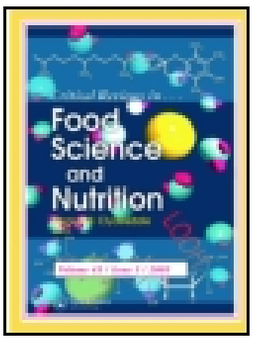

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CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
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REVIEW

Design and optimization of quercetin-based functional foods

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ABSTRACT

Quercetin is a flavonoid present in a wide variety of plant resources. Over the years, extensive efforts have been devoted to examining the potential biological effects of quercetin and to manipulating the chemical and physical properties of the flavonoid. However, limited studies have reviewed the opportunities and challenges of using quercetin in the development of functional foods. To address this necessity, in this review; we foremost present an overview of the chemical properties and stability of quercetin in food products followed by a detailed discussion of various strategies that enhance its oral bioavailability. We further highlight the areas to be practically considered during development of quercetin-based functional foods. By revisiting the current status of applied research on quercetin, it is anticipated that useful insights enabling research on quercetin can be potentially translated into practical applications in food product development.

KEYWORDS

Quercetin; flavonoids; health promotion; bioavailability; food development; bioactive agent delivery

Introduction

The development of functional foods has attracted heightened interest from the academic and industrial sectors, owing to the potential of functional foods in decreasing morbidity and mortality as well as increasing the quality of life of the public beyond the mere provision of essential nutrients. Among the different bioactive compounds with potential application in the supplementation or fortification during food production, flavonoids are one of the compounds that have garnered extensive interest. Flavonoids agents are heterocyclic natural compounds that, according to their structure, can be subdivided into flavonols, flavones, flavanones, isoflavones, flavan-3-ols, and anthocyanidins (Figure 1) (Goniotaki et al. 2004). Flavonoids play important roles in plant physiology by not only controlling the level of auxins to regulate plant growth and differentiation (Formica and Regelson 1995) but also serving as coloring agents that inhibit or stimulate insect feeding and hence the process of pollination (Formica and Regelson 1995). Flavonoids are also responsible for the texture and taste of edible plants, and function as antifeedants because of their unpleasant organoleptic characteristics and thus prevent ruminant animals from foraging (Formica and Regelson 1995). From a health perspective, flavonoids display various biological properties, including anti-inflammatory, antimicrobial, and anti-tumor properties (Narayana et al. 2001). Such properties are attributed to the ability of flavonoids to scavenge free radicals and interact with biological membranes (Saija et al. 1995a, 1995b). Among the different flavonoids, quercetin has received much attention for its nutraceutical and pharmaceutical applications (Formica and Regelson 1995). Quercetin is one among >4,000 naturally occurring plant phenolics, whose isolation was first documented in the late 1930s (Bentsáth, Rusznyák, and Szent-Györgyi 1936). According to the functional class assigned by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), quercetin is supposed to serve only as a coloring agent (World Health Organization 2019). However, it has been reported to have diverse biological effects, including its inhibitory action on the growth of various cancer cell lines in vitro (Middleton, Kandaswami, and Theoharides 2000) and its ability to activate AMP-activated protein kinase (AMPK) to ameliorate cognitive defects (Wang et al. 2014). More recently, the methanol leaf extract of *Erica multiflora*, in which quercetin-3-O-glucoside serves as a major compound, has been reported to modulate the metabolic and inflammatory pathways, alleviating high-fat and high-fructose diet-induced fatty liver disease in Wistar rats (Khlifi et al. 2020). Prominently, quercetin has the potential to promote oral health (Angellotti et al. 2020), partly by inhibiting the virulence of *Porphyromas gingivalis* to control the onset and progression of periodontal disease (He et al. 2020). Quercetin, therefore, has the potential to serve as a bioactive additive in a food product.

Regarding the health-promoting potential of quercetin and its possible use in functional food development, extensive efforts have been made to translate the benefits of this flavonoid from research into industrial practice in the context of nutrition. One example is quercetin-enriched cereal bars (containing 93.3% quercetin aglycone plus 6.7% quercetin-4-glucoside), which have been generated as functional food products to enhance the bioavailability of quercetin.

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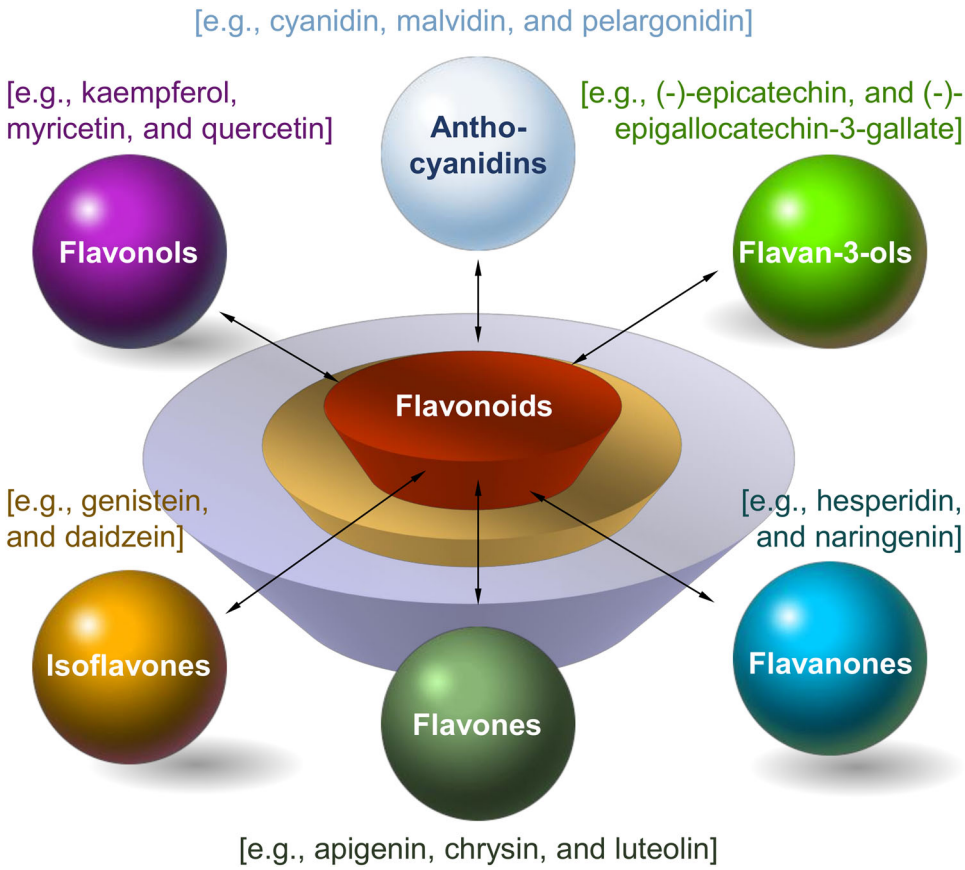

Figure 1. Sub-classes of flavonoids and representative examples in each subclass.

Compared to the oral consumption of quercetin powder-filled hard capsules (containing 100% quercetin aglycone), consumption of these cereal bars has been found to lead to a remarkably higher systemic availability of quercetin (Egert et al. 2012). Apart from cereal bars, quercetin has been used to enrich steamed bread to generate bread that displays an inhibitory effect against fluorescent advanced glycation end-products (AGEs) (Lin et al. 2018). Similar antioxidant effects have been observed in spreadable processed cheese (Přikryl et al. 2018) and bulk fish oil (Huber, Rupasinghe, and Shahidi 2009) upon the addition of quercetin. These results have verified the practicality of using quercetin as a functional food additive. Moreover, the health-promoting effects of quercetin are, indeed, a much-discussed topic in research and have already been extensively reviewed in literature (Russo et al. 2012, Khan et al. 2019, Gormaz, Quintremil, and Rodrigo 2015, Rather and Bhagat 2020, Kobylińska and Janas 2015). To avoid repeating the efforts to review the biochemistry and biological activity of quercetin, in this review; we aim to focus our discussions on the potential use of quercetin in food development and further streamline the design and optimization of quercetin-based functional foods.

Chemical properties and stability of quercetin in food products

There are five hydroxyl groups in quercetin, which has a flavonoid structure with two benzene rings (A and B) connected to an oxygen-containing pyrene ring (C) (Fig. 2). Glycoside structure is a frequent form of quercetin. Various types of sugar groups occupy one or more of these hydroxyl groups. Quercetin O-glycosides are the major derivatives of quercetin. In general, quercetin and its related derivatives commonly appear as yellow powder or crystals exhibiting poor aqueous solubility (Table 1) (National Center for Biotechnology Information 2021, FooDB 2021). Quercetin O-glycosides, a derivative of quercetin, have more than one O-glycosidic bond; they are commonly found in many fruits, vegetables, and food items (Table 2) (FooDB 2021). The glycosylation site of quercetin O-glycosides is generally located at the C-3 carbon. Quercetin 3-O-glucoside is found in plants such as beans (Chang and Wong 2004), salvia (Esmaeili and Sonboli 2010), and buckwheat (Kalinova and Vrchotova 2009); quercetin 3-O-galactoside is found in lingonberry (Heyman et al. 2014) and plum (Kim et al. 2003); and quercetin 3-O-xyloside is found in mango fruit (Masibo and He 2008). Quercetin derivatives in the form of disaccharides also exist widely in plants and vegetables. For instance, a large amount of rutin (quercetin 3-O-rhamnosylglucoside) has been found in cherries (Goncalves et al. 2004), spinaches (Kuti and Konuru 2004), grapes (Iacopini et al. 2008) and prunes (Gallaher and Gallaher 2008). In addition, quercetin 3-O-glycoside has been reported to contain three, four, or more saccharide groups (Williams and Grayer 2004). The hydroxyl groups at C-7 and C-4 can serve as glycosylation sites in quercetin derivatives, too. For example, quercetin 7-O-glucoside has a

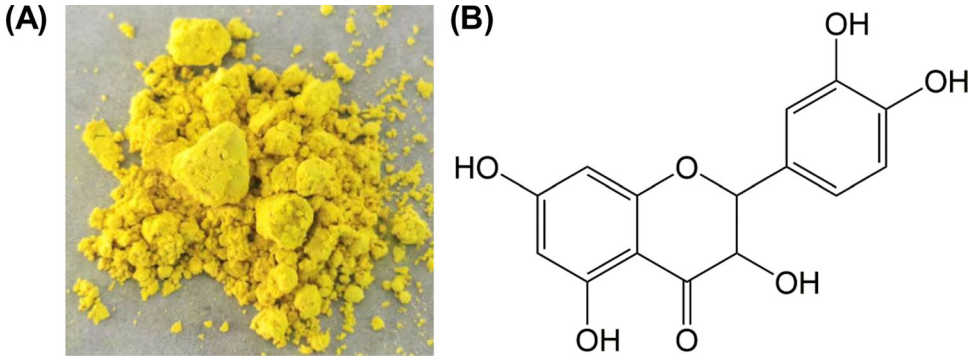

Figure 2. (A) A photo of quercetin powder and (B) the chemical structure of quercetin.

Table 1. Some of the basic information about quercetin.

Aspect	Information
IUPAC name	2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one
Synonym	2-(3,4-dihydroxy-phenyl)-3,5,7-trihydroxy-chromen-4-one; 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-1-benzopyran-4-one; 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-benzopyran-4-one; 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one; 2-(3,4-dihydroxyphenyl); 3,5,7-trihydroxychromen-4-one; 3′,4′,5,7-tetrahydroxyflavan-3-ol; 3′,4′,5,7; tetrahydroxyflavonol; 3′-hydroxykaempferol; 3,3′,4′,5,7-pentahydroxyflavone; 3,5,7,3′,4′-pentahydroxyflavone; 3,5,7-trihydroxy-2-(3,4-dihydroxyphenyl)-4H-chromen-4-on; 3,5,7; trihydroxy-2-(3,4-dihydroxyphenyl)-4H-chromen-4-one; 3′-hydroxykaempferol; dikvertin; flavin meletin; meletin; quercetin; quercetin dehydrate; quercetine; quercetol; quercitin; quertin; quertine; sophoretin; xanthaurine
Appearance	Yellow powder
Molecular formula	$C_{15}H_{10}O_7$
Average molecular weight	302.2357 g mol^{-1}
Monoisotopic molecular weight	302.042652674 g mol^{-1}
Hydrogen bond donor count	5
Hydrogen bond acceptor count	7
Water solubility	60 mg/L (at 16 °C)
Rotatable bond count	1
Refractivity	76.86 $m^3 \cdot mol^{-1}$
Polarizability	28.54 $Å^3$
Melting point	316.5 °C
JECFA functional class	Color
Flavor	Bitter

Data shown in the table are retrieved from (National Center for Biotechnology Information 2021) and (FooDB 2021).

glycosylation site at C-7 carbon (Chang and Wong 2004). However, quercetin derivatives with the glycosylation site at C-4 are only found in onion (Price, Bacon, and Rhodes 1997).

Industrially, quercetin receives the U.S. Food and Drug Administration (FDA) designation of "Generally Recognized as Safe (GRAS)" and hence is exempted from the Federal Food, Drug, and Cosmetic Act (FFDCA) food additive tolerance requirements. It is intended to be used as an ingredient in food items (including beverages and beverage bases, grain products and pastas, processed fruits and fruit juices, and soft candies) at levels of up to 500 mg per serving (U.S. Food and Drug Administration 2021). During food processing and storage, diverse chemical reactions (e.g. oxidation) occur in quercetin. In general, the chemical stability of quercetin can be affected by the oxygen concentration, pH, temperature, concentrations of other antioxidants, and the presence of metal ions. Upon oxidation, various oxidation products of quercetin, known as quercetin-quinones, can be generated; they contain one ortho-quinone and three quinone methides. The reactivity of quercetin-quinones with mercaptans is high, leading to an almost instant reaction between quercetin-quinones and glutathione (GSH)—which is the most abundant endogenous mercaptan (Pocernich and Butterfield 2012, Awad et al. 2002). Quercetin-quinone, at a low GSH concentration, can react with protein sulfhydryls (protein-SH), forming protein-quercetin adducts resulting in glutathionyl-quercetin (GSQ) (Boots et al. 2005). The chemical instability of GSQ leads to the dissociation into quercetin-quinones and GSH. Furthermore, quercetin is highly reactive in organic solutions (e.g. acetonitrile and methanol) at pH $>$ 7 (Moon et al. 2008, Buchner et al. 2006). Under alkaline conditions, the degradation rate of quercetin is remarkably higher than that in acidic and neutral environment (Moon et al. 2008, Buchner et al. 2006). The stability of quercetin is also influenced by the storage temperature (Moon et al. 2008, Buchner et al. 2006). A 70% loss of quercetin in *Phaseolus vulgaris* L. beans occurs upon boiling at atmospheric pressure (100 °C, 50 min) or at high pressure (121 °C, 10 min) (Ranilla, Genovese, and Lajolo 2009). A decline in the quercetin content (around 17%) in grapefruit juice occurs upon conventional pasteurization treatment

Table 2. Amount of quercetin in common food items.

Item	Average amount	Item	Average amount
Acerola	4.740 mg/100 g	Italian oregano	7.300 mg/100 g
Alfalfa	1.700 mg/100 g	Italian sweet red pepper	0.04820 mg/100 g
Allium	14.433 mg/100 g	Japanese pumpkin	0.32505 mg/100 g
Almond	0.12893 mg/100 g	Jujube	1.260 mg/100 g
Amaranth	0.88000 mg/100 g	Jute	23.530 mg/100 g
American cranberry	12.225 mg/100 g	Kai-lan	0.06500 mg/100 g
Angelica	41.529 mg/100 g	Kale	2.285 mg/100 g
Apple	3.157 mg/100 g	Kiwi	0.01333 mg/100 g
Apricot	1.006 mg/100 g	Kohlrabi	0.93333 mg/100 g
Arabica coffee	0.02500 mg/100 g	Lemon	0.39444 mg/100 g
Arctic blackberry	6.100 mg/100 g	Lettuce	6.669 mg/100 g
Asparagus	9.713 mg/100 g	Lime	0.40000 mg/100 g
Banana	0.01500 mg/100 g	Lingonberry	7.418 mg/100 g
Beer	0.85285 mg/100 g	Lovage	170.000 mg/100 g
Berry wine	0.49083 mg/100 g	Lowbush blueberry	6.700 mg/100 g
Bilberry	1.861 mg/100 g	Mandarin orange	0.07250 mg/100 g
Black cabbage	2.570 mg/100 g	Mexican oregano	42.000 mg/100 g
Black chokeberry	40.818 mg/100 g	Muskmelon	0.00333 mg/100 g
Black crowberry	4.927 mg/100 g	Napa cabbage	0.04000 mg/100 g
Black elderberry	42.000 mg/100 g	Nectarine	0.38000 mg/100 g
Black huckleberry	5.773 mg/100 g	New Zealand spinach	5.750 mg/100 g
Black mulberry	2.470 mg/100 g	Oat	31.000 mg/100 g
Blackcurrant	6.258 mg/100 g	Oval-leaf huckleberry	4.490 mg/100 g
Bog bilberry	17.364 mg/100 g	Pak choy	39.000 mg/100 g
Broad bean	1.517 mg/100 g	Parsley	0.28250 mg/100 g
Broccoli	2.035 mg/100 g	Parsnip	0.83812 mg/100 g
Brussel sprouts	2.263 mg/100 g	Pear	1.021 mg/100 g
Cabbage	5.100 mg/100 g	Pepper	8.819 mg/100 g
Capers	146.405 mg/100 g	Pepper (*C. frutescens*)	6.300 mg/100 g
Carrot	0.17365 mg/100 g	Pepper (Capsicum)	0.30000 mg/100 g
Cascade huckleberry	3.410 mg/100 g	Persian lime	0.45500 mg/100 g
Cashew nut	0.42333 mg/100 g	Pineapple	0.03500 mg/100 g
Cauliflower	0.49900 mg/100 g	Pistachio	0.94078 mg/100 g
Celeriac	0.18000 mg/100 g	Pitanga	5.800 mg/100 g
Cherry tomato	2.440 mg/100 g	Pomegranate	0.34012 mg/100 g
Chia	18.420 mg/100 g	Poppy	26.300 mg/100 g
Chinese cabbage	0.79000 mg/100 g	Potato	0.74214 mg/100 g
Chinese chives	0.16000 mg/100 g	Prickly pear	4.860 mg/100 g
Chinese mustard	8.800 mg/100 g	Prunus	6.040 mg/100 g
Chives	2.998 mg/100 g	Pummelo	0.24500 mg/100 g
Chocolate	25.000 mg/100 g	Purslane	0.39000 mg/100 g
Cloudberry	0.58500 mg/100 g	Rabbiteye blueberry	4.985 mg/100 g
Cloves	28.400 mg/100 g	Radish	35.185 mg/100 g
Cocoa powder	5.133 mg/100 g	Rapini	1.650 mg/100 g
Common bean	1.854 mg/100 g	Red beetroot	0.13400 mg/100 g
Common beet	0.13000 mg/100 g	Red huckleberry	0.93333 mg/100 g
Common buckwheat	6.841 mg/100 g	Red raspberry	0.98157 mg/100 g
Common cabbage	2.543 mg/100 g	Redcurrant	0.98200 mg/100 g
Common grape	1.008 mg/100 g	Robusta coffee	0.02500 mg/100 g
Common oregano	14.000 mg/100 g	Rocket salad (ssp.)	37.055 mg/100 g
Common pea	0.07600 mg/100 g	Romaine lettuce	0.08705 mg/100 g
Coriander	19.467 mg/100 g	Rowanberry	6.850 mg/100 g
Cowpea	11.360 mg/100 g	Saskatoon berry	16.640 mg/100 g
Cucumber	0.17144 mg/100 g	Savoy cabbage	0.24000 mg/100 g
Cucurbita	0.28250 mg/100 g	Sea-buckthorn berry	4.593 mg/100 g
Date	0.46500 mg/100 g	Shallot	2.000 mg/100 g
Dill	25.231 mg/100 g	Sherry	0.01250 mg/100 g
Dock	86.200 mg/100 g	Soft-necked garlic	20.000 mg/100 g
Eggplant	0.01343 mg/100 g	Sour cherry	3.810 mg/100 g
Elderberry	26.770 mg/100 g	Spinach	2.935 mg/100 g
European cranberry	8.454 mg/100 g	Strawberry	0.57466 mg/100 g
European plum	0.96118 mg/100 g	Swamp cabbage	1.650 mg/100 g
Evergreen huckleberry	8.410 mg/100 g	Swede	0.06500 mg/100 g
Fennel	24.857 mg/100 g	Sweet bay	1.595 mg/100 g
Fenugreek	0.78195 mg/100 g	Sweet cherry	1.705 mg/100 g
Fig	2.735 mg/100 g	Sweet orange	0.28861 mg/100 g
Garden onion	2405.000 mg/100 g	Sweet rowanberry	8.500 mg/100 g
Garden tomato	0.81587 mg/100 g	Swiss chard	2.943 mg/100 g
Garlic	0.59763 mg/100 g	Taro	0.78250 mg/100 g
Ginger	0.06333 mg/100 g	Tarragon	10.000 mg/100 g
Gooseberry	1.229 mg/100 g	Towel gourd	0.03000 mg/100 g
Grape	1.433 mg/100 g	Turmeric	7.085 mg/100 g
Grape wine	0.59542 mg/100 g	Turnip	0.31889 mg/100 g
Grapefruit	0.27783 mg/100 g	Vinegar	0.34495 mg/100 g

(*continued*)

Table 2. Continued.

Item	Average amount	Item	Average amount
Green bean	1.906 mg/100 g	Watercress	11.540 mg/100 g
Green bell pepper	1.316 mg/100 g	White cabbage	2.840 mg/100 g
Green zucchini	0.02415 mg/100 g	Wild leek	0.09000 mg/100 g
Half-highbush blueberry	10.247 mg/100 g	Yam	0.08333 mg/100 g
Highbush blueberry	9.312 mg/100 g	Yardlong bean	5.300 mg/100 g
Honey	0.31000 mg/100 g	Yellow bell pepper	0.23413 mg/100 g
Horseradish	0.28250 mg/100 g	Yellow wax bean	0.30841 mg/100 g

Data shown in the table are retrieved from (FooDB 2021).

(80 °C, 91 s) (Igual et al. 2011). Storage time also affects the stability of quercetin. Storing onion at 4 °C in darkness for 24 weeks causes a 100% drop in the quercetin content (Price, Bacon, and Rhodes 1997). After placing strawberry juice at 4 °C in darkness for 56 days, quercetin was also found to be reduced by 46.1% (Odriozola-Serrano, Soliva-Fortuny, and Martin-Belloso 2008). A 40% loss of quercetin conjugate in raspberry jam occurs after storing the jam in darkness at 20 °C for 180 days (Zafrilla, Ferreres, and Tomas-Barberan 2001). The reaction between quercetin and metal ions produces quercetin-metal complexes, and the quercetin oxidation potential is altered by the binding of metal ions to quercetin (Ravichandran, Rajendran, and Devapiriam 2014); this was confirmed as the presence of Cu^{2+} (Pękal, Biesaga, and Pyrzynska 2011) and Cr^{3+} (Chen et al. 2009) increased the diphenylpicrylhydrazyl (DPPH) radical scavenging activity of quercetin. However, quercetin activity was suppressed by the presence of Sn^{2+} (Dehghan and Khoshkam 2012) and Cd^{2+} (Ravichandran, Rajendran, and Devapiriam 2014). Pękal et al. (2011) have pointed out the preference of metal ions to bind to the carbonyl oxygen and 3-OH group (in the C ring) of quercetin, leading to a reduction in the radical scavenging activity.

Functional foods as effective means of quercetin supplementation

Upon oral intake, quercetin released from the food interacts with salivary proteins to generate soluble quercetin-protein binary aggregates (Manach et al. 2004). The formation of binary aggregates does not affect the absorption efficiency of quercetin (Cai and Bennick 2006). In the stomach, owing to the highly acidic conditions, quercetin may be degraded to phenolic acids (e.g. protocatechuic acid) (Weldin et al. 2003), followed by the absorption of phenolic acids (Konishi, Zhao, and Shimizu 2006, Farrell et al. 2012). In the small intestine, quercetin can undergo glucuronidation under the action of uridine diphosphate glucuronosyl-transferases as well as O-methylation under the activity of catechol-O-methyltransferase. Furthermore, quercetin glycosides (e.g. quercetin glucosides and quercetin galactoside) in the small intestine can be deglycosylated to form quercetin by the action of microbiota-derived β-glucosidase (Nemeth et al. 2003). In addition to the small intestine, the metabolism of quercetin also occurs in the large intestine. For instance, *Clostridium orbiscindens* has been found to cause fission of the C-ring in quercetin (Aura 2008). It is worth noting that the efficiency of absorption of different quercetin glycosides in humans is largely determined by the glycosidic moiety of the quercetin glycoside (Arts et al. 2004). An earlier study has found that, via the sodium-dependent SGLUT1 transporter in the small intestine, quercetin-3-O-glucoside can pass through enterocytes (Wolffram, Blöck, and Ader 2002). Quercetin-3-O-glucoside can serve as a substrate for lactase phloridzin hydrolase (LPH), which on one hand catalyzes the deglycosylation and; on the other hand, enables aglycone to get through enterocytes via passive diffusion (Day et al. 2003). Upon absorption, quercetin and its derivatives are subjected to glucuronidation, methylation, and/or sulfation in the small intestine, colon, liver, and kidney (Mullen, Edwards, and Crozier 2006, Spencer 2003, Murota and Terao 2005). Finally, quercetin can be decomposed into CO_2 and phenolic acids upon bacterial ring fission and is excreted via feces and exhalation (Guo and Bruno 2015, Abrahamse, Kloots, and van Amelsvoort 2005). CO_2, urine, or feces account for the excretion of 52.1%, 4.6%, and 1.9%, respectively, of absorbed quercetin in humans upon oral intake of quercetin (Walle, Walle, and Halushka 2001).

To ensure the attainment of the health-promoting effect of quercetin from food sources, achieving a plasma concentration of quercetin above the effective level is required. In general, shortly after the consumption of quercetin-rich foods, the overall plasma concentrations of free and conjugated quercetin, as well as its metabolites, have been found to range from 72 to 193 nmol/L in a human body (Petersen et al. 2016, Nguyen et al. 2015). However, such concentration of quercetin in plasma cannot effectively inhibit cancerous cells (Dajas 2012) and is also much lower than the dose used in clinical trials for tackling various pathological conditions (Table 3). Considering the low bioavailability of quercetin after oral administration owing partly to its rapid metabolism (Manach et al. 1998), practical application of quercetin, even as a nutraceutical, for health promotion remains a challenge (de Boer et al. 2005). This hindrance may be partially overcome by increasing the dose of quercetin; however, if we rely only on an increase in the administered dose to offset the low oral bioavailability of quercetin, the effective dose needed to exert the health-promoting effect may have to be unreasonably high.

Another strategy to solve this problem is to formulate quercetin as a functional food. This approach has two advantages. First, once quercetin is formulated into appetizing and savory food products, it will be easier to attain higher compliance for long-term quercetin intake. Such long-term intake is essential for attaining a therapeutic plasma concentration. The effect of long-term intake on the plasma concentration of quercetin has been partially

Table 3. Some clinical studies supporting the health benefits of oral intake of quercetin and its derivatives.

Disease	Study design	Subject gender	Results	Ref.
Hyperuricemia	Randomized, double-blind, placebo-controlled, crossover study	Male	Oral intake of quercetin at a dose of 500 mg/day has been found to lead to a decline in the concentration of uric acid in the plasma.	Shi and Williamson 2016
Polycystic ovary syndrome	Randomized, double-blind, placebo-controlled parallel study	Female	Oral intake of quercetin at a dose of 1 g/day has been reported to lead to a decline in the plasma concentrations of adiponectin, testosterone, luteinizing hormone, and insulin in female subjects suffering from polycystic ovary syndrome.	Rezvan et al. 2017
Obesity	Randomized, double-blind, placebo-controlled parallel study	Male and female	Oral intake of the onion peel extract (with the ultimate dose of quercetin being 100 mg/day) has been found to reduce body weight in overweight or obese human subjects.	Lee et al. 2016
Rheumatoid arthritis and other inflammatory conditions	Randomized, double-blind, placebo-controlled study	Female	Oral intake of quercetin at a dose of 500 mg/day has been reported to reduce morning pain and postoperative pain in patients suffering from rheumatoid arthritis.	Javadi et al. 2017
	Randomized, double-blind, placebo-controlled study	Male	Oral intake of quercetin at a dose of 500 mg/day has been found to reduce the plasma C-reactive protein (CRP) level.	Askari et al. 2012
Cardiovascular disease	Randomized, double-blind, placebo-controlled, crossover study	Male and female	Oral intake of quercetin at a dose of 162 mg/day from onion skin extract powder has been found to lead to a significant decline in systolic blood pressure in hypertensive individuals.	Brüll et al. 2015
	Randomized, double-blind, placebo-controlled, single center, cross-over study	Male	Oral intake of quercetin dehydrate at a dose of 150 mg/day has been found to decrease postprandial systolic blood pressure, to increase the HDL-cholesterol concentration, and to cause a reduction in the waist circumference.	Pfeuffer et al. 2013
	Randomized, double-blind, placebo-controlled study	Female	Oral intake of quercetin at a dose of 500 mg/day has been found to decrease systolic blood pressure.	Zahedi et al. 2013

suggested by an earlier clinical study (Guo, Mah, and Bruno 2014), in which daily ingestion of 1095 mg of quercetin for 3 days has been found to lead to a total plasma quercetin concentration of 1430 nmol/L (Guo, Mah, and Bruno 2014). Oral administration of the *Hypericum perforatum* extract to rats for 9 days also enabled the plasma concentration of quercetin to be much higher than that attained by short-term quercetin intake from an ordinary diet (Paulke et al. 2008). Apart from the ease of attaining long-term intake, another advantage of formulating quercetin into food products is the ease of achieving repeated administration, which can ultimately enhance the oral bioavailability of quercetin. This has been revealed by the observation that, after oral administration of 600 mg/kg of *Ginkgo biloba* to rats, the plasma concentration of quercetin reached a mean value of 582 nmol/L; however, upon repeated administration of the same dose, a 4.6-fold increase in the plasma concentration of quercetin was observed (Rangel-Ordonez et al. 2010). The increase in the bioavailability of orally administered quercetin upon repeated administration has been demonstrated in various studies (Rangel-Ordonez et al. 2010, Paulke et al. 2008, Guo, Mah, and Bruno 2014), although the accumulation of quercetin in the plasma does not occur even upon long-term intake of quercetin through diet (Bieger et al. 2008).

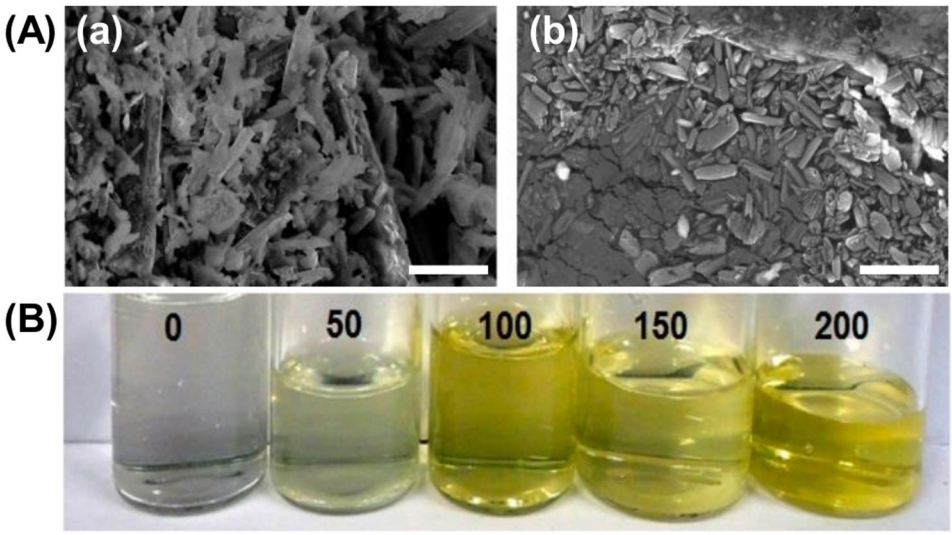

Figure 3. (A) SEM images of (a) pure quercetin and (b) a lyophilized HPH-treated quercetin nanosuspension. HPH was performed at 150 MPa for 20 cycles at 25 °C. Scale bar = 5 μm. (B) Aqueous solubility of a HPH-treated quercetin nanosuspension in water at different pressures at 25 °C for 20 cycles. The insoluble part of quercetin was removed by ultracentrifugation. Reproduced from (Karadag, Ozcelik, and Huang 2014) with permission from American Chemical Society.

Design of carriers for use in quercetin-based functional foods

Although formulation into functional foods can be a potentially favorable strategy to enhance the overall intake of quercetin, partly via the enhancement of oral bioavailability by the effect of long-term intake and by the effect of repeated administration; manipulating the pharmacokinetic profile of quercetin (or its derivatives) *per se* may further enhance the resultant oral bioavailability and can be achieved through physical or chemical modifications. Such feasibility has been verified by Sahoo et al. (2011), who applied high-pressure homogenization (HPH) to generate nanocrystals from conventional quercetin powder to enhance the dissolution rate of quercetin. Similar success in using HPH has been verified by a recent study, which has reported that HPH can, on the one hand, lead to the production of very fine suspensions and, on the other hand, cause a loss of crystallinity of quercetin (Fig. 3) (Karadag, Ozcelik, and Huang 2014), thereby enhancing the water dispersity, as predicted by the Ostwald-Freundlich theory (Muller and Peters 1998). Meanwhile, the synthesis of various derivatives of quercetin has also been reported to improve pharmacokinetic profiles (Mukherjee et al. 2019, Docampo-Palacios et al. 2020, Carullo et al. 2019, Bagavieva et al. 2019). However, these products need to be reevaluated as new compounds before human consumption, especially for efficiency and safety. An alternative method is to manipulate the properties of quercetin (or its derivatives) without changing the actual structure. Here, the importance of technologies for the delivery of bioactive agents becomes important. The possible role played by the delivery technologies has been supported by a previous study, in which liposomes have been adopted as carriers to enhance the oral bioavailability of quercetin (Priprem et al. 2008). More recently, using modified starch as an emulsifier, oil-in-water (O/W) emulsions have also been adopted as a delivery system to enhance the solubility of quercetin (Iqbal et al. 2020). Over the years, a large variety of delivery systems have been reported for improving the bioavailability and efficacy of quercetin (Fig. 4). These systems can be roughly classified into two types: lipid-based and polymer-based.

Lipid-based systems for oral delivery of quercetin

Lipids, as one of the major macronutrients and an important class of biological membrane constituents, have been widely exploited for the development of carriers to enhance the efficient oral delivery of quercetin. The potential of using lipid-based systems as quercetin carriers for oral administration has been demonstrated in an earlier study (Goniotaki et al. 2004), in which liposomes were generated from egg phosphatidylcholine (EPC) by using a thin-film hydration approach followed by sonication. Liposomes have been used as carriers of various flavonoids, including quercetin, rutin, isoscutellarein, and isoscutellarein diglycoside. The efficiency of the encapsulation of flavonoids into liposomes is known to be affected by the position of hydroxyl groups, as well as the presence and absence of a sugar moiety, on the flavonoid structure (Goniotaki et al. 2004). Because of the strong interactions between aglycones and EPC acyl chains, aglycones can interact more strongly with the lipophilic region of liposomes, leading to a greater encapsulation efficiency (Goniotaki et al. 2004). The biological activity of flavonoids can be affected by liposomal formulation to different extents. For instance, in SF268, MCF7, and H460 cells, the cytotoxicity of liposomal quercetin was found to be lower than that of free quercetin (Goniotaki et al. 2004), whereas in the case of isoscutellarein; the liposomal form has been shown to be more cytotoxic to these three cancer cell lines than that was free form (Goniotaki et al. 2004).

Cyclodextrins have been used to enhance the efficiency of liposome-encapsulated quercetin. This was revealed by the observation that upon complexation with cyclodextrins, the solubility of quercetin is enhanced (Azzi et al. 2018). In

Figure 4. Major roles played by carriers in improving the bioavailability and efficacy of quercetin.

addition, after complexing quercetin with cyclodextrins prior to encapsulation in liposomes, it was found to be more effectively protected from damage by UV irradiation (Azzi et al. 2018). Surface coating of liposomes has also been adapted to enhance the delivery efficiency of liposome-encapsulated quercetin. This has been demonstrated by Caddeo et al. (2016), who generated a hybrid system composed of liposomes coated with cross-linked chitosan to increase the bioavailability (and to optimize the release profile) of quercetin in the intestine. During preparation, cholesterol, quercetin, and various phosphatidylcholine-based phospholipids are first dispersed in PBS to generate negatively charged liposomes under sonication. The liposomes are then dispersed in a chitosan solution, followed by the addition of an aqueous solution of sodium tripolyphosphate for the formation of quercetin-loaded chitosan-coated liposomes. The size of the coated liposomes was estimated to be approximately 200 nm (Caddeo et al. 2016). Owing to the possibility of entrapping quercetin inside the polyelectrolyte shell, the quercetin encapsulation efficiency attained by the liposomes increased from approximately 55% to over 90% after the surface modification process (Caddeo et al. 2016). Along with their pH-release profiles, the coated liposomes have exhibited the potential for further exploitation in the oral delivery of quercetin for functional food development.

The composition of liposomes may also affect the properties and delivery performance of liposome-encapsulated quercetin. This has been demonstrated in an earlier study, in which three different types of phospholipids (unsaturated egg Lipoid E80, unsaturated soybean Lipoid S100, and saturated soybean Phospholipon 90H) were adopted to generate liposomes for quercetin microencapsulation (Azzi et al. 2018). Among all the liposomes tested, those generated from Lipoid E80 were found to have the smallest diameter, narrowest size distribution, and highest encapsulation efficiency of quercetin (Azzi et al. 2018). In addition, Lipoid E80-based liposomes were found to protect quercetin against UV irradiation (Azzi et al. 2018). This demonstrates the importance of a proper design of the liposome composition for optimized encapsulation and delivery of quercetin using liposomes. In addition to conventional liposomes, elastic liposomes have recently been employed for quercetin delivery. The concept of elastic liposomes was first introduced by Cevc and Blume (1992), who have generated liposomes with high deformability via association of phosphatidylcholine with sodium cholate or sodium deoxycholate. Compared to conventional liposomes, elastic liposomes can squeeze between cells despite their large vesicle size and show high adaptability (Gillet et al. 2009, Karande and Mitragotri 2009). To encapsulate quercetin and resveratrol into elastic

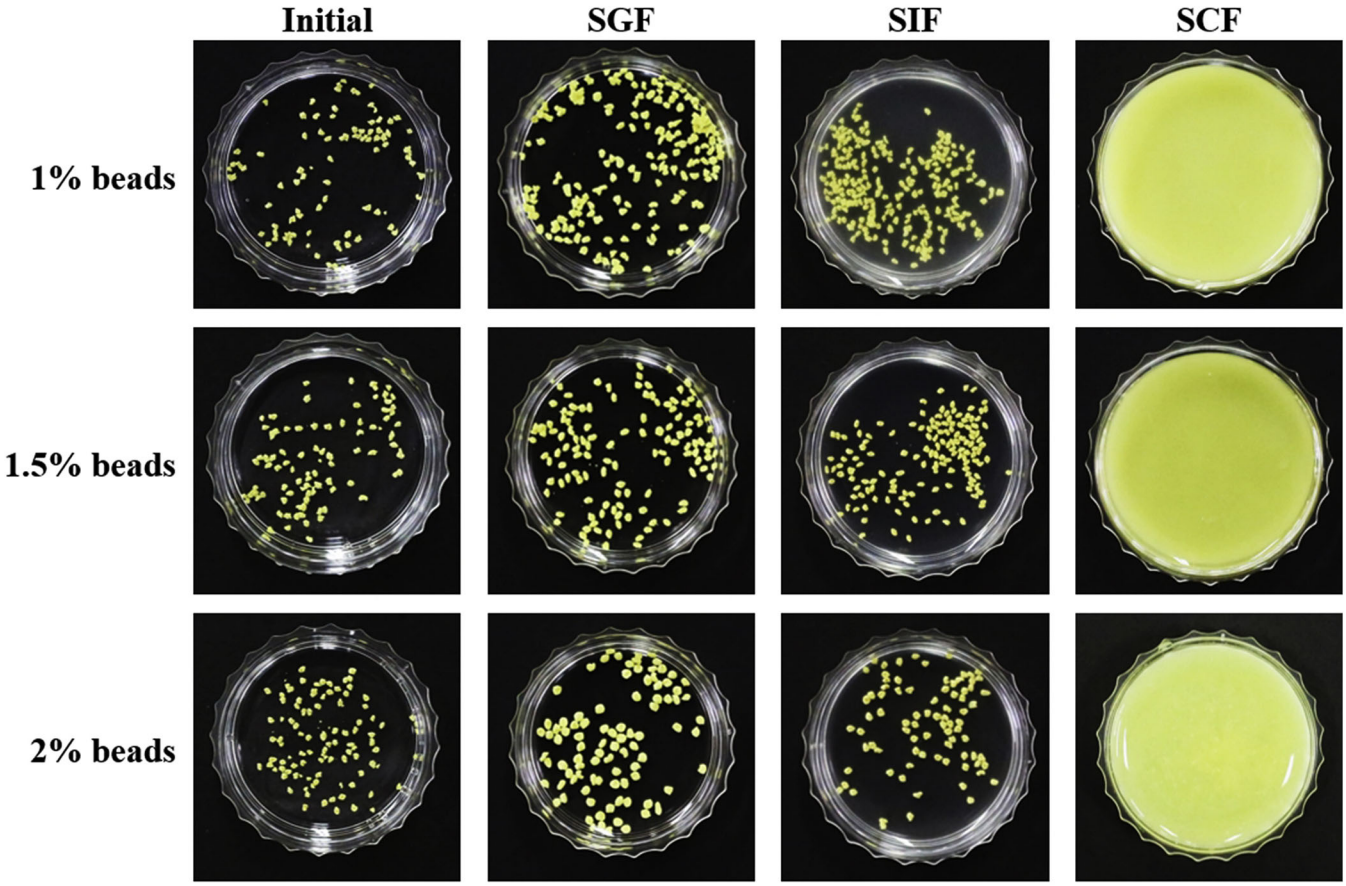

Figure 5. Images of hydrogel beads generated by using oligochitosan and different concentrations (1%, 1.5%, and 2%) of de-esterified pectin from yuzu (*Citrus junos*) peel. The images were taken in different locations of the simulated gastrointestinal tract. Abbreviation: SGF, simulated gastric fluid; SIF, simulated intestinal fluid; SCF, simulated colonic fluid. Reproduced from (Lee and Chang 2020) with permission from Elsevier B.V.

liposomes, the flavonoids are either entrapped inside the phospholipid bilayer (Cadena et al. 2013) or encapsulated in the aqueous phase of the liposomes as inclusion complexes with hydroxypropyl-β-cyclodextrin (Cadena et al. 2013). Recently, nanostructured lipid carriers loaded with quercetin have also been generated using the HPH approach (Ni et al. 2015). In a simulated beverage formulation (containing glucose, sodium benzoate, citric acid, and sodium citrate), although there was a remarkable increase in the particle size in the first 15 days, the size of the particles remained stable during the following two months (Ni et al. 2015). This reveals the high physical stability of the carriers for use in beverage formulations.

Polymer-based systems for oral delivery of quercetin

In addition to lipid-based systems, polymers have been widely used for the delivery of quercetin. In a previous study, hydrogel beads were generated from oligochitosan and yuzu peel pectin (YPP) for the oral delivery of quercetin in functional food development. During synthesis, YPP was first extracted from an alcohol-insoluble residue of yuzu peel powder under heating conditions (80 °C) in a shaking water bath (Lee and Chang 2020). After extraction, YPP was de-esterified by treatment with pectin methylesterase to generate low-methoxyl pectin which is more effective than that is the high-methoxyl counterpart for the preparation of hydrogel beads (Lee and Chang 2020). De-esterified YPP (DEYPP) was dissolved in water at different concentrations, followed by the addition of quercetin. Finally, the quercetin-containing DEYPP solution was dropped into a 1% (w/w) calcium chloride solution (pH 6) in which oligochitosan was present (Lee and Chang 2020). This led to the formation of hydrogel beads via both ionic crosslinking (between the $-COO^-$ of DEYPP and Ca^{2+}) and polyelectrolyte complexation (between the $-COO^-$ of DEYPP and the $-NH^{3+}$ of oligochitosan) (Lee and Chang 2020). Because both ionic crosslinking and polyelectrolyte complexation are stable in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF), the cumulative release of quercetin in these fluids has been found to be less than 1% (Lee and Chang 2020). Meanwhile, a slight increase in the mean particle diameter of the beads was observed (Fig. 5). This increase is due to the electrostatic repulsion of the protonated amine groups of oligochitosan in SGF and that of the deprotonated carboxyl groups of DEYPP in SIF. Moreover, upon exposure of the quercetin-loaded beads to simulated colonic fluid for 12 h, the mean particle diameter of the beads was substantially reduced due to hydrolysis of the beads caused by Pectinex Ultra SP-L. Accompanying this hydrolysis was the significant increase in the quercetin release rate, resulting in 65.37–99.54% of quercetin being released from the beads

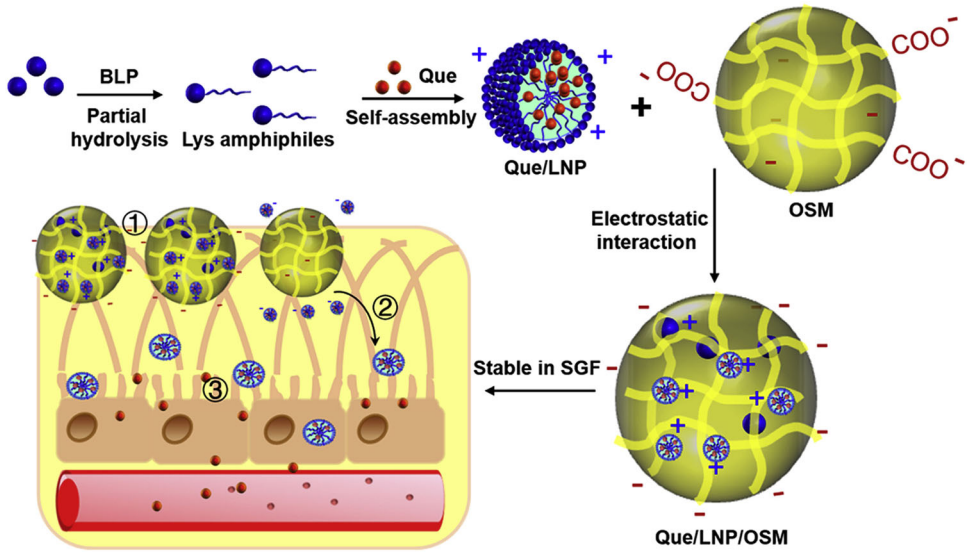

Figure 6. A schematic diagram depicting the generation, mucoadhesion, mucus penetration and responsive quercetin release of the intestine-responsive system. (1), (2), and (3) denote mucoadhesion, intestine-responsive release of quercetin-loaded nanoparticles, and mucus penetration, respectively. Abbreviation: BLP: *Bacillus licheniformis* protease; Que: quercetin; Lys: lysozyme; LNP: lysozyme-nanoparticles; OSM: oxidized starch microgels; SGF: stimulated gastric fluid. Reproduced from (Li et al. 2020a) with permission from Elsevier.

depending on the concentration of DEYPP used during bead fabrication (Lee and Chang 2020). This confirms the success in targeting quercetin delivery to the colonic region following oral intake.

With advances in the development of stimuli-responsive carriers, better control of quercetin release and absorption during the oral delivery process can be achieved. This is demonstrated by the recent development of an intestine-responsive system, which facilitates oral delivery and controlled release of quercetin (Fig. 6) (Li et al. 2020a). During microgel fabrication, nanoparticles, inside which quercetin is loaded, are first generated from the self-assembly of lysozyme amphiphiles, followed by electrostatic interactions between the nanoparticles and oxidized starch microgels (Li et al. 2020a). The microgels can protect the quercetin-loaded nanoparticles against acidic gastric conditions while enabling pH-responsive release of the nanoparticles in response to the intestinal conditions (Li et al. 2020a). The released nanoparticles can subsequently penetrate the mucus layer and be absorbed by the intestinal epithelium villi (Li et al. 2020a). Although the stability and use of the system have not yet been verified in food models, the capacity of the system to enhance the absorption of quercetin may warrant further exploitation of the system in functional food development. With advances in materials engineering, precise manipulation of systems for the delivery of quercetin has been made possible. Such success has been evidenced in the case of bacterial cellulose, which shows favorable properties (including high porosity, mechanical strength, chemical resistance, and biodegradability) and has been combined with molecular imprinting technology for sustained-release of quercetin (Jantarat et al. 2020). These advancements in microencapsulation and delivery of quercetin can potentially develop and enhance the bioavailability of quercetin-based functional foods.

Practical considerations for the development of quercetin-based functional foods

To translate the use of quercetin from concept to practice, several technical challenges must be overcome. One of these challenges is to elucidate the long-term safety of quercetin intake; this is particularly important because quercetin, upon oxidation, can generate quercetin-quinone (Fig. 7), which reacts with glutathione to form 6-glutathionyl quercetin and 8-glutathionyl quercetin. The formation of such adducts is so vigorous that ascorbate exhibits no inhibitory effect on the process (Boots et al. 2003, Awad et al. 2002, Galati et al. 2001), and these adducts are unstable, and at the end, quercetin-quinone may bind to other thiols, leading to an increase in membrane permeability or may even alter the activity of enzymes in which the availability of the thiol groups is vital for normal functioning (Yen et al. 2003, Boots, Haenen, and Bast 2008). Such adverse effects potentially led by quercetin have recently been known as the 'quercetin paradox' (Boots et al. 2007). Concerns regarding this paradox have been verified in lung cells (Boots et al. 2007), raising the awareness of the importance of considering the potential toxicity of metabolites formed by quercetin when it exerts its protective effect against oxidative stress. Although the apparent toxicity of quercetin-quinone has not yet been reported in in vivo and clinical contexts, a thorough evaluation of the safety of long-term intake, as well as the possible toxic effect of metabolites of quercetin in individuals with different physical conditions and daily doses of quercetin, is mandatory.

Another challenge that needs to be addressed before streamlining the development of quercetin-based functional foods is to determine the optimal dose of quercetin in food products. In fact, via fruit and vegetable consumption, the daily dose of ingested quercetin, on an average, by an ordinary person is approximately 15–40 mg. However, the actual ingested dose will vary significantly from one person to

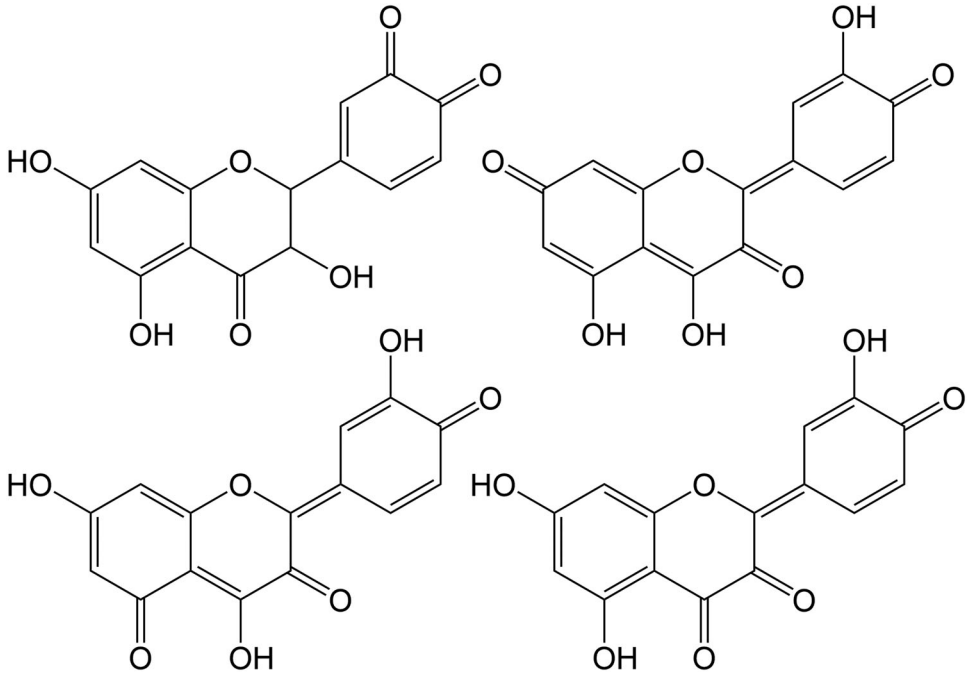

Figure 7. Chemical structures of the four tautomeric forms of quercetin-quinone formed upon oxidation of quercetin.

another due to the differences in their diet. This may partially explain why the daily dietary intake of quercetin varies substantially from country to country. In the US, 73–76% of the flavonoid intake (20–22 mg/d) has been found to be contributed by quercetin (Sampson et al. 2002); whereas in Japan and Germany, the quercetin intake has been estimated to be around 8.28 mg/d (Kimira et al. 1998) and 10.3 mg/d (Linseisen, Radtke, and Wolfram 1997), respectively. Furthermore, a higher dose of quercetin may be required by certain people, usually via the intake of quercetin in capsules (250 mg, 300 mg, and 500 mg) or tablets (50, 250, and 500 mg) for therapeutic purposes (e.g. allergy management and anti-inflammatory treatment) (Werbach 1993). Therefore, it is difficult to determine the optimal dose in functional foods to meet individual needs. This problem is further complicated if these foods are consumed by patients being administered other medications. Quercetin has already been found to alter the normal metabolic pathways for breaking down certain therapeutic agents, including felodipin (Miniscalco et al. 1992), estrogen (Schubert et al. 1994), cyclosporine (Choi, Choi, and Choi 2004), and digoxin (Hakkinen et al. 1999). This may lead to an expectedly high plasma concentration of the therapeutic agents, resulting in toxicity or other adverse drug reactions. Proper evaluation of the optimal daily intake of quercetin-based functional food products may have to be carried out for different groups of consumers.

As far as studies on the use of quercetin in functional foods are concerned, until now, most studies have been devoted to exploiting the physiological fate and biological effects of quercetin. The possible functional role of quercetin in food product development has been overlooked. The enrichment or fortification of quercetin may affect the nutritional content and sensory properties of food products; this has been demonstrated in a recent study (Li et al. 2020b), in which the effect of quercetin on the chemical profile of beef soup during stewing was investigated. Quercetin has been found to increase the quantity of unsaturated fatty acids and solid matter, decrease the content of methionine and total sugar, and increase the zinc content of the beef soup (Li et al. 2020b). The possible effect exerted by quercetin on liquid foods has been further confirmed by the observation that quercetin may help stabilize emulsions upon complexation with certain proteins (Han et al. 2021). One example of these proteins is found in black bean protein (BBP), whose aqueous solution was mixed with an ethanol solution of quercetin at different volumetric ratios to generate a series of BBP-quercetin nanocomplexes (Han et al. 2021). Compared with the oil-in-water (O/W) emulsion stabilized by using BBP alone, the emulsion stabilized by BBP-quercetin nanocomplexes was found to show smaller droplet size and lower viscosity (Han et al. 2021). In fact, O/W emulsions have been reported as possible delivery systems for functional oils or lipophilic active substances to enhance their bioavailability and enable controlled release (Adjonu et al. 2014). However, the addition of a substantial amount of a surfactant is usually involved in the preparation of O/W emulsions. The health concerns regarding long-term exposure to synthetic surfactants have impeded the wide application of such emulsions in food product development (He et al. 2011).

In addition to liquid foods, quercetin may affect the physical properties of solid foods. This has been evidenced by the effect of quercetin fortification on extending the development time of the dough (Lin and Zhou 2018). Such an effect is partially attributed to interactions of quercetin with gluten, leading to a slower rate of protein hydration and hence influencing the aggregation behavior of high-molecular-weight proteins in the flour (Miś et al. 2012). Quercetin can also serve as a reducing agent to impair the

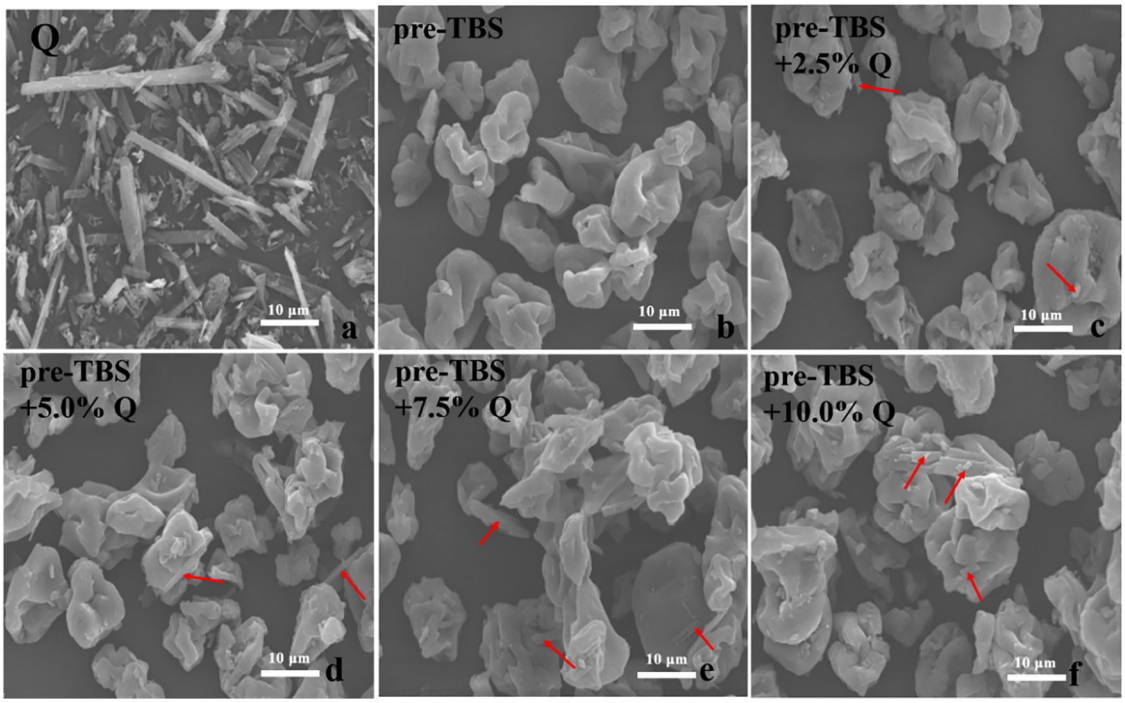

Figure 8. SEM images of (a) quercetin, (b) pre-TBS, as well as the complexes formed with different concentrations of quercetin: (c) 2.5%, (d) 5.0%, (e) 7.5%, and (f) 10.0%. "Q" designates quercetin. The arrows show quercetin on the starch granules. Reproduced from (Li et al. 2020c) with permission from Elsevier B.V.

establishment of the protein network in dough by disrupting the formation of disulfide bonds that account for dough stability, thereby reducing the dough elasticity and increasing the development time of the dough (Sivam et al. 2010, Rosell, Santos, and Collar 2006). The effect of quercetin on the physical properties of solid foods has been further demonstrated by a recent study, in which the rheological and thermal properties of pregelatinized Tartary buckwheat starch (pre-TBS) complexed with quercetin at various concentrations have been characterized (Fig. 8) (Li et al. 2020c). Upon quercetin complexation, the shearing resistance and viscosity of pre-TBS were found to be enhanced (Li et al. 2020c). In addition, compared to pre-TBS, the starch-quercetin complex displayed a more compact and stable structure, resulting in a lower digestion rate and digestion velocity constant (Li et al. 2020c). These results confirm the need to optimize the dose of quercetin and design the composition of the food to attain high-quality functional food products.

It is worth noting that the composition of the food product may affect the oral bioavailability of quercetin. This is shown by an earlier study (Goldberg, Yan, and Soleas 2003), which has found that upon administration of quercetin (with a dose of 0.14 mg/kg of body weight) dissolved in three beverages (including vegetable homogenate, grape juice, and white wine), the serum concentration of quercetin ranged from 10.8 to 25.3 ng/L. This reveals that, in functional food development, the bioavailability of quercetin should be assessed case by case rather than taking the dose of quercetin added to the food as the effective dose for consumption. Furthermore, while delivery technologies can enhance the oral bioavailability of quercetin, the conditions for the fabrication of the systems can influence the actual performance. This has been shown by Priprem et al. (2008), who formerly generated a lipid thin film consisting of egg phosphatidylcholine (EPC) and cholesterol, followed by the addition of a quercetin-containing polyethylene glycol (PEG) solution into the film for liposome formation. The size of the generated liposomal quercetin, as well as the encapsulation efficiency, has been found to be largely affected by experimental conditions (Priprem et al. 2008). For instance, by changing the molar ratio of EPC/cholesterol from 1:1 to 9:1, the mean size of the liposomes increased from approximately 210 nm to over 600 nm, with the surface charge changing from −32 mV to −13 mV (Priprem et al. 2008). In addition, by changing the order of incorporating quercetin into the liposomes (i.e. either incorporating quercetin into the lipid phase before the lipid thin film formation or incorporating quercetin into the film during liposome preparation), the encapsulation efficiency varied between 60% and 80% (Priprem et al. 2008). These results demonstrate the effect of fabrication conditions on the properties of liposomes.

Outlooks and concluding remarks

Quercetin is an important bioflavonoid present in a wide variety of plant materials, including *Morus alba*, *Prunus avium*, *Lactuca sativa*, *Capparis spinose, Brassica oleracea* var. italica, and *Centella asiatica* (Anand David, Arulmoli, and Parasuraman 2016). Its health benefits enable quercetin to emerge as a candidate for use in functional food development. Here, it is worth mentioning that although only the use of quercetin in functional food development has been discussed so far, quercetin has indeed been used as an additive for the fabrication of food-contact materials. For

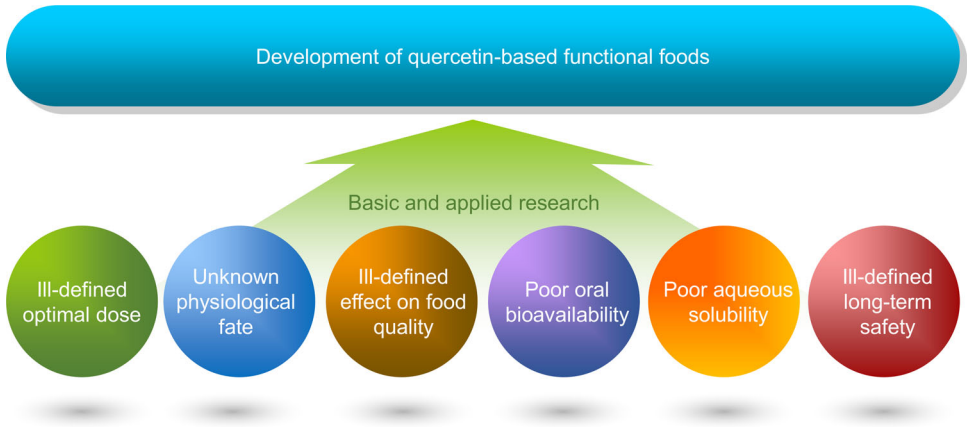

Figure 9. Major issues to be addressed to streamline the development of functional foods based on quercetin.

example, quercetin has been added as an active ingredient in a poly(vinyl alcohol) film obtained by solvent casting, and has been shown to enable the film to have anti-oxidative effects (Luzi et al. 2019). Recently, edible films have also been generated from kafirin and quercetin, with the latter being found to enhance the mechanical strength of films. The films have been applied as packaging films for cod fillets during cold storage to extend the shelf life. Nevertheless, a few issues (including more in-depth determination of the optimal dose, detailed evaluation of the safety of long-term quercetin intake, and the elucidation of the effect of quercetin on the chemical profiles and physical properties of foods) may have to be addressed before the use of quercetin can be streamlined in routine practice in food product development (Fig. 9). Some of these issues are further complicated when carriers are used, because while ingredients used to produce carriers of quercetin in the literature are largely biocompatible and nontoxic, the use of some organic agents (e.g. *n*-hexane (Li et al. 2020a)) may be involved. Residues of these agents may be brought into food products and cause safety concerns. In addition, functional groups (e.g. amine and hydroxyl groups) in carriers may interact with food components during food processing and storage, compromising the quality of food products. In-depth cost-benefit analysis, as well as a detailed evaluation of the safety of the carriers, should be performed on each carrier before the carrier is incorporated into foods. Nonetheless, owing to the high functionality in the food context and the well-supported health benefits of quercetin, it is expected to bring new opportunities and advances in food science in the future.

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Conflict of interest

The authors declare no conflict of interest.

References

Abrahamse, S. L., W. J. Kloots, and J. M. M. van Amelsvoort. 2005. Absorption, distribution, and secretion of epicatechin and quercetin in the rat. *Nutrition Research* 25 (3):305–17. doi: 10.1016/j.nutres.2004.10.013.

Adjonu, R., G. Doran, P. Torley, and S. Agboola. 2014. Formation of whey protein isolate hydrolysate stabilised nanoemulsion. *Food Hydrocolloids.* 41:169–77. doi: 10.1016/j.foodhyd.2014.04.007.

Anand David, A. V., R. Arulmoli, and S. Parasuraman. 2016. Overviews of biological importance of quercetin: A bioactive flavonoid. *Pharmacognosy Reviews* 10 (20):84–9. doi: 10.4103/0973-7847.194044.

Angellotti, G., D. Murgia, G. Campisi, and V. De Caro. 2020. Quercetin-based nanocomposites as a tool to improve dental disease management. *Biomedicines* 8 (11):504. doi: 10.3390/biomedicines8110504.

Arts, I. C. W., A. L. A. Sesink, M. Faassen-Peters, and P. C. H. Hollman. 2004. The type of sugar moiety is a major determinant of the small intestinal uptake and subsequent biliary excretion of dietary quercetin glycosides. *The British Journal of Nutrition* 91 (6):841–7. doi: 10.1079/BJN20041123.

Askari, G., R. Ghiasvand, A. Feizi, S. M. Ghanadian, and J. Karimian. 2012. The effect of quercetin supplementation on selected markers of inflammation and oxidative stress. *Journal of Research in Medical Sciences* 17 (7):637–41.

Aura, A. M. 2008. Microbial metabolism of dietary phenolic compounds in the colon. *Phytochemistry Reviews* 7 (3):407–29. doi: 10.1007/s11101-008-9095-3.

Awad, H. M., M. G. Boersma, S. Boeren, P. J. van Bladeren, J. Vervoort, and I. M. C. M. Rietjens. 2002. The regioselectivity of glutathione adduct formation with flavonoid quinone/quinone methides is pH-dependent. *Chemical Research in Toxicology* 15 (3):343–51. doi: 10.1021/tx010132l.

Azzi, J., A. Jraij, L. Auezova, S. Fourmentin, and H. Greige-Gerges. 2018. Novel findings for quercetin encapsulation and preservation with cyclodextrins, liposomes, and drug-in-cyclodextrin-in-liposomes. *Food Hydrocolloids.* 81:328–40. doi: 10.1016/j.foodhyd.2018.03.006.

Bagavieva, T. K., S. E. Yagunov, S. V. Kholshin, I. A. Emelyanova, O. I. Prosenko, and A. E. Prosenko. 2019. Synthesis and antioxidant properties of (dodecylsulfanyl)methyl quercetin derivatives. *Russian Chemical Bulletin* 68 (12):2283–9. doi: 10.1007/s11172-019-2701-2.

Bentsáth, A., S. Rusznyák, and A. Szent-Györgyi. 1936. Vitamin nature of flavones. *Nature* 138 (3497):798. doi: 10.1038/138798a0.

Bieger, J., R. Cermak, R. Blank, V. C. J. de Boer, P. C. H. Hollman, J. Kamphues, and S. Wolffram. 2008. Tissue distribution of quercetin in pigs after long-term dietary supplementation. *The Journal of Nutrition* 138 (8):1417–1420. doi: 10.1093/jn/138.8.1417.

Boots, A. W., J. M. Balk, A. Bast, and G. R. M. M. Haenen. 2005. The reversibility of the glutathionyl-quercetin adduct spreads oxidized

quercetin-induced toxicity. *Biochemical and Biophysical Research Communications* 338 (2):923–929. doi: 10.1016/j.bbrc.2005.10.031.

Boots, A. W., G. R. M. M. Haenen, and A. Bast. 2008. Health effects of quercetin: From antioxidant to nutraceutical. *European Journal of Pharmacology* 585 (2-3):325–337. doi: 10.1016/j.ejphar.2008.03.008.

Boots, A. W., N. Kubben, G. R. M. M. Haenen, and A. Bast. 2003. Oxidized quercetin reacts with thiols rather than with ascorbate: Implication for quercetin supplementation. *Biochemical and Biophysical Research Communications* 308 (3):560–565. doi: 10.1016/s0006-291x(03)01438-4.

Boots, A. W., H. Li, R. P. F. Schins, R. Duffin, J. W. M. Heemskerk, A. Bast, and G. R. M. M. Haenen. 2007. The quercetin paradox. *Toxicology and Applied Pharmacology* 222 (1):89–96. doi: 10.1016/j.taap.2007.04.004.

Brüll, V., C. Burak, B. Stoffel-Wagner, S. Wolffram, G. Nickenig, C. Müller, P. Langguth, B. Alteheld, R. Fimmers, S. Naaf, et al. 2015. Effects of a quercetin-rich onion skin extract on 24 h ambulatory blood pressure and endothelial function in overweight-to-obese patients with (pre-)hypertension: a randomised double-blinded placebo-controlled cross-over trial. *The British Journal of Nutrition* 114 (8):1263–1277. doi: 10.1017/S0007114515002950.

Buchner, N., A. Krumbein, S. Rohn, and L. W. Kroh. 2006. Effect of thermal processing on the flavonols rutin and quercetin. *Rapid Communications in Mass Spectrometry : RCM* 20 (21):3229–3235. doi: 10.1002/rcm.2720.

Caddeo, C.,. O. Diez-Sales, R. Pons, C. Carbone, G. Ennas, G. Puglisi, A. M. Fadda, and M. Manconi. 2016. Cross-linked chitosan/liposome hybrid system for the intestinal delivery of quercetin. *Journal of Colloid and Interface Science* 461:69–78. doi: 10.1016/j.jcis.2015.09.013.

Cadena, P. G., M. A. Pereira, R. B. S. Cordeiro, I. M. F. Cavalcanti, B. Barros Neto, M. d C. C. B. Pimentel, J. L. Lima Filho, V. L. Silva, and N. S. Santos-Magalhães. 2013. Nanoencapsulation of quercetin and resveratrol into elastic liposomes. *Biochimica et Biophysica Acta* 1828 (2):309–316. doi: 10.1016/j.bbamem.2012.10.022.

Cai, K. H., and A. Bennick. 2006. Effect of salivary proteins on the transport of tannin and quercetin across intestinal epithelial cells in culture. *Biochemical Pharmacology* 72 (8):974–980. doi: 10.1016/j.bcp.2006.06.026.

Carullo, G., M. Perri, F. Manetti, F. Aiello, M. C. Caroleo, and E. Cione. 2019. Quercetin-3-oleoyl derivatives as new GPR40 agonists: Molecular docking studies and functional evaluation. *Bioorganic & Medicinal Chemistry Letters* 29 (14):1761–1764. doi: 10.1016/j.bmcl.2019.05.018.

Cevc, G., and G. Blume. 1992. Lipid vesicles penetrate into intact skin owing to the transdermal osmotic gradients and hydration force. *Biochimica et Biophysica Acta (BBA) - Biomembranes* 1104 (1):226–232. doi: 10.1016/0005-2736(92)90154-E.

Chang, Q., and Y. S. Wong. 2004. Identification of flavonoids in Hakmeitau beans (Vigna sinensis) by high-performance liquid chromatography-electrospray mass spectrometry (LC-ESI/MS). *Journal of Agricultural and Food Chemistry* 52 (22):6694–6699. doi: 10.1021/jf049114a.

Chen, W. J., S. F. Sun, W. Cao, Y. Liang, and J. R. Song. 2009. Antioxidant property of quercetin-Cr(III) complex: The role of Cr(III) ion. *Journal of Molecular Structure* 918 (1-3):194–197. doi: 10.1016/j.molstruc.2008.08.008.

Choi, J. S., B. C. Choi, and K. E. Choi. 2004. Effect of quercetin on the pharmacokinetics of oral cyclosporine. *American Journal of Health-System Pharmacy : AJHP : official Journal of the American Society of Health-System Pharmacists* 61 (22):2406–2409. doi: 10.1093/ajhp/61.22.2406.

Dajas, F. 2012. Life or death: Neuroprotective and anticancer effects of quercetin. *Journal of Ethnopharmacology* 143 (2):383–396. doi: 10.1016/j.jep.2012.07.005.

Day, A. J., J. M. Gee, M. S. DuPont, I. T. Johnson, and G. Williamson. 2003. Absorption of quercetin-3-glucoside and quercetin-4 '-glucoside in the rat small intestine: The role of lactase phlorizin hydrolase and the sodium-dependent glucose transporter. *Biochemical Pharmacology* 65 (7):1199–1206. doi: 10.1016/S0006-2952(03)00039-X.

de Boer, V. C., A. A. Dihal, H. van der Woude, I. C. Arts, S. Wolffram, G. M. Alink, I. M. Rietjens, J. Keijer, and P. C. Hollman. 2005. Tissue distribution of quercetin in rats and pigs. *The Journal of Nutrition* 135 (7):1718–1725. doi: 10.1093/jn/135.7.1718.

Dehghan, G., and Z. Khoshkam. 2012. Tin(II)-quercetin complex: Synthesis, spectral characterisation and antioxidant activity. *Food Chemistry* 131 (2):422–426. doi: 10.1016/j.foodchem.2011.08.074.

Docampo-Palacios, M. L., A. Alvarez-Hernandez, O. Adiji, D. Gamiotea-Turro, A. B. Valerino-Diaz, L. P. Viegas, I. E. Ndukwe, A. de Fatima, C. Heiss, P. Azadi, et al. 2020. Glucuronidation of methylated quercetin derivatives: Chemical and biochemical approaches. *Journal of Agricultural and Food Chemistry* 68 (50):14790–14807. doi: 10.1021/acs.jafc.0c04500.

Egert, S., S. Wolffram, B. Schulze, P. Langguth, E. M. Hubbermann, K. Schwarz, B. Adolphi, A. Bosy-Westphal, G. Rimbach, and M. J. Müller. 2012. Enriched cereal bars are more effective in increasing plasma quercetin compared with quercetin from powder-filled hard capsules. *The British Journal of Nutrition* 107 (4):539–546. doi: 10.1017/S0007114511003242.

Esmaeili, M. A., and A. Sonboli. 2010. Antioxidant, free radical scavenging activities of Salvia brachyantha and its protective effect against oxidative cardiac cell injury. *Food and Chemical Toxicology : An International Journal Published for the British Industrial Biological Research Association* 48 (3):846–853. doi: 10.1016/j.fct.2009.12.020.

Farrell, T. L., M. Gomez-Juaristi, L. Poquet, K. Redeuil, K. Nagy, M. Renouf, and G. Williamson. 2012. Absorption of dimethoxycinnamic acid derivatives in vitro and pharmacokinetic profile in human plasma following coffee consumption. *Molecular Nutrition & Food Research* 56 (9):1413–1423. doi: 10.1002/mnfr.201200021.

FooDB2021. Compound Quercetin (FDB011904). Accessed January 20, 2021. https://foodb.ca/compounds/FDB011904.

Formica, J. V., and W. Regelson. 1995. Review of the biology of quercetin and related bioflavonoids. *Food and Chemical Toxicology : An International Journal Published for the British Industrial Biological Research Association* 33 (12):1061–1080. doi: 10.1016/0278-6915(95)00077-1.

Galati, G.,. M. Y. Moridani, T. S. Chan, and P. J. O'Brien. 2001. Peroxidative metabolism of apigenin and naringenin versus luteolin and quercetin: Glutathione oxidation and conjugation. *Free Radical Biology & Medicine* 30 (4):370–382. doi: 10.1016/S0891-5849(00)00481-0.

Gallaher, C. M., and D. D. Gallaher. 2008. Dried plums (prunes) reduce atherosclerosis lesion area in apolipoprotein E-deficient mice. *British Journal of Nutrition* 101 (2):233–239. doi: 10.1017/S0007114508995684.

Gillet, A., A. Grammenos, P. Compere, B. Evrard, and G. Piel. 2009. Development of a new topical system: Drug-in-cyclodextrin-in-deformable liposome. *International Journal of Pharmaceutics* 380 (1-2):174–180. doi: 10.1016/j.ijpharm.2009.06.027.

Goldberg, D. A., J. Yan, and G. J. Soleas. 2003. Absorption of three wine-related polyphenols in three different matrices by healthy subjects. *Clinical Biochemistry* 36 (1):79–87. doi: 10.1016/S0009-9120(02)00397-1.

Goncalves, B., A. K. Landbo, D. Knudsen, A. P. Silva, J. Moutinho-Pereira, E. Rosa, and A. S. Meyer. 2004. Effect of ripeness and post-harvest storage on the phenolic profiles of cherries (Prunus avium L.). *Journal of Agricultural and Food Chemistry* 52 (3):523–530. doi: 10.1021/jf030595s.

Goniotaki, M., S. Hatziantoniou, K. Dimas, M. Wagner, and C. Demetzos. 2004. Encapsulation of naturally occurring flavonoids into liposomes: Physicochemical properties and biological activity against human cancer cell lines. *The Journal of Pharmacy and Pharmacology* 56 (10):1217–1224. doi: 10.1211/0022357044382.

Gormaz, J. G., S. Quintremil, and R. Rodrigo. 2015. Cardiovascular disease: A target for the pharmacological effects of quercetin. *Current Topics in Medicinal Chemistry* 15 (17):1735–1742. doi: 10.2174/1568026615666150427124357.

Guo, Y., and R. S. Bruno. 2015. Endogenous and exogenous mediators of quercetin bioavailability. *The Journal of Nutritional Biochemistry* 26 (3):201–210. doi: 10.1016/j.jnutbio.2014.10.008.

Guo, Y., E. Mah, and R. S. Bruno. 2014. Quercetin bioavailability is associated with inadequate plasma vitamin C status and greater plasma endotoxin in adults. *Nutrition* 30 (11–12):1279–1286. doi: 10.1016/j.nut.2014.03.032.

Hakkinen, S. H., S. O. Karenlampi, I. M. Heinonen, H. M. Mykkanen, and A. R. Torronen. 1999. Content of the flavonols quercetin, myricetin, and kaempferol in 25 edible berries. *Journal of Agricultural and Food Chemistry* 47 (6):2274–2279. doi: 10.1021/jf9811065.

Han, L., K. Lu, S. Zhou, S. Zhang, F. Xie, B. Qi, and Y. Li. 2021. Development of an oil-in-water emulsion stabilized by a black bean protein-based nanocomplex for co-delivery of quercetin and perilla oil. *Lwt* 138:110644. doi: 10.1016/j.lwt.2020.110644.

He, W., Y. N. Tan, Z. Q. Tian, L. Y. Chen, F. Q. Hu, and W. Wu. 2011. Food protein-stabilized nanoemulsions as potential delivery systems for poorly water-soluble drugs: Preparation, in vitro characterization, and pharmacokinetics in rats. *International Journal of Nanomedicine* 6:521–533. doi: 10.2147/IJN.S17282.

Heyman, L., U. Axling, N. Blanco, O. Sterner, C. Holm, and K. Berger. 2014. Evaluation of beneficial metabolic effects of berries in high-fat fed C57BL/6J mice. *Journal of Nutrition and Metabolism* 2014: 403041. doi: 10.1155/2014/403041.

He, Z., X. Zhang, Z. Song, L. Li, H. Chang, S. Li, and W. Zhou. 2020. Quercetin inhibits virulence properties of Porphyromas gingivalis in periodontal disease. *Scientific Reports* 10 (1):18313. doi: 10.1038/s41598-020-74977-y.

Huber, G. M., H. P. V. Rupasinghe, and F. Shahidi. 2009. Inhibition of oxidation of omega-3 polyunsaturated fatty acids and fish oil by quercetin glycosides. *Food Chemistry* 117 (2):290–295. doi: 10.1016/j.foodchem.2009.04.007.

Iacopini, P., M. Baldi, P. Storchi, and L. Sebastiani. 2008. Catechin, epicatechin, quercetin, rutin and resveratrol in red grape: Content, in vitro antioxidant activity and interactions. *Journal of Food Composition and Analysis* 21 (8):589–598. doi: 10.1016/j.jfca.2008.03.011.

Igual, M., E. Garcia-Martinez, M. M. Camacho, and N. Martinez-Navarrete. 2011. Changes in flavonoid content of grapefruit juice caused by thermal treatment and storage. *Innovative Food Science & Emerging Technologies* 12 (2):153–162. doi: 10.1016/j.ifset.2010.12.010.

Iqbal, R., Z. Mehmood, A. Baig, and N. Khalid. 2020. Formulation and characterization of food grade O/W nanoemulsions encapsulating quercetin and curcumin: Insights on enhancing solubility characteristics. *Food and Bioproducts Processing* 123:304–311. doi: 10.1016/j.fbp.2020.07.013.

Jantarat, C., K. Attakitmongkol, S. Nichsapa, P. Sirathanarun, and S. Srivaro. 2020. Molecularly imprinted bacterial cellulose for sustained-release delivery of quercetin. *Journal of Biomaterials Science. Polymer Edition* 31 (15):1961–1976. doi: 10.1080/09205063.2020.1787602.

Javadi, F., A. Ahmadzadeh, S. Eghtesadi, N. Aryaeian, M. Zabihiyeganeh, A. R. Foroushani, and S. Jazayeri. 2017. The effect of quercetin on inflammatory factors and clinical symptoms in women with rheumatoid arthritis: A double-blind, randomized controlled trial. *Journal of the American College of Nutrition* 36 (1):9–15. doi: 10.1080/07315724.2016.1140093.

Kalinova, J., and N. Vrchotova. 2009. Level of catechin, myricetin, quercetin and isoquercitrin in buckwheat (Fagopyrum esculentum Moench), changes of their levels during vegetation and their effect on the growth of selected weeds. *Journal of Agricultural and Food Chemistry* 57 (7):2719–2725. doi: 10.1021/jf803633f.

Karadag, A., B. Ozcelik, and Q. R. Huang. 2014. Quercetin nanosuspensions produced by high-pressure homogenization. *Journal of Agricultural and Food Chemistry* 62 (8):1852–1859. doi: 10.1021/jf404065p.

Karande, P., and S. Mitragotri. 2009. Enhancement of transdermal drug delivery via synergistic action of chemicals. *Biochimica et Biophysica Acta* 1788 (11):2362–2373. doi: 10.1016/j.bbamem.2009.08.015.

Khan, H., H. Ullah, M. Aschner, W. S. Cheang, and E. K. Akkol. 2019. Neuroprotective effects of quercetin in Alzheimer's disease. *Biomolecules* 10 (1):59. doi: 10.3390/biom10010059.

Khlifi, R., Z. Dhaouefi, I. B. Toumia, A. Lahmar, F. Sioud, R. Bouhajeb, A. Bellalah, and L. Chekir-Ghedira. 2020. Erica multiflora extract rich in quercetin-3-O-glucoside and kaempferol-3-O-glucoside alleviates high fat and fructose diet-induced fatty liver disease by modulating metabolic and inflammatory pathways in Wistar rats. *The Journal of Nutritional Biochemistry* 86:108490. doi: 10.1016/j.jnutbio.2020.108490.

Kim, D. O., O. K. Chun, Y. J. Kim, H. Y. Moon, and C. Y. Lee. 2003. Quantification of polyphenolics and their antioxidant capacity in fresh plums. *Journal of Agricultural and Food Chemistry* 51 (22): 6509–6515. doi: 10.1021/jf0343074.

Kimira, M., Y. Arai, K. Shimoi, and S. Watanabe. 1998. Japanese intake of flavonoids and isoflavonoids from foods. *Journal of Epidemiology* 8 (3):168–175. doi: 10.2188/jea.8.168.

Kobylińska, A., and K. M. Janas. 2015. [Health-promoting effect of quercetin in human diet]. *Postepy Higieny i Medycyny Doswiadczalnej (Online)* 69:51–62. doi: 10.5604/17322693.1135423.

Konishi, Y., Z. H. Zhao, and M. Shimizu. 2006. Phenolic acids are absorbed from the rat stomach with different absorption rates. *Journal of Agricultural and Food Chemistry* 54 (20):7539–7543. doi: 10.1021/jf061554+.

Kuti, J. O., and H. B. Konuru. 2004. Antioxidant capacity and phenolic content in leaf extracts of tree spinach (Cnidoscolus spp.). *Journal of Agricultural and Food Chemistry* 52 (1):117–121. doi: 10.1021/jf030246y.

Lee, J. S., Y. J. Cha, K. H. Lee, and J. E. Yim. 2016. Onion peel extract reduces the percentage of body fat in overweight and obese subjects: A 12-week, randomized, double-blind, placebo-controlled study. *Nutrition Research and Practice* 10 (2):175–181. doi: 10.4162/nrp.2016.10.2.175.

Lee, T., and Y. H. Chang. 2020. Structural, physicochemical, and in-vitro release properties of hydrogel beads produced by oligochitosan and de-esterified pectin from yuzu (Citrus junos) peel as a quercetin delivery system for colon target. *Food Hydrocolloids.* 108 (106086): 106086. doi: 10.1016/j.foodhyd.2020.106086.

Li, Y. L., D. M. Fan, Y. L. Zhao, and M. F. Wang. 2020b. Effects of quercetin and cinnamaldehyde on the nutrient release from beef into soup during stewing process. *Lwt* 131:109712. doi: 10.1016/j.lwt.2020.109712.

Li, Y. L., S. S. Gao, X. L. Ji, H. Liu, N. Liu, J. C. Yang, M. Lu, L. Han, and M. Wang. 2020c. Evaluation studies on effects of quercetin with different concentrations on the physicochemical properties and in vitro digestibility of Tartary buckwheat starch. *International Journal of Biological Macromolecules* 163:1729–1737. doi: 10.1016/j.ijbiomac.2020.09.116.

Li, D., A. L. Liu, M. Y. Liu, X. Li, H. Y. Guo, C. C. Zuo, and Y. Li. 2020a. The intestine-responsive lysozyme nanoparticles-in-oxidized starch microgels with mucoadhesive and penetrating properties for improved epithelium absorption of quercetin. *Food Hydrocolloids.* 99:105309. doi: 10.1016/j.foodhyd.2019.105309.

Linseisen, J., J. Radtke, and G. Wolfram. 1997. Flavonoid intake of adults in a Bavarian subgroup of the national food consumption survey. *Zeitschrift Für Ernährungswissenschaft* 36 (4):403–412. doi: 10.1007/BF01617836.

Lin, J., Y. X. G. Tan, L. P. Leong, and W. B. Zhou. 2018. Steamed bread enriched with quercetin as an antiglycative food product: Its quality attributes and antioxidant properties. *Food & Function* 9 (6): 3398–3407. doi: 10.1039/c8fo00818c.

Lin, J., and W. B. Zhou. 2018. Role of quercetin in the physicochemical properties, antioxidant and antiglycation activities of bread. *Journal of Functional Foods* 40:299–306. doi: 10.1016/j.jff.2017.11.018.

Luzi, F., E. Pannucci, L. Santi, J. M. Kenny, L. Torre, R. Bernini, and D. Puglia. 2019. Gallic acid and quercetin as intelligent and active ingredients in poly(vinyl alcohol) films for food packaging. *Polymers (Polymers)* 11 (12):1999. doi: 10.3390/polym11121999.

Manach, C., C. Morand, V. Crespy, C. Demigné, O. Texier, F. Régérat, and C. Rémésy. 1998. Quercetin is recovered in human plasma as

conjugated derivatives which retain antioxidant properties. *FEBS Letters* 426 (3):331–336. doi: 10.1016/S0014-5793(98)00367-6.

Manach, C., A. Scalbert, C. Morand, C. Remesy, and L. Jimenez. 2004. Polyphenols: Food sources and bioavailability. *The American Journal of Clinical Nutrition* 79 (5):727–747. doi: 10.1093/ajcn/79.5.727.

Masibo, M., and Q. He. 2008. Major mango polyphenols and their potential significance to human health. *Comprehensive Reviews in Food Science and Food Safety* 7 (4):309–319. doi: 10.1111/j.1541-4337.2008.00047.x.

Middleton, E., Jr., C. Kandaswami, and T. C. Theoharides. 2000. The effects of plant flavonoids on mammalian cells: Implications for inflammation, heart disease, and cancer. *Pharmacological Reviews* 52 (4):673–751.

Miniscalco, A., J. Lundahl, C. G. Regardh, B. Edgar, and U. G. Eriksson. 1992. Inhibition of dihydropyridine metabolism in rat and human liver-microsomes by flavonoids found in grapefruit juice. *Journal of Pharmacology and Experimental Therapeutics* 261 (3): 1195–1199.

Miś, A., S. Grundas, D. Dziki, and J. Laskowski. 2012. Use of farinograph measurements for predicting extensograph traits of bread dough enriched with carob fibre and oat wholemeal. *Journal of Food Engineering* 108 (1):1–12. doi: 10.1016/j.jfoodeng.2011.08.007.

Moon, Y. J., L. Wang, R. DiCenzo, and M. E. Morris. 2008. Quercetin pharmacokinetics in humans. *Biopharmaceutics & Drug Disposition* 29 (4):205–217. doi: 10.1002/bdd.605.

Mukherjee, A., S. Mishra, N. K. Kotla, K. Manna, S. Roy, B. Kundu, D. Bhattacharya, K. D. Saha, and A. Talukdar. 2019. Semisynthetic quercetin derivatives with potent antitumor activity in colon carcinoma. *ACS Omega.* 4 (4):7285–7298. doi: 10.1021/acsomega.9b00143.

Mullen, W., C. A. Edwards, and A. Crozier. 2006. Absorption, excretion and metabolite profiling of methyl-, glucuronyl-, glucosyl- and sulpho-conjugates of quercetin in human plasma and urine after ingestion of onions. *The British Journal of Nutrition* 96 (1):107–116. doi: 10.1079/bjn20061809.

Muller, R. H., and K. Peters. 1998. Nanosuspensions for the formulation of poorly soluble drugs - I. Preparation by a size-reduction technique. *International Journal of Pharmaceutics* 160 (2):229–237. doi: 10.1016/S0378-5173(97)00311-6.

Murota, K., and J. Terao. 2005. Quercetin appears in the lymph of unanesthetized rats as its phase II metabolites after administered into the stomach. *FEBS Letters* 579 (24):5343–5346. doi: 10.1016/j.febslet.2005.08.060.

Narayana, K. R., M. Sripal Reddy, M. R. Chaluvadi, and D. R. Krishna. 2001. Bioflavonoids classification, pharmacological, biochemical effects and therapeutic potential. *Indian Journal of Pharmacology* 33: 2–16.

National Center for Biotechnology Information. 2021. PubChem Compound Summary for CID 5280343, Quercetin. Accessed January 20, 2021. https://pubchem.ncbi.nlm.nih.gov/compound/Quercetin.

Nemeth, K., G. W. Plumb, J. G. Berrin, N. Juge, R. Jacob, H. Y. Naim, G. Williamson, D. M. Swallow, and P. A. Kroon. 2003. Deglycosylation by small intestinal epithelial cell beta-glucosidases is a critical step in the absorption and metabolism of dietary flavonoid glycosides in humans. *European Journal of Nutrition* 42 (1):29–42. doi: 10.1007/s00394-003-0397-3.

Nguyen, M. A., P. Staubach, S. Wolffram, and P. Langguth. 2015. The influence of single-dose and short-term administration of quercetin on the pharmacokinetics of midazolam in humans. *Journal of Pharmaceutical Sciences* 104 (9):3199–3207. doi: 10.1002/jps.24500.

Ni, S. L., R. Sun, G. D. Zhao, and Q. Xia. 2015. Quercetin loaded nanostructured lipid carrier for food fortification: Preparation, characterization and in vitro study. *Journal of Food Process Engineering* 38 (1):93–106. doi: 10.1111/jfpe.12130.

Odriozola-Serrano, I., R. Soliva-Fortuny, and O. Martin-Belloso. 2008. Phenolic acids, flavonoids, vitamin C and antioxidant capacity of strawberry juices processed by high-intensity pulsed electric fields or heat treatments. *European Food Research and Technology* 228 (2): 239–248. doi: 10.1007/s00217-008-0928-5.

Paulke, A., M. Noldner, M. Schubert-Zslavecz, and M. Wurglics. 2008. St. John's wort flavonolds and their metabolites show antidepressant activity and accumulate in brain after multiple oral doses. *Pharmazie* 63 (4):296–302.

Pękal, A., M. Biesaga, and K. Pyrzynska. 2011. Interaction of quercetin with copper ions: Complexation, oxidation and reactivity towards radicals. *Biometals : An International Journal on the Role of Metal Ions in Biology, Biochemistry, and Medicine* 24 (1):41–49. doi: 10.1007/s10534-010-9372-7.

Petersen, B., S. Egert, A. Bosy-Westphal, M. J. Muller, S. Wolffram, E. M. Hubbermann, G. Rimbach, and K. Schwarz. 2016. Bioavailability of quercetin in humans and the influence of food matrix comparing quercetin capsules and different apple sources. *Food Research International (Ottawa, Ont.)* 88 (Pt A):159–165. doi: 10.1016/j.foodres.2016.02.013.

Pfeuffer, M., A. Auinger, U. Bley, I. Kraus-Stojanowic, C. Laue, P. Winkler, C. E. Rufer, J. Frank, C. Boesch-Saadatmandi, G. Rimbach, et al. 2013. Effect of quercetin on traits of the metabolic syndrome, endothelial function and inflammation in men with different APOE isoforms. *Nutrition, Metabolism, and Cardiovascular Diseases : NMCD* 23 (5):403–409. doi: 10.1016/j.numecd.2011.08.010.

Pocernich, C. B., and D. A. Butterfield. 2012. Elevation of glutathione as a therapeutic strategy in Alzheimer disease. *Biochimica et Biophysica Acta* 1822 (5):625–630. doi: 10.1016/j.bbadis.2011.10.003.

Price, K. R., J. R. Bacon, and M. J. C. Rhodes. 1997. Effect of storage and domestic processing on the content and composition of flavonol glucosides in onion (Allium cepa). *Journal of Agricultural and Food Chemistry* 45 (3):938–942. doi: 10.1021/jf9605916.

Přikryl, J., T. Hájek, B. Švecová, R. N. Salek, M. Černíková, L. Červenka, and F. Buňka. 2018. Antioxidant properties and textural characteristics of processed cheese spreads enriched with rutin or quercetin: The effect of processing conditions. *Lwt* 87:266–271. doi: 10.1016/j.lwt.2017.08.093.

Priprem, A., J. Watanatorn, S. Sutthiparinyanont, W. Phachonpai, and S. Muchimapura. 2008. Anxiety and cognitive effects of quercetin liposomes in rats. *Nanomedicine : nanotechnology, Biology, and Medicine* 4 (1):70–78. doi: 10.1016/j.nano.2007.12.001.

Rangel-Ordonez, L., M. Noldner, M. Schubert-Zsilavecz, and M. Wurglics. 2010. plasma levels and distribution of flavonoids in rat brain after single and repeated doses of standardized Ginkgo biloba extract EGb 761®. *Planta Medica* 76 (15):1683–1690. doi: 10.1055/s-0030-1249962.

Ranilla, L. G., M. I. Genovese, and F. M. Lajolo. 2009. Effect of different cooking conditions on phenolic compounds and antioxidant capacity of some selected Brazilian bean (Phaseolus vulgaris L.) cultivars. *Journal of Agricultural and Food Chemistry* 57 (13): 5734–5742. doi: 10.1021/jf900527v.

Rather, R. A., and M. Bhagat. 2020. Quercetin as an innovative therapeutic tool for cancer chemoprevention: Molecular mechanisms and implications in human health. *Cancer Medicine* 9 (24):9181–9192. doi: 10.1002/cam4.1411.

Ravichandran, R.,. M. Rajendran, and D. Devapiriam. 2014. Antioxidant study of quercetin and their metal complex and determination of stability constant by spectrophotometry method. *Food Chemistry* 146:472–478. doi: 10.1016/j.foodchem.2013.09.080.

Rezvan, N., A. Moini, L. Janani, K. Mohammad, A. Saedisomeolia, M. Nourbakhsh, S. Gorgani-Firuzjaee, M. Mazaherioun, and M. J. Hosseinzadeh-Attar. 2017. Effects of quercetin on adiponectin-mediated insulin sensitivity in polycystic ovary syndrome: A randomized placebo-controlled double-blind clinical trial. *Hormone and Metabolic Research* 49 (2):115–121.

Rosell, C. M., E. Santos, and C. Collar. 2006. Mixing properties of fibre-enriched wheat bread doughs: A response surface methodology study. *European Food Research and Technology* 223 (3):333–340. doi: 10.1007/s00217-005-0208-6.

Russo, M., C. Spagnuolo, I. Tedesco, S. Bilotto, and G. L. Russo. 2012. The flavonoid quercetin in disease prevention and therapy: Facts and fancies. *Biochemical Pharmacology* 83 (1):6–15. doi: 10.1016/j.bcp.2011.08.010.

Sahoo, N. G., M. Kakran, L. A. Shaal, L. Li, R. H. Muller, M. Pal, and L. P. Tan. 2011. Preparation and characterization of quercetin

nanocrystals. *Journal of Pharmaceutical Sciences* 100 (6):2379–2390. doi: 10.1002/jps.22446.

Saija, A., F. Bonina, D. Trombetta, A. Tomaino, L. Montenegro, P. Smeriglio, and F. Castelli. 1995b. Flavonoid-biomembrane interactions: A calorimetric study on dipalmitoylphosphatidylcholine vesicles. *International Journal of Pharmaceutics* 124 (1):1–8. doi: 10.1016/0378-5173(95)00051-J.

Saija, A., M. Scalese, M. Lanza, D. Marzullo, F. Bonina, and F. Castelli. 1995a. Flavonoids as antioxidant agents: Importance of their interaction with biomembranes. *Free Radical Biology and Medicine* 19 (4):481–486. doi: 10.1016/0891-5849(94)00240-K.

Sampson, L., E. Rimm, P. C. H. Hollman, J. H. M. de Vries, and M. B. Katan. 2002. Flavonol and flavone intakes in US health professionals. *Journal of the American Dietetic Association* 102 (10): 1414–1420. doi: 10.1016/S0002-8223(02)90314-7.

Schubert, W., G. Cullberg, B. Edgar, and T. Hedner. 1994. Inhibition of 17 beta-estradiol metabolism by grapefruit juice in ovariectomized women. *Maturitas* 20 (2-3):155–163. doi: 10.1016/0378-5122(94)90012-4.

Shi, Y., and G. Williamson. 2016. Quercetin lowers plasma uric acid in pre-hyperuricaemic males: A randomised, double-blinded, placebo-controlled, cross-over trial. *The British Journal of Nutrition* 115 (5): 800–806. doi: 10.1017/S0007114515005310.

Sivam, A. S., D. Sun-Waterhouse, S. Quek, and C. O. Perera. 2010. Properties of bread dough with added fiber polysaccharides and phenolic antioxidants: A review. *Journal of Food Science* 75 (8): R163–R174. doi: 10.1111/j.1750-3841.2010.01815.x.

Spencer, J. P. E. 2003. Metabolism of tea flavonoids in the gastrointestinal tract. *The Journal of Nutrition* 133 (10):3255S–3261s. doi: 10.1093/jn/133.10.3255S.

U.S. Food and Drug Administration. 2021. GRN No. 341 – Quercetin. Accessed January 20, 2021. https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=GRASNotices&id=341.

Walle, T., U. K. Walle, and P. V. Halushka. 2001. Carbon dioxide is the major metabolite of quercetin in humans. *The Journal of Nutrition* 131 (10):2648–2652. doi: 10.1093/jn/131.10.2648.

Wang, D. M., S. Q. Li, W. L. Wu, X. Y. Zhu, Y. Wang, and H. Y. Yuan. 2014. Effects of long-term treatment with quercetin on cognition and mitochondrial function in a mouse model of Alzheimer's disease. *Neurochemical Research* 39 (8):1533–1543. doi: 10.1007/s11064-014-1343-x.

Weldin, J., R. Jack, K. Dugaw, and R. P. Kapur. 2003. Quercetin, an over-the-counter supplement, causes neuroblastoma-like elevation of plasma homovanillic acid. *Pediatric and Developmental Pathology : The Official Journal of the Society for Pediatric Pathology and the Paediatric Pathology Society* 6 (6):547–551. doi: 10.1007/s10024-003-5061-7.

Werbach, M. R. 1993. *Nutritional Influences on Illness*. 2nd ed. Tarzana, California, US: Third Line Press.

Williams, C. A., and R. J. Grayer. 2004. Anthocyanins and other flavonoids. *Natural Product Reports* 21 (4):539–573. doi: 10.1039/b311404j.

Wolffram, S., M. Blöck, and P. Ader. 2002. Quercetin-3-glucoside is transported by the glucose carrier SGLT1 across the brush border membrane of rat small intestine. *The Journal of Nutrition* 132 (4): 630–635. doi: 10.1093/jn/132.4.630.

World Health Organization. 2021. Evaluations of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) - Quercetin and Quercitron. Accessed January 20, 2021. https://apps.who.int/food-additives-contaminants-jecfa-database/chemical.aspx?chemID=3047.

Yen, G. C., P. D. Duh, H. L. Tsai, and S. L. Huang. 2003. Pro-oxidative properties of flavonoids in human lymphocytes. *Bioscience, Biotechnology, and Biochemistry* 67 (6):1215–1222. doi: 10.1271/bbb.67.1215.

Zafrilla, P., F. Ferreres, and F. A. Tomas-Barberan. 2001. Effect of processing and storage on the antioxidant ellagic acid derivatives and flavonoids of red raspberry (Rubus idaeus) jams. *Journal of Agricultural and Food Chemistry* 49 (8):3651–3655. doi: 10.1021/jf010192x.

Zahedi, M., R. Ghiasvand, A. Feizi, G. Asgari, and L. Darvish. 2013. Does quercetin improve cardiovascular risk factors and inflammatory biomarkers in women with type 2 diabetes: A double-blind randomized controlled clinical trial. *International Journal of Preventive Medicine* 4 (7):777–785.