Review

Kidney Diseases

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An Overview on Renoprotective Effects of Thymoquinone

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Keywords
Kidney · Inflammation · Oxidative stress · Renoprotective effects · Thymoquinone

Abstract
Background: Kidneys as vital organs remove waste material from blood. Additionally, they may also have a role in the electrolyte balance, regulation of blood pressure, and red blood cell genesis. Kidney diseases may be caused by several factors such as ischemia/reperfusion injury, diabetes, and nephrotoxic agents. Oxidative stress and inflammation are involved in the pathogenesis and progression of kidney diseases. Traditionally, natural antioxidants are used for treatment of renal failure in various countries. ***Summary:*** People usually select natural antioxidants since they have an opinion that herbal medicine has not any important side effects. *Nigella sativa* is a flavoring herb that is widely used as a condiment and as a remedy for many disorders. Thymoquinone (TQ), the most important component of black seeds, mainly oil, is considered as an active agent responsible for a lot of the seed's useful effects. This review describes the protective roles and related mechanisms of TQ against renal disorders. The search terms, including TQ, antioxidant, renal ischemia-reperfusion, diabetic nephropathy, and nephrotoxic agent were searched in scientific databases. TQ showed anti-inflammatory and antioxidant properties in animal and in vitro models of several renal diseases caused by inflammation and oxidative stress. ***Key Messages:*** Experimental studies have shown beneficial effects of TQ against renal diseases; however, well-designed clinical trials in humans are required to confirm these effects.

Background

Nigella sativa, generally known as black seed or black cumin, is an annual flowering bush plant from the family Ranunculaceae which is growing in Southwest Asia, North Africa, and southern Europe [1, 2]. The main compounds that have been isolated from *N. sativa* seed include proteins, carbohydrates, fixed oils, essential oil, crude fiber, alkaloids, minerals, vitamins, ash, and moisture. The other components are tannins, resin, saponin, carotene, glucosides, and sterols [3]. One of the major components of the essential oil is thymoquinone (TQ) [4, 5]. Based on the use of *N. sativa* in traditional medicine

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as a natural treatment for some diseases, researchers have investigated its protective effects against asthma [6], hypertension [7], diabetes [8], and inflammation [9]. In addition, TQ is known to have antioxidant [10], analgesic, antipyretic [11], antischistosomal [12], antifungal [13], antibacterial [14], anticancer [15], anticonvulsant [16], hepatoprotective [17], and neuroprotective activities [18]. It has been found that TQ has beneficial protective effects against renal diseases through anti-inflammatory, antioxidant, and antiapoptotic activities [19]. The present review aimed to review the recent studies from 2007 to 2017 that describe the protective effects of TQ in the management of kidney diseases.

Evidence Acquisition

Online literature resources were checked using different search engines such as Medline, PubMed, Scopus, and Google Scholar from 2000 to 2017 to identify articles, editorials, and reviews about renoprotective effects of TQ. In this review article, the words TQ, antioxidant, renal ischemia-reperfusion, diabetic nephropathy, and nephrotoxic agents were applied to search the literature from scientific databases.

Results

Antioxidant and Anti-Inflammatory Effects of TQ

Reactive oxygen species (ROS) have been described as an important cause of renal disorders [20–23]. Reducing ROS improves graft maintenance and removal of acute inflammation. The scavenging function of free radicals is a property of black seeds which can prevent lipid peroxidation (LPO). The studies showed that TQ, a major constituent of *N. sativa* seeds, has strong antioxidant, anti-inflammatory, and cytoprotective abilities [24–28]. In this regard, Khattab and Nagi [29] studied the protective effect of TQ in the rats with hypertension induced by 4 weeks' administration of N (omega)-nitro-l-arginine methyl esters (l-NAME) (50 mg/kg/day p.o.). TQ treatment (0.5 and 1 mg/kg/day p.o.) decreased the increase in systolic blood pressure induced by l-NAME. Treatment of the rats with TQ brought increased creatinine (Cr) and glutathione (GSH) to normal levels. TQ prevented the production of superoxide radical in enzymatic and non-enzymatic systems. This study supported the effects of TQ in the rats against l-NAME-induced hypertension and kidney injury through its antioxidant activity [29]. The inhibitory effects of TQ (100, 200, 300, 400, 500, 750, 1,000 nM) on activation of interleukin-6 (IL-6) and redox-sensitive transcription factor nuclear factor kappa B (NF-κB) were investigated in vitro. An important reduction of advanced glycation end products induced high expression of IL-6 and NF-κB in the human proximal tubular epithelial cells. This result showed antioxidative properties of TQ [30].

Ozer et al. [31] investigated the protective effects of TQ on survival, vascular reactivity, mesenteric artery blood flow, oxidative, and inflammatory responses in rats subjected to cecal ligation and puncture (CLP). Intraperitoneal injection (i.p.) of TQ (1 mg/kg/day) for 3 days partially reduced aortic dysfunction and improved mesenteric hypoperfusion induced by CLP. TQ also prevented the increase in the serum levels of alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen (BUN), lactate dehydrogenase, Cr, and inflammatory cytokines (IL-1β, IL-6 and TNF-α) in the CLP group. The reduction of the GSH levels in spleen, liver, and kidney and the elevation of the malondialdehyde (MDA) levels in kidney, liver, lung, and spleen induced by CLP were prevented by TQ. Additionally, TQ showed the histopathological protective effects on multiple organ injury induced by CLP [31]. Another study supported the ameliorative effects of TQ in renal disorder caused by rheumatoid arthritis in rats. In this study, TQ (2 mg/kg dissolved in distilled water, i.p.) and methotrexate (MTX) (0.5 mg/kg, i.p.) importantly decreased the total clinical score of inflammation and leukocyte numbers, and ameliorated serum Cr and blood urea [32]. Hosseinian et al. [33] investigated the effects of TQ and renin-angiotensin system blockade on the renal expression of angiotensin II and renal tissue injury after unilateral ureteral obstruction (UUO) in rats. TQ (10 mg/kg, i.p.) 3 days before UUO and 2 weeks postoperatively importantly ameliorated apoptosis, TNF-α expression, and oxidative damage, but significantly reduced the upregulation of monocyte chemoattractant protein (MCP-1) and angiotensin II compared with the UUO group. This study showed the ability of TQ to improve UUO-induced renal tissue injury, which was comparable to the well-known renin-angiotensin system inhibitors such as losartan and captopril [33].

Ischemia/Reperfusion Injury

Renal ischemia-reperfusion (I/R) is known as a well-characterized model of acute renal injury that leads to both local and far organ damage [34–37]. Various studies have shown that TQ has protective effects against I/R injury to the several organs such as kidneys, lungs, and liver in different experimental models [38, 39]. The effect of

TQ on hepatic and renal changes induced by renal I/R in the rats was investigated. In this study, administration of TQ (10 mg/kg, p.o.) before I/R injury led to the reversal of increased MDA content and decreased activity of superoxide dismutase (SOD) and glutathione-S-transferase (GST) in renal and hepatic tissues. Additionally, it decreased the raised alanine aminotransferase and Cr serum levels and induced CYP3A1 mRNA expression by I/R. TQ also decreased spermidine/spermine N-1-acetyltransferase mRNA expression as a catabolic enzyme that participates in polyamine metabolism in the liver and kidney which was induced by I/R [40]. A study was done to investigate the effect of TQ on the changes in parameters of kidney function after the warm renal I/R injury (I/RI) in rats. Oral consumption of TQ (10 mg/kg/day) 4 days prior to the I/RI for 6 days improved the I/RI effects on the tubular renal functional and hemodynamic parameters as well as the expression of some renal damage markers, profibrotic and proinflammatory cytokines, which showed TQ has renoprotective effects on I/RI-induced renal disorders [39].

Diabetic Nephropathy

Diabetic nephropathy is the main reason of morbidity and death in diabetic people. To inhibit the expansion of this disease and to ameliorate progressed renal damage, effective remedies are needed [41–43]. Streptozotocin (STZ) is an antibiotic extensively applied in experimental models as an agent capable of inducing type 1 diabetes mellitus, which is known as insulin-dependent diabetes mellitus [44–46]. Studies show that *Nigella sativa* oil (NSO) and its main bioactive element TQ have, antihyperglycemic, antioxidant, and renoprotective properties in STZ-induced diabetes in the animal models [47, 48]. The study was done by Sayed [49], which showed that TQ reduced NF-κB activation induced by angiotensin II in a dose-dependent manner, with the maximum inhibitory effect of 500 nM. In addition, preincubation of the proximal tubular epithelial cells with TQ caused the disappearance of the second peak of NF-κB. The results demonstrated the therapeutic effect of TQ which can be administered to delay end-stage kidney disorders in diabetics. The study performed by Kanter [50] showed that the treatment with TQ (50 mg/kg body weight) by oral gavage in diabetic rats for 12 weeks decreased the capsular thickening, glomerular size, the tubular and glomerular basement membranes, the elevated content of mesangial matrix, and tubular dilatation and renal function as compared with the untreated diabetic rats. The findings showed that TQ treatment leads to the renal structural and functional progress in rats with STZ-induced diabetes. The study was carried out to investigate the feasible beneficial effects of proanthocyanidin (PA), TQ, and their combination to ameliorate the diabetic nephropathy in rats. Treatment of rats with PA (250 mg/kg), TQ (50 mg/kg), or PA + TQ (250 + 50 mg/kg, respectively) orally for 12 weeks showed a decrease in body weight, in addition to reduced SOD and GSH contents. The increased levels of nitric oxide (NO), urea, Cr, IL-6, and MDA were significantly decreased as a result of the treatment. The results indicated that PA and TQ treatment could be introduced as therapeutic protective agents in diabetes through reducing oxidative stress and ameliorating diabetic nephropathy. Therefore, TQ and PA may be clinically effective for supporting the diabetic kidney against oxidative stress [51]. Another study was done to investigate the effects of TQ in the rats with STZ-induced diabetes and to define the predictive cost of epithelial and mesenchymal markers in TQ treatment in rats with diabetic nephropathy. Treatment with TQ (50 mg/kg, orally) importantly ameliorated renal structural changes in both renal tubules and glomeruli and also the immunohistochemical expression of MMP-17 and mesenchymal markers Fsp1, desmin, and epithelial marker ZO-1 disappearance in the glomeruli of STZ-induced diabetic rats. These findings showed that both epithelial and mesenchymal markers act as good predictors of early renal injury and indexes of TQ reactivity in STZ-induced diabetic nephropathy [52]. A study was designed by Al-Trad et al. [53] to assess the effect of NSO and TQ treatment on podocyte injury, albuminuria, and the complex systems adjusting the extracellular angiogenesis and matrix protein accumulation in rats with STZ-induced diabetic nephropathy. The results indicated that treatment with 2 mL/kg NSO or 50 mg/kg TQ by oral consumption for 10 weeks importantly ameliorated increased albuminuria and the kidney weight/body weight ratio in STZ-induced diabetic nephropathy. The real-time PCR displayed that the treatment with NSO and TQ inhibited diabetes-induced mRNA overexpression of transforming growth factor-β1 (TGF-β1), vascular endothelial growth factor-A (VEGF-A) and collagen IV as well as down-regulation of mRNA expression of the podocyte-specific marker (podocin) in the diabetic kidney. NSO and TQ treatment reduced albuminuria in the diabetic nephropathy experimental models through the preservation of the podocyte function with the suppression of increased extracellular matrix gene expression by preventing TGF-β1 production and angiogenesis [53].

Nephrotoxic Agents

It is well defined that many drugs, such as the chemotherapeutic drug (cisplatin) and aminoglycoside antibiotics are able to cause nephrotoxicity [54–56].

Chemotherapy Drugs

Most chemotherapeutic drugs can lead to nephrotoxicity [57, 58]. Hence, recent strategies have been focused on preventing chemotherapy-induced nephrotoxicity. *N. sativa* or its isolated constituent TQ are introduced as the potential agent in fighting chemotherapy-induced nephrotoxicity [59].

Doxorubicin

The study carried out by Elsherbiny and El-Sherbiny [60] showed that oral consumption of TQ (50 mg/kg/day) for 3 weeks in rats that received doxorubicin (DOX) as a chemotherapeutic drug, reversed the increased levels of serum Cr, urea, and urinary albumin excretion, whereas animals that received DOX without TQ showed DOX-induced nephrotoxicity. Additionally, TQ ameliorated increased MDA and LPO, and also, it increased the decreased activities of SOD and GST in rats with DOX-induced nephrotoxicity. TQ also decreased the increased renal levels of IL-6, TNF-α, and NADPH oxidase 4, and increased the decrease in nuclear factor erythroid 2-related factor 2 (Nrf2) mRNA levels, interleukin-10 (IL-10) levels, and nuclear binding activity. Renal histopathological changes induced by DOX improved with TQ [60].

Cisplatin and Diesel Exhaust Particles

Ali et al. [61] studied the interaction between cisplatin (CP) nephrotoxicity and a single exposure to diesel exhaust particles and the concurrent treatment with TQ (20 mg/kg, orally) in rats. The results showed that several biochemical, physiological, and histopathological alterations contained decreased growth and Cr clearance and increased IL-6, plasma neutrophil gelatinase-associated lipocalin, C-reactive protein, urea and Cr concentrations, and urinary N-acetyl-b-D-glucosaminidase (NAG) activities induced by CP, and were significantly abrogated by TQ. Also, TQ significantly resolved potentiated indices of oxidative injuries in the kidney tissues, and induced renal tubular necrosis induced by CP and diesel exhaust particles [61].

Morphine

A study was designed by Jalili et al. [62] to investigate protective effects of TQ against morphine-induced renal toxicity in mice. The results showed that intraperitoneal administration of TQ (4.5, 9, and 18 mg/kg) and TQ with morphine importantly increased kidney weight, number, and mean diameter of the glomeruli. Additionally, TQ led to a decrease in BUN, serum NO and serum Cr levels in the groups treated with it compared to the morphine group. This study explained that the renoprotective effects of TQ against damage due to morphine toxicity may be related to its antioxidant and antiapoptotic effects [62].

Gentamicin

Sayed-Ahmed and Nagi [63] showed that TQ supplementation (50 mg/L in drinking water) in rat caused a complete reversal of the gentamicin (GM)-induced increase in BUN, Cr, thiobarbituric acid-reactive substances and total nitrate/nitrite and reduction in GSH, glutathione peroxidase (GPx), catalase (CAT), and ATP to control values. Furthermore, histopathological examination of renal tissues corroborated the biochemical data, wherein TQ supplementation protected kidney against GM-induced degenerative changes. The results of this study proposed that TQ is useful in preventing from the development of GM-induced acute renal failure by a mechanism related somewhat to its ability to reduce oxidative stress and to maintain the activity of the antioxidant enzymes, as well as its ability to prevent the energy reduction in renal tissues [63]. In another study, Samarghandian et al. [64] indicated that the significant elevation in the levels of serum Cr, BUN, MDA, IL-6, IL-18, IL-1β, and TNF-α and also the reduction of GSH, SOD, SOD, GPx, and IL-10 in the GM nephrotoxicity were improved by TQ (10, 20, 30 mg/kg), in a dose-dependent manner. These investigators proposed that TQ may improve acute renal failure by modulation of the oxidative stress and inflammatory responses.

Methotrexate

The study by El-Sheikh et al. [65] indicated that TQ treatment (10 mg/kg) concurrently with MTX in rats restored hepatorenal functions, as well as their normal histology. TQ also reversed oxidative and nitrosative stress, as well as inflammatory and apoptotic signs induced by MTX alone. This study proposed that TQ may be the useful adjuvant that gives hepatorenal protection to MTX toxicity through anti-inflammatory, antioxidant, antinitrosative, and antiapoptotic mechanisms.

Acetaminophen

Aycan et al. [66] studied the efficacy of TQ (10 mg/kg, i.p.) in acetaminophen (APAP)-induced renal toxicity in rat. The Cr and urea levels in the APAP + TQ treated

group were importantly lower than in the APAP-treated group. In contrast to the group treated with APAP, the MDA levels and serum NO activity were significantly lower in the TQ + APAP group. Histopathological study showed lower tissue damage scores in the APAP + TQ group compared with the APAP group.

Cyclosporine A

Farag et al. [38] investigated the effects of chronic cyclosporine A (CsA) treatment and acute renal I/R on the liver and kidney in rats treated with TQ. TQ treatment (10 mg/kg per day) decreased serum indicators back to control levels and improved CsA-induced renal and hepatic histopathological alterations. In renal and hepatic tissues, CsA and renal I/R induced considerable elevation of MDA levels with remarkable reduction in decreased GSH levels and SOD activities, as oxidative stress markers were neutralized by TQ therapy. This study showed that kidney and liver damage related to CsA or renal I/R can be significantly decreased by TQ.

Lead

Mabrouk and Ben Cheikh [67] investigated the possible beneficial effect of TQ on lead (Pb)-induced renal antioxidant defense system dysfunction in the rats. TQ treatment (5 mg/kg/day, p.o.) improved the decreased SOD and GSH level, CAT, GPx, and glutathione reductase activities in the kidney tissue induced by Pb [67].

Arsenic

A study was carried out on the protective role of TQ against renal injury induced by arsenic in rats. Renal degenerative changes induced by arsenic were decreased by TQ (10 mg/kg, intragastric gavage for 15 days). Also, TQ ameliorated the increased MDA levels and increased the reduced SOD, CAT, and GSH-Px enzyme activities [68].

Cadmium

Erboga et al. [69] showed that TQ (50 mg/kg body weight) once a day orally in rats reduced the nephrotoxicity of cadmium (Cd) (1 mg/kg body weight). TQ preserved the normal histological architecture of the renal tissue. Furthermore, the immunohistochemical analysis indicated that TQ importantly reduced the Cd-induced overexpression of NF-κB in the kidney and also decreased apoptotic cells. TQ significantly repressed LPO and compensated dearth in the antioxidant defenses of the kidney. These results proposed that the nephroprotective potential of TQ in Cd toxicity may be related to its antioxidant and antiapoptotic effects, which could be helpful for obtaining optimum results in the Cd-induced nephrotoxicity [69].

Mercuric Chloride

Fouda et al. [70] investigated protective effects of TQ in mercuric chloride ($HgCl_2$)-induced nephrotoxicity. Their results showed that the deterioration of antioxidant enzymes, increase in serum Cr and histological injury induced by $HgCl_2$ were markedly ameliorated by TQ therapy (10 mg/kg/day). Additionally, apoptosis and proliferative reactions were decreased. The maximal protective effect proposed by TQ was 48 and 72 h after administration of $HgCl_2$, when histological damage, renal cell apoptosis, and proliferative reactions reached their maximum. The findings showed the antioxidant effect of TQ.

Kidney Calculi

Kidney calculi are the term which is used to explain renal stones, which are formed in the urine that is made up of acid and mineral salts. They can block urine and cause renal infections, injury, and pain when they move around the body [71, 72]. A study was done to investigate the effects of TQ on ethylene glycol-induced renal calculi in rats. Intraperitoneal injection of TQ (5 mg/kg) caused fewer deposits. Also, TQ (5 mg/kg or 10 mg/kg, i.p.) importantly reduced the size and number of calcium oxalate sediments in the renal tubules [73]. Table 1 gives data on the protective effects of TQ on kidney diseases.

TQ Toxicity

Few studies reported TQ toxicity signs and symptoms in animal models. It was found that intraperitoneal injection of TQ caused peritonitis and abdominal muscle contractions and the oral administration of TQ caused dyspnea at different dose frequency exposure (acute, subacute, and subchronic) in rats and mice [74]. The maximum tolerated dose (MTD) of TQ, which is defined as the highest dose that is safe to administer to animal models in the absence of intolerable adverse effects, was determined in male and female Wistar rats [75]. The findings indicated that the MTD for intraperitoneal injection was 22.5 mg/kg in male rats and 15 mg/kg in females, whereas for oral administration it was 250 mg/kg in both male and female rats. Two rats died after administration of 500 mg/kg of TQ due to bowel obstruction. However, a possible mechanism of TQ toxicity was not fully understood [75].

Table 1. Protective effects of TQ on kidney diseases

Experimental model	Effect	Ref.
Rat	Decreased systolic blood pressure induced by l-NAME, and Cr and also elevated GSH levels	[29]
In vitro	Prevented from superoxide radical production in enzymatic and non-enzymatic systems	
	Prevented AGEs-induced Il-6 and NF-κB-activation in cultivated human pTECs	[30]
Rat	Decreased aortic dysfunction and improved mesenteric hypoperfusion induced by CLP, via decreasing the levels of inflammatory cytokines (IL-1, IL-6, TNF-α) and MDA and also increasing the GSH in kidney tissue	[31]
	Decreased the total clinical score of inflammation and leukocyte number and ameliorated serum Cr and blood urea in renal disorder caused by rheumatoid arthritis	[32]
	Prevented CsA-induced nephrotoxicity via decreasing the levels of MDA and increasing GSH level and SOD activity	[38]
	Prevented renal damage induced by unilateral ureteral obstruction via decreasing apoptosis, TNF-α expression, oxidative damage, upregulation MCP-1 and angiotensin	[33]
	Prevented renal damage induced by IR via decreasing profibrotic and proinflammatory cytokines	[39]
	Prevented renal damage induced by IR via decreasing MDA and SSAT mRNA expression as a catabolic enzyme that participates in polyamine metabolism	[40]
In vitro	Prevented renal tubular cells against tubular injury induced by AT II via decreasing NF-kB activation	[49]
Rat	Decreased the capsular thickening, glomerular size, tubular and glomerular basement membranes, elevated content of mesangial matrix and tubular dilatation, and renal function as compared untreated diabetic rats	[50]
	Prevented diabetic kidney via decreasing IL-6, NO, and MDA and also increasing SOD and GSH in kidney tissue	[51]
	Prevented renal structural changes induced by STZ via modulating the expression of the MMP-17 and mesenchymal markers Fsp1, desmin, and epithelial marker ZO-1 in the glomeruli	[52]
	Prevented diabetic nephropathy via inhibiting mRNA overexpression of TGF-β1, VEGF-A and collagen IV as well as downregulation of mRNA expression of the podocyte-specific marker (podocin) in the kidney	[53]
	Prevented DOX-induced nephrotoxicity via decreasing the levels of MDA, LPO, IL-6, TNF-α, and NOX-4 and also increasing the activities of SOD and GST, and Nrf2 mRNA l and IL-10 levels	[60]
	Prevented CP-induced nephrotoxicity via decreasing the plasma levels of IL-6, NGALa, CRP, and NAG activity	[61]
Mice	Prevented morphine-induced nephrotoxicity via decreasing the levels of blood urea nitrogen, NO, and serum levels of Cr	[62]
Rat	Prevented GM-induced nephrotoxicity via decreasing the serum levels of BUN, Cr, MDA, IL-6, IL-18, IL-1β, TNF-α and total NOx and increasing the levels of GSH, GPx, CAT, IL-10, and ATP	[63, 64]
	Prevented MTX-induced nephrotoxicity via modulating nitrosative stress, as well as inflammatory and apoptotic responses	[65]
	Prevented APAP-induced nephrotoxicity via decreasing the serum levels of MDA and NO	[66]
	Prevented Pb-induced nephrotoxicity via increasing the levels of SOD, GSH, CAT, GPx, and GR	[67]
	Prevented Ar-induced nephrotoxicity via decreasing the levels of MDA and increasing the activities of SOD, CAT and GSH-Px enzyme	[68]
	Prevented Cd-induced nephrotoxicity via modulating NF-κB in kidney	[69]
	Prevented $HgCl_2$-induced nephrotoxicity via increasing antioxidant enzymes and decreasing apoptosis and proliferative responses	[70]
	Prevented ethylene glycol-induced nephrotoxicity via reducing the size and number of calcium oxalate sediments in the renal tubules	[73]

l-NAME, N(omega)-nitro-l-arginine methyl esters; GSH, glutathione peroxidase; AGEs, advanced glycation end products; pTECs, proximal tubular epithelial cells; IL, interleukin; CLP, cecal ligation and puncture; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; LDH, lactate dehydrogenase; Cr, creatinine; MDA, malondialdehyde; TNF-α, tumor necrosis factor; MCP-1, monocyte chemoattractant protein; UUO, unilateral ureteral obstruction; SOD, superoxide dismutase; GST, glutathione-S-transferase; I/R, ischemia-reperfusion; SSAT, spermidine/spermine N-1-acetyltransferase; IRI, ischemia-reperfusion injury; AT II, angiotensin II; pTECs, proximal tubular epithelial cells; SOD, superoxide dismutase; NO, nitric oxide; STZ, streptozotocin; TGF-β1, transforming growth factor-β1, VEGF-A, vascular endothelial growth factor-A; VEGF-A, vascular endothelial growth factor-A; DOX, doxorubicin; LPO, lipid peroxidation; GST, glutathione-S-transferase; NOX-4, NADPH oxidase 4; Nrf2, nuclear factor erythroid 2-related factor 2; NGAL, neutrophil gelatinase-associated lipocalin; CRP, C-reactive protein; NAG, N-acetyl-b-D-glucosaminidase; GM, gentamicin; TBARS, thiobarbituric acid-reactive substances; NOx, nitrate/nitrite; GSH, glutathione peroxidase; GPx, glutathione peroxidase; CAT, catalase; ARF, acute renal failure; MTX, methotrexate; APAP, acetaminophen; CsA, cyclosporine A; Pb, lead; Cd, cadmium; NF-κB, nuclear factor kappa B; $HgCl_2$, mercuric chloride.

Conclusions

Scientific interest in medicinal plants and their ingredients has increased because of high efficiency of herb-derived drugs, increasing interest in natural products. *N. sativa* seeds (Ranunculaceae family), have been used for thousands of years as a condiment and food preservative. TQ as the bioactive component of fugacious oil of black seed has indicated potent medicinal effects in traditional medicine. The studies provided clear documents that TQ has antioxidant effects via strengthening the oxidant scavenging system, and thus antitoxic properties. Also, it has shown potential anti-inflammatory effects [76, 77]. This review indicated medicinal or protective features of TQ against inflammation and oxidative stress in renal disorders. TQ showed anti-inflammatory and antioxidant properties in animal and in vitro models of several renal diseases caused by inflammation and oxidative stress. TQ indicated anti-inflammatory effects through modulation of inflammatory molecules IL-1, IL-6, IL-18, IL-10, and TNF-α, and NF-κB activation. It also reduced the total clinical score of inflammation and leukocyte number. TQ decreased oxidative stress markers such as MDA and increased antioxidant content, including GSH, CAT, GST, and SOD, which have an important role in kidney disorders. It also ameliorated serum Cr and blood urea in renal disorder caused by rheumatoid arthritis or morphine in rats. In ethylene glycol-induced renal calculi, TQ led to lower deposits and decreased the size and number of calcium oxalate sediments in the renal tubules. Additionally, TQ improved the histopathological changes of the kidney induced by CLP, nephrotoxic agents, and diabetic nephropathies. Although experimental studies have shown the beneficial effects of TQ against renal diseases, well-designed clinical trials in humans are required to confirm these effects.

Conflict of Interest Statement

The authors declare that there is no conflict of interest regarding the publication of this article. There was no financial support or sponsorship for this work.

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