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Hepato- and reno-protective effects of thymoquinone, crocin, and carvacrol: A comprehensive review

Akbar Anaeigoudari✉

Department of Physiology, School of Medicine, Jiroft University of Medical Sciences, Jiroft, Iran

ABSTRACT

Medicinal plants are rich in nutrients and phytochemicals which prevent and treat a wide range of ailments. Accumulating experimental studies exhibit that some bioactive ingredients extracted from medicinal plants have suitable therapeutic effects on hepatic and renal injuries. This review focuses on the hepato- and reno-protective effects of thymoquinone, crocin, and carvacrol. The relevant literature was retrieved from PubMed, Scopus, Web of Science, and Google Scholar databases from the beginning of 2015 until the end of November 2021. According to the scientific evidence, the considered phytochemicals in this review have been applied with useful therapeutic effects on hepatic and renal damage. These therapeutic effects were mainly mediated through the amelioration of oxidative stress, suppression of inflammatory responses, and inhibition of apoptosis. Intracellular signaling pathways linked to nuclear factor kappa B (NF-κB), adenosine monophosphate-activated protein kinase, c-jun *N*-terminal kinase, and extracellular signal-regulated kinase 1/2 and Toll-like receptors are the most important pathways targeted by these phytochemicals. Up-regulation of transcription factor Nrf2 and down-regulation of transforming growth factor-beta 1 by these natural compounds also contribute to the alleviation of hepatic and renal injuries.

KEYWORDS: Carvacrol; Crocin; Thymoquinone; Hepatoprotective; Reno-protective; Inflammatory; Oxidative stress; NF-κB; Nrf2

1. Introduction

The liver and kidney have a key role in body hemostasis[1,2]. In normal conditions, these vital organs remove toxins and free radicals and prevent the accumulation of noxious substances threatening body organs[3]. Oxidative stress[4], inflammation[5], vascular dysfunction[6], and uncontrolled diabetes mellitus[7] have been shown to disturb liver and kidney function. Liver malfunction is recognized by increased blood levels of liver enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP)[8]. Kidney damage also can be characterized by a significant enhancement in serum level of creatinine and blood urea nitrogen as well as urinary excretion of proteins[9].

Medicinal plants are rich in nutrients and phytochemicals which prevent and treat a wide range of ailments[10]. Fruits and vegetables are considered the main source of phytochemicals[11]. Phytochemicals are divided into several groups according to their structure and function. These natural products include phenols, carotenoids, thiols, indoles, *etc*[12]. The therapeutic effects of phytochemicals have been well understood by conducting animal and clinical studies[13,14]. Antioxidant[15], anti-inflammatory[16], antihypertensive[17], anti-obesity[18], anti-cancer[19], anti-microbial[20], cardioprotective[21], neuroprotective[22], hepatoprotective[23] and reno-protective[24] effects are attributed to phytochemicals.

Thymoquinone (Figure 1) is a slightly water-soluble phytochemical compound that is mainly extracted from *Nigella sativa*. This natural compound has been demonstrated to have multiple therapeutic properties including antioxidant, anti-inflammatory, anti-diabetic, anti-sepsis, anti-carcinogenic, and anti-mutagenic effects[25]. The protective effects of thymoquinone on hepatotoxicity[26], cardiotoxicity[27], and renotoxicity[28] have been well studied. The positive impacts of thymoquinone on learning and memory

✉To whom correspondence may be addressed. E-mail: anaeiga317@gmail.com; Anaeia@jmu.ac.ir

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impairments resulting from hypothyroidism have also been documented[29].

Crocin (Figure 1) is a bioactive substance from *Crocus sativus*. In traditional medicine, it is employed for curing inflammation-related illnesses including bronchitis, diabetes, and cancer[30]. There are also ample pieces of evidence that show crocin scavenges free radicals and attenuates oxidative stress. Crocin can downregulate the levels of inducible nitric oxide synthase (iNOS), cyclooxygenase 2 (COX2), and interleukin-1β (IL-1β)[31]. Crocin has been also found to inhibit apoptosis *via* down-regulation of caspases-9 and 3 activity and reduction of Bax/Bcl2 ratio[32]. In addition, the effect of crocin against angiotensin II-triggered acute hypertension in rats has been confirmed[33].

Carvacrol (Figure 1) is a phenolic ingredient found in essential oils of some plants which possesses a wide range of biological and pharmacological properties such as anti-apoptosis, anti-cancer, anti-inflammation, and anti-proliferation[34]. Carvacrol can eliminate reactive oxygen species (ROS) and increase antioxidant activities including glutathione (GSH)[35]. Based on scientific findings, carvacrol has beneficial effects on depressive-like behaviors[36], high blood pressure[37], and diabetes[38]. Considering numerous beneficial effects of these compounds, in this review, the hepato- and reno-protective effects of thymoquinone, crocin, and carvacrol are focused on and summarized.

2. Methods

In the current review, findings were extracted from PubMed, Scopus, Web of Science, and Google Scholar databases from the beginning of 2015 until the end of November 2021 by searching key words incluing "hepatoprotective" or "renoprotective" and "thymoquinone", "crocin", and "carvacrol". Non-English papers and letters to the editor were excluded.

3. Hepatoprotective effects

3.1. Effects of thymoquinone

Hepatic damages resulting from ischemia-reperfusion (IR) are considered a basic obstacle in liver surgeries such as liver transplantation[39]. Oxidative and nitrosative stress has been considered important factors in the pathogenesis of IR-induced hepatic damages[40]. The protective effect of thymoquinone (20 mg/kg/day) was evaluated against IR-induced hepatic injury in rats. The previous study showed that pretreatment with thymoquinone mitigated the serum level of ALT, AST, myeloperoxidase (MPO), malondialdehyde (MDA), and nitric oxide (NO). In addition, overexpression of endothelial nitric oxide synthase (eNOS) and down-regulation of iNOS occurred after thymoquinone administration. The results suggested that the hepatoprotective effects of thymoquinone were probably mediated *via* regulating the NO signaling pathway and improving oxidative stress[41]. The liver plays a key role in lipid homeostasis. Some toxic substances such as ethanol damage the liver and consequently disturb lipid homeostasis[42]. In addition, AMP-activated protein kinase (AMPK) has a pivotal role in lipid homeostasis and its activation prevents the proliferation of hepatic stellate cells (HSC) and hepatic fibrosis[43]. Liver kinase B1 is a serine/threonine kinase linked to AMPK signaling pathway[44]. In addition, one of the basic regulators in hepatic lipid hemostasis is sirtuin 1 (SIRT1). Up-regulation of SIRT1-AMPK pathway has been shown to elevate fatty acids oxidation and suppress lipogenesis by affecting the activity of peroxisome proliferator-activated receptors (PPARs)[45]. On the other hand, it has been reported that alcohol damages the liver tissue by decreasing the activity of AMPK or SIRT1[46]. Oral administration of thymoquinone (20 and 40 mg/kg) could improve alcohol-caused liver dysfunction in mice *via* increased activity of liver kinase B1, AMPK, and PPARs and up-regulation of SIRT1[47].

Diabetes mellitus (DM) is a metabolic disorder associated with hyperglycemia which can be resulted from a defect in insulin secretion. The previous study demonstrated that liver injuries can be a consequence of DM. Hyperglycemia, hyperlipidemia, and inflammation resulting from DM contribute to liver damage[48]. It has been suggested that antioxidant agents can rescue liver cells from DM-triggered injuries[49]. In a study, administration of 20 mg/kg/day of thymoquinone along with beta-aminoisobutyric acid protected the hepatic tissue against streptozocin-induced diabetes. This therapeutic effect was due to antioxidant and anti-diabetic properties of thymoquinone[50].

Drug-stimulated hepatic injury has been shown to contribute to

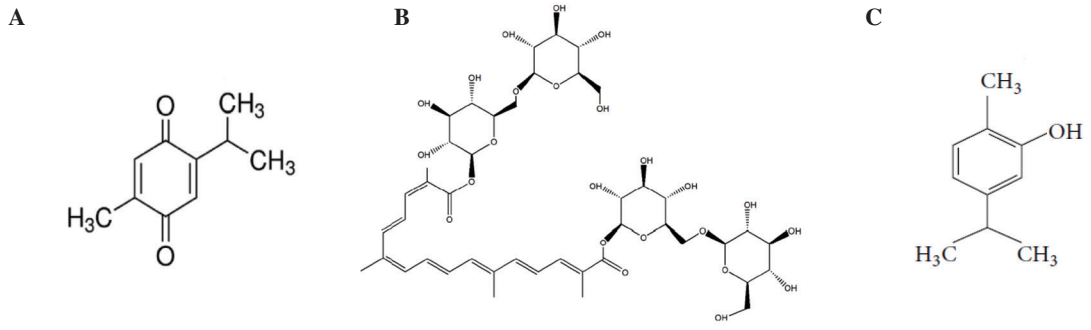

Figure 1. Molecular structure of (A) thymoquinone, (B) crocin, and (C) carvacrol.

acute liver failure[51]. Acetaminophen as a fever-reducing medication causes hepatic failure when it is used at a high dose for a long time[52]. Cytochrome 2E1 (CYP2E1) converts acetaminophen into *N*-acetyl-*p*-benzoquinone imine. *N*-Acetyl-*p*-benzoquinone imine reduces GSH level and promotes oxidative stress and consequently disarranges mitochondria function[53]. Researchers reported that thymoquinone (20 mg/kg) could alleviate hepatotoxicity resulting from acetaminophen overdose in mice by regulating the activity of c-jun *N*-terminal kinase (JNK) and AMPK signaling pathways and reducing the cytochrome 2E1 function[54].

Lipid accumulation in liver cells alters their normal function and induces nonalcoholic fatty liver disease (NAFLD). NAFLD can lead to liver fibrosis, cirrhosis, and hepatocarcinoma[55]. In a previous study, the effects of a low dose (10 mg/kg) and a high dose (20 mg/kg) of thymoquinone were evaluated against high-fat high-cholesterol diet-caused NAFLD in rats. The results demonstrated that both doses of thymoquinone ameliorated insulin resistance and blood glucose. In addition, the serum level of total cholesterol and triglyceride (TG) was reduced and the blood concentration of high-density lipoprotein (HDL) was elevated in thymoquinone-treated rats[56].

Hepatocellular carcinoma is one of the main causes of death resulting from cancer worldwide[57]. Binding of the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) to its receptors, TRAILR1 and TRAILR2, can be a spark for inducing programmed cell death by activating the caspase-8[58]. Production of B cell lymphoma (Bcl) anti-apoptotic proteins such as Bcl-2 and Bcl-XL also prevents apoptosis and increases the resistance of cancer cells against chemotherapy drugs[59]. Furthermore, transforming growth factor-beta 1 (TGF-β1) can prepare a suitable environment for the proliferation of tumor cells[60]. Thymoquinone (20 mg/kg) attenuated thioacetamide-caused hepatocellular carcinoma in rats *via* down-regulation of Bcl-2, Bcl-XL, and TGF-β1 expression, and up-regulation of TRAIL-linked apoptosis[61]. The hepatoprotective effects of thymoquinone are illustrated in Table 1.

3.2. Effects of crocin

IR can disturb liver tissue function by inducing the release of ROS and inflammatory cytokines[62]. Nuclear factor-erythroid 2-related factor 2 (Nrf2) is a transcription factor that protects organs such as the liver against oxidative stress damage[63]. Furthermore, the increased level of miR-122 that is expressed in liver cells has a relationship with liver enzymes in IR-induced hepatic damages[64]. The inhibition of miR-34a can prevent the hepatic injuries induced by IR[65]. P53 as a tumor suppressor protein also targets miR-34a[66]. It has been revealed that inhibition of p53 down-regulates miR-34a and finally castrates oxidative stress and ameliorates hepatic damage[67]. It has been recognized that crocin (200 mg/kg) can rescue liver tissue from IR-induced injury in rats, which is associated with the elevation of antioxidant enzymes activity including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), reduction of liver enzymes concentration, increase of Nrf2 expression and down-regulation of miR-122, miR-34a and p53[68].

Thioacetamide is an organosulfur carcinogenic compound that is employed in some industries including leader, paper, and textile. In addition, thioacetamide has been reported to have fungicidal properties. Therefore, it has been used to prevent the decay of some fruits such as oranges. However, thioacetamide has been revealed to have detrimental effects on different body organs such as the lungs, kidney, intestine, pancreas, and liver[69]. Intraperitoneally injection of crocin (10 mg/kg) exerted protective effects against thioacetamide-induced hepatocellular carcinoma in rats *via* modulating the oxidative stress status. In addition, treatment with crocin increased Nrf2 and heme oxygenase-1 (HO-1) expression, suppressed the level of c-JNK, stimulated TRAIL-mediated apoptosis, up-regulated the expression of caspase-8, p53, and Bax, and reduced the expression of Bcl-2[70]. Acrylamide is a potential carcinogenic and toxic compound that is formed at high temperatures and disturbs mitochondria function[71]. A previous study showed that crocin (50 mg/kg) improved acrylamide-induced liver injury in rats. This protective effect could be attributed to the antioxidant activity of crocin[72]. Bisphenol A is also a toxic substance that is used in production of polycarbonate plastics and epoxy resins[73]. Crocin (20 mg/kg for 30 d) has been found to decrease the bisphenol A-triggered liver toxicity in rats. The ameliorative effect of crocin against liver damage was mediated by the reduction of TG and liver enzymes, inhibition of oxidative stress, decrease of miR-122 expression, and up-regulation of JNK, extracellular signal-regulated kinase 1/2 (ERK1/2), and

Table 1. Hepatoprotective effects of thymoquinone.

Type of study	Animal	Dose	Mechanisms of action	Reference
IR-induced injury	Rat	20 mg/kg	Regulation of NO signaling pathway and oxidative stress status	[41]
Alcohol-caused injury	Mouse	20 and 40 mg/kg	Increase of LKB1, AMPK, and PPARs activity and up-regulation of SIRT1	[47]
Streptozocin-induced diabetes	Rat	20 mg/kg	Improvement of hepatic injury through alleviating streptozocin-induced diabetes	[50]
Acetaminophen-induced damage	Mouse	20 mg/kg	Modulation of JNK and AMPK signaling and inhibition of CYP2E1	[54]
High-fat high-cholesterol diet-induced damage	Rat	10 and 20 mg/kg	Amelioration of insulin resistance and blood glucose, reduction of total cholesterol and triglycerides, and elevation of HDL	[56]
Thioacetamide-induced damage	Rat	20 mg/kg	Down-regulation of Bcl-2, Bcl-XL, and TGF-β1 expression and up-regulation of TRAIL-linked apoptosis	[61]

IR: ischemia-reperfusion, NO: Nitric oxide, LKB1: Liver kinase B1, AMPK: AMP-activated protein kinase, PPARs: Peroxisome proliferator-activated receptors, SIRT1: Sirtuin 1, JNK: c-Jun *N*-terminal kinase, CYP2E1: Cytochrome 2E1, HDL: High-density lipoprotein, TGF: Transforming growth factor, TRAIL: Tumor necrosis factor-related apoptosis-inducing ligand.

mitogen-activated protein kinase (MAPK)[74]. Scientific evidence also demonstrated that oral administration of crocin (20 mg/kg for 8 weeks) suppressed lipogenesis and induced β-oxidation of fatty acids by activating the AMPK signaling pathway in diabetic and obese *db/db* mice[75].

Toll-like receptors (TLRs) are membrane receptors that play an important role in inflammation-caused tissue damage. They can be stimulated by exogenous and endogenous ligands[76]. TLRs were also expressed in hepatic parenchymal and non-parenchymal cells and contributed to the development of inflammatory responses resulting from alcoholic and non-alcoholic liver diseases, viral hepatitis, and drugs-linked liver disorders[77]. Some chemotherapeutic agents including cisplatin have been shown to induce hepatotoxicity *via* stimulating the inflammatory reactions when they are used at high doses[78]. Accumulating pieces of evidence exhibit that pretreatment with crocin (200 mg/kg) afford hepatoprotective effects against cisplatin-stimulated liver injury through antagonizing the activity of TLR4/nuclear factor kappa B (NF-κB) signaling pathway, elevating the level of anti-fibrogenic agents including activin membrane-bound inhibitor and miRNA-9 and miRNA-29 and inhibiting the expression of TGF-β1[79].

Liver fibrosis is a disorder followed by over-deposition of extracellular matrix ingredients. Malfunction of biliary system and accumulation of fat in the liver has been known as one of the most important causes of hepatic fibrosis[80]. Carbon tetrachloride (CCl_4) can induce hepatic fibrosis in animal studies[81]. Chhimwal *et al*. reported that crocin (20, 40, and 80 mg/kg) could alleviate the CCl_4-triggered hepatic fibrosis in rats through the improvement of PPAR-γ expression, modulation of inflammation, and suppression of fibrogenic signaling pathways[82].

Aging is considered an important factor in body organ dysfunction such as the liver. Oxidative stress and inflammation have been illustrated to play a key role in the harmful effects of aging on tissues[83]. Long-term injection of *D*-galactose can induce aging in animal studies[84]. The study of Omidkhoda *et al*. demonstrated that *D*-galactose (400 mg/kg) disturbed liver function with elevated levels of ALT, AST, ALP, MDA, and iNOS and reduced activity of GSH. Crocin at 7.5, 15, and 30 mg/kg could ameliorate *D*-galactose-stimulated hepatotoxicity *via* the suppression of lipid peroxidation and iNOS expression[85]. The hepatoprotective effects of crocin are summarized in Table 2.

3.3. Effect of carvacrol

Hippo-Yes-associated protein pathway (YAP)/Transcriptional coactivator with PDZ-binding motif (TAZ) as one of the most vital components of tissue homeostasis has been shown to modulate endothelial cell proliferation, vascular barrier establishment, and cell migration[86]. Meanwhile, interaction of Hippo and TGF-β signaling pathways can lead to fibrotic disorders[87]. It has been also reported that YAP and TAZ excite the HSC proliferation and promote the up-regulation of connective tissue growth factor as one of the principal players in tissue fibrosis induction[88]. Scientific evidence have proved that administration of 35 and 70 mg/kg of carvacrol prevented CCl_4-promoted hepatic fibrosis in rats by affecting the Hippo and TGF-β signaling pathways. Moreover, carvacrol normalized the level of liver enzymes, reduced the hepatic hydroxyproline, and down-regulated YAP/TAZ and TGF-β signaling pathways[89]. In another study, carvacrol (25 and 50 mg/kg) showed anti-fibrotic effects against thioacetamide through the mitigation of NF-κB, IL-1β, iNOS, matrix metalloproteinase-3 and 9 (MMP-3 and 9), autotaxin and TGF-β1 level in rats[90].

Lysyl oxidase, an extracellular copper-linked enzyme, catalyzes the covalent cross-linkage formation in collagen fibers and its overproduction can make a stable environment for induction of fibrotic processes[91]. It has been documented that carvacrol (70 mg/

Table 2. Hepatoprotective effects of crocin.

Type of study	Animal	Dose	Mechanisms of action	Reference
IR-induced injury	Rat	200 mg/kg	Amplification of SOD, catalase, and GPx activity, up-regulation of Nrf2, down-regulation of miR-122, miR-34a, and p53	[68]
Thioacetamide-induced injury	Rat	10 mg/kg	Enhancement of Nrf2 and heme oxygenase-1 expression, suppression of c-JNK, stimulation of TRAIL-mediated apoptosis, up-regulation of caspase-8, p53, and Bax, and down-regulation of Bcl-2	[70]
Acrylamide-induced injury	Rat	50 mg/kg	Potentiation of antioxidant defense	[72]
Bisphenol A-induced damage	Rat	20 mg/kg	Reduction of triglycerides and liver enzymes, inhibition of oxidative stress, decrease of miR-122 expression, and up-regulation of JNK, ERK1/2 and MAPK activity	[74]
Diabetic and obese condition	Mouse	20 mg/kg	Suppression of lipogenesis and induction of β-oxidation of fatty acids by the activation of AMPK signaling pathway	[75]
Cisplatin-induced damage	Rat	200 mg/kg	Opposition of TLR4/NF-κBp50 signaling, elevation of BAMBI and miRNA-9 and miRNA-29, and decrease of TGF-β1 level	[79]
CCl_4-induced damage	Rat	20, 40, and 80 mg/kg	Improvement of PPAR-γ expression and modulation of inflammatory and fibrogenic signaling pathways	[82]
D-galactose-induced aging	Rat	7.5, 15, and 30 mg/kg	Suppression of lipid peroxidation and iNOS expression	[85]

SOD: Superoxide dismutase, GPx: Glutathione peroxidase, ERK: Extracellular signal-regulated kinase, MAPK: Mitogen-activated protein kinase, TLR: Toll-like receptor, NF-κB: Nuclear factor kappa B, iNOS: Inducible nitric oxide synthase, BAMBI: Bone morphogenetic protein (BMP) and activin membrane-bound inhibitor.

kg) modified the oxidative stress status and decremented the level of lysyl oxidase homolog 2 and lysyl oxidase in CCl_4-exposed rats and consequently ameliorated liver tissue fibrosis[92]. Additionally, carvacrol administration (25, 50, 100 mg/kg) could exert ameliorative effects against fibrotic hepatic tissues in CCl_4-challenged mice through the inhibition of transient receptor potential melastatin 7, regulation of MAPK signaling pathway, and suppression of HSC proliferation[93].

Adriamycin as an antitumor antibiotic acts as a double-edged sword. It can inhibit cancer cells, but its high doses have toxic effects on organs such as the heart, liver, and kidney[94]. Oral administration of carvacrol (20 mg/kg) improved adriamycin-induced hepatic oxidative damage in rats by lowering the MDA concentration and elevating the CAT activity[95]. The anti-oxidant and anti-inflammatory effects of carvacrol against lipopolysaccharide (LPS)-induced liver injuries have been also confirmed. In an animal study, systemic injection of carvacrol (25, 50, and 100 mg/kg) reversed pernicious effects of LPS on liver function in rats by modulating liver enzymes concentration, diminishing NO, MDA, and IL-1β levels, and increasing total thiol content and SOD and CAT activities[96]. Carvacrol (20 mg/kg) also showed positive therapeutic impact on acetaminophen-prompted hepatotoxicity in rats, which was linked to its antioxidant properties[97]. The results of scientific works confirmed that the increase of cytochrome (Cyt) P450 activity by ethanol induces oxidative stress causing hepatic damage. It has been reported that carvacrol binds to the active site of Cyt P450 and suppresses its function. In animal research, carvacrol (50 mg/kg) ameliorated alcohol-induced hepatotoxicity with the inhibition of Cyt P450 and down-regulation of NF-κB, iNOS, and eNOS levels[98]. Some toxic heavy metals such as cadmium exert toxic effects on body tissues by disturbing the oxidative stress status. Treatment of rats with 25 and 50 mg/kg of carvacrol also attenuated the detrimental effects of cadmium on liver and kidney function by lowering the concentration of ALT, ALP, AST, urea, creatinine, and MDA and elevating the activity of SOD, CAT, and GPx. In addition, carvacrol alleviated the effects of cadmium on iNOS, COX-2, NF-κB, Bcl-3, Bax, Bcl-2, MAPK-14, MPO, prostaglandin E_2 (PGE_2), p53, caspase-6, caspase-3, and caspase-9[99].

The positive effects of carvacrol on liver dysfunction caused by type 2 diabetes mellitus (T2DM) in mice have been also explored. The results indicated that 10 mg/kg of carvacrol for 6 weeks could improve T2DM-caused liver malfunction *via* the reduction of ALT, AST, TG, and low-density lipoprotein cholesterol level, enhancement of high-density lipoprotein cholesterol content, and regulation of TLR 4/NF-κB signaling pathway[100]. One of the basic intracellular signaling pathways starting the hepatic regeneration after partial hepatectomy is IL-6/signal transducer and activator of transcription 3 (STAT3) signaling pathway. It has been exhibited that peripheral administration of carvacrol (73 mg/kg) could stimulate hepatocyte proliferation and hepatic regeneration 24 and 48 h after partial hepatectomy in mice by activating the IL-6/STAT3 and MAPK signaling pathways[101]. The hepatoprotective effects of carvacrol are displayed in Table 3.

4. Reno–protective effects

4.1. Effects of thymoquinone

In the kidneys, IR-induced injury contributes to pathological

Table 3. Hepatoprotective effects of carvacrol.

Type of study	Animal	Dose	Mechanisms of action	Reference
CCl_4-induced damage	Rat	35 and 70 mg/kg	Reduction of hydroxyproline, down-regulation of YAP/TAZ and TGF-β signaling pathway	[89]
Thioacetamide-induced damage	Rat	25 and 50 mg/kg	Mitigation of NF-κB, IL-1β, iNOS, MMP-3, MMP-9, and TGF-β1 level	[90]
CCl_4-induced damage	Rat	70 mg/kg	Decrement of lysyl oxidase homolog 2 and lysyl oxidase level and collagen fiber bundles	[92]
CCl_4-caused injury	Mouse	25, 50, 100 mg/kg	Inhibition of transient receptor potential melastatin 7, regulation of MAPK signaling pathway, and suppression of HSC proliferation	[93]
Adriamycin-induced injury	Rat	20 mg/kg	Decline of MDA concentration and elevation of catalase activity	[95]
Lipopolysaccharide-induced damage	Rat	25, 50, and 100 mg/kg	Diminution of NO, MDA, and IL-1β levels, enhancement of total thiol content, and increment of SOD and catalase activities	[96]
Acetaminophen-induced injury	Rat	20 mg/kg	Increase in antioxidant activity	[97]
Alcohol-induced injury	Rat	50 mg/kg	Inhibition of Cyt P450, and down-regulation of NF-κB, iNOS, and eNOS level	[98]
Cadmium-induced damage	Rat	25 and 50 mg/kg	Alleviation of the effects of cadmium on iNOS, COX-2, NF-κB, Bcl-3, Bax, Bcl-2, MAPK-14, MPO, PGE_2, p53, caspase-6, caspase-3, and caspase-9	[99]
Diabetes mellitus-induced damage	Mouse	10 mg/kg	Reduction of ALT, AST, triglycerides, and low-density lipoprotein cholesterol level, enhancement of high-density lipoprotein cholesterol content, and regulation of TLR4/NF-κB signaling pathway	[100]
Hepatectomy	Mouse	73 mg/kg	Activation of IL-6/STAT3 and MAPK signaling pathways	[101]

YAP: Yes-associated protein, TAZ: Transcriptional coactivator with PDZ-binding motif, IL: Interleukin, iNOS: Inducible nitric oxide synthase, MMP: Matrix metalloproteinase, HSC: Hepatic stellate cells, MDA: Malondialdehyde, Cyt: Cytochrome, eNOS: Endothelial nitric oxide synthase, COX: Cyclooxygenase, MPO: Myeloperoxidase, PGE_2: Prostaglandin E_2, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, STAT: Signal transducer and activator of transcription.

conditions such as acute kidney injury. IR-triggered renal injuries are due to overproduction of free radicals, pro-inflammatory and pro-fibrotic cytokines[102]. In a rat model of renal IR, oral administration of thymoquinone (10 mg/kg) ameliorated hemodynamic and tubular function indicators in the kidneys. These renoprotective effects of thymoquinone were associated with the decline of pro-inflammatory and pro-fibrotic mediators such as tumor necrosis factor (TNF)-α, TGF-1β, and plasminogen activator inhibitor-1[103]. Structural and functional abnormalities of the kidney can be a consequence of formation of fibrous tissues. Oxidative stress and inflammation are considered risk factors for renal fibrosis[104]. It has been demonstrated that thymoquinone (2, 5, and 10 mg/kg/day) protects against LPS-induced renal fibrosis through the inhibition of oxidative stress and inflammation responses. According to the results, treatment with thymoquinone decreased MDA concentration and increased total thiol content and SOD and CAT activity in kidney tissues[105]. Uncontrolled production of free radicals and inflammatory cytokines has been exhibited to have a central role in sepsis-linked renal damage[106]. It has been detected that thymoquinone (50 mg/kg) mitigated kidney injuries in septic ALB/c mice. The renal protective effects of thymoquinone were associated with the reduced expression of NF-κB, TNF-α, IL-1β, and IL-6, caspase-1, caspase-3, and caspase-8 and NOD-like receptor family pyrin domain-containing 3 (NLRP3)[107]. Ionizing radiations employed for management of some diseases damage DNA and stimulate the release of free radicals. Thymoquinone (50 mg/kg/day) as a natural antioxidant has been recognized to improve gamma-induced renal injuries in rats through the potentiation of antioxidant capacity and the inhibition of free radicals production[108].

Alteration of thyroid gland function, hyperthyroidism, and hypothyroidism, can disturb renal function[109]. It has been reported that hypothyroidism decrements the production of renin and enhances the blood level of creatinine and the permeability of glomerular capillaries[110]. It has been also found that hypothyroidism can induce renal failure by disturbing the function of intracellular antioxidant system. In a rat model of hypothyroidism induced by propylthiouracil, thymoquinone (50 mg/kg) balanced the oxidative status and up-regulated the gene expression of CAT in kidney tissues and finally improved renal function[111]. Kidney function can be threatened when they were exposed to heavy metals such as lead. The researchers reported that thymoquinone (5 mg/kg/day for 5 weeks) could ameliorate lead-induced nephropathy in rats through the reinforcement of intracellular antioxidant mechanisms[112]. In addition, thymoquinone (50 mg/kg) protected rats against manganese-induced nephrotoxicity *via* the down-regulation of TNF-α and IL-6 and the enhancement of SOD, GSH, and IL-10[113]. In an animal model of cisplatin-induced renal toxicity, systemic infusion of thymoquinone (50 mg/kg) along with curcumin reversed the harmful effects of this anti-cancer drug on the kidney of rats *via* attenuating the effect of NF-κB and kidney injury molecule 1, and amplifying the activity of Nrf2/HO-1 signaling pathway[114]. The improving effect of thymoquinone (20 mg/kg) against diclofenac-induced renal injury was also documented. In the study of Hashem *et al*., thymoquinone improved the antioxidant defense, suppressed the activity of caspase 3, and modulated the expression of mitofusin-2 and miR-34a in renal tissue of rats[115]. The renoprotective effects of thymoquinone are presented in Table 4.

4.2. Effects of crocin

Diabetic nephropathy is recognized as an important cause of renal failure. In this disease, renal cell function was disturbed by inflammation resulting from high blood sugar concentration[116]. In a mice model of nephropathy, crocin (50 mg/kg) exerted its renal protective effects *via* the attenuation of oxidative damage-related NF-κB signaling pathway and intensification of Nrf2 activity[117]. Moreover, hyperglycemia-caused inflammatory responses and NLRP3 inflammasome involve in the pathogenesis of diabetic nephropathy. Up-regulation of NLRP3 results in uncontrolled release of inflammatory cytokines such as IL-1β and IL-18 and ultimately disturbs renal function[118]. Administration of 50 mg/kg of crocin could alleviate diabetic nephropathy resulting from

Table 4. Renoprotective effects of thymoquinone.

Type of study	Animal	Dose	Mechanisms of action	Reference
IR-induced injury	Rat	10 mg/kg	Deletion of pro-inflammatory and pro-fibrotic mediators such as TNF-α, TGF-1β, and plasminogen activator inhibitor-1	[103]
LPS-induced injury	Rat	2, 5, and 10 mg/kg	Decrease of MDA concentration and elevation of total thiol content and SOD and catalase activity	[105]
Septic-induced damage	Mouse	50 mg/kg	Reduction of NF-κB, TNF-α, IL-1β, IL-6, caspase-1, caspase-3, caspase-8 and NLRP3 expression	[107]
Radiation-stimulated injury	Rat	50 mg/kg	Reinforcement of antioxidant defense	[108]
Hypothyroidism-induced damage	Rat	50 mg/kg	Up-regulation of gene expression of catalase	[111]
Lead-caused damage	Rat	5 mg/kg	Reinforcement of intracellular antioxidant mechanisms	[112]
Manganese-caused damage	Rat	50 mg/kg	Down-regulation of TNF-α and IL-6 and enhancement of SOD, GSH, and IL-10	[113]
Cisplatin-induced injury	Rat	50 mg/kg	Attenuation of the effect of NF-κB and kidney injury molecule 1 and amplification of Nrf2/HO-1 signaling pathway	[114]
Diclofenac-induced damage	Rat	20 mg/kg	Suppression of caspase 3 activity and modulation of Mfn2 and miR-34a expression	[115]

TNF-α: Tumor necrosis factor alpha, NLRP3: NOD-like receptor family pyrin domain-containing 3, GSH: Glutathione, HO: Heme oxygenase.

overexpression of TNF-α, IL-1β, and IL-18 in rats by decreasing NLRP3 inflammasome[119]. Treatment of rats with crocin (40 mg/kg) also suppressed the production of NADPH oxidase 4, p53, and IL-18 and repaired the diabetic nephropathy-induced renal damages[120]. In addition, daily administration of crocin (50 mg/kg) could inhibit nephropathy progression in pinealectomized diabetic rats by modulating the level of TGF-β1 and oxidative stress markers[121]. Moreover, crocin (12.5, 25, and 50 mg/kg) ameliorated the detrimental effects of methotrexate on the kidneys of rats by increasing antioxidant activity and lowering MDA levels[122].

Some anthracycline antibiotics such as doxorubicin have been reported to have side effects on the liver, kidney, neurons, and heart[123]. The toxic effect of these drugs can be a consequence of oxidative damage such as DNA and proteins. Scientific evidence illustrated that crocin (100 mg/kg/day for 3 weeks) as an antioxidant alleviated doxorubicin-caused nephrotoxicity in rats and decreased the gene expression of NF-κB, iNOS, TNF-α, and COX2[124].

Acute kidney injury is a clinical disorder without definitive treatment. One of the known causes of this disease is renal IR causing vascular endothelium dysfunction and inflammation[125]. In an experimental model of IR-excited acute kidney injury, intraperitoneal injection of crocin (100, 200, and 400 mg/kg) dose-dependently lessened leukocyte infiltration, intercellular adhesion molecule (ICAM)-1 and TNF-α in kidney tissues of rats[126]. In another research, crocin (20 mg/kg) restored the noxious effects of IR by modulating oxidative stress and TLR4-linked inflammation in rats[127]. The renoprotective effects of crocin are depicted in Table 5.

4.3. Effects of carvacrol

Nonsteroidal anti-inflammatory drugs are used for the relief of some ailments such as headache, flu, and arthritis[128]. Diclofenac is a nonsteroidal anti-inflammatory drug that is frequently used by people to remedy pain[129]. It has been propounded that there is a link between the use of diclofenac and renal damage[130]. Researchers evaluated the effect of carvacrol (10 mg/kg) against diclofenac-caused renal injury in rats. The results indicated that the reno-protective impact of carvacrol was associated with increased level of antioxidant indicators including GPx, GSH, CAT, and SOD and decreased production of oxidant and inflammatory indices such as MDA and TNF-α[131]. Sadeghi *et al*. reported that carvacrol reduced cisplatin-induced kidney toxicity by the reduction of NO metabolites and MDA concentration[132].

Antineoplastic compounds such as cyclophosphamide can trigger renal dysfunction by disturbing the oxidative status. Carvacrol (10 mg/kg) ameliorated cyclophosphamide-stimulated renal malfunction in rats through the attenuation of oxidative damage to renal tissues. Based on the results of Gunes *et al*., the concentration of MDA was decreased and GSH, SOD, and CAT activity and total antioxidant capacity levels were increased in the carvacrol-treated group compared to the cyclophosphamide group[133]. Systemic injection of 75 mg/kg of carvacrol also enhanced the SOD, CAT, GSH activity, down-regulated the eNOS expression, and decremented the MDA and MPO concentration, eventually mitigating the IR-caused disturbances in renal function of rats[134]. Restraint stress can be associated with oxidative stress resulting in body organs damage. It has been documented that carvacrol (30 and 40 mg/kg) protected the brain, liver, and kidney of rats against chronic stress-caused oxidative damage by reducing the level of MDA and increasing the activity of SOD and CAT in rats[135]. The renoprotective effects of carvacrol are summarized in Table 6.

Table 5. Renoprotective effects of crocin.

Type of study	Animal	Dose	Mechanisms of action	Reference
Hyperglycemia-induced nephropathy	Mouse	50 mg/kg	Attenuation of NF-κB signaling pathway and intensification of Nrf2 activity	[117]
Diabetic nephropathy	Rat	50 mg/kg	Overexpression of TNF-α, IL-1β, and IL-18 by decreasing NLRP3 inflammasome	[119]
Diabetic nephropathy	Rat	40 mg/kg	Suppression of NADPH oxidase 4, p53, and IL-18 production	[120]
Diabetic nephropathy	Rat	50 mg/kg	Modulation of the level of TGF-β1 and oxidative stress markers	[121]
Methotrexate-induced renal damage	Rat	12.5, 25 and 50 mg/kg	Decline of MDA level	[122]
Doxorubicin-induced nephrotoxicity	Rat	100 mg/kg	Decline of NF-κB, iNOS, TNF-α, and COX2 expression	[124]
IR-excited renal injury	Rat	100, 200 and 400 mg/kg	Decrease of leukocyte infiltration, ICAM-1 and TNF-α	[126]
IR-induced renal damage	Rat	20 mg/kg	Modification of oxidative stress, and inhibition of TLR4-linked inflammation	[127]

ICAM: Intercellular adhesion molecule.

Table 6. Renoprotective effects of carvacrol.

Type of study	Animal	Dose	Mechanisms of action	Reference
Diclofenac-caused injury	Rat	10 mg/kg	Increase in GPx, GSH, catalase, and SOD levels and decrease in MDA and TNF-α production	[131]
Cisplatin-induced damage	Rat	50 mg/kg	Reduction of NO metabolites and MDA concentration	[132]
Cyclophosphamide-stimulated injury	Rat	10 mg/kg	Decrease in MDA concentration, increase in GSH, SOD, catalase, and total antioxidant capacity level	[133]
IR-caused injury	Rat	75 mg/kg	Enhancement of SOD, catalase, and GSH activity, down-regulation of eNOS expression, and decrement of MDA and MPO concentration	[134]
Chronic stress-induced oxidative stress	Rat	30 and 40 mg/kg	Reduction of MDA level and increase of SOD and catalase activity	[135]

5. Conclusion

This review shows that inflammation and oxidative stress play a role key in hepatic and renal injuries. The activation of intracellular signaling pathways linked to NF-κB, MAPK, JNK, and ERK1/2 in response to inflammation stimuli can result in body organ damage. Thymoquinone, crocin, and carvacrol show hepato- and reno-protective effects through the inhibition of these signaling pathways. The transcription factor Nrf2 is also considered a very important cause in the protection of organs against oxidative stress. Thymoquinone, crocin, and carvacrol also exert their anti-oxidative effects against hepatic and renal injuries *via* up-regulating the Nrf2 pathway and amplifying the antioxidant defense. TGFβ1 makes a suitable environment for the growth and proliferation of cancer cells. According to the previous studies, TGF-β1 pathway is one of anti-tumor targets for thymoquinone and crocin in the protection of the liver and kidney.

Although accumulating evidence reveals that thymoquinone, crocin, and carvacrol exert protective effects against hepatic and renal damages in animal studies, the therapeutic effect of these phytochemicals in the clinical study needs to be further investigated. Therefore, preclinical studies are required to elucidate the safety and efficacy of these natural compounds.

Conflict of interest statement

The author declares that there is no conflict of interest.

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