1st International Multidisciplinary Conference on Nutraceuticals and Functional Foods
Current Research in Nutrition and Food Science Vol. 4(SI. 2), 146-151 (2016)

Bioavailability of Quercetin

MUZEYYEN BERKEL KASIKCI* and NERIMAN BAGDATLIOGLU

Department of Food Engineering, Faculty of Engineering,
Manisa Celal Bayar University, Manisa, Turkey.
*Corresponding author Email: muzeyyen.berkel@cbu.edu.tr

http://dx.doi.org/10.12944/CRNFSJ.4.Special-Issue-October.20

(Received: August, 2016; Accepted: September, 2016)

ABSTRACT

Quercetin is generally present as quercetin glycoside in nature and involves quercetin aglycone conjugated to sugar moieties such as glucose or rutinose. Quercetin has been reported to exhibit antioxidative, anti-carcinogenic, anti-inflammatory, anti-aggregatory and vasodilating effects. Unfortunately, quercetin bioavailability is generally poor and several factors affect its bioavailability. Quercetin bioavailability varies widely between individuals. Gender may affect quercetin bioavailability, but there is no clear evidence. There has been little research looking for the effects of age and vitamin C status on bioavailability of quercetin supplements, but there is no research seeking out the effects of age and vitamin C status on bioavailability of food-derived quercetin. Presence of sugar moieties increases bioavailability and differences in quercetin-conjugated glycosides affect bioavailability. For instance, onion-derived quercetin, which is mainly quercetin glucoside, is more bioavailable than apple-derived quercetin, which contains quercetin rhamnoside and quercetin galactoside. Quercetin is lipophilic compound, thus dietary fat enhances its bioavailability. Nondigestible fiber may also improve quercetin bioavailability. Quercetin bioavailability is greater when it is consumed as an integral food component. This study reviews and discusses factors affecting quercetin bioavailability.

Keywords: quercetin, bioavailability, sugar moiety, solubility, flavonoid, flavonol.

INTRODUCTION

Quercetin is a dietary flavonol found widely in fruits, vegetables and nuts in many different glycosidic forms. Major dietary sources are lettuce, chili pepper, cranberry, onion, black chokeberry, black elderberry, caper, tomato, broccoli and apple (Rothwell *et al*., 2013). In onions, quercetin is bound to 1 or 2 glucose molecules (quercetin-4´-glucoside and quercetin-3,4´-glucoside). Examples of dietary quercetin are quercetin galactosides, which are found in apples, quercetin arabinosides, which are present in berries, quercetin-3-rutinoside (rutin), which are found in capers (Erlund, 2004).

Quercetin has been reported to exhibit antioxidative, anti-carcinogenic, anti-inflammatory, anti-microbial, anti-viral, antiaging,anti-thrombotic, anti-aggregatory and vasodilating effects (Hayek *et al*., 1997; Chopra *et al*., 2000; Verma *et al*., 1988; Deschner *et al*., 1991; Pereira *et al*., 1996, Ferry *et al*., 1996; Erlund *et al*., 2004). Although quercetin has lots of health benefits, its bioavailability is relatively poor and highly variable. This study compiles and discusses bioavailability studies of food-derived quercetin and quercetin in supplements.

Bioavailability of quercetin

Bioavailability is the fraction of an orally administered substance that is absorbed and available for physiologic activity or storage (Jackson *et al*., 1997). Bioavailability is classified as absolute or relative based on its pharmacokinetics assessment (Toutain *et al*., 2004). Absolute bioavailability is more accurate, and is calculated as the area under the plasma concentration-time curve of an ingested substance (AUC_{oral}) relative to its intravenous administration ($AUC_{i.v}$) (Levine *et al*., 1996).

Alternatively, relative bioavailability is simpler, but less accurate, and is calculated as AUC_{oral}. However, studies examining relative bioavailability of quercetin are more common (Guo *et al*., 2015).

In contrast to the form in most supplements, most of the quercetin in foods is attached to a sugar molecule and this conjugate is known as a glycoside. The onion plant tends to attach glucose to form quercetin-3-glucoside (isoquercetin) while apple trees and tea plants tend to attach rutinose, yielding rutin (Heim *et al*.,2002; Yoo *et al*., 2010). Differences in quercetin-conjugated glycosides affect its bioavailability (Lee *et al*., 2012; Hollman *et al*., 1997a; Hollmann *et al*., 1997b). The size and polarities of these compounds can cause difficulty crossing membranes in the gut. Oppositely, this is not the case for isoquercetin. A clinical research compared quercetin bioavailability from different foods and supplements (Hollman *et al*., 1997a; Hollman *et al*., 1997b). Absorption from isoquercetin-rich onions was 52%, compared to 24% from a standard quercetin supplement (Hollman *et al*., 1997b). Likewise, animal studies showed superior bioavailability of isoquercetin relative to quercetin and rutin (Manach *et al*., 1997). Likewise, in another study, bioavailability of onion-derived quercetin, which is mainly quercetin glucoside, compared to apple-derived quercetin, which contains quercetin rhamnoside and quercetin galactoside (Yoo *et al*., 2010; Lee *et al*., 2012). In this study, $AUC_{0\text{-}24h}$ and C_{max} of quercetin following the consumption of onions were 2 and 3 times greater, respectively, than those following the consumption of apples (Lee *et al*., 2012). Quercetin T_{max} did not differ between dietary sources, but $t_{1/2}$ of apple-derived quercetin was more than 4 times shorter after consuming onions (15 h). These findings support that onion-derived quercetin is more bioavailable due to its greater absorption (Lee *et al*., 2012).

Studies in pigs showed that quercetin glucoside, compared to quercetin aglycone, had greater bioavailability. Some hypothesis may clarify this phenomenon. First of all, quercetin glucoside (0.76±0.01) is more water soluble than quercetin aglycone (1.82±0.32) on the basis of its lower octanol-water partition coefficient (Rothwell *et al*., 2005). Another hypothesis is quercetin glucoside is absorbed through sodium-dependent glucose transporter 1 (SLGT1), but it is not in use for quercetin aglycone (Wolffram *et al*., 2002). SGLT1-mediated absorption provides greater intestinal uptake of quercetin glucoside (Guo *et al*., 2015). The site and manner in which quercetin absorbed depends upon its chemical structure (Guo *et al*., 2015). *In vitro* studies put a hypothesis that the glucose moiety was using a transporter that normally pumps glucose across membranes of the intestinal wall (Gee *et al*., 2000). The rapid absorption observed with isoquercetin is consistent with this active transport. For quercetin and rutin, which cannot use the transporter, peak levels are riched within 2-4 and 6-8 hours respectively (Olthof *et al*., 2000; Erlund *et al*., 2000). Inversely, isoquercetin can reach peak concentrations in less than 40 minutes (Olthof *et al*., 2000). Mechanisms explaining gastric absorption of quercetin aglycone is unclear, but studies in Caco-2 cell monolayers support that intestinal absorption of quercetin aglycone occurs primarily by passive diffusion and secondarily by organic anion transporting polypeptide (OATP) (Nait *et al*., 2009). Contrasting quercetin aglycone, glycosylated forms of quercetin (quercetin glucoside, quercetin rutinoside) are not absorbed in the stomach (Crespy *et al*., 2002). Quercetin glycosides such as quercetin glucoside, quercetin galactoside, quercetin arabinoside, are deglycosylated to quercetin aglycone prior to absorption by lactase phlorizin hydrolase (LPH), a â-glucosidase residing at the brush border (Arts *et al*., 2004; Nemath *et al*., 2003). Afterwards, quercetin aglycone is passively absorbed (Day, A. J., 2003). Different from those, quercetin rutinoside is absorbed in the colon following deglycosylation, which appears to be mediated by gut microbiota-derived â-glucosidase that generates quercetin aglycone and facilitates its colonic absorption (Day, A.J., 2003; Jaganath, I. B., 2006, Kim, D.H., 2008).

The extent to which quercetin is absorbed in clinical studies can be estimated by multiplying the plasma maximum concentration (C_{max}) of quercetin by plasma volume (estimated at 3 L for adults) and dividing by the administered dose (Davy *et al*., 1994; Retzlaff, J. A., 1969; Guo *et al*.,2015). Healthy participants ingesting grape juice containing 10 mg quercetin aglycone had a quercetin C_{max} of 16 µM, which represents approximately 1.4% of the ingested dose (Golderg *et al*., 2003). Quercetin

glucoside is also poorly absorbed as evidenced by an estimated absorption of 6.9 in healthy participants who ingested onion-derived quercetin glucoside at a dose corresponding to 100 mg quercetin aglycone (Graefe *et al*., 2001).

Bioavailability of quercetin is related to its bioaccessibility and thereby solubility in the vehicle used for its administration. Quercetin is relatively lipophilic with low water solubility. The poor solubility of quercetin and crstalline form at body temperatures limitnits bioaccessibility and its bioavailability. Absolute bioavailability of quercetin was 16% in rats and its C_{max} was 2.01 µM following administration of quercetin suspended in aqueous solution. Administration of quercetin aglycone dissolved in an ethanol and PEG 200 solution increased its absolute bioavailability to 27.5% and C_{max} to 3.44 µM(Khaled *et al*., 2003; Pool *et al*., 2013). Octanol-water partition coefficient of quercetin (1.82±0.32) is nearly double that of quercetin-3-glucoside (0.76±0.01), but it is lower than that of kaempferol (3.11±0.54). Water solubility of quercetin is 1.53-12.5 mg/L at gastrointestinal pH levels (pH 2-7) (Pool *et al*., 2013).

Poor bioavailability of quercetin aglycone and glycosides is also related to their propensity, and that of their metabolites, to be effluxed back into the intestinal lumen following enterocyte uptake (Crespy *et al*., 1999; Crespy *et al*., 2001). Quercetin aglycone or glycosides are effluxed across the apical membrane of enterocytes, as indicated in Caco-2 cell monolayer studies showing that their permeability from the basolateral to apical side was more than 2 times greater than their apical to basolateral permeability (Nait *et al*., 2009; Walgren *et al*., 1998). Most of the absorbed quercetin aglycone is rapidly metabolized and secreted back into the intestinal lumen (Crespy *et al*., 2001).

Quercetin bioavailability is better when quercetin is consumed as a cereal bar ingredient instead of capsule (Egert *et al*., 2012). Its greater absorption may be related with manufacturing process that yields a homogenous solid dispersion of quercetin with other cereal ingredients. Solid dispersions have greater surface area that promotes dissolution in the intestinal lumen, thereby promoting bioavailability (Guo *et al*., 2015). Dietary fat improved quercetin bioavailability in a study with pigs (Lesser *et al*., 2004). Quercetin ingestion with short chain fructooligosaccharide (FOS) improves quercetin bioavailability (Matsukawa *et al*., 2009). Quercetin bioavailability of vacuum impregnated apple chips ($AUC_{0\text{-}1440\ min}$ = 104±24 µmol.min.L^{-1}) as functional food was similar to the supplementation with apple peel extract capsules ($AUC_{0\text{-}1440\ min}$ = 87±24 µmol. min.L^{-1}) in humans (Petersen *et al*., 2016). More research are needed to prove that quercetin in food matrix provides greater bioavailability than capsule forms.

Quercetin bioavailability is characterized by high intersubject variability (Kaushik *et al*., 2012). For instance, quercetin $AUC_{0\text{-}24\ h}$ was 8.9-89.1 µM.h following ingestion of onion-derived quercetin glucosides at a dose equivalent to 100 mg quercetin aglycone (Graefe *et al*., 2001). Quercetin C_{max} was 0.29-2.26 µM in adults who ingested a beverage containing 500 mg quercetin aglycone (Kaushik *et al*., 2002). Intersubject variations for time to C_{max} (T_{max}) and elimination half-life ($t_{1/2}$) of quercetin in adults were 69% and 122% respectively, following ingestion of 100 mg apple-derived quercetin glycosides (Lee *et al*., 2012). Likewise, 50 mg quercetin supplementation in adults results in highly variable plasma concentrations (38-194 nM) (Egert *et al*., 2008). Differences in â-glucosidase activity, a determinant of intestinal uptake of quercetin glucosides, promote intersubject variation in quercetin glycoside absorption (Nemeth *et al*., 2003; Day *et al*., 2003; Guo *et al*., 2015). Additionally, intersubject variations in intestinal and hepatic phase II quercetin –metabolizing enzymes (UGT, specifically UGT1A family; SULT, specifially SULT1A family; COMT) are speculated to contribute to interindividual differences in quercetin metabolism (Egert *et al*., 2008).

There is no clear evidence demonstrating that gender and age affect quercetin bioavailability (Guo *et al*., 2015). Exceptional finding was that quercetin from quercetin-3-rutinoside was more bioavailable in women compared with men (Erlund *et al*., 2000). A quercetin study in humans suggest that individual differences in plasma vitamin C status may contribute to intersubject variability in quercetin bioavailability (Guo *et al*., 2014). Some *in vitro* studies also showed that vitamin C protects

quercetin against oxidative degredation (Skaper *et al*., 1997; Takahama *et al*., 2003). More clinical studies are necessary to define if vitamin C status regulates quercetin bioavailability.

In conclusion, quercetin has several health effects and thereby, its bioavailability is really significant and unfortunately, is poor. Many factors such as glucose moieties, solubility, human factor, vitamin C status and food matrix can affect bioavailability. More research is warranted to evaluate and improve bioavailability of quercetin.

REFERENCES

1. Arts, I. C., Sesink, A. L., Faassen-Peters, M., Hollman, P.C. The type of sugar moiety is a major determinant of the small intestinal uptake and subsequent biliary excretion of dietary quercetin glycosides. *Br. J. Nutr.,* **91**: 841-847 (2009).
2. Chopra, M., Fitzsimons, P. E., Strain J. J., Thurnham, D.I., Howard A.N. Nonalcoholic red wine extract and quercetin inhibit LDL oxidation without affecting plasma antioxidant vitamin and carotenoid concentrations. *Clin. Chem*. **46**: 1162- 70 (2000).
3. Crespy,V., Morand, C., Besson, C., Manach, C., Demigne, C., Remesy, C. Comparision of the intestinal absorption of the quercetin, phloretin and their glucosides in rats. *J. Nutr.*, **14**: 2109-2114 (2001).
4. 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*., **50**: 618- 621 (2002).
5. Crespy, V., Morand, C., Manach, C., Besson, C., Demigne, C., Remesy, C. Part of quercetin absorbed in the small intestine is conjugated and further secreted in the intestinal lumen. *Am. J. Physiol.,* **277**: 120-126 (1999).
6. Davy, K. P., Seals, D. R. Total blood volume in healthy young and older men. *J. Appl. Physiol*., **76**: 2059-2062 (1994).
7. Day, A. J., Gee, J. M., DuPont, M. S., Johnson, I. T., Williamson, G. Absorption of quercetin-3-glucoside and quercetin-4´-glucoside in the rat small intestine: the role of lactase phlorizin hydrolase and the sodium-dependent glucose transporter. *Biochem. Pharmacol*., **65**: 1199-11206 (2003).
8. Deschner, E.E., Ruperto, J., Wong, G., Newmark, H.L. Quercetin and rutin as inhibitors of azoxymethanolinduced colonic neoplasia. Carcinogenesis, **12**:1193-1196 (1991).
9. Egert, S., Wolffram, S., Bosy-Westphal, A., Boesch-Saadatmandi, C., Wagner, A. E., Frank, J. Daily quercetin supplementation dpse-dependently increases plasma quercetin concentrations in healthy humans. *J. Nutr*., **138**: 1615-1621 (2008).
10. Egert, S., Wolffram, S., Schulze, B., Langguth, P., Hubbermann, E. M., Schwarz, K. Enriched cereal bars are more effective in increasing plasma quercetin compared with quercetin quercetin from powder-filled hard capsules. *Br. J. Nutr*., **107**: 539-546 (2012).
11. Erlund, I., Kosonen, T., Alfthan, G., Pharmacokinetics of quercetin from quercetin aglycone and rutin in healthy volunteers. *Eur. J. Clin. Pharmacol*., **56**: 545-553 (2000).
12. Erlund, I. Review of the flavonoids quercetin, hesperetin, and naringenin. Dietary sources, bioactivities, bioavailability and epidemiology. *Nutr. Res.,* **24**: 851-874 (2004).
13. Ferry, D.R., Smith, A., Malkhandi, J., Fyfe, D.W., de Takats, P.G., Anderson, D. Phase I clinical trial of the flavonoid quercetin: pharmacokinetics and evidence for in vivo tyrosine kinase inhibition. *Clin. Cancer Res*., **2**: 659- 68 (1996).
14. Gee, J. M., DuPont, M. S., Day, A. J. Intestinal transport of quercetin glycosides in rats involves both deglycosylation and interaction with the hexose transport pathway. *J. Nutr.,* **130**: 1200-1203 (2000).
15. Graefe, E. U., Witting, J., Mueller, S., Riethling, A. K., Uehleke, B., Drewelow, B. Pharmocokinetics and bioavailability of quercetin glycosides in humans. *J. Clin. Pharmacol.,* **41**: 492-499 (2001).

16. Goldberg, D. M., Yan, J., Soleas, G. J. Absorption of three wine-related polyphenols in three different matrices by healthy subjects. *Clin. Biochem.*, **36**: 79-87 (2003).
17. Guo, Y., Bruno, R. S. Endogenous and exogenous mediators of quercetin bioavailability. *J. Nutr. Biochem.,* **26**: 201-210 (2015).
18. Guo, Y., Mah., E., Bruno, R. S. Quercetin bioavailability is associated with inadequate plasma vitamin C status and greater plasma endotoxin in healthy adults. *Nutrition, 30*: 1279-1286 (2014).
19. Hayek, T., Fuhrman, B., Vaya, J., Rosenblat, M., Belinky, P., Coleman, R. Reduced progression of atherosclerosis in apolipoprotein E-deficient mice following consumption of red wine, or its polyphenols quercetin or catechin, is associated with reduced susceptibility of LDL to oxidation and aggregation. *Arterioscler Thromb. Vasc. Biol.* **17**: 2744-2752 (1997).
20. Heim, K., Tagliaferro, A. R., Bobilya, D. J. Flavonoid antioxidants: chemistry and structure-activity relationship. *J Nutr Biochem.*, **13**(10): 572-584 (2002).
21. Hollman, P. C., van Trijp, J. M., Buysman, M. N. Relative bioavailability of the antioxidant flavonoid quercetin from various foods in man. *FEBS Lett.*, **418**: 152-156 (1997).
22. Hollman, P. C., van Trijp, J. M., Mengelers, M. J. Bioavailability of the dietary antioxidant flavonol quercetin in man. *Cancer Lett.*, **114**: 139-140 (1997).
23. Jackson, M. J., The assessment of bioavailability of micronutrients: introduction. *Eur. J. Clin. Nutr.,* **51**: 1-2 (1997).
24. Jaganath, I.B., Mullen, W., Edwards, C. A., Crozier, A. The relative contribution of the small and large intestine to the absorption and metabolism of rutin in man. *Free Radic. Res.,* **40**: 1035-1046 (2006).
25. Kaushik, D., O'Fallon, K., Clarkson, P. M., Dunne, C. P., Conca, K. R., Michniak-Kohn, B. Comparision of quercetin pharmacokinetics following oral supplementation in humans. *J. Food Sci.*, **77**: 231-238 (2012).
26. Khaled, K. A., El-Sayed, Y. M., Al-Hadiya, B. M. Disposition of the flavonoid quercetin in rats after single intravenous and oral doses. *Drug Dev. Ind. Pharm.*, **29**: 397-403 (2003).
27. Kim, D.H., Jung, E. A., Sohng, I. S., Han, J.A., Kim, T. H., Han, M. J. Intestinal bacterial metabolism of flavonoids and its relation to some biological activities. *Arch. Pharm. Res.,* **21**: 17-23 (1998).
28. Lee, J., Mitchell, A. E. Pharmacokinetics of quercetin absorption from apples and onions in healthy humans. *J. Agric. Food Chem.*, **60**: 3874-3881 (2012).
29. Lesser, S., Cermak, R., Wolffram, S. Bioavailability of quercetin in pigs is influenced by the dietary fat content. *J. Nutr.*, **134**: 1508-1511 (2004).
30. Levine, M., Conry-Cantilena, C., Wang, Y., Welch, R. V., Washko, P. W., Dhariwal, K. R. Vitamin C pharmacokinetics in healthy volunteers: evidence for a recommended dietary allowance. *Proc. Natl. Acad. Sci.*, **93**: 3704-3709 (1996).
31. Manach, C., Morand, C., Demigne, C. Bioavailability of rutin and quercetin in rats. *FEBS Lett.*, **409**: 12-16 (1997).
32. Matsukawa, N., Matsumoto, M., Shinoki, A., Hagio, M., Inoue, R., Hara, H. Nondigestible saccharides supress the bacterial degradation of quercetin aglycone in the large intestine and enhance the bioavailability of quercetin glucoside in rats. *J. Agric. Food. Chem.,* **57**: 9462-9468 (2009).
33. Nait, C. M., Al., A. A., Peluso, J., Muller, C. D., Ubeaud, G. Quercetin and naringenin transport across human intestinal Caco-2 cells. *J. Pharm. Pharmacol.*, **61**: 1473-1483 (2009).
34. Nemeth, K., Plumb, G. W., Berrin, J. G., Juge, N., Jacob, R., Naim, H. Y. Deglycosylation by small intestinal epithelial cell beta-glucosidases is a critical step in the absorption and metabolism of dietary flavonoid glycosides in humans. *Eur. J. Nutr.*, **42**: 29-42 (2003).
35. Olthof, M. R., Hollman, P.C., Vree, T. B., Katan, M. B. Bioavailabilities of quercetin-3-glucoside and quercetin-4´-glucoside do not differ in humans. *J. Nutr.,* **130**: 1200-1203 (2000).
36. Pereira, M. A., Grubbs, C.J., Barnes, L.H., Li, H., Olson, G.R., Eto, I. Effects of the phytochemicals, curcumin and quercetin, upon azoxymethane-induced colon cancer and 7,12 dimethylbenz[a]anthracene-induced mammary cancer in rats. Carcinogenesis,

17:1305-1311 (1996).

37. Petersen, B., Egert, S., Bosy-Westphal, A., Müller, M. J., Wolffram, S., Hubbermann, E. M., Rimbach, G., Schwarz, K. Bioavailability of quercetin in humans and the influence of food matrix comparing quercetin capsules and different apple sources. *Food Res. Int.,* **88**: 159-165 (2016).
38. Pool, H., Mendoza, S., Xiao, H., McClements D. J. Encapsulation and release of hydrophobic bioactive components in nanoemulsion-based delivery systems: impact of physical form on quercetin bioaccessibility. *Food Func.*, **4**: 162-174.
39. Retzlaff, J. A., Tauxe, W. N., Kiely, J. M., Stroebel, C. F. Erythrocyte volume, plasma volume and, lean body mass in adult men and women. *Blood*, **33**:649-661 (1969).
40. Rothwell, J. A. Perez-Jimenez, J., Neveu, V., Medina-Remon, A., M´Hiri, N., Garcia-Lobato, P. Phenol explorer 3.0: a major update of the Phenol-Explorer database to incorporate data on the effects of food processing on polyphenol content. Database (Oxford) 2013. http://phenol-explorer.eu/contents/polyphenol/291
41. Skaper, S. D., Fabris, M., Ferrari, V., Dalle Carbonare, M., Leon, A. Quercetin protects cutaneous tissue-associated cell types including sensory neurons from oxidative stress induced by glutathione depletion: cooperative effects of ascorbic acid. *Free Radic. Biol. Med.*, **22**: 669-678 (1997).
42. Takahama, U., Yamamoto, A., Hirota, S., Oniki, T. Quercetin-dependent reduction of salivary nitrite to nitric oxide under acidic conditions and interactions between quercetin and ascorbic acid during the reduction. *J. Agric. Food Chem.*, **51**: 6014-6020 (2003).
43. Verma, A. K., Johnson, J.A., Gould, M. N., Tanner, M.A. Inhibition of 7,12-dimethylbenz(a) anthracene and N-nitrosomethylurea induced mammary cancer by dietary flavonol quercetin. Cancer Res., **48**:5754- 88 (1998).
44. Walgren, R. A., Walle, U. K., Walle, T. Transport of quercetin and its glucosides across human intastinal epithelial Caco-2 cells. *Biochem. Pharmacol.*, **55**: 1721-1727.
45. Wolffram, S., Block, M., Ader, P. Quercetin-3-glucoside is transported by the glucose carrier SLGT1 across the brush border membrane of rat small intestine. *J. Nutr.,* **132**: 630-635 (2002).
46. Yoo, K.S., Lee, E. J., Patil, B. S. Quantification of quercetin glycosides in 6 onion cultivars and comparisions of hydrolysis-HPLC and spectrophotometric methods in measuring total quercetin concentrations. *J. Food Sci.*, **75**: 160-165 (2010).