POLISH JOURNAL OF FOOD AND NUTRITION SCIENCES
Pol. J. Food Nutr. Sci. 2003, Vol. 12/53, SI 1, pp. 95–99

BIOAVAILABILITY OF QUERCETIN FROM FLESH SCALES AND DRY SKIN OF ONION IN RATS

Wiesław Wiczkowski[1], Kitti Nèmeth[2], Adam Buciński[1], Mariusz K. Piskuła[1]*

[1] Department of Food Technology; Institute of Animal Reproduction and Food Research of Polish Academy of Sciences, Olsztyn, Poland; [1, 2] Slovak University of Technology, Bratislava, Slovak Republic

Key words: quercetin, quercetin glucoside, bioavailability, onion, rat

Quercetin is a natural compound widely distributed in the plant food. It is still not certain which forms of quercetin, aglycone or glycosides, are better bioavailable. In this study, for the first time, the bioavailability of quercetin and quercetin β-glucosides was compared from dietary sources. As a source of quercetin glucosides, two outer fleshy onion scales of Błońska variety containing 21.30 mg Q/g d.m. (99.3% of quercetin as glucosides) were used, while quercetin aglycone originated from onion dry skin of the same variety containing 34.80 mg Q/g d.m. (53.2 % of quercetin as aglycone). The results showed that bioavailability of quercetin glucosides was 50% of that of quercetin aglycone ($p \leq 0.05$). A factor which may be the reason for differences in the determined bioavailabilities are the mechanisms of transportation and hydrolysis. It is suggested that more hydrophobic quercetin may pass through biological membranes to reach intestinal enterocytes *via* passive transport, while for more polar quercetin glucosides two mechanisms are proposed: prior to absorption they may be hydrolyzed in the intestinal lumen by β-glucosidases and released free quercetin is absorbed as above, or they may enter enterocytes *via* Na+/glucose transporter.

INTRODUCTION

Quercetin belongs to a large group of compounds called flavonoids. Flavonoids are polyphenolic compounds diverse in chemical structure and characteristics. Quercetin is a natural compound widely distributed in the plant kingdom [Aherne & O'Brien, 2002; Herrmann, 1976], occurring as various O-β-glycosides with D-glucose as the most common sugar residue [Herrmann, 1988]. Fruit, vegetables and beverages are the major sources of quercetin in diet [Crozier *et al.*, 1997; Hertog *et al.*, 1993c, 1992]. Daily consumption of flavonoids depends on dietary habits and flavonoid content in the food taken. The average intake of 5 main dietary flavonoids (quercetin, kaempferol, luteolin, apigenin, myricetin) is estimated to be 23 mg/day, with quercetin covering 70% of this value [Hertog *et al.*, 1993b].

Quercetin is a strong *in vitro* antioxidant with ability to chelate metals and scavenge free radicals, which in turn inhibits lipid peroxidation [Terao & Piskula, 1998; Ioku *et al.*, 1995; Terao *et al.*, 1994; Bors *et al.*, 1990; Chen *et al.*, 1990; Afanas'ev *et al.*, 1989]. Many studies have presented other biological activities of quercetin that may be beneficial to health. For example, it can inhibit platelet aggregation [Pace-Asciak *et al.*, 1995] and/or broad spectrum of enzymes [Cos *et al.*, 1998; Peterson & Dwyer, 1998] and has been demonstrated to have anti-inflammatory properties [Guardia *et al.*, 2001]. Through these actions quercetin may contribute to preventing "civilization diseases" [Keli *et al.*, 1996; Knekt *et al.*, 1996; Hertog *et al.*, 1995, 1993a]. However, to exhibit positive effects, quercetin has to enter the human systemic circulation. It is still not certain which forms of quercetin, aglycone or glycosides, are better absorbed. In experiment with ileostomic patients, Hollman *et al.* [1995] showed that quercetin absorption was 52% when taken as quercetin glycosides with onion, 24% when taken as quercetin aglycone, and 17% when taken as quercetin-3-rutinoside. The last two compounds were administered in capsules as pure substances. Manach *et al.* [1997] compared absorption of isolated quercetin and rutin. Rutinoside was absorbed more slowly than quercetin because, as it was concluded, prior to absorption rutinoside has to be hydrolyzed by the colon microflora, when quercetin aglycone was absorbed in the small intestine. In another study [Hollman *et al.*, 1999], it was shown that bioavailability of pure quercetin-4'--glucoside was better than that of quercetin-3-rutinoside. Again, the observed differences were attributed to the sites of hydrolysis and absorption; rutinoside was absorbed after deglycosylation by the more distant colon microflora whereas β-glucoside was absorbed after hydrolysis in the small intestine. Moreover, Hollman *et al.* [1997] showed that quercetin bioavailability from onions was 30% higher than that from apples or from pure rutinoside.

The above studies dealt with comparing absorption of quercetin as pure substance with its dietary sources in which it is present mostly as glycosides. In the presented work, the bioavailability of quercetin and quercetin β-glucosides originating from natural dietary sources was compared for the first time.

MATERIAL AND METHODS

Chemicals. Quercetin, quercetin-3-glucosides (Extrasynthese, Genay, France), quercetin-3,4'-O-glucoside and

*Author's address for correspondence: Wiesław Wiczkowski, Institute of Animal Reproduction and Food Reearch, ul. Tuwima 10, 10-747 Olsztyn, Poland; tel.: (48 89) 523 46 05; fax: (48 89) 524 01 24; e-mail: wiew@pan.olsztyn.pl

quercetin-4'-O-glucoside (generous gifts from Dr. T. Tsushida, National Food Research Institute, Tsukuba, Japan) were used for identification and calculation. Sulfatase type H-5 was purchased from Sigma Chemical Co. Methanol, acetonitrile, formic acid and acetic acid (supra-gradient) were from Merck KGaA, Darmstadt, Germany.

Determination of quercetin in onion. About 0.15 g of dried and pulverized onion tissue was extracted with 1 mL of 80% methanol by 30 s sonication. Next, the mixture was vortexed for 30 s, again sonicated and vortexed, and centrifuged for 5 min (5 000 x g at 4°C). Supernatant was collected in 5 mL flask. That step was repeated 5 times. Finally, extracts were directly submitted to HPLC analysis. Standard compounds were dissolved in 80% methanol and their concentration was confirmed by UV measurement.

Chromatographic determinations were done on Shimadzu HPLC system (Shimadzu, Kyoto, Japan) consisting of two pumps (LC-10 AD and LC-10 AD_{VP}), UV detector (SPD-10 A) set at 360 nm, MS detector (QP8000α), autosampler set to 5 μL injection (SIL-10 AD_{VP}), column oven (CTO-10 AS_{VP}) and system controller (SCL-10 A_{VP}). All chromatographic determinations were performed at 35°C with the flow rate of 0.2 mL/min on C18(2) Luna 3 μ column, 150 x 2 mm (Phenomenex, Torrance, CA, USA). The flavonoids were eluted in gradient system composed of water with 0.05% formic acid, pH 2.9 (solvent A), and acetonitrile (solvent B). Gradients were as follows: 17-80-80-17-17% B at gradient time, t_G = 0-17-27-28-55 min.

Confirmation of the analytes identity was done on a mass spectrometer with the following parameters: CDL temperature 240°C, CDL voltage (-50V), probe voltage (-3.5 kV), nebulizer gas (N_2) flow of 2.8 mL/min, and defragmentation voltage (-45 V).

Statistical analysis. All determinations were carried out in three replications. ANOVA analysis was performed for calculated parameters: $AUC_{0\text{-inf.}}$ (the Area Under the plasma Concentration-time curve), k_{el}, c_{max} and body weight. Assumptions of homogeneity of variances and normality of the distribution of a variable were tested with Levene Test and normal probability with W Shapiro-Wilk Test. The performed analysis showed that checked ANOVA assumptions were fulfilled.

Animals and diets. Four 6-week-old Wistar male rats weighing 210-270 g were used. Animals were kept in light- and temperature-controlled room in the Institute's animal facility with free access to tap water. The period before experiments was divided into two parts: first - when rats were kept for 5 days on standard diet, and second - when rats received synthetic diet for 4 days. The day before experiment at 2:00 p.m., the animals were food deprived. The next day at 7:00 a.m., two rats were orally administered (by direct stomach intubation) with lyophilised and pulverized Błońska onion fleshy tissues homogenized in 1.5 mL water. The other two rats were administered with pulverized dry Błońska onion skin also homogenized in 1.5 mL water. The dose was adjusted to 7 mg of quercetin per kg of body weight. After eight days the experiment was cross repeated.

Before (control) and after 10, 30, 60, 120, 240, 360, 480, 1 440 min of sample administration, tail vein blood was collected to heparinized tubes and centrifuged for 15 min (900 x g at 4°C) to obtain plasma.

Determination of plasma quercetin. Quercetin was determined by HPLC after extraction from blood plasma according to Piskula and Terao [1998]. Briefly, blood plasma was mixed with sulfatase solution in acetate buffer. The mixture was incubated at 37°C for 60 min, than quercetin released from conjugates was extracted with methanol/acetic acid (95:5, v:v) solution by vortexing and sonication. After centrifugation, supernatant was diluted with 100 mM lithium acetate and subjected to HPLC determination. A 20 μL sample was injected onto the HPLC column (TSKgel ODS-80TS, 5 μm, 150 x 4.6 mm, TOSOH, Japan) with mobile phase composed of water: methanol:acetic acid (52:46:2, v:v:v) and 50 mM lithium acetate set to the flow of 0.9 mL/min. Elution was monitored on electrochemical detector (ED 40, Dionex, USA) with a working potential of + 900 mV. Determination of quercetin was performed using an external standard curve.

Kinetic parameters. Pharmaco-kinetic parameters of quercetin (measured as quercetin aglycone): the area under the plasma concentration-time curve (AUC), the quercetin peak plasma level (c_{max}), the time to reach the peak plasma level (t_{max}), and the constant of elimination (k_{el}) were measured.

RESULTS

Content of quercetin in onion

Quercetin (Q) analysis in 4 onion varieties showed that Q content in onion dry skin was in the range of 25-35 mg Q/g d.m. while in onion fleshy parts it was on average 5 times lower, *i.e.* in the range of 4-7 mg Q/g d.m. (Table 1). Performed analysis of quercetin distribution within the onion fleshy scales revealed that over 50% of total onion quercetin is concentrated in the outer scale with sharp down gradient into the middle (Table 2). In onion flesh, quercetin was present as glucosides (Q3,4'G; Q4'G and Q3G (Figure 1)) and in trace amount as aglycone. In onion dry skin the predominant form of quercetin was aglycone (Table 3). Two outer fleshy scales of Błońska variety contained 21.30 mg Q/g d.m.

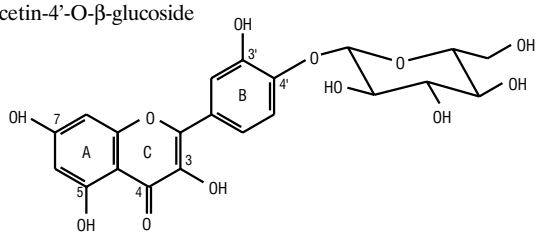
TABLE 1. Total quercetin concentration (mg Q/g d.m.) expressed as quercetin aglycone in onion flesh and onion dry skin in different varieties.

Variety	Onion flesh	Onion dry skin
Błońska	6.90	34.80
Sochaczewska	3.97	29.89
Efekt	4.85	28.79
Kristine	4.82	25.17

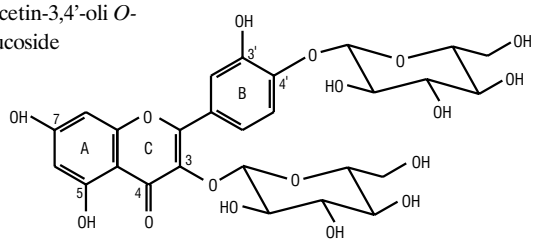
Plasma concentration of quercetin

Pharmaco-kinetic parameters of quercetin are presented in Table 4. The peak level (c_{max}) of quercetin was reached 10 min (t_{max}) after administration of both onion flesh or onion dry skin, and there were no significant differences between the two samples (Figure 2). Twenty four hours after administration, quercetin was still present in plasma. Its concentrations after onion skin and onion flesh

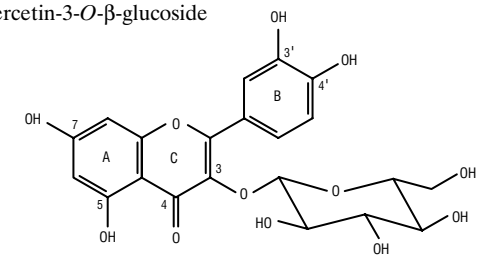
Quercetin-4'-O-β-glucoside



Quercetin-3,4'-oli *O*-
-β-glucoside



Quercetin-3-*O*-β-glucoside



Quercetin

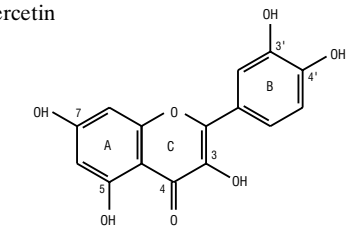


FIGURE 1. Structures of major quercetin glucosides and the aglycone found in onion.

administration were 0.25±0.10 μM, and 0.10±0.10 μM, respectively. The area under the curve (AUC) of absorption, a bioavailability marker of quercetin from onion flesh was 50% of that from onion skin. The constants of elimination of quercetin for onion skin and onion flesh were k_{el}=0.18 h^{-1} and k_{el}=0.12 h^{-1}, respectively.

TABLE 2. Distribution of quercetin within the onion fleshy scales of Błońska variety (%).

Onion scales							
1st scale[a]	2nd scale	3rd scale	4th scale	5th scale	6th scale	7th scale	8th scale
53.5	16.5	12.2	10.9	4.6	1.7	0.4	0.2

[a]- outer scale

TABLE 3. Quercetin content in fleshy scales of onion and onion dry skin (%) of Błońska variety.

	Quercetin aglycone	Quercetin glycosides			
		Q 4' G	Q 3 G	Q 3.4' G	Total
Onion flesh	0.7	68.3	1.0	30.0	99.3
Onion dry skin	53.2	40.5	0.2	6.1	46.8

It was demonstrated that $AUC_{0\text{-inf.}}$ describing bioavailability of quercetin from edible parts of onion and onion dry skin were significantly lower (p=0.015) and k_{el}, c_{max} body weight were not statistically different.

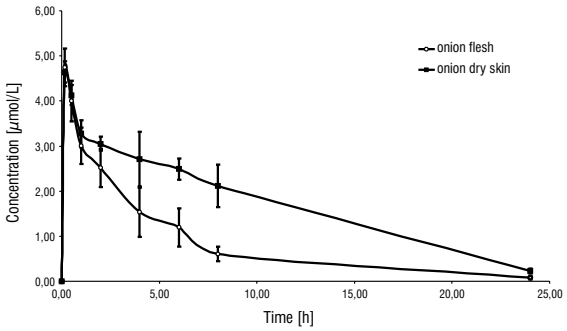


FIGURE 2. Quercetin concentration in rat plasma after administration of 7 mg quercetin per kg of b. wt. with freeze-dried onion flesh or onion dry skin.

DISCUSSION

The aim of this study was to compare bioavailability of quercetin and its β-glucosides. Earlier published papers report better bioavailability of β-glucosides [Hollman *et al.*, 1995]. In those studies, however, quercetin was offered in capsules as a pure crystalline substance which is very poorly soluble in water, while quercetin β-glucosides originated from onion, which means that bioavailability of quercetin from two different sources was compared. The application of only dietary sources rich in free quercetin or its glucosides for this comparison would be more relevant from the nutritional point of view.

Onion, a worldwide consumed vegetable, is a known dietary source rich in quercetin [Crozier *et al.*, 1997; Hertog *et al.*, 1992]. The performed analysis of distribution of this compound within different varieties (Table 1) showed that the richest in quercetin is the dry skin of onion where as much as 53.2% of total quercetin is present in the aglycone form (Table 3). Also the outer scale of onion flesh (Table 2), where 53.5% of total quercetin present in onion bulb is concentrated, is very rich in this compound. However, contrary to onion dry skin, onion flesh contains quercetin almost exclusively in the form of glycosides: quercetin-4'-glucoside, quercetin-3-glucoside, and quercetin-3,4'-glucoside (Table 3). A high level of quercetin in the outer layers of onion bulb results from exposure to the sunlight [Aherne & O'Brien, 2002]. Prevalence of the free form of quercetin in the onion dry skin is probably related with its protective function against UV B, where it acts as a filter protecting onion vegetative parts. These results show that because of high content of quercetin and its derivatives, the outer parts of onion bulb are a very attractive material for dietary experiments.

In the experiment on rats two outer flashy scales of Błońska variety containing only 0.7% of quercetin aglycone

TABLE 4. Kinetic parameters of quercetin in rat plasma after oral administration of onion flesh and onion dry skin.

Variable	Sources of quercetin	
	Onion flesh	Onion dry skin
Time to reach peak level [t_{max}, min]	10	10
Peak level [c_{max}, μM]	4.75 ± 0.85	4.65 ± 0.45
Elimination constants [k_{el}, h^{-1}]	0.18 ± 0.05	0.12 ± 0.05
$AUC_{0\text{-}24h}$ [μM x h/L]	20.47 ± 9.58	41.25 ± 9.69
$AUC_{0\text{-inf.}}$ [μM x h/L]	21.07 ± 10.17	43.44 ± 8.47

were used (Table 3) as a source of quercetin glucosides, and onion dry outer skin of the same variety, containing as much as 53.2% of quercetin in the free form (Table 3), was used as the source of quercetin aglycones. To compare the bioavailability of quercetin and its glucosides from the dietary sources, the impact of food matrix on absorption should be eliminated. Therefore, onion dry skin and outer fleshy scales were freeze-dried and powdered; additionally, prior to administration the doses were homogenized in water.

Assuming that the influence of food matrix was reduced, the obtained results do not confirm the previous report [Hollman *et al.*, 1995] that glucosides are more bioavailable than aglycones. As for the AUC value, which is a bioavailability marker, significant differences in bioavailability of quercetin from the sources used were found ($p \leq 0.05$) (Table 4, Figure 2). Quercetin from onion dry skin (53.2% aglycones) was twice as much bioavailable as that from outer fleshy scales (99.7% glucosides). In both cases maximum plasma quercetin concentrations c_{max} were reached 10 min following administration and were not significantly different ($p \leq 0.05$): c_{max} for onion dry skin and outer fleshy scales were 4.65 ± 0.45 μM and 4.75 ± 0.85 μM, respectively.

An increase in plasma quercetin concentration within the first 10 min after administration suggests that the absorption of quercetin from the used materials was similar (Figure 2). The observed decrease in quercetin concentration in the plasma starting 10 min following administration may result from the solubility drop of quercetin and its derivatives induced by lowering of pH in the stomach environment. In the other study it was shown that the solubility of quercetin is one of its absorption limiting factors [Piskula & Terao, 1998]. This phenomenon along with intensive elimination of quercetin metabolites from the blood common circulation in detoxification processes is probably the reason of the observation. Another factor which may be the reason for differences in the determined bioavailabilities are the mechanisms of transportation and hydrolysis. More hydrophobic quercetin than its glucosides may pass through biological membranes to reach intestinal enterocytes *via* passive transport. In the case of quercetin glucosides, two mechanisms are proposed: prior to absorption they may be hydrolyzed in the intestinal lumen by β-glucosidases and the released free quercetin is absorbed as above [Day *et al.*, 1998; Ioku *et al.*, 1998], or they may enter enterocytes *via* Na+/glucose transporter [Gee *et al.*, 2000, 1998]. Moreover, it is possible that these two mechanisms are the factors limiting quercetin glucosides absorption.

In this study, quercetin bioavailability may be also influenced by the degree of food matrix destruction. It must be pointed out here that despite a probably higher mechanical resistance of onion dry skin than that of freeze-dried fleshy scales the bioavailability of quercetin from onion dry skin is better (Table 4).

Quercetin solubility may be the main reason for contradiction of results reported by Hollman *et al.* [1995] and here. Pure crystalline quercetin is a substance with very low solubility in the digestive tract environment, therefore, with a low accessibility for the digestive media. In contrast to that, this limiting factor is not relevant in food where molecules of dietary quercetin are dispersed in the food matrix, which makes them very well accessible. In conclusion, the difference in the sources of free quercetin seems to be the main reason for the observed discrepancy between reports.

CONCLUSION

Taking into account absorption profiles of quercetin from dietary sources used in this study and the fact that the content of free quercetin in onion dry skin and in fleshy outer layers were about 50% and 1% (Table 3) respectively, one can conclude that dietary quercetin aglycone is better bioavailable than its glucosides.

ACKNOWLEDGEMENT

This work was in part funded by the State Committee for Scientific Research's project PBZ-KBN/020/P06/1999/09 and EU Centre of Excellence project ICA-CT-2000-70017.

REFERENCES

1. Afanas'ev I., Dorozhko A.I., Brodskii A.V., Kostyuk V.A., Potapovitch A.I., Chelating and free radical scavenging mechanisms of inhibitory action of rutin and quercetin in lipid peroxidation. Biochem. Pharmacol., 1989, 38, 1763–1769.
2. Aherne S.A., O'Brien N.M., Dietary Flavonols: chemistry, food content, and metabolism. Nutrition, 2002, 18, 75–81.
3. Bors W., Heller W., Michel Ch., Saran M., Flavonoids as antioxidants: determination of radical-scavenging efficiencies. Methods Enzymol., 1990, 186, 343–355.
4. Chen Y., Zheng R., Jia Z., Ju Y., Flavonoids as superoxide scavengers and antioxidants. Free Rad. Biol. Med., 1990, 9, 19–21.
5. Cos P., Li Y., Calomme M., Jia P.H., Cimanga K., van Poel B., Pieters L., Vlietinck A.J., Berghe D.V., Structure-activity relationship and classification of flavonoids as inhibitors of xanthine oxidase and superoxide scavengers. J. Nat. Prod., 1998, 61, 71–76.
6. Crozier A., Lean M.E.J., McDonald M.S., Black C., Quantitative analysis of the flavonoids content of commercial tomatoes, onions, lettuce, and celery. J. Agric. Food Chem., 1997, 45, 590–595.
7. 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 glucosides by human small intestine and liver β-glucosidase activity. FEBS Letters, 1998, 436, 71–75.
8. Gee J.M., DuPont M.S., Day A.J., Plumb G.W., Williamson G., Johnson I.T., Intestinal transport of quercetin glycosides in rats involves both deglycosylation and interaction with the hexose transport pathway. J. Nutr., 2000, 130, 2765–2771.
9. Gee J.M., DuPont M.S., Rhodes M.J., Johnson I.T., Quercetin glucosides interact with the intestinal glucose transport pathway. Free Radic. Biol. Med., 1998, 25, 19–25.
10. Guardia T., Rotelli A.E., Juarez A.O., Pelzer L.E., Anti-inflammatory properties of plant flavonoids. Effects of rutin, quercetin and hesperidin on adjuvant arthritis in rat. Il Farmaco, 2001, 56, 683–687.
11. Herrmann K., Flavonols and flavones in food plants; a review. J. Food. Technol., 1976, 11, 433–448.

12. Herrmann K., On the occurrence of flavonol and flavone glycosides in vegetables. Z. Lebensm. Unters. Forsch., 1988, 186, 1–5.
13. Hertog M.G.L., Feskens E.J., Hollman P.C., Katan M.B., Kromhnout D., Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly Study. The Lancet, 1993a, 342, 1007–1011.
14. Hertog M.G.L., Hollman P.C., Katan B., Kromhnout D., Intake of potential carcinogenic flavonoids and their determinants in adults in Netherlands. Nutr. Cancer, 1993b, 20, 21–29.
15. Hertog M.G.L., Hollman P.C., Katan M.B., Content of potentially anticarcinogenic flavonoids of 28 vegetables and 9 fruits commonly consumed in the Netherlands. J. Agric. Food Chem., 1992, 40, 2379–2383.
16. Hertog M.G.L., Hollman P.C., van de Putte B., Content of anticarcinogenic flavonoids of tea infusions, wines, and fruit juices. J. Agric. Food Chem., 1993c, 41, 1242–1246.
17. Hertog M.G.L., Kromhnout D., Aravanis Ch., Blackburn H., Buzina R., Fidanza F., Giampaoli S., Jansen A., Menotti A., Nedeljkovic S., Pakkarinen M., Simic B.S., Toshima H., Feskens E.J., Hollman P.C., Katan M.B., Flavonoid intake and long-term risk of coronary heart disease and cancer in the seven countries study. Arch. Intern. Med., 1995, 381–386.
18. Hollman P.C.H, Bijsman M.N.C.P., van Gameren Y., Cnossen E.P.J., de Vries J.H.M., Katan M.B., The sugar moiety is a major determinant of the absorption of dietary flavonoids glycosides in man. Free Rad. Res., 1999, 31, 569–573.
19. Hollman P.C.H., de Vries J.H.M., van Leeuwen S.D., Mengelers M.J.B., Katan M.B., Absorption of dietary quercetin glycosides and quercetin in healthy ileostomy volunteers. Am. J. Clin. Nutr., 1995, 62, 1276–1282.
20. Hollman P.C.H., van Trijp J.M.P., Buysman M.N.C.P., van de Gaag M.S., Mengelers M.J.B., de Vries J.H.M., Katan M.B., Relative bioavailability of the antioxidant flavonoid quercetin from various foods in man. FEBS Letters, 1997, 418, 152–156.
21. Ioku K., Pongpiriyadacha Y., Konishi Y., Takei Y., Nakatani N., Terao J., β-Glucosidase activity in the rat small intestine toward quercetin monoglucosides. Biosci. Biotechnol. Biochem., 1998, 67, 1428–1431.
22. Ioku K., Tsushida T., Takei Y., Nakatani N., Terao J., Antioxidative activity of quercetin and quercetin monoglucosides in solution and phospholipid bilayers. Biochem. Biophys. Acta, 1995, 1234, 99–104.
23. Keli S.O., Hertog M.G.L., Feskens E.J., Kromhnout D., Dietary flavonoids, antioxidant vitamins, and incidence of stroke. Arch. Intern. Med., 1996, 154, 637–642.
24. Knekt P., Järvinen R., Reunanen A., Maatela J., Flavonoid intake and coronary mortality in Finland: a cohort study. Br. Med. J., 1996, 312, 478–481.
25. Manach C., Morand Ch., Demingné Ch., Texier O., Régérat F., Rémésy Ch., Bioavailability of rutin and quercetin in rats. FEBS Letters, 1997, 409, 12–16.
26. Pace-Asciak C.R., Hahn S., Diamandis E.P., Soleas G., Goldberg D.M., The red wine phenolics trans-resveratrol and quercetin block human platelet aggregation and eicosanoid synthesis: implication for protection against coronary heart disease. Clinica Chimica Acta, 1995, 235, 207–219.
27. Peterson J., Dwyer J., Flavonoids: dietary occurrence and biochemical activity. Nutr. Res., 1998, 18, 1995–2018.
28. Piskula M.K., Terao J., Quercetin's solubility affects its accumulation in rat plasma after oral administration. J. Agric. Food. Chem., 1998, 46, 4313–4317.
29. Terao J., Piskula M. K., Yao Q., Protective effect of epicatechin, epicatechin gallate, and quercetin on lipid peroxidation. Arch. Biochem. Biophys., 1994, 308, 278–284.
30. Terao J., Piskula M.K., Flavonoids as inhibitors of lipid peroxidation in membranes. 1998, *In*: Flavonoids in Health and Disease. (eds. C. Rice-Evans, L. Packer). Dekker: New York, pp. 277–293.