Can dietary flavonoids influence the development of coronary heart disease?

By Helle Margrete Meltzer and Karl Egil Malterud

Abstract

The flavonoids constitute a large group of secondary plant metabolites being ubiquitous among higher plants. The biological activity of flavonoids was discovered during the 1930s, when it was found that several vegetables and fruits contained substances different from vitamin C and yet able to counteract the capillary fragility characteristic of scurvy. The “P vitamins” (as they were once called) were, however, not accepted as vitamins, and they are now regarded as members of the large and diffuse class of “non-nutrients”. Today, extensive research is directed towards the elucidation of the importance and the potential therapeutic value of flavonoids in the treatment of, e.g., cancer and cardiovascular diseases. In this paper, recent research on flavonoids is reviewed with emphasis on the possible correlation between dietary flavonoid content and reduced risk for cardiovascular disease.

Introduction

Recently, the preventive and therapeutic potential of food and beverages has received increased scientific attention. Large epidemiological surveys have shown a relationship between the consumption of fruit and vegetables and reduced risk of cancer and cardiovascular disease (1), and some of the works even indicate that raw vegetables give the strongest protection (2-4).

An expression like “the French paradox” has appeared, based on the interesting observation that the French have comparable plasma cholesterol levels to the Americans, and comparable fat intakes, but nevertheless a far lower incidence of coronary disease (5). The high French consumption of red wine has been implicated in these differences (6). Others claim that they can be explained by olive oil, or the consumption of garlic. Does red wine, olive oil and garlic have anything in common? (apart from “the good life” which such a consumption surely is an expression of, important in itself).

Several components in fruits and vegetables have drawn attention as possible candidates when the effects are to be explained, as illustrated in Table 1. For each of the candidates, there is evidence that they may have an effect. To assess their single and combined effects is an enormous task, which is only at its beginning. This article focuses on the flavonoids, a group of naturally occurring compounds which recently has attracted considerable attention as dietary constituents with potential importance for health (7-9) (Fact column 1).

Chemical structure

Flavonoids have a common skeleton of diphenylpyranes (C6-C3-C6), i.e., two benzene rings (A and B) connected by a heterocyclical pyran- or pyron ring (Figure 1). The flavonoids are often hydroxylated in the positions 3, 5, 7, 3’, 4’.

Table 1. Some dietary substances suggested to be associated with decreased risk of disease.

<table>
<thead>
<tr>
<th>Vitamins (e.g. ascorbic acid, α-tocopherol)</th>
<th>Minerals (e.g. selenium, zinc, manganese)</th>
<th>Dietary fibre</th>
<th>Glucosinolates</th>
<th>Indols</th>
<th>Flavonoids (including carotenoids)</th>
<th>Phytosterols</th>
<th>Proteinase inhibitors</th>
<th>Sulphur compounds from onion and garlic</th>
</tr>
</thead>
</table>

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FACT COLUMN 1: HISTORY

Flavonoids have been known as plant pigments for more than one hundred years. In periods, their biological effects and importance have been discussed intensively. Around 1940 the opinion was that flavonoids had vitamin properties. In the 1970s, the flavonoids were suspected of having mutagenic and carcinogenic effect, while in the 80s and 90s, considerable research has been directed towards their activity as antioxidants and radical scavengers, as well as their anti-mutagenic and anti-carcinogenic properties.

In a human context, interest in flavonoids originates from studies by the Nobel laureate Szent-Györgyi and co-workers in the 1930s (83,84), when they reported that a number of substances in vegetables and fruits (different from vitamin C) could heal the capillary fragility (with associated haemorrhage) characteristic of scurvy. For years there was an argument as to whether the flavonoids, often designated as bioflavonoids or vitamin P, had a direct, independent effect on tissue metabolism (especially capillary fragility), or if their role rather was of a synergistic nature. Around 1950 it was agreed that the flavonoids had physiological significance, but that their most important and possibly single role was their influence on capillary resistance. The effect seemed to be independent of vitamin C. In spite of this, flavonoids were taken off the list of effective drugs by the US Food and Drug Administration in 1962. At this point there were more than 200 flavonoid-containing preparations on the American market.

Interest in the biological effects of flavonoids has increased tremendously the last 15-20 years (85), and several thousand articles have been published on the theme. In addition to the more important effects mentioned in the main article, the are some more exotic ones. Among them are inhibition of tooth decay (86,87), protection against snake venom (88), or effect against dandruff (89)! Several books, such as (90-92) and reviews, e.g, (21,24,93) have been published.
and 5’. The presence or absence of a hydroxyl group in the 3 position determines the division into the two main subgroups of flavonoids: 3-hydroxyflavonoids (flavonols, flavanonols and catechins) and flavonoids with an unsubstituted 3-position (flavones and flavanones) (Figure 1). The most common flavonoid in food is quercetin, while catechins nutritionally are the most important of the flavonoids in beverages, due to their high concentration in tea. More than 4,000 flavonoids have been described, and the number of characterised substances is continually increasing (10).

From a nutritional point of view, flavonols and flavones are of special interest due to their potential protective role in carcinogenesis, atherosclerosis and thrombosis. Both flavonols and flavones are usually present in our food as glycosides, D-glucose being the most common sugar. Other sugars can be galactose, rhamnose, arabinose, xylose, in addition to glucuronic acid. The preferred binding site for the sugar unit is in the C3 position, glycosylation in the C7 position being somewhat less common (11,12). The sugar-free part of the molecule is called the flavonoid aglycone.

Due to the enormous variation in substitution types and substitution patterns, (hydroxylation-, methoxylation-, sulphation- and glycosidation patterns in addition to C-methylation, C-glycosylation and prenylation) more than 1,000 different flavonol and flavone glycosides have been described, and more than 20 million different combinations are theoretically possible (13).

**Function in plants**

Numerous functions of flavonoids in plants have been demonstrated or suggested. These include pigmentation (to attract pollinators), protection of the plant from UV light and micro-organisms, defence against grazing animals, regulation of enzyme activity and signal substances for nitrogen-fixing bacteria (14,15). The flavonoids are omnipresent in higher plants. In foods, we find flavonoids as natural colour substances and as antioxidants (16). Propolis, made by bees from plant exudates (usually from buds), is used to protect the hive entrance and is often rich in flavonoids. From old times the peoples of Asia have been drinking green tea as a medicinal remedy because of its presumed pharmacological effects. Green tea is an important source of flavonoids in the East (17).

Our knowledge about the dietary intake of flavonoids is sparse and partly contradictory. In 1976 Kühnau (18) estimated the daily flavonoid intake in the USA to be approximately 1 gram, 100 mg thereof being flavonols and flavones, but these estimates have not been confirmed. Hertog et al. (19) have improved the old analytical methods, and their results are shown in Table 2. Based on the analysis of five common flavonoids, the flavonoid content of the Dutch diet was estimated to be 28 mg/day (as aglycones). In areas with a very high intake of plants and herbs/spices, the intake of flavonoids is believed to be as high as 2-3 g/day. Many factors influence the flavonoid content of plants, among others the conditions of growth, ripeness and season. Growth beneath glass reduces the levels of flavonoids, and in general, processed foods have 50% lower concentrations than fresh (20). A subgroup of flavonoids, the isoflavonoids, are mainly found in the Leguminosae, soy beans being an example of a food with a substantial content of isoflavonoids.

**Biological effects**

Recently, the antioxidant properties of the flavonoids have become a subject of considerable interest (21-23), but in addition, several other properties have been reported, some of which are shown in Table 3 (13,16,24,25). Among the effects can be mentioned modulation of enzyme activity, e.g. cyclooxygenase, lipoygenases, phospholipase A2, hyaluronidase and 5’-nucleotidase. Inhibition of LAR (lens aldose reductase) and of ACE (angiotensin convertase) has also been described. These effects provide a broad potential for medical effects and usage, and in particular, work is presently being conducted with flavonoids and cancer (Fact column 2, p 53). In this paper, however, we will concentrate on the possible impact flavonoids may have on coronary heart disease. In this context, we will discuss the antioxidant properties of flavonoids.
There is some evidence that cellularity produced 15-lipoxygenase may be involved in the process (49).

Oxidised LDL has strong atherogenic properties, e.g. by chemotraction of monocytes and by the macrophages being inhibited from migrating back into the plasma. This leads to an accumulation of macrophages, saturated with cholesteryl esters, in intima. Gradually the macrophages are transformed to foam cells, which may then develop into fatty streaks. A fatty streak can further develop into fibrotic plaques, which become calcified and lead to reduction of the lumen (26).

Oxidised LDL is also cytotoxic, and may harm endothelial cells. This damage is accompanied by release of factors stimulating platelet aggregation and early growth of thrombosis. The combination of thrombogenesis and reduced intraluminal volume may lead to infarction.

Thus, substances protecting against the oxidation of LDL are of considerable interest in the prevention and treatment of coronary heart disease (27). In addition, substances with antithrombotic properties will be of interest. α-Tocopherol (vitamin E), retinyl stearate, γ-tocopherol and β-carotene have been reckoned among the most important antioxidants. All are fat-soluble. It is, however, well known that the content of antioxidants in an LDL particle can react directly with superoxide and the tocopheroxyl radical back to tocopherol.

Scavenging of free radicals participating in oxidative processes may thus be an explanation for some of the observed effects of flavonoids. Other mechanisms, such as protection of α-tocopherol, have also been suggested. In addition, quercetin reduces the cytotoxic effects of oxidised LDL (46,48). The mechanism underlying this effect is not known.

Because 15-lipoxygenase has been suggested to participate in the oxidation of LDL (49), it is of particular interest that several flavonoids inhibit this enzyme (50,51).

Frankel et al. have shown that phenols extracted from red wine inhibited Cu-catalysed oxidation of human LDL. ex vivo (52). This has been corroborated by other studies (53,54).

Recent experiments show that soybean isoflavonoids given to rhesus monkeys reduce LDL levels and increase the levels of HDL (high density lipoprotein) in plasma, and thus would be expected to have a beneficial effect in connection with coronary heart disease (107). So far, it is not known whether this effect also applies to humans.

Platelet aggregation

Since the 1950s it has been known that flavonoids may have an antithrombotic effect and inhibit platelet aggregation (55). The effect is well documented both in vitro and in vivo in animal experiments, as well as ex vivo in humans (56). The mechanisms behind the antiaggregatory effect seem complex. In many cases, inhibition of cyclic AMP phosphodiesterase, resulting in increased cAMP levels, seems to be important (57), but this is apparently not the case for the antiaggregatory flavonoids in green tea (58). A number of other mechanisms have
been suggested: an influence on the metabolism of arachidonic acid (with reduction in thromboxane levels) (59,60) – receptor antagonism to thromboxane receptors have also been reported (61), as well as an increase in the levels of prostacyclin (62). Many flavonoids are strong inhibitors of lipooxygenases, but have differing effect on cyclooxygenase (63, 64). Reduction of calcium levels (60), inhibition of “platelet activating factor” (58), scavenging of free radicals (65) and reduced liberation of proaggregatory receptors have also been reported. Apparently, the antiaggregatory effects of flavonoids are due to several more or less separate mechanisms. One would expect the substantial effect of flavonoids on arachidonic acid metabolism to result in antithrombotic properties, and this has indeed been demonstrated, mainly in animal experiments in vivo, but also in experiments with human cells in vitro (67–71). In this case, as well, several mechanisms seem to be involved. The literature is reviewed in, e.g. (24,72).

In summary, the antithrombotic, antiaggregatory and antioxidative/radical scavenging effects of flavonoids are well documented in in vitro systems, and the results point at several, partly independent, mechanisms. One can not disregard the possibility that still other effects may be of importance; inhibition of xanthin oxidase (produces superoxide radicals), myeloperoxidase (produces hypochlorite, another prooxidant) and angiotensin convertase (gives angiotensin II, which increases blood pressure) has also been reported for the flavonoids.

Therapeutic use
Medical use of plants rich in flavonoids goes back to ancient times. This practice was probably based on experience, and only lately has the use of flavonoids and flavonoid-containing preparations been based on rational biochemical knowledge.

The ability to counteract capillary permeability was the first biological effect shown for flavonoids. A number of pharmaceuticals, both with natural flavonoids and semisynthetic derivatives, take advantage of this effect, as shown in several clinical studies (73,74).

A flavonoid with an unusual structure, silybin (from the thistle Silybum marianum, “Marienstiel” – an ancient medical plant from central Europe (75), has hepatoprotective effect and is included in many pharmaceuticals. Its clinical effect is well documented (review, see (76)).

Another flavonoid, catechin (cyandinaol), also showed promising clinical activity against hepatic disease, but turned out to give serious side effects, probably of

<table>
<thead>
<tr>
<th>Table 3. Some biological effects reported for flavonoids (based mainly on in vitro experiments)</th>
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<tbody>
<tr>
<td><strong>Antioxidant effect / radical scavenging</strong></td>
</tr>
<tr>
<td><strong>Immunomodulating and antiinflammatory effects</strong></td>
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<tr>
<td>– probably mostly due to modulation of arachidonic acid metabolism:</td>
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<tr>
<td>Phospholipase A2 inhibition</td>
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<tr>
<td>Cyclooxygenase inhibition or activation</td>
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<tr>
<td>Lipoygenase (5-, 12-, 15-) inhibition</td>
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<tr>
<td><strong>Modulation of other enzyme activities (usually inhibition), e.g.:</strong></td>
</tr>
<tr>
<td>Lens aldose reductase (LAR)</td>
</tr>
<tr>
<td>Xanthin oxidase</td>
</tr>
<tr>
<td>5'-Iodothyronin deiodinase</td>
</tr>
<tr>
<td>Angiotensin convertase (ACE)</td>
</tr>
<tr>
<td>Cyclic AMP phosphodiesterase</td>
</tr>
<tr>
<td><strong>Antithrombocytic and antiinflammatory effects</strong></td>
</tr>
<tr>
<td><strong>Antiviral, antibacterial and antifungal effects</strong></td>
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<tr>
<td><strong>Oestrogenic activity</strong></td>
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<tr>
<td><strong>Effects on mutagenesis and carcinogenesis</strong></td>
</tr>
<tr>
<td><strong>Hepatoprotective effects</strong></td>
</tr>
<tr>
<td><strong>Effect on blood vessels; counteraction of vascular permeability</strong></td>
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</tbody>
</table>

Many of the activities listed above may be correlated; thus, hepatoprotective effects may be due to radical scavenging, antioxidant effects may (in some cases) be due to xanthin oxidase inhibition, and antiinflammatory effects may be due to inhibition of 5-lipoxygenase.

FACT COLUMN 2: FLAVONOIDS AND CANCER

Several natural substances and natural substance-derived preparations are used in the treatment of cancer – Vinca alkaloids, etoposid and Adriamycin are prominent examples. Flavonoids have also been studied in this connection. Flavone acetic acid, mentioned in the main article, once seemed very promising.

Many flavonoids have been reported to have cytostatic effect in various in vitro systems. These have, however, seldom translated into clinically relevant effects (100). Currently, the flavonoids draw considerable attention because they seem to be able to regulate certain processes important in the development of cancer. Examples of this are antipromotor activity, antiinvasive effect, and inhibition of enzymes like protein tyrosine kinase, TPA-dependent ornithin decarboxylase and DNA topoisomerases. Recently, a synergistic effect between fluorouracil and the flavonoid quercetin has been reported (101), although only in vitro.

Many animal studies have shown that isoflavonoids from soybeans (especially genistein) may have a protective effect against several forms of cancer (breast, colon, skin) (121). This has been related to the oestrogenic effect of isoflavonoids, and several biochemical mechanisms have been discussed (122).

Several flavonoids have antimutagenic effect (for reviews, see ref. 102,103). Although there are studies showing some flavonoids to have mutagenic activity in Ames test and other assay systems, very few results indicate that flavonoids have carcinogenic effect. In an early article, quercetin was claimed to induce cancer in rats (104), but this has not been confirmed generally by later work. Rather recently, however, it has been shown (123) that extremely large doses of quercetin (4% of the diet) over a long period of time (2 years) induced an increased incidence of kidney cancer in male rats (but not female rats). At lower dosages (1% or less) or shorter exposure time (maximum 15 months), there was no significant change in cancer incidence. Some of the methods used in this investigation have, however, been debated (124).

Summarising, the majority of researchers in this field seem to hold the view that the anticarcinogenic effects of flavonoids are more important than the procarcinogenic ones (124,125). For further references in this field, see, e.g. (126).

From in vitro data and biochemical knowledge, it appears that the flavonoids may be regarded as dietary constituents which may have beneficial effect (although of a preventive and not a curative nature) in relation to cancer. It should, however, be mentioned that Hertog et al. (82,105), did not find any correlation between flavonoid intake and reduced incidence of cancer, in contrast to what they found for coronary heart disease (7, 82). Thus it is too early to say if the many interesting in vitro results will turn out to be of clinical importance.
fact column 3: side effects

By and large, flavonoids are relatively non-toxic to higher animals (94-96,114), and seem to be devoid of teratogenic effects (97). As long as the diet is the sole source of flavonoids, the risk of becoming intoxicated seems small. Clinical trials with large doses of the flavonoid catechin (cyanadanol) have, however, showed serious side effects, probably due to immunological reactions (98,99). The dosages in these cases were more than 1 gram/day. The acute LD$_{50}$ for flavonoids tested in animal experiments normally seems to be above 1 gram/kg body weight. The mutagenic effect shown for a number of flavonoids in Ames test seems to be of less relevance in a cancer context than the antimutagenic effect shown for flavonoids (see fact column 2).

Dermatitis induced by flavonoids has been reported. In several of these reports raw extracts of plants were employed, and there is no direct evidence for flavonoids being the triggering factor. Some articles, however, describe tests using pure substances (115,116), and here it appears that certain flavonoids can produce dermatological reactions, although the large majority are inactive.

Propolis, well known for its allergic skin reactions (117), is normally rich in flavonoids, but other substances seem to be responsible for the allergy (118,119).

Some isoflavonoids are oestrogens. Their activity is relatively low, and consumption of soy beans, a rich source of isoflavonoids, does not seem to have adverse oestrogenic effects in humans. It has long been known that sheep grazing on isoflavonoid-rich clover species get hormone balance disturbances, and recently it has been shown that coumestrol, the most active iso-flavonoid oestrogen, (but only found in very small amounts in soy beans), disturbs oestrus in female mice and produces abnormal sexual behaviour in male mice (120).

immunological nature (Fact column 3). Preparations from Crataegus (hawthorn), containing oligomeric flavonoids as their (putative) main pharmacologically active ingredients, are used to treat immunological nature (Fact column 3). Preparations from Crataegus (hawthorn), containing oligomeric flavonoids as their (putative) main pharmacologically active ingredients, are used to treat immunological nature (Fact column 3). Preparations from Crataegus (hawthorn), containing oligomeric flavonoids as their (putative) main pharmacologically active ingredients, are used to treat immunological nature (Fact column 3). Preparations from Crataegus (hawthorn), containing oligomeric flavonoids as their (putative) main pharmacologically active ingredients, are used to treat
The Zutphen Study results have recently found support in a publication from Finland (111). Here, 5133 men and women between 30 and 69 years, with no signs of coronary disease at start, were followed for 26 years. The flavonoid intake was estimated on the basis of dietary reports at the start of the study, and the flavonoid values from the Dutch food item analysis. The intake was far below the Dutch: only 3.4 mg/day as a median, with a range from 0 to 41.4 mg. 64% of the flavonoids came from onions and apples. During the study period, 473 persons died of coronary disease. There was a significant inverse correlation between flavonoid intake and both total and coronary mortality among females, when corrected for age, smoking, serum cholesterol, blood pressure and body mass index. Among the men, the trend was the same, but significant only for total mortality.

The latest of the hitherto published epidemiological studies on dietary flavonoids also comes from Zutphen (112). In this work, 552 men between 50 and 69 years of age were followed in a prospective study investigating the relationship between flavonoid intake and stroke. After correction for confounders (including antioxidant vitamins) it was found that the quartile with the highest flavonoid intake (more than 28.6 mg/day) had significantly fewer cases of stroke than the quartile with the lowest flavonoid intake (less than 18.3 mg/d) (RR 0.27; 95% confidence interval 0.11-0.70; P for trend 0.004). Tea, being the main source of flavonoids in the investigation, gave similar results, while the reduction in stroke associated with increased intake of β-carotene and vitamin C was not significant. In fact, vitamin E seemed to have a positive correlation with the total amount of strokes, but this correlation was not statistically significant.

**Evaluation of dietary flavonoids is problematical**

1. Hitherto, it has been assumed that most flavonoids are broken down, to a larger or smaller degree, by intestinal bacteria, or that they undergo major structural changes in the gastrointestinal tract. Possibly, completely different metabolites are present in the body after absorption than those ingested. Thus, nutritional consequences of the flavonoids are not necessarily a result of the flavonoids in themselves, but of enteral or postabsorptive interactions and degradation products. For this reason, one has to distinguish sharply between experiments where flavonoids are given orally and by other routes, and also between *in vivo* and *in vitro* studies. So far we cannot disregard the possibility that the health impact of flavonoids primarily is a result of what happens in the intestine, *e.g.* through their influence on our immune system or intestinal bacteria.

2. Flavonoids usually co-occur with other active substances in foods, like vitamin C, and one has to consider that eventual effects of flavonoids are dependent on interactions with other dietary components.

3. The effects of flavonoids seem to be mainly preventive, and it is much more difficult to study (unknown) effects of prevention than treatment.

4. Flavonoids seem to have a broad spectrum of effects, and this may make rational applications more difficult, even if a broad-spectrum effect can be therapeutically beneficial. Furthermore, there does not seem to be any effect for which the flavonoids constitute the only responsible agent.

5. The metabolism and pharmacokinetics of flavonoids in humans is not very well understood. Flavonoids can be metabolised and degraded by the intestinal microflora, but they can also be metabolised heptatically and even enter the enterohepatical circuit. In flavonoid research, high priority is given to finding out how and to what degree flavonoids are absorbed in humans (22), and studies on this theme are presently performed by several research groups, *e.g.* (127,128). Some results concerning the biological activity of flavonoid metabolites have recently been published (45,113), but a lot still remains to be done in this field.

6. A standard method of approach to assess the function of dietary components has been to compose diets without the substance to be studied, follow an eventual modulation of metabolic processes, and then follow these processes when the substance is reintroduced (depletion/repletion studies). It is virtually impossible to compose a diet free of flavonoids but still adequate when it comes to regular nutrients. At the same time, such a diet has to be acceptable to the human subjects. These aspects make human experiments difficult to design. The emerging results from epidemiological and clinical studies indicate that these problems may be overcome, even though results may be difficult to interpret. The evidence obtained from clinical and epidemiological studies so far seem to indicate that flavonoids may, indeed, possess important biological activity.

### Table 4. Some results from the Zutphen study (7). In this study, diet, mortality and CHD incidence was studied in 805 men aged 65 to 84 years. The study started in 1985 and lasted five years. RR is adjusted for age, dietary factors, physical activity, body mass index, smoking, total serum cholesterol, HDL cholesterol, and systolic blood pressure. Abbreviations: RR = relative risk, CHD = coronary heart disease, MI = myocardial infarction.

<table>
<thead>
<tr>
<th>End point</th>
<th>Variable</th>
<th>RR</th>
<th>P for trend</th>
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<tbody>
<tr>
<td>CHD mortality</td>
<td>Flavonoid intake:</td>
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<tr>
<td></td>
<td>1-19 mg/d</td>
<td>1</td>
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<td></td>
<td>19.1-29.9 mg/d</td>
<td>0.32</td>
<td>0.003</td>
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<td></td>
<td>&gt;29.9 mg/d</td>
<td>0.32</td>
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<tr>
<td>Incidence of fatal</td>
<td>Flavonoid intake:</td>
<td></td>
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<tr>
<td>and non-fatal MI</td>
<td>1-19 mg/d</td>
<td>1</td>
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<tr>
<td></td>
<td>19.1-29.9 mg/d</td>
<td>0.89</td>
<td>0.15</td>
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<td></td>
<td>&gt;29.9 mg/d</td>
<td>0.52</td>
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<tr>
<td>Total mortality</td>
<td>Flavonoid intake:</td>
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<td></td>
<td>1-19 mg/d</td>
<td>1</td>
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<tr>
<td></td>
<td>19.1-29.9 mg/d</td>
<td>0.75</td>
<td>0.084</td>
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<tr>
<td></td>
<td>&gt;29.9 mg/d</td>
<td>0.72</td>
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<tr>
<td>CHD mortality</td>
<td>Tea intake*:</td>
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<tr>
<td></td>
<td>0-250 ml/d</td>
<td>1</td>
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<tr>
<td></td>
<td>251-500 ml/d</td>
<td>0.38</td>
<td>0.024</td>
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<tr>
<td></td>
<td>&gt;500 ml/d</td>
<td>0.45</td>
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<tr>
<td>CHD mortality</td>
<td>Apple intake:</td>
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<tr>
<td></td>
<td>0-18 g/d</td>
<td>1</td>
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<td></td>
<td>19-110 g/d</td>
<td>0.90</td>
<td>0.12</td>
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<td></td>
<td>&gt;110 g/d</td>
<td>0.51</td>
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* Correlation between flavonoid and tea consumption: r = 0.83.
Conclusion
Although no flavonoid-specific biological functions have been demonstrated so far, a growing amount of evidence indicates that the intake of flavonoids may be of considerable importance to health. A multitude of promising in vitro experiments have been carried out, but relatively few clinical trials or epidemiological studies. As natural substances with limited patentability, they have attracted only moderate interest from the pharmaceutical industry, and controlled for, in epidemiological studies of coronary heart disease. The assessment of the impact of the flavonoids on human health is difficult because of the high complexity of the antioxidant system of the body, and the picture is complicated further by the flavonoids also having mechanisms of action which are largely independent of the antioxidant system.

References


