Antioxidants (including polyphenols)

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Although essential for aerobic life, oxygen is also thought to be implicated in the process of ageing and to contribute towards the development of various degenerative diseases. The latter role is attributed to numerous oxidation reactions occurring in the body, resulting in a chronic accumulation of oxidative damage.

"Reactive species" include "free radicals" as well as other oxidizing agents that may easily be transformed into free radicals. Free radicals include oxygen, nitrogen or chlorine compounds and may be formed as natural products of metabolism, or can derive from exogenous sources. Although very important in neural transmission and cell signaling, free radicals are very reactive by possessing uncoupled electrons and may therefore damage other molecules. On the contrary, "antioxidants" are compounds that prevent the oxidation of susceptible molecules and can be produced endogenously (e.g. superoxide dismutase, catalase, uric acid) or can be provided through the diet (e.g. vitamins C and E, flavonoids). Disruption of the balance between free radical formation and their clearance by antioxidants leads to oxidative stress, a state that brings about excessive damage to biological molecules (proteins, lipids and DNA). There is evidence that the oxidation of low-density lipoprotein (LDL) is a key process implicated in the development of atherosclerosis, while the accumulation of DNA damage is thought to be a crucial step in carcinogenesis.

Dietary antioxidants fall into several groups, two of the main being antioxidant vitamins and polyphenols (including flavonoids). The following section on antioxidant vitamins has not been based on a specially commissioned scientific review. The section on polyphenols (Section 1.3.10.2) is based on a specially commissioned scientific review.

1.1.1.1   Antioxidant vitamins

There has been a longstanding theory that the antioxidant vitamins—E, C and beta carotene (a form of vitamin A)—may be protective against cardiovascular disease and may contribute to the protective effects of fruits, vegetables and the Mediterranean diet. While observational data comparing the health of people on antioxidant-rich diets with those with lower antioxidant intakes give support to this hypothesis, the results of clinical studies of high doses of antioxidant supplements to see if it works in practice have been contradictory. A 2009 review article reported that a total of nine primary and 11

secondary prevention trials (involving a total of 150,000 and 60,000 participants respectively) have been disappointing.[1]

Further research is needed to achieve a consensus on the associations between oxidation and chronic disease, and the extent to which antioxidants may reduce oxidative stress and protect health.

On the basis of the theoretical health benefits of antioxidants, antioxidant-rich foods and dietary supplements are today promoted by the industry and some health professionals as carriers of beneficial nutritional properties that may protect against premature aging. The European Food Safety Agency (EFSA) has recently reviewed a number of health claims in relation to vitamins A, C and E. The only one of the submitted claims directly related to cardiovascular health ("vitamin E can neutralise free radicals and help maintain a healthy heart") was rejected.[2] In contrast, claims that vitamin C and vitamin E can "protect DNA, proteins and lipids from oxidative damage" were approved.[2,3] EFSA rejected more general claims for "antioxidant activity", "antioxidant content", and "antioxidant properties".[4]

1.1.1.2 Polyphenols

1.1.1.2.1   Introduction

Polyphenols are phenolic phytochemicals widely distributed in plants, and are also present in significant amounts in a wide range of plant-derived foods and beverages. They constitute a very diverse group of secondary metabolites synthesised by plants and are ubiquitous throughout the plant kingdom. Several thousand molecules having a polyphenolic structure (i.e. several hydroxyl groups on aromatic rings) have been identified in higher plants, and several hundred are found in edible plants.[5] They are divided into several classes and subclasses according to their chemical structure. Flavonoids, phenolic acid, tannins, lignans and stilbenes are the most common polyphenolic classes in plant foods. Flavonoids are further classified as flavonols, flavones, flavanols (flavan-3-ols, catechins), flavanones, anthocyanidins and isoflavones (Table 1). Proanthocyanidins (also called condensed tannins) are oligomers and polymers of flavanols.

Table 1 Dietary flavonoids and examples of food sources

Flavonoid subclass	Food sources
Flavonols	apple, beans, berries, broccoli, kale, onion, red wine, tea, tomato
Flavones	celery, parsley
Flavanones	citrus fruit
Flavanols (catechins)	apple, berries, cocoa or dark chocolate, grape, red wine, tea
Proanthocyanidins	apple, berries, cocoa or dark chocolate, grape, red wine
Anthocyanidins	berries, cherry, plum, red cabbage, red onion, red grape, red wine
Isoflavones	soybean, soy foods, soy protein isolate

Polyphenols are an integral part of the human diet, and have been linked to improved human health through reduced risk of chronic diseases, especially cardiovascular disease. Unlike vitamins or other essential nutrients, polyphenols are not required for growth and development and for maintaining vital body functions throughout life, and do not cause classical deficiencies. However, they may be essential for maintaining body functions and health through the adult and later phases of life. Recently, they have been discussed as 'lifespan essentials' because they may increase the chance of reaching the full genetically determined lifespan and the quality of life during aging by reducing the incidence of chronic, age-related diseases.[6,7]

Polyphenols are the most abundant dietary antioxidants, with total intake of nearly 1 g/day, which is much higher than that of all other classes of phytochemicals and known dietary antioxidants. The intake of polyphenols is approximately 10 times higher than that of vitamin C and 100 times higher than that of vitamin E and carotenoids.[8]

Research on dietary flavonoids and other polyphenols, their bioactive properties, and their role in the prevention of chronic diseases truly began after 1995.[8] The diversity and complexity of their chemical structures as well as differences in bioavailability have delayed and complicated the research on their health benefits. The antioxidant properties of polyphenols have been extensively studied. However, the mechanisms of action go beyond radical scavenging or antioxidant functions. Polyphenols affect cell metabolism, physiology and health also through regulation of gene expression and interactions with receptors, enzymes and other proteins.

Today, there is an enormous amount of scientific literature on the potential cardioprotective properties of polyphenols, including data from *in vitro* studies, animal experiments and human intervention trials as well as prospective epidemiological studies. The data available supports the concept that certain polyphenols in the diet, especially flavonoids, may be associated with benefits on cardiovascular health.[9,10,11] Proposed mechanisms are presented in Table 2. However, it is important to understand that, in this relatively new area of investigation, the research that has been done to-date has limitations. Many of the studies on polyphenols are relatively small in size and short-term in nature. In addition, they have often measured intermediate end-points rather than health outcomes.

Table 2 Proposed mechanisms by which polyphenols may reduce the risk of CVD

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Oxidative stress
  o scavenge reactive oxygen and nitrogen species
  o chelate redox-active transition metal ions
  o spare and interact with other antioxidants
  o inhibit redox-sensitive transcription factors
  o inhibit pro-oxidant enzymes
  o induce antioxidant enzymes
Growth of atherosclerotic plaque
  o reduce adhesion molecule expression
  o reduce inflammation
  o reduce the capacity of macrophages to oxidatively modify LDL
Platelet function and haemostasis
  o inhibit platelet aggregation
Blood pressure and vascular reactivity
  o promote nitric oxide-induced endothelial relaxation
Plasma lipids and lipoproteins
  o reduce plasma cholesterol and triglycerides

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From: Manach et al. 2005[9]

This review provides a summary of the current scientific evidence on the effects of dietary polyphenols on CVD, based on recent critical reviews and meta-analyses of epidemiological studies and randomised controlled human trials (RCTs). In some cases, also original studies are cited. To date, the evidence is largely limited to certain groups of flavonoids and to foods or beverages rich in flavonoids, such as cocoa products, black and green tea, red wine, and soy products. Less evidence is currently available on other important dietary sources of polyphenols, such as fruits and berries.

1.1.1.2.2   Flavonoids and CVD

Prospective studies

Arts and Hollman[12] reviewed 12 prospective cohort studies on flavonoid intake and the risk of coronary heart disease (CHD), focusing on the flavonoid subclasses of flavonols, flavones and flavanols (catechins). Seven of the studies found protective effects of flavonols and flavones or of flavanols with respect to fatal and nonfatal CHD, and reductions of mortality were up to 65%. A similar result was obtained also in a 2007 systematic review conducted by Erdman and colleagues.[13]

A meta-analysis of prospective cohort studies indicated that intake of flavonols was inversely associated with non-fatal and fatal stroke.[14] Data from six cohorts involved 111,067 subjects with at least 2,155 non-fatal and fatal cases, and the persons were followed for from six to 28 years. This meta-analysis showed that a high intake of flavonols compared with a low intake was associated with a 20% lower risk of stroke incidence. It was concluded that flavonols may reduce stroke risk.

A large prospective study of 34,489 postmenopausal women with 16 years of follow-up investigated the associations between intakes of total flavonoids or seven subclasses of flavonoids and cardiovascular mortality.[15] Significant inverse associations were observed between anthocyanidin intake and CHD, CVD, and total mortality, between flavanone intake and CHD mortality, and between flavone intake and total mortality. No association was found between flavonoid intake and stroke mortality.

Randomised Controlled Trials (RCTs)

Erdman and colleagues[13] reviewed eight human intervention studies examining the effects of flavonols on markers for CHD. These studies used pure quercetin aglycone or glycosides, onions, or a variety of flavonol-rich foods. Duration of the interventions varied from one to 42 days, and the number of subjects from six to 19. The daily dose of quercetin equivalents varied from 20 to 250 mg. Favourable effects were found on antioxidant biomarkers. Plasma lipid profiles were not affected by flavonol supplements. The authors also reviewed studies on other flavonoids and concluded that the clinical evidence is encouraging but not sufficient to support a role of dietary flavonoids in reducing the risk of CVD.

The effect of oral isoflavone supplementation on endothelial function in postmenopausal women has been investigated in many studies. A meta-analysis of nine RCTs (including 525 subjects) showed that oral isoflavone supplementation did not improve endothelial function (measured as flow-mediated dilation, FMD) in postmenopausal women with high baseline FMD levels but led to significant improvement in women with low baseline FMD levels.[16] In these trials, the source of isoflavone was soy protein (six trials) or tablets (three trials), the doses of isoflavone ranged from 50 to 99 mg/day, and the duration of supplementation ranged from two weeks to 12 months. The result of this meta-analysis suggests that oral isoflavone supplementation should be applied to targeted subjects (with baseline FMD levels <5.2%), but not to all postmenopausal women.

1.1.1.2.3 Flavonoid-rich foods and CVD

1.1.1.2.3.1 Cocoa products

Chocolate and other cocoa products are made from beans of *Theobroma cacao*. Cocoa beans contain approximately 6-8% polyphenols by dry weight.[17] Cocoa is particularly rich in the flavanols epicatechin, catechin, and proanthocyanidins (oligomers of epicatechin and catechin).

Prospective studies

There are no meta-analyses available on epidemiological evidence relating to consumption of cocoa products and cardiovascular health. Therefore, four recent studies

examining the association of cocoa consumption with blood pressure (BP) and CVD risk are cited here.

The association of cocoa intake with BP and cardiovascular mortality was assessed in a Dutch cohort of 470 elderly men.[18] Men with habitual intakes of 4.2 g of cocoa per day (equal to 10 g of dark chocolate) had a 3.7 mmHg lower systolic BP and a 2.1 mmHg lower diastolic BP than non-consumers of cocoa. During 15 years of follow-up, cocoa intake was associated with 50% lower risk of cardiovascular and all-cause mortality.

The association of chocolate consumption with BP and the incidence of CVD (myocardial infarction and stroke) was investigated in a German cohort of 19 357 middle-aged men and women.[19] Systolic BP was 1.0 mmHg and diastolic BP 0.9 mmHg lower in the top quartile compared with the bottom quartile of chocolate consumption. After a mean follow-up of eight years, an increase in chocolate consumption of 6 g per day was associated with a 39% lower risk of the combined outcome of myocardial infarction (MI) and stroke. The inverse relation was stronger for stroke than for MI. Baseline BP explained 12% of the lower risk. Chocolate consumption had a strong inverse association with cardiac mortality also in a Swedish cohort of 1,169 patients surviving their first acute myocardial infarction.[20]

In addition to these European cohorts, the association between chocolate consumption and CVD has been evaluated in a large U.S. cohort of 34,489 postmenopausal women with a 16 year follow-up.[21] This study found a borderline significant inverse association between chocolate intake and CVD mortality.

RCTs

There are several recent reviews and meta-analyses on the effects cocoa products on cardiovascular health[22,23,24,25] and particularly on blood pressure.[26,27,28] In addition to BP, cardiovascular risk factors such as endothelial function, blood lipids, and platelet function have been investigated within these RCTs.

In their meta-analysis of the effectiveness of different flavonoid subclasses and flavonoid-rich foods on cardiovascular risk, Hooper and colleagues[29] reviewed 133 RCTs examining the effects on endothelial function (measured as flow-mediated dilatation, FMD), BP, and blood lipids. They found that chocolate or cocoa was the only group to show significant improvement of FMD. Daily consumption of 50 g dark chocolate increased FMD after acute (3.99%, six studies) and chronic (1.45%, two studies) intake. The time course suggested a peak effect at approximately two hours.

Chronic intake of chocolate or cocoa also had beneficial effects on blood pressure. Both systolic (5.88 mmHg) and diastolic BP (3.30 mmHg) was reduced.[29] This effect is similar to that identified earlier in a review by Taubert and colleagues.[30] These authors commented that the magnitude of the hypotensive effects of cocoa (dark chocolate 100

g/day) is clinically noteworthy; it is in the range that is usually achieved with monotherapy of β-blockers or angiotensin-converting enzyme inhibitors.[30]

Recently, Desch *et al* published a meta-analysis of RCTs assessing the antihypertensive effects of flavanol-rich cocoa products (dark chocolate or cocoa-containing beverages).[27] Ten RCTs comprising 297 individuals were included in the analysis. The populations studied were either normotensive adults or patients with prehypertension/stage 1 hypertension. Treatment duration ranged from two to 18 weeks. The mean BP reduction was 4.5 mmHg for systolic BP and 2.5 mmHg for diastolic BP. The meta-analysis confirms the BP-lowering capacity of flavanol-rich cocoa products in a larger set of trials than previously reported.

Also the meta-analysis by Ried and colleagues, including 15 trial arms, demonstrated a small but significant BP-reducing effect of dark chocolate and flavanol-rich cocoa products.[28] Compared with the previous meta-analyses with fewer trials, the size of the effects was smaller. The mean reduction was 3.2 mmHg for systolic and 2.0 mmHg for diastolic BP. However, subgroup meta-analysis revealed a significant reduction only for hypertensive or prehypertensive subgroups (5.0 mmHg for systolic and 2.7 mmHg for diastolic BP). Flavanol-rich cocoa products did not significantly reduce BP below 140/80 mmHg.

Hooper and colleagues concluded that there is sufficient evidence to suggest that chronic intake of chocolate or cocoa has no overall effect on blood LDL or HDL cholesterol.[29] In a more recent meta-analysis of the short-term effects of cocoa product consumption on lipid profile, Jia and colleagues found that cocoa consumption marginally lowered total cholesterol and significantly lowered LDL cholesterol (by 0.15 mmol/l).[31] However, no significant change was observed in LDL cholesterol in high-quality studies. There was no dose response and no effect in healthy subjects.

Ostertag and colleagues critically reviewed 25 well-controlled human intervention studies examining the effect of polyphenol-rich diets on platelet function.[32] One consistent finding was that cocoa-related products have platelet-inhibiting effects when consumed in moderate amounts. Significant inhibition of platelet aggregation and activation upon acute of chronic intake of flavanols from cocoa was observed. It was calculated that intake of 100 mg flavanols led to 3-11% inhibition of platelet function, and that 100 mg flavanols may be obtained from 11 g dark chocolate (cocoa content 70%), from 52 g milk chocolate, or from 50-100 ml cocoa drink (containing 8% pure cocoa). The authors concluded that the physiological relevance of the beneficial effects of cocoa consumption on platelet function is comparable to standard doses of aspirin: consumption of 100 g dark chocolate with 70% cocoa solids could result in similar effects to 81 mg of aspirin in an acute setting. The effect can be obtained in healthy subjects as well as in people at risk for CVD, and appears to be largest upon acute consumption.

1.1.1.2.3.2 Tea

Both green and black tea is made from leaves of the plant *Camellia sinensis*. Green tea is produced by steaming fresh leaves to inactivate polyphenol oxidase, followed by drying. It is a rich source of flavonoids, especially catechins such as epicatechin, epicatechin gallate, epigallocatechin, and epigallocatechin gallate. These catechins comprise 30-50% of the solids of green tea and 90% of total flavonoids.[33] Black tea undergoes a fermentation process in which the leaves are kept at room temperature for 16-24 hours and are then cut and dried. In the fermentation process polyphenol oxidase converts catechins to theaflavins and thearubigin polymers. The major fraction of black tea polyphenols is composed of thearubigins, which account for >20% of the solids and 47% of total flavonoids.[33] Black tea represents one of the main contributors to intake of flavonoids in European countries, while green tea is an important source of flavonoids in the Asian countries.

Prospective studies

The meta-analysis by Peters and colleagues reported that the incidence rate of MI was estimated to decrease by 11% with an increase in black tea consumption of three cups per day.[34] The analysis was based on 10 cohort and seven case-control studies. Gardner and colleagues reviewed 21 studies and found evidence that an intake of three or more cups of black tea per day was associated with reduction of CHD risk.[35] Grassi and colleagues reviewed 15 epidemiological studies and concluded that an inverse association between tea (black and green tea) intake and CVD has been demonstrated.[33]

Four prospective cohort studies reviewed by Kuriyama have shown that green tea consumption is inversely associated with mortality from CVD.[36] One of the studies reviewed included 40,530 individuals from Japan.[36] In that study the inverse association with CVD mortality was more remarkable than that with all-cause mortality, and was also more pronounced in women. Women who consumed five or more cups (500 ml or more) per day had 31% lower risk for CVD death compared to those who consumed less than one cup of green tea per day. There was no statistically significant association between green tea consumption and MI mortality. In women, green tea consumption was significantly associated with reduced mortality from stroke, especially cerebral infarction (62% lower risk in women who consumed five or more cups compared with those who consumed less than one cup/day).

A meta-analysis including nine studies involving 4,378 stroke incidents among 194,965 individuals demonstrated that drinking tea (black or green tea) daily significantly reduced risk of stroke.[37] In subjects drinking three cups or more of tea per day the risk of a fatal or non-fatal stroke was reduced by approximately 21% as compared with nondrinkers of tea. The effect does not appear to be specific to green or black tea or to Asian or non-Asian populations. The authors concluded that tea drinking might be one of the most actionable lifestyle changes to significantly reduce the risk of stroke.

Taubert and colleagues reviewed five RCTs on tea consumption involving a total of 343 subjects with a median duration of four weeks and showed that tea intake had no effects of blood pressure.[26] The data from black and green tea interventions were pooled. In the meta-analysis of Hooper and colleagues, ingestion of black tea resulted in an acute rise in systolic (5.69 mmHg) and diastolic BP (2.56 mmHg), independent of caffeine content.[29] However, chronic consumption of black tea did not show significant effects on BP.[29]

Chronic consumption of black tea also increased FMD by 3.40%, whereas the acute effect was modest (1.70%) and not significant.[29] Black tea had no effect on LDL or HDL cholesterol.

A meta-analysis of four interventional studies showed that green tea significantly reduced LDL cholesterol (−0.23 mmol/l) but had no overall effect on HDL cholesterol.[29] The authors estimated that two to five mugs of green tea per day (up to one-half of the usual fluid intake) would be required to achieve a clinically relevant reduction in LDL cholesterol concentration.

Kuriyama reviewed 30 RCTs and found that 17 studies indicated statistically significant beneficial effects of green tea on CVD risk profile, and 11 studies showed no such results.[36] Two studies on blood pressure or aortic stiffness showed acute harmful effects.

Ostertag and colleagues reviewed three studies examining black tea for its potential effect on platelet function. Consumption of one litre black tea per day inhibited platelet activation by 4-10%.[38] Two other studies did not find significant effects of tea consumption on platelet function.

1.1.1.2.3.3 Red wine

Red wine is produced by fermenting grape juice in the presence of grape solids. It is composed of more than 500 compounds, of which only a few are present at concentrations >100 mg/l.[39] Red wine contains a wide variety of polyphenols, most of which are derived from the skin and seeds of the grapes. Typical polyphenols include proanthocyanidins, anthocyanins, flavanols, flavonols, cinnamic derivatives, and resveratrol. White wine, on the other hand, is made by separating the juice from the solids by pressing and then allowing it to ferment. Therefore, white wine has a lower content of polyphenols than red wine. A typical commercial bottle of red wine contains approximately 1.8 g/l of total polyphenols, while a typical bottle of white wine has only 0.2-0.3 g/l of polyphenols.[39] One glass of red wine provides about 200 mg polyphenols, in comparison to 30 mg in a glass of white wine.

Prospective studies

Di Castelnuovo and colleagues performed a meta-analysis of 13 studies involving 209,418 subjects on the relationship between wine consumption (including red and white wine) and vascular risk.[40] A significant inverse association between light to moderate wine consumption and vascular risk was observed, with 32% reduction of overall vascular risk associated with drinking wine. Both non-fatal vascular endpoints and cardiovascular mortality were significantly reduced in wine drinkers. There was strong evidence from 10 studies involving 176,042 persons to support a J-shaped relationship between different amounts of wine intake and vascular risk. A statistically significant inverse association was found up to a daily intake of 150 ml of wine. The authors of this meta-analysis emphasised that the hazards of excess drinking should always be highlighted, and heavy drinkers should be pushed to cut their consumption.

In a large U.S. study of 34,489 postmenopausal women with 16 years of follow-up, consumption of red wine was inversely associated with CHD and CVD mortality.[41]

Opie and Lecour reviewed evidence for and against the "red wine hypothesis", which proposes that red wine is more likely to confer cardiovascular benefits than white wine.[42] There is strong epidemiological and mechanistic evidence for J-shaped relation between moderate alcohol consumption and total mortality. However, epidemiological data favouring a specific benefit of red over white wine is not strong and the "French paradox" (the inverse relation between CHD mortality and red wine consumption, with France having the lowest mortality despite its high-fat diet) could at least in part be explained by confounding factors. (See also Section 1.3.8 on alcohol and cardiovascular disease and Section 1.3.11 for this paper's recommended population goals in relation to alcohol consumption).

RCTs

Human studies have shown that there is incomplete and only indirect evidence that red wine might potentially be more cardioprotective than white wine.[42] The specific components of red wine that are active on cardiovascular endpoints, are the polyphenols, especially resveratrol and proanthocyanidins (which are high in pinot noir). In their comprehensive review Opie and Lecour concluded that red wine potentially has beneficial effects "beyond alcohol" and may be cardioprotective when consumed in moderate amounts and preferably with meals.[42]

The studies on the chronic effects of red wine do not suggest significant effects on endothelial function measured as FMD.[29] In acute studies red wine showed a modest (1.25%) but not significant benefit on FMD. Also another review found that data about the acute effects of red wine constituents on endothelial function is inconclusive.[43] The authors concluded that one should be very careful in suggesting red wine consumption in high-risk populations, such as patients with CHD, as the acute postprandial effect is not yet clear.

In the meta-analysis by Hooper and colleagues chronic consumption of red wine did not show significant effects on blood pressure, or LDL or HDL cholesterol.[29] Consumption of wine rich in polyphenols has produced inconsistent effects also on platelet function.[38]

1.1.1.2.3.4 Soy products

Soy foods are rich sources of isoflavones. Soybeans contain 35-40% protein on a dry-weight basis, and isoflavones are closely associated with the proteins. Soy foods contain 1-4 mg isoflavones/g, whereas soy isoflavone supplements contain up to 500 mg/g.[44]

The U.S. FDA approved a food-labelling health claim for soy proteins in the prevention of CHD in 1999 but clearly indicated that "the evidence did not support a significant role for soy isoflavones in cholesterol-lowering effects of soy protein".[44] Since then, similar health petitions for soy proteins have been approved also in the United Kingdom and some other countries. This has led to an enormous increase in the number of soy products, and to extensive research on the health effects of soy intake.

RCTs

The Nutrition Committee of the American Heart Association has assessed 22 RCTs published since 1999 and found that isolated soy protein with isoflavones significantly decreased LDL cholesterol but had no effect on HDL cholesterol, triglycerides, lipoprotein(a), or blood pressure.[45] The consumption of soy protein ranged from 25 to 135 g/day, and that of isoflavones from 40 to 318 mg. Isolated soy protein with isoflavones compared with milk or other proteins decreased LDL cholesterol concentrations by approximately 3%.

In the meta-analysis conducted by Hooper and colleagues soy protein isolate—but not other soy products or components—significantly reduced LDL cholesterol (–0.19 mmol/l) and diastolic BP (–1.99 mmHg).[29] Soy protein isolate or isoflavone extracts showed no statistically significant effects on HDL cholesterol, systolic BP or FMD.

It can be concluded that the beneficial effects observed in cardiovascular risk factors are very small compared with the large amount of soy protein required (studies all done on intakes above 25g per day). The evidence favours soy protein rather than soy isoflavones as the responsible nutrient. For this reason, use of isoflavone supplements in food or pills for cardiovascular health is not recommended.[46,45] In contrast, many soy products may be beneficial to cardiovascular and overall health because of their high content of polyunsaturated fats, fiber, vitamins, and minerals and low content of saturated fat.[45]

1.1.1.2.3.5 Fruits and berries

In a large U.S. study of 34,489 postmenopausal women with 16 years of follow-up, intakes of foods rich in flavonoids associated with reduction of mortality.[47] Consumption of apples and pears, oranges, grapefruit, blueberries, red wine, celery, strawberries,

Brussels sprouts, bran, chocolate, and fruit juices decreased the risk of CHD and CVD mortality. However, after multivariate adjustment, only apples and pears, grapefruit, and red wine remained significantly inversely associated with CHD mortality, and apples and pears, red wine, strawberries, bran, and chocolate for CVD mortality. Stroke mortality was reduced by consumption of apples and pears, red wine, bran and chocolate; only intake of bran remained statistically significant after multivariate adjustment.

Chong and colleagues reviewed RCTs investigating the effects of fruit polyphenols on four risk factors of CVD: platelet function, BP, vascular function and blood lipids.[48] They concluded that there is some evidence to suggest that fruits containing relatively high concentrations of flavonols, anthocyanins and proanthocyanidins, such as pomegranate, purple grapes and berries, are more effective than other fruits investigated in reducing CVD risk factors—particularly with respect to reducing BP, inhibition of platelet aggregation and increasing endothelial-dependent vasodilatation. Flavanone-rich fruits, such as oranges and grapefruits, may have some hypocholesterolaemic effects but little impact on other risk factors. However, to date the scientific evidence of beneficial effects of fruits and berries on CVD risk factors is limited, inconsistent and inconclusive. It should also be noted that besides being rich sources of various polyphenols, fruits and berries contain a wide range of other potentially cardioprotective components including fibre, folate, antioxidant vitamins and carotenoids.

1.1.1.2.4   Conclusions

There has been a lot of scientific interest in the potential cardioprotective properties of dietary polyphenols. However, due to the chemical diversity and complexity of these phytochemicals, the task is challenging. To date, certain groups of flavonoids as well as foods and beverages rich in flavonoids have been the main focus of attention. Although an extensive amount of information has been published, the overall evidence is still insufficient—not conclusive but promising. It must be stressed that the studies that have been done to date remain relatively small and short-term and do not always measure final health outcomes. The data presented in this review suggest the following conclusions:

o   Reviews and meta-analyses of epidemiological studies suggest that dietary intake of flavonols may be associated with a reduced risk of CHD and stroke; for other flavonoids the evidence is more limited. Flavonols are common constituents of our diet (Table 1), and increasing the consumption of fruits, berries, vegetables and tea would increase the intake of flavonols (and also the intakes of flavones, flavanols, flavanones, anthocyanidins, and proanthocyanidins).

o   Human intervention studies have shown that several biomarkers of cardiovascular risk are influenced by consumption of flavonoid-rich foods. Relatively consistent

and clinically relevant effects have been observed on endothelial function, blood pressure, and platelet function.

o Epidemiological studies have demonstrated that both black and green tea consumption may be associated with reduced risk of CVD, especially stroke. Beneficial effects from RTCs are less evident. Habitual consumption of green tea may have a small favourable effect on LDL cholesterol.

o According to the recommendations of The American College of Cardiology Foundation Task Force, moderate consumption (one to two cups/day) of tea is possibly useful for cardiovascular risk reduction.[46]

o Recent meta-analyses of RCTs have provided evidence that regular consumption of flavanol-rich dark chocolate (10-100 g/day) or other cocoa products may improve endothelial function, reduce blood pressure, and inhibit platelet function. The blood pressure lowering effects as well as reduction of CVD risk are supported by epidemiological evidence but one needs to remember there are other constituents in chocolate already known to reduce blood pressure including the minerals potassium, calcium and magnesium.

o It is also important to remember that chocolate and other cocoa products are usually high in sugar, fat, and energy—100g of plain chocolate provides over 500kcal, 28g of fat (predominantly saturated fat) and a substantial amount of sugar (62.6g).[49] Therefore, questions such as the optimal dose and long-term side effects (such as weight gain and adverse metabolic changes) warrant further investigation before cocoa products can be recommended for reduction of hypertension or other cardiovascular risk factors.

o There is epidemiological evidence on the inverse association between wine consumption and cardiovascular risk, but the evidence is weaker from randomised controlled trials. Thus the association may be nothing to do with polyphenols and may reflect the impact of other factors, such as, alcohol. (See also Section 1.3.8 on alcohol and cardiovascular disease and the recommended population goals for alcohol consumption).

o It should be noted that the polyphenols proposed to be responsible for the cardioprotective effects of dark chocolate (flavanols, proanthocyanidins) or red wine (proanthocyanidins, anthocyanins, flavanols, flavonols, and cinnamic derivatives) can be obtained also from many commonly consumed fruits, berries, and vegetables (Table 1) with no adverse effects on nutrition.

o Despite the interesting evidence that is emerging in relation to polyphenols, there is not currently sufficient conclusive evidence to justify a specific public health recommendation on polyphenols in relation to cardiovascular disease prevention.

1.1.1.3 Conclusions on antioxidants

The EHN's Nutrition Expert Group concluded that there is not currently sufficient conclusive evidence to justify making any public health recommendation in relation to antioxidants. This maintains the earlier conclusion of our 2002 report.

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