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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).