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Cardioprotective and nephroprotective effects of Quercetin against different toxic agents

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Abstract. – Quercetin (Qct) is a flavonoid that belongs to the group of the most bioactive polyphenolic compounds. It is abundantly found in our diet, and it has many beneficial effects on human health because of its potent antioxidant properties. Qct has shown cardioprotective effects against doxorubicin, cyclophosphamide, daunorubicin, and lindane and nephroprotective effects against methotrexate, doxorubicin, gentamicin, valproic acid, cadmium, potassium dichromate, fluoride, mercury chloride, 2,3,7,8-tetrachlorodibenzo-p-dioxin, titanium dioxide nanoparticles, and gold nanoparticles. In the current review, we discussed the molecular and biochemical mechanisms involved in the cardio- and nephroprotective effects of Qct. The main purpose of this review was to identify the cardio- and the nephroprotective mechanisms of Qct against several drugs and chemicals to encourage further studies to investigate the potential protective effect of Qct.

Key Words:
Quercetin, Flavonoids, Antioxidant, Cardiotoxicants, Nephrotoxicants, Apoptosis.

Introduction

Flavonoids are naturally occurring substances with various phenolic structures found in tea, flowers, fruits, roots, grains, stems, and bark. The basic structure of flavonoids has a 15-carbon skeleton consisting of two benzene rings (A and B) linked through a heterocyclic pyran ring (C) (Figure 1). Flavonoids can be divided into several classes, including flavonols (e.g., fisetin, kaempferol, quercetin and myricetin), flavanones (e.g., hesperetin and naringenin), and flavones (e.g., luteolin flavone and apigenin). These classes of flavonoids differ in the level of oxidation and replacement pattern of the C ring, whereas compounds inside a class differ in the replacement pattern of the A and B rings[1]. Over the past two decades, research on flavonoids has gained interest because it has been shown that flavonoids have beneficial effects by modulating multiple signaling pathways involved in various diseases. For instance, it has been reported that flavonoids have antioxidant, anti-inflammatory, anti-allergic, anti-thrombotic, analgesic, vasodilatory, and anti-bacterial effects[1-10].

Quercetin (Qct) (Figure 2) is a member of flavonols, which are subclass of flavonoids[10]. Qct is an aglycone that lacks an attached sugar. It is a brilliant citron-yellow needle crystal that is completely insoluble in cold water and poorly soluble in hot water. A Qct glycoside is formed when Qct is attached to a sugar moiety. In general, Qct glycoside is more water-soluble compared to Qct[11-14].

Qct is a key member of the polyphenolic family found primarily in several fruits and vegetables, such as lovage, capers, cilantro, dill, onions, several berries (e.g., cranberries, chokeberries, lingonberries), and apples. It is well known for its chemopreventive potential against different types of cancer, more specifically, prostate cancer. These chemopreventive properties of Qct are linked to several cell signaling mechanisms[15,16].

The beneficial effect of Qct has been documented in many studies because of its different pharmacological activities. Recently, it has been shown[17,18] that pro-inflammatory cytokine expression was suppressed through modulation of p38 mitogen-activated protein kinase (MAPK) and NF-kB signaling in a human mast cell line. Furthermore, it has been revealed that suppression of postmenopausal osteoporosis in rats was mediated through the downregulation of MAPK signaling pathways[19]. In the PC-3, PC-12, CT-26, and LNCaP cancer cell lines, cell growth was inhibited due to the induction of Qct mediated apoptosis. Qct also decreased CT-26 and MCF-7 tumor volume in mice, which increased animal survival rates[20].

Moreover, in other studies, Qct has shown modulatory effects on the Akt signaling pathway,

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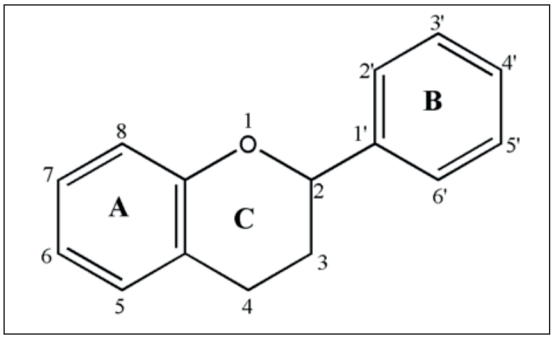

Figure 1. Structure of flavonoids.

suppressing vascular endothelial growth factor (VEGF), and hence, angiogenesis. It was also documented that Qct has an anti-metastatic property, as evidenced in lungs and ovarian cancer models[21-24]. Furthermore, Qct appears to have an anti-diabetic activity, as documented in streptozotocin-induced diabetes in rats[24]. Therefore, it is crucial to comprehensively understand the beneficial and protective effects of Qct against different toxic agents to assess the safety and efficacy of Qct.

In the current review, we discuss the cardio- and nephroprotective effects of Qct against various drug- and chemical-induced toxicities. Furthermore, we described the mechanisms of toxicity induced by different agents and the protective mechanism induced by Qct.

Protective effects of Quercetin against different drugs and toxic agents induced cardiotoxicity

Doxorubicin (Dox)

Dox is an effective and widely used chemotherapeutic agent to treat breast cancer, solid tumors, soft-tissue sarcomas, and leukemia. However, its use is associated with cardiotoxicity, limiting its clinical application[25,26]. The mechanisms by which Dox induces cardiotoxicity include production of the reactive oxygen species (ROS), mitochondrial dysfunction, inflammation, and alteration in the gene expression of different genes[27,28]. It has been reported that Qct induced protection against Dox-induced mitochondrial dysfunction, apoptosis, DNA damage, and ROS generation in H9C2 cells. In that study, Dong et al[29] indicated that the ameliorative effect of Qct against Dox-mediated cardiotoxicity was due to the decrease in the expression of Bid, p47, and Nox1 and the increase in the expression of Bcl-2 and Bmi-1.

Furthermore, Qct offered cardioprotection through the depletion of the lipid peroxidation and ROS levels and the elevation in the levels of superoxide dismutase (SOD)[29]. Chen et al[30] reported that Qct pretreatment in primary cardiomyocyte cells prevented the injury induced by DOX by producing antioxidant enzymes, inhibition of apoptosis, lipid peroxidation, and ROS generation[30]. In another study, it has been shown that Qct with Losartan synergistically attenuated the elevated serum levels of creatine kinase (CK), tumor necrosis factor-α (TNF-α), lactate dehydrogenase (LDH), and lipid peroxidation and restored the enzyme activities of catalase (CAT) and SOD. In that study, they suggested that Qct and Losartan can help reduce myocardial injury and leukocyte infiltration induced after Dox administration[31].

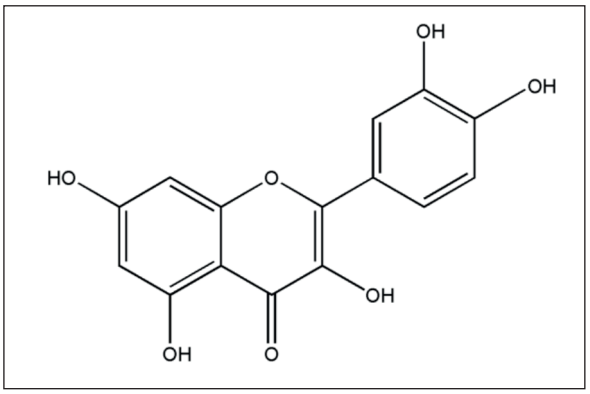

Figure 2. Structure of Quercetin (Qct).

Cyclophosphamide (CYP)

CYP is an effective chemotherapeutic drug used to treat lupus erythematosus, rheumatoid arthritis, multiple sclerosis, bone marrow transplantation, neuroblastoma, and some other types of cancers. However, CYP also has various highly toxic side effects. Dose-dependent cardiotoxicity is one of the most important toxic effects[32-35]. The exact mechanism by which CYP induces cardiotoxicity is still not clear. However, it has been shown that the toxic metabolite of CYP, acrolein, leads to excess ROS production, which in turn increased oxidative stress and decreased the antioxidant defense mechanism that causes CYP-induced cardiotoxicity. Furthermore, excess ROS production hampers the oxygen radical detoxifying ability of the mitochondria, having harmful effects on cardiomyocytes[36,37]. In addition, CYP-induced cardiotoxicity was found to be associated with the poor activity of Krebs cycle enzymes due to increased permeability of the inner mitochondrial membrane to calcium, resulting in the uncoupling of mitochondrial ATP synthesis[36]. In cardiac tissues, it has been demonstrated[38-40] that CYP reduced GSH levels and increased lipid peroxidation led to severe

cardiac damage. Furthermore, it has been reported that CYP-induced oxidative stress activated the nuclear factor-κB (NF-κB), which induced the release of numerous cytokines[38-40]. In another study, Sekeroğlu et al[41] reported that CYP increased the serum levels of LDH, which indicates cardiotoxicity[41]. However, Sekeroğlu et al[41] documented that Qct administration mitigated the increase in the LDH levels, as demonstrated also by Ikizler et al[39].

It is reported that the heart is susceptible to injury induced by ROS mainly because protective enzymes, such as GSH, CAT, and SOD, are present at a lesser value compared to other tissue[42]. SOD converts the toxic oxygen free radicals to H_2O_2, then H_2O_2 is converted to H_2O by CAT, hence, protects the cell from damage due to oxidative stress[43]. Many studies[44-48] have reported that xanthine oxidase (XO) catalyzes the conversion of hypoxanthine to xanthine through the oxidative process. Consequently, that generates uric acid and superoxide, which is considered one of the main sources of ROS generation enzymatically in the *in-vivo* system. Sekeroğlu et al[41] reported a significant increase in the XO activity in the heart of CYP-treated mice, which could be because of increased production of free radicals and decreased antioxidant enzymes[41]. Besides, they reported increased antioxidant enzyme activity in pretreated Qct animals, which may be attributed to an enhanced antioxidant status indicated by a rise in GSH and a decrease in LPO levels[41].

Additionally, inhibition of the XO activity in Qct treated mice in Sekeroğlu and colleagues' study[41] might be explained by its direct scavenging of the superoxide anion (O2-) or inhibition of O2 -generating enzymes, XO[41,49]. Furthermore, Sekeroğlu et al[41] documented nitrite levels in the myocardial tissue treated with Qct and Viscum album (VA) along with CYP indicated higher levels of NO[41]. This could be due to the ROS scavenging property of Qct and VA.

Moreover, published literature[50,51] has indicated that CYP administration enhances MPO activity in bladder and heart tissue. Furthermore, Qct and VA inhibits the MPO activity, hence restricting neutrophil infiltration[41,52]. It is proposed that the dominant mechanism for such protection is related to the increase in NO levels by Qct[41,52].

Daunorubicin (Dnr)

Dnr is an anthracycline antibiotic that is mostly used to treat solid tumors and leukemia. However, clinical use of Dnr is limited due to various undesirable effects, the most severe of which is cardiotoxicity associated with the production of highly reactive free radicals[53-56]. Guzy et al[57] reported the protective effect Qct against Dnr-induced cardiac changes[57]. In their study, they documented that Dnr treatment led to a significant increase in AT-Pase and glutathione reductase (GR) with a significant decrease in glutathione peroxidase (GPx). Conversely, Qct treatment restored these abnormalities and protected cardiomyocytes against the toxicity induced by Dnr[57].

Lindane

Solvents, pesticides, and heavy metals are the environmental toxins that cause most health-related problems. Lindane (γ-hexachlorocyclohexane) is a chlorinated pesticide used to control malaria, eliminate insects from crops, and treat louse infections in humans, livestock, and poultry[58]. Humans are exposed to lindane by various routes, such as dietary intake, dermal contact, drinking water, and breathing[59,60].

Overproduction of ROS leads to oxidative stress and mitochondrial dysfunction in the heart in response to disease and toxic processes, leading to the induction of lipids peroxidation and reactive aldehydes production[61]. During the normal physiological function, most of the generated ROS are eliminated by the antioxidant enzymes system present in our body[54]. However, low ROS levels are required to maintain several physiological functions, such as host defense, proliferation, gene expression, and signal transduction[62]. Lindane interacts with the cell membrane and triggers ROS generation leading to oxidative stress[59]. Ananya et al[63] reported that lindane treatment induced peroxidation of lipids and attenuated the activity of antioxidants enzymic, which led to oxidative stress in rats' hearts[63].

Recently, Padma et al[64] reported that Qct and Gallic acid (GA) improved the altered biochemical parameters and histopathological alteration in the heart, which suggested that Qct and GA can protect the heart[64]. In their study, they demonstrated that the levels of lipid peroxidation, CK, and LDH were significantly increased in the lindane treated group, which was linked to the cellular leakage due to necrotic damage in the cardiac membrane[64]. Furthermore, they demonstrated decreased CAT and SOD activity in the lindane-treated group, consistent with previous reports[63-66]. However, these abnormalities were restored in the group co-treated with lindane and Act, suggesting that Qct and GA have a preventive effect against lindane-induced cardiac damage. These findings were similar to a previously published report by Woo et al[66].

GSH, in conjunction with GPx, play an important role in protecting cells against various injuries by scavenging ROS[67]. It has been shown[64]

that oral lindane administration led to decrease in GSH levels in rats. In that study, Padma et al[64] reported an increase in GSH levels and GPx and GST activities in the Qct co-treated groups compared to the lindane alone group suggesting the protective effect of Qct[64].

According to Hazarika and Sarkar[68], peroxidation of membrane phospholipids alters the lipid milieu and the structural and functional integrity of cell membrane and affects the activities of numerous enzymes bound to the membrane, like Na^+/K^+-ATPase, Mg^{2+}-ATPase, and Ca^{2+}-ATPase[68]. In one study, Padma et al[64] reported that in the lindane treated group, the activities of Ca^{2+}-ATPase increased, while the activities of Mg^{2+}-ATPase and Na^+/K^+-ATPase decreased[64]. However, co-treatment with Qct restored the activities of these membrane-bound enzymes[64]. Their finding suggests that the Qct and GA have the membrane-stabilizing ability, and they can act as protective agents against lindane-induced cardiotoxicity[64].

Protective Effects of Quercetin Against Different Drugs and Toxic Agents Induced Nephrotoxicity

Methotrexate (MTX)

MTX is a folic acid antagonist with antiproliferative and anti-inflammatory effects; therefore, it is frequently used to treat different autoimmune disorders and malignant tumors[69-71]. MTX is an antimetabolite that hampers folic acid metabolism. Since it is polyglutamated, it can bind to dihydrofolate reductase (DHFR) with an affinity that is multiple folds higher than that of folate; hence, competitively inhibits tetrahydrofolate formation from dihydrofolate[72]. Tetrahydrofolate is essential for the biosynthesis of bases required for DNA synthesis and inhibiting cell proliferation[72].

Although MTX is used to treat several diseases and toxicity associated with its use limits its clinical application[73]. MTX sensitizes cells to ROS by decreasing NADPH, which plays an important role in the cellular antioxidant defense mechanism; hence, it is responsible for oxidative damage to the tissue[74,75]. It has been reported[74-78] that ROS mediated oxidative injury is associated with nephrotoxicity and hepatotoxicity.

Yuksel et al[75] explored the protective effects of Qct against MTX-induced kidney injury[75]. They found that Mtx treatment was associated with severe kidney damage, as validated by histopathological studies compared to the control group. In addition, MTX treatment induced the expression levels of caspase-3, MDA, and SOD. However, in the Qct group, these alterations were significantly restored, suggesting the antioxidant property of Qct[75]. Another study[76] showed that MTX treatment was associated with alterations in the renal architecture described as tubular dilation and degeneration. In addition to that, they also documented that MTX caused an increase in oxidative stress, as indicated by a significant elevation in MDA levels and reduction in GPx, CAT, and SOD activities. However, these alterations were restored significantly when MTX was given along with Qct.

Doxorubicin (Dox)

Dox is a highly effective chemotherapy agent for malignant neoplasms, including solid tumors, such as the cervix, breast, ovary, uterine and pulmonary cancer, and hematopoietic tumors because it shows remarkable efficiency and wide spectrum effects[79,80]. Nevertheless, its use is limited because of its toxicity, especially the nephrotoxicity associated with its clinical use[80,81]. The important indicator of kidney damages is increased lipid peroxidation and protein oxidation[81]. Yagmurca et al[82] evaluated the protective effect of Qct against Dox-induced kidney toxicity in rats[82]. They revealed significant tissue injuries in the Dox-treated animals. These injuries included interstitial infiltration, renal tubular dilation, decreased bowman space, and glomerular vacuolization. Nevertheless, these abnormalities were mitigated with the administration of Qct[82]. In another study, Kocahan et al[83] also reported the protective action of Qct against Dox-induced hepato- and nephrotoxicity through its antioxidant effects[83]. Additionally, Heeba and Mahmoud[84] reported that Qct has both beneficial and harmful effects on the kidney in a dose-dependent manner[84]. Several other studies[30,85-91] documented that Qct prevented Dox-induced damage in the liver, kidney, and heart via its antioxidant property. At a low dose, Qct acted as a preventive agent against Dox-mediated nephrotoxicity via antioxidant, anti-apoptotic, and anti-inflammatory actions[84]. Furthermore, Qct at high doses significantly augmented the cytotoxic effects of Dox in several human cancer cell lines, HEPG2, PC3, MCF7, and HELA[84]. Allam et al[92] reported the synergistic effect of Qct and berberine (BER) against Dox-induced nephrotoxicity through antioxidant mechanism[92].

Gentamicin (GM)

GM-induced nephrotoxicity has been characterized by direct tubular necrosis predominantly

located in the proximal tubule[93]. Although the exact mechanism by which GM causes nephrotoxicity is still unclear, several studies have demonstrated that GM induced cellular generation of ROS, causing an imbalance in the intrinsic antioxidant enzymes[93-98].

Abdel-Raheem et al[95] showed that oxidative stress was mainly associated with GM-induced kidney injury as evidenced by a significant increase in kidney toxicity markers, such as high total urinary protein excretion, serum creatinine, and blood urea nitrogen (BUN)[95]. Moreover, they found that induction of oxidative stress was responsible for the observed nephrotoxicity as they reported that GM treatment resulted in a significant reduction in the activity of CAT, GSH, and SOD and a remarkable increase in lipid peroxidation levels (LPO). Additionally, they demonstrated progressive alterations in the tubules and glomeruli, as evidenced by histopathological examination. These abnormal changes were restored when rats were co-treated with Qct[95]. These findings confirmed the antioxidant and the nephroprotective effect of Qct.

Valproic Acid (VPA)

VPA is an antiepileptic drug that is most widely used to treat epilepsy worldwide[99]. Clinicians support the use of VPA as an anticonvulsant agent, but its adverse effects and toxicity limit its uses[100]. Although VPA is a relatively safe drug when used at low doses, at high doses, it can have serious un-

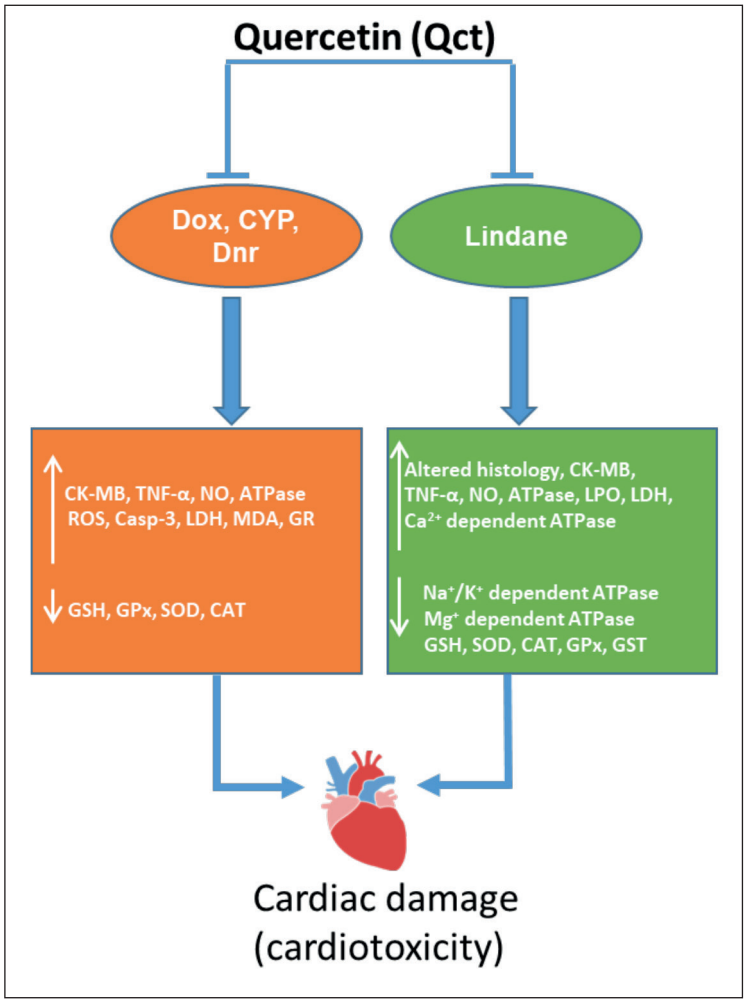

Figure 3. Schematic representation of the protective mechanisms of quercetin to mitigate cardiac toxicity. Qct; Quercetin; Dox; Doxorubicin, CYP; Cyclophosphamide, Dnr; Daunorubicin, CK-MB; Creatine kinase-MB, TNF-α; Tumor Necrosis Factor-alpha, NO; Nitric Oxide, ROS; Reactive Oxygen Species, Casp-3; Caspase-3, LDH; Lactate Dehydrogenase, MDA; Malondialdehyde, GR; Glutathione reductase, GSH; Glutathione, GPx; Glutathione Peroxidase, SOD; Superoxide dismutase, CAT; Catalase, LPO; Lipid Peroxidation, GST; Glutathione S-transferase.

wanted effects on the biological system[101]. Many studies[102,103] confirmed that VPA promotes ROS formation, which is mainly responsible for its unwanted effects. Chaudhary et al[104] investigated the protective effects of Qct against the nephrotoxic potential of VPA[104]. They measured the oxidative stress indices, such as LPO and protein carbonyl (PC), supporting their causative effect on VPA-induced neurotoxicity[104]. Furthermore, they reported that VPA treatment significantly altered enzymatic and non-enzymatic antioxidants. Pretreatment with Qct, however, mitigated the toxic effect induced by VPA[104]. Therefore, based on these findings, they suggested that Qct should be considered an effective treatment for reducing the harmful effects of VPA.

Cadmium (Cd)

Cd is a natural toxic metal that affects most organs. Cd, a well-known pollutant present in the environment, can induce kidney damage, as reported elsewhere[105-107]. It has been reported[105-107] that chronic exposure to Cd, found in drinking water, air, soil, animal products, and plants, damages different organs, primarily the kidney. Humans can get exposed to this metal through beverages, fish, and cigarette smoking. Cd cannot generate free radicals directly; however, several free radicals, including nitric oxide (NO) and superoxide radicals, have been documented[108] to be generated indirectly. Oxidative stress is mainly responsible for Cd-induced renal damage[105,106]. In the cytosol, Cd indirectly produces ROS, which can deplete the endogenous antioxidant status of cells and trigger peroxidative damage to biological membrane lipids and number of proteins, including Na^+/K^+-ATPase, which has been reported to be reduced in response to Cd, suggesting that renal ATPase may be involved in Cd-induced nephrotoxicity[109].

Published studies have reported that Cd forms a complex with endogenous metal-binding protein metallothionein (MT) in the liver. This Cd-MT complex is released slowly from the liver and reaches the kidney through circulation. In renal cells, Cd is released from the Cd-MT complex and absorbed in proximal tubules. If the defense and detoxification system of the kidney is suppressed, free Cd can damage renal tubules[105,106,110]. Renugadevi and Prabu[111] reported that oral administration of $CdCl_2$ significantly induced renal damage, which was evident by increased serum creatinine, uric acid, and urea levels and decreased creatinine clearance [111]. They reported an increase in the levels of renal LPO and the protein carbonyl content with a significant reduction in non-enzymatic antioxidants (vitamin E, vitamin C, reduced GSH, and total sulfhydryl group) and enzymatic antioxidants (GR, GST, GPx, G6PD, CAT, and SOD) in rat treated with Cd[111]. Additionally, they also reported numerous abnormalities in the Cd-treated rats, ranging from tubular dilation to necrosis. Qct treatment markedly mitigated the Cd-induced biochemical changes in urine serum and kidney tissue[111]. In another study, Morales et al[112] reported that induction of inflammation was associated with Cd-induced kidney toxicity and an increase in BUN levels, a well-documented, reliable, and important marker of nephrotoxicity. Moreover, they reported that Cd treatment altered the expression of iNOS and Cox2, a mediator of inflammation. Qct treatment, however, mitigated these alterations[112]. It can be assumed that Qct may have a protective effect against nephrotoxicity and oxidative stress induced by Cd administration.

Potassium Dichromate (K2Cr2O7)

People working in textile manufacturing, spray paint, photography and photoengraving, cooling system, and stainless-steel industries can get exposed to chromium (Cr) compounds[113]. Nephrotoxic effects of K2Cr2O7 have been associated with the intracellular reduction of Cr (VI) to Cr (III). As a result, ROS and reactive nitrogen species (RNS) are overproduced[114-118].

Becerra et al[118] reported that K2Cr2O7 produced a significantly increased systemic LPO and reduced renal removal of para-amino hippuric acid (PAH) and inulin one day after K2Cr2O7 administration. Moreover, they reported Qct attenuated the damage caused by K2Cr2O7 probably due to free radical scavenging effects and synergistic effects with endogenous antioxidants[118].

Fluoride

Drinking water and food are natural sources of fluoride for humans[119]. Recent studies[120-124] have estimated that about 30-40% of agrochemicals and 20% of pharmaceuticals products are in the form of organofluorines. As the kidney plays an important role in fluoride metabolism, as mainly 50-80% of the fluoride is removed *via* excretion through urine, the kidney is the major organ affected by fluoride intoxication[119,122]. NaF has been shown[119,125] to cause histological alterations in the kidney tissues and increased ROS generation and LPO production. Recently, Nabavi et al[126] reported an association of oxidative stress with Sodium Fluoride-Induced toxicity in rat kidneys[123,126]. Moreover, they found that fluoride administration

resulted in a significant downregulation of antioxidant defenses coupled with increased serum levels of glomerular damage markers (BUN, creatinine, and urea), consistent with a previous study by Yu et al[127]. Additionally, NaF caused kidney damage through increased oxidative stress, as evidenced by decreased SOD activity, CAT activity, GSH levels, and elevated lipid peroxidation. However, the antioxidant-oxidant balance was normalized to the control level when Qct administration was given before fluoride administration[126].

Mercury chloride (HgCl2)

Mercury (Hg) is one of the major environmental pollutants responsible for nephrotoxicity in animals and humans[128-133]. Mercury is a potent nephrotoxic substance commonly used to induce acute kidney injury (AKI) in animal models because the kidney is the main site of mercury accumulation following acute exposure[129,134,135]. It is important to comprehensively understand the biotransformation mechanism of Hg to induce protection against Hg-induced AKI. Several nephroprotective mechanisms against Hg-induced toxicity have been proposed. Some reports[136-139] suggested that $HgCl_2$ exposure induced oxidative stress in the proximal tubules because of disturbance in the antioxidant capacity.

Recently, the protective effect of Qct against $HgCl_2$-induced AKI was assessed[140]. In that study, Shin et al[140] demonstrated that $HgCl_2$ induced kidney injury, as evidenced by the accumulation of $HgCl_2$ in the kidney and increase in creatinine and BUN. Furthermore, $HgCl_2$ treatment induced the urinary excretion of high mobility group box 1 protein (HMGB1), neutrophil gelatinase-associated lipocalin (NGAL), tissue inhibitor of metalloproteinases 1(TIMP-1), kidney injury molecule-1 (KIM-1), and netrin-1. However, Qct pretreatment mitigated these effects and protected the kidney against HgCl2 induced AKI[140].

Tetrachlorodibenzo-p-Dioxin (TCDD)

TCDD is a dioxin formed by the burning of metals and waste materials during the production of herbicides and in several industrial processes, like plastics and paper manufacturing[141,142]. Humans are exposed to TCDD through food sources like bovine adipose tissue, milk, milk products, fish, and hen's eggs[143]. TCDD is responsible for causing several toxicities, including wasting syndrome, reproductive toxicity, generalized carcinogenesis, immune dysfunction, nephrotoxicity, and hepatotoxicity[141-145]. The mechanism of TCDD toxicity is mainly explained through its binding to the aryl hydrocarbon receptor (AhR), an intracellular ligand-dependent transcription factor[146]. Oxidative stress is an important mechanism of toxicity induced by TCDD, and many studies[142,144,145,147,148] showed that exposure to TCDD leads to oxidative damage of many tissues, such as the liver, kidney, and testis. Published studies[144,149,151] have confirmed the link between TCDD-induced kidney toxicity and oxidative stress. Lu et al[144] reported that TCDD treatment increased lipid peroxidation and induced significant alterations in the antioxidant enzymes in the kidney[144]. It has also been demonstrated[151] that Qct and Chrysin (CH) showed antioxidant activity against TCDD-induced nephrotoxicity. In this study[151], they reported that Qct and CH successfully protected the kidney from the injury induced by TCDD, as they significantly attenuated Lipid peroxidation (TBARS) levels and induced the levels of SDO, CAT, GSH, and GPx enzymes activity.

Titanium Dioxide Nanoparticles ($NTiO_2$)

The microscopic particles with less than 100 nm size in one dimension are known as nanoparticles (NPs). Toxicological studies confirmed that some NPs, such as $NTiO_2$, are potentially harmful because of their unique physicochemical properties and the high surface-to-volume ratio[152]. Besides, these $NTiO_2$ are commonly used in a wide range of consumer products, including clothing, cosmetics, sunscreens, paints, electronics, and surface coating[153]. $NTiO_2$ is also used in food colorants, nutritional supplements, and toothpaste. It has been reported[154-157] that $NTiO_2$ can induce nephrotoxicity due to their accumulation in the kidney. Hadis et al[158] documented that Qct protected the kidney against $NTiO_2$ through its antioxidant, anti-inflammatory, and anti-apoptotic properties[158]. Moreover, they demonstrated that the induction of oxidative stress-mediated $NTiO_2$-induced kidney damage, as indicated by increased levels of malondialdehyde (MDA) and reduced levels of SOD and CAT. When rats were pretreated with Qct, it attenuated the infiltration of inflammatory cells, reduced the glomerular diameter, and restored the abnormalities induced by $NTiO_2$[158].

Gold Nanoparticles (GNPs)

GNPs' shape and characteristics make them attractive materials for a wide range of biological applications. Nonetheless, a thorough under-

standing of their bioaccumulation and systemic toxicity is needed to apply GNPs in medicine and drug delivery[159]. The kidneys are extremely susceptible to xenobiotics because of the high volume of blood flow that passes through them and because they filter a considerable amount of toxins. These toxins can accumulate in the kidney. Despite multiple beneficial effects of GNPs, many studies have found that smaller GNPs at the same mass concentration cause huge cytotoxic and inflammatory responses relative to larger GNPs because of their high reactivity with biological components, the harmful effects of their huge surface area, and the large numbers of NPs[159,160].

Abdelhalim et al[160] reported that Qct had nephroprotective potential against GNPs[160]. They reported that administration of GNPs compromised kidney functions, as evidenced by elevation in serum levels of toxic markers (creatinine, BUN, and uric acid), reduction in the levels of GSH, and induction of the lipid peroxides levels. When rats were co-treated with Qct, these alterations were attenuated significantly, protecting the kidney from the damage induced by GNPs[160].

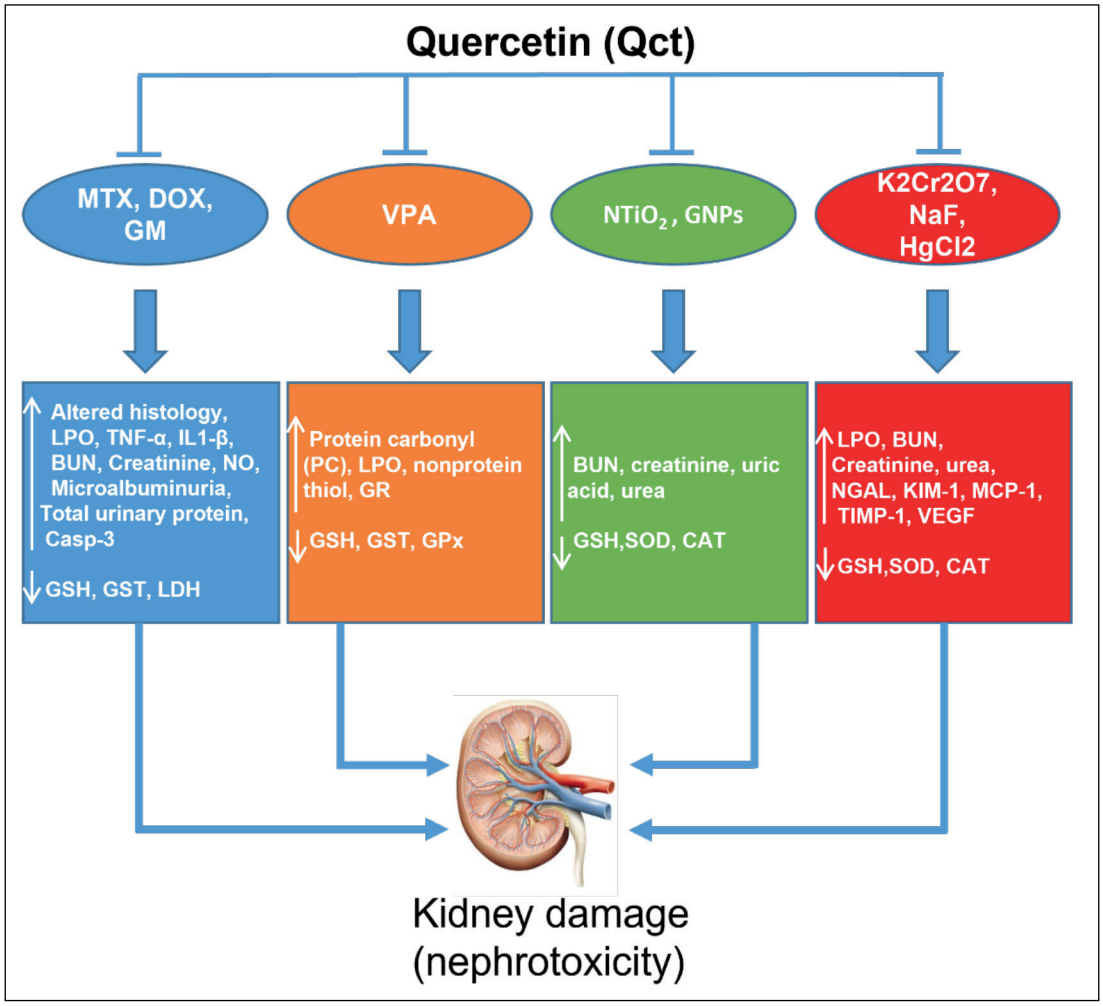

Figure 4. Schematic representation of the protective mechanisms of quercetin to mitigate nephrotoxicity. Qct; Quercetin; MTX; Methotrexate, Dox; Doxorubicin, GM; Gentamicin, VPA; Valproic acid, K2Cr2O7; Potassium dichromate, NaF; Sodium Fluoride, HgCl2; Mercuric Chloride, NTiO2; Titanium Dioxide Nanoparticles, GNPs; Gold Nanoparticles, TNF-α; Tumor Necrosis Factor-alpha, NO; Nitric Oxide, Casp-3; Caspase-3, LDH; Lactate Dehydrogenase, GR; Glutathione reductase, GSH; Glutathione, GPx; Glutathione Peroxidase, SOD; Superoxide dismutase, CAT; Catalase, LPO; Lipid Peroxidation, GST; Glutathione S-transferase. IL-1β; Interleukin 1-beta, BUN; blood urea nitrogen, NGAL; Neutrophil gelatinase-associated lipocalin, KIM-1; Kidney Injury Molecule-1, MCP-1, Monocyte chemoattractant protein-1, TIMP-1; Tissue Inhibitor of Metalloproteinases, VEGF; Vascular Endothelial Growth Factor.

Table I. Cardioprotective effect of Quercetin (Qct).

Cardiotoxicant, dose & duration	Animal/Tissue/Cell	Qct dose, duration	Mechanisms of protection	Ref.
Dox: 1 μM for 24 hrs.	Primary cardiomyocytes	Qct: 10, 20, 40 & 80 μM for 22 hrs. before Dox treatment	Antioxidant	30
Dox: 2.5 mg/kg, i.p., 6 doses for 2 weeks, (accumulative dose of 15 mg/kg)	Wistar rats (male, 190-220 g)	Qct: 10 mg/kg/day, oral, for 6 weeks, started with the 1st dose of Dox	Antioxidant	31
CYP: 40 mg/kg/day, i.p., for 2 days	Swiss albino mice (male, 30-45 g)	Qct: 50 mg/kg/day, oral, for 10 days	Antioxidant Anti-inflammatory	41
Dnr: 15 mg/kg (single dose), i.g	Wistar rats (male, 190-200 g)	Qct: 100 mg/kg, oral, for 24 hrs.	Antioxidant	57
Lindane :100 mg/kg, oral for 30 days	Wistar rats (male, 180-200 g)	Qct: 10 mg/kg, oral, for 30 days	Antioxidant	64

Dox; Doxorubicin, Qct; Quercetin, CYP; Cyclophosphamide, Dnr; Daunorubicin, hrs.; hours, i.p; Intraperitoneal injection, i.g; Intragastric injection.

Table II. Nephroprotective effect of Quercetin (Qct).

Nephrotoxicant, dose, duration	Animal/Tissue/Cell	Qct dose, duration	Mechanisms of protection	Ref.
MTX: 20mg/kg, i.p, single dose	Sprague Dawley rats (male, 200-250 g)	- Qct: 50 mg/kg, oral, for 8 days (2 days prior to MTX treatment and 6 days after it).	Antioxidant	75
MTX: 20mg/kg, i.p	Sprague Dawley rats (male, 8-10-week-old)	Qct: 5 mg/kg, i.p., for 6 days	Anti-apoptotic Antioxidant	76
Dox: 20 mg/kg (single dose), i.p	Wistar rats (male)	Qct: 50 mg/kg, oral, for 10 days	Prevented histological alterations	82
GM: 80 mg/kg, i.p, for 7 days	Wistar rats (female, 150-200 g)	Qct: 50 mg/kg/day, oral, for 7 days	Antioxidant	95
VPA: 20 mg for 2 hrs.	PNS of kidney tissues from Wistar rats (male, 3-4-week-old) weighing 100-120 g	Qct: 0.05 mM, for 1h prior to VPA treatment	Antioxidant	104
Cd: 5 mg/kg/day, oral, for 4 weeks	Wistar rats (male, 120-150 g)	Qct: 50 mg/kg/day, oral, for 4 weeks	Antioxidant	111
Cd: 1.2 mg/kg, s.c., 5 times per week for 9 weeks	Wistar rats (male, 8-week-old, 200 g)	Qct: 50 mg/kg/day, i.p., for 9 weeks	Antioxidant	112
$K_2Cr_2O_7$: 15 mg/kg, i.p.	Wistar rats (male)	Qct: 50 mg/kg, i.p., for 5 days	Antioxidant	118
NaF: 600 ppm for 7 days	Wistar rats (male, 200-250 g)	Qct: 10 & 20 mg/kg/day, i.p., for 7 days	Antioxidant	126
$HgCl_2$: 20 mg/kg, oral, single dose	Sprague Dawley rats (male)	Qct: 250 mg/kg/day, oral, for 3 days	Anti-apoptotic Antioxidant	140
$NTiO_2$: 50 mg/kg, oral, for 2 weeks	Wistar rats (female, 180-200 g)	Qct: 75 mg/kg, oral, for 3 weeks prior to $NTiO_2$ treatment	Anti-apoptotic Antioxidant	158
GNPs: 50 μL of 10 nm GNPs, i.p., for 7 days	Wistar Kyoto rats (male, 12-week-old, 220-240 g)	Qct: 100 mg/kg/day, i.p., for 7 days	Anti-apoptotic Antioxidant	160

MTX; Methotrexate, Dox; Doxorubicin, GM; Gentamicin, VPA; Valproic acid, Cd; Cadmium, K2Cr2O7; Potassium dichromate, NaF; Sodium Fluoride, HgCl2; Mercuric Chloride, NTiO2; Titanium Dioxide Nanoparticles, GNPs; Gold Nanoparticles, Qct; Quercetin, hrs.; hours, i.p; Intraperitoneal injection, S.c; Sub-cutaneous injection, PNS; Post-nuclear supernatant, ppm; Parts per Million.

Discussion

This review summarized the findings reported by different research teams regarding Qct and its protective effects against toxicities caused by various drugs and toxic agents (Tables I and II). According to the findings documented by several studies, Qct has a cardioprotective effect against Dox, CYP, Dnr, and lindane (Figure 3), and nephroprotective effects against MTX, Dox, GM, VPA, Cd, K2Cr2O7, Fluoride, HgCl2, TCDD, NTiO2, and GNPs (Figure 4). Qct offered protection against various chemicals and toxicants through different mechanisms by acting as antioxidants, modulating cardiac and renal enzymes, improving antioxidant defense mechanisms, and inhibiting apoptosis-mediated toxicities.

Conclusions

Qct has a broad spectrum of beneficial properties against different toxicants. However, most of these beneficial effects have not been verified on humans in a clinical trial. Although this review will help pharmacologists, toxicologists, and chemists to develop new safer pharmaceutical products in combination with Qct against different Cardio and nephrotoxicants, more studies are needed to confirm the protective properties of Qct against several toxicants in case of human toxicity.

Conflicts of Interest

The authors declare no conflicts of interest.

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