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REVIEW ARTICLE

Hepatoprotective effects of quercetin against natural and chemical toxicities: A review

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ABSTRACT

Liver metabolizes and detoxifies xenobiotics and toxicity in this organ can lead to dysfunctionality. Flavonoids such as quercetin (QRC) have been shown to possess protective effects against different liver disorders. This flavonol exerts its hepatoprotective effects via different mechanisms including increase of nuclear factor (erythroid-derived 2)-like 2 protein expression, sirtuin 1, thioredoxin and thioredoxin reductase and decrease in nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and myeloid differentiation primary response gene 88 (MYD88). The aim of the current review was to examine the possible protective effects of QRC against different natural and chemical toxic agents-induced hepatotoxicity, so that it could be considered as a hepatoprotective agent in clinical trials. Based on a variety of keywords, Medline, Scopus, Web of Science and Google scholar were searched for all related published literature. Because of insufficient clinical trials on this topic, this review contains only *in vivo* and *in vitro* investigations. In this regard, more clinical trials are required to be performed to confirm QRC beneficial properties in human hepatotoxicity. Collectively, QRC could be a promising natural compound in reversing the toxic effects of different toxic agents in the liver.

KEY WORDS: liver; antioxidant; Nrf2; FoxP3; NF-κB; Beclin-1

ABBREVIATIONS

2-BE: 2-butoxyethanol; **4-HNE:** 4-hydroxynonenal; **ACN:** acrylonitrile; **ACR:** acrylamide; **ADH:** alcohol dehydrogenase; **AHR:** aryl hydrocarbon receptor; **ALP:** alkaline phosphatase; **ALT:** alanine aminotransferase; **APAP:** N-acetyl-para-aminophenol; **AST:** aspartate aminotransferase; **B.C.:** before Christ; **Bcl-2:** B-cell lymphoma 2; **CO:** carbon monoxide; **COX-2:** cyclooxygenase; **CRP:** C-reactive protein; **CTGF:** connective tissue growth factor; **CYP2E1:** cytochrome 2E1; **D-GalN:** D-galactosamine; **DMN:** dimethylnitrosamine; **DNMTs:** DNA methyltransferases; **DPPH:** 2-2-diphenyl-1-picrylhydrazyl; **EPV:** *Echis pyramidum* venom; **ERK:** extracellular receptor kinase; **EtOH:** Ethanol; **Fe-NTA:** ferric nitrilotriacetate; **FoxP3:** forkhead box P3; **GCL:** glutamate-cysteine ligase; **GCLC:** glutamate-cysteine ligase-catalytic subunit; **GGT:** gamma-glutamyl transpeptidase; **GPX:** glutathione peroxidase; **GSH:** glutathione; **GST:** glutathione-S-transferase; **HCV:** Hepatitis C virus; **HepG2:** hepatocellular carcinoma G2; **HMGB1:** high-mobility group box 1 protein; **HO-1:** heme oxygenase 1; **HSP:** heat shock protein; i.v.- intravenously; **IF-γ:** interferon-γ; **IgG:** immunoglobin g; **IL-1β:** interleukin 1 beta; **IL-6:** interleukin 6; **iNOS:** inducible nitric oxide synthase; **IRES:** internal ribosome entry site; **IκBα:** inhibitor of kappa B protein-alpha; **Keap1:** kelch-like ECH-associated protein-1; **LDH:** lactate dehydrogenase; **LMP:** lysosomal membrane permeabilization; **LPS:** lipopolysaccharide; **MAP Kinase:** mitogen-activated protein kinase; **MAP1LC3:** microtubule-associated proteins 1A/1B light chain 3B; **MMP:** metalloproteinase; **MPO:** myeloperoxidase; **MYD88:** myeloid differentiation primary response gene 88; **NAPQI:** N-acetyl-p-benzoquinone imine; **NF-κB:** nuclear factor kappa-light-chain-enhancer of activated B cells; **NPs:** nanoparticles; **NQO1:** NADPH: Quinone Oxidoreductase 1; **Nrf2/ARE:** nuclear factor (erythroid-derived 2)-like 2/antioxidant response element; **p.o.:** per os; **PCBs:** polychlorinated biphenyls; **P-JNK:** phosphorylated c-Jun N-terminal kinase; **PLA2:** phospholipase A2; **PLIN2:** perilipin 2; **PON1:** paraoxonase 1; **Prx:** peroxiredoxin; **QRC:** quercetin; **ROR-γt:** retinoid related orphan receptor-γt; **ROS:** reactive oxygen species; **SDH:** sorbitol dehydrogenase; **SOD:** superoxide dismutase; **STAT1:** signal transducer and activator of transcription 1; **SULTs:** sulfotransferases; **TAA:** thioacetamide;

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s.c.: subcutaneously; **TAC:** total antioxidant capacity; **TB:** total bilirubin; **TBARS:** thiobarbituric acid reactive substances; **t-BHP:** tert-butyl hydroperoxide; **TG:** tripterygium glycosides; **TGF-β1:** transforming growth factor-β1; **Th17:** T helper 17; **Tim-3:** T-cell immunoglobulin and mucin domain 3; **TLR:** toll-like receptor; **TNF-α:** tumor necrosis factor alpha; **TOC:** total oxidant capacity; **TP:** total protein; **TRAF6:** TNF receptor associated factor 6; **Treg:** T regulatory; **Trx:** thioredoxin; **TrxR:** thioredoxin reductase; **T-SH:** total sulfhydryls; **UGTs:** UDP-glucuronosyltransferases; **WCPE:** Wu-Chia-Pi solution; **XO:** xanthine oxidase; **γ-GT:** gamma glutamyl transferase

Introduction

Considering it as one of the most vital biological structures in the body, liver plays a critical role in regulating various physiological processes such as blood volume, immune and endocrine systems, lipid and cholesterol homeostasis, nutrient metabolism, and also the breakdown of xenobiotics (Trefts *et al.*, 2017). Liver possesses a very high capacity to detoxify endogenous and exogenous chemicals, synthesize beneficial compounds and store excess nutrients (Madrigal-Santillán *et al.*, 2014). Hepatotoxicity can be defined as toxic damage to the cells and structure of the liver which affects its normal functions (Kaplowitz, 2005). There are many natural toxins such as aflatoxin B1 (El-Nekeety *et al.,* 2014), lipopolysaccharide (LPS) (Peng *et al.,* 2017) and snake venom (Al-Asmari *et al.,* 2018), and chemical toxins such as cadmium (Renugadevi & Prabu, 2009), cisplatin (Verma *et al.,* 2018) and ethanol (Chen, 2010), which can lead to hepatotoxicity.

In spite of improvement in our knowledge about hepatic development, metabolism, and repair, hepatotoxicity induced by various natural and chemical toxins leads to substantial morbidity and mortality worldwide (Schiano, 2003). On the other hand, there is no efficacious medicine without any side effects, which entirely protects the liver, stimulate hepatic function and facilitate the regeneration of hepatic cells (Chattopadhyay, 2003). Therefore, this drive the need to seek the best therapy and to find complementary and alternative medicines for the prevention and/or treatment of hepatotoxicity.

Consumption of diverse plants and fruits have played pivotal roles in human health for centuries (Adewusi & Afolayan, 2010). From 2600 B.C. to now, the medicinal use of plants has been recorded (Balandrin *et al.*, 1985). Considerable evidence implicates that the beneficial effects of medicinal plants could be ascribed to the presence of biologically-active compounds that are called phytochemicals (Gupta, 1994). Phytochemicals show a wide range of biological properties, and are considered pharmaceutically important (Osbourn & Lanzotti, 2009).

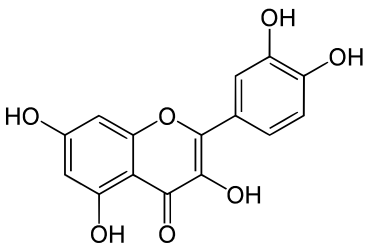

Figure 1. Chemical structure of quercetin.

Among different naturally occurring compounds, polyphenols are the most abundant antioxidants in the diet and are present in a variety of fruits, cereals and vegetables such as apple, grapes, corn, walnut, cinnamon, ginger and many others (Keerthi *et al.*, 2014; Srivastava *et al.,* 2016). Natural polyphenols are reported to have hepatoprotective properties (Kemelo *et al.*, 2017).

Quercetin (QRC), with the IUPAC name of "2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one", is a flavonol that belongs to the flavonoid group of polyphenols (flavus means yellow, which is their common color) (Figure 1) (D'Andrea, 2015). The primary sources of dietary QRC in a typical diet are fruits and vegetables such as onions, apples grapes, cherries and blueberries (Zou *et al.*, 2018). Several lines of experimental evidence have demonstrated that QRC exerts a substantial number of pharmacological properties including hepatoprotective (Miltonprabu *et al.,* 2017), hypocholesterolemic (Kang *et al.*, 2016), anti-inflammatory, anti-obesity, anti-diabetic (Chen *et al.*, 2016), anti-cancer (Hashemzaei *et al.,* 2017), cardioprotective (Chen *et al.,* 2013), renoprotective, antioxidant and anti-apoptotic effects (Gomes *et al.,* 2014). Among the proposed underlying mechanisms for the antioxidant effect of QRC, Nrf2 signaling pathway has been highlighted to have fundamental role in protecting liver against xenobiotics (Iranshahy *et al.*, 2018).

A large amount of the research papers have focused on the effects of different naturally occurring compounds and natural and chemical toxins-induced organ toxicity, particularly liver (Dorri *et al.*, 2018; Fanoudi *et al.*, 2018; Hedayati *et al.,* 2018; Tabeshpour *et al.*, 2018). However, as far as we know, there is no comprehensive review, which presents information on the hepatoprotective effects of QRC, a natural flavonoid, against natural and chemical toxicities.

Literature search strategy

Scientific databases including Medline, Scopus, Web of Science and Google scholar were thoroughly searched on the hepatoprotective effects of QRC against natural and chemical toxicities. The search terms included: "hepatoprotection", "liver protective effects", "liver toxicity" and "quercetin". The reference list of related articles was searched for more relevant articles. The search in the databases was carried out from inception until September 2019.

Hepatoprotective effects of quercetin against natural toxins-induced toxicity

The hepatoprotective effects of QRC against natural toxins-induced toxicity are summarized in Table 1.

Table 1. Natural toxins and the hepatoprotective effects of quercetin.

Toxin	Animal/Cell line	Dosage of QRC	Duration and route of dministration	Consequences	Bibliography
Aflatoxin B1	Rats	1.4 mg/kg	21 days, p.o.	↑TP, GPX, SOD, DNA and RNA content, fatty acid synthase and TNFα gene expression	(El-Nekeety *et al.*, 2014)
Aflatoxin B1	Rats	10 mg/kg	30 days, p.o.	↓ROS, lipid peroxidation, AST, ALT and ALP ↑cell viability, and GSH	(Eftekhari *et al.*, 2018)
Aflatoxin B1	Rats	50 mg/kg	4 weeks, p.o.	↓serum cytokines, procollagen III, nitric oxide, lipid peroxidation and DNA fragmentation ↑GPx, copper- and zinc-containing SOD-mRNA gene expression	(Abdel-Wahhab *et al.*, 2015)
Lipopolysaccharides	Mice	25, 50 and 100 mg/kg	6 days, i.p.	↓TNF-α, IL-6, IL-1β, NF-κB	(Peng *et al.*, 2017)
Lipopolysaccharides	rats	25 mg/kg	2 weeks, i.p.	↓ALT, AST and TBARS ↑TB, GSH and SOD	(Pilkhwal *et al.*, 2010)
Concanavalin A	Mice	100 and 200 mg/kg	5 days, p.o.	↓ALT and AST, and TNF-α and IL-6, Beclin-1 and LC3, Bax, caspase 3 and caspase 9, TRAF6, and P-JNK ↑P62, Bcl-2	(Wu *et al.*, 2017)
Concanavalin A	Mice	50 mg/kg	Single administration, i.p.	↓AST and ALT, TNF-α, IF- γ and IL-4, HMGB1, TLR2 and TLR4 ↑IκBα	(Li, X *et al.*, 2016)
Hepatitis C virus	293T, Huh-7 and Huh-7.5	50 μM	-	↓HSP40 and HSP70, IRES translation	(Gonzalez *et al.*, 2009)
Echis pyramidum venom	Rats	10 mg/kg	Single administration, i.p.	↓AST, ALT, ALP, TBARS ↑T-SH	(Al-Asmari *et al.*, 2018)
Tripterygium glycosides	Mice	10, 20 and 40 mg/kg	1 week, p.o.	↓ALT, AST, ALP, γ-GT, TNF-α ↑GSH, GST, GPx, IL-10, copper- and zinc-containing SOD and CAT	(Wang *et al.*, 2015)
Tripterygium glycosides	Mice	20, 50 and 80 mg/kg	10 days, p.o.	↓Th17-related IL-17 and IL-6, ROR-γt, protein and mRNA expression of TLR4, and MYD88, NF-κB, and IL-6 and IL-17 ↑IL-10, FoxP3, Tim-3	(Wei CB *et al.*, 2017)
Tripterygium glycosides	Mice	20, 50 and 80 mg/kg	10 days, p.o.	↓AST and ALT, and MDA ↑GSH and SOD, Nrf2 protein, HO-1, NQO1 and GCLC	(Wei C *et al.*, 2017)

Aflatoxin B_1

Aspergillus flavus and *Aspergillus parasiticus* are two species which produce aflatoxins. They are major class of mycotoxins (Abdel-Wahhab *et al.*, 2006) and one of the most potent toxic compounds that exist in a big scale in agricultural crops, particularly nuts and grains (Taghizadeh *et al.,* 2018). In a study, aflatoxin B_1 (1.4 mg/kg, in the diet, for 21 days) reduced the levels of total protein (TP), glutathione peroxidase (GP_X), superoxide dismutase (SOD), DNA and RNA content, fatty acid synthase and tumor necrosis factor alpha (TNF-α) gene expression in the liver of rats. QRC at the dose of 50 and 100 mg/kg (per os (p.o.), for 21 days) was able to normalize these alterations. From these results, the authors concluded that QRC revealed its hepatoprotective effect *via* exerting antioxidant activity and regulating the alteration of genes expression induced by aflatoxin B_1 (El-Nekeety *et al.,* 2014). In another study, significant hepatoprotective activity of QRC nanoparticles (NPs) (10 mg/kg, p.o., for 30 days) was observed against aflatoxin B_1 (80 μg/kg, p.o., for 30 days) in rats (*in vivo*) and hepatocytes (*in vitro*). QRC NPs showed this effect *via* diminishing the rate of reactive oxygen species (ROS) formation and lipid peroxidation, improving cell viability, mitochondrial membrane potential and glutathione (GSH) level, and decreasing the levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) (Eftekhari *et al.,* 2018). The results of an investigation showed that aflatoxin B_1 caused a substantial elevation in serum cytokines, procollagen III, nitric oxide, lipid peroxidation and DNA fragmentation as well as a considerable reduction in GPx and copper- and zinc-containing SOD-mRNA gene expression in rat liver. QRC alone (50 mg/kg, p.o., for 4 weeks) or in combination with chitosan NPs (140 and 280 mg/kg, p.o., for 4 weeks) could reverse these effects. The researchers came to the conclusion that chitosan NPs were able to improve the protective effect of QRC against the cytogenetic effect of aflatoxin B_1 (Abdel-Wahhab *et al.,* 2015).

Lipopolysaccharides

LPS are known as main constituents of the outer membrane of gram-negative bacteria that triggers the immune system throughout infection (Startek *et al.*, 2018).

The results of a study revealed that pretreatment of mice with QRC (25, 50 and 100 mg/kg, intraperitoneally (i.p.), for 6 days) ameliorated the survival rate, reduced the liver histopathological changes, attenuated the hepatic damage, decreased the production of oxidative markers and inflammatory cytokines (tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6) and interleukin 1 beta (IL-1β)), suppressed the activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), mitogen-activated protein kinase (MAP Kinase) signaling pathways and the expression of apoptotic proteins mediated by LPS (50 μg/kg, i.p., for 6 days)/D-galactosamine (D-GalN) (300 mg/kg, i.p., for 6 days) . The proposed mechanisms included antioxidant, hepatocyte anti-apoptotic and cytokines anti-inflammatory activities *via* the IKK/NF-κB and MAP Kinase signaling pathways. Therefore, QRC could be a promising therapeutic agent against acute liver injury in mice (Peng *et al.,* 2017). In another study, LPS (1 mg/kg, i.p., single administration) resulted in hepatotoxicity *via* escalation in serum levels of ALT, AST, thiobarbituric acid reactive substances (TBARS), and reduction in total bilirubin (TB), GSH and SOD in rat liver. QRC (25 mg/kg, i.p., for 2 weeks) significantly counteracted these changes. Taken these results together, QRC was able to attenuate LPS-elicited hepatotoxicity *via* preventing cytotoxic effects of cytokines, nitric oxide and ROS (Pilkhwal *et al.*, 2010).

Concanavalin A

A *Canavalia* extract, concanavalin A is a plant lectin that is capable of promoting the mitosis of T cells and results in acute autoimmune hepatitis (Gantner *et al.*, 1995). Concanavalin A (25 mg/kg, single administration) elevated the serum levels of ALT and AST, and TNF-α and IL-6, increased the expression of autophagy markers (Beclin-1 and LC3), decreased the expression of P62, upregulated Bax, caspase 3 and caspase 9, and downregulated B-cell lymphoma 2 (Bcl-2) in mice. It also augmented the expression of TNF receptor associated factor 6 (TRAF6) and phosphorylated c-Jun N-terminal kinase (P-JNK). QRC (100 and 200 mg/kg, p.o., for 5 days) attenuated apoptosis and autophagy in concanavalin A-elicited autoimmune hepatitis *via* inhibiting TRAF6/JNK pathway (Wu *et al.,* 2017). In addition, pretreatment of mice with QRC (50 mg/kg, i.p., single administration) decreased the concanavalin A-elicited rises in the serum levels of AST and ALT and liver necrosis, as well as reduced serum concentrations of pro-inflammatory cytokines (TNF-α, interferon-γ (IF-γ) and IL-4). Moreover, expression of high-mobility group box 1 protein (HMGB1), toll-like receptor (TLR)-2, TLR-4 mRNA and protein in mice liver were decreased by QRC. Pretreatment with QRC also prevented degradation of inhibitor of kappa B protein-alpha (IκBα) and modulated concanavalin A-elicited nuclear translocation in the liver of NF-κB p65. Finally, it was demonstrated that QRC provided protection against concanavalin A-mediated hepatitis in mice *via* attenuating the HMGB1–TLRs–NF-κB signaling pathway (Li *et al.,* 2016).

Hepatitis C virus

Hepatitis C virus (HCV) is a significant public health concern with a worldwide prevalence of 3% and the resulting infection leads to chronic hepatitis and liver cirrhosis (Khan *et al.,* 2014; Shepard *et al.*, 2005). Gonzalez *et al.* demonstrated that QRC (50 μM) significantly inhibited HCV production possibly *via* a decrease in heat shock protein 40 (HSP40) and HSP70 and their potential involvement in internal ribosome entry site (IRES) translation, as well as viral morphogenesis or secretion in 293T, Huh-7, and Huh-7.5 cell lines. The inhibition of HCV production could be a promising therapeutic target, since it does not block a viral-encoded protein directly but rather a cellular cofactor (Gonzalez *et al.,* 2009).

Snake venom

An extremely poisonous viper snake, *Echis pyramidum* is endemic to northeast Africa and the Arabian Peninsula (Al Asmari *et al.*, 2014). Its venom phospholipase A2 (PLA2) has been shown to induce hepatotoxicity (Mukherjee & Maity, 1997). *Echis pyramidum* venom (EPV) at the dose of 4.76 mg/kg (i.p., single administration) resulted in a substantial elevation in serum biomarkers of liver (ALT, AST and ALP), increased lipid peroxidation, fat accumulation, focal degeneration and cytoplasmic vacuolation of hepatocytes in rats. QRC (10 mg/kg, i.p., 1 hour before EPV injection) was able to counteract these alterations. The proposed protective mechanisms of QRC were antioxidant, anti-inflammatory, anti-edema, anti-hemorrhagic and PLA2-inhibitory properties (Al-Asmari *et al.,* 2018).

Tripterygium glycosides

The main chemical components of *Tripterygium wilfordii* Hook F, tripterygium glycosides (TG) are associated with a high occurrence of liver injury (Li *et al.,* 2011). The observations of the study indicated that TG (270 mg/kg, p.o., 12 hours after QRC treatment) led to increase in the serum levels of ALT, AST, ALP, gamma glutamyl transferase (γ-GT), and pro-inflammatory cytokine TNF-α, as well as hepatic lipid peroxidation in mice. TG also considerably decreased the levels of hepatic GSH, glutathione-S-transferase (GST), GPx, and the anti-inflammatory cytokine IL-10, as well as the enzyme activity and mRNA expression of copper- and zinc-containing SOD and CAT. Pre-administration of QRC (10, 20 and 40 mg/kg, p.o., for 1 week) counteracted these changes. This study proposed that QRC alleviated TG-elicited acute liver injury, possibly *via* antioxidant and anti-inflammatory activities (Wang *et al.,* 2015). In another study, TG (500 μg/kg, i.p., single administration) noticeably increased the expression level of the T helper 17 (Th17)-related IL-17 and IL-6, as well as the Th17 transcription factor retinoid related orphan receptor-γt (ROR-γt) in mice. Additionally, it downregulated the expression of IL-10. QRC (20, 50 and 80 mg/kg, p.o., for 10 days) restored the expression of T regulatory (Treg) transcription factor forkhead/winged-helix family transcriptional repressor P3 (FoxP3). Moreover, QRC was able to drastically decrease both protein and mRNA

expression of TLR-4. Consequently, myeloid differentiation primary response gene 88 (MYD88), NF-κB, and IL-6 and IL-17 were inactivated, and the levels of T-cell immunoglobulin and mucin domain 3 (Tim-3) were elevated. QRC showed its hepatoprotective effect through a shift in the balance of Th17 and Treg cells to Treg dominance, which was regulated by Tim-3 and TLR4-MyD88-NF-κB signaling pathway (Wei *et al.,* 2017). Besides, QRC (20, 50 and 80 mg/kg, p.o., for 10 days) was concluded to prevent immunological liver injury mediated by TG *via* activation of nuclear factor (erythroid-derived 2)-like 2 (Nrf2)/antioxidant response element (ARE) signaling pathway in a dose-dependent way. In this study, QRC reduced the serum levels of AST and ALT, and MDA content but was able to increase GSH and SOD contents in mice liver. Histopathological alterations of the liver tissue were improved by this flavonol. Additionally, the expression of Nrf2 protein in the nucleus as well as mRNA expressions of heme oxygenase 1 (HO-1), NADPH quinone oxidoreductase 1 (NQO1) and glutamate-cysteine ligase catalytic subunit (GCLC) increased by QRC (Wei *et al.,* 2017).

Hepatoprotective effects of quercetin against chemicals-induced toxicity

Solvents

2-Butoxyethanol

As one of the most commonly used glycol ethers in production of domestic and industrial products, 2-butoxyethanol (2-BE) is an ethylene glycol monobutyl ether that is also used as a solvent (Hung *et al.*, 2011). Treatment of rats with 2-BE (225 mg/kg, p.o., for 28 days) increased the serum levels of AST, ALT, ALP and albumin while decreased TB levels. It also induced histopathological changes of liver tissue. Concomitant administration of QRC (50 mg/kg, p.o., for 21 days) with 2-BE reversed these alterations. It was concluded that QRC exerted its hepatoprotective properties *via* antioxidant mechanism (Eldin *et al.*, 2015).

Ethanol

Ethanol (EtOH), also known as ethyl alcohol, grain alcohol and drinking alcohol, is a simple alcohol with the chemical formula C_2H_5OH. It is a flammable, volatile and colorless liquid, identified as a major risk factor for different kinds of liver diseases (Williams *et al.*, 2014). In an *in vitro* study, QRC (100 μM/l) was able to counteract ethanol-elicited (100 mM/l) GSH depletion, MDA, ROS, cellular AST and lactate dehydrogenase (LDH) elevation, and SOD inactivation in rat hepatocytes. The results indicated the antioxidant and anti-inflammatory effects of bilirubin released from QRC/HO-1 and biliverdin reductase pathway against ethanol hepatotoxicity (Jie *et al.,* 2013). In another *in vitro* study, pre-treatment of rat hepatocytes with QRC (50 μM) substantially decreased EtOH-mediated hepatotoxicity *via* stimulating HO-1 expression at both mRNA and protein levels. Extracellular receptor kinase (ERK) protein was also involved in inducing HO-1 expression. These observations proposed that QRC was able to diminish ethanol-mediated oxidative stress *via* a pathway which involves ERK activation and HO-1 upregulation (S. Liu *et al.,* 2012). Lee *et al.* in 2017 studied the possible protective effects of 3′-O-methyl QRC (3′MQRC) and QRC-3-O-glucuronide (QRC3GA), two metabolites of QRC, against EtOH-mediated hepatotoxicity. The results showed that QRC, 3′MQRC and QRC3GA (5, 5 and 10 μM, respectively) escalated cell viability in hepatocellular carcinoma G2 (HepG2) cells treated with EtOH. This effect was evidenced by reduced levels of ROS and lowered lipid peroxidation, and increased levels of GSH, SOD and CAT. Besides, QRC, 3′MQRC and QRC3GA restored the expression of HO-1 *via* the activation of Nrf2 and activator protein-1 (AP-1). These results proposed that QRC, 3′MQRC and QRC3GA mitigate oxidative stress in hepatocytes exposed to EtOH (2.5%) through upregulating HO-1 expression (Lee *et al.*, 2018). Besides, QRC (100 mg/kg, p.o., for 90 days) attenuated CYP2E1-mediated EtOH (10 ml/kg) hepatotoxicity *via* inducing HO-1. Decreased heme pool and carbon monoxide (CO) releasing restricted protein synthesis and suppressed enzymatic activity of CYP2E1. Collectively, QRC alleviated EtOH-induced oxidative liver damage and microsomal lipid peroxidation (Tang *et al.,* 2013). Exposure of mice with EtOH (30% of total calories in the diet, for 15 weeks) led to a considerable elevation in lysosomal redox-active iron resulting in liver oxidative damage. Iron-induced ROS production was able to stimulate lysosomal membrane permeabilization (LMP) and following mitochondria apoptosis. QRC (100 mg/kg, p.o., for 15 weeks) was capable of relieving EtOH-induced liver oxidative damage and apoptosis *via* reducing lysosome iron and improving iron-induced LMP (Li *et al.,* 2016). In another investigation, EtOH-incubated (100 mM/l) rat hepatocytes were co-exposed to QRC (100 μM/l) and different doses of ferric nitrilotriacetate (Fe-NTA) for 24 hours. The results indicated that Fe-NTA in a dose-dependent manner led to the elevation of AST and LDH, depletion of GSH and SOD, and increase of MDA and ROS in both intact and EtOH-incubated hepatocytes. QRC normalized intercellular labile iron pool (LIP) level and alleviated oxidative stress mediated by EtOH. Excessive iron might aggravate EtOH-mediated hepatotoxicity *via* Fenton-active LIP, and QRC mitigated ethanol-induced iron and oxidative stress. Thus, intercellular LIP may contribute to the hepatoprotective action of QRC in addition to its direct ROS-scavenging property (Li *et al.,* 2014). In an EtOH-mediated liver injury model, rats were administered 50% ethanol (5 g/kg, p.o., after 2.5 h of QRC administration from the fifth day, for 10 days), which led to cell necrosis, fibrosis and inflammation. EtOH elevated the levels of AST, ALT, alcohol dehydrogenase (ADH), γ-GT, triglyceride in plasma and MDA in liver tissue while diminished GSH content in liver tissue. Furthermore, it significantly increased the plasma levels of IL-1β, IL-1, IL-6, IL-8, and TNF-α, but decreased the level of IL-10 in rat plasma. QRC (5, 10 and 20 mg/kg, for 2 weeks) could reverse these alterations. From these results, it was concluded that QRC *via* multiple mechanisms,

showed hepatoprotective action mediated by EtOH (X. Chen, 2010). Feeding of rats with liquid diets containing ethanol (28% of total calories, for 12 weeks) caused hepatotoxicity evidenced by lipid droplets accumulation and histopathological changes, elevated levels of triglyceride in serum and liver, and increased levels of ALT and AST in serum. QRC not only counteracted these changes, but also elevated the number of autolysosome and restoration of autophagy-related protein expression. Besides, QRC improved lipophagy characterized by the reduced level of perilipin 2 (PLIN2), increased AMPK activity and elevated co-localization of liver microtubule-associated proteins 1A/1B light chain 3B (MAP1LC3) and PLIN2 proteins. Together, these data recommend that consistent consumption of dietary QRC can lead to prevention of hepatic steatosis mediated by EtOH (Zeng *et al.,* 2019).

Acetaminophen

Intoxication with acetaminophen (also known as N-acetyl-para-aminophenol (APAP) or paracetamol) is the most important cause of acute liver failure worldwide. APAP hepatotoxicity is elicited by producing its most active and toxic metabolite, N-acetyl-p-benzoquinone imine (NAPQI) (Barman *et al.,* 2016). 3,4-dihydroxyphenylacetic acid (DOPAC), a predominant biologically-active catabolite of QRC, was administered to mice to investigate its possible protective effect against APAP-induced hepatotoxicity. APAP (300 mg/kg, i.p., 1 h after the last administration of DOPAC) elevated the serum levels of AST and ALT. It also increased oxidative stress *via* augmenting lipid peroxidation and diminishing antioxidant enzyme activities, which resulted in hepatocellular necrosis and reduced liver function. DOPAC (10, 20 or 50 mg/kg/day, i.g., for 3 days) escalated Nrf2 translocation to the nucleus and elevated the expression of phase II enzymes and antioxidant enzymes, and as a consequence, depleted APAP-induced hepatotoxicity and improved antioxidant activity (Xue *et al.,* 2016). In another study, APAP (1.0 mg/kg, i.p., on day 5) increased the serum levels of AST and ALT, elicited lipid peroxidation *via* elevating TBARS in serum and liver of rats. QRC (50 and 100 mg/kg, p.o., for 7 days) counteracted all the measured parameters, indicating its antioxidant property (Valcheva-Kuzmanova, 2015). Ahmed *et al.* suggested that QRC was able to protect against APAP-mediated hepatotoxicity by quenching free radicals, mitigating lipid peroxidation, and increasing the activity of antioxidants. In addition, the inflammatory infiltrations elicited by APAP were considerably alleviated (Ahmed *et al.,* 2014). Besides, rats treated with APAP (500 mg/kg, p.o., for 5 days) showed elevated levels of liver AST, ALT, ALP, and TB, along with levels of TNF-α, and decreased hepatic TP and albumin concentrations. Elevated levels of MDA and reduced activities of SOD, CAT, GSH, GP_X and GST were also observed. On the other hand, QRC (50 mg/kg, p.o., for 3 weeks) was capable of reversing these alterations (El Faras & Elsawaf, 2017). In the study, the encapsulated form of QRC (0.18 mg/kg p.o., for 7 days) was investigated against APAP-provoked liver injury. QRC demonstrated to alleviate the elevated levels of AST and ALT, mitigate the lipid peroxidation and increase the depleted content of GSH. The authors concluded that QRC in chitosan/alginate nanoformulations could manifest hepatoprotective effects against liver oxidative stress elicited by APAP (Tzankova *et al.,* 2017). In an investigation, isoQRC was able to drastically alleviate APAP-elicited liver oxidative stress (elevation in GSH, GPx and SOD activities, and reduction in H_2O_2 and MDA levels), nitrosative stress (inhibition of protein 3-nitrotyrosine formation), inflammation (reduction in IL-6, IL-1β and TNF-α; inhibition of inducible nitric oxide synthase (iNOS) expression, IκBα phosphorylation and NF-κB p65 translocation, suppression in phosphorylation of ERK, JNK and P38 MAP Kinases) and centrilobular necrosis. IsoQRC also led to increase in activities of UDP-glucuronosyltransferases (UGTs) and sulfotransferases (SULTs) and inhibition of cytochrome 2E1 (CYP2E1). These results demonstrated that IsoQRC afforded protection against APAP-elicited hepatotoxicity *via* suppression of oxidative stress, nitrosative stress and inflammation, along with regulation of APAP metabolism (Xie *et al.*, 2016). Barros *et al.* concluded that treating of rats with QRC (50 mg/kg, p.o., for 8 days) reduced the serum levels of AST and ALT and attenuated the hepatotoxicity caused by APAP (3 g/kg, p.o., on the 8th day, single administration) (Barros *et al.,* 2017). In an *in vitro* and *ex vivo* investigation, it was proved that QRC and piperine promoted antioxidant and protective effect of curcumin in APAP-mediated hepatotoxicity. Rats were pretreated with combination of QRC, piperine and curcumin (500, 1,000 and 2,000 mg/kg, p.o., for 7 days), and then APAP (2 g/kg, p.o., single administration) was administered on the 7th day. The combination therapy reduced the serum levels of AST, ALT and ALP, inhibited 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals, and depleted MDA levels (Mehta *et al.*, 2012). In another combination treatment (QRC and curcumin), rats were given APAP (650 mg/kg b.w, p.o., for 15 days). APAP resulted in an increase in TBARS along with a substantial depletion in GP_X, GST, SOD, CAT activities, and GSH content. In addition, it led to hepatic necrosis, augmentation in plasma AST, ALT and ALP, reduction in plasma TP, albumin and globulin. On the other hand, QRC and curcumin were able to counteract these changes. Overall, it was concluded that the hepatoprotective effects of QRC and curcumin were comparable with N-acetylcysteine (Yousef *et al.*, 2010).

Organic Compounds

Carbon Tetrachloride

An extremely potent hepatotoxic compound, carbon tetrachloride (CCl_4) is metabolized by CYP2E1 to trichloromethyl ($^{\bullet}OCCl_3$) and peroxy trichloromethyl ($^{\bullet}OOCCl_3$) radicals. Lipid peroxidation is known as one of the leading cause of CCl_4-elicited hepatotoxicity, which is enhanced by free radical derivatives of CCl_4 (Sajid *et al.,* 2016). QRC (20 mg/kg, i.p., for 15 days) has been demonstrated to possess prophylactic properties against CCl_4-mediated hepatotoxicity (1.0 ml/kg, i.p, every 3 days for 15 days) in rats, evidenced by normalizing the

increased levels of serum AST, ALT, ALP, bilirubin, and TP, concomitant with SOD, CAT, GPx, and GST activities. These effects could be attributed to the antioxidant action of QRC (Krishnappa, *et al.*, 2014). In another study, pre-administration of mice with QRC (50 mg/kg, i.p., for 5 days) markedly depleted the serum levels of AST and ALT, and ameliorated histological changes in CCl_4-elicited hepatotoxicity (2 ml/kg CCl_4 in olive oil, 10% v/v, i.p.). It also increased the activity of copper- and zinc-containing SOD and inhibited nitrotyrosine formation. QRC mitigated the inflammation in the liver *via* decreasing NF-κB, TNF-α, cyclooxygenase (COX-2) and iNOS. This flavonol led to an elevation in Nrf2 and HO-1 expression, and inhibited the expression of transforming growth factor-β1 (TGF-β1). These findings indicated that QRC possesses anti-nitrosative stress, antioxidant, anti-inflammatory and anti-fibrotic effects (Domitrovic *et al.,* 2012). Besides, treatment of rats with CCl_4 (0.5 ml, diluted 1:6 in vegetable oil, i.p., for 16 weeks) elicited cell necrosis, fibrosis, and inflammatory infiltration. It also increased hepatic content of collagen and TBARS, as well as iNOS. Administration of QRC (150 μM/kg, i.p., for 3 weeks) reversed all these alterations. The authors concluded that QRC was effective in ameliorating CCl_4-induced hepatotoxicity (Pavanato *et al.,* 2003).

Oxidative state, inflammation and fibrosis were induced by CCl_4 (The 1st week, 0.2 ml of a mix 1:6 CCl_4 in mineral oil, 2nd week a mix of 1:5, 3rd week a mix of 1:4 and from the 4th to 8th week a mix of 1:3, i.g.). Administration of QRC (100 mg/kg/day, i.g., for 8 weeks) to rats depleted oxidative status and inflammation, and inhibited liver fibrosis in hepatic stellate cells as well as metalloproteinase 2 (MMP2) and MMP9 activation. The results showed that QRC decreased the levels of AST, ALT along with gamma-glutamyl transpeptidase (GGT), TGF-β, collagen 1α and connective tissue growth factor (CTGF). In addition, QRC elevated the gene expression and functional activities of SOD and CAT, and restored the elevated expressions of TNF-α and IL-6, and NF-κB activity. It also decreased the activated hepatic stellate cells number while increased MMP2 and MMP9 activities (Hernandez-Ortega *et al.,* 2012). The data from an investigation indicated that treatment of mice with QRC (40 and 80 mg/kg/day, p.o., for one week) considerably inhibited CCl_4-mediated liver injury (2 ml of a mix 1:1 CCl_4 in olive oil, i.p., twice a week, for one week). QRC resulted in a reduction in oxidative stress, which is consistent with reducing of lipid peroxidation level and elevating the antioxidant enzyme activities in mice liver. Furthermore, it diminished the expression of CYP2E1 and production of iNOS, IL-1β, COX-2 and nitric oxide. More importantly, QRC suppressed TLR2 and TLR4 activation and MAP Kinase phosphorylation, which in turn inactivated NF-κB and the inflammatory cytokines. These data prove that QRC exerted its effect *via* its antioxidant property and modulatory effect on TLR2/TLR4 and MAP Kinase/NF-κB signaling pathways (Ma *et al.*, 2015). In another investigation, CCl_4 (0.5 ml/kg, i.p., once every 3 days for 2 weeks) significantly raised plasma ALT and AST, and bilirubin levels as well as markers of oxidative stress, TBARS, conjugated dienes, nitrites and CAT activity. It also upregulated expression levels of HO-1 and sirtuin 1. QRC (100 mg/kg, i.g., once every day, for 2 weeks) significantly counteracted these alterations except for HO-1 and bilirubin. Accordingly, QRC *via* affecting sirtuin 1 expression could exert its hepatoprotective effect (Kemelo *et al.*, 2017). Besides, in rats administered with CCl_4 (15 ml/kg, i.p.), increased serum levels of AST, ALT and MDA content of mice' liver, and 4-hydroxynonenal (4-HNE), and decreased mRNA expression of peroxiredoxin (Prx) 1, 2, 3, 5, 6, thioredoxin reductase 1 and 2 (TrxR1/2), thioredoxin 1 and 2 (Trx1/2), Nrf2, and HO-1 along with reduced content of GSH were observed. QRC (20 or 80 mg/kg, p.o.) was able to counteract all these changes *via* its antioxidant activity (Zhang *et al.,* 2014).

In an experiment, QRC-phospholipid complex (7 mg/kg, p.o., for 7 days) was developed to improve the bioavailability and protective properties of QRC against CCl_4-mediated hepatotoxicity (2 ml/kg CCl_4, i.p., single administration, on 7th day) in rats. Biochemical alterations and histopathological evaluations showed that QRC-phospholipid complex manifested better protection of rat liver in comparison with free QRC at the same dose. Thus, QRC-phospholipid complex better protects against CCl_4-mediated hepatotoxicity than free QRC at the same dose (K. Zhang *et al.,* 2016). A similar study indicated that QRC in liposomal carrier (75 mg/kg, p.o., for 10 days) showed better ameliorative effect on oxidative stress, initiated by CCl_4 (1.0 ml/kg in olive oil, i.p., for 7 days), leading to a cytoprotective effect and reversed the CCl_4-mediated changes in the rat liver structure (Shaji & Iyer, 2012). A Chinese wine, Wu-Chia-Pi solution (WCPE) is known for its health-beneficial properties and contains QRC and acteoside. In this study, WCPE (1.0 and 5 ml/kg/day, p.o., for 28 days) was able to decrease the elevated levels of MDA and DPPH produced by CCl_4, (0.4% CCl_4 in soybean oil, i.p., single administration) and increase CAT activity in mice liver. Collectively, the antioxidant and hepatoprotective properties of WCPS could be attributed to QRC and acteoside (Huan *et al.,* 2012). Besides, QRC (10 mg/kg) and caffeic acid (6 mg/kg) were studied for their probable protective effects against CCl_4- and APAP-mediated hepatotoxicity (1.5 ml/kg, p.o., in rats and 1 g/kg, p.o., in mice, respectively). CCl_4 led to a pronounced increase in serum levels of AST and ALT. QRC and caffeic acid were able to exhibit hepatoprotective action possibly *via* antioxidants, free radical scavenging, reducing inflammation, calcium channel blocking and/or microsomal enzyme inhibitory activity (Janbaz *et al.*, 2004). The synergistic effects of chitosan NPs (140 and 280 mg/kg, p.o.) plus QRC (50 mg/kg, p.o.) for 3 weeks were evaluated in an investigation. This combination represented noticeable improvements in biochemical and histological alterations in CCl_4-induced hepatotoxicity (1.0 ml/kg CCl4 in corn oil, p.o., twice a week, for 3 weeks) in rats. In fact, the mentioned combination resulted in a decrease in levels of AST, ALT, ALP, carcinoembrionic antigen (CEA) and alpha fetoprotein (AFP), and MDA

content paralleled with an increase in GPx, SOD and CAT activities (El-Denshary *et al.,* 2015). In another combination treatment study, it was proved that both QRC-5',8-disulfonate (a novel synthetic compound, with elevated bioavailability) and the parent QRC (100, 200 and 500 mg/kg, p.o., for 14 days) remarkably mitigated serum levels of AST, ALT, LDH and hepatic MDA content which were elevated by CCl_4 (0.3 ml in peanut oil, ip, on 15th day, single administration). QRC-5',8-disulfonate and QRC also increased GPx and total SOD. These observations demonstrated that this combination has hepatoprotective effects against CCl_4-elicited hepatotoxicity in mice (Cui *et al.*, 2013).

In an *in vitro* study, CCl_4 (0.4% v/v, for 24 hour) lowered the viability of HepG2 cells as well as GSH content while escalated AST, ALT and LDH activities, and lipid peroxidation. *Psidium guajava* and its QRC fractions (100, 200 and 300 μg/ml) were able to reverse these alterations and alleviate the cytotoxicity mediated by CCl_4 (Vijayakumar *et al.,* 2018).

Acrylamide

According to IARC (International Agency for Research on Cancer) and rodent studies, acrylamide (ACR) is classified as a possible human carcinogen (Hogervorst *et al.*, 2016). It was found for the first time in 2002 in high-temperature-heated carbohydrate-rich foods e.g. french fries and potato chips (Hosseinzadeh *et al.*, 2014). ACR (50 mg/kg, i.p., single administration) was shown to increase 8-OH guanosine level, decrease GST activity, and induce DNA damage by measuring tail length, tail DNA, and tail moment when administered to rats. On the other hand, QRC (10 mg/kg, i.p., for 5 days) was able to prevent the ACR-induced hepatotoxicity *via* reversing these alterations, suppressing DNA damage, and improving liver histopathological changes (Ansar *et al.*, 2016).

Acrylonitrile

Acrylonitrile (ACN), as an anticipated human carcinogen, develops tumors in a number of tissues including liver (M. Chen *et al.,* 2019). Treatment of rats with ACN (50 mg/kg/day, p.o., for 5 weeks) led to a substantial increase in MDA, diminution in GSH content as well as SOD and GP_X activities in rats' liver. It also elevated the levels of AST, ALT, direct bilirubin and TB. Pre-administration of rats with QRC (70 mg/kg/day, p.o., for 6 weeks) reversed all these changes. It was suggested that QRC through its antioxidant action could manifest protective activity against ACN-mediated hepatotoxicity (Abo-Salem *et al.*, 2011).

Alloxan

An organic compound alloxan is classified as a derivative of pyrimidine, which exhibits a variety of biological activities (Djurasevic *et al.,* 2018). It has been proven that exposure of alloxan-induced diabetic mice (75 mg/kg, intravenously (i.v.), single administration) to QRC (50 mg/kg/ day, i.p., for 7 days) and chrysin (50 mg/kg/ day, i.p., for 7 days) depleted lipid peroxidation as well as number of vacuolated cells and degree of vacuolization of the liver tissue. The proposed mechanism was their ROS scavenging action (Sirovina *et al.,* 2013).

Bisphenol A

An important and all-purpose industrial chemical, bisphenol A, is known to provoke alterations in antioxidant status and in biochemical parameters in liver (Mahmoudi *et al.,* 2015). Treatment of mice with bisphenol A (60 and 120 mg/kg, p.o., for 30 days) escalated the serum levels of AST, ALT, ALP and acid phosphatase (ACP) activities, while decreased protein content. All these alterations were reversed by QRC (60 mg/kg, p.o., for 30 days). Antioxidant potential of QRC was surmised to be the major mechanism (Sangai & Verma, 2012).

Dimethylnitrosamine

Dimethylnitrosamine (DMN) is known as a hepatotoxin in animal models and interestingly its hepatic fibrosis model manifests most of the clinical symptoms noticed in human liver fibrosis (Pan *et al.,* 2015). Rats exposed to DMN (10 mg/kg/day, i.p., for 3 consecutive days per week for 4 weeks) exhibited a pronounced reduction in body and liver weight, albumin and hepatic GSH levels as well as an increase in serum levels of AST, ALT, bilirubin, and MDA content. Besides, it augmented hydroxyproline content accompanied with a reduction in type I collagen mRNA production. An increase in hepatic stellate cell activation and TGF-β1 expression was also observed. QRC (10 mg/kg, p.o., for 4 weeks) was capable of reversing all these alterations. Collectively, hepatoprotective and anti-fibrogenic effects of QRC were demonstrated against DMN-mediated liver injury, suggesting that it could be used as a preventive agent for hepatic fibrosis (Lee *et al.*, 2003).

Polychlorinated Biphenyl

Extensively spread environmental pollutants, polychlorinated biphenyls (PCBs), are broadly used in numerous industrial products, which develop a variety of health effects including various liver disorders (Buha *et al.,* 2015). In an experimental design, rats were administered with PCB (2 mg/kg/day, i.p., for 30 days) and a considerable increase in H_2O_2 and MDA, concomitant with a significant reduction in GSH level, were shown. Moreover, PCB resulted in apoptosis *via* upregulating aryl hydrocarbon receptor (AHR), p53 and apoptotic proteins (Bax, caspase 3, caspase 9) and downregulating Bcl-2 expression. By counteracting all these changes, QRC (50 mg/kg/day, p.o., for 30 days) exerted its hepatoprotective effect (Sekaran *et al.,* 2012).

Tert-butyl hydroperoxide

Tert-butyl hydroperoxide (t-BHP), a radical oxidizing chemical, has been described to directly induce oxidative stress (Kim *et al.*, 2015). With the same mechanism as H_2O_2, it affects cellular GSH but it is not degraded by CAT (Mezera *et al.,* 2016). In a model of t-BHP-mediated hepatotoxicity (1.5 mM/kg, i.p., single administration), mice that were treated with hydroalcoholic fraction of *Capparis spinosa* L. (400 mg/kg, p.o., for 5 days) and QRC (20 mg/kg, p.o., for 5 days) showed a significant reduction in AST, ALT and ALP, sleeping time and MDA as well as an elevation in the activities of GSH, SOD and CAT. This study proposed that free radical hunting action

of *Capparis spinosa* L. and QRC could be the possible hepatoprotective mechanism (Kalantari *et al.,* 2018).

Thioacetamide

A hepatotoxin and hepatocarcinogenic compound, thioacetamide (TAA), is extensively used as a model of acute and chronic liver disease (Salama *et al.,* 2013). In an experimental design, rats received a single dose of TAA (350 mg/kg, i.p., twice with 24 hours' interval in the last two days of the experiment) and the serum levels of AST, ALT and ammonia increased. Piecemeal necrosis, focal necrosis, apoptosis, and focal inflammation were also observed. Interestingly, QRC (350 mg/kg/day, i.p., for 10 days) was able to attenuate the liver damage (Ashkani-Esfahani *et al.,* 2016). In another experiment, administration of TAA resulted in a drastic increase in AST, ALT and ALP enzymes activity, and MDA, and a significant reduction in total antioxidant capacity (TAC) and GP_X enzyme activity. In addition, MMP9 and MMP2 markers were overexpressed. Pretreatment of rats with QRC (100 mg/kg, p.o., for 45 days) and ellagic acid (100 mg/kg, p.o., for 45 days) reversed all these alterations and exhibited hepatoprotective effects *via* their antioxidant, metal chelating capacity and anti-inflammatory properties (Afifi *et al.*, 2018).

Heavy Metals

Cadmium

As an industrial pollutant and toxic metal, cadmium has been demonstrated to affect human health because it is accumulated in liver and other tissues (Casalino *et al.*, 2002). Exposure of rats to cadmium chloride (5 mg/kg, p.o., for 28 days) led to a remarkable raise in activities of AST, ALT, ALP, LDH, GGT, and bilirubin in serum as well as TBARS, lipid hydroperoxides and protein carbonyl in liver. Cadmium also lowered GSH content, total sulfhydryl groups, vitamin C and vitamin E as well as the activities of SOD, CAT, GPx, GST, glutathione reductase and glucose-6-phosphate dehydrogenase (G6PD). QRC (50 mg/kg, p.o., for 28 days) considerably ameliorated cadmium-mediated anomalies in biochemical indices (Milton *et al.*, 2010). In another study, QRC (100 mg/kg, i.p., single administration) was able to augment the content of GSH and vitamin C as well as TP and the activities of SOD and CAT. QRC was also capable of reversing atrophic, noticeably nodular, inflamed and necrotic liver tissue induced by cadmium fluoride (2 mg/kg, i.p., single administration) in mice (Zargar *et al.*, 2015). Renugadevi *et al.* demonstrated that treatment of rat with cadmium chloride (5 mg/kg/day, p.o., for 4 weeks) substantially increased the serum levels of AST, ALT, ALP, LDH, GGT as well as TBARS and lipid hydroperoxides and protein carbonyl content in liver. Furthermore, it considerably decreased the activities of SOD, CAT, GP_X and GST as well as GSH, vitamin C and vitamin E in rats' liver. Exposure of intoxicated rats with QRC (50 mg/kg/day, p.o., for 4 weeks) counteracted these changes. The obtained results indicated that QRC, *via* its antioxidant activity, could protect the liver from cadmium-elicited hepatotoxicity (Renugadevi & Prabu, 2009).

Arsenic

One of the most abundant elements in the environment, arsenic, accumulates in vital organs such as liver (Bodaghi-Namileh *et al.,* 2018). Arsenic (13 mg/kg in 0.5 ml of physiological saline, subcutaneously (s.c.), single administration) noticeably lowered the antioxidant levels in hepatic cells which were reversed by nanocapsulated QRC (8.98 μM/kg, p.o., single administration, 90 min prior to the arsenic injection). Arsenic also produced a considerable diminution in liver cell membrane microviscosities and treatment with nanocapsulated QRC prevented this loss. The authors concluded that oral route of administration of nanocapsulated QRC could be a beneficial route for possible prevention against liver cell damage (Ghosh *et al.*, 2009). Same researchers found that administration of arsenic to rats drastically decreased the antioxidant levels in hepatic cells. Arsenic (12 mg/kg in water, p.o., twice a week, for 4 months) also elevated hepatic hydroxyproline and upregulated cytochrome *C* expression in liver. All these anomalies were alleviated by liposomal QRC (5 ml/kg suspension containing 2.71 mg/kg of QRC, s.c., twice a week, for 4 months) proposing that its protective effect could be due to QRC ability to decrease arsenic deposition in liver. Consequently, liposomal QRC might be considered as a therapeutic agent against arsenic-elicited hepatic cell damage in rats (Ghosh *et al.*, 2011).

Other Metals

According to the results of the experiment in copper oxide NPs-treated rats (3 and 50 mg/kg, i.p., for 7 days), the activities of AST, ALT, and ALP as well as nitric oxide were elevated significantly in serum, while GSH level, CAT activity, and TAC were decreased in the liver. This metal also led to an increase in DNA damage. However, QRC (200 mg/kg, p.o., for 30 days), *via* its free radical scavenging effect, exhibited therapeutic activity against hepatotoxicity (Arafa *et al.*, 2017).

Administration of gold NPs (50 μl, i.p., for 7 days) to rats resulted in a substantial elevation in the activities of ALT, ALP, GGT and TP along with MDA levels while the content of GSH diminished in liver. QRC (200 mg/kg/day i.p., for 7 days) exhibited its hepatoprotective effect by reversing all these alterations. It was concluded that QRC exerted its effect *via* antioxidant activity (Abdelhalim *et al.*, 2018).

Based on the data obtained from Liu *et al.* in 2015, QRC (40 and 80 mg/kg/day, i.g., for 20 days) was able to ameliorate nickel-elicited hepatotoxicity (20 mg/kg/day, i.p., for 20 days) in mice *via* reducing the activity of DNA methyltransferases (DNMTs) and DNA methylation level of Nrf2. In addition, QRC led to the induction of Nrf2 translocation and HO-1 activity and decreasing TNF-α, IL-1β and iNOS. Moreover, it suppressed p38 MAP kinase and signal transducer and activator of transcription 1 (STAT1) activation. Collectively, the ability of QRC to regulate Nrf2/HO-1 and p38/STAT1/NF-κB signaling pathway was considered as its anti-inflammatory action (C. M. Liu *et al.,* 2015).

In the experimental design, rats were treated with zinc oxide NPs (600 and 1000 mg/kg, p.o., for 5 days) and following alterations were observed: substantial elevation

in ALT activity, glucose, TNF-α, IL-6, C-reactive protein (CRP), and immunoglobin g (IgG). QRC (200 mg/kg, p.o., for 3 weeks) was shown to have mitigating effect on these biochemical markers and ameliorate the hepatic oxidative damage in DNA provoked by zinc oxide. These findings suggested the use of QRC as a therapeutic agent against metal oxide NPs-induced hepatotoxicity (Baky *et al.*, 2013).

Pesticides

Pesticides are known as chemicals, which aim to destroy different types of pests such as insects, microorganisms and etc. Liver, as the principle organ for metabolizing pesticides, is greatly affected in this way (VoPham *et al.,* 2017). Atrazine (120 mg/kg in corn oil, p.o., for 16 days), as an herbicide, was administered to rats and elevation in serum levels of AST, ALP, ACP, sorbitol dehydrogenase (SDH), and content of MDA was noticed. It also decreased the activities of SOD, CAT, and GSH content. Administration of QRC (10 mg/kg, p.o., for 16 days) reversed all these changes demonstrating its hepatoprotective effects (Abarikwu, 2014).

Rats exposed to lindane (100 mg/kg in olive oil, p.o., for 30 days) showed a considerable increase in AST, ALT, ALP and LDH serum levels and MDA content, while a substantial decrease in GSH content and CAT, SOD, GPx and GST activities were observed. Co-treatment of QRC (10 mg/kg in 50% ethanol, p.o., for 30 days) together with lindane meaningfully diminished these biomarkers. From these results, it could be deducted that QRC had ameliorative effects on lindane-evoked oxidative stress in liver (Padma *et al.*, 2012).

Rotenone administration (1.5 mg/kg in corn oil, s.c., for 10 days) to rats induced hepatotoxicity as evidenced by a marked increase in activities of AST, ALT, ALP, LDH, GGT, direct bilirubin and TP as well as protein carbonyl content and xanthine oxidase (XO) activity (as lipid peroxidation markers). Besides, rotenone significantly decreased GSH content, GST, SOD and myeloperoxidase (MPO) activities as well as ferric reducing antioxidant power. As a promising agent to prevent hepatotoxicity, QRC (5, 10 and 20 mg/kg in corn oil, s.c., for 3 days) reversed all these imbalances (Akinmoladun *et al.,* 2018).

Toosendanin, the main active compound in *Toosendan Fructus* and *Meliae Cortex*, is used as parasiticide and insecticide. Toosendanin-induced hepatotoxicity (10 mg/kg in 10% propylene glycol, i.p., single administration) in mice was characterized by an elevation in AST, ALT, ALP serum levels, and TB content as well as liver content of ROS and MDA. But toosendanin reduced GSH content and Nrf2 expression. For the *in vitro* part of the study, L-02 cells were treated with 2 μM TSN and decreased glutamate-cysteine ligase (GCL) activity and cellular expression of the catalytic/modify subunit of GCL (GCLC/GCLM) were observed. Furthermore, cellular GSH content and Nrf2 expression were decreased while ROS formation and the expression of the Nrf2 inhibitor protein kelch-like ECH-associated protein-1 (Keap1) increased. All these anomalies were counteracted by QRC (40 and 80 mg/kg, i.g., for 7 days). Overall, by inducing the Nrf2/GCL/GSH antioxidant signaling pathway, QRC exerted its hepatoprotective activity (Jin *et al.,* 2019).

Anti-cancers

Cisplatin

As one of the most active cytotoxic drugs in the therapy of cancer such as testicular, bladder and ovarian, cisplatin has been demonstrated to provoke hepatotoxicity (Yüce *et al.*, 2007). Administration of cisplatin (12 mg kg, i.p., single administration) in rats led to a substantial increase in the activities of AST, ALT, ALP, LDH and indirect bilirubin, while decreased activities of paraoxonase 1 (PON1), arylesterase, CAT, SOD, GPx and GST in hepatic tissue, manifesting acute hepatotoxicity. Cisplatin also decreased TAC while increased total oxidant capacity (TOC) resulting in an elevation of liver MDA content. QRC improved the imbalance in oxidant and antioxidant system induced by cisplatin and protected the hepatic tissue through direct quenching of free radicals and increasing antioxidant defense system (Verma *et al.,* 2018).

Epirubicin

Belonging to the class of anthracyclines, epirubicin is metabolized by the liver and induces toxicity in this organ (Sasu *et al.,* 2016). Rats that received a single dose of epirubicin (9 mg/kg, i.v., single administration) showed acute hepatotoxicity evidenced by a remarkable augmentation in serum levels of AST, ALT, and MDA content, accompanied by a considerable reduction in the activities of CAT, SOD, and cytosolic GSH levels. QRC (0.33 mg/kg, p.o., single administration) counteracted these changes and exerted its ameliorative effect *via* preventing cellular membrane perforation and the antioxidant defense system of mitochondria in the liver (Kebieche *et al.,* 2009).

Methotrexate

Due to its hepatotoxic effect in cancer chemotherapy, methotrexate' use in the treatment of different types of cancers has been limited (Ali *et al.,* 2017). Oral administration of methotrexate (0.125 and 0.25 mg/kg, for 14 days) to rats drastically elevated the serum levels of AST, ALT, ALP and TP content. Methotrexate also induced histopathological changes in liver tissue. QRC, (500 mg/kg, p.o., for 14 days) by reversing all these alterations, significantly inhibited the methotrexate-elicited hepatotoxicity (David *et al.*, 2016).

Streptozotocin

A naturally occurring compound produced by the gram-positive bacterium *Streptomyces achromogenes*, streptozotocin, has been shown to have toxic effects on liver (Bell *et al.*, 1984). Treatment of rats with streptozotocin (70 mg/kg, i.p., single administration) led to a pronounced increase in hepatic TBARS concentration, chemiluminescence, and SOD and CAT activities. It also activated NF-κB, induced IKKα and iNOS, and elevated the degradation of IκBα. All these anomalies were abolished by QRC (50 and 80 mg/kg, i.p., for 8 weeks). Thus, QRC *via* inhibiting the IKK/NF-κB signaling pathway, prevented the generation of harmful mediators and protected the liver from streptozotocin (Dias *et al.*, 2005). In another study, the MDA content of liver as well as the

serum activities of AST, ALT and ALP were shown to be increased in streptozotocin-administered rats (40 mg/kg, i.p., single administration) while GPx activity and serum albumin were decreased. In addition, apoptotic index in hepatic tissue elevated. QRC (15 mg/kg, i.p., 5 days after the administration of streptozotocin, for 8 weeks) was capable of counteracting these imbalances. Taken these results together, QRC has been demonstrated to possess hepatoprotective effects in rats possibly *via* antioxidant and anti-apoptotic properties (El Gohary *et al.*, 2013).

Miscellaneous

Dimethylhydrazine

A parent form of azoxymethane and a well-known carcinogen, dimethylhydrazine, is commonly used in experimental models of colorectal carcinogenesis in rodents (Punvittayagul *et al.*, 2018). In an investigation, dimethylhydrazine (30 mg/kg, i.p., twice on weeks 2 and 3) resulted in a marked elevation in 8-OH guanine formation in the rats' liver, which was suppressed by QRC (0.2% and 2% QRC diet, p.o., for 12 weeks). Collectively, it can be deduced that QRC possessed hepatoprotective effect against dimethylhydrazine (No *et al.*, 2007).

Perflurooctanic Acid

A member of the class of contaminants known as perfluoroalkyl acids, perfluorooctanoic acid, is toxic to a variety of organs including liver (Yu *et al.*, 2016). Zou *et al.* demonstrated that administration of mice with perflurooctanic acid (10 mg/kg/day, i.g., for 14 days.) substantially increased the serum levels of AST, ALT, ALP, LDH, and total bile acids. It also prevented the generation of MDA, H_2O_2, and 8-OH-2′-deoxyguanosine, decreased COX-2, IL-6 and

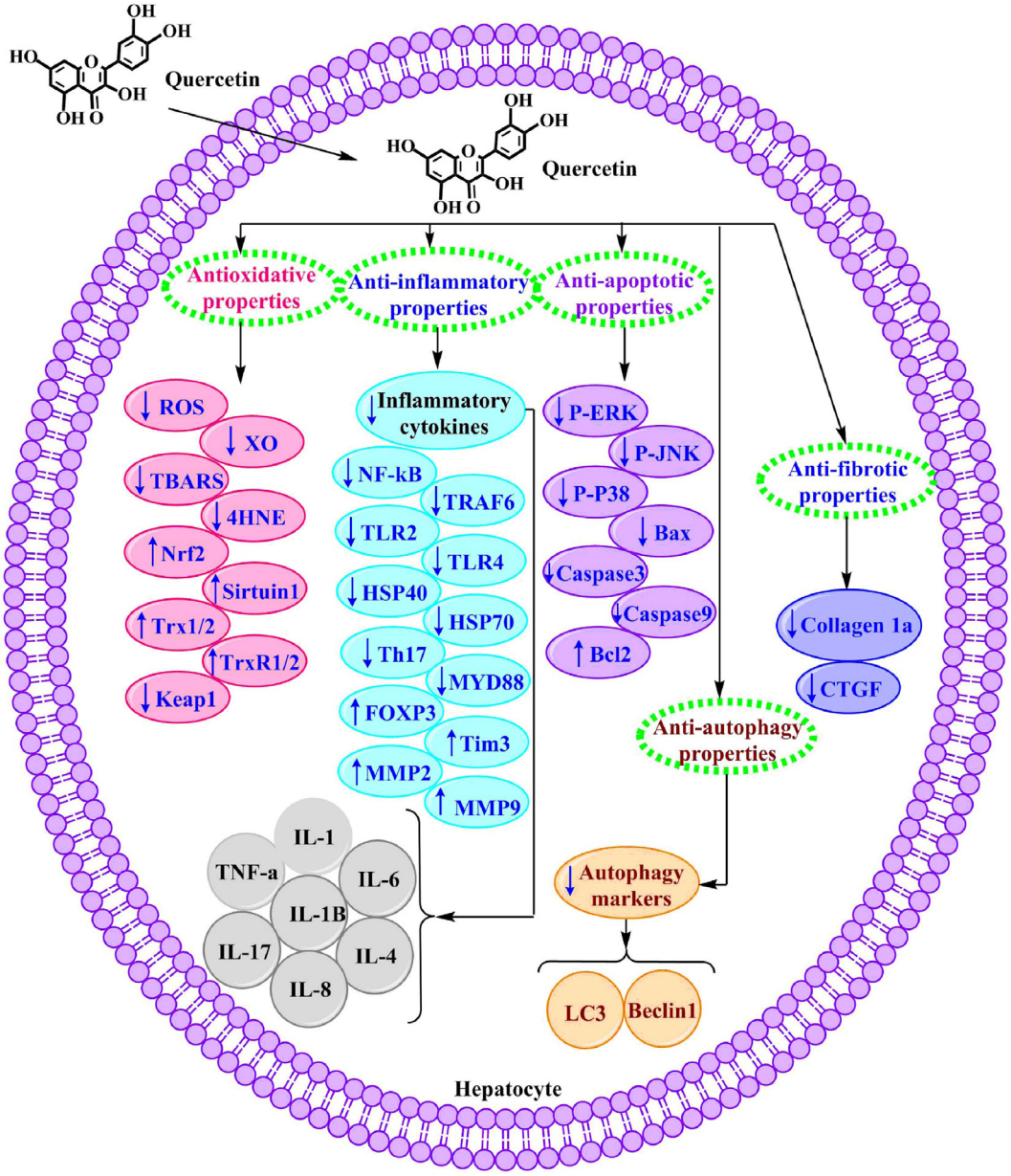

Figure 2. A schematic presentation of different beneficial effects of quercetin against natural and chemical toxic agents.

CRP, and reduced the number of TUNEL-positive cells. QRC (75 mg/kg/day, i.g., for 14 days.) counteracted all these imbalances and showed its hepatoprotective effects *via* antioxidant, anti-inflammatory and anti-apoptotic properties (W. Zou *et al.*, 2015).

Sodium Azide

A colorless and inorganic salt compound, sodium azide, is known to be hepatotoxic (A. O. Williams, 1967). When sodium azide (20 mg/kg, i.p., single administration for 2 days) was administered to rats, the activities of AST, ALT, GGT, and hepatic MDA content elevated, while CAT, GPx, GST activities and GSH levels decreased. QRC (100 mg/kg, p.o., for 7 days) abolished all these alterations and revealed its hepatoprotective effect *via* antioxidant activity (Somade *et al.*, 2016).

Conclusion

Large amount of the research papers has focused on the hepatoprotective effects of QRC against a broad range of natural toxins such as aflatoxin B1, LPS, concanavalin A, snake venom and chemical toxic agents such as solvents (ethanol), organic compounds (CCl_4), heavy metals, pesticides, chemotherapy agents etc. Considerable evidence implicates that QRC exerts its hepatoprotective effects *via* antioxidant, anti-inflammatory and anti-apoptotic activities. In exploring the underlying mechanisms of QRC action, QRC showed its antioxidant properties *via* elevation in Trx, TrxR, Nrf2 andsirtuin 1, accompanied with reduction in ROS, TBARS, 4HNE and XO. ORC anti-inflammatory effects were evidenced by decrease in NF-κB, MYD88, TRAF6, TLR2, TLR4, HSP40, HSP70, along with increase in FoxP3 and Tim-3. Anti-apoptotic actions were reflected by inhibition in phosphorylation of ERK, JNK and P38. QRC also exhibited anti-fibrotic properties through decrease in collagen 1α and CTGF, and anti-autophagic effects *via* reduction in Beclin-1 and LC3 (Figure 2). Briefly, QRC can be considered as a promising natural compound in counteracting or improving the toxic effects of diverse natural toxins and chemical toxic agents in the liver. The main goal of this review was to consider QRC as a therapeutic potential for human health but there are not too many clinical trials on this subject. This could be due to low bioavailability of QRC in human beings. Consequently, more clinical trials are needed to be accomplished to make sure of QRC safety as a therapeutic agent.

Disclosure statement

No potential conflict of interest was reported by the authors.

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