Dietary Flavonols and O-Glycosides

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Abstract

Flavonols are the most widespread subgroup of the flavonoids. Quercetin, kaempferol, myricetin, and isorhamnetin are the major dietary flavonol aglycones, which most commonly occur as *O*-glycosides in dietary sources including fruits, vegetables, tea, and wine. The role of flavonols and *O*-glycosides

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in human nutrition has gained increased interest due to their associated health beneficial effects for a number of chronic diseases, including cardiovascular diseases, diabetes, and cancer. However, the potential bioactivity of flavonols and *O*-glycosides will depend on their bioavailability. Following digestion, flavonol glycosides are cleaved to their aglycones, which may be metabolized in the enterocytes and further in the liver, forming glucuronidated, sulfated, and/or methylated metabolites, or they may be passively permeate the intestinal epithelial barrier. Flavonols that reach the colon may be degraded by the colonic microbiota to different metabolites, which may also contribute to the observed biological effects. In this chapter, the recent findings on the bioavailability, metabolism, bioactivity, and benefits of dietary flavonols and *O*-glycosides are highlighted. In addition, the recent information on food applications, safety issues, marketed products, and patents are also presented.

Keywords

Quercetin · Kaempferol · Myricetin · Isorhamnetin · Bioavailability · Metabolism · Cardiovascular diseases · Diabetes · Cancer · Toxicity

3.1 Introduction

Flavonols belong to a large group of compounds collectively known as flavonoids, which are a subgroup of an even larger group of compounds known as polyphenols. They are the most widespread subgroup of the flavonoids, being dispersed throughout the plant kingdom with the exceptions of algae and fungi (Crozier et al. 2009). Flavonols not attached to sugar moieties are referred as the aglycone form, whereas flavonols with sugar moieties are called flavonol glycosides. The major dietary flavonol aglycones are quercetin (3,5,7,3′,4′-pentahydroxyflavone), kaempferol (3,5,7,4′-tetrahydroxyflavone), myricetin (3,5,7,3′,4′,5′-hexahydroxyflavone), and isorhamnetin (3,5,7,4′-tetrahydroxy-3′-methoxyflavone), which most commonly occur as *O*-glycosides. Fruits, vegetables, and beverages are important dietary sources of these flavonol *O*-glycosides. In particular, berries, onion, and *Brassica* vegetables including cabbage, kale and broccoli, buckwheat, tea, and red wine are among the well-known sources of quercetin and kaempferol aglycones and *O*-glycosides (Table 1). Apples also contain quercetin glycosides including quercetin 3-*O*-galactoside, quercetin 3-*O*-glucoside, quercetin 3-*O*-rhamnoside, quercetin 3-*O*-arabinoside, and quercetin 3-*O*-xyloside. However, as apple flavonols are almost exclusively present in the peel of the fruit (Jakobek and Barron 2016), the flavonol content of whole fruit is low (5.73 mg/100 g fresh weight) compared to berries (www.phenol-explorer.eu) (Table 1).

Dietary intake of flavonols varies between countries. In the Netherlands, the average intake of flavonols was reported to be approximately 23 mg/day, of which quercetin contributed 16 mg/day, kaempferol 3.9 mg/day, and myricetin 1.4 mg/day. Tea was the major source in this population (48% of total intake), followed by onions (29%) and apples (7%) (Hollman and Arts 2000). The same foods and beverages are

Table 1 Dietary sources of flavonols and *O*-glycosides

Category	Food or beverage	Flavonols and *O*-glycosides	Content (mg/100 g FW or mg/100 mL)
Fruits	Black chokeberry	Quercetin 3-*O*-galactoside	46.46
		Quercetin 3-*O*-glucoside	41.95
		Σ	**88.41**
	Black elderberry	Quercetin	**42.00**
	Highbush blueberry	Kaempferol 3-*O*-glucoside	0.62
		Myricetin 3-*O*-arabinoside	12.21
		Myricetin 3-*O*-rhamnoside	1.03
		Quercetin 3-*O*-acetyl-rhamnoside	5.66
		Quercetin 3-*O*-arabinoside	7.09
		Quercetin 3-*O*-galactoside	8.99
		Quercetin 3-*O*-glucoside	1.49
		Quercetin 3-*O*-xyloside	1.60
		Σ	**38.69**
	Lingonberry	Kaempferol	0.53
		Kaempferol 3-*O*-glucoside	1.23
		Quercetin 3-*O*-arabinoside	4.29
		Quercetin 3-*O*-galactoside	13.22
		Quercetin 3-*O*-rhamnoside	12.20
		Σ	**31.47**
	Bog bilberry	Myricetin	13.65
		Quercetin	17.03
		Σ	**30.68**
Vegetables	Red onion	Isorhamnetin	1.51
		Isorhamnetin 4′-*O*-glucoside	6.00
		Quercetin	1.31
		Quercetin 3,4′-*O*-diglucoside	77.08
		Quercetin 3-*O*-glucoside	1.80
		Quercetin 3-*O*-rutinoside	0.21
		Quercetin 4′-*O*-glucoside	38.80
		Quercetin 7,4′-*O*-diglucoside	1.80
		Σ	**128.51**
	Black olive	Quercetin 3-O-rhamnoside	4.07
		Quercetin 3-O-rutinoside	45.36
		Σ	**49.43**
	Chinese cabbage (pak choy)	Kaempferol	9.60
		Myricetin	0.10
		Quercetin	39.00
		Σ	**48.70**
	Kale	Kaempferol	26.74
		Quercetin	7.71
		Σ	**34.45**

(continued)

Table 1 (continued)

Category	Food or beverage	Flavonols and *O*-glycosides	Content (mg/100 g FW or mg/100 mL)
	Chili pepper	Quercetin	**32.59**
	Broccoli	Kaempferol 3,7-*O*-diglucoside	1.50
		Kaempferol 3-*O*-glucoside	1.40
		Kaempferol 3-*O*-sophoroside	16.60
		Quercetin 3-*O*-glucoside	1.80
		Quercetin 3-*O*-sophoroside	6.50
		Σ	**27.80**
Cereals	Buckwheat	Quercetin	0.11
		Quercetin 3-*O*-rutinoside	36.14
		Σ	**36.25**
Pulses	Beans	Kaempferol 3-*O*-acetyl-glucoside	16.40
		Kaempferol 3-*O*-glucoside	39.88
		Kaempferol 3-*O*-xylosyl-glucoside	11.50
		Σ	**67.78**
Seasonings	Caper	Kaempferol	104.29
		Kaempferol 3-*O*-rhamnosyl-rhamnosyl-glucoside	19.53
		Kaempferol 3-*O*-rutinoside	165.76
		Quercetin	32.82
		Quercetin 3-*O*-rutinoside	332.29
		Σ	**654.69**
	Saffron	Kaempferol 3,7,4′-*O*-triglucoside	103.92
		Kaempferol 3-*O*-sophoroside	150.75
		Kaempferol 3-*O*-sophoroside 7-*O*-glucoside	255.32
		Σ	**509.99**
	Mexican oregano	Galangin	188.00
		Methylgalangin	42.07
		Quercetin	42.00
		Σ	**272.07**
Coffee and cocoa	Dark chocolate	Quercetin	**25.00**
Beverages	Black tea	Kaempferol	0.13
		Kaempferol 3-*O*-galactoside	3.08
		Kaempferol 3-*O*-glucoside	12.20
		Kaempferol 3-*O*-glucosyl-rhamnosyl-glucoside	1.03
		Kaempferol 3-*O*-rutinoside	17.36
		Quercetin	0.09
		Quercetin 3-*O*-galactoside	4.17

(continued)

Table 1 (continued)

Category	Food or beverage	Flavonols and *O*-glycosides	Content (mg/100 g FW or mg/100 mL)
		Quercetin 3-*O*-glucoside	10.87
		Quercetin 3-*O*-glucosyl-rhamnosyl-galactoside	0.64
		Quercetin 3-*O*-glucosyl-rhamnosyl-glucoside	6.51
		Quercetin 3-*O*-rhamnoside	0.93
		Quercetin 3-*O*-rutinoside	19.68
		Σ	**76.69**
	Red wine	Isorhamnetin	0.33
		Isorhamnetin 3-*O*-glucoside	0.26
		Kaempferol	0.23
		Kaempferol 3-*O*-glucoside	0.79
		Myricetin	0.83
		Quercetin	0.83
		Quercetin 3-*O*-arabinoside	0.49
		Quercetin 3-*O*-glucoside	1.14
		Quercetin 3-*O*-rhamnoside	1.15
		Quercetin 3-*O*-rutinoside	0.81
		Σ	**6.86**

The data presented in this table is extracted from Phenol-Explorer database (www.phenol-explorer.eu)

also the most predominant dietary sources of flavonols in Denmark and the USA. However, eating habits and cultural differences may significantly influence the dietary source of flavonols. For example, while green tea is the superior source of flavonols in Japan, berries are reported to be the most important dietary sources in Finland. Variations of dietary sources also can be observed among different regions within the same country. For instance, in Italy, red wine is known to be the most significant source of dietary flavonols. On the other hand, in the northern villages of Italy, the major sources of flavonols are reported to be fruits and vegetables (Aherne and O'Brien 2002). In addition to the above, the methods of culinary preparation also have a marked impact on the flavonol content of foods and hence their intake. For example, peeling of fruits and vegetables can eliminate a significant portion of flavonols because these compounds are often present in higher concentrations in the outer parts than in the inner parts, as in case of apples. Moreover, many fresh fruits and vegetables are subjected to a form of processing, e.g., cooking, before consumption, which may also significantly affect the flavonol content. Accordingly, it has been demonstrated that the quercetin content of onions and tomatoes reduced by 75–80% after boiling for 15 min, 65% after cooking in a microwave oven, and 30% after frying (Briones-Labarca et al. 2011).

In 1936, Szent-Györgyi found that quercetin 3-*O*-rutinoside, also known as rutin, had vitamin properties and termed this flavonol as "vitamin P." At that time, dietary

flavonols are believed to have a poor bioavailability, and therefore nutritional scientists excluded vitamin P from the category of vitamins. In 1970s, quercetin and other plant flavonols are assumed to be potential carcinogens as these compounds were found to possess mutagenic activity (Terao 2009). On the other hand, a great number of recent scientific studies based on in vivo experiments reported the benefits of flavonol consumption with respect to cardiovascular diseases, diabetes, inflammation, viral infections, enhanced physical strength, and cancer prevention (Ahmad et al. 2015; Gormaz et al. 2015; Chen et al. 2016a; Kashyap et al. 2016; Bazzucchi et al. 2019). However, the potential bioactivity of flavonols and *O*-glycosides will depend on their bioavailability. Following digestion, flavonol glycosides are cleaved to their aglycones, which may be metabolized in the enterocytes and further in the liver, forming glucuronidated, sulfated, and/or methylated metabolites, or they may passively permeate the intestinal epithelial barrier (Day et al. 2001). Furthermore, flavonols that reach the colon may be degraded by the colonic microbiota to different phenolic acids, e.g., phenylacetic acid and protocatechuic acid (Serra et al. 2012), which may also contribute to the observed biological effects.

Considering the above, in this chapter, bioactive constituents, bioavailability, metabolism, bioactivity, and benefits of dietary flavonols and *O*-glycosides are highlighted. In addition, the recent information on food applications, safety issues, marketed products, and patents are also presented.

3.2 Bioactive Constituents

Flavonols are formed from the combination of derivatives synthesized from phenylalanine via the shikimic acid pathway and acetic acid. The initial step of flavonol biosynthesis includes the formation of amino acid phenylalanine from phenylpyruvate. Then, by the action of phenylalanine ammonia-lyase (PAL) enzyme, phenylalanine is transformed to *trans*-cinnamic acid, which is hydrolyzed to *p*-coumaric acid (C9). The C9 acids condense with three malonyl-CoA molecules (C2) by chalcone synthase (CHS) to form chalcones (C15) (Aherne and O'Brien 2002; Survay et al. 2011). The C15 chalcones are then isomerized into (2*S*)-flavanones by chalcone isomerase (CHI). (2*R*, 3*R*)-*trans*-dihydroflavonols are subsequently formed from (2*S*)-flavanones by flavanone 3β-hydroxylase (FHT). Lastly, flavonol synthase (FLS), 2-oxoglutarate-dependent dioxygenase, catalyzes the desaturation of dihydroflavonols to flavonols (Leonard et al. 2006).

The structure of the flavonols is based on the flavonoid nucleus, which consists of three phenolic rings referred to as the A, B, and C rings. The benzene ring A is condensed with a six-member ring C, which carries a phenyl benzene ring B as a substituent in the 2-position. The term *4-oxo-flavonoids* is often used to describe the structure of flavonols (Aherne and O'Brien 2002), which can be distinguished from other flavonoids with the presence of (i) a double bond at the 2–3-position, (ii) a carbonyl group at the 4-position, and (iii) a hydroxyl group at the 3-position of C ring (Fig. 1). Azaleatin, fisetin, galangin, gossypetin, kaempferide, kaempferol,

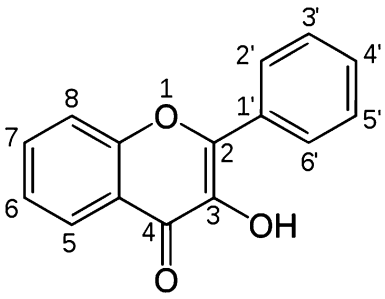

Fig. 1 Chemical structure of flavonols

isorhamnetin, morin, myricetin, natsudaidain, pachypodol, quercetin, rhamnazin, and rhamnetin are the common flavonol aglycones, which structurally differ from each other by variations in the number and position of hydroxyl and methyl groups (Table 2).

In nature, the majority of flavonols are present as *O*-glycosides. Glycosylation occurs frequently at the 3-position of the C ring, but substitutions can also take place at the 5-, 7-, 4′-, 3′-, and 5′-carbons (Crozier et al. 2009). The glycosidic sugars are generally glucose; however other carbohydrate substitutions including arabinose, galactose, rutinose, lignin, rhamnose, and xylose are also present (Aherne and O'Brien 2002). There are several flavonol glycosides, comprising mono-, di-, and tri-glycosides based upon quercetin, kaempferol, azaleatin, kaempferide, myricetin, and rhamnetin, and various permutations of glucose, galactose, rhamnose, arabinose, and rutinose. Some examples of flavonol glycosides and their glycosylation positions are given in Table 3; however it is noteworthy to mention that there are numerous flavonol conjugates, with 179 different glycosides of quercetin alone (Hollman and Arts 2000). The classification of the structures requires the knowledge of the nature of α or β aglycon sugar bonds as well as the optical configuration of the involved sugar (dextro or levo). As a rule, D-configured sugars, i.e., glucose, galactose, xylose, and glucuronic acid, form β bonds, while the α bonds are made of L-sugars such as arabinose and rhamnose. For example, this arrangement can be observed in the composition of apple flavonols, which are composed of quercetin glycosides, including α-L-arabinoside, β-D-galactoside, β-D-glucoside, α-L-rhamnoside, and β-D-xyloside (Escarpa and Gonzalez 2001).

3.3 Bioavailability and Metabolism

Several factors affect the bioavailability of a compound, including degradation by gut microflora and enzymes, decomposition in the gut lumen, and first pass metabolism by the liver. In addition, the physicochemical properties of the compound will also influence its bioavailability, consisting molecular weight, partition coefficient, and pKa (Choudhury et al. 1999). The absorption of dietary aglycones and *O*-glycosides has been the subject of many studies, and most of them have been related with quercetin and its glycosides.

Table 2 Flavonols and their hydroxylation and methylation positions

Flavonol	IUPAC name	5	6	7	8	2′	3′	4′	5′	6′
Azaleatin	2-(3,4-dihydroxyphenyl)-3,7-Dihydroxy-5-methoxychromen-4-one	OCH_3	H	OH	H	H	H	OH	OH	H
Fisetin	3,3′,4′,7-Tetrahydroxy-2-phenylchromen-4-one	H	H	OH	H	H	OH	OH	H	H
Galangin	3,5,7-Trihydroxy-2-phenylchromen-4-one	OH	H	OH	H	H	H	H	H	H
Gossypetin	2-(3,4-dihydroxyphenyl)-3,5,7,8-Tetrahydroxychromen-4-one	OH	H	OH	OH	H	OH	OH	H	H
Kaempferide	3,5,7-Trihydroxy-2-(4-methoxyphenyl) chromen-4-one	OH	H	OH	H	H	H	OCH_3	H	H
Kaempferol	3,4′,5,7-Tetrahydroxy-2-phenylchromen-4-one	OH	H	OH	H	H	H	OH	H	H
Isorhamnetin	3,5,7-Trihydroxy-2-(4-hydroxy-3-methoxyphenyl) chromen-4-one	OH	H	OH	H	H	OCH_3	OH	H	H
Morin	2-(2,4-dihydroxyphenyl)-3,5,7-Trihydroxychromen-4-one	OH	H	OH	H	OH	H	OH	H	H
Myricetin	3,3′,4′,5′,5,7-Hexahydroxy-2-phenylchromen-4-one	OH	H	OH	H	H	OH	OH	OH	H
Natsudaidain	2-(3,4-dimethoxyphenyl)-3-Hydroxy-5,6,7,8-tetramethoxychromen-4-one	OCH_3	OCH_3	OCH_3	OCH_3	H	H	OCH_3	OCH_3	H
Pachypodol	5-Hydroxy-2-(4-hydroxy-3-methoxyphenyl)-3,7-dimethoxychromen-4-one	OH	H	OCH_3	H	H	OCH_3	OH	H	H
Quercetin	3,3′,4′,5,7-Pentahydroxy-2-phenylchromen-4-one	OH	H	OH	H	H	OH	OH	H	H
Rhamnazin	3,5-Dihydroxy-2-(4-hydroxy-3-	OH	H	OCH_3	H	H	OCH_3	OH	H	H

(continued)

Table 2 (continued)

Flavonol	IUPAC name	5	6	7	8	2′	3′	4′	5′	6′
	methoxyphenyl)-7-methoxychromen-4-one									
Rhamnetin	2-(3,4-dihydroxyphenyl)-3,5-Dihydroxy-7-methoxychromen-4-one	OH	H	OCH_3	H	H	OH	OH	H	H

Reproduced from Survay et al. (2011)

Table 3 Flavonol glycosides and their glycosylation positions

Aglycone	Flavonol glycoside	3	7	8	3′	4′
Azaleatin	Azalein	Rhamnose				
Kaempferide	Icariin	Rhamnose	Glucose	tert-Amyl		
Kaempferol	Amurensin		Glucose	tert-Amyl		
	Astragalin	Glucose				
	Kaempferitrin	Rhamnose	Rhamnose			
	Robinin	Robinose	Rhamnose			
Myricetin	Myricitrin	Rhamnose				
Quercetin	Hyperoside	Galactose				
	Isoquercetin	Glucose				
	Quercitrin	Rhamnose				
	Rutin	Rutinose				
	Spiraeoside					Glucose
	Troxerutin	Rutinose	Hydroxyethyl		Hydroxyethyl	Hydroxyethyl
Rhamnetin	Xanthorhamnin	Trisaccharide				

Reproduced from Survay et al. (2011)

The bound sugar moiety is also known to influence the bioavailability of flavonoids. For instance, Morand et al. (2000) examined the effect of the type/nature of the sugar on the absorption of glycosides. They found that quercetin 3-glucose (33.2 μM) absorbed in the small intestine and was better absorbed than quercetin (11.7 μM) itself. In contrast, glycosides containing a rhamnose moiety could not be absorbed in the small intestine. These researchers suggested that the 3-O-glucosylation improves the absorption of quercetin in the small intestine.

In another study, Manach et al. (1995) studied the bioavailability and the plasma transport of flavonols in rats fed with quercetin or rutin diets. They also investigated the flavonol concentrations in plasma, ileal and cecal contents, and feces. They suggested that the rate of elimination of quercetin metabolites was relatively low and

high plasma concentrations can be easily maintained with a regular supply of flavonoids in the diet. In contrast, Gugler et al. (1975) showed that quercetin was poorly absorbed (1%) across the gastrointestinal tract in a human trial. However, they observed that recovery in feces after the oral dose was 53% degraded by microorganisms in the gut.

Choudhury et al. (1999) investigated the absorption and excretion of the aglycone quercetin and compared with its 3-glucoside (isoquercitrin) and 3-rhamnoglucoside (rutin) in the rat. They reported that isoquercitrin (0.48% of administered dose) orally absorbed was bioavailable. On the other hand, their results revealed that neither unchanged rutin, quercetin, nor the conjugated metabolites in the form of glucuronide or sulfate were detected in the urine after oral dosing. They also found that all the flavonoids studied produced low total urinary recoveries after intravenous administration, 9.2% for quercetin-3-rhamnoglucoside, 6.7% for the 3-glucoside, and 2.4% for the aglycone, indicating that extensive metabolism to low molecular weight compounds or excretion via other routes may be occurring. The differences in the metabolism of each compound could be linked to their physicochemical properties. Quercetin is the most lipophilic compound enabling its entry by passive diffusion into the liver. Very little unchanged quercetin and a greater number of metabolites and their conjugates were observed in the urine. However, rutin (less lipophilic compound) would not be distributed into the liver as readily. This lead to a greater proportion of unchanged compound and fewer metabolites being detected in the urine (Choudhury et al. 1999). Erlund et al. (2001) showed that quercetin-3-rutinoside was more bioavailable in women compared to men, and plasma levels were the highest in women using oral contraceptives. This could be related to interindividual variation in the gastrointestinal microflora or absorption or biotransformation mechanisms which affect the bioavailability. Another study conducted by Hollman et al. (1999) reported that the peak concentration of quercetin (C_{max}) in plasma was 20 times higher and reached T_{max} more than 10 times faster after the intake of glucoside ($C_{max} = 3.5$ μM; $T_{max} < 0.5$ h) than the rutinoside ($C_{max} = 0.18$ μM; $T_{max} = 6.0$ h). They also suggested that quercetin glucoside is actively absorbed from the small intestine, whereas quercetin rutinoside is absorbed from the colon after deglycosylation. Reinboth et al. (2010) investigated the bioavailability of quercetin in dogs, administering oral doses of 30 mmol/kg b.w. of the aglycone, isoquercitrin, or rutin, equivalent to 10 mg quercetin/kg b.w. They have reported that quercetin and isoquercitrin were mainly absorbed in the small intestine with isoquercitrin being one and a half times more bioavailable than quercetin. Dang et al. (2014) indicated that the bioavailability of myricetin was found to be 9.62% and 9.74% at two oral doses (50 mg/kg and 100 mg/kg, respectively), showing that it was poorly absorbed after oral administration.

In general, the first part of metabolism consists of tissues including the small intestine, liver, and kidneys, whereas the second part of the metabolism occurs in the colon. Studies on humans have clearly shown that metabolism in human body is vital to determine which ones are better absorbed and which ones cause formation of bioactive metabolites. Sugar moieties, such as quercetin-3-glucoside, are cleaved from the phenolic backbone in the small intestine and absorbed here through the

ingestion of flavonoids. Moreover, enzymes play an important role in the absorption. For instance, lactase phlorizin hydrolase (at enterocyte membrane) or β-glucosidase (cytosolic, for polar glycosides) hydrolyze glycosylated flavonoids and then aglycones enter epithelial cells by passive diffusion. On the other hand, some flavonoids linked to a rhamnose moiety must reach the colon and hydrolyzed by the colon microbiota (Marín et al. 2015). When the aglycon or the new bioactive metabolites formed are absorbed at small intestine, they go through some degree of phase II metabolism at enterocyte level, such as glucuronidation, methylation, and sulfation (Hollman 2004; Marín et al. 2015). Afterward, these products enter the bloodstream by the portal vein, reaching the liver. If a flavonoid glycoside is not absorbed in the small intestine, it can be metabolized by the colonic microflora into its aglycone in the large intestine (Xiao 2017). It is also worth emphasizing that tissue distribution can help predict a variety of events related to the efficacy. Xu et al. (2014), for example, reported that the highest level of kaempferide was observed in heart, whereas tamarixetin was observed in the lung of rats when their distribution in different tissues (heart, liver, lung, spleen, kidney, prostate, and brain) was investigated.

3.4 Bioactivities

Dietary flavonols and *O*-glycosides have many important biological activities, including antioxidant, anti-inflammatory, antiangiogenic, hypolipidemic, neuroprotective, and anticancer effects (Table 4). All these studies significantly indicated that dietary flavonols and *O*-glycosides may help treating some critical health problems.

Epilepsy is a common neurological disorder in which brain activity becomes abnormal, causing unpredictable seizures. Das et al. (2017), after investigating the effects of fisetin in traumatic epilepsy in rats for its antiepileptic activity, reported that fisetin pretreatment was found to inhibit the development of iron-induced electrical seizure and significantly decrease the corresponding multiple unit activity in the cortex and in the hippocampus. Moreover, it significantly reduced the production of malondialdehyde suggesting the antilipidperoxidative action of fisetin. Another worldwide health problem is food allergy for which present medications have many side effects and do not stop the progression of hypersensitivity reactions. Elkholy et al. (2019) showed that fisetin exerted potent immunomodulatory and anti-inflammatory activities, thus abled them to alleviate OVA-induced food allergy in mice. This alleviation could be due to their capability to rebuild the normal T-helper 1/T-helper 2 cytokine balance and AT1 blockade activity. In addition, Kim et al. (2014b) reported that administration of spiraeoside to mice suppressed the passive cutaneous anaphylaxis reaction. Thus, they supposed that spiraeoside can be utilized as an anti-allergic agent.

Even though there are many researches on acute lung injury and acute respiratory distress syndrome, the mortality rate as a result of these diseases still remains high. In the study of Feng et al. (2016), fisetin was injected (1, 2, and 4 mg/kg, i.v.) 30 min

Table 4 Recent animal studies on chronic disease

Components	Chronic disease	Animal model	Key outcomes	References
Fisetin	Epilepsy	Wistar rats	Antiepileptic action of fisetin in iron-induced model of epileptic rats by inhibiting oxidative stress	Das et al. (2017)
	Food allergy	BALB/c mice	Fisetin alleviated food allergy and shows potent anti-inflammatory and immunomodulatory effects	Elkholy et al. (2019)
	Acute lung injury	Sprague-Dawley rats	Fisetin may regulate the inflammatory process in lipopolysaccharide-induced acute lung injury	Feng et al. (2016)
	Ischemic heart disease	Wistar rats	Fisetin attenuates isoproterenol-induced cardiac ischemic injury	Garg et al. 2019
	Neurotoxicity	Pregnant Wistar rats	Fisetin reduced the toxic effects of MeHg in the developing rat brain	Jacob and Thangarajan (2017)
	Depression	ICR mice Ahi1$^{loxp/loxp}$ mice	Fisetin provided antidepressant effects	Wang et al. (2017)
	Acute pancreatitis	C57BL/6mice	Fisetin reduced pancreatitis and pancreatitis-associated lung injury	Jo et al. (2014)
	Atopic dermatitis	NC/Nga mice	Fisetin exhibited as a potential therapeutic for atopic dermatitis	Kim et al. (2014)
	Alcohol-induced acute liver	C57BL/6 mice	Fisetin at 5 and 10 mg/kg can attenuate the adverse effects of alcohol in liver tissues	Koneru et al. (2016)
	Glaucoma	DBA/2 J mouse	Fisetin was able to promote the visual functions of DBA/2 J mice	Li et al. (2019)
	Cardiac hypertrophy	SHR and control Wistar Kyoto rats	Fisetin inhibited cardiac hypertrophy in hypertension rats	Lin et al. (2019)
	Hyperglycemia	Wistar rats	Fisetin ameliorated hyperglycemia in diabetic rats	Althunibat et al. (2019)
	Aging	Wistar rats	Fisetin could be considered as an antiaging compound	Singh et al. 2019
Galangin	Hypertrophic scar	BALB/c mice	Galangin was a novel anti-hypertrophic scar compound	Zhang et al. (2016)

(continued)

Table 4 (continued)

Components	Chronic disease	Animal model	Key outcomes	References
Hyperoside	Osteoporosis	Kunming mice	Hyperoside was effective in preventing osteoporosis	Chen et al. (2018)
	Chronic liver fibrosis	Kunming mice	Hyperoside has a potential anti-fibrosis and protective physiological function of livers	Zou et al. (2017)
Isoquercetin	Diabetes mellitus	Wistar rats	Isoquercetin regulated nuclear factor erythroid 2-related factor 2, inflammatory, and AMP-activated protein kinase pathway genes	Jayachandran et al. (2019)
	Cerebral ischemic stroke	Sprague-Dawley rats	Isoquercetin has a neuroprotective effect against I/R brain injury	Dai et al. (2018)
Isoquercitrin	Liver injury	Kunming mice	Isoquercitrin protected liver from APAP induced injury	Xie et al. (2016)
	Type 2 diabetes mellitus	Kunming mice	Isoquercitrin significantly inhibited postprandial blood glucose changes in a dose-dependent manner	Zhang et al. (2018)
Kaempferol	Myocardial ischemia/ reperfusion injury	Sprague-Dawley rats	Kaempferol provided cardioprotection via antioxidant activity and inhibition of phospho-GSK-3β activity in rats with I/R	Zhou et al. (2015)
Morin	Schizophrenia	Swiss mice	Morin exhibited antipsychotic-like activity	Ben-Azu et al. (2018)
Myricetin	Ischemic stroke	Sprague-Dawley rats	Myricetin attenuated brain injury and neurological deficits	Wu et al. (2016)
Myricitrin	Liver damage	BALB/ cN mice	Myricitrin showed a significant hepatoprotective activity	Domitrović et al. (2015)
Quercetin	Rheumatoid arthritis	C57BL/6 mice	Quercetin decreased the severity of arthritic inflammation, protecting joints from degradation	Haleagrahara et al. (2017)
	Liver injury	ICR mice	Quercetin inhibited CCl_4-induced liver injury	Ma et al. (2015a)
	Liver injury	Kunming mice	Quercetin showed a potential protective effect against perfluorooctanoic acid-induced liver damage via attenuation of oxidative stress and inflammation	Zou et al. (2015)

(continued)

Table 4 (continued)

Components	Chronic disease	Animal model	Key outcomes	References
Spiraeoside	Type I allergy	Balb/c mice	Spiraeoside prevented mast cell activation and allergic responses	Kim et al. (2014)
Troxerutin	Hepatic gluconeogenesis	ICR mice	Troxerutin markedly reduced high-fat diet-induced enhancement of hepatic gluconeogenesis	Zhang et al. (2017)
	Liver cancer	Wistar rats	Troxerutin exerted a significant therapeutic effect against liver cancer by modulating liver function enzymes, xenobiotic enzymes	Thomas et al. (2017)
Icariin	Parkinson's disease	C57BL/6 mice	Icariin showed neuroprotective effect on dopaminergic neurons in Parkinson's disease mice	Chen et al. (2017)
	Bone infection	Rabbits	Icariin exhibited osteoplastic properties on osteoblasts and enhanced bone repair	Zhang et al. (2017)
	Depression	Sprague-Dawley rats	Icariin showed protective effects against corticosterone-induced depression and metabolic dysfunction	Gong et al. (2016)
	Ischemic stroke	Sprague-Dawley rats	Icariin exhibited neuroprotective effect on ischemic stroke in rats	Xiong et al. (2016)
	Acute kidney injury	C57BL/6 N mice	Icariin protected against kidney injury	Xie et al. (2018)

before lipopolysaccharide (LPS) administration (5 mg/kg, i.v.) in rats. They demonstrated that fisetin effectively reduced the inflammatory cytokine release and total protein in bronchoalveolar lavage fluids and the lung wet/dry ratios. Fisetin, moreover, inhibited LPS-induced increases of neutrophils and macrophage infiltration and attenuated myeloperoxidase activity in lung tissues. Additionally, the protective effect of fisetin in acute lung injury may be due to its ability to inhibit the expression Toll-like receptor 4 and the activation of nuclear factor-κB (NF-κB) in lung tissues. In addition, Jo et al. (2014) showed that pre- and posttreatment with fisetin attenuated the severity of cerulein-induced pancreatitis and pancreatitis-associated lung injury, inhibiting the activation of NF-κB and c-Jun NH_2-terminal kinase. Atopic dermatitis (AD) is a chronically relapsing and pruritic inflammatory skin disease. Kim et al. (2014a) investigated whether fisetin relieves AD-like clinical symptoms induced by repeated dinitrofluorobenzene treatment in NC/Nga mice. They reported

that fisetin significantly inhibited infiltration of inflammatory cells and suppressed the expressions of various inflammatory mediators. Furthermore, fisetin also inhibited phosphorylation of NF-κB p65, which associated with inflammation. Recent researches on alcohol consumption indicated that production of reactive oxygen species (ROS) and improvement of lipid peroxidation are the prime causes in the initiation of acute liver injury. Furthermore, the involvement of matrix metalloproteinases (MMPs) plays role in the pathogenesis of alcoholic liver diseases. Koneru et al. (2016), for instance, investigated the protective effect of fisetin on the liver from binge alcohol-induced toxicity and to explore the underlying mechanisms of inhibition of MMP and oxidative stress. They demonstrated that pretreatment with fisetin (5 and 10 mg/kg) ameliorated the alcohol-induced alterations in liver function, antioxidant defense, histological changes, mitochondrial respiratory enzymes, and MMP activities.

Coronary microvascular disease is another type of ischemic heart disease in its severest form, i.e., myocardial infarction, which continues to be a major cause of morbidity and mortality all throughout the world. Garg et al. (2019) reported via an in vivo study that flavonols like fisetin had a cardioprotective effects in the heart at doses of 10 and 20 mg/kg via suppression of oxidative stress-mediated apoptosis and inflammation and suppressed the receptor for advanced glycation end products (RAGE)/NF-κB. Methyl mercury (MeHg) is a neurotoxin causing irreversible cognitive damage in offspring of gestationally exposed mothers. Accordingly, Jacob and Thangarajan (2017) evaluated the effect of gestational intake of fisetin on MeHg neurotoxicity in F1 generation rats. They reported that intake of fisetin during pregnancy in rats ameliorated in utero MeHg exposure induced neurotoxicity outcomes in postnatal weaning F1 generation rats. Same group further investigated the mechanism behind the mitigating action of fisetin against prenatal MeHg exposure-induced neurotoxicity. They concluded that fisetin regulates the expression of regulatory genes and proteins involved in plasticity and synaptic transmission and decreases MeHg neurotoxicity in the developing rat brain (Jacob and Sumathi 2019). Fisetin has been reported to play an important role in depression, causing a series of physiological abnormalities including decreased tropomyosin receptor kinase B (TrkB) phosphorylation. Wang et al. (2017) indicated that fisetin increased phosphorylated TrkB level without altering total TrkB. Gong et al. (2016) also carried out studies on antidepressant-like effect and the possible mechanisms of icariin in a rat model of corticosterone-induced depression. They observed that icariin remarkably increased sucrose intake and hippocampal brain-derived neurotrophic factor levels and decreased the immobility time in forced swim test in corticosterone-induced depressive rats. Icariin pretreatments reversed the pathological process of corticosterone-induced depression via regulation of the disturbed metabolic pathways.

Glaucoma is another common chronic neurodegenerative disease, which could cause visual loss, especially in aged people. Li et al. (2019) carried out studies on whether fisetin is able to mitigate glaucoma. They reported that fisetin is able to promote the visual functions of DBA/2 J mice by inhibiting NF-κB activation. In addition, they found that both mRNA levels and secretory of tumor necrosis

factor alpha (TNFα), interleukin (IL-1β), and IL-6 were dramatically decreased in fisetin-treated DBA/2 J mice compared to untreated mice. In a recent study, Lin et al. (2019) investigated the effect of fisetin extenuates hypertension-associated cardiac hypertrophy in spontaneously hypertension rats. They showed that fisetin inhibits cardiac hypertrophy by effectively suppressing calcineurin-NFATC3, hypertrophic marker, in SHR hearts. In a recent study, Althunibat et al. (2019) observed that fisetin prevented cardiomyopathy via restoration of hyperglycemia and attenuation of oxidative stress, inflammation, and apoptosis in the diabetic heart. In another recent study, Shi et al. (2018b) found that the underlying mechanisms of fisetin could be attributable to suppression of NF-κB and activation of the nuclear factor erythroid 2-related factor 2 pathway. In parallel with these studies, Jayachandran et al. (2019) investigated the effects of streptozotocin (STZ) on Nrf2, NF-kB, and AMPK pathway and how the isoquercetin treatment at a molecular level overcame the burden of diabetes mellitus. They showed that isoquercetin prevented the oxidative stress and regulation of the expression of Nrf2 pathway-associated proteins and genes.

Aging is the time-related deterioration, characterized by different molecular hallmarks at the cellular and organismal level. More recently, Singh et al. (2019) observed that fisetin suppressed the aging-induced elevation in levels of reactive oxygen species, eryptosis, lipid peroxidation, and protein oxidation, whereas it significantly increases the levels of antioxidants and activates plasma membrane redox system. Based on these findings, the authors proposed that fisetin-rich diet might be a potential antiaging intervention strategy.

Hypertrophic scar is a complex fibroproliferative disorder, causing pain, burning, and itching. Zhang et al. (2016) revealed that galangin effectively extenuated hypertrophic scar formation, suppressing proliferation and inhibiting activin receptor-like kinase 5/Smad2/3 signaling, thus suggesting that galangin is as a potential agent for the treatment of hypertrophic scar or other fibroproliferative disorders.

Osteoporosis is a bone disease, causing loss in bone mass, micro-architectural deterioration of bone tissue, and predisposition to fracture. Accordingly, Chen et al. (2018) concluded that hyperoside was effective in preventing osteoporosis, inhibiting the TNF-receptor-associated factor 6, mediating receptor activator of nuclear factor-κB ligand (RANKL)/RANK/NF-κB signaling pathway and elevating the osteoprotegerin/RANKL ratio. Another study conducted by Zou et al. (2017) demonstrated that hyperoside has hepatoprotective action upon CCl_4-induced chronic liver fibrosis in mice, improving the expression of Nrf2 in nucleus, decreasing the MDA content and GOT/GPT/serum monoamine oxidase activity, and increasing the anti-oxidase (GSH-Px/SOD/CAT) activity toward the formation of trichloromethyl radicals.

Ischemic stroke, leading cause of death, is characterized by an obstruction within a blood vessel supplying blood to the brain. Dai et al. (2018) investigated the effect of isoquercetin on ischemia/reperfusion (I/R) brain injury. They found that isoquercetin has a neuroprotective effect against I/R injury in vivo, mediated by extenuating both oxidative stress and neuronal apoptosis via Nrf2-mediated

inhibition of the NOX4/ROS/NF-κB pathway. Similarly, Zhou et al. (2015) found that kaempferol provided cardioprotection via antioxidant activity and inhibition of phospho-GSK-3β activity in rats with I/R. Moreover, Wu et al. (2016) observed that administration of myricetin mitigated brain injury and neurological deficits via improvement of mitochondrial function and activation of Nrf2 pathway. In addition, Xiong et al. (2016) showed that icariin has neuroprotective effect on ischemic stroke in rats, inhibiting inflammatory responses mediated by NF-κB and peroxisome proliferator-activated receptors (PPARα and PPARγ).

Acetaminophen (APAP) causes serious liver damage. Recently, many researches have been performed in mice for their ability to prevent APAP-induced liver injury. Xie et al. (2016) reported that isoquercitrin pretreatments effectively extenuated APAP-induced hepatic oxidative stress via inhibition NF-κB and MAPK pathways and amelioration of iNOS, TNF-α, IL-1β, and IL-6 production. Accordingly, Domitrović et al. (2015) reached similar results; they reported that myricitrin ameliorated toxic liver damage by several mechanisms, increasing glutathione, cytochrome P450 2E1 level, proliferating cell nuclear antigen expression in regenerating liver tissue and reducing hepatic lipid peroxidation, cyclooxygenase-2, and tumor necrosis factor-alpha overexpression and inflammation in the liver, and inhibiting hepatic expression of transforming growth factor-beta1, alpha-smooth muscle actin, and liver fibrosis. Another study conducted by Ma et al. (2015a) demonstrated that quercetin prevented the CCl_4-induced inflammation via modulation of the TLR2/TLR4 and MAPK/NF-κB signaling pathway.

Schizophrenia is a chronic and severe mental disorder. Ben-Azu et al. (2018) examined the possible mechanisms involved in the antipsychotic-like activity of morin in ketamine model of schizophrenia and observed that morin may demonstrate antipsychotic-like therapeutic effect via modulation of oxidative/nitrergic, cholinergic actions and neuroprotection.

Rheumatoid arthritis is a chronic inflammatory disease. Haleagrahara et al. (2017) showed that quercetin reduced the severity of arthritic inflammation disease in animals, decreasing levels of TNF-α, IL-1β, IL-17, and MCP-1.

Zhang et al. (2017) showed that troxerutin effectively decreased high-fat diet-induced enhancement of hepatic gluconeogenesis via its inhibitory effects on endoplasmic reticulum stress-mediated nucleotide oligomerization domain activation and consequent inflammation.

Parkinson's disease is a neurodegenerative disorder, which is related to the dysfunctions of nigrostriatal dopaminergic systems. Chen et al. (2017) examined the neuroprotective effects of icariin on dopaminergic neurons and the possible mechanisms of Parkinson's disease. They reported that icariin has neuroprotective effect on dopaminergic neurons in Parkinson's disease mice model. The potential mechanisms might be related to PI3K/Akt and MEK/ERK pathways.

Acute kidney injury is a complication of sepsis and increases mortality. Xie et al. (2018) research group indicated that icariin ameliorated cecal ligation and perforation-induced mortality and acute kidney injury, inhibiting renal oxidant damage, inflammatory responses, apoptosis, and vascular permeability.

3.5 Benefits

Studies on humans have clearly shown that drug treatment for diseases often causes severe side effects. Therefore, natural compounds, dietary flavonols and *O*-glycosides, exert a significant therapeutic effect against inflammatory, cancer, and diabetes. However, the protective effects of flavonols and *O*-glycosides on human studies are limited, whereas human cell studies are more common (Table 5).

Osteoarthritis is a common disorder, causing pain and stiffness. Moreover, inflammatory cytokines, IL-1β, induce the production of other inflammatory mediators such as NO and PGE2. Ma et al. (2015b) after investigating the anti-inflammatory effects and mechanisms of astragalin on IL-1β-stimulated human osteoarthritis chondrocytes reported that astragalin inhibited IL-1β-induced NO and PGE2 production by activating PPAR-γ, which subsequently inhibited IL-1β-induced NF-κB and MAPK activation in chondrocytes.

Colorectal cancer is the second leading cause of cancer death in women and the third for men. Chemotherapy, which is the most widely used treatment for cancer, may induce a wide range of adverse effects in patients. Recently, Farsad-Naeimi et al. (2018) investigated the effects of fisetin supplementation on inflammatory and metastatic factors in colorectal cancer patients. They demonstrated that fisetin supplementation markedly attenuated the plasma levels of interleukin (IL)-8 and high-sensitivity C-reactive protein. Therefore, fisetin supplementation can ameliorate the inflammatory status in colorectal cancer patients. In another study, Youns and Hegazy (2017) showed that fisetin inhibited cellular proliferation and viability of hepatic (HepG-2, IC50: 3.2 μM), colorectal (Caco-2, IC50: 16.4 μM), and pancreatic (Suit-2, IC50:8.1 μM) cancer cell lines mediated through activation of CDKN1A, SEMA3E, GADD45B, and GADD45A and downregulation of TOP2A, KIF20A, CCNB2, and CCNB1 genes. Moreover, Wang and Huang (2018) suggested that fisetin effectively inhibited cell proliferation and migration and induced apoptosis in NSCLCs. Huang et al. (2015) showed that galangin and myricetin inhibit angiogenesis induced by ovarian cancer cell lines, inhibiting secretion of vascular endothelial growth factor by the Akt/p70S6K/ hypoxia-inducible factor-1α (HIF-1α) pathway. Another study conducted by Zou and Xu (2018) investigated the effects of galangin on the suppression of retinoblastoma. They observed that galangin suppressed the growth of retinoblastoma tumor through inactivating protein kinase B and promoting Caspase-3 pathway. Thyroid cancer is a thyroid malignant tumor causing enlarged lymph node and pain in the anterior region of the neck. More recently, Fang et al. (2019) demonstrated that icariin showed antitumor effect via downregulating miR-625-3p. Moreover, icariin blocked phosphoinositide 3-kinase/protein kinase B and mitogen-activated protein extracellular signal-regulated kinase kinase/extracellular signal-regulated kinase signaling pathways. Another study found that icariin inhibits both inducible and constitutive signal transducer and activator of transcription 3 activation, making suppressor of tumor cell survival, angiogenesis, and proliferation (Jung et al. 2018). Cisplatin is a valuable chemotherapy agent in clinical studies. However, adverse side effects notably nephrotoxicity limit the use of cisplatin which seriously limits

Table 5 Recent human/cell studies on chronic disease

Components	Chronic disease	Human/cell model	Key outcomes	References
Astragalin	Osteoarthritis	25 patients (age, 57)	Astragalin inhibited IL-1β-induced inflammatory mediators NO and PGE2 production in chondrocytes	Ma et al. (2015b)
Fisetin	Colorectal cancer	37 colorectal cancer patients (100 mg fisetin ($n = 18$) or placebo ($n = 19$) for 7 consecutive weeks)	Fisetin could improve the inflammatory status in colorectal cancer patients	Farsad-Naeimi et al. (2018)
	Hepatic, colorectal, and pancreatic cancer	Hepatic (HepG-2), colorectal (Caco-2) and pancreatic (Suit-2) cancer cell lines	Fisetin inhibited cellular proliferation and viability of hepatic, colorectal, and pancreatic cancer cell lines	Youns and Hegazy (2017)
	Lung cancer	A549 human NSCLC cell line	Fisetin inhibited the growth of A549 cells in a dose- and time-dependent manner	Wang and Huang (2018)
	Chronic obstructive pulmonary disease	NCI-H292 (CRL-1848) and HEK293T (CRL-3216)	Fisetin is a good therapeutic drug candidate for the treatment of inflammatory lung diseases	Lee et al. (2018)
Galangin	Ovarian cancer	A2780/CP70 and OVCAR-3	Galangin inhibited angiogenesis induced by ovarian cancer cell lines	Huang et al. (2015)
	Osteosarcoma	MG-63 and U2-OS	Galangin attenuated osteosarcoma cell proliferation	Liu et al. (2017)
	Laryngeal cancer	TU212 and M4e	Galangin suppressed laryngeal cancer cell proliferation, migration, and invasion, inactivating PI3K/AKT and p38 signaling pathways	Wang and Tang (2017)
	Kidney cancer	A498 cells	Galangin inhibited the proliferation of the kidney cancer A498 cells via inhibition of the PI3K/AKT/mTOR signaling pathway	Zhu et al. (2018)

(continued)

Table 5 (continued)

Components	Chronic disease	Human/cell model	Key outcomes	References
	Retinoblastoma	Y-79, C-33A, WERI-Rb-1, ARPE-19	Galangin exhibited a suppressive effect on human retinoblastoma cell proliferation and migration	Zou and Xu (2018)
Icariin	Bipolar disorder Alcohol use disorder	Ten participants with bipolar I or bipolar II disorders	Icariin may reduce depressive symptoms and decrease alcohol consumption	Xiao et al. (2016)
	Cisplatin-induced cytotoxicity	HEK-293 cell	Icariin exerted protective effect on cisplatin-induced cytotoxicity	Zhou et al. (2019)
	Thyroid cancer	SW579 and TPC1 cells	Icariin showed antitumor effect on thyroid cancer	Fang et al. (2019)
	Myeloma	MMcell and U266	Icariin exhibited as a signal transducer and activator of transcription 3 blocker in myeloma therapy	Jung et al. (2018)
Isoquercitrin	Bladder cancer	5637 and T24 cells	Isoquercitrin inhibits the progression of human bladder cancer	Chen et al. (2016b)
Isorhamnetin	Colon cancer	HT-29 and $Caco_2$	Isorhamnetin glycosides induced a higher percentage of apoptosis in HT-29 than in $Caco_2$, whereas isorhamnetin was more apoptotic in $Caco_2$	Antunes-Ricardo et al. (2014)
Kaempferide	Cervical cancer	HeLa (cervical), MDA-MB-231 (breast), HCT 116 (colon), and HL60 (leukemia)	Kaempferide induced apoptosis in cervical cancer cells	Nath et al. (2015)
Kaempferol	Atherosclerosis	HUVECs	Kaempferol alleviated ox-LDL-induced cell apoptosis	Che et al. (2017)

(continued)

Table 5 (continued)

Components	Chronic disease	Human/cell model	Key outcomes	References
	Human cancer	Human breast carcinoma (MCF-7) cells, human stomach carcinoma (SGC-7901) cells, human cervical carcinoma (Hela) cells, and human lung carcinoma (A549) cells	Kaempferol showed antiproliferative activity on a panel of human cancer cell lines	Liao et al. (2016)
Morin	Kidney injury	HK-2 cells	Morin acted as an ER stress inhibitor	Mo et al. (2019)
Myricetin	Colon cancer	HCT-15	Myricetin treatment reduced cell proliferation and induced apoptotic death of HCT-15 human colon cancer cells via BAX/BCL2-dependent pathway	Kim et al. (2014)
Quercetin	Blood pressure	Meta-analysis of randomized controlled trials ($n = 587$)	Quercetin significantly reduced blood pressure	Serban et al. (2016)
Quercitrin	Periodontal disease	hGF, hMSC	Quercitrin increased both soft and hard tissue regeneration of the periodontium	Gómez-Florit et al. (2015)
Rhamnazin	Inflammation	RAW264.7 cell	Rhamnazin was protective against LPS-induced cytotoxicity in macrophage cells	Kim (2016)
Robinin	Ox-LDL and inflammatory stress	Peripheral blood mononuclear cells were isolated from healthy human volunteers	Robinin ameliorates oxLDL-induced inflammatory insult through TLR4/NF-κB pathway	Janeesh et al. (2014)
Troxerutin	Acute cerebral infarction	Acute cerebral infarction patients ($n = 456$)	Troxerutin could improve neurological defects and promote functional recovery	Liang et al. (2017)

its clinical application. Zhou et al. (2019) investigated the protective effect and possible mechanism of icariin on cisplatin-induced nephrotoxicity on HEK-293 cells. They observed that icariin prevented cisplatin-induced HEK-293 cell injury via regulating NF-κB and PI3K/Akt signaling pathways. Chen et al. (2016b) reported that isoquercitrin inhibited bladder cancer via regulation of the PI3K/Akt and PKC signaling pathways. Antunes-Ricardo et al. (2014) showed that isorhamnetin glycosides showed cytotoxic effect against colon cancer cells, but their activity was affected by glycosylation. Nath et al. (2015), furthermore, demonstrated that kaempferide induced apoptosis in cervical cancer cells through activation of the caspase cascade.

Chronic obstructive pulmonary disease is another chronic inflammatory lung disease and is predicted to be the third leading cause of death worldwide by 2030. Lee et al. (2018) suggested that fisetin is a good drug candidate for improving the lung function of patients with chronic obstructive pulmonary disease, suppressing the TNF-α/NF-κB signaling pathway. Liu et al. (2017) observed that galangin extenuated osteosarcoma cells proliferation via selective activation of the transforming growth factor (TGF)-β1/Smad2/3 signaling pathway. Bipolar disorder is a common and severe psychiatric illness. Xiao et al. (2016) after investigating the effects of icariin on comorbid bipolar and alcohol use disorder in humans reported that icariin may decrease depressive symptoms and reduce alcohol consumption in persons with bipolar disorder and alcohol use. Atherosclerosis is a common disease in which plaque builds up inside your arteries. In addition, endothelial cells, macrophages, and smooth muscle cells have been demonstrated as the main cell types participating in atherosclerosis (Che et al. 2017). Che et al. (2017) observed that kaempferol abated ox-LDL-induced cell apoptosis by upregulation of autophagy via inhibiting PI3K/Akt/mTOR pathway in human endothelial cells. Endoplasmic reticulum (ER) stress may cause various kidney diseases. In a recent study, Mo et al. (2019) found that morin acted as an antioxidant and ameliorated ER-induced cytotoxicity in HK-2 cells. Rhamnazin was protective against LPS-induced cytotoxicity in macrophage cells via modulation of reactive oxygen species/reactive nitrogen species (Kim 2016). In short, dietary flavonols and *O*-glycosides are good candidates to prevent chronic diseases due to their pharmacological properties.

3.6 Application in Food

Food processing often causes losses in bioactive compounds, due to oxidation, enzymatic action, removal of skin or seeds, and leaching into water or oil that is then discarded (Rickman et al. 2007). On the other hand, the concentration of simpler derivatives may increase upon the breakdown of larger molecules. In the literature, there are several reports on the changes of contents of the flavonols, in particular quercetin, rutin, and kaempferol, due to different processing methods (Dos Reis et al. 2015; Nayak et al. 2015; Kamiloglu et al. 2016). A systematic review (Rothwell et al. 2015) collected extensive data and expressed the results as retention

factors (RFs), fold changes in flavonol content due to processing. According to this study, kaempferol and quercetin monoglycosides from broccoli were lost significantly as a result of boiling and frying (RF < 0.3); however steaming caused milder loss (RF $= 0.64$). Steaming also resulted in fewer losses of quercetin derivatives from carrot compared to boiling (RF $= 0.89$ and 0.37, respectively). On the other hand, similar losses of quercetin derivatives from onion were observed upon blanching, boiling, frying, and microwaving (RF $= 0.42$–0.54). Blanched and steamed cabbage and cauliflower contained increased amount of free quercetin; however free quercetin often represents only a small amount of all quercetin derivatives. Although different cooking methods caused a variation in the loss of rutin content in peeled potatoes (RF $= 0.39$–0.54), rutin content in carrots was affected similarly by boiling and steaming. On the contrary, almost all rutin was lost in cauliflower upon boiling, whereas steaming induced no significant change (RF $= 0.08$ and 0.76, respectively) (Rothwell et al. 2015).

In addition to food processing effect, interaction of flavonols with other components in the diet is also critical. Both macroconstituents, i.e., carbohydrates, lipids, and proteins, and microconstituents, i.e., minerals and vitamins, most often occur in foods in combination in a food matrix and are consumed together, which has an impact on the bioavailability of flavonols (Singh and Gallier 2014). Accordingly, a study carried out with rats (Matsumoto et al. 2007) reported that difructose anhydride III, i.e., an indigestible saccharide, promotes the absorption of αG-rutin, a soluble flavonol glycoside. The mechanism behind this observation may be the inhibition of αG-rutin conversion to rutin, a hardly absorbable compound due to its insolubility, by difructose anhydride III (Matsumoto et al. 2007). Another study assessing the effect of pectin on plasma quercetin levels and the fecal flora in mice supplemented with rutin found that the plasma quercetin and isorhamnetin concentrations were significantly higher in the pectin-rutin diet group compared to cellulose-rutin diet group. The authors suggested that pectin might increase the bioavailability of quercetin from rutin by changing the metabolic activity of the intestinal flora and/or the physiological function of the gut. Another explanation is that soluble fiber, e.g., pectin, could increase the gastrointestinal transit time, improving the absorption of flavonols (Tamura et al. 2007). In the study of Azuma et al. (2002), the effects of lipids and emulsifiers on the absorption of orally administered quercetin were investigated in rats. Co-administration of lipids such as lecithin and soybean oil or emulsifiers including sucrose fatty acid ester, polyglycerol fatty acid ester, and sodium taurocholate with quercetin had statistically no significant effects on absorption of quercetin, whereas, the combination of lipids and emulsifiers significantly enhanced the absorption of quercetin (Azuma et al. 2002). The same research group (Azuma et al. 2003) also examined the effects of co-ingestion of quercetin glucosides from onion with different sources of lipids including soybean oil, fish oil, beef tallow, and lecithin. The diet containing soybean oil significantly enhanced the accumulation of quercetin metabolites in plasma of rats. Fish oil and beef tallow also increased the plasma concentration to a similar extent to that with soybean oil, whereas lecithin was the most effective among all the lipids. Moreover, emulsifiers also showed an enhancing effect on the accumulation

of quercetin metabolites (Azuma et al. 2003). Later, another research group (Lesser et al. 2004) investigated the influence of dietary fat on oral bioavailability of quercetin in pigs. Quercetin was administered either as aglycone or as quercetin 3-*O*-glucoside in test meals differing in fat content (3, 17, or 32%). The results revealed that regardless of the chemical form applied, quercetin bioavailability was higher in the 17% fat diet compared to the 3% fat diet ($p < 0.05$) and no additional effect on bioavailability was observed when the flavonols were administered with diets containing 32% fat (Lesser et al. 2004). Same group further investigated the influence of fatty acid pattern of dietary fats on the oral bioavailability of quercetin, which was enhanced after intake of medium-chain and long-chain triacylglycerols, compared to the standard diet (Lesser et al. 2006). In a more recent in vivo study (Guo et al. 2013), overweight men and postmenopausal women ingested quercetin with a fat-free, low-fat, or high-fat diet. During high-fat diet, plasma quercetin maximum concentration and area under curve increased, compared to fat-free diet. Isorhamnetin and tamarixetin, the methylated metabolites of quercetin, were also increased during high-fat diet. The authors reported that it is likely that dietary lipids enhanced the micellarization of quercetin in the small intestine, which favored its solubility and absorption (Guo et al. 2013). In another study, healthy volunteers consumed supplements containing quercetin and kaempferol glycosides together with black tea, black tea with milk, green tea, and water. The addition of milk to black tea did not affect the plasma concentration of quercetin or kaempferol, and hence flavonols from tea were absorbed, and their bioavailability was not affected by the addition of milk (Hollman et al. 2001). Moreover, in the study of Ferri et al. (2015), effect of co-administration of α-tocopherol with quercetin and rutin is evaluated using a rat model. The concentrations of flavanols in plasma and brain indicated that α-tocopherol was able to promote quercetin and rutin transport. The authors indicated that the potential mechanism of enhanced transport of quercetin, rutin, and their putative metabolites might be due to the P-glycoprotein action and/or impairment of the phosphorylation/dephosphorylation mechanism, which controls the in-/outflux of metabolites across the blood-brain barrier (Ferri et al. 2015).

Besides the macro- and micronutrients given above, presence of other flavonoids can also affect the bioavailability of flavonols. For instance, Silberberg et al. (2005) performed a study on rats adapted to diets containing quercetin, or (+)-catechin, or both. When quercetin and (+)-catechin were fed together, their respective plasma concentration significantly decreased, whereas the urinary and hepatic concentrations were only reduced in case of quercetin. On the other hand, co-administration of quercetin and (+)-catechin had no effect on the formation of their metabolites, i.e., glucurono- and sulfo-conjugates (Silberberg et al. 2005). Similarly, Orrego-Lagarón et al. (2016) studied the simultaneous administration of naringenin and quercetin, which are common constituents of tomatoes and other fruits and vegetables, using an in situ model of intestinal perfusion in mice. The results showed that when naringenin and quercetin are administered together, the permeability coefficient values were decreased, whereas the levels of phase II metabolites were increased (Orrego-Lagarón et al. 2016).

3.7 Safety: Toxicity and Side Effects

Majority of studies on safety of flavonols are performed with quercetin. Several scientific bodies and national authorities declared information about the safety and recommended doses of quercetin. International Agency for Research on Cancer, the specialized cancer research agency of World Health Organization (WHO), declared that quercetin is not classifiable as to its carcinogenicity to humans. The Food and Drug Administration (FDA), the federal agency of the US Department of Health and Human Services, also approved quercetin as Generally Recognized As Safe (GRAS) under the intended conditions of use (Ożarowski et al. 2018). The average daily intake of quercetin was estimated as 200 mg and of approximately 460 mg for high consumers. Similarly, in Italy, based on a regulation, the amount of quercetin aglycone in dietary supplements is restricted to 200 mg per day. On the other hand, in Canada, 1200 mg quercetin was defined as the daily limit. However, in case of daily administration of 40–1200 mg quercetin, it has to be separated into two or three doses and consumed together with the meal. Furthermore, for uses over 12 weeks or during pregnancy and breastfeeding, the consumer should consult to a healthcare practitioner (Andres et al. 2018).

Several clinical trials showed that oral intake of quercetin in humans rarely results in adverse effects. Yet, no adverse incidences were reported in human intervention studies, in which volunteers were given quercetin at daily doses of 500 mg for 4–8 weeks (Javadi et al. 2014; Shi and Williamson 2016), 730 mg for 4 weeks (Edwards et al. 2007), or 1000 mg for 5 days, for at least 2 weeks or for 12 weeks (Ganio et al. 2010; Rezvan et al. 2017). On the other hand, in a study conducted with chronic pelvic pain syndrome patients for 1 month, one individual experienced headaches after taking a 1000 mg daily doses of quercetin for a few days. In addition, another patient complained about mild tingling sensation after each quercetin dose (Shoskes et al. 1999). In another study, in which the patients suffering from chronic hepatitis C were treated with daily doses of 250–5000 mg quercetin for 4 weeks, some patients developed mild stomach discomfort when quercetin was taken without a meal (Lu et al. 2016). Information on the safety of quercetin based on clinical trials is limited as there is no data considering long-term treatments ($>$12 weeks) with high dose of quercetin ($\geq$1000 mg per day) (Andres et al. 2018).

Animal studies showed that under certain conditions, quercetin might cause some implications including organ toxicity, cancer, and effects on endocrine system. According to chronic toxicity studies carried out with rats, consumption of approximately 1900–2100 mg quercetin per kg body weight per day resulted in reduced body weight, elevated organ weight (including liver and kidney), increased incidence of hyperplastic polyposis syndrome, presence of calcium oxalate crystals in urine, and existence of yellow-brown pigmentation in the stomach and small intestine (Ito et al. 1989; Dunnick and Hailey 1992; Program 1992). Furthermore, studies using different carcinogens showed that in rodents treated with 150–3400 mg quercetin per kg body weight per day, tumor development was observed in kidney (Zhu and Liehr 1994), colon (Pereira et al. 1996), pancreas (Barotto et al. 1998; Valentich et al. 2006), duodenum (Matsukawa et al. 2002), and mammary glands

(Singh et al. 2010). The possible mechanism behind the carcinogenic effect of quercetin was explained by the inhibition of catechol-*O*-methyltransferase enzyme resulting in increased formation of 4-hydroxyestradiol, which is a carcinogenic metabolite, as well as decreased formation of anti-carcinogenic metabolite 2-methoxyestradiol (Zhu and Liehr 1994; Singh et al. 2010). In addition, in male rats administration of 50–150 mg quercetin per kg body weight per day for 10 days increased the testosterone concentrations in the serum (Ma et al. 2004). In another study, Abd-Ellah et al. (2016) also demonstrated increased serum testosterone levels in male rats fed with 90 mg quercetin per kg body weight per day for 16 days. However, as some other studies conducted for longer periods did not report any effect of quercetin on serum testosterone levels in male rats, it is assumed that this increase in testosterone concentrations in the serum might be considered as a temporary effect of quercetin (Andres et al. 2018).

In addition to the above, both human and animal studies demonstrated that quercetin may interact with drugs and hence modulate their bioavailability. In humans, single or multiple administration of 300–1500 mg quercetin per day decreased the bioavailability of midazolam (sedative) (Duan et al. 2012; Nguyen et al. 2015) and talinolol (antihypertensive drug) (Wang et al. 2013; Nguyen et al. 2014), whereas enhanced bioavailability of cyclosporine (immunosuppressant drug) (Choi et al. 2004), fexofenadine (antihistamine drug) (Kim et al. 2009), and pravastatin (cholesterol-lowering drug) (Wu et al. 2012) was observed. Similarly, in some studies with rats, rabbits, and pigs, animals were fed with 0.6–100 mg quercetin per kg body weight per day for several days, and as a result, the bioavailabilities of many drugs including irinotecan, etoposide, tamoxifen, paclitaxel, doxorubicin (anticancer drugs), digoxin (heart failure drug), verapamil, diltiazem (hypertension, angina pectoris, and heart arrhythmia drugs), valsartan (antihypertensive drug), ranolazine (angina pectoris drug), and paracetamol were enhanced (Ożarowski et al. 2018). On the other hand, the bioavailability of simvastatin (cholesterol-lowering drug) and cyclosporine was reduced when taken together with quercetin (Hsiu et al. 2002; Cermak et al. 2009; Yu et al. 2011). Increased bioavailability of drugs may cause enhanced effectiveness of the drug; however it may also give rise to the potential side effects. In case of a possibility of an increased side effect, the dosage of drug should be adjusted (Andres et al. 2018).

Besides quercetin, kaempferol is also reported to possess some adverse effects including mutagenic and genotoxic effects (Galati and O'Brien 2004; Elgorashi et al. 2008). In addition, it has been reported that the consumption of kaempferol reduces the bioavailability of iron and/or folic acid and hence may cause some undesirable effects in iron and/or folic acid deficient patients (Lemos et al. 2007; Chen and Chen 2013). On the other hand, despite numerous in vitro studies on carcinogenic effects of kaempferol, there are no data from in vivo studies evidencing this effect (Devi et al. 2015). Similarly, for another flavonol, myricetin and its glycoside myricitrin, acute studies in mice did not provide evidence of genotoxicity, supporting the opinion of WHO's expert committee on food additives (JECFA) that myricitrin poses no safety concern for humans when consumed at current estimated dietary exposures (Hobbs et al. 2015).

3.8 Marketed Products

Nowadays, flavonol supplements, in particular quercetin supplements, are widely available in markets for affordable prices. The labels of these marketed products contain some health claims including support of immune and skin health, anti-inflammatory responses, cardiovascular and cholesterol health, and reduction of symptoms of arthritis. Additionally, these marketed products may help fight against allergies and pain; support circulation, mood, and energy levels; and help protect the kidneys, brain, and liver. The scientific studies related to these health claims of flavonols are given in detail in the previous sections. In some marketed products, flavonols are combined with other compounds to increase their low bioavailability. For example, there are a few quercetin supplements enhanced with 20–50% bromelain, which is an enzyme derived from the stems of pineapples. Although quercetin supplements enhanced with bromelain may provide increased absorption of quercetin, these products may not be suitable for those with pineapple allergies. In another product, quercetin is combined with vitamin C to ease the gastrointestinal discomfort that the consumed may experience and also to increase the antioxidant activity. Many of the products available on the market contain 500 mg of flavonol on average; however products with less or more amount of flavonols are also available.

3.9 Patents

In recent years, numerous patents have been published as a result of inventions related to applications of flavonols, in particular quercetin and its *O*-glycosides. These patents include methods of extraction of flavonols from natural sources (Zhang 2016; Cao et al. 2018; Shi et al. 2018a), production of nanocapsules (Wang et al. 2015; Krolevets 2016; Zhang et al. 2019), and prevention and treatment of various diseases including immune diseases (Park et al. 2017), liver disease (Kim et al. 2018), breast cancer (Lee 2018), and many others.

In Table 6, some recent US patents on health promoting effects of flavonols are presented. Mbikay et al. (2015) claimed that a therapeutically effective amount of quercetin-3-*O*-β-D-glucoside and, optionally, a therapeutically effective amount of a statin reduce the plasma cholesterol levels of patients. In another study, it has been suggested that quercetin combined with one or more of vitamin B3, vitamin C, and folic acid can be used to treat cancer together with a chemotherapy agent (Lines 2015). Same researcher also used a similar formulation, i.e., quercetin, vitamin B, vitamin C, and *Bauhinia forficata* extract, to treat metabolic syndrome and diabetes (Lines 2016). Moreover, a composition containing quercetin or isoquercetin, one or more of vitamin B3, vitamin C, and a folate, has been used to treat Zika virus infection. This formulation may also prevent microcephaly and treat and prevent infections of other *Flaviviridae* viruses (Lines 2017). Similarly, Bakar (2016) also claimed that quercetin, or analogues, or derivatives thereof have antiviral activity for prophylaxis or treatment of flavivirus infection or a disease resulting therefrom in humans or animals. The antiviral activity included the inhibition of virus attachment

Table 6 Recent US patents on health promoting effects of flavonols

Patent no	Date	Inventors (country)	Title	Major claims
US 2015/0190369 A1	Jul. 9, 2015	Mbikay et al. (Canada)	Quercetin-3-glucoside and uses thereof	Quercetin-3-*O*-β-D-glucoside (Q3G) increases the amount of cell surface low-density lipoprotein receptor (LDLR) on a cell and reduces the amount of functional protein convertase subtilisin/kexin type 9 (PCSK9) secreted by the cell Plasma cholesterol levels are reduced in patients treated with a therapeutically effective amount of Q3G and, optionally, a therapeutically effective amount of a statin
US 2015/0283112 A1	Oct. 8, 2015	Kim et al. (Korea)	Composition comprising myricetin as active ingredient for enhancing exercise performance or fatigue recovery	Myricetin or a pharmaceutically available salt thereof increases exercise capacity and enhances physical strength. Energy efficiency is increased by improving the function of mitochondria The composition comprising myricetin as active ingredient prevents aging and recovers from fatigue The composition also has an anti-obesity effect by increasing energy consumption
US 2015/0366838 A1	Dec. 24, 2015	Lines (Switzerland)	Method for treating cancer with a combination of quercetin and a chemotherapy agent	Combination of a chemotherapy agent and a composition that includes quercetin, one or more of vitamin B3, vitamin C, and folic acid may be used to treat cancer
US 2016/0000749 A1	Jan. 7, 2016	Bakar (Malaysia)	Method of inhibiting or treating a dengue virus infection with quercetin	Quercetin, or analogues, or derivatives thereof have antiviral activity for prophylaxis or treatment of *flavivirus* infection (that may comprise dengue virus types 1, 2, 3, and 4) or a disease resulting therefrom in humans or animals. The antiviral activity includes the inhibition of virus attachment to host cells and inhibition of intracellular virus replication

(continued)

Table 6 (continued)

Patent no	Date	Inventors (country)	Title	Major claims
US 2016/0129064 A1	May 12, 2016	Lines (Switzerland)	Method for treating metabolic syndrome and diabetes using quercetin and *Bauhinia forficata* extract	Composition containing quercetin, vitamin B, vitamin C, and *Bauhinia forficata* extract may be used to treat metabolic syndrome and diabetes
US 2016/0317442 A1	Nov. 3, 2016	Dajas et al. (Uruguay)	Nanosomal preparation of the complex formed by quercetin (or another flavonol, flavone, or a derivative thereof) and 2-hydroxypropyl-beta-cyclodextrin for intravenous use in cerebral pathological conditions	Cholesterol lecithin nanosomes, without propylene glycol, from the complex formed by quercetin (or another flavonol or flavone or a derivative thereof) and 2-hydroxypropyl-β-cyclodextrin, by means of a process that allows the safe, effective intravenous use thereof in the treatment of cerebral pathological conditions in adults and newborns The preparation stabilizes altered hemodynamic parameters in severe neonatal hypoxia in newborn pigs and is effective in protecting cerebral function in experimental Parkinson's disease models and in newborn pigs subject to hypoxia
US 2017/0007632 A1	Jan. 12, 2017	Lai and Lai (Taiwan)	Method for alleviating radiation injury with isorhamnetin-3-*O*-β-D-glucoside	Administration of a composition containing isorhamnetin-3-*O*-β-D-glucoside to a subject in need thereof alleviates the radiation injury
US 2017/0042924 A1	Feb. 16, 2017	Otsuka et al. (Japan)	Muscle atrophy inhibitor containing quercetin glycoside	Quercetin glycosides, which are safely ingestible for a long time, have inhibitory activity on the expression of myostatin involved in muscle atrophy
US 2017/0196834 A1	Jul. 13, 2017	Bei and Guo (China)	Preparation and application of flavonol as brain-targeting synergist	Kaempferide, rutin, troxerutin, myricetin, and hydroxy derivatives thereof, in particular their glycoside, ester, ether derivatives, can promote the drug molecules that have therapeutic or healthcare effect, such as ginsenoside, stilbene glucoside, resveratrol, levodopa, edaravone, vinpocetine, nicergoline, citicoline, oxiracetam, to enter brain tissues, to dramatically

(continued)

Table 6 (continued)

Patent no	Date	Inventors (country)	Title	Major claims
				enhance drugs concentrations in the brain tissues and effectively enhance the efficacy of drugs without increasing the plasma concentration
US 2017/0216246 A1	Aug. 3, 2017	Lines (Switzerland)	Method for treating Zika virus infection with quercetin-containing compositions	Composition containing quercetin or isoquercetin, one or more of vitamin B3, vitamin C, and a folate may be used to treat Zika virus infection. Composition may also prevent microcephaly and treat and prevent infections of other *Flaviviridae* viruses

to host cells and inhibition of intracellular virus replication. According to Otsuka et al. (2017), quercetin glycosides have inhibitory activity on the expression of myostatin involved in muscle atrophy. Likewise, another flavonol, myricetin or a pharmaceutically available salt thereof, has been shown to increase the exercise capacity and to enhance the physical strength. Increase in energy efficiency was due to the improved function of mitochondria. Myricetin is also claimed to prevent aging and recover from fatigue and has an anti-obesity effect by increasing energy consumption (Kim et al. 2015). In another study, nanosomal preparation of the complex formed with quercetin and 2-hydroxypropyl-beta-cyclodextrin was used in the treatment of cerebral pathological conditions in adults and newborns. The preparation was effective in protecting cerebral function in experimental Parkinson's disease models and in newborn pigs subject to hypoxia (Dajas et al. 2016). Similarly, kaempferide, rutin, troxerutin, myricetin, and hydroxy derivatives thereof, in particular their glycoside, ester, and ether derivatives, can promote the drug molecules that have therapeutic or healthcare effect, such as ginsenoside, stilbene glucoside, resveratrol, levodopa, edaravone, vinpocetine, nicergoline, citicoline, and oxiracetam, to enter brain tissues, to dramatically enhance drugs concentrations in the brain tissues and effectively enhance the efficacy of drugs without increasing the plasma concentration (Bei and Guo 2017). In addition to the above, administration of a composition containing isorhamnetin-3-*O*-β-D-glucoside to a subject in need thereof alleviates the radiation injury (Lai and Lai 2017).

3.10 Perspectives

In addition to the research already performed in the literature, new strategies need to be addressed to gain additional information. Below, a number of important points are highlighted as to how, in the future, one might approach to this topic differently, in order to maximize the knowledge gained from this chapter.

- Recently, the role of interindividual variability on the impact of flavonols on bioefficacy attracted great attention. So far, studies investigating this effect could not correlate the observed bioactivity with the bioavailability due to lack of data (Menezes et al. 2017). Hence, future studies, which include the parent compound and known metabolites, together with details of the individuals, i.e., age, gender, genotype, composition of gut microbiota, diet, lifestyle, and health status, are needed to address the effect of interindividual variation on bioavailability of flavonols and *O*-glycosides (Almeida et al. 2018).
- Encapsulation technology can be used to enhance the bioavailability of flavonols or to achieve controlled release of these compounds during digestion. Spray drying, coacervation, liposome entrapment, inclusion complexation, cocrystallization, nanoencapsulation, freeze-drying, yeast encapsulation, and nanoemulsion are some of the current technologies that are used to encapsulate bioactive compounds (Fang and Bhandari 2010). Although there are several reports in the literature that studied the encapsulation of flavonols (Hao et al. 2017; Azzi et al. 2018), the effect of this processing technique on the human body is not fully established yet. Therefore, further research on this topic is necessary.
- One of the factors affecting the bioavailability of flavonols is their interaction with other components in the diet. Co-digestion of flavonols with other macro- and microconstituents in foods will affect their bioavailability. In general, while indigestible carbohydrates, e.g., dietary fiber, proteins, and minerals, are likely to cause unfavorable effects on flavonol bioavailability, digestible carbohydrates, lipids, vitamins, and some other micronutrients, e.g., other flavonoids, alkaloids, and carotenoids, may enhance the bioavailability of flavonols. Interaction between flavonols and food matrix is a complex phenomenon that should be further investigated to provide maximum beneficial health effects to the consumers.
- Scientific information on the safety evaluation of flavonols from clinical trials is limited due to lack of relevant safety data, especially considering high-dose flavonol treatments for longer terms. Therefore, in future human intervention studies, it is important to investigate the safety and possible side effects of flavonols considering long-term treatments with high dose of flavonols (e.g., for quercetin >12 weeks and ≥ 1000 mg per day).

3.11 Conclusions

The focus of this chapter was the bioactive constituents, bioavailability, metabolism, bioactivity, benefits, food applications, safety issues, marketed products, and patents of dietary flavonols and *O*-glycosides. Flavonols, e.g., quercetin, kaempferol, myricetin, and isorhamnetin, most commonly occur as *O*-glycosides in dietary sources. In the human body, flavonol glycosides are cleaved to their aglycones and further metabolized to their glucuronidated, sulfated, and methylated conjugates. Moreover, compounds that reach the colon may be degraded by the colonic

microbiota to different metabolites, which may also contribute to the health beneficial effects of flavonol consumption with respect to cardiovascular diseases, diabetes, inflammation, viral infections, enhanced physical strength, and cancer prevention. Dietary intake of flavonols may be affected by the food processing, which often results in significant losses. Although rare adverse effects of flavonol consumption are reported, majority of the clinical trials and animal studies indicated that flavonol consumption is safe under the intended conditions of use.

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