Polyphenols and prevention of cardiovascular diseases

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Purpose of review

Polyphenols are the most abundant dietary antioxidants and research on their role in the prevention of degenerative diseases has developed quickly over these last few years. This paper reviews the recent studies on the prevention of cardiovascular diseases by polyphenols, focusing on human studies.

Recent findings

A large number of recent intervention studies have shown that several biomarkers of cardiovascular risk are influenced by the consumption of polyphenol-rich foods. Effects on biomarkers of oxidative stress, lipemia and inflammation appear so far unconclusive. More-consistent effects have been observed on endothelial function and haemostasis and support a reduction of risk by polyphenols in agreement with the few epidemiological studies already published. All clinical studies have used foods or beverages containing a mixture of different polyphenols and the exact nature of the most active compounds remains largely unknown. Absorption, metabolism and elimination vary widely between polyphenols. These data on bioavailability should be taken into account to improve the experimental design and the interpretation of the observed effects.

Summary

Future intervention studies should include a detailed assessment of the bioavailability of polyphenols. Beyond clinical trials carried out with polyphenol-rich foods, more studies with pure polyphenols will also be needed to establish their role in the prevention of cardiovascular diseases.

Keywords

antioxidant, bioavailability, cardiovascular diseases, clinical trials, endothelial function, flavonoids, haemostasis, lipemia, polyphenols

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Abbreviations

FMD	flow-mediated dilation
HDL	high-density lipoprotein
LDLlow-density	lipoprotein

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Introduction

Polyphenols are common constituents of the human diet, present in most foods and beverages of plant origin. They are considered to contribute to the prevention of various degenerative diseases, including cardiovascular diseases. This assumption originally came from *in vitro* studies, showing the antioxidant properties of several polyphenols and their ability to modulate the activity of various enzymes. More evidence for a protective role of polyphenols against cardiovascular diseases arose from a number of epidemiological studies, clinical trials, experiments on animal models and mechanistic studies. However, data are still often contradictory. Two reasons in particular can be inferred. The first one is that the polyphenol family encompasses very diverse compounds with highly different bioavailabilities. Hence the results obtained for one polyphenol cannot be generalized to others. The second point is that polyphenols are now known to be largely metabolized in the body and native compounds most often tested in *in vitro* studies are virtually absent in the tissues. The relevance of these *in vitro* studies with respect to the reduction of cardiovascular risk must therefore be questioned.

This paper reviews the recent studies on the prevention of cardiovascular diseases by polyphenols, focusing on *in vivo* studies. Results are discussed in the light of our knowledge on bioavailability.

Polyphenols in animal models of atherosclerosis

The effect of polyphenol-rich foods or polyphenol extracts on the development of atherosclerotic lesions has been studied in apolipoprotein $E^{-/-}$ mice and hamsters. A reduction of the lesion was observed upon consumption of a tea extract [1], green and black tea [2], pomegranate juice [3], grape extracts [4], red wine, dealcoholized wine and wine polyphenols [4,5,6•]. The atheroprotective effect of dietary soy isoflavones in apolipoprotein $E^{-/-}$ mice was shown to require the presence of estrogen receptor-α and was unrelated to plasma cholesterol [7••]. Only a few studies have evaluated and demonstrated an antiatherosclerotic effect of pure polyphenols (for example quercetin and catechin) [8]. The reduction of atherosclerotic lesion by polyphenol intake is not necessarily related to the modifications in the oxidative stress biomarkers and lipid parameters. This suggests that other mechanisms, for example the anti-inflammatory action of polyphenols, could be involved. These animal experiments suggest a protective

effect of polyphenols but they cannot be extrapolated directly to humans. In particular, the doses applied are often higher than those to which humans are commonly exposed with their diet.

Polyphenols and cardiovascular diseases in epidemiological studies

Various epidemiological studies have shown an inverse association between the consumption of polyphenols or polyphenol-rich foods and the risk of cardiovascular diseases. A meta-analysis including seven case-control and 10 cohort studies suggested a reduction of the risk of myocardial infarction of 11% upon consumption of three cups of tea per day [9]. One more recent prospective study and three cross-sectional studies tend to confirm these protective effects of tea against cardiovascular risk [10–13].

A moderate wine consumption has consistently been associated with a reduced risk of cardiovascular diseases. However, the respective contribution of alcohol and polyphenols to these effects was not well clarified. A meta-analysis based on 26 cohort and case-control studies showed that light to moderate intake of both wine and beer was associated with a reduction of vascular risk [14•]. The reduction was more pronounced for wine, possibly due to its higher polyphenol content. Two recent cohort studies in which wine was compared to beer and spirits or red wine compared to white wine also suggested that wine, and more particularly red wine, which is about 10 times richer in polyphenols than white wine, were more protective than beer or spirits [15•]. An inverse association between ischemic stroke and wine but not beer and spirit consumption was also observed in a prospective study [16].

Correlation between the intake of flavonols, flavones, catechins and lignans and the risk of coronary heart diseases and stroke have been looked for [17]. Out of 18 prospective studies on coronary heart diseases or stroke, 10 showed an inverse association between intake and risk, and the other no association. A cross-sectional study showed a reduction of cardiovascular risk in US postmenopausal women consuming the largest amounts of isoflavones [18]. More studies are needed, in particular on the more abundant anthocyanins, proanthocyanidins and phenolic acids polyphenol classes. They have not been studied so far due to the lack of appropriate food-composition tables or their too-recent publication.

Clinical studies

Altogether, animal experiments and epidemiological studies suggest a protective role of polyphenols. Several mechanisms of action have been proposed and explored in clinical studies (Table 1). Most intervention studies in humans have been carried out with polyphenol-rich foods and in particular tea, wine, cocoa or soy. These foods and beverages do not only contain polyphenols and only the properly controlled studies are considered here (soy with or without isoflavones, tea versus caffeine, wine versus alcohol).

Table 1. Proposed mechanisms by which polyphenols may reduce risk for cardiovascular diseases

Antioxidants
Scavenge reactive oxygen and nitrogen species
Chelate redox-active transition metal ions
Spare and interact with other antioxidants
Inhibition of the redox-sensitive transcription factors
Inhibition of pro-oxidant enzymes
Induction of antioxidant enzymes
Growth of atherosclerotic plaque
Reduce adhesion molecule expression
Anti-inflammatory
Reduce the capacity of macrophages to oxidatively modify LDL
Platelet function and haemostasis
Inhibit platelet aggregation
Blood pressure and vascular reactivity
Promote nitric oxide-induced endothelial relaxation
Plasma lipids and lipoproteins
Reduce plasma cholesterol and triglycerides

LDL, low-density lipoprotein.

Antioxidant effects of polyphenols

Antioxidant effects of polyphenols have been reviewed elsewhere [19,20]. The most recent human intervention trials are discussed here (Table 2). When the source of polyphenols was consumed for 1–12 weeks, an increase in the plasma antioxidant capacity or in the concentration of antioxidants such as vitamin E, vitamin C, β-carotene and uric acid was observed in some studies, whereas no change were observed in other studies. The same contrasting results were obtained for lipid-oxidation products in plasma and low-density lipoprotein (LDL) oxidizability measured *ex vivo*. These discrepancies could be explained by kinetic effects, polyphenols being largely eliminated in the 2 to 8 hours following ingestion [21], and therefore virtually absent in fasting plasma samples collected after a night washout.

In acute studies, polyphenols are ingested alone or with a meal and blood samples are collected in the few hours following ingestion. Coffee, red wine and grape-seed extract all increased the postprandial plasma antioxidant capacity (Table 2). Olive oil showed no effect, probably due to the phenol intake being too low. A decrease of the level of plasmatic F_2-isoprostane, a marker of lipid oxidation, was also observed after ingestion of a cocoa drink [22•]. This last result is important as it shows a diminution of lipid damage shortly after the consumption of polyphenols. In these acute studies, the maximum plasma antioxidant capacity is usually reached 1–4 h after ingestion of the polyphenol source. This delay is similar to the time needed to reach the maximal concentration in plasma for most antioxidant polyphenols [23•].

Table 2. Intervention studies with polyphenols and effects oxidative stress biomarkers

Food	Food quantity (polyphenol intake)	Control	Subjets (number)	Duration of intervention	Biomarkers affected	Biomarkers not significantly affected	Reference
Chronic studies							
Black tea+fried onions	300 ml/day+150 g/day (131 mg flavonoids/day)	Isocaloric low-flavonoid diet	Healthy subjects (32)	1 week		Plasma F_2-isoprostane, LDL-MDA, vitamin C, vitamin E, β-carotene, iron	[27]
Green or black tea	1000 ml/day	Caffeine solution	Healthy subjects (13)	1–4 weeks		Urinary F_2-isoprostane	[28]
Black tea	5 servings/day	Caffeinated drink	Hypercholesterolemic patients (15)	3 weeks		Plasma AOC, oxidized LDL, LDL-TBARS, F_2-isoprostanes; urinary 8-OHdG	[29]
Red wine	250 ml/day	White wine, champagne	Healthy subjects (18)	3 weeks	Plasma AOC ↑	Plasma TBARS, uric acid, vitamin E	[30]
Dealcoholized red wine	375 ml	White wine, red wine	Smokers (18)	2 weeks	Plasma F_2-isoprostane ↓, urinary F_2-isoprostane ↓, serum γ-GT ↓, serum uric acid ↓, β-carotene ↑	Plasma vitamin C, vitamin E	[31]
Extra-virgin olive oil	20 g/day	Regular olive oil	Hyperlipidemic patients (10)	6 weeks	LDL oxidizability ↓	LDL-vitamin E	[32]
Virgin olive oil	25 ml/day	Refined olive oil	Healthy subjects (30)	3 weeks	Oxidized LDL ↓, LDL oxidizability ↑		[33]
High-phenol olive oil	70 g/day (18 mg phenols/day)	Low-phenol olive oil	Smokers (25)	3 weeks		Plasma AOC, MDA, lipid hydroperoxides, protein carbonyl	[34]
Cocoa powder+dark chocolate	22 g/day+16 g/day (466 mg proanthocyanidins/day)	No cocoa, no chocolate	Healthy subjects (23)	4 weeks	Serum AOC ↑, LDL oxidizability ↓		[35]
Cocoa extract	(234 mg flavanols/day)	Placebo	Healthy subjects (32)	4 weeks	Plasma vitamin C ↑, uric acid ↑	Plasma AOC, MDA, vitamin C, vitamin E, F_2-isoprostanes	[36]
Bilberries, lingonberries+ black currants	100 g/day	No berries	Healthy subjects (20), 60 years old	8 weeks	Serum vitamin C ↑	Serum AOC, vitamin E; LDL oxidizability	[37]
Acute studies							
Red wine	250 ml	No wine	Healthy subjects (15)	<1 day	Plasma AOC ↑, uric acid ↑		[38]
Red wine	300 ml	No wine	Healthy subjects (3)	<1 day	Plasma AOC ↑		[30]
Red wine	400 ml	Hydroalc. sol.	Healthy subjects (6)	<1 day	Plasma AOC ↑, vitamin E ↑, protein thiols ↑	Plasma vitamin C, uric acid	[39]
Grape-seed extract	300 mg	No grape seed extract	Healthy subjects (8)	<1 day	Plasma AOC ↑, lipid hydroperoxyde ↓	LDL oxidizability	[40]
Virgin olive oil	50 ml	Baseline	Healthy subjects (16)	<1 day	LDL oxidizability ↓	Plasma vitamin E	[41]
Fortified olive oil	47 g (31 mg phenols)	Olive oil with no phenols	Healthy subjects (12)	<1 day		LDL oxidizability	[42]
Cocoa drink	100 ml (187 mg flavanols)	Low-flavonoid cocoa drink	Healthy subjects (20)	<1 day	Plasma F_2-isoprostane ↓	Plasma AOC, MDA, vitamin C, vitamin E	[22•]

In the acute studies in the second half of the table, the source of polyphenols is ingested together with bread, breakfast or a meal. AOC, antioxidant capacity; γ-GT, γ-glutamyl transpeptidase; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; LDL, low-density lipoprotein; MDA, malondialdehyde; TBARS, thiobarbituric acid-reactive substances.

Polyphenols thus affect transiently some markers of oxidative stress. However, the link between these effects and the risk of cardiovascular diseases remains to be established. A direct scavenging of free radicals by polyphenols, as often suggested, may not be the key mechanism explaining their effects on oxidative stress biomarkers and cardiovascular risk factors. Polyphenol concentrations in plasma are low (usually 1 μM or less) and much lower than those of uric acid, an endogenous antioxidant (150–450 μM). The extensive conjugation of polyphenols to glucuronic acid and sulfate groups in the tissues may markedly decrease their antioxidant capacity, as described for quercetin and isoflavones [24,25•]. Red-wine polyphenols were shown to limit the development of atherosclerotic lesions in apolipoprotein E-deficient mice, independently of the lipid peroxidation [6•,26•]. A better knowledge of the mechanisms involved in cell-mediated modulation of the redox status by polyphenol exposure is needed to better evaluate the significance of these antioxidant effects in the prevention of cardiovascular diseases.

Polyphenols and lipemia

Out of 12 recent intervention studies with different polyphenol sources lasting 1–13 weeks, six showed no effects on lipids in plasma (Table 3). In the other six studies, polyphenol ingestion resulted in a decrease of the level of total cholesterol, LDL-Cholesterol, apolipoprotein B or lipoprotein (a), or an increase of the level of high-density lipoprotein (HDL)-cholesterol and apolipoprotein A-I. Such an improvement in the lipid parameters were observed after ingestion of polyphenols from tea, virgin olive oil, cocoa, soybean or red clover. Both normo- and hypercholesterolemic subjects showed improvement or no change in the lipid parameters.

Six trials were carried out with either soy proteins differing in their isoflavone contents or with isoflavone extracted from red clover against placebo (Table 3). Three of these studies showed an improvement of some lipid parameters. In a recent meta-analysis of 10 human trials, soy proteins were shown to effectively reduce LDL-Cholesterol and increase HDL-Cholesterol but the extent of these effects could not be related to the dose of isoflavones ingested together with the proteins [43••]. In ovariectomized monkeys, the consumption of soy but not of isolated isoflavone reduced cholesterolemia [44]. More studies with isolated isoflavones are needed to establish the hypolipidemic effects of isoflavones.

Polyphenols and endothelial function

Dysfunction of the vascular endothelial cells can be measured by flow-mediated dilation (FMD) of the brachial artery. The large majority of studies testing red wine [51–53], grape juice [54], black tea [55,56], soy [57,58] or cocoa [59] have shown a net beneficial effect on FMD.

Table 3. Intervention studies with polyphenols and effects on plasma lipids

Food	Amount of food ingested (polyphenol intake)	Control	Subjects (number)	Duration of intervention	Lipid parameters affected	Lipid parameters not affected	Reference
Black tea+fried onions	300 ml/day+150 g/day (131 mg flavonoids/day)	Isocaloric low-flavonoid diet	Healthy subjects (32)	1 week		Total fat, SFAs, PUFAs, MUFAs, C	[27]
Black tea	5 servings/day	Caffeinated drink	Hypercholesterolemic subjects (15)	3 weeks	C ↓, LDL-C ↓, apoB ↓, lipoprotein (a) ↓		[29]
Red wine	250 ml/day	White wine, champagne	Healthy subjects (18)	3 weeks		TG, C, PL, apoA-I, apoB	[30]
Dealcoholized red wine	375 ml	White wine, red wine	Smokers (18)	2 weeks		TG, C, LDL-C, HDL-C	[31]
Virgin olive oil	25 ml/day	Refined olive oil	Healthy subjects (30)	3 weeks	HDL-C ↑	TG, C, LDL-C	[33]
Cocoa powder+dark chocolate	22 g/day+16 g/day (466 mg proanthocyanidins/day)	No cocoa, no chocolate	Healthy subjects (23)	4 weeks	HDL-C ↑	LDL/HDL	[35]
Isoflavone-rich soy protein	63 g/day (123 mg isoflavones/day)	Isoflavone-poor soy protein	Hypercholesterolemic (36)	6 weeks		LDL size, C concentration in LDL	[45]
Isoflavone-rich soy protein	25 g/day (50 mg isoflavones/day)	Isoflavone-poor soy protein	Hypercholesterolemic (42)	6 weeks		TG, C, LDL-C, HDL-C, apoB, apoA-I	[46]
Isoflavone-rich soy protein	(56 mg isoflavones/day)	Isoflavone-poor soy protein	Healthy subjects (22)	17 days	HDL-C ↑, apoA-I ↑	TG, C, LDL-C, apoA-II, apoB	[47]
Isoflavone-rich soy protein	(132 mg isoflavones/day)	Isoflavone-poor soy protein	Healthy women (18)	13 weeks	LDL-C ↓	TG, C, HDL-C, apoA-I, apoB, lipoprotein (a)	[48]
Red clover extract	(86 mg isoflavones/day)	Placebo	Premenopausal women (12)	12 weeks		TG, C, LDL-C, HDL-C, lipoprotein (a)	[49]
Biochanin-rich red clover extract	(40 mg isoflavones/day)	Placebo	Healthy subjects (40)	6 weeks	LDL-C ↓	TG, C, HDL-C	[50]

apo, apolipoprotein; C, cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MUFA, mono-unsaturated fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; TG, triglycerides.

These effects were observed in both healthy adults and coronary patients.

The positive effect of wine should be attributed to polyphenols rather than to alcohol. Dealcoholized red wine showed similar effect compared to whole red wine, whereas vodka did not affect the FMD of healthy volunteers [51,52]. Purple grape juice was also reported to improve the FMD in patients with coronary heart disease [54]. On the other hand, Whelan *et al.* [53] showed that in spite of a 6-fold lower polyphenol content, white wine equally improved the impaired endothelium function observed in adults with coronary heart disease, compared to red wine. If this result is confirmed, it implies that the active molecules might not be proanthocyanidins or anthocyanins, which are characteristic of red wine.

Consumption of black tea has also been shown to improve FMD in 50 patients with coronary heart disease [56]. After acute or long-term (30-day) tea intake, FMD increased to reach values comparable to that of healthy volunteers. Improvement of FMD upon long-term consumption of black tea was also observed in subjects with mild hyperlipemia [60]. A preliminary study on 10 young healthy volunteers suggested that black tea may also improve coronary endothelial function, as measured by a non-invasive transthoracic Doppler echocardiography method [61].

Cuevas *et al.* [58] observed a significant improvement of FMD in postmenopausal women having mild hypercholesterolemia with a short (4-week) supplementation with soy isolate protein providing isoflavones at 80 mg/day. Two recent double-blind studies merit particular attention because they used pure genistein [57,62]. Consumption of a genistein supplement (54 mg/day) for 6 or 12 months improved FMD in healthy postmenopausal women compared to placebo, increased levels of nitrites/nitrates and decreased plasma endothelin-1 levels. Steinberg *et al.* [63] compared the effect of isolated soy proteins with high or low isoflavone contents in healthy postmenopausal women. After 6 weeks, a non-significant trend for increased vasodilatory response was observed in the high isoflavone group compared to the low-isoflavone and control groups.

Polyphenols and inflammation

Polyphenols have a variety of anti-inflammatory and immune-modulating effects that may be of relevance to atherosclerosis. Even if *in vitro* studies have extensively provided arguments for anti-inflammatory effects of various polyphenols, human studies provide only a few tangible results. Supplementation with black tea, green tea, green tea polyphenol isolate, red wine, grape juice and cocoa affected only a few blood parameters related to inflammation, such as circulating adhesion molecules, cytokines and mediators [35,64•,65–67]. Soy isoflavone supplementation for 6 weeks did not significantly affect concentrations of circulating adhesion molecules in postmenopausal women [63]. However, reduction of circulating vascular cell-adhesion molecule (VCAM)-1 concentrations was observed after 6-week administration of formononetin (daidzein precursor)-enriched isoflavones [68]. The limited anti-inflammatory effects of polyphenols observed in these human studies undoubtedly result from the fact that they were carried out on healthy subjects and rarely studied immune cell functions.

Polyphenols and haemostasis

Supplementation of the diet of experimental animals with polyphenols is known to increase bleeding time and to reduce *ex vivo* platelet aggregation [20]. Similarly, different clinical trials carried out on healthy subjects have shown an improvement of haemostasis after acute or chronic (2–4 weeks) consumption of red wine, tea or cocoa powder. With one exception [69], all recent studies run with red wine, black tea or cocoa against proper controls showed an inhibition of *ex vivo* collagen- or ADP-induced platelet aggregation [36,70–72].

Bioavailability and bioefficacy of polyphenols

Bioavailability differs greatly between polyphenols. Some polyphenols like soy isoflavones are well absorbed through the gut barrier whereas others such as proanthocyanidins, abundant in wine or cocoa, or thearubignins, the main polyphenols in black tea, are hardly absorbed [21]. Furthermore, each polyphenol may be present in foods in different forms, which can affect the intestinal absorption. Quercetin glucosides from onions are much more efficiently absorbed than other quercetin glycosides such as rutin present in tea or apple [73]. The total polyphenol content of tested food sources, generally stated in clinical trials, should be thus completed by a precise description of their polyphenol composition. This may avoid misleading interpretations. For example, effects of proanthocyanidin-rich extracts are systematically attributed to the major polymers whereas minor compounds may be better absorbed and more efficient.

Determination of plasma concentrations or urinary excretion of the polyphenol metabolites may facilitate the interpretation of clinical studies. High inter-individual variability has been frequently reported in the efficiency of intestinal absorption and metabolism, especially where the gut microflora are involved. For example, Meyer *et al.* [74•] recently reported that only the volunteers who were able to convert daidzein into the microbial metabolite equol (35% of the subjects), gained benefit from consumption of soy products with significant reductions of cholesterol, LDL-Cholesterol, plasma triglycerides and lipoprotein (a). No significant effect was observed when the whole group of subjects was considered.

The peak of absorption and the elimination rate have also been shown to differ markedly among polyphenols. Catechins which are rapidly absorbed and eliminated from plasma (within 4 h) should have a more transient impact than other compounds such as isoflavones, which have a higher life span in the arteries. This kinetic data, now known for most polyphenols, could usefully be correlated with the observed effects.

The doses applied in animal experiments or in *in vitro* studies often exceed those to which human tissues may be exposed. According to the maximum concentrations obtained in human plasma after nutritional intakes [21], all the effects observed with doses above 2 μM are unlikely to occur *in vivo*. Furthermore, polyphenols are present in plasma as glucuronide and sulfate ester derivatives. Biological activities of the conjugated metabolites are known to be influenced by conjugation. For example the affinities of daidzein and genistein for estrogen receptors are 10 and 40 times higher than those of their respective glucuronides [75]. It is thus crucial that all studies on the mechanisms of action of polyphenols, using very sophisticated methods but non-physiological compounds, can be complemented by studies using the metabolites actually found in the body. Non-absorbed polyphenols such as proanthocyanidins should never be tested in cultured cells or isolated organs since they have no chances of reaching the inner tissue level as such. Unfortunately, very few studies used relevant metabolites and doses so that our knowledge of the mechanisms of action of polyphenols are still very limited [76••].

Conclusion

Several biomarkers of cardiovascular risk are influenced by the consumption of polyphenol-rich foods. Effects on biomarkers of oxidative stress, lipemia and inflammation appear unconclusive. More-consistent effects have been observed on endothelial function and haemostasis and support a reduction of risk by polyphenols in agreement with the few epidemiological studies so far published.

All clinical studies have used foods or beverages containing a mixture of different polyphenols and the exact nature of the most active polyphenols remains largely unknown. Some polyphenols are highly bioavailable whereas others are hardly absorbed through the gut barrier. Until we know more about the activity of pure polyphenols in humans and targets of action of circulating polyphenols, it remains difficult to predict their protective efficacy against cardiovascular diseases. The lack of effects of polyphenols in some studies could be explained by rapid elimination of polyphenols once absorbed. Indeed, their effects are often more easily seen in the postprandial stages rather than in fasting conditions as often done. Together with the nature of the most active polyphenols, optimal doses to prevent cardiovascular diseases need to be determined to formulate reliable nutritional recommendations.

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