	Baicalein	Flavonoid; roots of *Scutellaria*	Pristine - injected BALB/c	LN	OS, inflammation	Attenuation of kidney	↓IL-1b, ↓IL-18, ↓$O_2^{-\cdot}$,	[40]

No.	Modulator	Chemical Class and Natural Sources	Experimental Model	Disease Model	Pathobiology Involved	Major Research Outcomes	Molecular Markers	Ref.
		baicalensis Georgi	mice			dysfunction, antioxidation, anti-inflammation, inhibition of MDSC expansion	↑ GPx, ↑Nrf2, ↑HO-1, ↓ NLRP3, ↓Casp-1, ↓mIL-1 β, ↓p-NF-kB	
			LPS-primed spleen-derived MDSCs	OS, inflammation			↓ROS, ↓IL-1β, ↓IL-18, ↑Nrf2, ↑HO-1, ↓NLRP3, ↓mIL-1β/pro-IL-1β, ↓Casp-1-p20/pro-casp-1-p45, ↓p-NF-kB/NF-kB, ↓Ang-1, ↓p47phox, ↓GP91phox, ↓iNOS	
5	Calycosin	Isoflavone; root of *Astragalus membranaceus*	HFD-fed/ STZ-injected SD rat	DKD	Inflammation, OS, fibrosis	Inhibition of inflammatory, oxidative, and fibrotic events	↓IL-33, ↓ST2, ↓NF-kB p65, ↓TNFα, ↓IL-1 β, ↓IL-6, ↑Nrf2, ↓MDA, ↓TGFβ	[41]
6	Chlorogenic acid	Cinnamate ester; coffee, fruits, and vegetables	STZ-injected and HFD-fed SD rat	DKD	OS, inflammation	Relieve kidney injury, mitigation of OS, inflammation	↓MDA, ↑SOD, ↑GSH-Px, ↑n-Nrf2, ↑HO-1, ↓IL-6, ↓TNFα, ↓IL-1 β, ↑c-NF-kB, ↓n-NF-kB, ↑IkBα, ↓p-IkBα,	[42]
			HG-treated rat mesangial cell line (HBZY-1)			Mitigation of OS, inflammation, increase in cell proliferation	↑n-Nrf2, ↑HO-1, ↑c-NF-kB, ↓n-NF-kB, ↑IkBα, ↓p-IkBα, ↓IL-6, ↓TNFα, ↓IL-1 β	
7	Cryptotanshinone	Quinoid diterpene; *Salvia miotiorrhiza* bunge	UUO-operated mice	Kidney fibrosis	OS, inflammation	Attenuation of OS and inflammation	↓collagen-1, ↓FN, ↓CD68, ↓CD3, ↑IkBα, ↓NF-kB p65, ↑SOD2, ↑CAT, ↑GSH, ↓MDA, ↑Nuclear Nrf2, ↓cytosolic Nrf2, ↑HO-1	[43]

No.	Modulator	Chemical Class and Natural Sources	Experimental Model	Disease Model	Pathobiology Involved	Major Research Outcomes	Molecular Markers	Ref.
8	Curcumin	Curcuminoid; turmeric (*Curcuma longa*)	5/6 nephrectomy Wistar rat	CKD	OS, inflammation	Protection of kidney function, antioxidant, anti-inflammation	↓Nox4, ↑eNOS, ↓nitrotyrosine, ↓MCP-1, ↓Keap-1, ↑Nrf2, ↑GPx-1, ↑CAT, ↑SOD-1, ↓phospho serine D1R	[44]
			0.25% Adenine -diet rat	CKD	OS, inflammation	Amelioration of kidney function and OS	↓IL-1 β, ↓IL-6, ↓TNFα, ↑cycstatin C, ↓adiponecitn, ↑sclerostin, ↑SOD, ↑Nrf2, ↑GSH reductase. ↓ caspase3	[45]
			HG-treated NRK-52E cells	OS	OS	Increase in cell viability, inhibition of EMT	↑E-cadherin, ↓α-SMA, ↑Nrf2, ↑HO-1	[46]
9	Epigallocatechin-3 - Gallate	Polyphenol; Dried leaves of tea plant (*Camellia sinensis*)	STZ-injected mice	DKD	Oxidative damage, inflammation,	Anti-OS	↓TGFβ1, ↓PAI-1, ↓ICAM-1, ↓VCAM-1, ↓MDA, ↓iNOS, ↓3-NT, ↑Nqo1, ↑HO-1, ↑t-Nrf2, ↑c-Nrf2, ↑n-Nrf2, ↑n-Nrf2/t-Nrf2	[47]
			HG-cultured MMC				↑t-Nrf2, ↑c-Nrf2, ↑n-Nrf2, ↑Nqo1, ↑HO-1, ↓MDA, ↓iNOS, ↓VCAM-1, ↓ICAM-1, ↓COL4, ↓FN	
			NZB/W F1 lupus-prone mice	LN	OS	Antioxidant and anti-inflammation	↑Nrf2, ↓p47phox, ↑Nqo1, ↑HO-1, ↑GPx, ↓CD3, ↓F4/80, ↓NF-kB, ↓NLRP3, ↓IL-1	[48]

No.	Modulator	Chemical Class and Natural Sources	Experimental Model	Disease Model	Pathobiology Involved	Major Research Outcomes	Molecular Markers	Ref.
							β, ↓IL-18, ↓casp1-p20,	
			UUO mice	CKD	OS, inflammation	Kidney function improvement, prevention of OS and inflammation	↑SOD, ↑CAT, ↑GSH-Px, ↓MPO, ↓TNFα, ↓IL-6, ↓IL-1 β, ↑IkBα, ↓p-IkBα, ↓NF-kB, ↑n-Nrf2, ↑HO-1, ↑t-bilirubin	[49]
10	Ethyl acetate extract of *Saliva miltiorrhiza*	Diterpenoids, phenolic compounds, flavonoids, triterpenoids; dried root of *Salvia miltiorrhiza* Bunge	STZ-injected mice	DKD	Oxidative stress	Antioxidation, attenuation of kidney dysfunction	↑Nrf2, ↑HO-1, ↑Nqo1, ↓Keap1	[50]
			HG-treated SV40-MES-13 MMCs	hyperglycemia		Antioxidation	↓ROS, ↑Nrf2, ↑HO-1, ↑Nqo1, ↓Keap1	
11	Isoliquiritin	Flavonoid glycoside; Chinese licorice (*Glycyrrhiza uralensis*)	Cationic BSA-injected SD rat	MGN	Inflammation and OS	Antioxidative, anti-inflammatory activities	↓Keap1, ↑Nrf2, ↓n-Nrf2, ↑c-Nrf2, ↑HO-1, ↑Nqo1, ↓MDA, ↓NO, ↑SOD, ↑CAT, ↑GPx, ↑GSH, ↓NF-kB p65, ↓nuclear NF-kB p65, ↑cyclic NF-kB, ↓IKKb, ↓p-IKKb, ↓TNFα, ↓IL-1 β, ↓COX2, ↓iNOS, ↓p38 MAPK, ↓p-p38 MAPK	[51]
12	Oleuropein, peracetylatedoleuropein	Secoiridoid; olive leaves, roots, and unprocessed olive drupes	Pristine - injected BALB/c mice	LN	Inflammation and OS	Amelioration of kidney abnormalities, inhibition of proinflammation, antioxidation	↓MMP-3, ↓iNOS, ↓mPGEs-1, ↓PGE2, ↑Nrf2, ↑HO-1, ↓pSTAT3, ↓NF-kB-p65, ↑IkBα, ↓pp38, ↓pJNK, ↓pERK1/2 ↓NLRP3, ↓ASC, ↓IL-18, ↓	[52]

No.	Modulator	Chemical Class and Natural Sources	Experimental Model	Disease Model	Pathobiology Involved	Major Research Outcomes	Molecular Markers	Ref.
							IL-1β, ↓cleaved caspase-1, ↓cleaved caspase 11	

f2-HO-1

No.	Modulator	Chemical Class and Natural Sources	Experimental Model	Disease Model	Pathobiology Involved	Major Research Outcomes	Molecular Markers	Ref.
			Non-phenolic compounds					
1	Akebia Saponin D	triterpenoid saponin; *Dipsaci Radix*	STZ-injected mice	DKD	OS, inflammation	Amelioration of kidney damage, inflammation, OS, and apoptosis	↓TNFα, ↓IL-1β, ↓IL-6, ↓MCP-1, ↓ROS, ↓MDA, ↓LDH, ↑SOD, ↑Bcl2, ↓Bax, ↓cleaved caspase3/caspase3, ↓cleaved caspase9/caspase9, ↑n-Nrf2, ↓p-NF-kB/t-NF-kB, ↑HO-1, ↑Nqo1, ↓p-IkBα/t-IkBα	[62]
			HG-treated HK-2 cells				↓TNFα, ↓IL-1β, ↓IL-6, ↓MCP-1, ↓ROS, ↓MDA, ↓LDH, ↑SOD, ↑Bcl2, ↓Bax, ↓cleaved caspase3/caspase3, ↓cleaved caspase9/caspase9, ↑Nrf2, ↓p-NF-kB/t-NF-kB, ↑HO-1, ↑Nqo1, ↓p-IkBα/t-IkBα	
2	Allicin	Diallyl thiosulfinate; garlic (*Allium sativum* L.)	5/6 nephrectomy Wistar rat	CKD	Fibrosis, OS	Antihypertensive and antioxidant effects	↑AT1R, ↑AT2R, ↑Nrf2, ↓Keap1, ↑CAT, ↑SOD, ↓HO-1, ↑eNOS	[63]
3	Antroquinonol	Enone; mushroom (*Antrodia camphorate*)	Adriamycin - injected BALB/c mice	FSGS	OS	Decrease in kidney dysfunction, anti-OS, anti-inflammation	↓desmin, ↓$O_2^{\bullet-}$, (serum, urine ↓ $O_2^{\bullet-}$, ↓NO), ↓DHE, ↓p47phox, ↑Nrf2, ↑GPx, ↓NF-kB p65, ↓MCP-1, ↓IL-6, ↓CD3, ↓F4/80, ↓Col I, ↓Col III, ↓Col IV, ↓TGFβ1	[64]
4	Artemisinin	sesquiterpene lactones; *Asteraceae*	STZ-injected rat	DKD	OS	Amelioration of kidney	↓MDA, ↑t-SOD, ↑GPx, ↓TGFβ1, ↑t-	[65]

No.	Modulator	Chemical Class and Natural Sources	Experimental Model	Disease Model	Pathobiology Involved	Major Research Outcomes	Molecular Markers	Ref.
		Artemisia annua				dysfunction and OS	Nrf2, ↑n-Nrf2, ↑HO-1, ↑Nqo1	
5	Aucubin	iridoid glycoside; leaf of *Eucommia ulmoides*	HFD-fed and STZ-injected mice	DKD	OS, inflammation	Amelioration of kidney dysfunction, anti-inflammation, anti-OS	↓FN, ↓collagen IV, ↓MDA, ↑SOD, ↑CAT, ↑GSH/T-GSH, ↓TNFα, ↓IL-6, ↓IL-1β, ↓p65, ↓IkBα, ↑Nrf2, ↑HO-1, ↑Nqo1, ↑FOXO3α, ↓p-FOXO3α/FOXO3α, ↑SIRT1, ↑SIRT3, ↓Ac-FOXO3α/FOXO3α	[66]
6	Berberine	isoquinoline alkaloid; *Coptidis Rhizoma* and *Cortex Phellodendri*	STZ-injected mice	DKD	OS	Anti-fibrosis	↓α-SMA, ↓collagen-1, ↑Nrf2, ↑NQO1, ↑HO-1	[67]
			HG-treated NRK 52E cells	EMT			↓E-cadherin, ↓α-SMA, ↑n-Nrf2, ↑Nqo1, ↑HO-1, ↓p-Smad2, ↓p-Smad3	
7	Betulinic acid	pentacyclic triterpenoid; from the outer bark of white birch trees (*Betula alba*)	STZ-injected SD rat	DKD	OS	Anti-OS	↓IL-1 β, ↓IL-6, ↓MDA, ↑SOD, ↑CAT, ↑p-AMPK/AMPK, ↓p-IkBα/IkBα, ↓p-NF-kB/NF-kB, ↑Nrf2, ↑HO-1	[68]
8	Citral	Terpeonids; *Litsea cubeba*	Adriamycin - injected BALB/c mice	FSGS	OS	Amelioration of kidney dysfunction, anti-OS, anti-inflammation, anti-apoptosis	↓$O_2^{-\cdot}$, (serum, urine ↓$O_2^{-\cdot}$, ↓NO), ↓DHE, ↓p47phox, ↑Nrf2, ↑Nqo1, ↑HO-1, ↓desmin, ↓TUNEL, ↓Casp-3p17, ↓Casp-9p37, ↓Bax/Bcl2, ↓pNF-kB p65, ↓MCP-1, ↓ CD3, ↓F4/80	[69]
			LPS-treated RAW 264.7 macrophages	OS			↓NO, ↓NF-kB, ↓IL-6, ↓TNFα, ↓IL-1β, ↓p-ERK1/2(10min), ↓p-JNK1/2(15,30min)	

No.	Modulator	Chemical Class and Natural Sources	Experimental Model	Disease Model	Pathobiology Involved	Major Research Outcomes	Molecular Markers	Ref.
9	Dioscin	Steroid saponin; *Dioscoreae rhizoma*	10% fructose -fed mice	CKD	Oxidative damage, lipid metabolism, fibrosis	Inhibition of inflammation, lipid metabolism, OS, kidney fibrosis	↓MDA, ↑SOD, ↑GSH-Px, ↓α-SMA, ↑SIRT3, ↑SOD2, ↓IL-1β, ↓IL6, ↓TNFα, ↓NF-kB, ↓HMGB1, ↓COX2, ↓c-Jun, ↓c-Fos, ↓SREBP-1c, ↓SCD-1, ↓FASn, ↓p-Akt, ↓p-FoxO1A, ↓ACC, ↑CPT1, ↑Nrf2, ↓Keap1, ↑GST, ↓TGFβ1, ↓p-Smad3, ↑Smad7	[70]
10	Ergone (alisol B 23-acetate, pachymic acid B)	steroid; *Polyporus umbellatus*, surface layer of *Poria cocos, Alisma orientale*	AngII- treated HK-2 and conditionally immortalized MPC5 cells	CKD	OS, inflammation, impaired Nrf 2 activation	inhibition of the RAS/Wnt/b-catenin signaling cascade	(HK-2) ↓Snail1, ↓MMP-7, ↓Twist, ↓FSP-1, ↓Col I, ↓Col III, ↓α-SMA, ↓vimentin, ↑E-cadherin, ↓NF-kB, ↓MCP-1, ↓COX2, ↑Nrf2, ↑HO-1 (podocyte) ↓Snail1, ↓MMP-7, ↓Twist, ↓FSP-1, ↑podocin, ↑nephrin, ↑podocalyxin, ↑synaptopodin, ↓desmin, ↑WT1, ↓Akt2, ↓NF-kB, ↓MCP-1, ↓COX2, ↑Nrf2, ↑HO-1	[71]
11	L-mimosine	Amino acid; *Mimosa pudica*	Rats with remnant kidneys after subtotal nephrectomy (5/6 nephrectomy)	CKD	Fibrosis	Improvement of kidney function, inhibition of fibrosis	↑HIF-1α, ↑HIF-2α, ↑VEGF, ↑HO-1, ↑GLUT-1, ↓α-SMA, ↓collagen III	[72]
12	Melatonin	Endogenous indoleamine, coffee, walnut, etc.	Pristine - injected BALB/c mice	LN	OS, inflammation	Attenuation of OS, inflammation	↑SIRT1, ↑Nrf2, ↓TNFα, ↓NF-kB, ↓iNOS, ↓NLRP3, ↑CD31	[73]
13	Notoginsenoside R1	Saponin; *Panax notoginseng*	db/db mice	DKD	OS	Anti-OS, decrease in apoptosis	↓Collagen I, ↓TGFβ1, ↑Nrf2, ↑HO-1, ↓Bax/Bcl2,	[74]

, chronic
acellular
; GMCs,
fat diet;
ric oxide
nonocyte
branous
P3, NLR
2-related
hibitor-1;
unilateral

No.	Modulator	Chemical Class and Natural Sources	Experimental Model	Disease Model	Pathobiology Involved	Major Research Outcomes	Molecular Markers	Ref.
							↓Caspase-3, ↓Caspase-9	
			AGEs-treated HK-2 cells	Mitochondria injury			↓LDH, ↓ROS, ↑n-Nrf2, ↑HO-1, ↓Bax/Bcl2, ↓Cspase-3, ↓Caspase-9, ↓TGFβ1, ↓collagen I	
14	Obacunone	Triterpenoid limonoid; citrus and other plants of the *Rutaceae* family	HG-treated NRK-52E cells	OS	OS	Inhibition of OS, mitochondrial injury, and apoptosis	↑SOD, ↑GSH, ↑CAT, ↓ROS, ↓JC-1 monomer/aggregate, ↑p-GSK3β/GSK3β, ↓n-Fyn, ↑n-Nrf2, ↑Nqo1, ↑HO-1, ↑SOD, ↑GSH, ↑CAT, ↓c-CytC/m-CytC, ↓cleaved caspase3	[75]
15	Oleanolic acid	Triterpenoid; olive oil, *Phytolacca Americana, Syzygium* spp, garlic, etc.	Cyclosporine -treated ICR mice	Chronic nephropathy	Inflammation, fibrosis	Antioxidation, anti-inflammation	↓α-SMA, ↑HO-1, ↑nuclear/total Nrf2, ↑SOD1, ↓MDA, ↓urinary 8-iso-PGF2α, ↓urine 8-oxo-dG, ↓Bax/Bcl2, ↓active caspase-3	[76]
16	Pyrroloquinoline quinone	In soil and foods such as kiwifruit and human breast milk	HG-treated HK-2 cells	OS	OS	Decrease in OS, inflammation and cellular senescence	↓IL-1β, ↓TNFα, ↓NF-kB, ↓p16, ↓p21, ↓ROS, ↑SOD2, ↑CAT, ↓keap1, ↑Nrf2, ↑HO-1, ↑Nqo1, ↑GST, ↑GPx3,	[77]
			UUO-operated ICR mice				↑E-cadherin, ↓α-SMA, ↓FN, ↑HO-1, ↑Nqo1, ↑Nrf2, ↑SOD, ↑GPx, ↑CAT, ↑SOD2, ↓p-Smad3, ↓β-catenin	
17	Sinomenine	Alkaloid; *Sinomenium acutum*	TGFβ-treated/H_2O_2-treated HEK293 cells, TGFβ-treated RAW264.7 cells	CKD	Fibrosis, OS	Anti-fibrosis, antioxidation	↑E-cadherin, ↓α-SMA, ↓FN, ↑HO-1, ↑Nqo1, ↑Nrf2, ↑SOD, ↑GPx, ↑CAT, ↑SOD2, ↓p-Smad3, ↓β-catenin	[78]

1. Carrero, J.J.; Hecking, M.; C r, K.J. Sex and gender ne
64.
20.
nd its
926.
urinary
34.
.;
erm
unsen,
What
9. Cruz, M.C.; Andrade, C.; Ortutia, M.; Draibe, S.; Nogueira-Martins, L.A.; Sesso, R.C.C. Quality of life in patients with chronic kidney disease. Clinics 2011, 66, 991–995.
10. Lee, H.B.; Yu, M.R.; Yang, Y.; Jiang, Z.; Ha, H. Reactive oxygen species-regulated signaling pathways in diabetic nephropathy. J. Am. Soc. Nephrol. 2003, 14, S241–S245.
11. Podkowińska, A.; Formanowicz, D. Chronic kidney disease as oxidative stress-and inflammatory-mediated cardiovascular disease. Antioxidants 2020, 9, 752.
12. Noh, H.; Ha, H. Reactive oxygen species and oxidative stress. In Contributions to Nephrology; Karger: Basel, Switzerland, 2011; Volume 170, pp. 102–112.
13. Ha, H.; Hwang, I.A.; Park, J.H.; Lee, H.B. Role of reactive oxygen species in the pathogenesis of diabetic nephropathy. Diabetes Res. Clin. Pract. 2008, 82, S42–S45.

No.	Modulator	Chemical Class and Natural Sources	Experimental Model	Disease Model	Pathobiology Involved	Major Research Outcomes	Molecular Markers	Ref.
18	Sulforaphane	Isothiocyanate (organosulfur compound); Cruciferous vegetables such as broccoli, brussels sprouts, and cabbages	STZ-injected and meglumine diatrizoate-injected Wistar rats	DKD, CIN	OS	Renoprotective	↓MDA, ↓8-oxo-dG, ↑Nrf2, ↑HO-1, ↓IL6, ↑Caspase3	[79] [80]
			Meglumine diatrizoate-treated NRK-52E cells			Cell viability	↑Nrf2, ↑HO-1, ↓IL6	
			F344 rat kidneys transplanted Lewis rat	CRAD	OS	OS alleviation, kidney functional and morphological improvements	↓MDA, ↓8-isoprostane, ↓ox-LDL, ↓8-oxo-dG, ↑SOD, ↑CAT, ↑GPx, ↑GR, ↑ γ-GCS, ↑Nrf2, ↑HO-1, ↑Nqo-1	[80]
19	Trigonelline	Alkaloid; traditional herbs (especially fenugreek), coffee bean, soybean, and other edible food plants	Oxalate-induced MDCK cells	EMT	Fibrosis	Attenuation of EMT, prevention of cell migration and ROS overproduction,	↓FN, ↓vimentin, ↓α-SMA, ↑ E-cadherin, ↑ZO-1, ↓MMP9, ↓ROS, ↑Nrf2	[81]

AGEs, advanced glycation end products; AngII, angiotensin II; α-SMA, α-smooth muscle actin; AT1R, angiotensin II receptor type 1; CAT, catalase; CIN, contrast induced nephropathy; CKD, chronic kidney disease; COX2, cyclooxygenase-2; CRAD, chronic renal allograft dysfunction; DKD, diabetic kidney disease; EMT, epithelial-to-mesenchymal transition; eNOS, endothelial nitric oxide synthase; FSGS, focal segmental glomerulosclerosis; γ-GCS, γ-glutamine cysteine synthase; GPx, glutathione peroxidase; GR, glutathione reductase; GSK3β, glycogen synthase kinase 3β; GST, Glutathione-S-transferase; HFD, high fat diet; HG, high glucose; HIF, hypoxia-inducible factor; HMGB1, high-mobility group box 1; HO-1, Heme oxygenase-1; iNOS, inducible nitric oxide synthase; LDH, lactate dehydrogenase; LN, lupus nephritis; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; MDCK, Madin-Darby canine kidney; MMP, matrix metalloproteinase; NLRP3, NLR family pyrin domain containing 3; Nqo1, NADPH quinone oxidoreductase; Nrf2, nuclear factor erythroid 2-related factor 2; OS, oxidative stress; ox-LDL, oxidized low-density lipoprotein; RAS, renin-angiotensin system; SOD, superoxide dismutase; STZ, Streptozotocin; UUO, unilateral ureteral obstruction.

1 ... Park, ... y in ... 5.

1 ... dative ... enal

1 ... gnaling ... s.

1 ... cent

1 ... prevention and treatment of kidney disease. Phytomedicine 2018, 50, 50–60.

20. Rapa, S.F.; Di Iorio, B.R.; Campiglia, P.; Heidland, A.; Marzocco, S. Inflammation and oxidative stress in chronic kidney disease-potential therapeutic role of minerals, vitamins and plant-derived metabolites. Int. J. Mol. Sci. 2019, 21, 263.

21. Nezu, M.; Suzuki, N.; Yamamoto, M. Targeting the KEAP1-NRF2 system to prevent kidney disease progression. Am. J. Nephrol. 2017, 45, 473–483.

22. Lu, M.; Wang, P.; Qiao, Y.; Jiang, C.; Ge, Y.; Flickinger, B.; Malhotra, D.K.; Dworkin, L.D.; Liu, Z.; Gong, R. GSK3β-mediated Keap1-independent regulation of Nrf2 antioxidant response: A molecular rheostat of acute kidney injury to chronic kidney disease transition. Redox Biol. 2019, 26, 101275.

23. Yamawaki, K.; Kanda, H.; Shimazaki, R. Nrf2 activator for the treatment of kidney diseases. Toxicol. Appl. Pharmacol. 2018, 360, 30–37.

24. Choi, B.H.; Kang, K.S.; Kwak, M.K. Effect of redox modulating NRF2 activators on chronic kidney disease. Molecules 2014, 19, 12727–12759.

25. Kanda, H.; Yamawaki, K. Bardoxolone methyl: Drug development for diabetic kidney disease. Clin. Exp. Nephrol. 2020, 24, 857–864.

26. Abraham, N.G.; Kappas, A. Heme oxygenase and the cardiovascular–renal system. Free Radic. Biol. Med. 2005, 39, 1–25.

27. Li, S.; Qiu, B.; Lu, H.; Lai, Y.; Liu, J.; Luo, J.; Zhu, F.; Hu, Z.; Zhou, M.; Tian, J.; et al. Hyperhomocysteinemia accelerates acute kidney injury to chronic kidney disease progression by downregulating Heme Oxygenase-1 expression. Antioxid. Redox Signal. 2019, 30, 1635–1650.

28. Demirogullari, B.; Ekingen, G.; Guz, G.; Bukan, N.; Erdem, O.; Ozen, I.O.; Memis, L.; Sert, S. A comparative study of the effects of hemin and bilirubin on bilateral renal ischemia reperfusion injury. Nephron Exp. Nephrol. 2006, 103, e1–e5.
29. Chang, T.T.; Chen, Y.A.; Li, S.Y.; Chen, J.W. Nrf-2 mediated heme oxygenase-1 activation contributes to the anti-inflammatory and renal protective effects of Ginkgo biloba extract in diabetic nephropathy. J. Ethnopharmacol. 2020, 266, 113474.
30. Di Noia, M.A.; Van Driesche, S.; Palmieri, F.; Yang, L.M.; Quan, S.; Goodman, A.I.; Abraham, N.G. Heme oxygenase-1 enhances renal mitochondrial transport carriers and cytochrome C oxidase activity in experimental diabetes. J. Biol. Chem. 2006, 281, 15687–15693.
31. Bolisetty, S.; Traylor, A.; Zarjou, A.; Johnson, M.S.; Benavides, G.A.; Ricart, K.; Boddu, R.; Moore, R.D.; Landar, A.; Barnes, S.; et al. Mitochondria-targeted heme oxygenase-1 decreases oxidative stress in renal epithelial cells. Am. J. Physiol. Ren. Physiol. 2013, 305, F255–F264.
32. Kwak, J.Y.; Takeshige, K.; Cheung, B.S.; Minakami, S. Bilirubin inhibits the activation of superoxide-producing NADPH oxidase in a neutrophil cell-free system. Biochim. Biophys. Acta 1991, 1076, 369–373.
33. Nath, K.A. Heme oxygenase-1: A provenance for cytoprotective pathways in the kidney and other tissues. Kidney Int. 2006, 70, 432–443.
34. Lever, J.M.; Boddu, R.; George, J.F.; Agarwal, A. Heme oxygenase-1 in kidney health and disease. Antioxid. Redox Signal. 2016, 25, 165–183.
35. Funes, S.C.; Rios, M.; Fernández-Fierro, A.; Covián, C.; Bueno, S.M.; Riedel, C.A.; Mackern-Oberti, J.P.; Kalergis, A.M. Naturally derived Heme-Oxygenase 1 inducers and their therapeutic application to immune-mediated diseases. Front. Immunol. 2020, 11, 1467.
36. Dong, C.; Wu, G.; Li, H.; Qiao, Y.; Gao, S. Ampelopsin inhibits high glucose-induced extracellular matrix accumulation and oxidative stress in mesangial cells through activating the Nrf2/HO-1 pathway. Phytother. Res. 2020, 34, 2044–2052.
37. Zhang, J.; Zhao, X.; Zhu, H.; Wang, J.; Ma, J.; Gu, M. Apigenin protects against renal tubular epithelial cell injury and oxidative stress by high glucose via regulation of NF-E2-related factor 2 (Nrf2) pathway. Med. Sci. Monit. 2019, 25, 5280–5288.
38. Xie, X.; Chen, Q.; Tao, J. Astaxanthin promotes Nrf2/ARE signaling to inhibit hg-induced renal fibrosis in GMCs. Mar. Drugs 2018, 16, 117.
39. He, L.; Liu, G.; Shi, Y.; Peng, X.; Liu, H.; Peng, Y. Astaxanthin attenuates adriamycin-induced focal segmental glomerulosclerosis. Pharmacology 2015, 95, 193–200.
40. Li, D.; Shi, G.; Wang, J.; Zhang, D.; Pan, Y.; Dou, H.; Hou, Y. Baicalein ameliorates pristane-induced lupus nephritis via activating Nrf2/HO-1 in myeloid-derived suppressor cells. Arthritis Res.

Ther. 2019, 21.

41. Elsherbiny, N.M.; Said, E.; Atef, H.; Zaitone, S.A. Renoprotective effect of calycosin in high fat diet-fed/STZ injected rats: Effect on IL-33/ST2 signaling, oxidative stress and fibrosis suppression. Chem. Biol. Interact. 2020, 315.
42. Bao, L.; Li, J.; Zha, D.; Zhang, L.; Gao, P.; Yao, T.; Wu, X. Chlorogenic acid prevents diabetic nephropathy by inhibiting oxidative stress and inflammation through modulation of the Nrf2/HO-1 and NF-κB pathways. Int. Immunopharmacol. 2018, 54, 245–253.
43. Wang, W.; Wang, X.; Zhang, X.S.; Liang, C.Z. Cryptotanshinone attenuates oxidative stress and inflammation through the regulation of Nrf-2 and NF-κB in mice with unilateral ureteral obstruction. Basic Clin. Pharmacol. Toxicol. 2018, 123, 714–720.
44. Tapia, E.; García-Arroyo, F.; Silverio, O.; Rodríguez-Alcocer, A.N.; Jiménez-Flores, A.B.; Cristobal, M.; Arellano, A.S.; Soto, V.; Osorio-Alonso, H.; Molina-Jijón, E.; et al. Mycophenolate mofetil and curcumin provide comparable therapeutic benefit in experimental chronic kidney disease: Role of Nrf2-Keap1 and renal dopamine pathways. Free Radic. Res. 2016, 50, 781–792.
45. Ali, B.H.; Al-Salam, S.; Al Suleimani, Y.; Al Kalbani, J.; Al Bahlani, S.; Ashique, M.; Manoj, P.; Al Dhahli, B.; Al Abri, N.; Naser, H.T.; et al. Curcumin ameliorates kidney function and oxidative stress in experimental chronic kidney disease. Basic Clin. Pharmacol. Toxicol. 2018, 122, 65–73.
46. Zhang, X.; Liang, D.; Guo, L.; Liang, W.; Jiang, Y.; Li, H.; Zhao, Y.; Lu, S.; Chi, Z.H. Curcumin protects renal tubular epithelial cells from high glucose-induced epithelial-to-mesenchymal transition through Nrf2-mediated upregulation of heme oxygenase-1. Mol. Med. Rep. 2015, 12, 1347–1355.
47. Sun, W.; Liu, X.; Zhang, H.; Song, Y.; Li, T.; Liu, X.; Liu, Y.; Guo, L.; Wang, F.; Yang, T.; et al. Epigallocatechin gallate upregulates NRF2 to prevent diabetic nephropathy via disabling KEAP1. Free Radic. Biol. Med. 2017, 108, 840–857.
48. Tsai, P.Y.; Ka, S.M.; Chang, J.M.; Chen, H.C.; Shui, H.A.; Li, C.Y.; Hua, K.F.; Chang, W.L.; Huang, J.J.; Yang, S.S.; et al. Epigallocatechin-3-gallate prevents lupus nephritis development in mice via enhancing the Nrf2 antioxidant pathway and inhibiting NLRP3 inflammasome activation. Free Radic. Biol. Med. 2011, 51, 744–754.
49. Wang, Y.; Wang, B.; Du, F.; Su, X.; Sun, G.; Zhou, G.; Bian, X.; Liu, N. Epigallocatechin-3-Gallate attenuates oxidative stress and inflammation in obstructive nephropathy via NF-κB and Nrf2/HO-1 signalling pathway regulation. Basic Clin. Pharmacol. Toxicol. 2015, 117, 164–172.
50. An, L.; Zhou, M.; Marikar, F.M.M.T.; Hu, X.W.; Miao, Q.Y.; Li, P.; Chen, J. Salvia miltiorrhiza lipophilic fraction attenuates oxidative stress in diabetic nephropathy through activation of nuclear factor erythroid 2-related factor 2. Am. J. Chin. Med. 2017, 45, 1441–1457.

51. Liu, Y.; Xu, X.; Xu, R.; Zhang, S. Renoprotective effects of isoliquiritin against cationic bovine serum albumin-induced membranous glomerulonephritis in experimental rat model through its anti-oxidative and anti- inflammatory properties. Drug Des. Dev. Ther. 2019, 13, 3735–3751.
52. Castejon, M.L.; Sánchez-Hidalgo, M.; Aparicio-Soto, M.; Montoya, T.; Martín-LaCave, I.; Fernández-Bolaños, J.G.; Alarcón-de-la-Lastra, C. Dietary oleuropein and its new acyl-derivate attenuate murine lupus nephritis through HO-1/Nrf2 activation and suppressing JAK/STAT, NF-κB, MAPK and NLRP3 inflammasome signaling pathways. J. Nutr. Biochem. 2019, 74.
53. Huang, T.; Dong, Z. Osthole protects against inflammation in a rat model of chronic kidney failure via suppression of nuclear factor-κB, transforming growth factor-β1 and activation of phosphoinositide 3-kinase/protein kinase B/nuclear factor (erythroid-derived 2)-like 2 signaling. Mol. Med. Rep. 2017, 16, 4915–4921.
54. Koca, H.B.; Pektas, M.B.; Koca, S.; Pektas, G.; Sadi, G. Diabetes-induced renal failure is associated with tissue inflammation and neutrophil gelatinase-associated lipocalin: Effects of resveratrol. Arch. Biol. Sci. 2016, 68, 747–752.
55. Bae, E.H.; Joo, S.Y.; Ma, S.K.; Lee, J.U.; Kim, S.W. Resveratrol attenuates 4-hydroxy-2-hexenal-induced oxidative stress in mouse cortical collecting duct cells. Korean J. Physiol. Pharmacol. 2016, 20, 229–236.
56. Sun, Y.; Zhang, Y.; Zhao, D.; Ding, G.; Huang, S.; Zhang, A.; Jia, Z. Rotenone remarkably attenuates oxidative stress, inflammation, and fibrosis in chronic obstructive uropathy. Mediat. Inflamm. 2014, 2014.
57. Lu, H.; Li, Y.; Zhang, T.; Liu, M.; Chi, Y.; Liu, S.; Shi, Y. Salidroside reduces high-glucose-induced podocyte apoptosis and oxidative stress via upregulating heme oxygenase-1 (HO-1) expression. Med. Sci. Monit. 2017, 23, 4067–4076.
58. Wu, P.; Yan, Y.; Ma, L.L.; Hou, B.Y.; He, Y.Y.; Zhang, L.; Niu, Z.R.; Song, J.K.; Pang, X.C.; Yang, X.Y.; et al. Effects of the Nrf2 protein modulator salvianolic acid a alone or combined with metformin on diabetes-associated macrovascular and renal injury. J. Biol. Chem. 2016, 291, 22288–22301.
59. Wang, J.H.; Zhang, H.F.; Wang, J.H.; Wang, Y.L.; Gao, C.; Gu, Y.T.; Huang, J.; Zhang, Z. Salvianolic acid A protects the kidney against oxidative stress by activating the Akt/GSK-3 β /Nrf2 signaling pathway and inhibiting the NF- B signaling pathway in 5/6 nephrectomized rats. Oxidative Med. Cell. Longev. 2019, 2019.
60. Prabu, S.M.; Muthumani, M. Silibinin ameliorates arsenic induced nephrotoxicity by abrogation of oxidative stress, inflammation and apoptosis in rats. Mol. Biol. Rep. 2012, 39, 11201–11216.
61. Alaofi, A.L. Sinapic acid ameliorates the progression of streptozotocin (STZ)-induced diabetic nephropathy in rats via NRF2/HO-1 mediated pathways. Front. Pharmacol. 2020, 11.

62. Lu, C.; Fan, G.; Wang, D. Akebia Saponin D ameliorated kidney injury and exerted anti-inflammatory and anti-apoptotic effects in diabetic nephropathy by activation of NRF2/HO-1 and inhibition of NF-KB pathway. Int. Immunopharmacol. 2020, 84.

63. García Trejo, E.M.Á.; Buendía, A.S.A.; Reyes, O.S.; Arroyo, F.E.G.; García, R.A.; Mendoza, M.L.L.; Tapia, E.; Lozada, L.G.S.; Alonso, H.O. The beneficial effects of Allicin in chronic kidney disease are comparable to Losartan. Int. J. Mol. Sci. 2017, 18, 1980.

64. Tsai, P.Y.; Ka, S.M.; Chao, T.K.; Chang, J.M.; Lin, S.H.; Li, C.Y.; Kuo, M.T.; Chen, P.; Chen, A. Antroquinonol reduces oxidative stress by enhancing the Nrf2 signaling pathway and inhibits inflammation and sclerosis in focal segmental glomerulosclerosis mice. Free Radic. Biol. Med. 2011, 50, 1503–1516.

65. Zhang, H.; Qi, S.; Song, Y.; Ling, C. Artemisinin attenuates early renal damage on diabetic nephropathy rats through suppressing TGF-β1 regulator and activating the Nrf2 signaling pathway. Life Sci. 2020, 256.

66. Ma, B.; Zhu, Z.; Zhang, J.; Ren, C.; Zhang, Q. Aucubin alleviates diabetic nephropathy by inhibiting NF-κB activation and inducing SIRT1/SIRT3-FOXO3a signaling pathway in high-fat diet/streptozotocin-induced diabetic mice. J. Funct. Foods 2020, 64.

67. Zhang, X.; He, H.; Liang, D.; Jiang, Y.; Liang, W.; Chi, Z.H.; Ma, J. Protective effects of berberine on renal injury in streptozotocin (STZ)-Induced diabetic mice. Int. J. Mol. Sci. 2016, 17, 1327.

68. Xie, R.; Zhang, H.; Wang, X.Z.; Yang, X.Z.; Wu, S.N.; Wang, H.G.; Shen, P.; Ma, T.H. The protective effect of betulinic acid (BA) diabetic nephropathy on streptozotocin (STZ)-induced diabetic rats. Food Funct. 2017, 8, 299–306.

69. Yang, S.M.; Hua, K.F.; Lin, Y.C.; Chen, A.; Chang, J.M.; Kuoping Chao, L.; Ho, C.L.; Ka, S.M. Citral is renoprotective for focal segmental glomerulosclerosis by inhibiting oxidative stress and apoptosis and activating Nrf2 pathway in mice. PLoS ONE 2013, 8, e74871.

70. Qiao, Y.; Xu, L.; Tao, X.; Yin, L.; Qi, Y.; Xu, Y.; Han, X.; Tang, Z.; Ma, X.; Liu, K.; et al. Protective effects of dioscin against fructose-induced renal damage via adjusting Sirt3-mediated oxidative stress, fibrosis, lipid metabolism and inflammation. Toxicol. Lett. 2018, 284, 37–45.

71. Chen, L.; Chen, D.Q.; Wang, M.; Liu, D.; Chen, H.; Dou, F.; Vaziri, N.D.; Zhao, Y.Y. Role of RAS/Wnt/β-catenin axis activation in the pathogenesis of podocyte injury and tubulo-interstitial nephropathy. Chem. Biol. Interact. 2017, 273, 56–72.

72. Yu, X.; Fang, Y.; Ding, X.; Liu, H.; Zhu, J.; Zou, J.; Xu, X.; Zhong, Y. Transient hypoxia-inducible factor activation in rat renal ablation and reduced fibrosis with L-mimosine. Nephrology 2012, 17, 58–67.

73. Bonomini, F.; Dos Santos, M.; Veronese, F.V.; Rezzani, R. NLRP3 inflammasome modulation by melatonin supplementation in chronic pristane-induced lupus nephritis. Int. J. Mol. Sci. 2019, 20,

3466.

74. Zhang, B.; Zhang, X.; Zhang, C.; Shen, Q.; Sun, G.; Sun, X. Notoginsenoside R1 protects db/db mice against diabetic nephropathy via upregulation of Nrf2-mediated HO-1 expression. Molecules 2019, 24, 247.
75. Zhou, J.; Wang, T.; Wang, H.; Jiang, Y.; Peng, S. Obacunone attenuates high glucose-induced oxidative damage in NRK-52E cells by inhibiting the activity of GSK-3β. Biochem. Biophys. Res. Commun. 2019, 513, 226–233.
76. Hong, Y.A.; Lim, J.H.; Kim, M.Y.; Kim, E.N.; Koh, E.S.; Shin, S.J.; Choi, B.S.; Park, C.W.; Chang, Y.S.; Chung, S. Delayed treatment with oleanolic acid attenuates tubulointerstitial fibrosis in chronic cyclosporine nephropathy through Nrf2/HO-1 signaling. J. Transl. Med. 2014, 12.
77. Wang, Z.; Han, N.; Zhao, K.; Li, Y.; Chi, Y.; Wang, B. Protective effects of pyrroloquinoline quinine against oxidative stress-induced cellular senescence and inflammation in human renal tubular epithelial cells via Keap1/Nrf2 signaling pathway. Int. Immunopharmacol. 2019, 72, 445–453.
78. Qin, T.; Yin, S.; Yang, J.; Zhang, Q.; Liu, Y.; Huang, F.; Cao, W. Sinomenine attenuates renal fibrosis through Nrf2-mediated inhibition of oxidative stress and TGFβ signaling. Toxicol. Appl. Pharmacol. 2016, 304, 1–8.
79. Khaleel, S.A.; Raslan, N.A.; Alzokaky, A.A.; Ewees, M.G.; Ashour, A.A.; Abdel-Hamied, H.E.; Abd-Allah, A.R. Contrast media (meglumine diatrizoate) aggravates renal inflammation, oxidative DNA damage and apoptosis in diabetic rats which is restored by sulforaphane through Nrf2/HO-1 reactivation. Chem. Biol. Interact. 2019, 309.
80. Lv, D.; Zhou, Q.; Xia, Y.; You, X.; Zhao, Z.; Li, Y.; Zou, H. The association between oxidative stress alleviation via sulforaphane-induced Nrf2-HO-1/NQO-1 signaling pathway activation and chronic renal allograft dysfunction improvement. Kidney Blood Press. Res. 2018, 43, 191–205.
81. Peerapen, P.; Thongboonkerd, V. Protective roles of trigonelline against oxalate-induced epithelial-to-mesenchymal transition in renal tubular epithelial cells: An in vitro study. Food Chem. Toxicol. 2020, 135.