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QUERCETIN AND ITS DERIVATIVES: CHEMICAL STRUCTURE AND BIOACTIVITY – A REVIEW

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Key words: quercetin, phenolic compounds, bioactivity

Quercetin is one of the major dietary flavonoids belonging to a group of flavonols. It occurs mainly as glycosides, but other derivatives of quercetin have been identified as well. Attached substituents change the biochemical activity and bioavailability of molecules when compared to the aglycone. This paper reviews some of recent advances in quercetin derivatives according to physical, chemical and biological properties as well as their content in some plant derived food.

INTRODUCTION

In recent years, nutritionists have shown an increased interest in plant antioxidants which could be used in unmodified form as natural food preservatives to replace synthetic substances [Kaur & Kapoor, 2001]. Plant extracts contain various antioxidant compounds which occur in many forms, thus offering an attractive alternative to chemical preservatives. A small intake of these compounds and their structural diversity minimize the risk of food allergies. Additionally, the substances isolated from edible plants are the least toxic to a human body. For this reason, the naturally occurring bioactive compounds, that may act in synergy with drugs in pharmacological applications, can be adapted in "combination therapy", thus enabling the use drugs at lower concentration but with an increased efficiency [Russo, 2007]. This strategy can play a major role in the future of cancer prevention [Reddy *et al.*, 2003]. This aspect of research is presently at the developmental phase, but the search for new substances occurring naturally in plants to be used as food preservatives or as a new therapeutic agents shifts the scientists' focus to, among others, phenolic compounds [Singh, 2002].

Quercetin, a flavonol occurring in fruit and vegetables is a food component with proven beneficial impact on health [Kaur & Kapoor, 2001]. Its biochemical activity is well documented. It is one of the most potent antioxidants among polyphenols [Formica & Regelson, 1995; Prior, 2003; Rice-Evans *et al.*, 1997]. Quercetin has also been demonstrated to display the antiviral, antibacterial, anticarcinogenic and antiinflammatory effects [Di Carlo *et al*., 1999; Formica & Regelson, 1995; Harborne & Williams, 2000]. The anticarcinogenic properties of quercetin result from its significant impact on an increase in the apoptosis of mutated cells, inhibition of DNA synthesis, inhibition of cancerous cell growth, decrease and modification of cellular signal transduction pathways [Erkoc *et al*., 2003].

In food, quercetin occurs mainly in a bounded form, with sugars, phenolic acids, alcohols *etc*. After ingestion, derivatives of quercetin are hydrolyzed mostly in the gastrointestinal tract and then absorbed and metabolised [Scalbert & Williamson, 2000; Walle, 2004; Wiczkowski & Piskuła, 2004]. Therefore, the content and form of all quercetin derivatives in food is significant for their bioavailability as aglycone. Progress in highly sensitive and high-precision testing equipment made scientists able to isolate and identify compounds which sometimes occur in marginal quantities and are characterised by a highly complex structure. The number of new natural plant substances described in literature, including quercetin derivatives, is still increasing. This progress is illustrated by the fact that in the flavonol group, more than 230 new compounds were identified in the years 1986-1992 [Harborne 1994], while 180 new structures were isolated in the years 2001-2003 [Williams & Grayer, 2004]. Research into the biological properties of the flavonoid derivatives has become popular as well. The list of investigated substances includes compounds with antioxidant properties as a potential source of food preservatives [Smith-Palmer *et al.*, 2001; Vurma *et al.*, 2006], compounds with antibacterial and antiviral properties as an alternative to antibiotics [Chun *et al*., 2005; Shetty, 2004] as well as substances with allelopathic properties which could replace pesticides and insecticides [Simmonds, 2001; Souto *et al*., 2000]. This paper focuses on quercetin derivatives most frequently occurring in the nature to determine the impact of their chemical structure on the physical properties and biological activity.

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CHEMISTRY OF QUERCETIN DERIVATIVES

Structure

A molecule of quercetin (1) (Figure 1), contains five hydroxyl groups whose presence determines the compound's biological activity and the possible number of derivatives. The main groups of quercetin derivatives are glycosides and ethers as well as the less frequently occurring sulfate and prenyl substituents [Harborne, 1994; Williams & Grayer, 2004]. More than half of flavonol structures identified in the past decade are compounds containing alkyl substituents in their molecules [Williams & Grayer, 2004]. The content of few common quercetin derivatives in some fruits and vegetables is shown in Table 1. The main groups of quercetin derivatives are characterized below, while their chemical structure is shown in Figure 1, the number of compound is labeled in parenthesis.

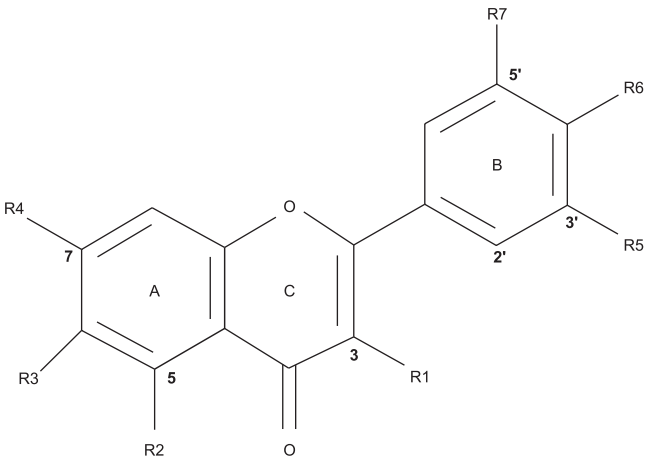
Glycosides

Quercetin *O*-glycosides are quercetin derivatives with at least one *O*-glycosidic bond which are widely distributed in the plant kingdom. Practically every plant contains compounds of this group, and some, like onion, contain vast quantities of these substances in highly diversified forms [Fossen *et al*., 1998]. The most common quercetin glycosylation site is the hydroxyl group at C-3 carbon. Quercetin 3-*O*-glycosides occur as monosaccharides with glucose, galactose, rhamnose or xylose. These compounds are found in various fruits and vegetables (Table 1) and other anatomical parts of plants [Wiczkowski & Piskuła, 2004]. Quercetin 3-*O*-glucoside (2) was found, among others, in sage [Lu & Foo, 2002] and mango fruit [Berardini *et al*., 2005], whereas quercetin 3-*O*-rhamnoside (3) was detected in spinach [Kuti & Konuru, 2004], olive oil [Ryan *et al*., 1999] and peppers [Materska *et al*., 2003]. Quercetin bounded to disaccharides is also frequently detected in plants, an example of such derivative is rutin: 3-*O*-rhamnosylglucoside (4). Significant quantities of this compound are found in tea [Erlund, 2000], spinach [Kuti & Konuru, 2004], chokeberries [Slimestad *et al*., 2005a] and buckwheat [Kalinova *et al*., 2006; Oomah & Mazza, 1996]. In addition to monosaccharides and disaccharides, sugar chains with three-, four- and five saccharide moieties have also been identified in quercetin 3-*O*-glycoside derivatives [Harborne, 1994; Williams & Grayer, 2004]. Another glycosylation site which occurs in quercetin derivatives is hydroxyl group at C-7 carbon. Quercetin 7-*O*-glucoside (5) which is found *e.g*. in beans [Chang & Wong, 2004], is an example of this derivative. Yet, glycosylation at C-7 is more frequently accompanied by C-3 substitution of –OH group, 3-*O*-rhamnoside-7-*O*-glucoside (6) is such a compound found in peppers [Materska *et al*., 2003].

C-glycosides are another type of quercetin derivatives, but these compounds occur relatively rarely in nature. The most

TABLE 1. Contents of some quercetin derivatives in plant derived products.

Quercetin derivatives	Source	Content (mg/kg)		References
		d.m.	f.m.	
Quercetin 3-*O*-galactoside	Mango – fruits	76-1470		Berardini *et al.* [2005]
	Plums		~ 35	Kim *et al.* [2003]
	Blueberry		146	Zeng & Wang [2003]
	Cranberry		97	Zeng & Wang [2003]
	Chokeberry		415	Zeng & Wang [2003]
	Lingonberry		118	Zeng & Wang [2003]
Quercetin 3-*O*-glucoside	Mango-fruits	77-1045		Berardini *et al.* [2005]
	Beans	100-690		Chang & Wong [2004]
	Plums		12-22	Kim *et al.* [2003]
	Onions		9-37	Nemeth & Piskuła [2007]
Quercetin 3-*O*-xyloside	Mango – fruits	10-278		Berardini *et al.* [2005]
Quercetin 3-*O*-rhamnoside	Mango – fruits	0-116		Berardini *et al.* [2005]
	Pepper – fruits	113-993		Materska & Perucka [2005]
	Cranberry		55	Zeng & Wang [2003]
	Lingonberry		109	Zeng & Wang [2003]
Quercetin 3-*O*-glucuronide	Lettuce	0-730		Nicolle *et al.* [2004]
	Chicory		81-1065	Innocenti *et al.* [2005]
Quercetin 7-*O*-glucoside	Beans	20-120		Chang & Wong [2004]
Quercetin 3-*O*-diglucoside	Beans	120-640		Chang & Wong [2004]
Quercetin 3,4'-diglucoside	Onions		169-1372	Nemeth & Piskuła [2007]
Quercetin 3-*O*-rhamnoside-7-*O*-glucoside	Pepper – fruits	130-365		Materska & Perucka [2005]
Quercetin 3-*O*-rutinoside (rutin)	Plums		28-77	Kim *et al.* [2003]
	Cherries		18-137	Goncalves *et al.* [2004]
	Tomatoes		3.2-9.2	Slimestad *et al.* [2005b]
	Buckwheat – leaves	35-98 x 10^3	10-49 x 10^3	Kalinova *et al.* [2006]
	Buckwheat – seeds	442-511		Oomah & Mazza [1996]
	Chokeberry		710	Slimestad *et al.* [2005a]
Quercetin 3-*O*-6''-acetylglucoside	Beans	10-50		Chang & Wong [2004]
Quercetin 3-methyl ether	Honey		2-3.3	Yao *et al.* [2003]
Quercetin 3,3'-dimethyl ether	Honey		0.3-2.1	Yao *et al.* [2003]



Systematic name (common name)	Substituents						
	R1	R2	R3	R4	R5	R6	R7
(1). 3, 5, 7, 3', 4'-pentahydroxyflavon (quercetin)	OH	OH	H	OH	OH	OH	H
(2). Quercetin 3-*O*-glucoside (izoquercetin)	O-Glc	OH	H	OH	OH	OH	H
(3). Quercetin 3-*O*-rhamnoside (quercitrin)	O-Rha	OH	H	OH	OH	OH	H
(4).Quercetin 3-*O*-rhamnozyl-(1→6)-glucoside (rutin)	O-X	OH	H	OH	OH	OH	H
(5). Quercetin 7-*O*- glucoside	OH	OH	H	O-Glc	OH	OH	H
(6). Quercetin 3-*O*-rhamnoside-7-*O*-glucoside	O-Rha	OH	H	O-Glc	OH	OH	H
(7). Quercetin 6-*C*- glucoside	OH	OH	Glc	OH	OH	OH	H
(8). Quercetin 3-(2''-acetylgalactoside)	O-Y	OH	H	OH	OH	OH	H
(9). Quercetin 3-sulfate-7-*O*-arabinoside	O-Sul	OH	H	O-Ara	OH	OH	H
(10). Quercetin 3-*O*-glucoside-3'-sulfate	O-Glc	OH	H	OH	O-Sul	OH	H
(11). Quercetin 5-methyl ether (azaleatin)	OH	O-M	H	OH	OH	OH	H
(12). Quercetin 7- methyl ether (rhamnetin)	OH	OH	H	O-M	OH	OH	H
(13). Quercetin 3'- methyl ether (isohramnetin)	OH	OH	H	OH	O-M	OH	H
(14). Quercetin 4'- methyl ether (tamarixetin)	OH	OH	H	OH	OH	O-M	H
(15). Quercetin 7-methoxy-3-*O*-glucoside	O-Glc	OH	H	O-M	OH	OH	H
(16). Quercetin 3'- methoxy -3-*O*-galactoside	O-Gal	OH	H	OH	O-M	OH	H
(17). 6,5'-Di-*C*-prenylquercetin	OH	OH	Z	OH	OH	OH	Z

Glc: glucose; Rha: rhamnose; Ara: arabinose; X: rhamnosylglucose; M: $-CH_3$; Sul: $-SO_3Na$; Y: 2-acetylgalactose; Z: prenyl.

FIGURE 1. Quercetin and its derivatives.

frequent site of C-glycosylation is the C-6 carbon, *e.g.* in 3, 4, 7, 3', 4'-pentahydroxy-6-glucose flavon (7) which was first identified in *Ageratina calophylla* [Harborne, 1994].

The number of naturally occurring quercetin glycosides may be higher due to the fact that sugar moiety can additionally contain acyl and sulfate substituents [Williams & Grayer, 2004]. Acyl derivatives include links with aliphatic acids, such as acetic, malonic and 2-hydroxypropionic acid, or aromatic acids, including benzoic, gallic, caffeic and ferulic acid [Harborne, 1994]. Quercetin 3-(2''-acetylgalactoside) (8), found in St. John's wort, is an example of an acyl derivative of quercetin which was identified in the last decade [Jürgenliemk & Nahrstedt, 2002]. Sulfate derivatives of quercetin occur relatively rarely in nature. The compounds identified in the recent years include 3-sulfate-7-*O*-arabinoside (9), found in saltbush [Williams & Grayer, 2004] and quercetin 3-*O*-glucoside-3'-sulfate (10), found in the cornflower [Flamini *et al*., 2001].

Ethers

Ether bonds may be formed between every hydroxyl group of a quercetin molecule and an alcohol molecule, mostly methanol [Harborne, 1994]. Quercetin may contain up to five ether groups in various configurations. Wide distribution of quercetin ethers is indicated by the fact that nearly every monoether derivative has a common name (Figure 1, compounds 11-14) [Harborne, 1994]. Ether derivatives of quercetin which also contain sugar substituents are frequently found in nature. Such compounds were identified in sage, they were: quercetin 7-methoxy-3-glucoside (15) and quercetin 3'-methoxy-3--galactoside (16) [Lu & Foo, 2002]. In addition there are also derivatives containing alkyl substituents. The most common hydrocarbon forming such derivatives is prenyl (3-methylbut-2-en). The lipophilic derivative of quercetin identified in the past decade is 6,5'-di-C-prenyl quercetin (17) found in paper mulberry [Son *et al*., 2001].

Physical properties

Despite the presence of five hydroxyl groups, the quercetin molecule has a lipophilic character. Quercetin derivatives can be both lipo- and hydrophilic, depending on the type of substituents in the molecule. In general, *O*-methyl, *C*-methyl and prenyl derivatives of flavonoids, including quercetin derivatives, are lipophilic. They are synthesized by glands located on the surface of leaves, flowers or fruits. These compounds are particularly widespread in the families *Labiatae* or *Compositae*. They can be easily isolated from hydrophilic compounds by immersing plant tissue in acetone [Williams & Grayer, 2004].

Glycosylation of at least one hydroxyl group of quercetin derivatives results in an increase of its hydrophilicity. This change in character from lipophilic to hydrophilic is very significant to plants for glycosidic derivatives of quercetin, which are cytosol-soluble, can be easier transported to various parts of the plant and stored in vacuoles [Rice-Evans *et al*., 1997; Williams & Grayer, 2004].

Chemical properties

The most extensively investigated chemical property of phenolic compounds is their antioxidant activity. Antioxidants are capable of neutralizing free radicals which are always present in food as well as in cells of a human body [Bartosz, 1995]. The antioxidant properties of phenolic compounds are linked with their ability to transfer a hydrogen or an electron, as well as with chelation of metal ions and inhibition of the activity of oxidases [Bartosz, 1995; Rice-Evans *et al.*, 1997]. Additionally, antioxidant activity is often accompanied by antiviral and antibacterial activity of these compounds [Chun *et al.,* 2005; Rotelli *et al*., 2003].

There are many methods for determining antioxidant activity, and most of them involve the description of antioxidant relative ability to scavenge free radicals in comparison with a known antioxidant [Rice-Evans *et al.,* 1997]. Trolox is a synthetic antioxidant frequently applied as a reference compound, but generally recognized antioxidants, such as vitamin C and quercetin, are also used to this end. The most popular tests are: determination of antiradical activity in reaction with DPPH synthetic radical (1,1-diphenylpicrylhydrazyl radical), determination of antioxidant activity of compounds in relation to radicals generated in the lipid phase, *e.g.* β-carotene emulsion system or TEAC (Trolox Equivalent Antioxidant Capacity), determination of antiradical activity in relation to peroxide radical, $OH^{\cdot}$ hydroxyl radical, *etc*. Indirect method to determine antioxidant activity is metal ions chelation power. Flavonoids, which are able to chelate Fe^{2+} or Cu^{2+} ions render them inactive to participate in free radical reactions [Morel *et al*., 1993].

Research investigating relationships between the structure and antioxidant activity of phenolic compounds has been conducted for many years. Results obtained so far have enabled determining general relationships, *i.e.* it has been shown that the antioxidant activity of a compound is determined by the presence of free hydroxyl groups and their mutual location [Rice-Evans *et al*., 1997; Wang *et al*., 2006]. In addition, analyses carried out in various model systems have led to the determination of functional groups in flavonoid molecules

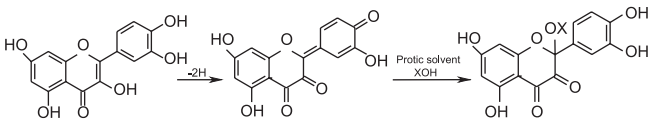


FIGURE 2. Pathway of oxidative changes in quercetin reaction with DPPH radical in protic solvents [Goupy *et al*., 2003].

responsible for the activity in the investigated system [Wang *et al*., 2006]. Regarding quercetin reaction with DPPH radical, its high antiradical activity has been shown to be determined by the presence of 1,2 dihydroxybenzene (catechol) in the B ring [Burda & Oleszek, 2001; Goupy *et al.,* 2003]. It was supported by a research comparing the antiradical activity of quercetin and its C(3)-OH and C(4')-OH glycoside derivatives. In reaction with DPPH, quercetin donates two hydrogen atoms and is transformed into a quinone intermediate (Figure 2). Even though the presence of a hydroxyl group at the C-3 carbon of quercetin enables the regeneration of the catechol ion through the addition of the proton from the solution [Goupy *et al*., 2003]. In the case of quercetin derivatives, glycosilation at C(4')-OH markedly decreased the H-donating ability [Goupy *et al.,* 2003], while C(3)-OH derivatives of quercetin showed reducing potential comparable with that of free aglycone [Burda & Oleszek, 2001; Matetrska & Perucka, 2005].

Wang *et al.* [2006], investigating the antioxidant activity of flavonoid aglycones, including fisetin, kaempferol, morin, myricetin and quercetin, concluded that in reference to superoxide radicals, the highest reduction potential is demonstrated by the 4'-OH group in B-ring. On the other hand, a research investigating the scavenging activity of quercetin derivatives in relation to radicals does not fully support the theory that 4'-OH in B ring is mainly responsible for high scavenging power. Quercetin 3-*O*-glycoside derivatives such as rutin and quercitrin are characterised by much lower, in comparison to quercetin, scavenging activity in a xanthine/xanthine oxidase system despite a free 4'-OH group in B-ring [Materska *et al*., *in press*]. In other model systems, quercetin derivatives were also demonstrated to display a lower activity in comparison with free aglycone [Cos *et al*., 1998; Burda & Oleszek 2001; Materska & Perucka, 2005]. The lower antioxidant activity of quercetin derivatives is mainly due to the blocking of hydroxyl groups by sugar or alkoxyl substituents. In addition, the increased hydrophilicity of quercetin glycosides modifies the coefficients of distribution between the aqueous and lipid phase, which is of great significance in lipid systems such as TEAC or β-carotene emulsion [Burda & Oleszek, 2001]. In view of the number of factors which determine the chemical properties of quercetin derivatives, empirical research is needed to confirm or exclude the specific activity. To date, only isolated derivatives of both quercetin and other flavonoids have been investigated, but the availability of relevant information has been on the rise in the recent years.

ABSORPTION AND METABOLISM OF QUERCETIN DERIVATIVES

Absorption and metabolism of quercetin and its derivatives has attracted much attention in relation to their pro-healthy

value. The total flavonoid intake from dietary sources is estimated to be from several hundred miligrams to 1 gram per day [Formica & Regelson, 1995; Hertog *et al.,* 1993]. Quercetin derivatives, glycosides in particular, represent a considerable part of these food constituents. It is common knowledge that having been ingested both quercetin as quercetin derivatives undergo many metabolic conversions and appear in body tissues almost as glucuronated, sulfated and methylated forms [Day *et al.,* 1998; Graf *et al.*, 2006; Scalbert *et al.,* 2002; Williams *et al*., 2004].

Investigations on the bioavailability and metabolism of quercetin derivatives focused mostly on glycosides, because in this form quercetin predominates in diet. It has been clearly shown that quercetin aglycone and glycosides are absorbed from the gastrointestinal tract to a different extent, additionally absorption of quercetin glycosides depends on the position and nature of sugar substitutions [Cermak *et al*., 2003; Scalbert & Williamson, 2000]. A lipophilic quercetin molecule can be easily absorbed by the stomach and then secreted in the bile [Crespy *et al.*, 2002]. Quercetin glycosides are not affected by pH conditions of the stomach and pass through the small intestine where they are partially deglycosylated and absorbed [Gee *et al.*, 1998]. There are two mechanism enabling intestinal absorption of quercetin glycosides. In the first, they are a potential substrate for lactose phlorizin hydrolaze (LPH) in the brush border membrane [Day *et al.*, 2000]. This β-glycosidase had a high affinity particularly towards flavonol glucosides, and preferred the sugar group at the 3-position [Day *et al.,* 1998; 2000]. It has been shown that LPH-mediated hydrolysis was the main absorption pathway of quercetin–3-glucoside. The second mechanism enabling intestinal absorption of quercetin glycosides assumes the possibility of interacting with sodium-dependent glucose transporter SGLT1 [Wolfram *et al.*, 2002]. After absorption, glycosides are hydrolysed by β-glycosidases present in cytosole of small intestine mucosa cells [Day *et al.*, 1998]. Glycosides of quercetin with a substituent other than glucose, *e.g.* quercetin 3-*O*-rhamnoglucoside and quercetin-3-*O*-rhamnoside, are not hydrolyzed by endogenous human enzymes and pass through the small intestine and enter the cecum and colon, where they are hydrolyzed by colon microflora to quercetin and sugar [Scalbert & Williamson, 2000]. For this reason absorption of those compounds is delayed.

After hydrolysis and absorption, quercetin is metabolised in analogy with drugs and other extrinsic compounds [Scalbert & Williamson, 2000]. The successive stages of quercetin metabolism include enzymatically controlled reconjugation reactions, as: glucuronidation, methylation, sulfation or hydroxylation [Scalbert & Williamson, 2000].

Information on the absorption and metabolism of other than glycosidic derivatives of quercetin in a human body is sparse. Yet it is likely that lipophilic ethers of quercetin are absorbed in analogy to quercetin aglycone, while hydrophilic derivatives with acyl or sulphate substituents must be deconjugated before absorption.

BIOACTIVITY

Research into the bioactivity of quercetin derivatives and its impact on human health is still at the developmental stage. It is common knowledge that metabolic modification of quercetin derivatives alters their antioxidant properties. In addition, *in vivo* concentrations of flavonoids and their metabolites are lower than those of antioxidant nutrients such as ascorbic acid and α-tocopherol [Williams *et al*., 2004]. On this basis it has been suggested that cellular effects of flavonoids may be mediated by their interactions with intracellular signalling cascades [Williams *et al*., 2004]. Ample investigations have confirmed a beneficial effect of quercetin derivatives, but the exact mechanism of their action is still unresolved.

Simple derivatives such as quercetin mono-glycosides: 3-*O*-glucoside and 3-*O*-rhamnoside as well as diglycoside – rutin, have been best investigated to date. A human body needs these substances to absorb and use vitamin C. Investigators have also found that quercetin 3-*O*-glucoside and rutin contribute to the relaxation of smooth muscles in mammals. Similar properties were observed in methoxyl derivatives of quercetin: 3,4'-dimethoxyquercetin and 3,7-dimethoxyquercetin [Harborne & Williams, 2000].

Due to its antioxidant activity, rutin protects liver cells [Janbaz *et al*., 2002] and suppresses hemoglobin oxidation [Grinberg *et al*., 1994]. Rutin has also anti-inflammatory properties which are displayed mostly in respect of chronic diseases [Obied *et al.*, 2005; Rotelli *et al*., 2003]. When administered to rats, rutin has also been found to display chemopreventive properties, acting as an agent blocking carcinogenesis induced by heterocyclic amines [Hirose *et al*., 1999].

Two other quercetin derivatives – quercetin 3-*O*-xylose (1→2)–rhamnoside and 3-*O*-rhamnoside – decreased the swelling caused by chemically-induced inflammation in mice [Harborne & Williams, 2000]. In addition, quercetin 3-*O*-rhamnoside minimized damage to the colon, prevented diarrhea and stabilized the transport of fluids in the colon of rats [DiCarlo *et al*., 1999].

When investigating the less known methoxyl derivatives of quercetin, Miyazawa *et al*. [2000] concluded that obuine (3,5,3'-trihydroxy-7,4'-dimetoxyflavon) and pachypodol (5,4'-dihydroxy-3,7,3'-trimetoxyflavon) showed the antimutagenic activity towards chemically-induced mutagens (*umu* test). The anticarcinogenic activity of tetrasaccharide derivative of quercetin: quercetin 3-*O*-rhamnosyl (1→6) –*O*-[glucosyl (1→3) rhamnosyl (1→2) – *O*-glactoside was also demonstrated by Vilegas *et al*. [1999].

On the other hand, investigations of protective mechanism of quercetin and its derivatives on oxidative damages of *in vitr*o rat C6 glioma cells showed that quercetin but neither rutin and quercitrin [Chen *et al*., 2006], nor 3-*O*-glucoside and 3-*O*-acetylglucoside [Zielińska *et al*., 2003] were active as cells protectors.

CONCLUSIONS

It is common knowledge that flavonoid antioxidants are related to various beneficial effects exerted on human health. Yet, as for many flavonoids, metabolism of quercetin derivatives in the enterocyte is the rate-limiting step of their bioactivity. The *in vivo* investigations of the beneficial and/or toxic action of flavonoids tend toward a theory that products of fla-

vonoid metabolism may modulate lipid and protein kinases, acting as signalling molecules rather than as antioxidants [Williams *et al.,* 2004]. On the other hand, while considering quercetin derivatives as food protectors, the antioxidant and antimicrobial activity of unchanged compounds must be confirmed.

REFERENCES

1. Bartosz G., Druga twarz tlenu (The Second Face of Oxygen). 1995, PWN, Warszawa, pp. 179–203 (in Polish).
2. Berardini N., Fezer R., Conrad J., Beifuss U., Carle R., Schieber A., Screening of mango (*Mangifera indica* L.) cultivars for their contents of flavonol O- and xanthone C-glycosides, anthocyanins and pectin. J. Agric. Food Chem., 2005, 53, 1563–1570.
3. Burda S., Oleszek W., Antioxidant and antiradical activities of flavonoids. J. Agric. Food Chem., 2001, 49, 2774–2779.
4. Cermak R., Landgraf S., Wolffram S., The bioavailability of quercetin in pigs depends on the glycoside moiety and on dietary factors. J. Nutr., 2003, 133, 2802–2807.
5. Cos P., Ying L., Calomme M., Hu J.P., Cimanga K., Poel B., Pieters L., Vlietinck A.J., Berghe D.V., Structure-activity realtionship and classification of flavonoids as inhibitors of xanthine oxidase and superoxide scavengers. J. Nat. Prod., 1998, 61, 71–76.
6. Chang Q., Wong Y.S., Identification of flavonoids in Hakmeitau beans (*Vigna sinensis*) by high performance liquid chromatography-electrospray mass spectrometry (LC-ESI/MS). J. Agric. Food Chem., 2004, 52, 6694–6699.
7. Chen T.J., Jeng J.Y., Lin Ch.W., Wu Ch.Y., Chen Y.Ch., Quercetin inhibition of ROS- dependent and –independent apoptosis in rat glioma C6 cells. Toxicology, 2006, 223, 113–126.
8. Chun S.S., Vattem D.A., Lin Y.T., Shetty K., Phenolic antioxidants from clonal oregano (*Origanum vulgare*) with antimicrobial activity against *Helicobacter pylori*. Proc. Biochem., 2005, 40, 809–816.
9. Crespy V., Morand C., Besson C., Manach C., Demigne C., Remesy C., Quercetin, but not its glycosides is absorbed from the rat stomach. J. Agric. Food Chem., 2002, 50, 618–621.
10. Day A.J., DuPont M.S., Ridley S., Rhodes M., Rhodes M.J.C., Morgan M.R.A., Williamson G., Deglycosylation of flavonoid and isoflavonoid glycosides by human small intestine and liver β-glucosidase activity. FEBS Lett., 1998, 436, 71–75.
11. Day A.J., Canada F.J., Diaz J.C., Kroon P.A., Mclauchlan R., Faulds C.B., Plumb G.W., Morgan M.R.A., Williamson G., Dietary flavonoid and isoflavone glycosides are hydrolysed by the lactase site of lactase phlorizin hydrolase. FEBS Lett., 2000, 468, 166–170.
12. Di Carlo G., Mascolo N., Izzo A.A., Capasso F., Flavonoids: old and new aspects of a class of natural therapeutic drugs. Life Sci., 1999, 65, 337–353.
13. Erkoc S., Erkoc F., Keskin N., Theoretical investigation of quercetin and its radical isomers. J. Mol. Struct., 2003, 631, 141–146.
14. Erlund I., Kosonen T., Alfthan G., Maenpaa J., Perttunen K., Kenraali J., Parantainen J., Aro A., Pharmacokinetics of quercetin from quercetin aglycone and rutin in healthy volunteers. Eur. J. Clin. Pharmacol., 2000, 56, 545–553.
15. Flamini G., Antognoli E., Morelli I., Two flavonoids and other compounds from the aerial parts of *Centaurea brakteata* from Italy. Phytochemistry, 2001, 57, 559–564.
16. Formica J.F., Regelson W., Review of the biology of quercetin and related bioflavonoids. Food Chem. Tox., 1995, 33, 1061–1080.
17. Fossen T., Pedersen A.T., Andersen O.M., Flavonoids from red onion (*Allium cepa*). Phytochemistry, 1998, 47, 281–285.
18. Gee J.M., DuPont M.S., Rhodes M.J., Johnson I.T., Quercetin glucosides interact with the intestinal glucose transport pathway. Free. Rad. Biol. Med., 1998, 25, 19–25.
19. Goncalves B., Landbo A.K., Knudsen D., Silva A.P., Moutinho-Pereira J., Rosa E., Meyer A.S., Effect of ripeness and postharvest storage on the phenolic profiles of cherries (*Prunus avium* L.). J. Agric. Food Chem., 2004, 52, 523–530.
20. Goupy P., Dufour C., Loonis M., Dangles O., Quantitative kinetic analysis of hydrogen transfer reactions from dietary polyphenols to the DPPH radical. J. Agric. Food Chem., 2003, 51, 615–622.
21. Graf B.A., Ameho C., Dolnikowski G.G., Milbury P.E., Chen Ch.Y., Blumberg J.B., Rat gastrointestinal tissues metabolize quercetin. J. Nutr., 2006, 136, 39–44.
22. Grinberg L.N., Rachmilewitz E.A., Newmark H., Protective effects of rutin against hemoglobin oxidation. Biochem. Pharmacol., 1994, 48, 643–649.
23. Harborne J.B., ed., The Flavonoids, Advances in Research Since 1986. 1994, Chapman & Hall, London, pp. 378–382.
24. Harborne J.B., Williams Ch.A., Advances in flavonoid research since 1992. Phytochemistry, 2000, 55, 481–504.
25. Hertog M.G.L., Hollman P.C.H., Katan M.B., Kromhout D., Estimation of daily intake of potentially anticarcinogenic flavonoids and their determinants in adults in The Netherlands. Nutr. Cancer, 1993, 20, 21–29.
26. Hirose M., Takahashi S., Ogawa K., Futakuchi M., Shirai T., Phenolics: blocking agents for heterocyclic amine-induced carcinogenesis. Food Chem. Toxicol., 1999, 37, 985–992.
27. Innocenti M., Gallori S., Giaccherini C., Ieri F., Vincieri F.F., Mulinacci N., Evaluation of the phenolic content in the aerial parts of different varieties of *Cichorium intybus* L. J. Agric. Food Chem., 2005, 53, 6497–6502.
28. Janbaz K.H., Saeed S.A., Gilani A.H., Protective effect of rutin on paracetamol- and CCl_4 –induced hepatotoxicity in rodents. Fitoterapia, 2002, 73, 557–563.
29. Jürgenliemk G., Nahrstedt A., Phenolic compounds from *Hypericum perforatum*. Planta Medica, 2002, 68, 88.
30. Kalinova J., Triska J., Vrchotova N., Distribution of vitamin E, squalene, epicatechin and rutin in common buckwheat plants (*Fagopyrum esculentum* Moech). J. Agric. Food Chem., 2006, 54, 5330–5335.
31. Kaur Ch., Kapoor H.C., Antioxidants in fruits and vegetables – the millennium's health. Int. J. Food Sci. Technol., 2001, 36, 703–725.
32. Kim D.O., Chun O.K., Kim Y.J., Moon H.Y., Lee Ch.Y., Quantification of polyphenolics and their antioxidant capacity in fresh plums. J. Agric. Food Chem., 2003, 51, 6509–6515.
33. Kuti J.O., Konuru H.B., Antioxidant capacity and phenolic content in leaf extracts of tree spinach (*Cnidoscolus* spp.). J. Agric. Food Chem., 2004, 52, 117–121.
34. Lu Y., Foo L.Y., Polyphenolics of *Salvia* – a review. Phytochemistry, 2002, 59, 117–140.
35. Materska M., Perucka I., Antioxidant activity of the main phenolic compounds isolated from hot pepper fruit (*Capsicum annuum* L.). J. Agric. Food Chem., 2005, 53, 1750–1756.

36. Materska M., Perucka I., Stochmal A., Piacente S., Oleszek W., Quantitative and qualitative determination of flavonoids and phenolic acid derivatives from pericarp of hot pepper fruit cv. Bronowicka Ostra. Pol. J. Food Nutr. Sci., 2003, 12/53, 72–76.
37. Materska M., Perucka I., Konopacka M., Rogoliński J., Ślosarek K., Effect of 3-*O*-glycosylation of quercetin in 3-O rhamnosidic derivative on superoxide radical scavenging activity and reduction of DNA damages after X-ray radiation of human lymphocytes. Planta Medica (in press).
38. Miyazawa M., Okuno Y., Nakamura S., Kosaka H., Antimutagenic activity of flavonoids from *Pogostemon cablin*. J. Agric. Food Chem., 2000, 48, 642–647.
39. Morel I., Lescoat G., Cogrel P., Sergent O., Pasdeloup N., Brissot P., Cillard P., Cillard J., Antioxidant and iron-chelating activities of the flavonoids catechin, quercetin and diosmetin on iron-loaded rat hepatocyte cultures. Biochem. Pharmacol., 1993, 45, 13–19,
40. Nemeth K., Piskuła M.K., Food content, processing, absorption and metabolism of onion flavonoids. Crit. Rev. Food Sci. Nutr., 2007, 47, 397–409.
41. Nicolle C., Carnat A., Fraisse D., Lamaison J-L., Rock E., Michel H., Amouroux P., Remesy Ch., Characterisation and variation of antioxidant micronutrients in lettuce (*Lactuca sativa* folium). J. Sci. Food Agric., 2004, 84, 2061–2069.
42. Obied H.K., Allen M.S., Bedgood N.R., Prenzler P.D., Robards K., Stockman R., Bioactivity and analysis of biofenols recovered from olive mill waste. J. Agric. Food Chem., 2005, 53, 823–837.
43. Oomah B.D., Mazza G., Flavonoids and antioxidative activities in buckwheat. J. Agric. Food Chem., 1996, 44, 1746–1750.
44. Prior R.L., Fruits and vegetables in the prevention of cellular oxidative damage. Am. J. Clin. Nutr., 2003, 78, 570–578.
45. Reddy L., Odhav B., Bhoola K.D., Natural products for cancer prevention: a global perspective. Pharmacol. Ther., 2003, 99–113.
46. Rice-Evans C.A., Miller J., Paganga G., Antioxidant properties of phenolic compounds. Trends Plant Sci., 1997, 2, 4, 152–159.
47. Rotelli A.E., Guardia T., Juarez A.O., De la Rocha N.E., Pelzer L.E., Comparative study of flavonoids in experimental models of inflammation. Pharmacol. Res., 2003, 48, 601–606.
48. Russo G.L., Ins and outs of dietary phytochemicals in cancer chemoprevention. Bioch. Pharm., 2007, 74, 533–544.
49. Ryan D., Robards K., Lavee S., Determination of phenolic compounds in olives by reversed-phase chromatography and mass spectrometry. J. Chrom. A, 1999, 832, 87–96.
50. Scalbert A., Morand Ch., Manach C., Remesy Ch., Absorption and metabolism of polyphenols in the gut and impact on health. Biomed. Pharmacother., 2002, 56, 276–282.
51. Scalbert A., Williamson G., Dietary intake and bioavailability of polyphenols. J. Nutr., 2000, 130, 2073–2085.
52. Shetty K., Role of proline-linked pentose phosphate pathway in biosynthesis of plant phenolics for functional food and environmental applications: a review. Proc. Bioch., 2004, 39, 789–803.
53. Simmonds M.S.J., Importance of flavonoids in insect-plant interactions: feeding and oviposition. Phytochemistry, 2001, 56, 245–252.
54. Singh R.P., Murthy C.K.N., Jayaprakasha G.K., Studies on the antioxidant activity of pomegranate (*Punica granatum*) peel and seed extracts using in vitro models. J. Agric. Food Chem., 2002, 50, 81–86.
55. Slimestad R., Torskangerpoll K., Nateland H.S., Johannessen T., Giske N.H., Flavonoids from black chokeberries, *Aronia melanocarpa*. J. Food Comp. Anal., 2005a, 18, 61–68.
56. Slimestad R., Verheul M.J., Seasonal variations in the level of plant constituents in greenhouse production of Cherry tomatoes. J. Agric. Food Chem., 2005b, 53, 3114–3119.
57. Smith-Palmer A., Stewart J., Fyfe L., The potential application of plant essential oils as natural food preservatives in soft cheese. Food Microbiol., 2001, 18, 463–470.
58. Son K.H., Kwon H.W., Chang H.W., Kim H.P., Kang S.S., Papyriflavonol A, a new prenylated flavonol from *Broussonetia papyrifera*. Fitoterapia, 2001, 72, 456–458.
59. Souto X.C., Chiapusio G., Pellissier F., Relationships between phenolics and soil microorganisms in spruce forests: significance for natural regeneration. J. Chem. Ecol., 2000, 26, 2025–2034.
60. Vilegas W., Sanommiya M., Rastrelli L., Pizza C., Isolation and structure elucidation of two new flavonoid glycosides from the infusion of *Maytenus aquifolium* leaves. Evaluation of the antiulcer activity of the infusion. J. Agric. Food Chem., 1999, 47, 403–406.
61. Vurma M., Chung Y.K., Shellhammer T.H., Turek E.J., Yousef A.E., Use of phenolic compounds for sensitizing *Listeria monocytogenes* to high-pressure processing. Int. J. Food Microbiol., 2006, 106, 263–269.
62. Walle T., Absorption and metabolism of flavonoids. Free Rad. Biol. Med., 2004, 36, 829–837.
63. Wang L., Tu Y.Ch., Lian T.W., Hung J.T., Yen J.H., Wu M.J., Distinctive antioxidant and antiinflammatory effects of flavonols. J. Agric. Food Chem., 2006, 54, 9798–9804.
64. Wiczkowski W., Piskuła M.K., Food flavonoids. Pol. J. Food Nutr. Sci., 2004, 13/54, 101–114.
65. Williams Ch.A., Grayer R.J., Anthocyanins and other flavonoids. Nat. Prod. Rep., 2004, 21, 539–573.
66. Williams R.J., Spencer P.E., Rice-Evans C. Flavonoids: antioxidants or signalling molecules? Free Rad. Biol. Med. 2004, 36, 838–849.
67. Wolfram S., Blöck M., Ader P., Quercetin-3-glucoside is transported by the glucose carrier SGLT1 across the brush border membrane of rat small intestine. J. Nutr., 2002, 132, 630–635.
68. Yao L., Datta N., Tomas-Barberan F.A., Ferreres F., Martos I., Singanusong R., Flavonoids, phenolic acids and abscisic acid in Australian and New Zeland *Leptospermum* honeys. Food Chem., 2003, 81, 159–168.
69. Zeng W., Wang S.Y., Oxygen radical absorbing capacity of phenolics in blueberries, cranberries, chokenberries and lingonberries. J. Agric. Food Chem., 2003, 51, 502–509.
70. Zielińska M., Gülden M., Seibert H., Effects of quercetin and quercetin-3-*O*-glycosides on oxidative damage on rat C6 glioma cells. Env. Tox. Pharm., 2003, 13, 47–53.

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