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Review

The biological activities, chemical stability, metabolism and delivery systems of quercetin: A review

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ABSTRACT

Background: Quercetin, one of the most well-known flavonoids, has been included in human diet for a long history. The use of quercetin has been widely associated with a great number of health benefits, including antioxidant, anti-inflammatory, antiviral and anticancer as well as the function to ease some cardiovascular diseases (i.e., heart disease, hypertension, and high blood cholesterol). However, poor water solubility, chemical instability and low bioavailability of quercetin greatly limit its applications. Utilization of delivery systems can improve its stability, efficacy and bioavailability.

Scope and approach: In this review, biological activities, chemical stability, metabolism and toxicity of quercetin and different delivery systems for quercetin were discussed.

Key findings and conclusions: Quercetin digested in human body (e.g., mouth, small intestine, liver, kidneys) undergoes glucuronidation, sulfation or methylation. During the food processing and storage, many factors such as heat, pH, metal ions, could affect the chemical stability (including oxidation and degradation) of quercetin. Utilization of delivery systems including lipid-based carriers, nanoparticles, inclusion complexes, micelles and conjugates-based encapsulation has the potential to improve both the stability and bioavailability and thus health benefits of quercetin. Each delivery system has its unique advantages and shortcomings, and the specific selection should be based on the application domains. Moreover, the exploration of natural food-grade ingredients as main compositions of delivery systems for quercetin might be required in the future.

1. Introduction

Quercetin (3,5,7-trihydroxy-2-(3,4-dihydroxyphenyl)-4Hchromen-4-one) is a dietary flavonoid, which widely existed in caper, black chokeberry, onion, tomato and lettuce (Bischoff, 2008). In plants, quercetin is usually in a bound form with sugars, ethers or phenolic acids and etc. Different forms of quercetin derivatives seem to influence their rate of absorption in the small intestine and stomach (Mullen et al., 2008; Walle, 2004). The content and form of its derivatives play a key role in their absorption (Rahman, Biswas, & Kirkham, 2006; Wiczkowski & Piskuła, 2004).

Quercetin has attracted increasing attention due to its antioxidant (Dueñas, González-Manzano, González-Paramás, & Santos-Buelga, 2010), anti-obesity (Nabavi, Russo, Daglia, & Nabavi, 2015), anti-carcinogenic (Kumari, Yadav, Pakade, Singh, & Yadav, 2010), antiviral (Anandam & Selvamuthukumar, 2014; Ganesan et al., 2012), antibacterial (Rattanachaikunsopon & Phumkhachorn, 2010) and anti-inflammatory effects (Kleemann et al., 2011). Moreover, quercetin has been reported to have a strong potential in the treatment of cancers. Globally, it is estimated that about 1.68 million new cases of cancer are expected to be diagnosed in 2016 (Siegel, Miller, & Jemal, 2016). As documented, quercetin can inhibit the proliferation of different types of cancer cells (e.g. colorectal cancer cells, prostate cancer cells, liver cancer cells, pancreatic cancer cells and lung cancer cells) by modulating their cellular processes and restraining them from growning (Lee, Bode, & Dong, 2011; Shan; Wang & Li, 2009; Kim, Choi, et al. 2013; Kim, Seo, et al., 2013). It is also reported that the anti-cancer function of quercetin is essentially associated to its strong antioxidant capacity (Conklin, 2000). Due to its potential health benefits for human, quercetin has come into the focus of utilization as a nutraceutical ingredient in food and pharmaceutical industries.

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Stability of quercetin has been extensively studied to investigate its chemical changes during food processing and storage. The content of quercetin or quercetin derivatives could be dramatically reduced as a result of oxidation and degradation during food processing and storage (Buchner, Krumbein, Rohn, & Kroh, 2006; Odriozola-Serrano, Soliva-Fortuny, & Martín-Belloso, 2008). The stability of quercetin in different food matrixes could be influenced by pH, temperature, metal ions, and also other compounds such as glutathione (GSH) (Boots, Balk, Bast, & Haenen, 2005; Dehghan & Khoshkam, 2012; Moon, Wang, DiCenzo, & Morris, 2008; Price, Bacon, & Rhodes, 1997).

However, quercetin has low water solubility and bioavailability, chemical instability and short biological half-life, which may reduce its efficacy when used in the food and pharmaceutical fields (Cai, Fang, Dou, Yu, & Zhai, 2013). Quercetin is a lipophilic compound, and it is moderately soluble in ethanol (4.0 mg/mL, 37 °C) (Priprem, Watanatorn, Sutthiparinyanont, Phachonpai, & Muchimapura, 2008), and highly soluble in dimethyl sulfoxide (150 mg/mL, 25 °C) (Ferry et al., 1996). However, its solubility in water is only approximately 0.01 mg/mL (25 °C) (Gao et al., 2011). It is therefore difficult to directly incorporate high levels of quercetin into water-based food matrix.

Delivery systems are generally designed to efficiently encapsulate an appreciable amount of the functional components to protect them against the chemical degradation (e.g. oxidation or degradation) during the processing and storage, and the nutraceuticals incorporated can be released at a controlled rate and at particular site of action or within a particular region of the gastrointestinal tract (GIT) (des Rieux, Fievez, Garinot, Schneider, & Préat, 2006; McClements, Decker, Park, & Weiss, 2009; Joye & McClements, 2016). Many types of delivery systems such as polymeric nanoparticles (Ensign, Cone, & Hanes, 2012; Chang-Bravo, Lopez-Cordoba, & Martino, 2014; Nayak, Tiyaboonchai, Patankar, Madhusudhan, & Souto, 2010), liposomes (Jeon, Yoo, & Park, 2015; Koudelka et al., 2015), microparticles (Soto & Ostroff, 2010; Wan, Sun, Sun, & Tan, 2012), and emulsions (Liu, Hou, Lei, Chang, & Gao, 2012; McClements, 2011; Lu, Kelly, & Miao, 2016) have been shown to significantly enhance the therapeutic efficacy of many nutraceuticals by increasing their bioavailability. Moreover, delivery systems can also protect the bioactive compounds from being enzymatically metabolized and thermal- or light-degradation, thus, increasing its stability (Sharma et al., 2015). Moreover, the utilization of delivery systems has the potential to reduce side effects and control the release of bioactive compounds, which makes this approach more attractive (Grill, Johnston, Sadhukha, & Panyam, 2009; Mainardes, Urban, Cinto, Chaud, Evangelista, & Gremião, 2006). Many nutrients and bioactive agents (e.g. resveratrol, luercetin, curcumin and vitamin C) have been loaded into delivery systems, which improved water solubility, chemical stability and bioavailability (Chen, Li, & Tang, 2015; Li et al., 2009; Matos, Gutiérrez, Coca, & Pazos, 2014; Zhou et al., 2014). However, each of those delivery systems has its own weakness, such as high cost in preparation and the difficulty to scale up, and further investigation is required for better application (Singh, Tiwari, & Tawaniya, 2013).

The objective of this article is to give an overview of recent findings regarding the main biological properties and chemical stability of quercetin, as well as the different metabolic pathways. Special attention is paid to the development of delivery systems for the incorporation of quercetin to enhance its water solubility, chemical stability and bioavailability.

2. Chemical structures of quercetin and its derivatives

Quercetin has a typical flavonoid structure and contains five hydroxyl groups. Fig. 1 displays the structural characteristics of flavonoids: 2 benzene rings (A and B) connected by an oxygen-containing pyrene ring (C). Quercetin is commonly found in its glycoside form, in which one or more hydroxyl group is replaced by different types of sugar groups. The main groups of quercetin derivatives are quercetin *O*-glycosides and some other common derivatives are summarized in Fig. 1. The molecular structure and some physicochemical properties of quercetin and its derivatives are shown in Table 1. In general, all these compounds have poor solubility in water. Quercetin and its derivatives usually exist in the form of yellow colored powder or crystals.

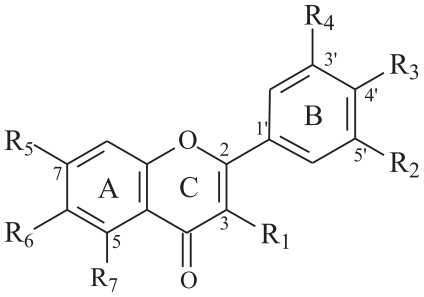
Quercetin *O*-glycosides are the derivatives with at least one *O*-glycosidic bond. Many plants and vegetables contain quercetin *O*-glycosides and the most common glycosylation site is located at the C-3 carbon. The associated monosaccharides may include glucose, galactose and xylose. Quercetin 3-*O*-glucoside has been found in beans (Chang & Wong, 2004), salvia (Esmaeili & Sonboli, 2010) and buckwheat (Kalinova & Vrchotova, 2009). Quercetin 3-*O*-galactoside is found in lingonberry (Heyman et al., 2014) and plum (Kim, Chun, Kim, Moon, & Lee, 2003), whereas quercetin 3-*O*-xyloside is presented in mango fruit (Masibo & He, 2008). Quercetin derivatives in the form of disaccharides are also widely existed in plants and vegetables. For example, rutin (quercetin 3-*O*-rhamnosylglucoside) has been founded in abundance in cherries (Goncalves et al., 2004), spinaches (Kuti & Konuru, 2004), grapes (Iacopini, Baldi, Storchi, & Sebastiani, 2008) and prunes (Gallaher & Gallaher, 2009). Moreover, three, four or more saccharide groups have also been detected in quercetin 3-*O*-glycoside (Williams & Grayer, 2004). Other glycosylation sites in quercetin derivatives can be on the hydroxyl group at C-7 carbon and C-4 carbon. For examples, Quercetin 7-*O*-glucoside in beans (Chang & Wong, 2004) has the glycosylation site at C-7 carbon. The quercetin derivative with glycosylation site at C-4 carbon is only found in onion (Price et al., 1997).

3. Biological activities of quercetin

In this section, a number of main biological activities for quercetin are reviewed (Table 2).

3.1. Antioxidant activity

Quercetin has been shown to be a strong antioxidant *in vitro* and is one of the most powerful scavengers of reactive oxygen species, such as $O_2^{\bullet -}$ (Kukongviriyapan, Sompamit, Pannangpetch, Kukongviriyapan, & Donpunha, 2012), NO•·(Luangaram, Kukongviriyapan, Pakdeechote, Kukongviriyapan, & Pannangpetch, 2007), and $ONOO^-$ (Kim, Choi, et al. 2013; Kim, Seo, et al., 2013). Oxidative damage induced by $O_2^{\bullet -}$, NO•and $ONOO^-$ can create deleterious effects on cells and tissues in human body and may cause many diseases such as cardiovascular diseases, diabetes and cancers (Valko, Rhodes, Moncol, Izakovic, & Mazur, 2006; Waris, & Ahsan, 2006). Fortunately, peroxidation can be terminated by antioxidants, such as quercetin, which can interfere peroxidation by reacting with the radicals formed (Hollman & Katan, 1997). Its antioxidative activity is ascribed to: (a) a catechol group in the B ring; (b) a 2,3-double bond in conjugation with a 4-oxo function in the C ring; and (c) −OH group at positions 3 and 5 in heterocyclic ring (Heijnen, Haenen, Minou Oostveen, Stalpers, & Bast, 2002; Silva et al., 2002). Moreover, quercetin could significantly enhance the endogenous antioxidant capacity of scavenging ABTS radicals by 6.2 folds compared to that of trolox, which can be ascribed to its contribution to the total antioxidant capacity of plasma (Arts, Dallinga, Voss, Haenen, & Bast, 2004).



Systematic name	R_1	R_2	R_3	R_4	R_5	R_6	R_7
Quercetin	OH	OH	OH	H	OH	H	OH
Quercetin 3-*O*-rhamnoside (quercitrin)	O-Rha	OH	OH	H	OH	H	OH
Quercetin 3-*O*-rhamnozyl-(1→6)-glucoside (rutin)	O-RG	OH	OH	H	OH	H	OH
Quercetin 3-*O*-glucoside (isoquercitrin)	O-Glu	OH	OH	H	OH	H	OH
Quercetin 3-*O*-galactoside (Hyperoside)	O-Gal	OH	OH	H	OH	H	OH
Quercetin 7-*O*-glucoside	OH	OH	OH	H	OH	H	O-Glu
Quercetin 3-*O*-rhamnoside-7-*O*-glucoside	O-Rha	OH	OH	O-Glu	OH	H	OH
Quercetin 6-C- glucoside	OH	OH	OH	H	OH	Glu	OH
Quercetin 3'- methyl ether (isohramnetin)	OH	O-Met	OH	H	OH	H	OH
Quercetin 7- methyl ether (rhamnetin)	OH	OH	OH	H	OH	H	O-Met
Quercetin 4'- methyl ether (tamarixetin)	OH	OH	O-Met	H	OH	H	OH

Gal: galactose; Glu: glucose; Rha: rhamnose; RG: rhamnosyl glucose; Met: methyl

Fig. 1. Chemical structures of quercetin and its main derivatives.

3.2. Anti-inflammatory activity

As noted by Rubió, Motilva, and Romero (2013) and Ruma, Kumar, and Prakash (2013), quercetin exhibites a strong anti-inflammatory capacity. Some researchers suggest that quercetin could suppress lipopolysaccharide (LPS)-induced cytokine production in different cells. For example, quercetin can inhibit LPS-induced tumor necrosis factor production in macrophages (Sah, Tirkey, Kuhad, & Chopra, 2011) and LPS-induced interleukin (IL)-8 production in lung cells (Geraets et al., 2007). Furthermore, Bureau, Longpré, and Martinoli (2008) reported that quercetin can inhibit LPS-induced mRNA levels of cytokines in colloid cells, such as tumor necrosis factor (TNF)-α and IL-1α. They also found that the apoptosis of neuronal cell was decreased in a microglial–neuronal coculture by the addition of quercetin.

The anti-inflammatory effect of quercetin is associated with its antioxidative and free radical scavenging properties in some reports (Comalada et al., 2005; Nijveldt et al., 2001). Reactive oxygen species not only exist in the oxidation process, but are also involved in inflammatory response by activation of transfer factors such as nuclear factor-κ-gene binding (NF-κB) (MacNee, 2001). Moreover, NF-κB could induce the production of TNF-α cytokines (Xu et al., 2007). Therefore, eliminating reactive oxygen species could prevent oxidation and inhibit inflammation simultaneously. Furthermore, Nair et al. (2006) interpreted that quercetin could inhibit the gene expression of TNF-α by adjustment of NF-κB in peripheral blood mononuclear cells.

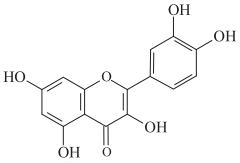
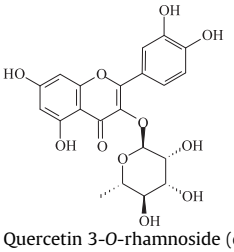
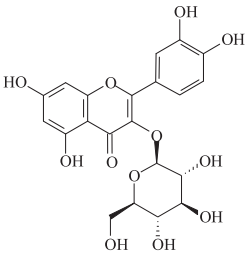
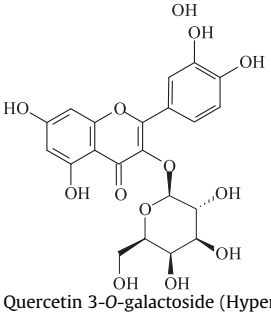
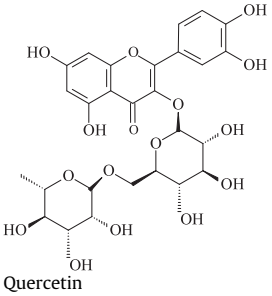
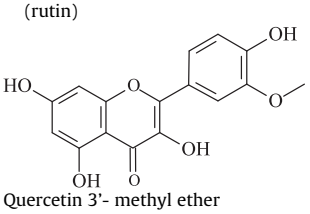
3.3. Anticancer activity

Quercetin has been proven to be a strong anticancer agent from *in vitro* studies in various cancer cells, e.g. U138MG, Hep-2 cells and A549 lung cancer cells, and also from *in vivo* tests (Dajas, 2012; Gibellini et al., 2011). Quercetin can prevent cancer induced by oxidative stress due to its antioxidant activity and suppression of many kinases involved in the growth of cancer cells, proliferation and metastasis (Baghel, Shrivastava, Baghel, Agrawal, & Rajput, 2012; Gibellini et al., 2011). In terms of human breast carcinoma cells, such as SK-Br3 and MDA-MB cells, a low dose of quercetin inhibited their proliferation (Jeong, An, Kwon, Rhee, & Lee, 2009). Quercetin was also found to induce the death receptor-mediated apoptosis in ascite cells of Dalton's lymphoma-bearing rats (Li et al., 2016). Moreover, quercetin restrained the activity of protein kinase C, which contributed to cancer progression (Maurya & Vinayak, 2015).

3.4. Prevention of cardiovascular diseases

Recently, some studies reported that regular intake of flavonoids in foods can decrease the risk of coronary artery disease (Hooper

Table 1
Summary of physicochemical properties of quercetin and its derivatives.

Chemical structure	Molecular weight	Melting point (°C)	logP	Water solubility (mg/ml)	Physical state	UV–Vis max(nm)	Reported biological activities	References
 Quercetin	302.23	314–316	1.48	0.001	Yellow powder	258, 360	Antioxidant, anti-inflammation, antiviral, anti-obesity, antidepressant as well as preventing cancer, diabetes, asthma, hypertension and cardiovascular diseases	Polychniatou & Tzia, 2016; Lemańska et al., 2004; D'Andrea, 2015; Nabavi et al., 2015; Gao et al., 2011
 Quercetin 3-*O*-rhamnoside (quercitrin)	448.38	174–179	0.90	0.024	Yellow powder	256, 346	Antioxidant, anti-inflammation, anticancer as well as inhibiting lipid peroxidation	Peng et al., 2003; Gonzales et al., 2015; Wattenberg et al., 1968; Shimoi, Yoshizumi, Kido, Usui, & Yumoto, 2003; Uppugundla et al., 2009; Cincin et al., 2014
 Quercetin-3-*O*- glucoside (isoquercitrin)	464.38	188–189	0.83	0.095	Yellow powder	257, 362	Antioxidant, anti-inflammatory, antihypertensive, as well as cytoprotection; inhibiting melanogenesis and Ca^{2+}-induced lipid peroxidation	Kwon et al., 2009; Valentová, Vrba, Bancířová, Ulrichová, & Křen, 2014; Gonzales et al., 2015; Ohguchi et al., 2010;
 Quercetin 3-*O*-galactoside (Hyperoside)	464.38	227–230	0.43	NA	Yellow powder	256, 358	Antioxidant, antimicrobial anti-inflammation, as well as preventing hypertension and cardiovascular diseases	Ola et al., 2009; Khanavi et al., 2013; Li et al., 2013; Sujatha & Kantida, 2012
 Quercetin 3-*O*-rhamnozyl-(1 → 6)-glucoside (rutin)	610.52	190–192	−2.02	0.034	Faint yellow powder	256, 351	Antioxidant, anticancer, anti-inflammation, cardioprotection as well as anticonvulsive	Calabro et al., 2005; Diniz et al., 2008; Nassiri-Asl, Shariati-Rad, & Zamansoltani, 2008; Hu, Zhang, Pan, Li, & Kong, 2012
 Quercetin 3'- methyl ether (isohramnetin)	316.26	305–307	2.79	0.037	Yellow crystal	255, 356	Antioxidant, anti-tumor as well as preventing endothelial dysfunction, hypertension and cardiovascular diseases	Hughey et al., 2012; Zhao et al., 2013; Igarashi & Ohmuma, 1995; Ibarra et al., 2003

NA: Not available.

Table 2
Main biological activities of quercetin.

Biological activities	Study model	Method	Effective or tested concentration of quercetin	Results	References
Antioxidative	ICR rats	$O_2^{\bullet -}$ production was determined by lucigenin-enhanced chemiluminescence method	50 mg/kg and100 mg/kg	Quercetin (100 mg/kg) reduced the production rate of $O_2^{\bullet -}$ by 50%	Kukongviriyapan et al., 2012
	Sprague–Dawley rats	Accumulation of NO_2 and NO_3 were measured	25 mg/kg and 50 mg/kg	Quercetin at doses of 25 mg/kg and 50 mg/kg suppressed plasma NO_x concentration 50.4% and 45.5%, respectively	Luangaram et al., 2007
	Zymosan-induced murine macrophages	Amounts of $ONOO^-$ were measured as relative fluorescence units with emission at 530 nm and excitation at 485 nm	1, 3, 10 and 30 μM	Quercetin exhibited inhibitory activity on $ONOO^-$ with $IC_{50} = 8.6$ μM	Kim et al., 2013
	Zymosan-induced murine macrophages	UV spectrophotometry: measured at 517 nm using microplate reader	3, 10, 30 and 100 μM	Quercetin exhibited inhibitory activity on $DPPH^{\bullet}$ with $IC_{50} = 27.6$ μM	Kim et al., 2013
Anti-inflammatory	A549 lung epithelial cells	IL-8 was measured using ELISA kits (CLB/Sanquin)	10 μM	Quercetin significantly reduced IL-8 production	Geraets et al., 2007
	Macrophages of Wistar albino rat lung tissue	Cytokines were measured from brain homogenate using commercially available ELISAs for rat IL-1β, TNF-α, and IL-6	2 and 25 mg/kg	Quercetin significantly decreased IL-6 and TNF-α levels but no significant decrease was observed in levels of IL-1β	Sah et al., 2011
	PC12 cells	PCR products were analyzed by electrophoresis	0.1 μM	Quercetin significantly reduced LPS-induced IL-1α and TNFα gene expression; Quercetin prevented the apoptosis of neuronal cells caused by microglia activation	Bureau et al., 2008
	Peripheral blood mononuclear cells	TNF-α and NF-κB gene expressions were quantitated using real-time PCR	1, 5, 10, 25, and 50 μM	Quercetin inhibited the proinflammatory cytokine TNF-α via modulation of NF-κB	Nair et al., 2006
Anticancer	Human breast carcinoma SK-Br3, MDA-MB-453, and MDA-MB-231	Cell proliferation was assayed by cell counts using a hemocytometer or Z1 Coulter Counter	5 and 10 μM	A low dose of quercetin inhibit proliferation of cancer cell and this inhibition resulted from cell cycle arrest at the G1 phase	Jeong et al., 2009
	Ascite cells of Dalton's lymphoma-bearing rats	Total protein kinase C activity was measured using a PepTag non-radioactive assay kit	25, 50 and 75 mg/kg	Activity of protein kinase C was downregulated after quercetin treatment	Maurya & Vinayak, 2015
Prevention of cardiovascular diseases	Hypertensive patients	Blood pressure was obtained by a trained observer using an Omron random zero automatic blood pressure analyzer	730 mg/day for 4 weeks	Quercetin was found to reduce 7 mm Hg systolic pressure, 5 mm Hg diastolic pressure and 5 mm Hg mean arterial pressures	Edwards et al., 2007
	Obese and hypertensive subjects	Blood pressure measurements were obtained with a standard manual sphygmomanometer under standardized conditions; LDL-cholesterol was measured using the Konelab 20i analyzer with the manufacturer's assay kits	150 mg/day for 42 days	Quercetin decreased systolic blood pressure by 2·9 mmHg	Egert et al., 2009
	Wistar rats	Not shown in detail	10 mg/kg for one week	Quercetin decreased the levels of lipid peroxidation products in plasma and adtevak	Prince & Sathya, 2010
	Human intracutaneous cells and ApoE*3-Leiden mice	H_2O_2-induced lipid peroxidation was assessed with a fluorescence assay using fluorophore C11-BODIPY$^{581/591}$; Atherosclerosis was analyzed blindly in 4 cross-sections from each specimen	0.1%, w/w in diet	Quercetin protected against H_2O_2-induced lipid peroxidation in human intracutaneous cells, as well as significantly attenuated atherosclerosis by 40% in ApoE*3-Leiden mice	Kleemann et al., 2011

Table 3
Effects of heat treatment, pH and storage condition on quercetin content.

Food processing	Food product	Processing condition	Results	References
Thermal	Bean (*Phaseolus vulgaris* L.)	Atmospheric (100 °C) and pressure boiling (121 °C) with and without soaking	70% degradation of quercetin	Ranilla et al., 2009
	Onion bulbs	Atmospheric boiling (100 °C) for 60 min	43.2% degradation of quercetin	Makris & Rossiter, 2001
	Solutions	Heating at 97 °C for 240 min under pH 8	The presence of oxygen caused 100% degradation of quercetin, while the degradation without oxygen was only 15%	Makris & Rossiter, 2000
	Grapefruit juices	Conventional thermal pasteurization heating at 80 °C for 91 s	17% degradation of quercetin	Igual et al., 2011
Alkali or acid	Solutions	Treatment with different pH values (pH = 5 and 8) with air or nitrogen perfusion for 300 min	Complete degradation of quercetin after 180 min at pH 8; The presence of oxygen accelerated the degradation of quercetin	Buchner et al., 2006
	Solutions	Treatment with different pH values (pH = 2.7, 7 and 10) for 96 h	Complete degradation of quercetin after 120 min at pH 10	Moon et al., 2008
Storage	Onions (*Allium cepa*)	Long-term storage (168 days, 20 °C)	100% degradation of quercetin	Price et al., 1997
	Strawberry juice	Storage in darkness (56 days, 4 °C)	46.1% degradation of quercetin	Odriozola-Serrano et al., 2008
	Raspberry jams	Storage (180 days, 20 °C)	40% degradation of quercetin 3-glycoside	Zafrilla et al., 2001
Metal ions	Solutions	Quercetin and $CuCl_2$ solutions mixed in three ratios (0.5, 1 and 2)	Increase the antioxidant activity	Pękal et al., 2011
	Solutions	In the presence of Cr^{3+}	Increase DPPH radical scavenging activity	Chen et al., 2009
	Solutions	In the presence of Sn^{2+}	Reduced DPPH radical scavenging activity	Dehghan & Khoshkam, 2012

et al., 2008; Wang, Ouyang, Liu, & Zhao, 2014; Yamagata, Tagami, & Yamori, 2015). Results from some studies also indicated the effect of quercetin on inhibiting cardiovascular diseases. For hypertensive patients, the intake of quercetin (730 mg/day, 4 weeks) was found to reduce systolic pressure (by 7 mm Hg), diastolic pressure (by 5 mm Hg) and mean arterial pressure (by 5 mm Hg) (Edwards et al., 2007). In a similar study, the systolic pressure and atherogenic LDL level were reduced for some obese subjects with metabolic syndrome symptoms after being supplemented with 150 mg quercetin/day for 42 days. However, the supplementation of quercetin scarcely affects the level of TNF-α and C-reactive proteins, even though fasting plasma quercetin concentration was increased from

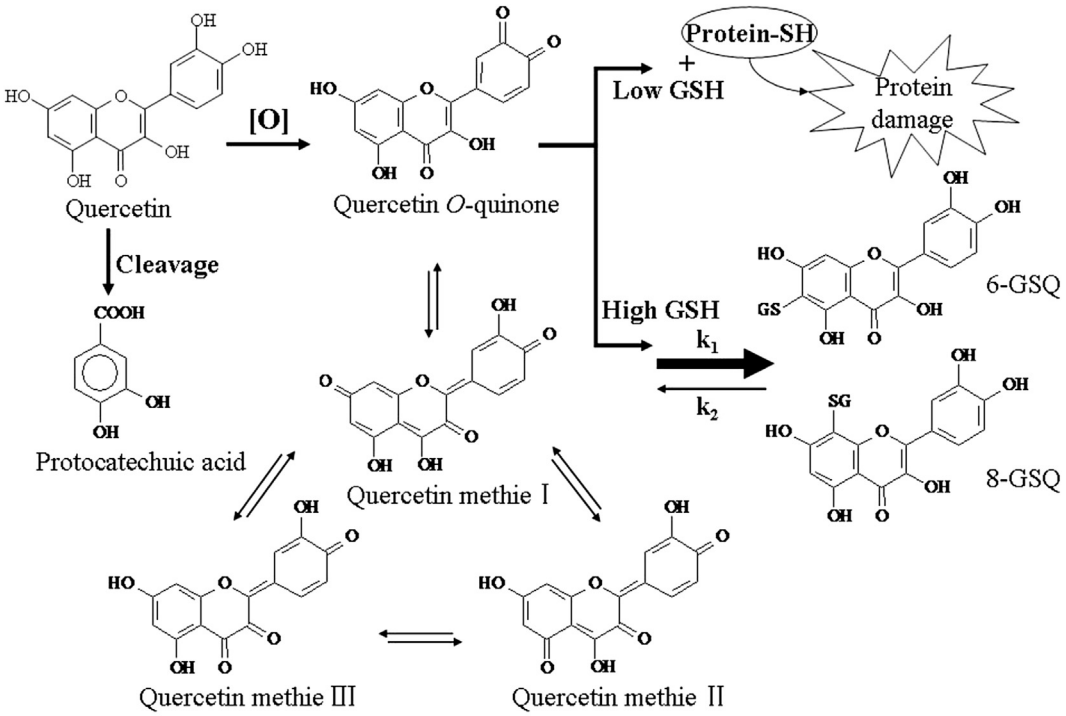


Fig. 2. Oxidation and degradation pathways of quercetin (adapted from Boots et al., 2003).

71 to 269 nmol/L (Egert et al., 2009).

In order to evaluate the beneficial effect of quercetin supplementation on heart disease and elucidate a potential mechanism for this protective action, some studies were performed using cells and animal models. Treating macrophagocytes with quercetin could decrease the basic expression of inflammatory genes, including TNF-α, IL-6, IL-8, IL-10 and epoxidase-2 (a marker of prostaglandin production) (Overman, Chuang, & McIntosh, 2011). In human adipose cells, quercetin inhibited the expression of inflammatory genes and reduced the secretion of IL-6, IL-8 and monocyte chemoattractant protein-1. At the same time, it suppressed the NF-κB transcriptional activity induced by TNF-α (Chuang et al., 2010). In the animal model, Wistar rats were administered orally with quercetin (10 mg/kg) for one week. The results revealed that quercetin protected the rats from myocardial infarction (induced by hypodermic injection of isoprenaline) by reducing the lipid peroxidation products such as lipid hydroperoxides and conjugated dienes in heart and plasma (Prince & Sathya, 2010). Cardiovascular disease of human model was also investigated. Cultured human intracutaneous cells incubated with quercetin (0.1%, w/w in diet) were testified to have a lower level of H_2O_2-induced lipid peroxidation and attenuated atherosclerosis by 40% in ApoE*3-Leiden mice (Kleemann et al., 2011).

4. Chemical stability of quercetin: oxidation and degradation

Quercetin undergoes many chemical changes such as oxidation, during food processing and storage. Chemical stability of quercetin is influenced by oxygen concentration, pH value, temperature, concentration of other antioxidants, as well as the presence of metal ions. Table 3 summarizes the effects of heat treatment, pH and storage condition on quercetin degradation.

Quercetin can be oxidized into various oxidation products, namely quercetin-quinones, which contain one ortho-quinone and three quinone methides. The reversible change between quercetin and quercetin-quinones is illustrated in Fig. 2. A cleavage of quercetin leading to protocatechuic acid is also existent. Quercetin-quinones are highly reactive towards mercaptans and can immediately react with GSH, which is the most abundant endogenous mercaptans (Awad et al., 2002; Pocernich, & Butterfield, 2012). Boots et al. (2005) reported that at a low GSH concentration, quercetin-quinone reacted with protein sulfhydryls (protein-SH) to form protein-quercetin adducts namely glutathionyl-quercetin (GSQ). They also found that GSQ was not stable, and could continuously dissociate into quercetin-quinones and GSH. At a high GSH concentration, the dissociated quercetin-quinones reacted again with GSH and turned into GSQ. However, at a low GSH concentration the dissociated quercetin-quinones would react with other mercaptans, e.g. protein-SH (Boots et al., 2005).

The stability of quercetin is pH and temperature dependent. Quercetin is very unstable in organic solutions (e.g. acetonitrile and methanol) at pH > 7 (Buchner et al., 2006; Moon et al., 2008). Buchner et al. (2006) and Moon et al. (2008) showed that degradation rate of quercetin was higher under alkaline conditions. Storage temperature also affects the stability of quercetin significantly. Atmospheric (100 °C, 50 min) or pressure boiling (121 °C, 10 min) could induce a 70% loss of quercetin in *Phaseolus vulgaris* L. beans (Ranilla, Genovese, & Lajolo, 2009). Conventional pasteurization treatment (80 °C, 91 s) reduced approximately 17% of quercetin in grapefruit juice (Igual, García-Martínez, Camacho, & Martínez-Navarrete, 2011).

The stability of quercetin is also influenced by storage time. Storage at 4 °C in darkness for 24 weeks resulted in 100% loss of quercetin in onion (*Allium cepa*) (Price et al., 1997). At 4 °C in darkness for 56 days, quercetin in strawberry juice was reported to decrease by 46.1% (Odriozola-Serrano, Soliva-Fortuny, & Martin-Belloso, 2008). Storage in darkness at 20 °C for 180 days induced a 40% loss of quercetin conjugate in raspberry jam (Zafrilla, Ferreres, & Tomás-Barberán, 2001).

Quercetin can react with metal ions to form quercetin-metal

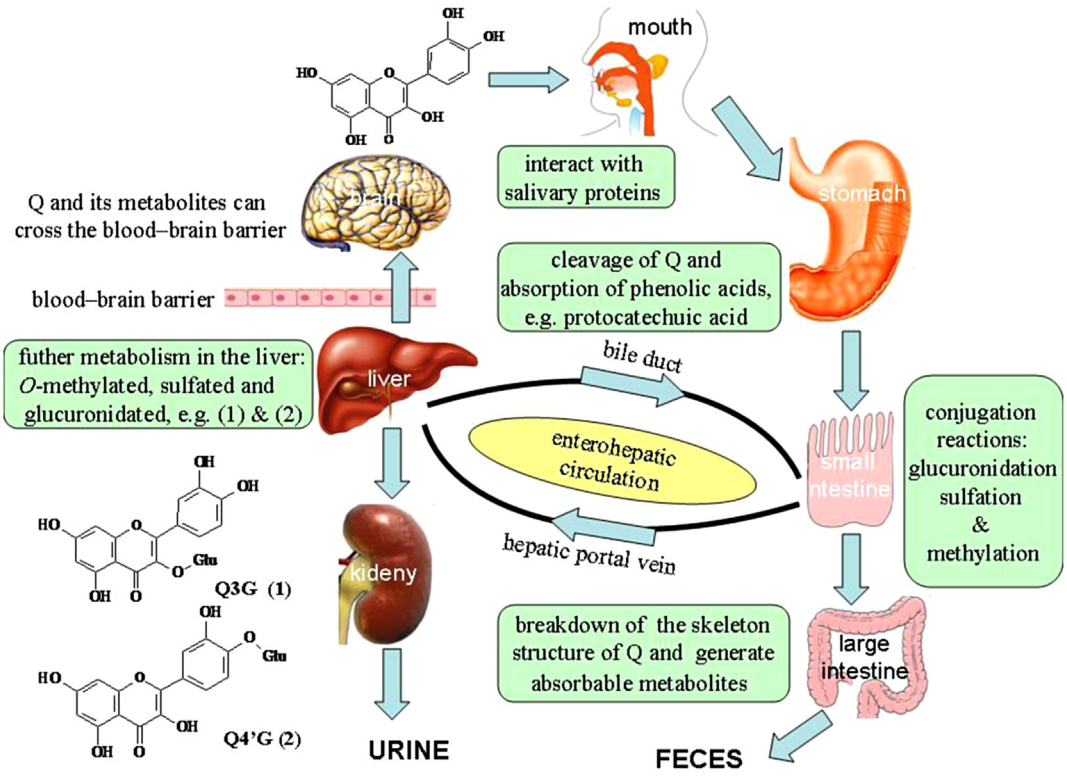


Fig. 3. Schematic illustration of the metabolism and absorption of quercetin. Q represents quercetin.

complexes, and metal ions bound to quercetin changed the quercetin oxidation potential (Ravichandran, Rajendran, & Devapiriam, 2014). According to reports in literature, DPPH radical scavenging activity of quercetin increased in the presence of Cu^{2+} (Pękal, A., Biesaga, M., & Pyrzynska, 2011) and Cr^{3+} (Chen, Sun, Liang, & Song, 2009). However, Sn^{2+} (Dehghan & Khoshkam, 2012) and Cd^{2+} (Ravichandran et al., 2014) reduced this activity of quercetin. Pękal, Biesaga, and Pyrzynska (2011) reported that metal ions were more likely bound to the carbonyl oxygen and 3-OH group (in C ring) of quercetin leading to its decrease of radical scavenging activity.

5. Absorption, metabolism and bioavailability

5.1. Absorption and metabolism

The *in vivo* absorption, distribution, metabolism, and bioavailability of quercetin have been extensively studied in animal models and in human. Schematic illustration of the absorption and metabolism of quercetin is shown in Fig. 3.

In the mouth, quercetin released from the food can interact with salivary proteins, and form soluble quercetin-protein binary aggregates (Manach, Scalbert, Morand, Rémésy, & Jiménez, 2004). However, it was reported that the absorption of quercetin hardly changed despite the formation of the binary aggregates (Cai & Bennick, 2006).

In the stomach, quercetin is exposed to the strong acidic condition, and may be degraded to phenolic acids (e.g. protocatechuic acid) by bacterial ring fission, leading to the breakdown of the skeleton structure of quercetin (Weldin, Jack, Dugaw, & Kapur, 2003). Furthermore, phenolic acids could also be absorbed in the stomach (Farrell et al., 2012; Konishi, Zhao, & Shimizu, 2006).

In the small intestine, there is an efficient glucuronidation of quercetin by the action of uridine diphosphate glucuronosyltransferases and extensive *O*-methylation of quercetin by the action of catechol-*O*-methyltransferase. In addition, quercetin glycosides (e.g. quercetin glucosides and quercetin galactoside) can be deglycosylated to quercetin in the small intestine, which is mediated by microbiota-derived β-glucosidase (Nemeth et al., 2003). Subsequently, those quercetin and quercetin derivatives are transported by the hepatic portal vein to the liver. In the liver, quercetin is further metabolized, including *O*-methylation, sulfation and glucuronidation (Murota & Terao, 2005; Spencer, 2003). The conjugation of quercetin with sulfate is carried out by sulfotransferases. When quercetin is *O*-methylated, its major product is 3′-*O*-methylquercetin (isorhamnetin) and 4′-*O*-methylquercetin (tamaraxetin) to a lesser extent. The resulted quercetin derivatives and the un-metabolized quercetin are released into blood circulation via the portal vein of liver. Subsequently, quercetin and its derivatives can be conjugated in the liver, resulting in the formation of sulfate or glucuronide (Boersma et al., 2002; Shali, Curtis, Powell, & Roy, 1991). Moreover, the catechol-*O*-methyl transferase in the liver and kidney could also take part in further methylation of quercetin and its derivatives (De Santi, Pietrabissa, Mosca, & Pacifici, 2002).

The adsorption of quercetin and its conjugates takes place in the large intestine, where colonic microorganisms can disassimilate those compounds. For example, *Clostridium orbiscindens* plays a key role in executing the fission of the C-ring in quercetin (Aura, 2008). The metabolites formed by the colonic microorganisms are absorbed and transported via the portal vein to the liver and undergo the conjugation reactions.

A recent study estimates the distribution of quercetin after the intravenous and oral administration in rats. After an oral administration of quercetin to male Sprague-Dawley rats, about 93% of quercetin was metabolized in the intestine before being absorbed, whereas only 3.1% was metabolized in the liver (Chen, Yin, Zuo, & Chow, 2005). The report also revealed that about 59.1% of total quercetin including free and conjugated quercetin as well as its metabolites was adsorbed after an oral administration of a single dose of 10 mg quercetin/kg body weight in rats. A long-term treatment (11 weeks) of rats with quercetin fed in diet (500 mg/kg BW rat) demonstrated that quercetin and its metabolites were distributed in several organs (e.g., lung, kidney, heart and liver), with the highest level of quercetin in the lung and the lowest level in the brain and spleen. It implies that the intake of quercetin from daily diet can lead to the accumulation of quercetin throughout the body (de Boer et al., 2005).

5.2. Bioavailability

In human, the total plasma concentration of free and conjugated quercetin as well as its metabolites was in the range of 72 and 193 nmol/L, following the short-term intake of quercetin-rich foods (Nguyen, Staubach, Wolffram, & Langguth, 2015; Petersen et al., 2016; Pfeuffer et al., 2013). This result implies that a short-term treatment of quercetin could not reach the threshold plasma concentration of quercetin that is effective in inhibiting cancerin cells (Dajas, 2012). However, a long-term supplement of quercetin could be a different situation. Guo, Mah, and Bruno (2014) interpreted that a daily ingestion of 1095 mg quercetin for 3 days led to a total plasma quercetin concentration of 1430 nmol/L. Similarly, approximately 2317 nmol/L of plasma quercetin concentration is detected after an oral administration of *Hypericum perforatum* extract for a period of 9 days (Paulke, Nöldner, Schubert-Zsilavecz, & Wurglics, 2008). When 600 mg/kg of *Ginkgo biloba* extract is administered orally to rats, a mean plasma quercetin concentration of 582 nmol/L is detected, whereas a repeated adminstration of the same dose resulted in a 4.6-fold increase (Rangel-Ordóñez, Nöldner, Schubert-Zsilavecz, & Wurglics, 2010). A good deal of literature showed that a repeated quercetin administration obviously increased its bioavailability (Guo et al., 2014; Paulke et al., 2008; Rangel-Ordóñez et al., 2010). However, Bieger et al. (2008) reported that the long-term dietary intake of quercetin did not lead to its plasma accumulation.

Following a single-dose administration of 10 mg quercetin/70 kg of body weight dissolved in three beverages, i.e. vegetable homogenate, grape juice and white wine, the subsequent serum quercetin concentrations were 10.8, 25.3 and 12.7 ng/L, respectively (Goldberg, Yan, & Soleas, 2003). Supplementation of the capsule containing 22 mg quercetin resulted in 109 nmol/L plasma concentration of quercetin (Petersen et al., 2016). Therefore, food matrix also seems to play an important role in the bioavailability of quercetin.

In this context, the fact that plasma levels of quercetin can be enhanced upon a long-term supplementation is interesting. Although abundant studies both *in vitro* and *in vivo* provide the evidence that the supplementation of quercetin could prevent cardiovascular diseases and cancers, little information about the effect of quercetin on the treatment of human cardiovascular diseases and cancer is available.

5.3. Excretion

The absorbed quercetin and its derivatives were excreted in the urine (Nishijima, Takida, Saito, Ikeda, & Iwai, 2015) or excreted into the bile and eliminated in the excrement (Shi & Williamson, 2015). In the other case, quercetin was suffered from bacterial ring fission and decomposed into phenolic acids and CO_2, which was excreted through feces and breath (Abrahamse, Kloots, & van Amelsvoort,

2005; Guo & Bruno, 2015). In human experiments following an oral administration, absorbed quercetin was excreted via CO_2, urine or the feces as glucuronide or sulfate conjugates, and accounted for 52.1%, 4.6% and 1.9%, respectively (Walle, Walle, & Halushka, 2001). Although quercetin underwent extensive metabolism and was mostly recovered in the form of metabolic products, Moon et al. (2008) demonstrated that a trace level of unchanged quercetin (varied from 0.25 to 18 μg within 10 healthy subjects) also existed in the urine after the ingestion of 500 mg Quercetin 500-Plus® capsules.

6. Toxic effects

Many reports showed that the oxidation products such as semiquinone and quinones displayed several toxic effects, because the oxidated products could alter redox homeostasis and deplete cellular protein-SH by arylation (Russo, Spagnuolo, Tedesco, Bilotto, & Russo, 2012; Metodiewa, Jaiswal, Cenas, Dickancaite, & Segura Aguilar, 1999). By reacting with free radical of human body, quercetin can form toxic oxidation products, namely quercetin-quinine which is highly reactive with thiols and GSH might be the principal reactant (Boots, Kubben, Haenen, & Bast, 2003). Boots, Haenen, & Bast (2008) has proven that if the GSH concentration was high enough, it could trap quercetin-quinine as GSQ. However, at low concentration of GSH, it might be ineffective to trap quercetin-quinine which could react with other sulfhydryl compounds such as protein-SH. Once it happened, it might produce toxic effects, e.g. causing cell injury by destroying the integrity of cell membrane and proteins (Wagner et al., 2010; Yen, Duh, Tsai, & Huang, 2003), or destroying the function of enzymes containing sulfhydryl structure (Kalyanaraman, Premovic, & Sealy, 1987). In a model system of isolated mice liver nuclei, quercetin decreased the nuclear GSH content in a dose-dependent manner and might lead to DNA damage (Sahu & Gray, 1996). Ramos & Aller (2008) used quercetin cooperating with arsenic to induce apoptosis in human leukemia cell lines (THP-1, HL-60) and found that GSH content was decreased during the process. Considering that arsenic is highly reactive towards GSH, reduction of GSH may increase the free arsenic concentration, and hence resulted in DNA and cellular damage.

There are also numerous reports about the mutagenic/genotoxic effect of quercetin. *In vitro*, quercetin was tested positively for mutagenic effects in bacteria (Joseph & Priya, 2011). It could also induce reverse mutations (Resende, Vilegas, Dos Santos, & Varanda, 2012), and prevent DNA strand breakage (Özyurt et al., 2014). The mutagenicity of quercetin was observed in hamster ovary cell, at concentrations ranging from 0.2 μM to 1 mM (Engen et al., 2015). Quercetin induced significant frequencies of sister chromatid exchange in ovary cells compared to spontaneous occurrences. However, the mutagenicity/genotoxicity effect of quercetin has not been full confirmed *in vivo*. Supplementation of quercetin

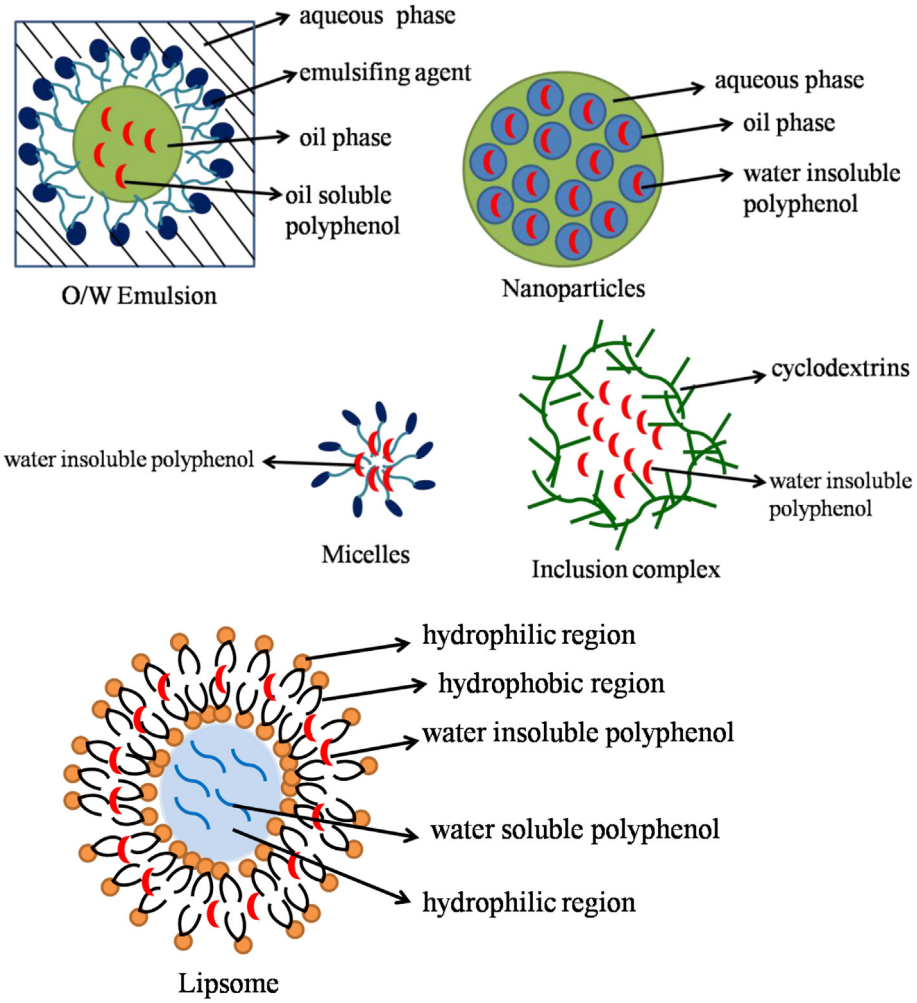


Fig. 4. Schematic representation of the different kinds of colloidal delivery systems. (adapted from McClements, 2010).

Table 4
Advantages and disadvantages of different delivery systems for enhancing bioavailability of quercetin.

Delivery systems	Advantages	Disadvantages	References
Solid lipid nanoparticles (SLNs)	Good tolerability an biodegradability High encapsulation efficiency Targetability	Potential for aggregation Recrystallization risk Low encapsulation loading	Müller, Maassen, Schwarz, & Mehnert, 1997; Yang et al.,1999; Cavalli, Gasco, Chetoni, Burgalassi, & Saettone, 2002
Nanostructure lipid carriers (NLCs)	Smaller particle sizes than SLNs High encapsulation loading High stability	Slightly faster release in comparison to SLNs	Fang, Fang, Liu, & Su, 2008; Zhuang et al., 2010; Fryd & Mason, 2012; Ezhilarasi, Karthik, Chhanwal, & Anandharamakrishnan, 2013
Nanoemulsions (NEs)	Stable system to gravitational separation and aggregation Small droplet size and higher liquid droplet interface area High encapsulation efficiency Targetability	Rapid release Low stability in gastric condition	Gregoriadis, 2006; Takahashi et al., 2007
Lipsomes	Carriers for both lipophilic and hydrophilic molecules Targetability	Low stability at acidic pH High cost of raw materials	Fathi et al., 2012; Hauss, 2007
Biopolymer-particles	Preparing from natural ingredients Small size (10–1000 nm) Effective penetration ability Prolonged release Targetability	Poor stability against aggregation and gravitational separation	Sahoo & Labhasetwar, 2003; Parveen & Sahoo, 2008; Dutta & Green, 2008
Inclusion complexes	Thermo-oxidative stability Strong photo-protectors Controlled release	Potential for disruption Not stable in the presence of competitive compounds and in polar solvents	Kalogeropoulos, Yannakopoulou, Gioxari, Chiou, & Makris, 2010; López-García, López, Maya, & Fernández-Bolaños, 2010
Micelles	Small size (typically < 10 nm) Thermodynamic stability Colloidal stability	Limited solubilization capacity High amount of surfactants or surface active agents Undesirable taste to the formulation	Torchilin, 2007; Boyd, 2008; Sahu, Kasoju, & Bora, 2008
Conjugates-based carriers	No surfactant High loading capacity	Complex preparation methods Being sensitive to pH	Kim et al., 2015; Gupta et al., 2015

consistently resulted in no significant change in several genotoxicity endpoints (e.g. micronuclei and chromosomal aberrations) in bone marrow cells of rats (Cierniak, Papiez, & Kapiszewska, 2004). However, it is recently reported that female rats intraperitoneally supplemented with quercetin suggested a protective effect of quercetin against genotoxic damage induced by Cr (VI) (del Carmen García-Rodríguez, Nicolás-Méndez, Montaño-Rodríguez, & Altamirano-Lozano, 2014). While positive results were also obtained in some *in vivo* mutagenicity/genotoxicity assays, following up a treatment with quercetin (da Silva et al., 2002). Because of the discrepancy in different studies, further research work is required to better understand the potential risk or safety of dietary quercetin.

7. Delivery systems for quercetin

In the past decades, most efforts have been undertaken to improve the bioavailability of poorly water-soluble bioactive compounds (Cai et al., 2013; Lu et al., 2016). Different delivery systems were developed to incorporate the bioactive compounds to modify the dispersed states, improve their chemical stabilities, and finally fulfill their health benefits (McClements et al., 2009). Currently available delivery systems can be classified into five types: (i) lipid-based carriers (Fathi, Mozafari, & Mohebbi, 2012; Yao, Xiao, & McClements, 2014), (ii) Polymer nanoparticles (Jones & McClements, 2010; Kumari, Yadav, & Yadav, 2010; Lee, Yun, & Park, 2015; Parveen, Misra, & Sahoo, 2012; Wilczewska, Niemirowicz, Markiewicz, & Car, 2012); (iii) inclusion complexes (Joye, Davidov-Pardo, & McClements, 2014, 2015); (iv) micelles (Kim et al., 2003; Munin & Edwards-Lévy, 2011) and (v) conjugates-based capsulations (Kim, Park, Choo, & Chong, 2015; Kim et al., 2010; McClements et al., 2009; Weiss, Takhistov, & McClements, 2006). These systems exhibited individual advantages, yet disadvantages were also identified in terms of limited physical stability, low loading capacity, leakage during the storage, organic solvent residue issues, complexity of manufacturing, lack of cost-effective large-scale production, difficulty in the regulatory acceptance of certain constituent materials, cytotoxicity and/or unpredictable safety issues. A detailed description of these carriers is provided below, a variety of carriers are shown schematically in Fig. 4, and the advantages and disadvantages of different delivery systems for quercetin are presented in Table 4.

7.1. Lipid-based delivery systems

Lipid-based formulations, such as solid lipid nanoparticles (SLNs), nanostructure lipid carriers (NLCs), nanoemulsions (NEs) and liposomes, have been applied to enhance the oral absorption and bioavailability of lipophilic and hydrophilic bioactive compounds (Hauss, 2007; Pouton, 2000).

7.1.1. NEs

Emulsion-based encapsulation is one of the most promising techniques for the protection and delivery of polyphenols, particularly nano-emulsions (NEs) (Lu et al., 2016). NEs (O/W) consist of spherical lipid particles dispersed within an aqueous medium, with the particles having a core-shell structure. The hydrophobic core consists of oil molecules and the nonpolar parts of emulsifiers, whereas the polar shell consists of the polar parts of the emulsifiers (Davidov-Pardo & McClements, 2014). Lipophilic bioactive components could be encapsulated within the hydrophobic core of the lipid particles in emulsions (Donsì, Sessa, Mediouni, Mgaidi, & Ferrari, 2011). Compared with conventional emulsions, NEs have been reported to show better stability against particle aggregation and gravitational separation, higher optical transparency, and increased bioavailability of the encapsulated components (McClements, 2010; 2013). NEs were utilized to improve the bioavailability of quercetin. The solubility of quercetin in NEs was

increased markedly to 4.138 mg/mL, compared with 0.17–7.7 μg/mL in water, and a significant absorption enhancing effect of NEs was implicated (Gao et al., 2009).

7.1.2. SLNs

SLNs are composed of lipids that are solid at ambient temperature (Schäfer-Korting, Mehnert, & Korting, 2007), and usually created by preparing an O/W nanoemulsion at a temperature above the melting point of the lipid phase, and then cooling it down to induce lipid crystallization (Joye et al., 2014; Mehnert & Mader, 2012). As a type of submicron particulate drug delivery system, SLNs possess the advantages of high biocompatibility, high bioavailability, controlled release and minimal problems with multiple routes of administration, such as oral, intravenous, pulmonary and transdermal administration (Mehnert & Mäder, 2001). SLNs have been applied to enhance gastrointestinal absorption of quercetin by Li et al. (2009) who reported that the bioavailability of quercetin-loaded SLNs was 5.71-fold greater than that of the quercetin-loaded suspension in 4% CMC-Na (sodium carboxymethyl cellulose) in rats. Bose and Michniak-Kohn (2013) developed a solvent-free solid lipid based nanosystem, which was evaluated for topical delivery of quercetin, and *in vitro* release studies showed the biphasic release of quercetin from the SLNs formulation, with an initial burst release followed by prolonged release for up to 24 h. In spite of the distinct advantages like high encapsulation efficiency and slower degradation rate for quercetin, it has to be noted that SLNs also display some shortcomings such as the potential for aggregation, recrystallization risk and possibility of explusion (Fathi et al., 2012).

7.1.3. NLCs

NLCs are the second-generation lipid-based nanoparticles and composed of a solid matrix entrapping variable oils in the nanocompartments as solubilizing medium for lipophilic bioactive compounds (Müller, Radtke, & Wissing, 2002). Sun et al. (2014) synthesized biocompatible and biodegradable quercetin-nanostructured lipid carriers (quercetin-NLCs) by using the phase inversion-based process method, and found that quercetin-NLCs exhibited a good thermal stability and a sustained release pattern. The study also indicated that solubility of quercetin in water was improved by at least 1000 folds and the activity to inhibit breast cancer was dramatically enhanced. *In vitro* and *in vivo* investigations performed by Tan, Liu, Guo, and Zhai (2011) interpreted that quercetin-NLCs could promote the permeation of quercetin into the cell, increase the level of quercetin retention in epidermis and dermis, and enhance anti-oxidation and anti-inflammation functions. Liu et al. (2014) formulated a novel quercetin-loaded cationic nanostructured lipid carriers consisting of desired amounts of quercetin, lipids (the compound of glycerol monostearate and medium chain triglycerides) and soy lecithin, which exhibited an average particle size of 126.6 nm, a zeta potential of 40.5 mV and 89.3% entrapment efficiency of quercetin with slower release *in vitro* during the digestion compared with those of quercetin suspended in 0.5% (w/v) sodium carboxymethylcellulose aqueous solution.

7.1.4. Lipsomes

Liposomes are mainly composed of phospholipids and steroids or other surfactants (Wilczewska et al., 2012). They are biocompatible spherical vehicles with a 80–300 nm size range and can entrap water-soluble, lipid-soluble, and amphiphilic materials (Landi-Librandi et al., 2012; Mignet et al., 2012). Lipsomes could improve the water solubility, reduce the toxic effects and control the release of the entrapped drugs. Moreover, Liposemes are also reported to possibly protect the encapsulated compounds from external stimuli, such as light, enzymes, extreme temperature, and pH fluctuations (Xia, Hu, Jin, Zhao, & Liang, 2012). Gang et al. (2012) explored the application of polyethyleneglycol-2000-distearoyl phosphatidyl ethanolamine (PEG2000-DSPE) to prepare quercetin-loaded nanoliposomes (PEG-DSPE-Q-NLs). The results showed that quercetin/PEG2000-DSPE formulation was more effective than pure quercetin in inhibiting the growth of glioma cancer cells, suggesting nanomaterials (PEG2000-DPSE) could be effective drug delivery vehicles as tumor-targeted drug carriers. According to the report of Jeon et al. (2015), multilayered liposomes with up to 10 alternating layers were successfully developed using a layer-by-layer deposition technique. The results revealed that an increase in the number of layers resulted in a more sustained release of quercetin with improved skin permeation.

7.2. Polymer nanoparticles

Polymer nanoparticles can be fabricated from a variety of ingredients, including natural polymers such as proteins and polysaccharides, systhetic polymers like poly lactide (PLA) and poly lactide co-glycolide (PLGA), and inorganic materials mainly referring to the silica. The compositions of the nanoparticles have a pronounced influence on many of their functional attributes, for examples the protective properties and release characteristics for bioactive components (Joye & McClements, 2013).

7.2.1. Natural polymers-based nanoparticles

7.2.1.1. Protein-based nanoparticles. Proteins, of both plant and animal origins, are often used to prepare nanoparticles, due to their easy digestion within the human GIT (Joye & McClements, 2014). Fang et al. (2011) developed a nanoparticle using bovine serum albumin (BSA) as a matrix to encapsulate quercetin, and found that BSA nanoparticles could maintain the bioactive properties of quercetin under both acidic and neutral conditions for a long period. Patel, Heussen, Hazekamp, Drost, and Velikov (2012) developed quercetin-loaded zein nanoparticles with the average particle size below 200 nm and they found that chemical stability of quercetin entrapped in the colloidal particles was improved under the alkaline condition and exposition to UV-light irradiation.

7.2.1.2. Polysaccharide-based nanoparticles. Polysaccharides, same as proteins, are commonly applied to fabricate biopolymer particles. There are three major gelation mechanisms for polysaccharides, i.e. ionotropic, cold- and heat-set gelation (Burey, Bhandari, Howes, & Gidley, 2008). Ha, Kim, Lee, and Lee (2013) prepared quercetin-loaded linoleic acid (LA) modified chitosan oligosaccharide/β-lactoglobulin (CSO-LA/β-lg) nanoparticles and suggested that the encapsulation efficiency of quercetin was enhanced with increased charged amount of LA. In comparison with pure quercetin solution, the quercetin-loaded lecithin-chitosan nanoparticles showed a higher cell permeation ability, and significantly increased the accumulation of quercetin in the skin, especially in the epidermis (Zhang, Yang, Tang, Hu, & Zou, 2008). Water solubility of quercetin was also improved when it was entrapped in polymeric microparticulates formed by sodium alginate and chitosan through an ionic cross-linking method, as the embedded quercetin was present in the amorphous form instead of its original crystalline one. The authors claimed that quercetin molecules were encapsulated or dispersed into the chitosan-alginate polymers during the ionic cross linking, and it was included in an amorphous complex with intermolecular interactions within the matrix (Hazra, Mandal, Mandal, Bhuniya, & Ghosh, 2015; Xing, Zhang, & Tan, 2007).

7.2.2. Synthetic polymer-based nanoparticles

Being a FDA-approved biocompatible polymer, poly (lactic-co-glycolic acid) (PLGA) has been widely explored in different drug delivery applications. Jain, Thanki, and Jain (2013) prepared the orally administrable PLGA nanoparticles (NPs) encapsulating quercetin, and confirmed that the free radical scavenging ability of quercetin was retained in freeze-dried NPs. Poly (caprolactone, PCL) nanoparticles formed by nano-precipitation method was able to improve the bioavailability of quercetin probably because of the submicron size of nanoparticles and the controlled release of quercetin from the particles (Kumar, Verma, & Singh, 2015). Pandey et al. (2015) utilized the emulsified nanoprecipitation technique to synthesize quercetin embedded poly (lactic acid) (PLA) nanoparticles (PLA-quercetin), and they found delayed diffusion and stronger interaction between PLA and quercetin resulted in the sustained delivery of quercetin from the polymer matrix. Quercetin could react with glycerol diglycidyl ether (GDE) to form poly (quercetin) particles (p(quercetin)) via a microemulsion polymerization/crosslinking method. The formed p(quercetin) particles were more thermally stable in comparison to pure quercetin and the particles were found to have significant antioxidant capacity equal to that of 82.5 mg/L gallic acid (Sahiner, 2014).

7.2.3. Inorganic material-based nanoparticles

Quercetin-loaded silica nanoparticles modified by cetyltrimethylammonium bromide prohibited quercetin degradation and decreased its cytotoxicity (Nday, Halevas, Jackson, & Salifoglou, 2015). Sapino et al. (2015) evaluated the potential of aminopropyl functionalized mesoporous silica nanoparticles (NH_2-MSN) as a topical carrier system for quercetin. They found that the complex with NH_2-MSN at a concentration of 60 μM was more effective than quercetin alone and the cell proliferation was reduced to a 50% level. Kumar et al. (2014) confirmed that the quercetin conjugated Fe_3O_4 nanoparticle was a promising anticancer agent for targeted drug delivery.

7.3. Inclusion complex

A great number of studies have shown that flavonoids and carotenoids can form inclusion complexes with cyclodextrins (CD). CD has a truncated cone structure and relatively hydrophobic internal cavity and hydrophilic external faces, which could facilitate the formation of non-covalent inclusion complexes with different foreign compounds (guest). The complexes were reported to improve stability, solubility and/or dissolution rate and ultimately the bioavailability of many bioactive compounds (Borghetti, Lula, Sinisterra, & Bassani, 2009; Tsao et al., 2012). Jullian, Moyano, Yanez, and Olea-Azar (2007) investigated the complexation of quercetin with three types of cyclodextrins, i.e. β-cyclodextrin (β-CD), hydroxypropyl-β-cyclodextrin (HP-βCD) and sulfobutyl ether-β-cyclodextrin (SBE-βCD). The results indicated that all complexes showed a higher scavenging capability than that of quercetin in water, and quercetin-SBE-βCD complex was the most reactive form. Aytac, Kusku, Durgun, and Uyar (2016) found that the inclusion complex of β-CD and quercetin formed at the ratio of 1:1 exhibited its higher weight loading with a much lower release, and also improved its solubility, antioxidant activity and photostability properties. Kale, Saraf, Juvekar, and Tayade (2006) reported a quercetin-CD inclusion complex using a kneading and co-evaporation method, with which quercetin showed enhanced aqueous solubility (90–120 μg/mL) and dissolution rate, and the complex exhibited significantly higher anti-cancer activity *in vivo* with a much lower dose.

7.4. Micelles

Micelles are based on the colloidal assemblies of amphiphilic molecules, which can form micelles with a size of 100 nm or smaller (Trautwein et al., 2003). Micellar systems have significant advantages as effective delivery systems, for example, they have very small particle size, and usually thermodynamically stable (Boyd, 2008). Therefore, micelles were well investigated for the solubilization, encapsulation efficiency, loading capacity and targeted delivery of hydrophobic drugs (Oerlemans et al., 2010). Zhao et al. (2011) developed quercetin-loaded mixed micelles as delivery systems for quercetin, which were composed of Pluronic P 123 and D-α-tocopheryl polyethyleneglycol succinate (TPGS) at the ratio of 7:3. Zhou and Wang (2015) studied the interactions between quercetin and sodium cholate (NaC), and confirmed that quercetin could strongly bind with NaC aggregates through hydrophobic forces. The binding constant of quercetin with NaC secondary micelles was found to be higher than that with NaC primary ones, which obviously enhanced the radical scavenging ability of quercetin.

7.5. Conjugates-based delivery carriers

Polyphenol can be incorporated into the backbone of the polymer matrix, which allowed a slow release of the guest polyphenol (Wattamwar et al., 2012). A single-phase reaction-precipitation method was developed to formulate quercetin conjugated poly (β-amino esters) nanogels, which had a quercetin loading of 25–38 wt %. Quercetin in the conjugate presented a consistent release over 45–48 h, and its antioxidant activity was retained over the extended period (Gupta, Authimoolam, Hilt, & Dziubla, 2015). Du, Liu, Yang, and Zhai (2015) developed GA (glycyrrhetinic acid) -CMCA (O-carboxymethylated chitosan + cholic acid) conjugates for the delivery of quercetin, and they testified that quercetin-GA-CMCA carrier could alter the *in vitro* release pattern of quercetin, enhance cell apoptosis rate and prolong quercetin circulation time in rats. The bioactivity of quercetin could be improved when it was conjugated with a hydrolysable pivaloxymethyl (POM) group. Quercetin-POM conjugate could enhance the multidrug resistance modulating effect of quercetin (Kim et al., 2015).

7.6. Other types of delivery systems

It was reported that hydrogels and hyper-branched polymers could be used to improve the solubility of quercetin (Althans, Schrader, & Enders, 2014). Quercetin-loaded maltodextrin films were also confirmed to be able to enhance the oral bioavailability of quercetin (Lai et al., 2015). Quercetin nanocapsules, formed by emulsion-diffusion-evaporation method, were demonstrated to notably reduce arsenic-induced oxidative damage in liver and brain tissues than unformulated free quercetin (Ghosh, Mandal, Sarkar, Panda, & Das, 2009). In another study, the anti-tumorigenic activity of quercetin was significantly enhanced when encapsulated in lecithin-based cationic nanocarrier (Leciplex). The growth of mice (C57BL/6) tumor from subcutaneously injected B16F10 melanoma cells was more effectively suppressed by quercetin leciplex than that by quercetin suspension since the least tumor volumes were observed in all measurements (Date et al., 2011). Guazelli et al. (2013) compared the efficacy of microencapsulated quercetin with its suspension, and found that the microencapsulated quercetin reduced the oxidative damage, and prevented the inflammatory progress and microscopic damage score in the mice model.

8. Conclusions and future trends

Quercetin is widely present in the human's daily diet. Therefore, it is important to clearly understand the effects of quercetin on human health. From studies performed so far, it has been proven that quercetin is an excellent antioxidant, and it has anti-inflammatory, anti-cancer and anti-cardiovascular disease effects. Interestingly, the anti-inflammatory effect of quercetin seems to be linked with its antioxidant activity. This indicates that the supplementation of quercetin might become a potential alternative to the treatments of diseases induced by inflammation and oxidative stress, e.g. sarcoidosis.

Oxidation was reported as the main cause of changes in quercetin during food production and storage. Avoiding high oxygen exposure, high temperature and alkaline conditions during processing and storage is important to minimize the degradation of quercetin. Toxicity problems of quercetin arise particularly in the case of the formation of oxidation products namely quercetin-quinone, which has high reactivity with sulfydryl. Therefore, it could influence the function of several critical enzymes in human body (e.g. coenzyme A) in the human metabolic process. As a result, quercetin supplementation should be taken with caution because of its potential toxicity. In addition, the biological activities, stability and potential toxicity of quercetin are largely dependent on its transformation during the absorption and metabolism in GIT, which includes *O*-methylation, sulfation and glucuronidation.

In order to improve water solubility, chemical stability and bioavailability of quercetin, different types of delivery systems were introduced in this review, including lipid-based carriers, polymer nanoparticles, inclusion complexes, micelles and conjugates-based delivery systems. Each delivery system has its own advantages and shortcomings, and the specific selection should be based on the application fields. On the basis of the current review, the future development of novel delivery systems for quercetin should focus on the following three aspects: (i) development of natural food-grade ingredients as the main compositions of delivery systems for quercetin to obtain a higher encapsulation and retention efficiencies; (ii) the investigation into interactions between food matrix and encapsulated quercetin; (iii) the potential application of co-encapsulation, where two or more bioactive ingredients may be combined to generate a synergistic effect.

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A list of abbreviations

BSA	bovine serum albumin
CA	cholic acid
CD	cyclodextrins
CMCA	O-carboxymethylated chitosan (OCMC) hydrophobically modified with cholic acid (CA)
CMC-Na	sodium carboxymethyl cellulose
CSO-LA/β-lg	chitosan oligosaccharide/β-lactoglobulin
GA	glycyrrhetinic acid
GIT	gastrointestinal tract
GSH	glutathione
GSQ	qlutathionyl-quercetin
HP-βCD	hydroxypropyl-β-cyclodextrin
IL	interleukin
LA	linoleic acid
LPS	lipopolysaccharide
NaC	sodium cholate
NEs	nanoemulsions
NH2-MSN	aminopropyl functionalized mesoporous silica nanoparticles
NLCs	nanostructure lipid carriers
NPs	nanoparticles
NF-κB	nuclear factor-κ-gene binding
OCMC	O-carboxymethylated chitosan
PCL	poly (caprolactone)
PEG2000-DSPE	polyethyleneglycol-2000-distearoyl phosphatidyl ethanolamine
PEG-DSPE-quercetin-NLs	quercetin-loaded nanoliposomes composed of polyethyleneglycol-2000-distearoyl phosphatidyl ethanolamine
PLA	poly lactide
PLGA	poly lactide co-glycolide
POM	pivaloxymethyl
SBE-βCD	sulfobutyl ether-β-cyclodextrin
SLNs	solid lipid nanoparticles
TPGS	D-α-tocopheryl polyethyleneglycol succinate
TNF	tumor necrosis factor; βCD, β-cyclodextrin

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