J. Korean Soc. Appl. Biol. Chem. **54**(1), 1-18 (2011) **Review**

New Genera of Flavonols and Flavonol Derivatives As Therapeutic Molecules

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Received May 12, 2010; Accepted October 11, 2010

Natural products from plants and microorganisms traditionally have provided the pharmaceutical industry with one of the most important sources of "lead" compounds in the search for new drugs and medicines. The diversity of polyphenol structure is enormous. They are classified into several classes, the most important polyphenol in our food being phenolic acids and flavonoids, which include flavonol as one of subgroups. Flavonols are a group of plant secondary metabolites containing hydroxyl in 3rd position of chromone ring of a '6+3' flavonoid ring structure. Several health beneficial activities have been attributed to these naturally occurring plant flavonols, including antioxidative, anticarcinogenic, vasoprotective, anti-inflammatory, neurodegenerative, antidiabetic, antiplatelet activities, among which antioxidative properties remain the main topic investigated in recent years. The main aim of this review is to put forward the pharmacological importance of major flavonols and newly found flavonol derivatives from the last 10 years and their related bioactivity as lead compounds. The bioactivity of these flavonoids depends on structure-activity relationship (SARs), the flavonols being one of the structurally active compounds. Most studies have demonstrated their occurrence and their absorption in humans, but the question remains as to which form is actually absorbed: aglycone, glycosidic or both. The major flavonols such as quercetin, kaempferol, myricetin, rutin, isorhamnetin, and galangin were found to exhibit anticancer activity. These flavonols also have positive effects on major diseases such as cardiovascular disease, type-2 diabetes, and Alzheimer's disease. They are also found to have therapeutic value against osteoporosis, platelet aggregation, and antioxidant activity, the major action of prevention.

Key words: antioxidants, biosynthesis, flavonols, secondary metabolites

Studies published during the last 10 years on the flavonoids as flavonols were searched using MEDLINE and PUBMED. Flavonoids are ubiquitous plant secondary metabolites found in almost all parts of plants. So far more than 4000 flavonoids have been discovered, and the list is expanding. They have been described to occur mainly in plants as *O*-, *C*-glycosides, free aglycones, and as methylated and sulfated derivatives [Bruneton, 1999]. They have been found to be an important part of the human diet and principle physiological active constituents used to treat human diseases [Bruneton, 1999]. Several biological activities have been attributed to flavonoids such as antioxidative [Dugas *et al*., 2000; Leenen *et al*., 2000], anticarcinogenic [Warngard *et al*, 1987], vasoprotective [Woodman and Chan, 2004; Roghani *et al*., 2005], anti-inflammatory [Boots *et al*., 2008], neurodegenerative [Hou *et al*., 2009; Zhu *et al*., 2009], antidiabetic [Soobrattee *et al*., 2005; Lee *et al*., 2009b], and antiplatelet [Watson *et al*., 2005] activities, among which the antioxidative property remains the main topic investigated in recent years. Hence, these are described as ubiquitous molecules or nutraceuticals. Flavonoids and their analogs can be subdivided into several classes: flavones, flavonols, flavanones, isoflavones, flavans, flavanols, and anthocyanins [Mojca *et al*., 2005]. The bioactivity of these flavonoids depends on SARs, the flavonols being one of the structurally active compounds.

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doi:10.3839/jksabc.2011.001

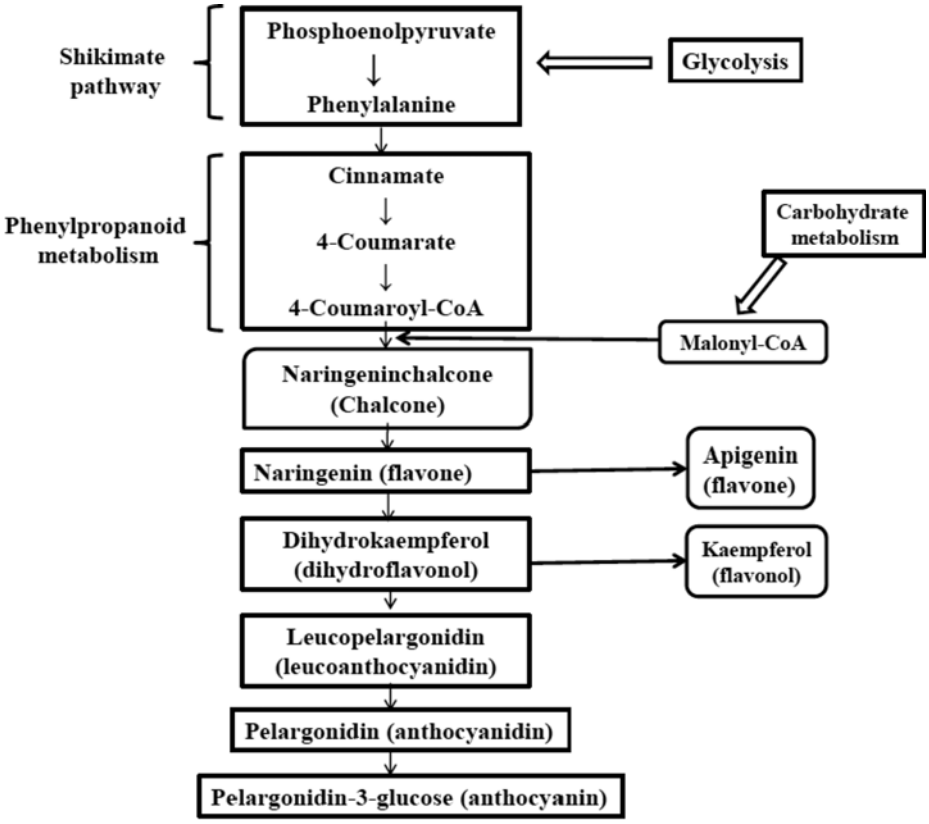

Fig. 1. Biosynthesis of flavonoids.

Fruits, vegetables, and beverages such as tea and red wine are major sources of flavonols in the human diet. Food sources, dietary intakes, and bioavailability of flavonols are strongly influenced by variations in plant type, growth period of plants, season, light, degree of ripeness, food preparation, and processing [Ahrene and O'Brien, 2002]. The health effects of flavonols though reviewed by several authors [Duthie *et al*., 2000; Graf *et al*., 2005], there was no updated review on major flavonols and new derivatives of flavonol. Thus, the main aim of the present review is to summarize bioactivity of flavonols and their derivatives mentioned in the literature during the last 10 years (2000 to 2010) and their role as therapeutic molecules in the treatment of various major diseases.

Biosynthesis and Chemistry of Flavonols

The flavonoids are a group of low-molecular-weight polyphenolic substances that are formed from the combination of derivatives synthesized from phenylalanine (via the shikimic acid pathway) and acetic acid [Heller, 1986]. The first step involves the formation of phenylalanine from phenylpyruvate. Phenylalanine is transformed into trans-cinnamic acid, which is then hydrolyzed into *p*-coumaric acid (C-9). The C-9 acids condense with three C-2 (malonyl-coA) units to form a C-15 chalcone. Three subsequent ring closure and hydration give rise to compounds such as the 3-hydroxyflavonoids (catechins) and 3, 4-diolflavonoids (flavonols) [Crozier *et al*., 1997]. The biosynthesis of flavonols and major classes are described in Figs. 1 and 2. The structure of the flavonoids is based on the flavonoid nucleus (Fig. 3a), which consists of three phenolic rings referred to as the A, B, and C rings [Harborne, 1986]. The term *4-oxo-flavonoids* is often used to describe flavonoids, such as flavanols (catechins), flavanones, flavonols, and flavones, which carry a carbonyl group on C-4 of ring C (Fig. 3b).

Types of flavonols. Flavonoids depend on structural class, degree of hydroxylation, other substitutions and conjugations, and degree of polymerization [Harborne, 1986]. In plants, they are relatively resistant to heat, oxygen, dryness, and moderate degrees of acidity, but can be modified by light [Crozier *et al*., 1997]. Photostability of the flavonoid molecule depends on the nature of the hydroxyl group attached to C-3 of ring C. The absence or glycosylation of this hydroxyl group results in high photostability of the molecule [Smith *et al*., 2000].

Classification. The biological activities of flavonoids and their metabolites depend on their chemical structure and relative orientation of various moieties on the molecule. The basic structure of the flavonoid nucleus allows for different substitution patterns in the A, B, and

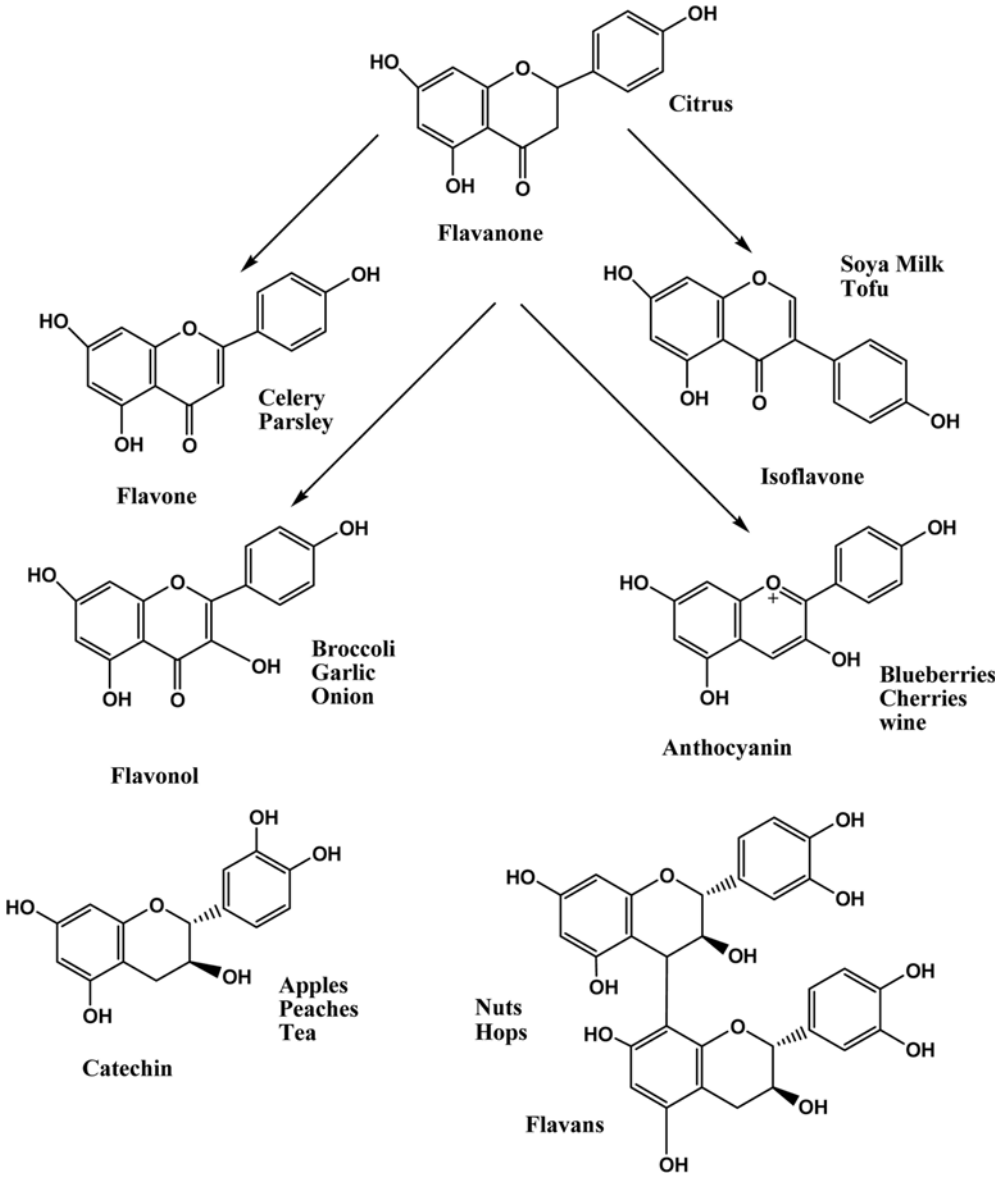

Fig. 2. Major classes of flavonoids and their sources [Yao *et al*., 2004].

C rings, resulting in various subgroups. The flavonoids are divided into different classes according to their oxidation level on the C-ring, which include, among others, anthocyanidins, flavanols (catechins), flavones, flavonols, flavanones, and isoflavonoids [Harborne, 1986] (Fig. 3). Flavones and flavonols are found most frequently with B-ring hydroxylation in the C-3' and C-4' positions [Kühnau, 1976] in most of the plants (Table 1).

Flavonoid glycosides. Major classifications and substitutions of flavonoids include glycosylation, hydrogenation, hydroxylation, malonylation, methylation, and sulfation [Harborne, 1986] and complex pattern of conjugation, glycosylation or methylation can modify the hydrophilicity of the molecule and its biological properties, and markedly increase the molecular weight of the flavonoid. Flavonoid without sugar moieties are *aglycones*, whereas with sugar moieties are called *flavonoid* glycosides [Harborne, 1986]. Except for catechins, flavonoids do not occur in plants as aglycones; the most frequently occurring forms are the glycoside derivatives in plants [Crozier *et al*., 1997].

The preferred glycosylation site on the flavonol molecule is the C-3 position and, less frequently, the C-7 position during glycoside formation [Fossen *et al*., 1998]. D-glucose is the most usual sugar residue, whereas arabinose, galactose, glucorhamnose, lignin, L-rhamnose, and xylose are the least preferred [Kühnau, 1976]. For instance, quercetin can be linked to the 3-*O*-glycoside rhamnose to yield quercitrin, or to glucorhamnose to yield rutin. The checklist of flavonol-glycosides [Harborne and Mabry, 1988] is available (Table 2 and Fig. 4).

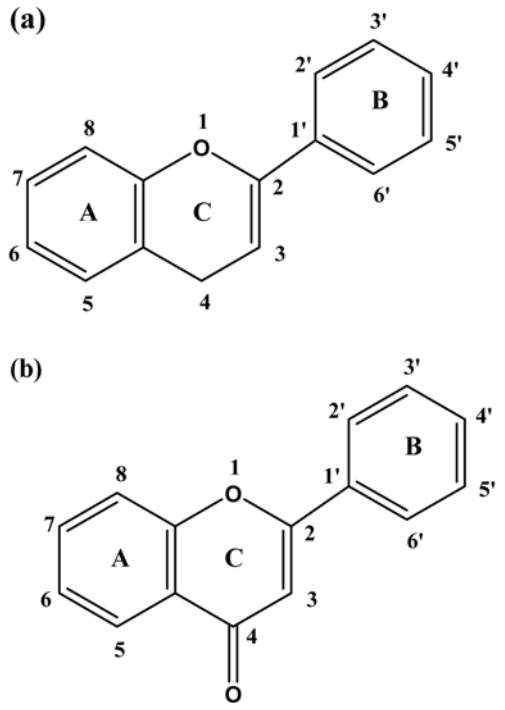

Fig. 3. (a) Flavan nucleus and (b) 4-oxo-flavonoid nucleus basic structure [Ahrene and O'Brien, 2002].

Flavonols in the Human Diet

Fruits, vegetables, and beverages such as tea and red wine are especially rich sources of quercetin, myricetin, and kaempferol as flavonols [Crozier *et al*., 1997]. Tea, onions, and apples are the most predominant food sources of flavonols in the Denmark [Justesen *et al*., 1997] and United States [Rimm *et al*., 1996]. However, the dietary sources can differ significantly depending on the country of origin. Predominant source of dietary flavonoids is red wine in Italy, whereas fruits, vegetable soups, and salads in a northern Italian villages [Pietta, 2000].

Lowest intake (1 to 9 mg/d) of flavonoids was from a South American diet, whereas highest flavonoid intake (75 to 81 mg/d) was from a Scandinavian diet [deVries *et al*., 1997]. The daily consumption of flavonols is difficult to determine as values depend on availability of food composition tables, dietary habits and preferences, and flavonol content in foods. Total flavonoid intake and content in foods can be assumed greater than values reported as dietary flavonoid content, and intakes have been based mostly on the content of only three flavonols (Tables 3 and 4).

Metabolism of Flavonoids

In the past few years, there has been an increase in the number of studies on flavonoid absorption, metabolism, and excretion both *in vivo* and *in vitro*. This section reviews studies on the absorption and metabolism of flavonoids in human subjects and tissues only. The detailed mechanism of flavonoids metabolism is explained in Fig. 5 (a and b).

Absorption of flavonoids as flavonols. Nowadays, concentrations as low as 10 nM can be detected in human plasma samples as analytical methods have greatly improved [Manach *et al*., 1998]. Over the past few years, researchers have studied flavonol absorption in humans by providing subjects with various sources of flavonols, such as a flavonol-rich food, flavonol aglycone capsules, and other encapsulated flavonol glycosides [Aziz *et al*., 1998; McAnlis *et al*., 1998]. Most studies have demonstrated the occurrence of flavonol absorption in humans, but the question remains as to which form is actually absorbed: aglycone, glycosidic or both.

For instance, 52% of quercetin glucosides were absorbed in an onion-rich meal [Hollman *et al*., 1995], which led to the conclusion that humans could absorb significant amounts of quercetin in aglycone and glycosidic forms. However, quercetin glucosides are efficiently hydrolyzed into quercetin in the small intestine by β-glucosidases, which is then mostly absorbed [Walle *et al*., 2000]. The attached sugar moiety on flavonol affects the rate of metabolic absorption [Hollman *et al*., 1999]. The nature of glycosides can differ in type and position depending on the food source. For example, quercetin-3-glucoside and quercetin-4'-glucoside are two forms of quercetin rapidly absorbed in humans irrespective of the position of the glucose moiety [Olthof *et al*., 2000].

However, flavonoid aglycones are hydrophobic in nature and can be transported across membranes by both passive diffusion and active transport. It was also speculated that the intestinal sodium–glucose transporter can transport glucose attached to quercetin through the intestinal cell wall [Hollman *et al*., 1995].

Kaempferol and galangin flavonols are absorbed and conjugated inside the cells then transported across. Kaempferol showed passive diffusion, whereas it was not the case with other conjugates.

Hydrolysis of flavonoids. Deglycosylation of flavonoid glycosides has been quoted as the first stage of metabolism. Human small intestine and liver cell-free extracts were used to study glucosidases activity toward flavonoid glycosides, in which some but not all flavonoid glycosides were hydrolyzed [Day *et al*., 2000a]. Similarly, lactase phlorizin hydrolase, which can deglycosylate dietary flavonoid glycosides, is suggested to have a role in flavonoid metabolism [Manach *et al*., 1996]. After absorption, flavonoids are bound to albumin and transported to the liver via the portal vein [Manach *et al*.,

Table 1. 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	2,3',4',7-tetrahydroxy-2-phenylchromen-4-one	H	H	OH	H	H	H	OH	OH	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) cgrinbe-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
Isorhamnetic	3,5,7-trihydorxy-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	H	OH	OCH_3	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-methoxyphenyl)-7-methoxyphenyl)-4-one	OH	H	OCH_3	H	H	OCH_3	OH	H	H
Rhamnetin	2-(3,4-dihydroxyphenyl)-3,5-dihydroxy-7-methoxychromen-4-one	OH	H	OCH_3	H	H	OH	OH	H	H

Table 2. Flavonol derivatives and their glycosylation positions

Flavonol	Aglycone	3	5	6	7	8	2'	3'	4'
Astragalin	Kaempferol	Glc	-	-	-	-	-	-	-
Azalein	Azaleatin	Rha	-	-	-	-	-	-	-
Hyperoside	Quercetin	Gal	-	-	-	-	-	-	-
Isoquercetin	Quercetin	Glc	-	-	-	-	-	-	-
Kaempferitrin	Kaempferol	Rha	-	-	Rha	-	-	-	-
Myricitrin	Myricetin	Rha	-	-	-	-	-	-	-
Quercitrin	Quercetin	Rha	-	-	-	-	-	-	-
Robinin	Kaempferol	Robinose	-	-	Rha	-	-	-	-
Rutin	Quercetin	Rutinose	-	-	-	-	-	-	Glc
Spiraeoside	Quercetin	-	-	-	-	-	-	-	-
Xanthorhamnin	Rhamnetin	trisachharide	-	-	-	-	-	-	-
Amurensin	Kaempferol	-	-	-	Glc	tert-amyl	-	-	-
Icariin	Kaempferide	Rha	-	-	Glc	Tert-amyl	-	-	-
Troxerutin	Quercetin	Rutinose	-	-	hydroxyethyl		-	-	hydroxyethyl

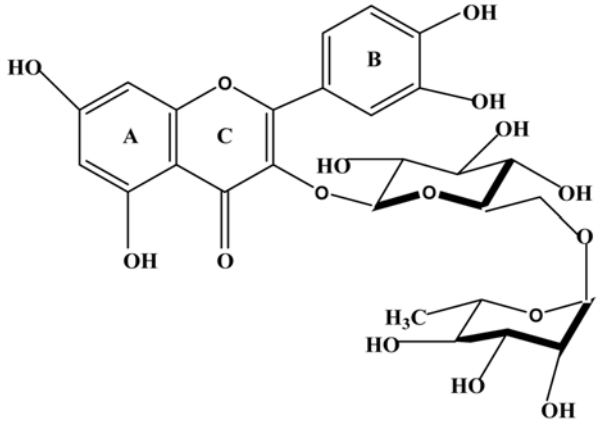

Fig. 4. Example of flavonol glycoside.

1996] as well as to the intestinal mucosa and/or kidneys [Hackett, 1986]. Flavonoids and their derivatives may undergo reactions such as hydroxylations, methylations, and reductions. Isorhamnetin (3' methyl-quercetin) present in human plasma after consumption of various fruits and vegetables [Manach *et al*., 1998] and quercetin glucosides can be methylated to form isorhamnetin immediately after absorption in the liver cell (Fig. 4b) [Olthof *et al*., 2000].

Conjugation reactions with glucuronic acid and/or sulfate appear to be the most common type of metabolic pathways for the flavonoids. For instance, glucuronidation of flavonols occurs in human microsomes (UGT-1A9) [Oliveira and Watson, 2000] and liver [Yilmazer *et al.*, 2001], and uridine diphosphate-glucuronosyltransferase plays an important role in this process [Oliveira and Watson, 2000]. Glucuronidation, *O*-methylation, and *O*-methyl-glucuronidation occur in flavonoid metabolism in the small intestine [Kuhnle *et al*., 2000], and *O*-methyl-transferases are involved. In humans after ingestion of *Gingko biloba* extract, no flavonoid metabolites were detected in blood. The structural requirements of flavonols for the formation of advanced glycation end-product are hydroxyl groups at 3', 4', 5, 7 and methylation of 3' hydroxy exhibiting inhibitory activities against free radicals [Matsuda *et al*., 2003]. This activity was explained by SAR [Day *et al*., 2000b].

Bacterial degradation of flavonoids. Flavonoid metabolism in humans depend on the participation of intestinal microflora [Matsuda *et al*., 2003], and flavonoids that are not absorbed in the small intestine can be metabolized by colonic microflora into aglycones and phenolic acids. This process takes place in the large intestine and the cecum [Winter *et al*., 1989] and produces a series of phenolic compounds that have been identified as aromatic acids (Fig. 5a and b).

Excretion of flavonoids. Flavonoid glucuronides and sulfates are polar, water-soluble compounds that are readily excreted by mammals in the urine and bile. When excreted in bile, the flavonoids are passed into the duodenum and metabolized by intestinal bacteria, which results in the production of fragmentation products and/or the hydrolysis of glucurono- or sulfoconjugates [Winter *et al*., 1989]. The resulting metabolites that are released may be reabsorbed and enter the enterohepatic cycle. Substitution on the flavonoid molecule, degree of polarity, and molecular weight determine the extent of biliary excretion [Griffiths, 1982]. They also are eliminated by renal excretion after conjugation in the liver [McDonald *et al.*, 1983]. Studies have shown that the amount of flavonols excreted, as a proportion of intake, can vary from 0.8 to 1.4% [Aziz *et al*., 1998] depending on the source of dietary flavonols.

Bioactivity of Flavonols

The bioactivity of flavonols mainly due the antioxidant activity was compared to SAR. Studies showed a direct relationship between the flavonol content [Yen *et al*., 2008] and antioxidant activities in ethanol fractions and flavonol derivatives [Mariani *et al*., 2008]. These molecules of nutritional interest play an important role in cellular response for preventing pathologies. In particular, they interact directly with nuclear receptors and can modulate the activity of key enzymes involved in cell signaling and antioxidant responses. Moreover, nutri-genomics, which may be defined as the application of genomic tools to study the integrated effects of nutrients on gene regulation, however, holds great promise in increasing the understanding of how nutrients affect molecular events in organisms [Moskaug *et al*., 2004]. Some of these mechanisms are discussed below.

Anti-carcinogenic properties of flavonols. Skin is the first barrier of defense, and many research studies indicate that exposure of human skin to physical carcinogens such as UV light may damage cells, leading to skin cancer. It has been shown that reactive oxygen species (ROS) such as superoxide anion (O_2·), hydroxyl radical (·OH), and hydrogen peroxide (H_2O_2) are responsible for UV-induced oxidative damage. Skin cancer, cutaneous aging, and many inflammatory disorders are interrelated [Nishi *et al*., 1991]. It has been reported that the flavonol quercetin exhibits antitumor activity by inhibition of calmodulin and oxidative stress, thus preventing photobiological damage [Takahama, 1985].

The flavonol myricetin was found to inhibit wrinkle formation in UVB-induced mouse skin and exhibited anti-photoaging effect [Jung *et al*., 2010] by regulating MMP-9 expression. It can stimulate transcription of

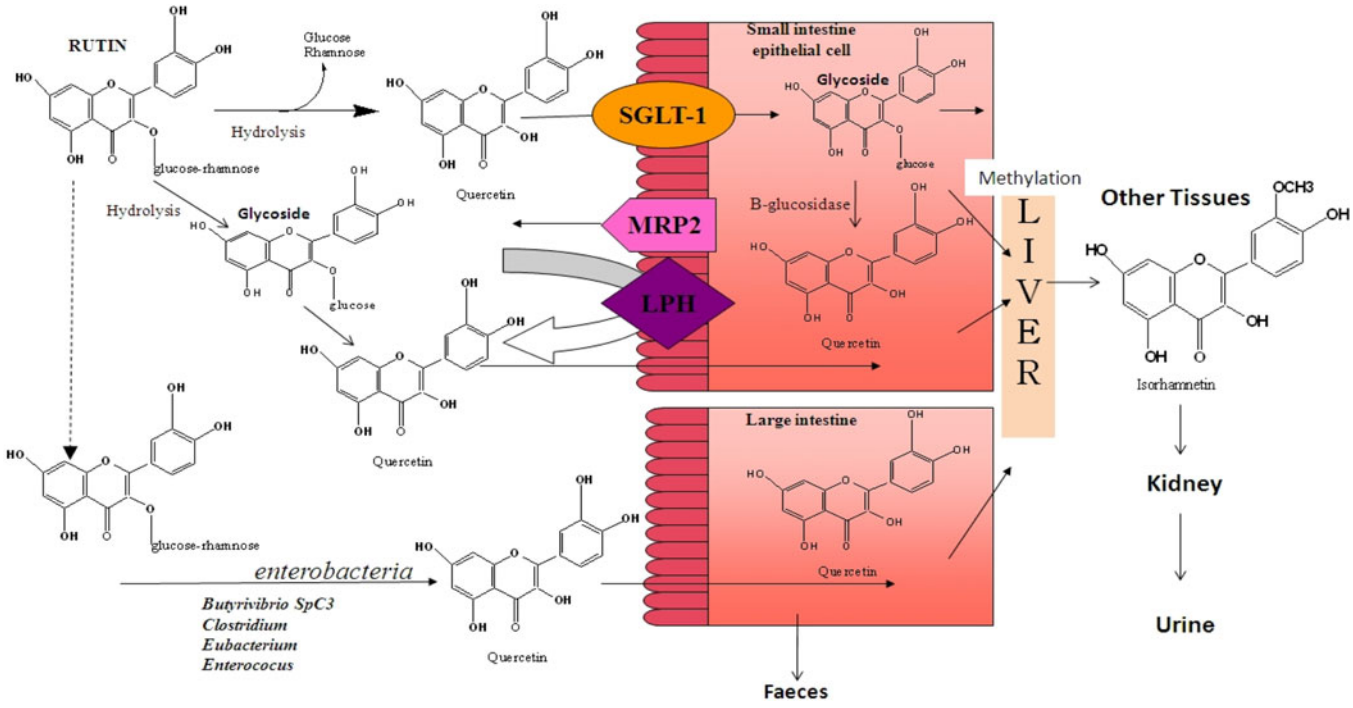

Fig. 5. (a) Microbial flora assisted metabolism of flavonols in humans [Hollman, 2000].

phase II detoxifying systems and act as anti-carcinogen [Jung *et al*., 2010] and inhibit carcinoma cell growth. The difference in flavonol action may be due to the greater uptake by cell membrane of the less hydrophilic poly-methoxylated flavonoids. Quercetin also arrests tumor growth by inhibiting mitosis [Giulia *et al*., 1999] and cell cycle, as well as by blocking or competing for hormone receptor sites [Komori *et al*., 1993; Lea *et al*., 1993; Larocca *et al*., 1994]. The flavonols quercetin and rutin when administered by diet were reported to inhibit azoxymethanol-induced colonic neoplasia in mice [Avila *et al*., 1994]. The flavonol glucoside kaempferol-3-*O*-β-D-glucopyranoside derived from the traditional Chinese medicinal plant *Wikstroemia indica* demonstrated antileukemic activity in the P-388 leukemic mice [Deschner *et al*., 1991]. Including this quercetin was also found to have anti-proliferative effects (~40%) in serous ovarian cancer cells [Ye *et al*., 2007] and colorectal cancer cells. Quercetin and some of the quercetin conjugates were also found to reduce COX-2 expression at the transcription level [Bao *et al*., 2004]. Gliszyńska-Świgło *et al*. [2003] also investigated the involvement of the pro-oxidant quinone chemistry of quercetin.

The flavonol kaempferol, could be a potent candidate for apoptosis in human lung carcinoma cells (H460) [Leung *et al*., 2007], human HCT116 colon cancer cells [Li *et al*., 2009], and rat H4IIE cells [Niering *et al*., 2005]. Among three flavonols (myricetin, quercetin and kaempferol), myricetin directly targets one of the four members of this family JAK1 and blocks cell transformation in mouse JB6 cells [Takuma *et al*., 2009]. The DNA topoisomerases (topos) is considered as the target of several drugs commonly used in cancer chemotherapy [López-Lázaro *et al*., 2010]. Few new flavonols like morin shows protective effect against colon carcinogenesis [Kumar *et al*., 2010], apoptosis in DEN (diethylnitrosamine)-induced hepatocellular carcinogenesis model [Sivaramakrishnan and Devaraj, 2010] and anticancer through COX-2, NFkB, and matrix in metalloproteinase-mediated pathways [Sivaramakrishnan and Devaraj, 2009]. This naturally available dietary agent is believed to impede cancer promotion and progression.

The results of MTT assay showed that flavonols such as quercetin, kaempferol, and myricetin were all able to induce cytotoxicity on human oesophageal adenocarcinoma OE33 cell line [Zhang *et al*., 2008] and squamous cell carcinoma (KYSE-510) cell line [Zhang *et al*., 2009] in a dose- and time-dependent manner. The cytotoxicity induced by these flavonols was mediated by G2/M cell cycle arrest and apoptosis in both of the above cell types.

Four Flavonols-myricetin, quercetin, kaempferol, and galangin with different numbers of hydroxyl moieties present in flavan rings A, B, and C, are responsible for their antioxidant activity, cytotoxicity on human umbilical vein endothelial cells, and for their potential antiangiogenic and cell adhesion effects [Kim *et al*., 2006]. Flavonols as dietary compounds strongly upregulate the activity of p-glycoprotein in cancer cell lines [Elisabetta *et al*., 1995].

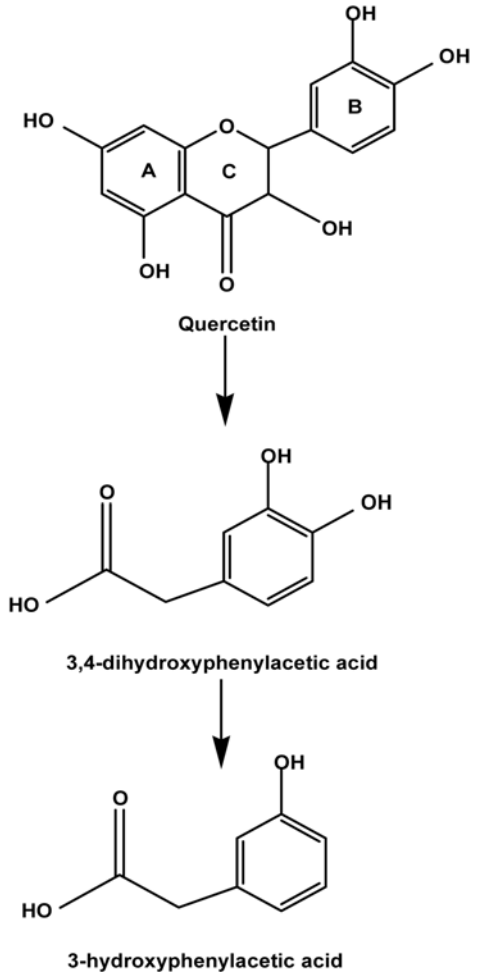

Fig. 5. (b) Quercetin (a flavonol) hydrolysis products formed by human microflora [Day *et al*., 2000a].

Dietary flavonol quercetin acts as anti-tumor agent against β-catenin/Tcf signaling in SW480 cells [Park *et al*., 2005], inhibit the activation of phophatidylinositol 3-kinase, which is required for tumor necrosis factor-α-induced upregulation of matrix metalloproteinase-9 [Hwang *et al*., 2009], and quercetin-deglucosidated derivatives beneficial for EpRE-mediated gene expression effects [Lee-Hilz *et al*., 2008] are the major metabolites present in the systemic circulation. The action mechanisms of most flavonoids are inhibition of cell proliferation, differentiation, inhibition of angiogenesis, cell cycle arrest, and apoptosis.

Vasoprotective effects. Flavonoids, long been acknowledged for their unique antioxidant properties, possess other activities that may be relevant to heart ischemia-reperfusion [Akhlaghi and Bandy, 2009]. They may prevent production of oxidants, and inhibit oxidants from attacking cellular targets, ultimately resulting in lower oxidant production and better re-establishment of blood in the ischemic zone (Fig. 6).

Epidemiological studies indicating that high dietary intake of flavonols reduces the risk of mortality due to coronary heart disease have provoked interest in the mechanism of this cardioprotective effect [Akhlaghi and Bandy, 2009; Middleton *et al*., 2000; Woodman and Chan, 2004]. The biological effects include lowering plasma levels of low-density lipoproteins, inhibiting platelet aggregation, scavenging free radicals, and reducing cell proliferation. The order of potency for relaxation was flavonols>flavones>flavanones [Ajay *et al*., 2003]. The flavonol quercetin has capacity to relax the preconstricted rings of aorta in subchronic STZ-diabetic rats through nitric oxide and prostaglandin-mediated pathways, which could be considered as endothelium-dependent [Roghani *et al*., 2005]. In recent years proliferation in blood vessels has been the focus of major studies. In addition, flavonols enhance the production of vasodilating factors and inhibit the expression of two major pro-angiogenic factors. Taken together, all these mechanisms are triggered by flavonols with specific structures, although the structural requirements may be different from one effect to the other, and that they all contribute to the vasoprotective, anti-angiogenic, anti-atherogenic, vasorelaxant and anti-hypertensive effects of acute or chronic administration of plant polyphenols found *in vivo* in animals and in human patients. Flavonoids may contribute to the vascular protection by scavenging peroxynitrite-derived radical, and high intake of fruits and vegetables reduces coronary risk [Stoclet *et al*., 2004; McCarty, 2008]. Finally, flavonoids are vasodilatory through a variety of mechanisms, one of which is likely to interact with ion channels. These multifaceted activities of flavonoids raise their utility as possible therapeutic interventions to ameliorate ischemia-reperfusion injury [Kaliora *et al*., 2006].

Anti-inflammatory activity. Anti-inflammatory properties of flavonoids have been studied successfully both *in vitro* and *in vivo*. Rheumatoid arthritis (RA) is one of the chronic inflammatory diseases, which are characterized by leukocyte recruitment and activation, cell proliferation, angiogenesis, and pannus formation, ultimately resulting in joint destruction [Boots *et al*, 2008]. Flavonol-rich RVHxR (*Rhus verniciflua* Stokes) have significant anti-inflammatory activities on vascular permeability, leukocyte migration, and cellular immunity and acts as a potential therapeutic agent in the treatment of inflammatory and angiogenesis-related diseases [Lee *et al*., 2009a].

Kaempferol, afzelin, kaempferitrin, quercetin, isoquercetrin, rutin, and pterogynoside act as myeloperoxidase inhibitors [Regasini *et al*., 2008]. Inflammatory pathways induced by co-planar polychlorinated biphenyls (PCBs) can be down-regulated by the dietary flavonoid quercetin through mechanisms associated with functional caveolae

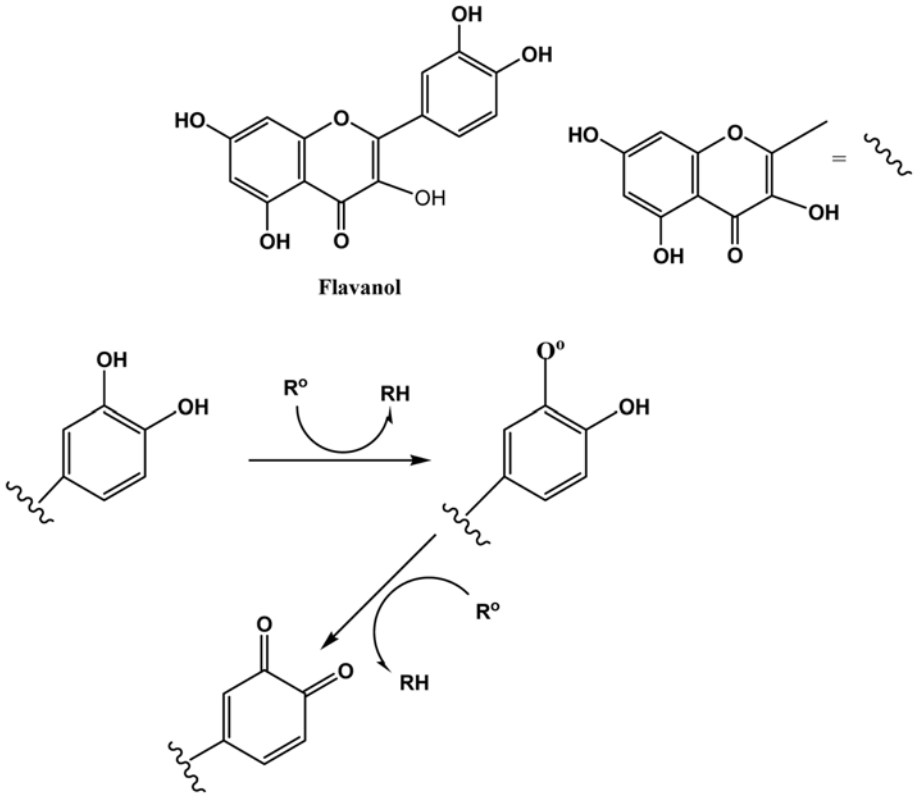

Fig. 6. Radical scavenging capacity of flavonols [Pietta, 2000].

(membrane domains) [Jung *et al*., 2010]. Quercetin suppressed the induction of GRP78 expression by various ER stressors, except brefeldin A at both the mRNA and protein levels [Natsume *et al*., 2009]. The flavonol myricitrin can act as a substrate and inhibitor of myeloperoxidase, which is the predominant peroxidase present at sites of inflammation [Meotti *et al*., 2006]. The flavonols and flavonol glycosides present in *Punica granatum* (pomegranate) possess anticancer activities associated with anti-inflammation effects [Lansky and Newman, 2007]. The flavonol quercetin and 3-*O*-methyl quercetin found in *Achyrocline satureioides* (Lam.) has anti-inflammatory effects against edema [De Souza *et al*., 2007]. These studies demonstrate that quercetin remains functionally stable in the formulations of non-ionic emulsion with high lipid content and anionic emulsion with low lipid content [Casagrande *et al*., 2007]. The dihydroflavonols were also found to have effects on inflammation and enzymes involved in arachidonic acid metabolism [Hernández *et al*., 2007]. The compounds sakuranetin, 7-*O*-methylaromadendrin, and 3-acetyl-7-*O*-methylaromadendrin present in *Inula viscosa* have been tested both *in vitro* and *in vivo* as selective inhibitors of 5-LOX [Hernández *et al*., 2007]. The flavonols such as myricitrin were found to have anti-allodynic property in animal models of persistent inflammatory and neuropathic pain in mice [Morikawa *et al*., 2003]. Quercetin, isoquercetin, and rutin were found to modulate the inflammatory response by modulating the prostanoid synthesis, as well as cytokine production [Rotelli *et al*., 2003]. The contents of PGE2, TNF-α, RANTES, MIP-2 and the mRNA for cyclooxygenase-2 were also found to be decreased in rats. In a comparative study of anti-inflammatory activities of flavonols in animal models of acute and chronic inflammations, the compound quercetin was able to reduce paw oedema induced by carrageenan [Morikawa *et al*., 2003]. An intraperitoneal administration of rutin inhibited both acute and chronic phases of experimental model of inflammation [Pelzer *et al*., 1998].

Flavonols and neurodegenerative diseases. Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive impairment of memory and cognition. The present study on cortical neurons isolated from double transgenic (TgAPP/PS1e9) AD mice shows that the ginkgo flavonols, quercetin and kaempferol, stimulate depression-related signaling pathways, which involves brain-derived neurotrophic factor BDNF/phosphorylation of cyclic AMP response element-binding protein CREB/postsynaptic density proteins PSD95, and reduces amyloid-β-peptide (Ab) [Hou *et al*., 2009]. Hibifolin, a flavonol glycoside, prevents β-amyloid-induced neurotoxicity in cultured cortical neurons, thus providing protection

Table 3. Contents of major flavonols in fruits and vegetables

Fruit/Vegetable	Major Flavonol Content (mg/100 g fresh weight)		
	Kaempferol	Myricetin	Quercetin
Apple (Fuji)	0.01	0-0.03	0-4.91
Apricot	0	0	1.15-2.60
Artichokes	0	0	0
Asparagus	-	-	2.31-28.72
Avocados	-	-	-
Banana	-	-	-
Beans	8.00-44.37	-	0-0.01
Beets	0	0	0-0.67
Bilberry	0	0-2.10	1.70-4.12
Blackberries	0-0.21	0-9.99	0-10.76
Blueberries	0-3.72	0-8.62	0-14.60
Broccoli	0.70-9.15	0-0.03	0-13.70
Brussel sprouts	0.74-1.28	0	0-0.60
Chinese Cabbage	0.01-16.30	0-0.10	0-39.00
Carrots	0-0.60	0-0.40	0-1.50
Cauliflower	0-1.25	0	0-3.90
Celery	-	0	0-3.50
Chard Swiss	0.50-9.20	0-3.10	0.30-7.50
Cherries (sweet)	0	0	0.86-3.93
Chicory (green)	0-11.10	0	0-25.20
Chinese Chives	15.07-19.16	-	-
Cowpeas	1.92	2.60	17.22
Cranberries	0-0.27	0.40-23	7.30-25
Crowberries	0	4.40-4.90	5.30-5.60
Crowndaisy (leaves)	0	0.02	0.16
Cucumber (with peel)	0	0-0.33	0
Currants (European, black)	0-1.50	0-14	4.40-8.60
Currants (red)	0-0.04	0-4.29	0-1.30
Currants (white)	0-0.70	0-0.70	0.50-6.30
Dates	-	0	0-2.40
Egg plant	0.01	0.03	0
Elderberry	-	-	29-60
Figs	-	0	0-3.20
Garlic Chives	2.12	-	0.12
Goose berries	0-1.90	0	0-2.20
Grapefruit	0.40	-	0.50
Grapes (black)	0	0.45	1.26-3.70
Grapes (red)	0-0.01	0-0.03	0-3.98
Grapes (white)	0	0-0.45	0.20-3.87
Horseradish (roots)	0.60-2.57	0	0-0.57
Kale	0.48-47	0	0-12
Kiwifruit	0	0	0
Kohlrabi	2.43	0	0.40
Leeks	0.64-4.58	0	0-0.50
Lemons	0	0	0-3.47
Lettuce	0-0.04	0	0-14.56
Mangos	0.01	0.03	0
Melon (Cataloupe)	0	0	0

Table 3. Continued

Fruit/Vegetable	Major Flavonol Content (mg/100 g fresh weight)		
	Kaempferol	Myricetin	Quercetin
Mulberries	0	-	2.47
Mushrooms	0	0	0
Nectarines (white)	-	-	0.10-0.66
Onions (raw)	0-1	0-0.03	1.50-118.70
Onion (red)	0-4.50	0-3.80	0-191.70
Oranges (all varieties)	0-0.01	0-0.03	0-0.90
Papaya (raw)	0.01	0.03	0
Parsley	0-2.50	8.08	0-1
Peache (raw)	0	0	0-1.23
Pear (raw)	0	0	0-20.50
Pear (green)	0	0	0-19.03
Pepper (green, hot chilli)	0	1.20	10.50-21.02
Pepper (yellow)	0	0	28.83-78.38
Pepper (sweet, red)	0	0	0-1.20
Perilla leaves	0	0.43	0.53
Pineapple (raw)	0.01	0-0.03	0
Plum (red)	0-0.01	0-0.03	0-7.04
Pomegranate	0	0	0
Potato (flesh & skin)	0-0.05	0	0-3.41
Pumpkin (raw)	0	0	0
Radish (raw)	0.40-2.11	0	0
Raspberries (raw)	0-0.66	0	0-4.58
Spinach (raw)	0-55	0-0.04	0-27.22
Strawberries (raw)	0-1.61	0-0.03	0-3.20
Sweetpotato (raw)	0.01	0.03	0.01
Tagerines (mandarin)	0	0	0
Tomato (cherry)	0-0.27	-	0.17-20.30
Watercress	1-1.50	0.20	4-8.30

The table contents were extracted from USDA data of Flavonoids 2007.

against cell death. This principle could be useful in developing potential drugs or food supplements for treating AD [Zhu *et al*., 2009]. Rutin was also found to have anticonvulsive effects when injected intracerebroventricularly [Butterfield *et al*., 2002; Nassiri-Asl *et al*., 2008]. Kaempferol and rhamnocitrin can augment cellular antioxidant defense capacity through regulation of HO-1 expression and MAPK signal transduction in PC12 cells [Hong *et al*., 2009]. In addition, the compound fisetin was found to be good neuroprotective agent that significantly reduces the behavioral deficits following an ischemia of brain [Maher *et al*., 2007].

Flavonols and anti-diabetic property. Diabetes mellitus (DM) has been a subject of extensive research, but the prevention and control of type 2 DM have not been resolved. Kaempferol glycosides isolated from *Cinnamomum osmophloeum* leaves were found to have insulin-like anti-diabetic mechanism [Lee *et al*., 2009b].

Myricetin improves insulin sensitivity through the enhancement of insulin action on IRS-1-associated PI 3-kinase and GLUT 4 activity in soleus muscles of animals exhibiting insulin resistance [Grundy, 2007]. The flavonol quercetin was found to exhibit anti-obesity properties through anti-adipogenesis activity by activating the AMPK signal pathway in 3T3-L1 preadipocytes [Ahn *et al*., 2008]. The compound kaempferitrin (kaempferol-3, 7-O-(α)-L-dirhamnoside) found in the *Bauhinia forficate* leaves has long-term effects on glycaemia in diabetic rats, as well as on ^{14}C-D-glucose uptake and ^{14}C-leucine incorporation into protein in normal rat soleus muscle [Muthukumaran *et al*., 2008].

Flavonols and platelet aggregation. Platelets perform a central role in hemostasis and thrombosis. They adhere to subendothelial collagens exposed at sites of blood vessel injury via glycoprotein (GP) GPV1 and integrin $\alpha_2\beta_1$, thus inducing inside-out signaling. GPVI binding to

Table 4. Contents of major flavonols in beverages

Beverage	Major Flavonol Content (mg/100 mL)		
	Kaempferol	Myricetin	Quercetin
Berry wine (colored)	0-0.33	0.13-2.26	0.14-2.43
Berry wine (white)	0	0	0-0.41
Apple cider (European)	-	-	0-0.96
Apple juice (unsweetened)	0	0-0.05	0-3.01
Blackberry (concentrate)	-	20.85	22.85
Coffee (in water)	0	0.05	0.05
Cranberry juice (raw)	-	4.41	16.41
Crowberry juice	-	3.46-3.51	3.76-3.99
Grape juice (white)	-	-	0.36
Grapefruit juice (pink)	-	-	0
Grapefruit juice (white)	0	0.05	0-0.47
Lemon juice (raw)	0	0-0.05	
Orange juice	0	0.05	0-2.20
Tangerine juice (raw)	0	-	0-1.44
Tea (black, in water)	0.25-2.41	0.17-0.90	0.41-4.75
Tea (Green)	0.67-3.31	0.52-1.60	1.40-4.10
Tea (oolong)	0.90	0.49	1.30

The contents of table were extracted from USDA data of Flavonoids 2007.

collagen performs distinct functions in the regulation of cell signaling involving non-receptor tyrosine kinases (e.g. Src, Fyn, Lyn, Syk), adaptor proteins, phospholipase C, and lipid kinases such as phosphoinositide 3-kinase (PI3K) [Ruggeri and Mendolicchio, 2007; Watson *et al*., 2005]. Some recent studies suggested that quercetin or the combined use of adenosine diphosphate and thromboxane A2 inhibitors abrogated platelet spreading on these surfaces to a similar extent [Navarro-Núñez *et al*., 2010]. In the study on the inhibitory effect of quercetin on platelet kinases, Dai *et al*. [2006] reported that the addition of 2,2'-azobis(2-methylpropionamidine) dihydrochloride (AAPH) at 37°C to the suspension of RBCs caused fast hemolysis after a short period of inhibition, and addition of flavonols and their glycosides (FOHs) bearing ortho-dihydroxyl functionality significantly suppressed hemolysis. Other studies on bioactive compounds such as quercetin and dihydroquercetin showed that inhibition of platelet aggregation may not be directly mediated by the removal of free radicals possibly due to their interaction with cell membrane [Chen and Deuster, 2009].

The novel derivatives of flavonols from plant sources and some of their biological effects are summarized in Table 5.

Toxicological Issues

Phytochemicals are traditionally used as herbal drugs to prevent disorders in the human body. The flavonol phytochemical may be a chemical compound or mixtures of chemical compounds that act individually or in combination to maintain human health. In practice, standardization of the dosage as herbal drugs is important, and very low doses may have no therapeutic value. Thus, plant materials, which have therapeutic value, are often used in overdose. An upper limit is necessary with highly active or potentially harmful ingredients, as most plants have wide therapeutic window (e.g. effect of a toxic compound is considerably higher than the therapeutic dose).

At the international level, some of the existing Legal Frameworks for plant-derived ingredients with medicinal properties are maintained by the World Health Organization (WHO), EU, and the Food and Drug Administration (FDA) of USA. According to FDA, natural products are regulated as foods under the requirement for ingredients to be generally recognized as safe (GRAS). Natural products generally have GRAS status, provided that this is supported by expert consensus. Hence, dietary supplements and herbs are considered to be foods provided that they have GRAS status and do not make medicinal claims.

Botanical secondary compounds are not benign molecules; ecologically speaking, they evolved as chemical defenses that can repel, stun, poison or kill other species. It would be naïve to think that all plant extracts are necessarily safe for human consumption. It is precisely for these reasons that poison centers have been established across several

Table 5. Effective novel flavonol derivatives identified from the plant sources

Flavonol/ Flavonol derivative	Plant Source	Analysis/Bioactivity	Reference
Quercetin 3,3',4'-tri-*O*-β-D-glucopyranosides Quercetin 3'-(6-sinapoyl-*O*-β-D-glucopyranosyl)-3,4'-di-*O*-β-D-glucopyranoside Quercetin 3-(2-sinapoyl-*O*-β-D-glucopyranosyl)-3'-(6-sinapoyl-*O*-β-D-glucopyranoside	*Eruca sativa* leaves	1D and 2D analysis of ^{1}H and ^{13}C NMR and ESI MS/MS	Weckerle *et al*., 2001
Quercetin 3-O-[2'''-*O*-β-D-glucopyranosyl-(1→6)-β-D-glucopyranoside Quercetin 3-O-[2''', 6'''-*O*-diacetyl-β-D-glucopyranosyl-(16)-β-D-glucopyranoside Isorhamnetin 3-O-[2'''-*O*-β-D-glucopyranosyl-(1→6)-β-D-glucopyranoside Quercetin 3-O-[2'''-*O*-acetyl-α-L-arabinopyranosyl-(1→6)-β-D-glucopyranoside	Meconopsis quintuplinervia	HRFABMS, ^{1}H-^{1}H COSY, HSQC and HMBC	Shang *et al*., 2006
Kaempferol 3-*O*-[(6'''-*O*-acetyl-β-D-glucopyranosyl)-(1→4)-3'''-*O*-(4'''', 4''''-dimethyl-3-oxo-butyl)-α-L-rhamnopyranoside] Kaempferol 3-*O*-[(3'''-*O*-acetyl-β-D-glucopyranosyl)-(1→4)-3'''-*O*-(4'''', 4''''-dimethyl-3-oxo-butyl)-α-L-rhamnopyranoside] Kaempferol 3-*O*-[(2'''-*O*-acetyl-β-D-glucopyranosyl)-(1→4)-α-L-rhamnopyranoside]	*Neocheiropteris palmatopedata* roots	^{1}H NMR, ^{13}C NMR and DEPT/cancer cell line	Hong *et al*., 2010
Quercetin 3-*O*-rutinoside Quercetin 3-*O*-galactoside Quercetin 3-*O*-glucuronide Kaempferol 3-*O*-robinobioside Keampferol 3-*O*-galactoside Isorhamnetin 3-*O*-rutinoside Kaempferol 3-*O*-glucoside Kaempferol 3-*O*-glucuronide Kaempferol 3-*O*-pentose	Petals of lotus (Nelumbo) cultivars	HPLC/PDA/ESI	Yang *et al*., 2009
Kaempferol-3-*O*-α-L-(3'''-*E*, 4''-*Z*-di-p-coumaroyl)-rhamnopyranoside Quercetin-3-*O*-α-L-(3''-*E*, 4''-*Z*-di-p-coumaroyl)-rhamnopyranoside Quercetin-3-*O*-α-L-(3''-*Z*, 4''-*E*-di-p-coumaroyl)-rhamnopyranoside Kaempferol-3-*O*-α-L-(3'', 4''-di-*Z*-p-coumaroyl)-rhamnopyranoside	Machilus philippinensis	HPLC-SPE-NMR/type II diabetes	Lee *et al*., 2008
Kaempferol 3-*O*-(2'', 4''-*O*-diacetyl-α-L-rhamnopyranoside) Kaempferol 3-*O*-(3'', 4''-*O*-diacetyl-α-L-rhanmopyranoside) Kaempferol-3-*O*-(4''-*O*-acetyl-α-L-rhamnopyranoside)	Forsteronia refracta	P^{90} RSK inhibitors	Xu *et al*., 2006
Quercetin-3-arabinose Quercetin-3-galactoside	American craneberry fruit	HPLC & GC-MS	Chen and Zuo, 2007
Myricetin hexoside Myricetin deoxyhexoside Quercetin hexoside-gallate Kaempferol hexoside Quercetin deoxyhexoside Myricetin deoxyhexoside-gallate	*Myrica rubra Sieb. et Zucc.*	HPLC-DAD-ESIMS	Fang *et al*., 2007
Galangin	Plant origin/*Alpinia officinarum*	Inhibitory effect on rat vas deferens (Partly Vanilloid receptors) Leukeaemia therapy (HL-60 cell), /cancer chemoprevention,	Capasso and Mascolo, 2003; Bestwick, 2006; Heo *et al*., 2001
Morin	Plant origin/Standard	Anti-heptocellualr transformation agent/Supressed Th1 immune response in mice	Hsiang *et al*., 2005; Fang *et al*., 2005
Isorhamnetin, Kaempferol	Ginkgo biloba	Inhibitor of CYP1B1	Chang *et al*., 2006
Quercetin	*Ginkgo biloba*/others	Inhibitor of CYP1B1/Enhance osteogenic differentiation in adipose tissues, bone engineering, stem cell research	Chang *et al*., 2006; Kim *et al*., 2006
Myricitrin	Standard	Anti-inflammatory and antinociceptive action	Meotti *et al*., 2006
Kaempferitrin (Kaempferol-3,7-*O*-(α)-L-dirhamnoside)	Bauhinia forficata	Insulinomimetic effect	Jorge *et al*., 2004
Fisetin	Standard	Inhibits T_H2-type cytokine	Higa *et al*., 2003

continents [Gurib-Fakim, 2006].

While the pharmaceutical industry in the developed world will continue to investigate promising leads from natural products in their effort to produce new drug entities, the production of new medicines in the developing world may have quite different priorities; when a plant is readily available and has the potential to provide inexpensive therapy for the treatment of a disease, then a product may well be developed. Thus, a close collaboration is expected between clinical doctors and scientists with a common endeavor-production of safe, quality and efficacious products, making worthwhile contribution to healthcare.

Conclusion

Flavonols as flavonoids are dietary factors, and humans consume about 1-2 g of flavonoids daily. Flavonoids are abundantly present in fruits, vegetables, seeds, nuts, tea, and red wine. The major flavonol consumed is quercetin, which is believed to act as health-promoting substances. It is generally nontoxic and manifests a diverse range of beneficial biological activities such as antioxidative, anti-carcinogenic, vasoprotective, anti-inflammatory, neuro-degenerative, antidiabetic, and antiplatelet activities. Among all flavanols, quercetin, myricetin and kaempferol play the most important role in controlling of various diseases.

Acknowledgment. This work was carried out with the support of "Cooperative Research Program for Agriculture Science & Technology Development (Project No. PJ005453)" Rural Development Administration, Republic of Korea.

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