

## ORIGINAL COMMUNICATION

# Consumption of black currants, lingonberries and bilberries increases serum quercetin concentrations

I Erlund<sup>1\*</sup>, J Marniemi<sup>2</sup>, P Hakala<sup>2</sup>, G Alfthan<sup>1</sup>, E Meririnne<sup>3</sup> and A Aro<sup>1</sup>

<sup>1</sup>Biomarker Laboratory, National Public Health Institute, Helsinki, Finland; <sup>2</sup>Research and Development Centre, The Social Insurance Institution, Turku, Finland; and <sup>3</sup>Research Unit of Substance Abuse, National Public Health Institute, Helsinki, Finland

**Objective:** To study serum quercetin concentrations of subjects consuming berries or habitual Finnish diets.

**Design:** Randomized parallel dietary intervention.

**Subjects:** Forty healthy men (age 60y).

**Intervention:** Twenty subjects consumed 100 g/day of berries (black currants, lingonberries and bilberries) for 8 weeks. Twenty subjects consuming their habitual diets served as controls. Fasting blood samples were obtained 2 weeks prior to the study, at baseline, and at 2, 4 and 8 weeks. Intake of quercetin was assessed from 3 day food records collected at baseline and at 8 weeks.

**Results:** The serum quercetin concentrations were significantly higher in the subjects consuming berries compared to the control group ( $P=0.039$  ANCOVA with repeated measures). During the berry consumption period the mean serum concentrations of quercetin ranged between 21.4 and 25.3  $\mu\text{g/l}$  in the berry group, which was 32–51% higher compared with the control group. According to 3 day food records, there was no difference in quercetin intake at baseline, but at 8 weeks the intake was  $12.3 \pm 1.4$  mg/day (mean  $\pm$  s.e.m.) in the berry group and  $5.8 \pm 0.6$  mg/day in the control group ( $P=0.001$ ).

**Conclusions:** The results indicate that the berries used in this study are a good source of bioavailable quercetin.

**Sponsorship:** The study was supported by the Academy of Finland, Juho Vainio Foundation and the Finnish Foundation for Cardiovascular Research.

European Journal of Clinical Nutrition (2003) 57, 37–42. doi:10.1038/sj.ejcn.1601513

**Keywords:** human; dietary intervention; berries; quercetin; flavonoids

### Introduction

Flavonoids are polyphenolic compounds widely occurring in plants. One of the most studied flavonoids is the flavonol quercetin. The compound exhibits a wide range of biological activities, such as antioxidative (Aviram & Fuhrman, 1998; Chopra *et al*, 2000), anticarcinogenic (Pereira *et al*, 1996; Caltagirone *et al*, 1997) and enzyme-inhibiting (Siess *et al*, 1995; Peet & Li, 1999) activities. Furthermore, although the results are somewhat controversial, several epidemiological

studies indicate a protective effect for quercetin on cardiovascular disease (Hertog *et al*, 1995; Knekt *et al*, 1996; Yochum *et al*, 1999).

According to data from the Seven Countries Study, the main dietary sources of quercetin are onions, tea, apples and red wine (Hertog *et al*, 1995). However, in Nordic countries, such as Finland, where berries are commonly consumed, berries are a more important source of quercetin than, for instance, red wine (Hirvonen, 2001). In Finland, the berries contributing most significantly to the total intake of quercetin are lingonberries (*Vaccinium vitis-idaea*), which are closely related to cranberries (*Vaccinium oxycoccus*), bilberries (*Vaccinium myrtillus*), which are closely related to blueberries, and black currants (*Ribes nigrum*; Häkkinen *et al*, 1999). Quercetin concentrations of 74–146 mg/kg have been found in lingonberries (Häkkinen *et al*, 1999; Mattila *et al*, 2000), in black currants the concentration ranges between 52 and 122 mg/kg (Mikkonen *et al*, 2001), and a concentration of 30 mg/kg has been reported in bilberries (Häkkinen *et al*, 1999).

\*Correspondence: I Erlund, Biomarker Laboratory, National Public Health Institute (KTL), Mannerheimint. 166, 00300 Helsinki, Finland.  
E-mail: iris.erlund@ktl.fi

Guarantors: AA and JM

Contributors: IE performed quercetin analyses, interpreted the data and wrote the article. PH and JM designed and executed the dietary intervention. PH calculated quercetin intake. EM performed statistical analyses. GA and AA supervised quercetin analyses. All authors read and commented on the manuscript.

Received 9 October 2001; revised 17 April 2002;  
accepted 18 April 2002

Quercetin is mainly present in plants as glycosides and different plants contain different quercetin glycosides. Onions, for instance, contain quercetin glucosides, while in lingonberries the compound is present at least as arabinosides and rutosides. No data is available on the bioavailability of quercetin from berries or some of the quercetin glycosides present in berries. Previous supplementation studies have shown that quercetin is bioavailable from foods such as onions and apples (Hollman *et al*, 1997), tea and red wine (de Vries *et al*, 2001), and from capsules containing quercetin aglycone or quercetin-3-rutinoside (Erlund *et al*, 2000). The bioavailability of the compound and the site of absorption in the gastrointestinal tract seems to depend on the type of sugar it is bound to. Quercetin from quercetin glucosides from onions are rapidly and efficiently absorbed from the proximal parts of the small intestine (Hollman *et al*, 1997), while quercetin from quercetin-3-rutinoside is absorbed from the distal parts of the small intestine or the colon (Erlund *et al*, 2000). In a pharmacokinetic study the bioavailability of quercetin from quercetin-3-rutinoside varied remarkably between individuals and was poorest in men (Erlund *et al*, 2000, 2001).

The aims of the present study were to determine the impact of daily consumption of 100 g of berries (black currants, lingonberries and bilberries) on serum quercetin concentrations in healthy middle-aged men, and to study serum quercetin concentrations in subjects consuming their habitual diets. Indices of antioxidant capacity were also measured from the samples, and the results have been published previously (Marniemi *et al*, 2000).

## Subjects and methods

### Subjects

The study population consisted of 60 male volunteers, all 60 y of age, living in the city of Turku. The subjects were checked to be in good health and were free of medication. The subjects were asked to refrain from dietary supplements for one month prior to and during the study. Their weights were within the normal range or their overweight was less than 20% (body mass index (BMI) < 30 kg/m<sup>2</sup>).

The subjects were randomized into three groups ( $n=20$  in each group; Marniemi 2000). One group received berries, one group vitamin supplements, and one group served as a control group. Subjects from the berry and the control groups were included in this study ( $n=40$ ). The vitamin supplements did not contain quercetin, and therefore serum samples from that group were not analyzed for quercetin.

### Study design

The subjects in the berry group were given 2 kg each of deep-frozen black currants, lingonberries and bilberries. The berries were packed in 100 g portions in plastic bags. The subjects were instructed to take one bag out of the freezer

each day and eat one portion of berries per day. They were also instructed to eat the different berries in turns to ensure an even distribution over the 8 week intervention period. The berries were eaten fresh and heating of the berries was not allowed. The control group received 500 mg daily of calcium gluconate. It is unlikely that calcium affects the absorption of quercetin (Hollman *et al*, 2001). The subjects were instructed not to alter their normal dietary habits during the study. The study protocol was approved by the Ethics Committee of the Social Insurance Institution and all subjects gave their informed written consent prior to participation.

The subjects were asked to record any deviations from instructions regarding diet and berry consumption. Compliance was emphasized and each subject was asked about it separately when they came in for the blood samplings.

### Intake of quercetin

The subjects filled out 3 day dietary records right before the beginning of the study and at 8 weeks. The average daily intakes of quercetin were calculated with the Nutrica computer program developed at the Social Insurance Institution (Knuts *et al*, 1987). The database of this program has been validated by Hakala *et al* (1996). Quercetin data from the Fineli database (provided by M-L Ovaskainen from the National Public Health Institute) were added to the Nutrica database.

### Blood sampling and chemical analyses

Blood samples were taken 2 weeks prior to the study, at baseline and at weeks 2, 4 and 8. Blood was drawn from the antecubital vein in the morning after an overnight fast. The serum was separated immediately and was kept frozen at  $-70^{\circ}\text{C}$  until analyzed.

Serum quercetin concentrations were analyzed using a validated method developed at our laboratory (Erlund *et al*, 1999). In this method potential conjugates of quercetin are hydrolyzed and therefore the results represent total quercetin (unconjugated quercetin, quercetin conjugated with glucuronic acid, sulfate or glycoside groups, and quercetin either bound or not bound to protein). In brief, quercetin conjugates were hydrolyzed by incubating 1 ml of serum with 110  $\mu\text{l}$  of 0.78 M sodium acetate buffer (pH 4.8), 100  $\mu\text{l}$  of 0.1 M ascorbic acid and 40  $\mu\text{l}$  of a crude preparation from *Helix pomatia* containing 4000 U of  $\beta$ -glucuronidase and 200 U of sulfatase activity (type HP-2, Sigma), for 17 h at 37°C. The sample was diluted with 2 ml of phosphate buffer (70 mM, pH 2.4) and added to a Bond Elut C<sub>18</sub> solid-phase extraction column, preconditioned with 6 ml of methanol and 6 ml of phosphate buffer. The column was washed with 9 ml of phosphate buffer and 0.5 ml of water. Quercetin was eluted into a conical glass tube with 2 ml of methanol and dried. For removal of additional interferences, 1 ml of toluene-dichloromethane (80:20, v/v) and 200  $\mu\text{l}$  of 5.3 M

acetic acid–32 mM oxalic acid (80:20, v/v; pH 2.4) were added. The tubes were vortexed and centrifuged. The lower phase was used for HPLC analysis.

Chromatographic analysis was performed with a system consisting of an HP 1090 liquid chromatograph (Hewlett-Packard, Palo Alto, CA, USA), a Coulochem 5100A electrochemical detector with a model 5011 analytical cell (ESA Inc., Chelmsford, MA, USA) and an Inertsil ODS-3 analytical HPLC column (250×4.0 mm i.d., 5 µm; GL Sciences, Tokyo, Japan). The mobile phase consisted of 59% of methanol in phosphate buffer (70 mM, pH 2.4). The detector potential was set to 100 mV.

Quantitation of the quercetin peak was based on the standard additions method using serum standards containing 0, 10, 30, 90 or 150 µg/l of added quercetin. The reproducibility of the method was followed by analyzing a pooled reference sample with a concentration of 72 µg/l in triplicate in each run. Day-to-day variation (CV%) of the reference was 6.4%.

### Statistical methods

Statistical significance of the difference between serum quercetin concentrations of the two dietary groups was assessed by analysis of covariance (ANCOVA) for repeated measures. The baseline values served as covariates and time (weeks 2, 4, 8) as repeated measure. *Post-hoc* comparisons were performed using contrast analysis. Whether the intake of quercetin differed between the groups at 8 weeks was tested by ANCOVA. The baseline values served as covariates. *Post-hoc* comparisons were performed by Tukey's test. Whether the baseline values of serum quercetin or quercetin intake differed between the two groups was tested by Student's *t*-test. The paired *t*-test was used to test the difference in quercetin intake between baseline and 8 weeks within the two groups. A *P*-value of less than 0.05 was considered statistically significant.

## Results

### Intake of quercetin

In the berry group the mean calculated intake of quercetin was significantly higher at the end of the 8 week study compared with baseline ( $P=0.001$ , paired *t*-test; Table 1). In the control group the intake did not change ( $P>0.1$ , paired *t*-test). Quercetin intake was slightly higher at baseline in the berry group compared to the control group but the

**Table 1** The intake of quercetin (mg/day, mean ± s.e.m.) assessed by 3 day food records

	Baseline	8 weeks
Berry group (n=20)	7.6 ± 1.1	12.3 ± 1.4 <sup>a</sup>
Control group (n=20)	5.5 ± 0.5	5.8 ± 0.6

<sup>a</sup>Intake between groups at 8 weeks with baseline values as covariates,  $P=0.001$ , Tukey's test.

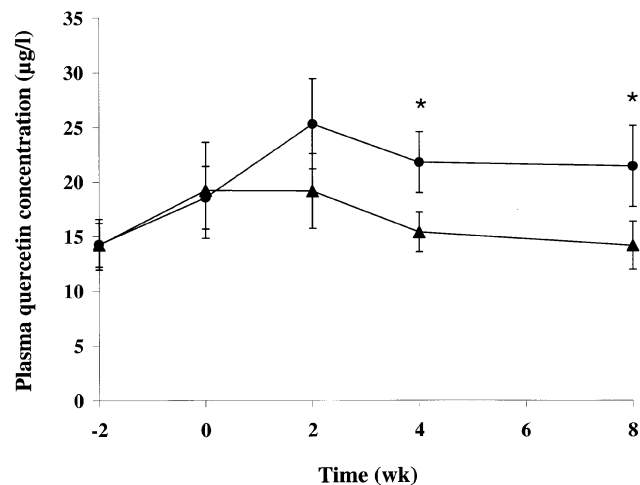
difference was non-significant ( $P>0.1$ , Student's *t*-test). At the end of the study the intake of quercetin was significantly higher in the berry group compared with the control group ( $P=0.001$ , ANCOVA). The intake of quercetin from the background diet (when intake from berries was disregarded), did not change within groups during the study ( $P>0.1$  ANCOVA). In the berry group the mean estimated intake of quercetin from the berries was 6.2 mg/day.

### Compliance

Compliance appeared to be good in this study. No deviations from the instructions regarding diet or berry consumption were reported in the 3 day dietary records or at other times. Also, serum vitamin C concentrations increased in the berry group from  $9.4 \pm 2.9$  mg/l (mean ± s.d.) at baseline to  $11.9 \pm 2.5$  mg/l at 8 weeks ( $P<0.001$ , analysis of variance for repeated measures), while no significant changes occurred in the control group. This further supports the interpretations that the subjects actually ate the berries.

### Serum quercetin concentrations

Serum quercetin concentrations were significantly higher in the berry group during the berry consumption period than in the control group ( $P=0.039$  ANCOVA with repeated measures). According to contrast analysis the differences were significant at 4 weeks ( $P=0.034$ ) and 8 weeks ( $P=0.046$ ). In the berry group the mean concentrations ranged between 21.4 and 25.3 µg/l between weeks 2 and 8. These values were 32–51% higher compared with the control group at the corresponding timepoints. Two weeks prior to the study and at baseline the mean concentrations of the two groups were very similar (Figure 1). At these two time-



**Figure 1** Serum quercetin concentrations (mean ± s.e.m.) in middle-aged men consuming 100 g/day of berries as a part of their habitual diets (n=20) or their habitual diets (n=20). \*  $P<0.05$  between groups at the time-point, contrast analysis.

points, when the men still followed their habitual diets, the mean quercetin concentration for all subjects was  $16.3 \pm 12.9 \mu\text{g/l}$  (mean  $\pm$  s.d.).

## Discussion

The aims of this study were to investigate plasma quercetin concentrations after long-term consumption of berries and in subjects consuming their habitual diets. The effects of berry consumption and antioxidant supplementation on serum antioxidant capacity were also studied, but the results have been published elsewhere (Marniemi *et al*, 2000).

Daily consumption of 100 g of berries (black currants, lingonberries and bilberries) significantly increased fasting serum quercetin concentrations. Compared with the control group, the concentrations were 32–51% higher in the berry group during the berry consumption period. The increase in serum quercetin was similar to or higher than what was previously reported in 12 men consuming 375 ml of black tea or 750 ml of red wine for 4 days, but less than half of what was found when the subjects consumed 50 g of fried onions (de Vries *et al*, 2001). However, in our study the serum samples were taken after an overnight fast, while in the study by de Vries *et al* they were taken twice during the last day they consumed the quercetin-containing foods. Therefore, the results are not quite comparable, but they do suggest that more quercetin reaches the systemic circulation after consumption of 100 g of these berries than after consumption of 750 ml of red wine or 375 ml of black tea.

Few reports have been published regarding plasma quercetin concentrations in subjects following their habitual diets. In most studies, the subjects have followed a flavonoid-restricted diet prior to ingestion of quercetin-containing foods or supplements. In this study, the prestudy concentrations of quercetin in all subjects were  $16 \pm 13 \mu\text{g/l}$  (mean  $\pm$  s.d.), which is similar or slightly lower than what we found previously in subjects consuming their habitual diets; in 100 healthy university students and employees the concentration was  $24 \pm 17 \mu\text{g/l}$  (Freese *et al*, 2002) and in 37 healthy female hospital employees it was  $16 \pm 24 \mu\text{g/l}$  (Erlund *et al*, 2002). The results are similar to those of Noroozzi *et al* (2000), who reported plasma concentrations of  $23 \pm 4 \mu\text{g/l}$  (mean  $\pm$  s.e.m.) in five men and five women with diabetes, also following their habitual diets.

The duration of supplementation was 8 weeks. This time was considered long enough to allow changes to occur in antioxidant capacity. A shorter time-period would have sufficed to reach a steady-state concentration for quercetin. Usually, the time needed for this is four to five elimination half-lives. For quercetin, half-lives between 15 and 28 h have been reported (Hollman *et al*, 1997; Erlund *et al*, 1999), which indicates that steady-state levels are reached within 3–6 days. However, to our knowledge, no studies actually showing that this applies to quercetin have been performed and most bioavailability or pharmacokinetics studies with quercetin have involved one-time ingestion of quercetin-

rich foods or supplements. For some compounds following nonlinear kinetics, the kinetic behavior changes during long-term administration or is disproportional to what is expected based on single-dose studies (Ludden, 1991). Therefore, a longer study time is an advantage when investigating a compound with poorly known kinetic behavior. In this study, serum quercetin concentrations remained relative stable during the berry consumption period.

Based on the results of this study no conclusions can be made about which of the berries contributed most to the increase in serum quercetin concentrations. Preliminary studies in our laboratory have shown that quercetin is bioavailable from all of the berries used in this study (data not shown), but whether the bioavailability of the compound is different from the different berries is not known. Lingonberries, black currants and bilberries contain partly different quercetin glycosides (Kühnau, 1976; Koeppen & Herrmann, 1977, Häkkinen & Auriola, 1998) and no information is available on the bioavailability of for instance quercetin arabinosides. Also, differences in the distribution of quercetin in the different compartments of berries and the thickness of the skin could affect its availability from berries.

The estimated intake of quercetin from the berries was 6.2 mg/day. Intake was calculated from a food database, to which values for quercetin concentrations had been added. The calculated intake values are rough estimations, because the quercetin concentrations of, for instance, black currants vary a great deal depending on the cultivar, ripeness and growing conditions (Mikkonen *et al*, 2001). Furthermore, the berries used in this study were purchased from a berry dealer (Pakkasmarja Ltd), after which they were stored at  $-20^\circ\text{C}$  for 7–8 months until they were consumed. Reductions of 18, 25 and 19% have been reported to occur for black currant, bilberry and lingonberry during storage at  $-20^\circ\text{C}$  for 6 months (Häkkinen, 2000) and it is likely that similar degradation of quercetin occurred during storage in this study. Therefore, the plasma quercetin concentrations after berry consumption would probably have been higher if fresh berries had been used. However, the harvesting season for each of the berries is only a few weeks in the autumn and most berries are eaten from the freezer. Our approach was therefore a more realistic one.

In general, berries are an important source of quercetin in the Finnish diet. According to a recent estimate, which was based on Finnish 1998 annual food consumption data, berries account for 25% of the total quercetin intake (9.5 mg/day; Häkkinen, 2000). In the Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) Study 8.3% of the total quercetin intake (7.4 mg) in Finnish middle-aged male smokers was estimated to originate from berries (Hirvonen, 2001). In other Scandinavian countries, berries probably contribute similarly or less to the total quercetin intake. The annual per capita consumption of fresh berries in Norway, Finland, Denmark, Iceland and Sweden has been estimated as 9.6, 9.6, 3.4, 2.2 and 1.3 kg, respectively (Johansson *et al*, 1998). However, at least in Finland, con-

sumption varies between persons living in different parts of the country (Kleemola *et al*, 1994) and between urban and rural areas. In the 1992 Dietary Survey of Finnish Adults, the median daily consumption of unprocessed berries was 14 and 26 g for men and women, respectively (M-L Ovaskainen, personal communication). In the 90% quartile, the corresponding values were 93 and 111 g, which are similar to the amount consumed in this study.

Increased intake of berries can be recommended because, in addition to quercetin, they are rich sources of many other potentially beneficial compounds as well, and are low in fat and energy. Anthocyanins, for instance, are present in berries in high concentrations and are potent antioxidants *in vitro*. However, their bioavailability appears to be quite low and they are excreted very rapidly (Murkovic *et al*, 2000). Therefore compounds such as quercetin and phenolic acids, together with vitamin C, could play a more important role in the possible health effects of berries.

In conclusion, the results of this study indicate that berries are a good source of bioavailable quercetin, and that in the Finnish population the mean fasting serum quercetin concentration is about 20 µg/l.

#### Acknowledgements

We would like to thank Dr M-L Ovaskainen for providing data on quercetin concentrations of foods and for calculating berry consumption in the 1992 Dietary Survey of Finnish Adults.

#### References

- Aviram M & Fuhrman B (1998): Polyphenolic flavonoids inhibit macrophage-mediated oxidation of LDL and attenuate atherosclerosis. *Atherosclerosis* **137** (Suppl), S45–50.
- Caltagirone S, Ranelletti FO, Rinelli A, Maggiano N, Colasante A, Musiani P, Aiello FB & Piantelli M (1997): Interaction with type II estrogen binding sites and antiproliferative activity of tamoxifen and quercetin in human non-small-cell lung cancer. *Am. J. Respir. Cell Mol. Biol.* **17**, 51–59.
- Chopra M, Fitzsimons PE, Strain JJ, Thurnham DI & Howard AN (2000): Nonalcoholic red wine extract and quercetin inhibit LDL oxidation without affecting plasma antioxidant vitamin and carotenoid concentrations. *Clin. Chem.* **46**, 1162–1170.
- de Vries JH, Hollman PC, van Amersfoort I, Olthof MR & Katan MB (2001): Red wine is a poor source of bioavailable flavonols in men. *J. Nutr.* **131**, 745–748.
- Erlund I, Alfthan G, Siren H, Ariniemi K & Aro A (1999): Validated method for the quantitation of quercetin from human plasma using HPLC with electrochemical detection. *J. Chromatogr. B Biomed. Applic.* **727**, 179–189.
- Erlund I, Kosonen T, Alfthan G, Mäenpää J, Perttunen K, Kenraali J, Parantainen J & Aro A (2000): Pharmacokinetics of quercetin from quercetin aglycone and rutin in healthy volunteers. *Eur. J. Clin. Pharmacol.* **56**, 545–553.
- Erlund I, Alfthan G, Mäenpää J & Aro A (2001): Tea and coronary heart disease: the flavonoid quercetin is more bioavailable from rutin in women than in men. *Arch. Intern. Med.* **161**, 1919–1920.
- Erlund I, Silaste ML, Alfthan G, Rantala M, Kesäniemi YA & Aro A (2002): Plasma concentrations of the flavonoids naringenin, hesperetin and quercetin in human subjects following their habitual diets, or diets high or low in fruits and vegetables. *Eur. J. Clin. Nutr.* (in press).
- Freese R, Alfthan G, Jauhainen M, Basu S, Erlund I, Salminen I, Aro A & Mutanen M (2002): High intake of vegetables, berries and apple combined with high intake of linoleic or oleic acid only slightly affects markers of lipid peroxidation and lipoprotein metabolism in healthy subjects. *Am. J. Clin. Nutr.* (in press).
- Hakala P, Marniemi J, Knuts L-R, Kumpulainen J, Tahvonen R & Plaami S (1996): Calculated vs. analysed nutrient composition of weight reduction diets. *Food Chem.* **57**, 71–75.
- Häkkinen S & Auriola S (1998): High-performance liquid chromatography with electrospray ionization mass spectrometry and diode array ultraviolet detection in the identification of flavonol aglycones and glycosides in berries. *J. Chromatogr. A.* **829**, 91–100.
- Häkkinen SH, Kärenlampi SO, Heinonen IM, Mykkänen HM & Törrönen AR (1999): Content of the flavonols quercetin, myricetin, and kaempferol in 25 edible berries. *J. Agric. Food Chem.* **47**, 2274–2279.
- Häkkinen S (2000): Flavonols and phenolic acids in berries and berry products (dissertation). Kuopio: University of Kuopio.
- Hertog MGL, Kromhout D, Aravanis C, Blackburn H, Buzina R, Fidanza F *et al* (1995): Flavonoid intake and long-term risk of coronary heart disease and cancer in the Seven Countries Study. *Arch. Intern. Med.* **155**, 381–386.
- Hirvonen T (2001): Flavonol and flavone intake and risk of cardiovascular disease and cancer in male smokers (dissertation). Helsinki: Publications of the National Public Health Institute (KTL) A19/2001.
- Hollman PC, van Trijp JM, Buysman MN, van der Gaag MS, Mengelers MJ, de Vries J & Katan MB (1997): Relative bioavailability of the antioxidant flavonoid quercetin from various foods in man. *FEBS Lett.* **418**, 152–156.
- Hollman PC, Van Het Hof KH, Tijburg LB & Katan MB (2001): Addition of milk does not affect the absorption of flavonols from tea in man. *Free Radic. Res.* **34**, 297–300.
- Johansson L, Becker W, Fagt S, porgeirsdóttir H & Valsta L (1998): *Grønnsak-og fruktinntaket i Norden* (in Norwegian). Uppsala: Nordiska Ministerrådet.
- Kleemola P, Virtanen M & Pietinen P (1994): *The 1992 dietary survey of Finnish adults*. Helsinki: Publications of the National Public Health Institute B2/1994.
- Knekt P, Jarvinen R, Reunanen A & Maatela J (1996): Flavonoid intake and coronary mortality in Finland: a cohort study. *Br. Med. J.* **312**, 478–481.
- Knuts L-R, Rastas M, Haapala P, Seppänen R, Karveti R-L & Aro A (1987): Nutrica—a computer program for calculation of food and nutrient intake. *Abstracts of the Third Meeting of Eurofoods*, Warsaw, 24–27 May 1987, p 16.
- Koeppe BH & Herrmann K (1977): Flavonoid glycosides and hydroxycinnamic acid esters of blackcurrants (*Ribes nigrum*). Phenolics of fruits 9. *Z Lebensm Unters Forsch.* **164**, 263–268.
- Kühnau J (1976): The flavonoids. A class of semi-essential food components: their role in human nutrition. *World Rev. Nutr. Diet* **24**, 117–191.
- Ludden TM (1991): Nonlinear pharmacokinetics. Clinical implications. *Clin. Pharmacokinet.* **20**, 429–446.
- Marniemi J, Hakala P, Mäki J & Ahotupa M (2000): Partial resistance of low density lipoprotein to oxidation in vivo after increased intake of berries. *Nutr. Metab. Cardiovasc. Dis.* **10**, 331–337.
- Mattila P, Astola J & Kumpulainen J (2000): Determination of flavonoids in plant material by HPLC with diode-array and electro-array detections. *J. Agric. Food Chem.* **48**, 5834–5841.
- Mikkonen TP, Määttä KR, Hukkanen AT, Kokko HI, Törrönen AR, Kärenlampi SO & Karjalainen RO (2001): Flavonol content varies among black currant cultivars. *J. Agric. Food Chem.* **49**, 3274–3277.

- Murkovic M, Adam U & Pfannhauser W (2000): Analysis of anthocyanine glycosides in human serum. *Fresenius J. Anal. Chem.* **366**, 379–381.
- Noroozi M, Burns J, Crozier A, Kelly IE & Lean ME (2000): Prediction of dietary flavonol consumption from fasting plasma concentration or urinary excretion. *Eur. J. Clin. Nutr.* **54**, 143–149.
- Peet GW & Li J (1999): IkappaB kinases alpha and beta show a random sequential kinetic mechanism and are inhibited by staurosporine and quercetin. *J. Biol. Chem.* **274**, 32655–32661.
- Pereira MA, Grubbs CJ, Barnes LH, Li H, Olson GR, Eto I, Juliana M, Whitaker LM, Kelloff GJ, Steele VE & Lubet RA (1996): 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.
- Siess MH, Leclerc J, Canivenc-Lavier MC, Rat P & Suschetet M (1995): Heterogenous effects of natural flavonoids on monooxygenase activities in human and rat liver microsomes. *Toxicol. Appl. Pharmac.* **130**, 73–78.
- Yochum L, Kushi LH, Meyer K & Folsom AR (1999): Dietary flavonoid intake and risk of cardiovascular disease in postmenopausal women. *Am. J. Epidemiol.* **149**, 943–949.