

## Flavonoids and heart disease<sup>1,2</sup>

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Flavonoids are secondary plant metabolites; plants use them to attract pollinators and repel predators, to color flowers and fruits, and for other functions. Subclasses include isoflavones or phytoestrogens, catechins, anthocyanidins, and flavonols. Flavonoids contain benzene rings with multiple hydroxyl groups and they are therefore known as polyphenols.

In 1936, Ruzsnyak and Szent-Györgyi (1) proposed that intake of flavonoids decreased the capillary fragility seen in scurvy and named flavonoids vitamin P. Flavonoids were stripped of vitamin status around 1950, but interest in them has resurged because of possible links with cancer and cardiovascular disease. Epidemiologic studies have shown an inverse association between fruit and vegetable intake and cancer risk; plants may therefore contain anticarcinogenic compounds. Animal experiments made the flavonol quercetin a plausible candidate. The antioxidant properties of flavonols and catechins suggested that their intake might prevent atherosclerosis, and the low incidence of heart disease in France has been ascribed to a high intake of flavonoids from red wine. The hypothesis that flavonoids prevent heart disease received a boost when Hertog et al (2) reported an inverse association between the intake of the flavonol quercetin and coronary mortality in men in Zutphen, Netherlands. The major sources of quercetin and related flavonols turned out to be tea and onions rather than fruits or green vegetables. Great Britain, with its high tea intake, was therefore an obvious choice for further studies.

In this issue, Hertog et al (3) report on the association of flavonol intake at baseline with morbidity and mortality over 14 y in 1900 men in Caerphilly, Wales, United Kingdom. There was no association of flavonol or tea intake with ischemic heart disease incidence. On the contrary, heart disease and total mortality rose with tea intake.

The authors offer two explanations for this. One is that subjects used milk in their tea and that the proteins from milk form complexes with flavonoids that inhibit their absorption. Intake of black tea indeed raised plasma antioxidant capacity in volunteers whereas tea with milk did not (4). However, plasma concentrations of catechins and quercetin in volunteers given tea were the same whether the tea contained milk or not (K Van het Hof, J Weststrate, L Tijburg, personal communication, 1997; PCH Hollman, K Van het Hof, personal communication, 1997). Thus, lack of absorption is an insufficient explanation.

The second explanation is confounding. The men with the highest intake of tea and flavonols tended to be manual workers; they smoked more, consumed less alcohol, and ate more fat (Table 1 in reference 3). Hertog et al corrected for these

confounders, but confounders that have been measured with less than perfect precision cannot be completely eliminated by multivariate analysis. Measurements of diet, smoking, and alcohol intake were necessarily crude, and no data were available on physical activity or psychosocial factors. Therefore, the most plausible explanation for the higher mortality in tea drinkers is confounding by unmeasured or imperfectly measured coronary risk factors that clustered with tea intake.

Where does this leave flavonoids?

The food table is the central paradigm of nutrition science and health effects of foods should be explained in terms of defined food components. However, different sources of flavonols show different associations with disease: onion intake is associated with decreased cancer risk (5) but tea intake is not (6), and in the present study, the incidence of heart disease mortality went up with tea but down with onion consumption (Table 3 in reference 3). Such differences can be due to confounding or to other substances present in these foods, but the same substance could also be present in different forms. Metabolic studies show that quercetin compounds from onions have a higher bioavailability than do those from tea. Such studies also suggest that *in vivo* antioxidant activity of dietary quercetin remains feasible; quercetin is absorbed well from foods and plasma concentrations  $\leq 0.5 \mu\text{mol/L}$  can be reached (7). Addition of flavonols to blood plasma *in vitro* reduces the oxidizability of low-density lipoprotein (LDL), although effects of administration *in vivo* are less clear. Flavonols probably do not accumulate inside LDL particles, which explains why consumption of tea by volunteers has only minimal effects on the oxidizability of LDL isolated from plasma. Addition of red wine to blood plasma reduced the oxidizability of LDL, but *in vivo* data are conflicting (8, 9).

The epidemiologic findings on flavonols and cardiovascular disease are summarized in Table 1. Inverse associations were seen in Zutphen (2, 10) and in elderly persons in Rotterdam, Netherlands, where high tea consumption was inversely associated with noninvasively assessed measures of atherosclerosis (JCM Witteman, personal communication, 1997). A modest protective effect was also seen in Finland (11). However, in a large cohort of US health professionals there was no associa-

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**TABLE 1**  
Prospective studies of flavonol intake and cardiovascular disease (CVD)

Reference	Location	Follow-up	Number and type of events	Relative risk <sup>1</sup>
Hertog et al (2)	Zutphen, Netherlands	y		
		5	43 deaths from CHD 38 first myocardial infarctions	0.3 0.5
Keli et al (10)	Zutphen, Netherlands	15	42 strokes	0.3
Knekt et al (11)	Finland	20	473 deaths from CHD	0.7
Rimm et al (12)	United States	6	486 nonfatal myocardial infarctions	1.1
			140 deaths from CHD	0.8
Hertog et al (3)	Caerphilly, United Kingdom	10	186 cases of CHD	1.0
		14	131 deaths from CHD	1.6

<sup>1</sup> Relative risk in the highest versus lowest tertile (2), quartile (10, 11), or quintile (12) of intake of quercetin and related flavonols and flavones; risks were corrected for age, diet, and conventional risk factors for coronary heart disease (CHD).

tion of flavonol intake with incidence of nonfatal coronary disease (12). The overall picture is thus conflicting.

The problems involved in detecting an association of a dietary factor with a disease that develops over the course of decades are huge, and failure to observe such an association does not prove that none exists. Thus, saturated fat intake does not correlate with heart disease within populations, even though metabolic studies and clinical trials provide proof for a causal relation. The question whether flavonoids protect against atherosclerosis can only be answered definitively by a randomized clinical trial. Future research would also be helped by development of better markers for in vivo oxidation of LDL, by reliable biomarkers for long-term consumption of flavonoids, and clarification of the metabolism of flavonoids in humans. For flavonoids and heart disease the glass is thus half full. More research is needed to either empty it or fill it to the brim. ☞

## REFERENCES

- Rusznayk S, Szent-Györgyi A. Vitamin P: flavonols as vitamins. *Nature* 1936;138:27.
- Hertog MGL, Feskens EJM, Hollman PCH, Katan MB, Kromhout D. Dietary antioxidant flavonoids and risk of coronary heart disease. The Zutphen elderly study. *Lancet* 1993;342:1007-11.
- Hertog MGL, Sweetnam PM, Fehily AM, Elwood PC, Kromhout D. Antioxidant flavonols and ischemic heart disease in a Welsh population of men: the Caerphilly Study. *Am J Clin Nutr* 1997;65:1489-94.
- Serafini M, Ghiselli A, Ferro Luzzi A. In vivo antioxidant effect of green and black tea in man. *Eur J Clin Nutr* 1996;50:28-32.
- Dorant E, Van den Brandt PA, Goldbohm RA, Sturmans F. Consumption of onions and a reduced risk of stomach carcinoma. *Gastroenterology* 1996;110:12-20.
- Kohlmeier L, Weterings KGC, Steck S, Kok FJ. Tea and cancer prevention: an evaluation of the epidemiological literature. *Nutr Cancer* 1997;27:1-13.
- Hollman PCH, Van der Gaag MS, Mengelers MJB, Van Trijp JMP, De Vries JHM, Katan MB. Absorption and disposition kinetics of the dietary antioxidant quercetin in man. *Free Radic Bio Med* 1996;21:703-7.
- Fuhrman B, Lavy A, Aviram M. Consumption of red wine with meals reduces the susceptibility of human plasma and low-density lipoprotein to lipid peroxidation. *Am J Clin Nutr* 1995;61:549-54.
- De Rijke YB, Demacker PNM, Assen NA, Sliotoos LM, Katan MB, Stalenhoef AFH. Red wine consumption does not affect oxidizability of low-density lipoproteins in volunteers. *Am J Clin Nutr* 1996;63:329-34.
- Keli SO, Hertog MGL, Feskens EJ, Kromhout D. Dietary flavonoids, antioxidant vitamins, and incidence of stroke: the Zutphen study. *Arch Intern Med* 1996;156:637-42.
- Knekt P, Järvinen R, Reunanen A, Maatela J. Flavonoid intake and coronary mortality in Finland: a cohort study. *Br Med J* 1996;312:478-81.
- Rimm EB, Katan MB, Ascherio A, Stampfer MJ, Willett WC. Relation between intake of flavonoids and risk for coronary heart disease in male health professionals. *Ann Intern Med* 1996;125:384-9.