Evidence that the antioxidant flavonoids in tea and cocoa are beneficial for cardiovascular health
Penny M. Kris-Etherton and Carl L. Keen

Epidemiologic studies suggest an inverse association of tea consumption with cardiovascular disease. The antioxidant effects of flavonoids in tea (including preventing oxidative damage to LDL) are among the potential mechanisms that could underlie the protective effects. Other possible mechanisms include attenuating the inflammatory process in atherosclerosis, reducing thrombosis, promoting normal endothelial function, and blocking expression of cellular adhesion molecules. Cocoa and chocolate can also be rich sources of flavonoids. Flavanols and procyanidins isolated from cocoa exhibit strong antioxidant properties in-vitro. In acute feeding studies, flavanol-rich cocoa and chocolate increased plasma antioxidant capacity and reduced platelet reactivity. Based on limited data, approximately 150 mg of flavonoids is needed to trigger a rapid antioxidant effect and changes in prostacyclin. Some dose-response evidence demonstrates an antioxidant effect with approximately 500 mg flavonoids. Brewed tea typically contains approximately 172 mg total flavonoids per 235 ml (brewed for 2 min); hence, consumption of 1 and 3.5 cups of tea would be expected to elicit acute and chronic physiologic effects, respectively. Chocolate is more variable with some products containing essentially no flavonoids (0.09 mg procyanidin/g), whereas others are high in flavonoids (4 mg procyanidin/g). Thus, approximate estimates of flavonoid rich chocolate needed to exert acute and chronic effects are 38 and 125 g, respectively. Collectively, the antioxidant effects of flavonoid-rich foods may reduce cardiovascular disease risk.


Introduction
During the past 2 decades the field of nutrition has evolved from establishing the role of nutrients in deficiency diseases such as rickets and pellagra that were common in the early 20th century, to focusing on how diet can be used in the prevention and treatment of chronic diseases such as cardiovascular disease, age-related loss of vision, and osteoporosis. Although the classic essential nutrients are still widely studied, interest in evaluating the effects of a myriad of bioactive compounds on health is growing. Inherent to the evolution of nutrition as a field has been the pursuit of ways in which nutrition can optimize human health. We are now at a juncture at which we have established the nutrient basis and molecular mechanisms of numerous nutrient deficiency diseases, and we have made impressive progress in identifying nutrients, dietary factors, and dietary patterns that can modulate risk for certain chronic diseases such as hypertension and diabetes.

These advances have moved us to the current era, in which we are undertaking efforts to unravel how the thousands of bioactive factors in food affect health. As we gain a better understanding of how these bioactive compounds affect health, we will become positioned to make improved food-based dietary recommendations. For example, programs such as National Cancer Institute’s 5-A Day are widely recognized as positive efforts to improve the nutrition habits of the general population. Such programs are based on epidemiologic evidence that diets rich in fruits and vegetables are associated with reduced risk for several chronic diseases. To date, however, there is a poor appreciation of the identity of the factors in fruits and vegetables that confer these protective effects. In the absence of this knowledge, it is difficult to identify specific fruits and vegetables (or other plant foods) that may be particularly rich in these biofactors. Similarly, until these factors are identified, the agricultural industry and food manufacturers cannot work on ways to improve the content of such agents in target foods.

The present review summarizes the research that has been conducted recently in tea and cocoa, two foods that are rich sources of flavonoids. Flavonoids represent a class of bioactive compounds that may have multiple beneficial effects on cardiovascular health.
Tea
Both green and black tea are made from the leaves of the plant *Camellia sinensis*. Other than water, tea is consumed more than any other beverage worldwide. Three billion kilograms of tea are produced each year. Green tea is produced by steaming fresh leaves for 1 min (to inactivate polyphenol oxidase) followed by drying [1]. Black tea, in contrast, undergoes a fermentation procedure in which the leaves are kept at room temperature for 16–20 h, and then cut and dried.

Green tea is a rich source of polyphenols called flavonoids, the predominant being catechins, and flavanols. These polyphenols share a similar molecular structure based on diphenylpropane. The primary catechins are epicatechin, epicatechin gallate, epigallocatechin, and epigallocatechin gallate (Fig. 1) [2,3]. Collectively, these catechins comprise 30–50% of the solids in green tea [4] and 90% of the total flavonoids [5]. The fermentation process used to produce black tea results in the conversion of catechins to theaflavins (including theaflavin, theaflavin-3-gallate, theaflavin-3′-gallate, and theaflavin-3,3′-digallate) and thearubigin polymers (Fig. 1) [2,6]. The major fraction of black tea polyphenols is composed of thearubigin, which accounts for more than 20% of the solids [6] and approximately 47% of the total flavonoids [5].

**Epidemiologic studies**
A number of epidemiologic studies have evaluated the effect of tea consumption on the incidence of cardiovascular disease [5,7]. In general, the findings are inconclusive, with some studies showing a beneficial effect of tea consumption on cardiovascular disease whereas other studies have shown no effect, or even adverse effects.

In an attempt to resolve the inconsistencies in the literature, Peters *et al.* [8] conducted a meta-analysis of 10 cohort studies [9–18] and seven case–control studies [19–25] that assessed the association between the rate of cardiovascular disease with increasing tea consumption (Table 1, Fig. 2). Three outcome categories were studied: myocardial infarction, stroke,

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**Figure 1. Chemical structures of flavanols in tea and cocoa**

Reprinted with permission from Yang *et al.* [2] and Borchers *et al.* [3].
and the broader category of coronary heart disease. The relative risk estimates for myocardial infarction appeared to be reasonably homogeneous, and those investigators found that the incidence rate of myocardial infarction was reduced by 11% with an increase in tea consumption of three cups per day [8]. Because the results for the coronary heart disease and stroke categories were too heterogeneous, effect estimates were not summarized.

Thus, it appears that there may be a favorable effect of tea consumption on myocardial infarction, but Peters et al. [8] were careful to point out limitations of epidemiologic studies. They noticed a bias toward

### Table 1. Summary of 17 observational epidemiologic studies of tea consumption and cardiovascular diseases

<table>
<thead>
<tr>
<th>Reference</th>
<th>Outcome</th>
<th>Follow-up (years)</th>
<th>All subjects (n)</th>
<th>Cases (n)</th>
<th>Cups of tea drunk</th>
</tr>
</thead>
<tbody>
<tr>
<td>[9]</td>
<td>Stroke</td>
<td>6</td>
<td>26145</td>
<td>736</td>
<td>17.7% ≥ 0.7 cup/day</td>
</tr>
<tr>
<td>[10]</td>
<td>CHD</td>
<td>10</td>
<td>34492</td>
<td>438</td>
<td>25.0% ≥ 0.7 cups/day</td>
</tr>
<tr>
<td>[11]</td>
<td>Stroke</td>
<td>8</td>
<td>11567</td>
<td>206</td>
<td>66.6% ≥ 1.3 cups/day</td>
</tr>
<tr>
<td>[12]</td>
<td>CHD</td>
<td>14</td>
<td>1900</td>
<td>131</td>
<td>85.8% ≥ 1.3 cups/day</td>
</tr>
<tr>
<td>[13]</td>
<td>CHD</td>
<td>15</td>
<td>44303</td>
<td>279</td>
<td>91.2% ≥ 2 cups/day</td>
</tr>
<tr>
<td>[14]</td>
<td>Stroke</td>
<td>5</td>
<td>552</td>
<td>42</td>
<td>75.7% ≥ 1.4 cups/day</td>
</tr>
<tr>
<td>[15]</td>
<td>CHD</td>
<td>8</td>
<td>805</td>
<td>43</td>
<td>66.7% ≥ 1.1 cups/day</td>
</tr>
<tr>
<td>[16]</td>
<td>MI</td>
<td></td>
<td>12893</td>
<td>539</td>
<td>19.4% ≥ 1 cup/day</td>
</tr>
<tr>
<td>[17]</td>
<td>Stroke</td>
<td></td>
<td>12893</td>
<td>275</td>
<td></td>
</tr>
<tr>
<td>[18]</td>
<td>CHD</td>
<td>12</td>
<td>20089</td>
<td>159</td>
<td>25.9% ≥ 1 cup/day</td>
</tr>
<tr>
<td>[19]</td>
<td>MI</td>
<td></td>
<td>680</td>
<td>340</td>
<td>32.0% ≥ 1 cup/day</td>
</tr>
<tr>
<td>[20]</td>
<td>Stroke</td>
<td></td>
<td>662</td>
<td>331</td>
<td>67.1% ≥ 1 cup/day</td>
</tr>
<tr>
<td>[21]</td>
<td>MI</td>
<td></td>
<td>936</td>
<td>287</td>
<td>23.3% ≥ 1 cup/day</td>
</tr>
<tr>
<td>[22]</td>
<td>MI</td>
<td></td>
<td>351</td>
<td>146</td>
<td>39.0% ≥ 1 cup/day</td>
</tr>
<tr>
<td>[23]</td>
<td>MI</td>
<td></td>
<td>1423</td>
<td>472</td>
<td>40.9% ≥ 1 cup/day</td>
</tr>
<tr>
<td>[24]</td>
<td>MI</td>
<td></td>
<td>12759</td>
<td>440</td>
<td>1.9% ≥ 5 cups/day</td>
</tr>
<tr>
<td>[25]</td>
<td>MI</td>
<td></td>
<td>1300</td>
<td>276</td>
<td>60.8% ≥ 1 cup/day</td>
</tr>
</tbody>
</table>

*aPercentage of subjects who drink at least the given number of cups per day (in case–control study, only for control individuals). Data from the meta-analysis of Peters et al. [8]. CHD, coronary heart disease; MI, myocardial infarction.

### Figure 2. Summary of 17 observational epidemiologic studies of tea consumption and cardiovascular diseases

Numbers in brackets are reference numbers. Data from Peters et al. [8]. CHD, coronary heart disease; MI, myocardial infarction.
preferential publication of smaller studies that suggest protective effects, heterogeneity in disease classification, imprecision of the exposure measurement (i.e. quantifying tea consumption), and a number of uncontrolled variables that could confound the results reported. For example, in an attempt to explain inconsistent epidemiologic studies, Arts et al. [26•] controlled for catechin intake in a cohort of 806 men in the Zutphen Elderly Study, and found an inverse association between tea consumption and ischemic heart disease. Thus, as Katan noted [27], controlled clinical studies are the only way to resolve definitively whether tea consumption reduces risk for cardiovascular disease. A key component of future studies on tea should be a careful documentation of the polyphenolic profile of the teas being studied to the greatest possible extent.

Clinical studies
To date, no randomized controlled clinical trials have been conducted to evaluate the effects of tea on the incidence of cardiovascular disease. However, a number of clinical studies evaluated the effects of tea consumption on various cardiovascular disease risk factors. A focal point of this research has been to explore the effects of tea consumption on antioxidant end-points.

Antioxidant effects
The flavonols and flavonoids found in tea have been shown to have potent antioxidant effects. The overall antioxidant capacity of black tea is similar to that of green tea, demonstrating that thearubigens and the catechin monomers have comparable antioxidant properties [28,29]. These antioxidant effects are believed to be a primary mechanism that mediates the cardioprotective effects of tea.

In addition, there is a growing appreciation of the role of the endothelium as a regulator of vascular health. Nitric oxide (NO) is integral to normal endothelial function, which in turn modulates vasomotor tone, platelet activity, leukocyte adhesion, and vascular smooth muscle cell proliferation [30]. Early in the atherosclerotic process there is a loss of endothelium-derived NO production. Loss of NO bioactivity is attributable to increased oxidative stress, and there is some evidence that increasing antioxidant availability restores nitric-oxide-dependent responses [31]. In other words, providing antioxidant treatment in response to endothelial dysfunction and atherosclerosis may be a means to decrease oxidative stress and improve endothelial health.

The first step in evaluating this hypothesis with regard to tea consumption is to ascertain whether tea consumption increases plasma antioxidant levels. In support of this, Langley-Evans [32] found that consumption of black tea increased plasma antioxidant potential in human subjects by 50–76%. It remains to be seen, however, whether the increase in antioxidant levels in plasma is associated with a change in endothelial function.

The hypothesis that tea consumption reverses endothelial dysfunction was recently evaluated by Duffy et al. [33••]. Those investigators found that both short-term (2 h after consumption of 450 ml black tea) and long-term (900 ml black tea daily for 4 weeks) improved flow-mediated dilatation (i.e. vasomotor function) of the brachial artery in 66 patients with proven coronary artery disease. Both short-term and long-term tea consumption resulted in flow-mediated dilatation values that were comparable to those of healthy persons, suggesting that tea consumption reverses endothelial vasomotor dysfunction in patients with coronary artery disease. If confirmed by subsequent studies, then this will be an important clinical finding because it establishes a major mechanism of action by which tea may confer beneficial effects on cardiovascular disease risk. Significantly, in the study reported by Duffy et al., the improvement in endothelial function was associated with an increase in plasma catechin concentrations.

Mechanisms unrelated to antioxidant activity
Mechanisms other than increasing plasma antioxidant activity that may contribute to the beneficial effects of tea consumption on cardiovascular disease are presented in Table 2. There is evidence that flavonoids protect against in-vitro LDL oxidation [5], an event that plays a key role in atherogenesis. Catechins also have been shown to prevent LDL from oxidative damage [29,34–36]. It remains to be established whether tea consumption inhibits LDL oxidation in vivo. There is also some evidence that catechins can interfere with the atherosclerotic inflammatory process [30,37] and reduce thrombosis [38]. In addition, green tea polyphenols (100 mg/day; primarily catechins) have been shown to decrease adenosine diphosphate (ADP)-induced platelet aggregation [39].

Summary
In summary, there is a growing database from clinical studies that provides more than suggestive evidence that tea has beneficial effects on multiple mechanisms that appear to play important roles in the initiation and progression of cardiovascular disease. Further studies

<table>
<thead>
<tr>
<th>Table 2. Potential mechanisms by which tea confers cardioprotective effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevent oxidative damage to LDL</td>
</tr>
<tr>
<td>Interfere with the inflammatory process in atherosclerosis</td>
</tr>
<tr>
<td>Reduce thrombosis</td>
</tr>
<tr>
<td>Promote normal endothelial function</td>
</tr>
<tr>
<td>Block expression of adhesion molecules</td>
</tr>
</tbody>
</table>
will be needed to substantiate these findings and identify the particular bioactive factor(s) involved.

**Cocoa**

Cocoa represents another example of a potentially rich dietary source of flavonoids. High concentrations of flavonoids are present in certain cocoas, predominately as the flavanol monomers (−)-epicatechin (epicatechin) and (+)-catechin (catechin), and as oligomers of these monomeric base units, which are known as the procyanidins [Fig. 1] [40,41].

Cocoa is derived from the beans of *Theobroma cacao*, a tree native to South America [42]. Historically, the Olmec, Maya, and Aztec peoples considered cacao to have strong medicinal properties. Numerous applications for the use of cacao in these cultures are well documented, including the treatment or prevention of infection, inflammation, heart palpitations, and angina [42]. After the 16th century conquest of Central America by Spain, Cortes introduced cacao to Europe, where it was typically viewed as a healthy and nutritious beverage. Today, although cocoa and chocolate are still widely consumed as beverages, they are most commonly consumed as confectioneries. With respect to confectioneries, concern regarding the fat content of chocolate may be over-emphasized, because the primary form of fat in chocolate (stearic acid) is cholesterol-neutral when it is present in the diet in moderate amounts [3,43].

Numerous investigators are currently studying the biologic effects of cocoa and its flavanol and oligomer components. *In vitro*, it has been reported that cocoa, and isolated cocoa flavanols and their oligomers have the following actions. They can increase the antioxidant capacity of solutions and slow the oxidation of LDL [44–47]. They may also induce endothelial-dependent vessel relaxation [48]. Mao and coworkers [49,50] reported that cocoa procyanidins can reduce the production of inflammatory cytokines, while increasing the production of anti-inflammatory cytokines. Schramm et al. [51*] reported that cocoa procyanidins can increase the synthesis of the antithrombotic lipid prostacyclin, while reducing the production of the proinflammatory cysteinyl leukotrienes. Cocoa polyphenol oligomers have been reported to protect against peroxynitrate-dependent oxidation and nitration reactions [52]. Finally, cocoa was shown to decrease the expression of the activated conformation of glycoprotein IIb/IIIa and CD62P (P-selectin) on epinephrine-activated platelets [53].

While the flavonols and procyanidins isolated from cocoa clearly have a number of interesting properties *in vitro*, the critical question is whether the same effects can be observed *in vivo*. In this regard, Spencer et al. [54] recently reported that, *in vitro*, there is significant decomposition of the procyanidins isolated from cocoa when they are incubated in simulated gastric juice. Given the above, it can be argued that many of the *in vitro* effects reported for these compounds may not occur *in vivo*. Critical to this issue is the extent to which the flavanols and procyanidins in cocoa are absorbed.

**Flavanol bioavailability**

During the past few years, several laboratories have begun to address the issue of the bioavailability of the flavonoids in chocolate and cocoa. Richelle et al. [55] monitored the plasma kinetics of epicatechin over an 8-h time period after volunteers consumed two different doses (40 and 80 g) of black chocolate. Those investigators reported that there was a dose-dependent increase in plasma epicatechin following the consumption of the chocolate, with plasma epicatechin reaching its peak approximately 2 h after consumption. Similar to the above, Wang et al. [56] reported a dose-dependent increase in plasma epicatechin concentrations after the consumption of increasing amounts (0, 27, 53, and 80 g) of a flavanol-rich chocolate (6.9 mg flavonoids/g). Significantly, a dose–response relationship was also observed between the levels of epicatechin in the plasma and serum antioxidant capacity. In contrast, the concentration of plasma lipid oxidation products was inversely related to plasma epicatechin [Fig. 3] [56]. Similar to the findings of Wang et al., Baba et al. [57] reported a rapid rise in plasma epicatechin following the consumption of a flavonoid-rich cocoa drink.

Complementing the above work, Osakabe et al. [58] recently reported a study in which participants consumed 36 g cocoa, which provided 2610 mg total polyphenols (measured using a nonspecific assay) daily for 2 weeks. A control group consumed an equivalent amount of sugar as contained in the cocoa beverage. Using both 2-2′-azobis 4-methoxy-2,4-dimethylvaleronitrile (V-70) and copper chloride to initiate radical formation, susceptibility of LDL to oxidation was determined in LDL isolated from the plasma. Compared with baseline, lag time to oxidation of LDL was significantly increased in the cocoa group by 29% using the V-70 radical initiator, and by 14% using the copper ion initiator. It is important to note that those investigators were unable to detect epicatechin in the plasma samples obtained from these individuals, although an increased urinary excretion of epicatechin was observed 1 and 2 weeks after cocoa consumption. It is likely that the timing of blood draws explains the lack of epicatechin in the plasma because the blood samples in this study were taken following a 12-h fast. Several investigators have reported that the majority of
absorbed epicatechin is cleared from the blood by 8 h [55–57].

Wan et al. [59] also observed a rapid clearance of epicatechin in subjects fed 22 g cocoa powder and 16 g dark chocolate. Those investigators also reported an 8% increase in LDL oxidation lag time. Osakabe et al. [58] observed that there was a significant increase in lag time to LDL oxidation after 1 and 2 weeks of cocoa consumption, independent of a concurrent presence of plasma epicatechin. This suggests that the protective effect on LDL oxidation may have been due to an effect of the cocoa flavanols on the amount of vitamin E, or other antioxidants, associated with the LDL particle. Regardless of the mechanisms involved, these results provide additional evidence for the concept that the intake of dietary flavonoids can be associated with improvements in the oxidative defense system.

Although the bioavailability of the flavanols has been well documented, there is still limited information concerning procyanidin absorption. Radiolabeling techniques have indicated that the procyanidins are bioavailable, although those studies did not demonstrate whether the procyanidins were intact or depolymerized before absorption [60]. Recently, Holt et al. [61] reported that cocoa procyanidin dimer B2 [epicatechin-(4β-8)-epicatechin] can be detected in the plasma of humans within 30 min of consuming a cocoa beverage, reaching a maximum concentration in the plasma approximately 2 h after consumption. The physiologic consequences of nanomolar concentrations of the dimer with respect to cardiovascular health remain to be determined.

**Platelet effects**

Similar to tea flavonoids, cocoa flavanols and their related oligomers can inhibit platelet activation in vitro, following stimulation with epinephrine [53]. Importantly, these effects have also been observed following the consumption of a flavanol-rich cocoa beverage. Using flow cytometry, and monoclonal and secondary fluorescent antibodies, Rein et al. [62] determined the expression of specific platelet surface receptors (P-selectin and glycoprotein IIb/IIIa) in persons who consumed one of three beverages: water; cocoa containing 897 mg flavanols and related oligomers; and a caffeine-containing beverage. Blood was drawn immediately before consumption of the test beverage and after consumption at 2 and 6 h. Flow cytometry was performed on either unstimulated platelets, or after ex vivo stimulation using epinephrine or two concentrations of ADP. At 2 and 6 h following the consumption of the cocoa beverage, platelets stimulated with ADP had significantly less P-selectin expression. Additionally, there was a trend (P = 0.053) toward less P-selectin expression in the unstimulated platelets 6 h after the consumption of cocoa. However, there was no effect on P-selectin in the other treatment groups. Similarly, at 2 and 6 h following the consumption of the cocoa beverage, glycoprotein IIb/IIIa expression on unstimulated platelets and those stimulated with epinephrine and ADP (at 20 μmol/l) was significantly decreased. There was also a trend toward decreased expression when platelets were stimulated with a higher concentration of ADP (100 μmol/l). In contrast, glycoprotein IIb/IIIa expression was significantly increased following stimulation with epinephrine in persons who consumed the caffeine-containing beverage, and there was a trend toward increased expression when platelets were stimulated with ADP (20 μmol/l).

In the same study [62], platelet primary hemostasis was measured using a platelet function analyzer, which measures the ability of platelets to form a hemostatic plug in a collagen membrane. Following stimulation of platelets with collagen and ADP or epinephrine, closure
time (i.e. the time that it takes for blood to occlude an aperture) was measured. Compared with the caffeine beverage, when platelets were stimulated with collagen-epinephrine primary hemostasis (as measured by closure time) significantly increased by 31% at 6 h following the consumption of the cocoa beverage.

Although the mechanisms for the observed antiplatelets effects are unknown, one possible explanation may be the increased production of prostacyclin, an eicosanoid that is known to inhibit platelet aggregation via increasing cyclic adenosine monophosphate levels. Schramm et al. [51] reported that plasma prostacyclin was significantly \( (P<0.05) \) higher in participants following the consumption of 36 g of a high-flavanol (4.0 mg/g) chocolate bar relative to participants who consumed the same amount of a low-flavanol (0.9 mg/g) chocolate bar \( (554 \pm 37 \text{ pmol/l versus } 397 \pm 40 \text{ pmol/l}) \).

Collectively, the data obtained during the past 5 years on the biologic effects of flavonoid-rich cocoas and chocolate support the concept that the consumption of flavonoid-rich foods may be associated with positive cardiovascular effects. It is important to note that clear epidemiologic data concerning the influence of cocoa/chocolate consumption on the risk for cardiovascular disease are lacking. Unfortunately, such data will be difficult to collect because the flavonoid content of these foods can be markedly influenced by food processing. For example, dutching, a common treatment used in the production of cocoa, results in a marked reduction in its flavonoid content.

**Conclusion**

Even in a ‘balanced’ diet that meets macronutrient recommendations and micronutrient requirements, there is a growing body of evidence that bioactive compounds play an important role in optimizing health. Flavonoids, such as those occurring in tea and cocoa, are an example of a class of bioactive compounds that may confer beneficial effects on a number of important risk factors for cardiovascular disease. As discussed in the present review, there is now a reasonable body of literature that supports the concept that the flavonoids present in tea and chocolate may provide positive health benefits. Other flavonoid-rich foods and beverages, such as apples, certain nuts and purple grape juice, clearly may also provide similar benefits. A better understanding of the mechanisms that underlie the biological effects of flavonoids following their absorption will provide important clues regarding the biopotency of the different classes of flavonols and procyanidins.

Currently, there is a dearth of information concerning the amount of flavonoids that are needed on an acute or chronic basis to trigger the positive health effects discussed herein. A best approximation based on the studies reviewed is that 150 mg of flavonoids is needed to observe an acute effect and 500 mg for a chronic effect. The average brewed tea contains about 172 mg total flavonoids per 235 ml (brewed for 2 min) [63]; hence, consumption of 1 to 3.5 cups of tea would be expected to elicit acute and chronic physiological effects, respectively. Commercially available chocolate is more variable, with some products containing essentially no flavonoids \( (0.09 \text{ mg procyanidin/g}) \), whereas others are high in flavonoids \( (4 \text{ mg procyanidin/g}) \). Thus, based on flavonoid-rich chocolate, approximate estimates of the amounts needed to elicit acute and chronic effects are 38 and 125 g of chocolate, respectively. However, until we have a better understanding of the dose–response relationship, it is not possible to make dietary recommendations concerning the amount of flavonoids to consume on a daily basis.

The message that individuals should try to consume a variety of food products that are rich in flavonoids on a daily basis is one that could be defended on the basis of current information. The identification of foods that are high in these nutrients and the amounts needed to elicit physiologic effects will be a valuable public health message. Perhaps even more important is that agricultural and food scientists develop and implement processing techniques that retain the flavonoids that are naturally present in many plant foods. As the message on the positive health benefits of flavonoids continues to build, it is easy to envision food labels in the future that provide information about this important class of nutrients.

We are now at a juncture at which it is important to unravel the intriguing mysteries of which bioactive compounds are important and of how they work, individually and in synergy, to enhance health. As we gain a better understanding of how bioactive compounds in various foods improve health, we will need to devise strategies for increasing their intake within the context of a healthy diet that meets energy requirements. Essential to this will be consumption of a greater variety of plant foods [64]. Tea, as a noncalorie beverage, can be an ideal delivery vehicle for select bioactive compounds. Similarly, flavonoid-rich chocolate or cocoa may also be a component of a healthy diet when consumed in moderation. Chocolate can be part of the flavonoid ‘cocktail’ that is consumed along with other flavonoid-rich foods; however, its high energy density (provided by fat and sugar) is a key factor in determining the quantity of flavonoids that can be derived from this food. Other flavonoid-rich beverages, such as purple grape juice [65,66], may also be valuable in reducing one’s risk for certain chronic diseases.
Nutrition and metabolism

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
• of outstanding interest


25 Boston Collaborative Drug Surveillance Program. Coffee drinking and acute myocardial infarction. Report from the Boston Collaborative Drug Surveil-


Decreased plasma leukotrienes by 29% \( (P<0.01) \) and 16% less leukotriene \( (P<0.05) \) 2 h after ingestion. Aortic endothelial cultures treated with procyanidin synthesized twice as much 6-keto-prostaglandin \( F_1 \alpha \) \( (P<0.01) \) and 16% less leukotriene \( (P<0.05) \) versus control cultures.

This study evaluated the effect of cocoa procyanidins on eicosanoid synthesis in humans and cultured human aortic endothelial cells. A randomized, cross-over, blinded study design was employed, and 10 healthy persons consumed 37 g low-procyanidin \( (0.09 \text{mg/g}) \) and high procyanidin \( (4.0 \text{mg/g}) \) chocolate. The high procyanidin chocolate increased plasma prostacyclin by 32% \( (P<0.01) \) and 16% less leukotriene \( (P<0.05) \) versus control cultures.