Polyphenols for Cholesterol Management

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Introduction

Coronary heart disease (CHD) is still a major health problem in many countries. It is well known that an increased serum concentration of low-density lipoprotein (LDL) cholesterol is a powerful risk factor for CHD. Epidemiological studies also suggest that high serum concentrations of high-density lipoprotein (HDL) cholesterol may protect against CHD, although results from recent intervention studies with drugs do not support a causal relationship between HDL and CHD risk. Traditionally, reducing saturated and *trans*-fatty acids intake has been the cornerstone in the management of dyslipidemia. However, in recent years, many other dietary components have attracted much interest. This has led, with different degrees of success, to the search and testing of specific foods and food components that may help to improve the serum lipoprotein profile. However, evidence is emerging that diet also affects other risk markers for CHD, such as endothelial function, blood pressure, inflammation, and platelet function.

This chapter reviews the role of polyphenols in dyslipidemia management. In addition, the relation between polyphenols and endothelial function is briefly addressed. Focus is on flavonoids from cocoa and the stilbene *trans*-resveratrol, as flavonoids from cocoa have been extensively studied in the past, while recent studies have ascribed possible cardioprotective effects to *trans*-resveratrol. Metabolism of these polyphenols is discussed as well.

History

Polyphenols are metabolites produced by higher plants and are important for pigmentation, reproduction, growth, and protection against pathogens. It has for long been recognized that foods rich in polyphenols may possess healthy properties, such as anti-oxidative, antibacterial, antihypertensive and anti-inflammatory effects. In humans, the potential beneficial effect of polyphenols on cardiovascular disease has generated a great amount of scientific interest during the past decades. Hertog et al. were among the first to suggest a strong protective effect of flavonoids, a subgroup of polyphenols found in tea, onions, and apples, on CHD-related deaths [1]. The French paradox, the observation that the incidence of CHD is low in the French population, despite a high dietary intake of saturated fat, also supported the notion that polyphenols may have beneficial effects on cardiovascular disease. This association has been attributed to increased intakes of resveratrol, a polyphenol found in foods such as red wine and grapes. This French paradox has formed the basis for numerous papers on the relation between polyphenol intake, and, more specifically, polyphenols from grapes, and

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cardiovascular health. Also studies in the Kuna Indians of the San Blas Islands of Panama supported the idea that polyphenols may improve cardiovascular health. This population consumed on average three 10-ounce cups of cocoa beverage each day. The prevalence of hypertension among Kuna Indians was very low (2.2%), blood pressure did not increase with age, and a lower rate of myocardial infarction and stroke was found as compared to mainland Panamanians [2]. In another study, an inverse relation was found between cocoa intake and cardiovascular mortality in men aged 65–84 years from Zutphen, a city in the Netherlands [3]. Men in the highest tertile of cocoa intake consumed on average 4.2 g cocoa daily, which is equal to a daily intake of 10 g dark chocolate, and had a 50% lower risk than men in the lowest tertile, who did not consume cocoa at all. An inverse relation between cocoa intake and systolic and diastolic blood pressure was also found, but this was not the main explanation for the observed lower cardiovascular risk in this group. In another epidemiologic study in survivors (45–70 years of age) of an acute myocardial infarction, an inverse association was found between chocolate consumption and cardiac mortality [4]. These examples have certainly contributed to the immense growth of scientific interest in the relation between polyphenol intake, dyslipidemias, and cardiovascular health during the past decades.

Chemical Structure

Each structure that includes several hydroxyl groups on aromatic rings can be defined as a polyphenol. Polyphenolic compounds can be divided into distinct groups based on the number of phenol rings and by the structural elements attached to these rings. In this way, four main polyphenol groups have been identified: (1) phenolic acids, (2) flavonoids, (3) stilbenes, and (4) lignans (Fig. 22.1).

Several products rich in these compounds and their estimated daily intakes are listed in Table 22.1 [5].

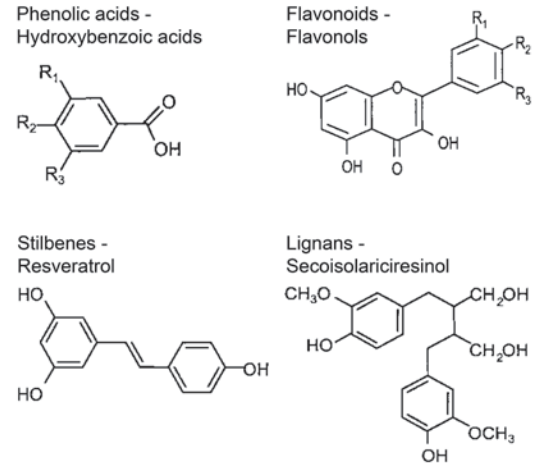

Fig. 22.1 Chemical structure of the four main polyphenolic compounds. Hydroxybenzoic acids is drawn as an example of a subgroup of phenolic acids, the flavonols as the subgroup of the flavonoids, resveratrol belongs to the stilbenes, and secoisolariciresinol is an example of the lignans

Phenolic Acids

Phenolic acids can be classified into derivatives of benzoic acid or derivatives of cinnamic acid. Hydroxybenzoic acids are found in only a few plants eaten by humans. Caffeic acid is the major representative of a hydroxycinnamic acid and occurs in foods mainly as an ester with chlorogenic acid. Coffee consumers have an intake of 0.5–1 g of chlorogenic acid. Hydroxycinnamic acid is also found in amounts varying from 0.5 to 2 g/kg fresh weight, mainly in the skin of mature fruits. Wheat grain contains on average 0.8–2.0 g of ferulic acid—also a hydroxycinnamic acid—per kilogram dry weight. Phenolic acids are also present in rice, wheat, and oat flour in quantities of 70–90 mg/kg fresh weight, whereas corn flour may contain up to 300 mg/kg fresh weight.

Flavonoids

The flavonoids are divided into six subclasses, depending on the oxidation status and saturation of the heterocycle group that is part of the

Table 22.1 Products rich in polyphenols and their estimated daily intakes. (Based on ref. [5])

Main compound	Subgroup	Products rich in this compound	Estimated daily intake (mg/day)
Phenolic acids	Benzoic acids	Red fruits, black radish, onions, tea leaves	
	Cinnamic acids	Grains and seeds, coffee, apples, blueberries, cherries, kiwis, and plums	
Flavonoids	Flavonols	Tea, onions, curly kale, leek, broccoli, tomatoes	13
	Flavones	Parsley, chamomile tea, celery, tangerines	1.6
	Isoflavones	Soybeans, soy milk, tofu, tempeh	USA/Netherlands: 1.2 Asia: 25–50
	Flavanones	Grapefruits, oranges, lemons, tomatoes, mint	14.4
	Anthocyanidins	Cranberries, blackberries, eggplant, cabbage, beans, onions, radishes	3.1
	Flavanols	Tea leaves, cocoa beans, dark chocolate, apples, blueberries, grapes, apricots	156
Stilbenes		Red wine, black grapes	
Lignans		Cereals, berries, vegetables, flaxseed	

flavonoid skeletal structure: (1) flavonols, (2) flavones, (3) isoflavones, (4) flavanones, (5) anthocyanidins, and (6) flavanols. These subclasses share a common structure that consists of two aromatic rings, bound by three carbon atoms that form an oxygenated heterocycle. Flavonoids naturally occur mostly as glycosides rather than as aglycones.

Flavonol The most widely known flavonols are quercetin and kaempferol. Flavonols mainly accumulate in the skin and leaves of vegetables, due to the fact that the biosynthesis of flavonols is stimulated by light. Therefore, the flavonol content of the same species can be very different; cherry tomatoes for instance have a higher flavonol content than regular tomatoes, caused by the different ratios of skin to whole fruit.

Flavones are present in herbs such as parsley, but also chamomile tea, celery, tangerines, and some other citrus fruits contain flavones.

Isoflavones Soybeans are a main source of isoflavones, whereas its content in other beans and peas like kidney beans, black beans, and chickpeas is low. The level of the isoflavones genistein and daidzein in soybeans varies and depends on the geographic zone where the beans are cultivated. Growing conditions and processing also influence the isoflavone content of soybeans, which varies between 580 and 3800 mg/kg fresh weight. In soy milk, this content lies between 30 and 175 mg/L. The intake of isoflavones differs widely around the world. In Asian countries, more soy products are consumed compared to Western countries, which is reflected in a higher estimated daily intake, as indicated in Table 22.1.

Flavanones are mainly found in the solid parts and the membranes separating the segments of citrus fruits. Therefore, a five times higher flavanone content is found in whole fruits compared to juice.

Anthocyanidin is present in fruits and vegetables that have red, blue, and purple pigments. Black currants and blackberries contain about 2–4 g of anthocyanidin per kilogram fresh weight. The amount of anthocyanidins in a food product relates to its color intensity. Furthermore, anthocyanidin is found in fruit skin and its content becomes higher as a fruit ripens.

Flavanol/flavan-3-ol The main flavanols are catechin and epicatechin, which are present in cocoa beans, dark chocolate, and green tea. A cup of green tea can provide up to 200 mg catechins. Several processes and conditions affect

the flavanol content of cocoa, such as the variety and country of origin. Also the fermentation and roasting process, that has been applied, determines the flavanol content of cocoa beans.

Stilbenes

The most widely known and studied stilbene is *trans*-resveratrol, which is found in low quantities in red wine and in the skin of black grapes. The average *trans*-resveratrol content of red wines is 1.9 mg/L, varying from nondetectable levels up to 14.3 mg/L. *Trans*-resveratrol is thought to play a role in explaining the "French paradox."

Lignans

A rich dietary source of lignans is flaxseed (>300 mg/100 g). Other sources are cereals, grains, fruits, and certain vegetables. Lignan content of grain products varies from 7 to 764 mg/100 g [6].

Effects of Polyphenols on Lipid and Lipoprotein Metabolism

In the following paragraphs, effects of chocolate and cocoa on lipid and lipoprotein metabolism are reviewed. Chocolate and cocoa are main sources of flavanols, such as epicatechin. In addition, attention will be paid to the stilbene resveratrol, a polyphenol with supposed cardioprotective effects. Finally, the effects of tea catechins and soy isoflavones are discussed.

Flavonoids

In a recent meta-analysis, effects of flavanol-rich cocoa products or dark chocolate on the serum lipid profile were summarized [7]. Ten controlled intervention studies were identified, including 320 subjects. Daily flavanol intake between the studies varied widely (88–963 mg). Compared with control, it was estimated that consumption of the cocoa products or dark chocolate for 2 weeks significantly decreased LDL cholesterol by −0.15 mmol/L (95% confidence interval, CI: −0.27, −0.03 mmol/L). No significant effect on LDL cholesterol was observed in longer-term studies (4–12 weeks). Total cholesterol concentrations were significantly reduced by 0.16 mmol/L (95% CI: −0.30, −0.02 mmol/L). In both short-term and longer-term studies, no significant effects on serum HDL cholesterol and triglyceride levels were observed (Fig. 22.2).

A possible dose–effect relationship was examined by dividing the studies based on the intake of flavanols (either <500 mg or >500 mg flavanol daily). Surprisingly, a daily flavanol

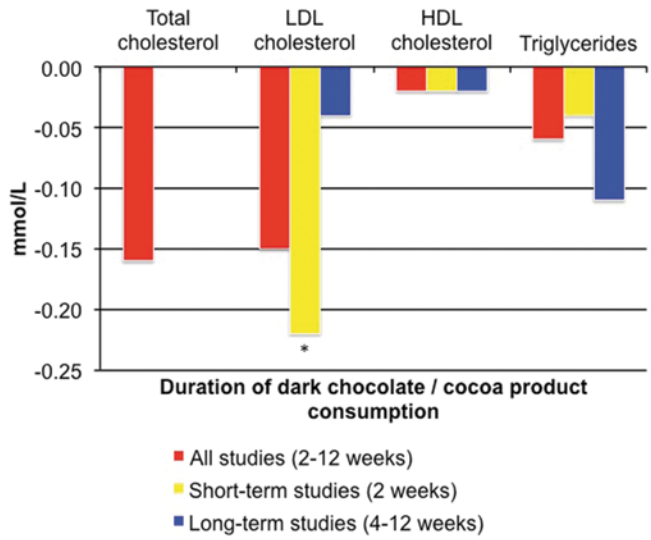

Fig. 22.2 Effects of dark chocolate/cocoa product consumption on serum total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride concentrations. A statistically significant (*) reduction in serum LDL cholesterol was found in short-term studies, while other lipids and lipoproteins did not change. In longer-term (4–12 weeks) studies, effects did not reach statistical significance. Effects of study duration on serum total cholesterol levels were not reported. *LDL* low-density lipoprotein, *HDL* high-density lipoprotein. (Results are from ref. [7])

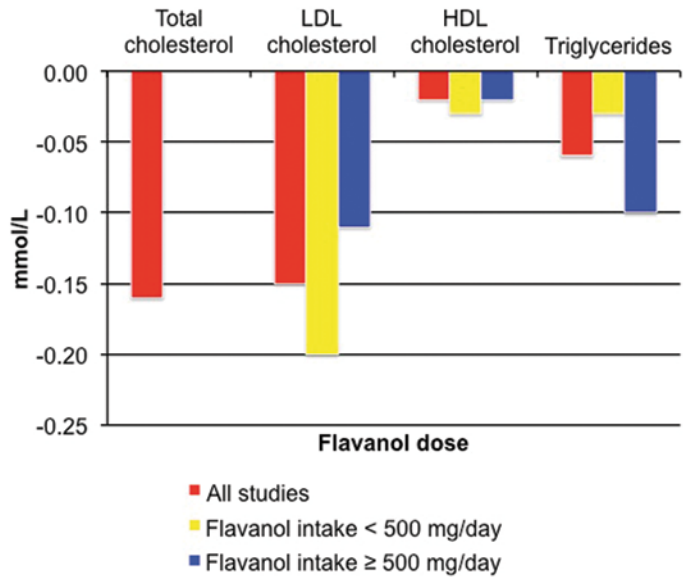

Fig. 22.3 Effects of flavanol intake on serum total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride concentrations. Differences in effects between the two levels of intakes did not reach statistical significance. Effects of different intake level on serum total cholesterol levels were not reported. *LDL* low-density lipoprotein, *HDL* high-density lipoprotein. (Results are from ref. [7])

intake of < 500 mg appeared to lower LDL cholesterol more efficiently than intakes ≥ 500 mg (−0.20 mmol/L vs. −0.11 mmol/L, respectively), but the differences between these effects were not statistically significant (Fig. 22.3).

A comparable LDL cholesterol-lowering effect of −0.07 mmol/L (95% CI: −0.14, 0.00 mmol/L) was found in a more recent meta-analysis that included 21 studies and 986 subjects [8]. In studies that lasted maximally 3 weeks, a mean effect on serum LDL cholesterol of −0.22 mmol/L was observed. However, no effect was observed in longer-term studies (3–26 weeks), which raises questions on the clinical usefulness of these observations. Without considering study duration, HDL cholesterol was increased by 0.03 mmol/L (95% CI: 0.00, 0.06 mmol/L). Beneficial effects on HDL cholesterol were more pronounced in longer-term trials (> 3–26 weeks; Fig. 22.4). In this meta-analysis, the effects of epicatechin (and not of total flavanols) were also examined, but no significant effects on serum total, LDL, and HDL cholesterol were found.

Human studies have also shown an increased in vitro resistance of LDL to oxidation after intake of polyphenol-rich fractions from cocoa [9, 10]. Furthermore, polyphenol-rich cocoa fractions increased fecal cholesterol excretion in rats [11].

Trans-resveratrol

The most widely known stilbene, resveratrol, is thought to exert several cardioprotective effects, among others the modulation of lipid and lipoprotein metabolism. Indeed, many in vitro or animal studies suggest that resveratrol has positive effects on proteins that are involved in reverse cholesterol transport. These proteins include peroxisome proliferator-activated receptor gamma (PPARγ), liver X receptor alpha (LXRα), 27-hydroxylase, and ATP-binding cassette A1 (ABCA1) [12], which are involved in cholesterol efflux. In hamsters, resveratrol may in vitro protect LDL against oxidation, downregulate 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, and increase the apolipoprotein A-I (apoA1) to apoB ratio [13]. Furthermore, resveratrol might enhance cholesterol efflux by preventing HDL particles from oxidation (Fig. 22.5) [14]. The possible anti-atherosclerotic effect of resveratrol might also be related to lower a reduced transfer of cholesteryl esters from HDL to very-low-density lipoprotein (VLDL) and LDL through an inhibitory effect on cholesteryl ester transfer protein (CETP) activity [15].

In humans, a recent meta-analysis using seven studies showed no statistically significant

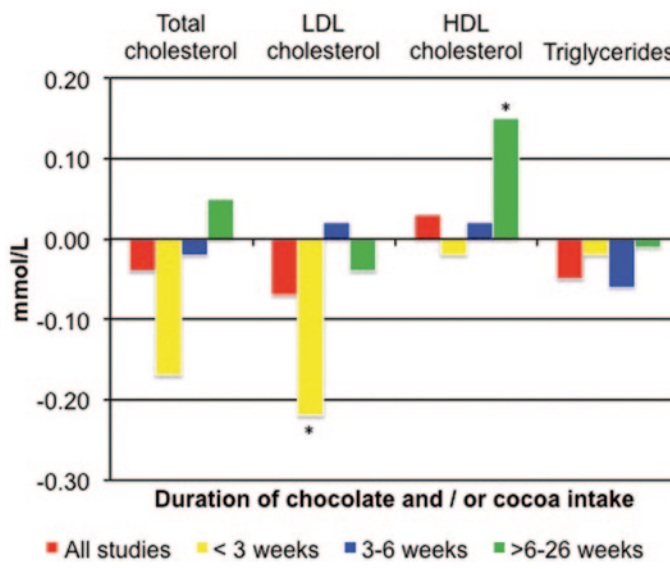

Fig. 22.4 Effect of duration of chocolate and/or cocoa intake on serum total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride concentrations. Statistically, significant differences between the groups with different study durations are indicated with an asterisk. *LDL* low-density lipoprotein, *HDL* high-density lipoprotein. (Results are from ref. [8])

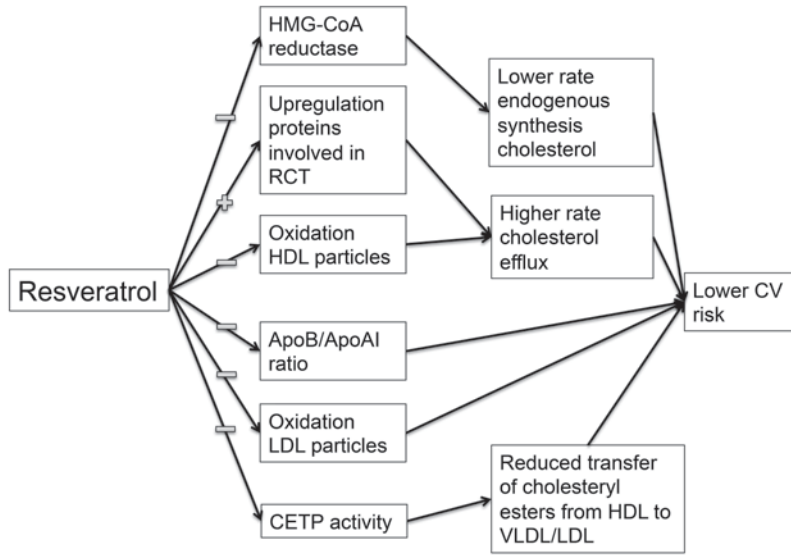

Fig. 22.5 Proposed effects of resveratrol on cholesterol and apolipoprotein metabolism and cardiovascular risk as seen in animals. + stimulating effect, − inhibiting effect, *RCT* reverse cholesterol transport, *HDL* high-density lipoprotein, ApoB apolipoprotein B100, ApoAI apolipoprotein AI, *LDL* low-density lipoprotein, *CETP* cholesteryl ester transfer protein, *VLDL* very-low-density lipoprotein, *CV* cardiovascular

effect of the intake of purified *trans*-resveratrol and extracts containing resveratrol on serum total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride concentrations [16]. Results were not related to the dose of resveratrol used, study duration, or cardiovascular risk profile of the participants. However, the number of studies may have been too few to examine these potential sources of heterogeneity into detail. Also, none of the studies was specifically designed to examine the effects of resveratrol on the serum lipoprotein profile. Finally, in some of the studies, subjects were on statin therapy, which may have masked any potential effects of

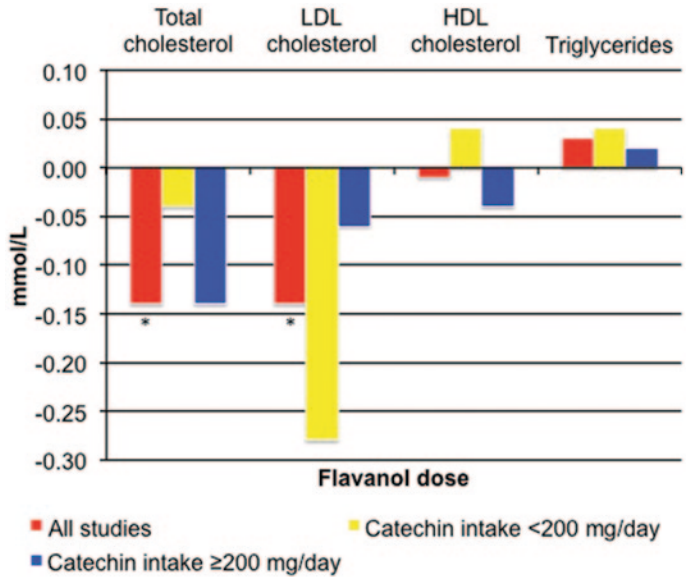

Fig. 22.6 Effects of catechin intake on serum total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride concentrations. A statistically significant (*) reduction in serum total and LDL cholesterol was found in all studies, while HDL and triglyceride concentrations did not change. Differences in effects between the two levels of intakes did not reach statistical significance. *LDL* low-density lipoprotein, *HDL* high-density lipoprotein. (Results are from ref. [17])

resveratrol. Thus, before more definitive conclusions can be drawn, more powerful trials on the effects of *trans*-resveratrol supplementation on lipid metabolism in hyperlipidemic subjects are needed.

Catechins and Isoflavones

Animal studies have shown positive effects on lipid metabolism of green tea catechins, of which epigallocatechin is the most abundantly present. These effects include reducing intestinal lipid absorption, promoting fecal cholesterol excretion, and inhibiting enzymes involved in hepatic cholesterol synthesis.

In humans, a significant reduction in total and LDL cholesterol after green tea catechin intake was found in a meta-analysis, including 1415 subjects in 20 trials. This meta-analysis included studies with green tea catechin doses ranging between 145 and 3000 mg, while study duration varied between 3 and 24 weeks. Green tea catechins significantly lowered total cholesterol (−0.14 mmol/L; 95% CI: −0.25, −0.03 mmol/L), and LDL cholesterol (−0.14 mmol/L; 95% CI: −0.26, −0.02 mmol/L). No significant effects on HDL cholesterol and triglycerides were observed ([17]; (Fig. 22.6).

Regarding the effects of isolated soy isoflavones (in which the soy protein is absent) on lipid metabolism, a meta-analysis with 10 studies and 959 subjects did not suggest that these components do affect serum lipoprotein concentrations [18]. However, soy protein containing intact isoflavones showed a beneficial effect on the lipid profile in two meta-analyses [19, 20].

Effects of Polyphenols on Endothelial Function

The main focus of this paragraph is on the polyphenol epicatechin, because this flavonol from cocoa has been studied most widely with respect to endothelial function. Furthermore, many recent studies have focused on the stilbene *trans*-resveratrol. Therefore, effects of this compound on endothelial function are discussed as well.

Flavonoids

Regarding the positive effects of flavanols on endothelial function, a recent meta-analysis found a beneficial effect of chocolate, cocoa, and/or cocoa flavanols on flow-mediated dilatation (FMD) [8]. An acute effect—2 h after intake of chocolate or cocoa—of on average 3.19% (95% CI: 2.04%, 4.33%) on FMD was reported. Epicatechin dose

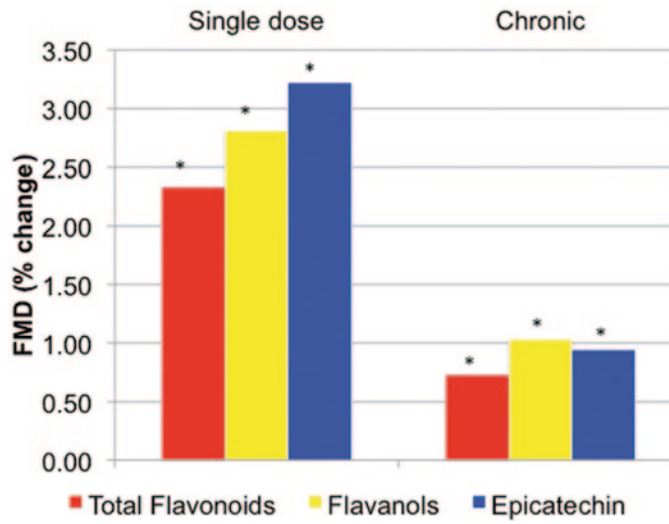

Fig. 22.7 Effect of single-dose and chronic (minimum of 2 weeks intervention) flavonoid intake on % change in FMD. All results were statistically significant (*). *FMD* flow-mediated dilation. (Results are from ref. [22])

might play a role in this beneficial effect, as an increased epicatechin dose (>100 mg/day) from the experimental products showed a more pronounced effect on acute FMD compared to lower epicatechin doses. A mean difference in FMD of 1.34% (95% CI: 1.00%, 1.68%) was observed after chronic intake (3–26 weeks) of chocolate/cocoa.

Another meta-analysis also reported beneficial effects of the intake of flavonoid-rich cocoa on several cardiovascular risk factors. In this study, an increase of 1.53% (95% CI: 0.67%, 2.40%) in FMD after chronic (2–18 weeks) consumption of flavonoid-rich cocoa was found [21]. One meta-analysis examined the effect of flavonoid subclasses on FMD. The acute mean effect of epicatechin on FMD was 3.22% (95% CI: 1.94%, 4.50%), whereas for total flavonoids (the sum of flavanols, catechol flavonoids, procyanidins, epicatechin, and catechins) an acute effect of 2.33% (95% CI: 1.58%, 3.08%) was reported. Also, in studies that reported the longer-term effects (≥2 weeks intervention), epicatechin intake from the experimental products showed a somehow larger improvement (0.94%; 95% CI: 0.47%, 1.42%) on FMD than total flavonoid intake (0.73%; 95% CI: 0.17%, 1.30%) (Fig. 22.7) [22].

The mechanisms to explain the beneficial effect of cocoa polyphenols in general or of epicatechin in particular on FMD have not been elucidated yet. It has been suggested that epicatechin enhances nitric oxide (NO) bioavailability and therefore exerts a positive effect on FMD. This increase in NO might be the result of an increased expression and/or activity of endothelial nitric oxide synthase (eNOS), but also of changes in NO bioavailability or changes in the expression of eNOS-related proteins. This eNOS activation is likely to be mediated via the calcium/calmodulin pathway, as described in Fig. 22.8 [23].

Other suggested pathways that positively influence endothelial function include the antioxidant capacity of flavonoids, which leads to lower oxidative stress levels in vivo and a reduced endothelial adhesion molecule expression in vitro [24]. Furthermore, cocoa and chocolate showed positive effects on fasting insulin and homeostatic model assessment-insulin resistance (HOMA-IR) [8][25]. This finding might be related to the positive effect of chocolate and cocoa on endothelial function, as these processes share common pathways [25].

The upregulation of NO production has several positive effects on the vasculature. First, NO exerts antihypertensive effects through vasodilation. Second, the antithrombotic effect of NO is reflected by the inhibition of platelet aggregation. This effect might be mediated by the inhibition of cyclooxygenase-2 (COX-2), which catalyzes the synthesis of prostaglandin E_2 (PGE_2). Decreas-

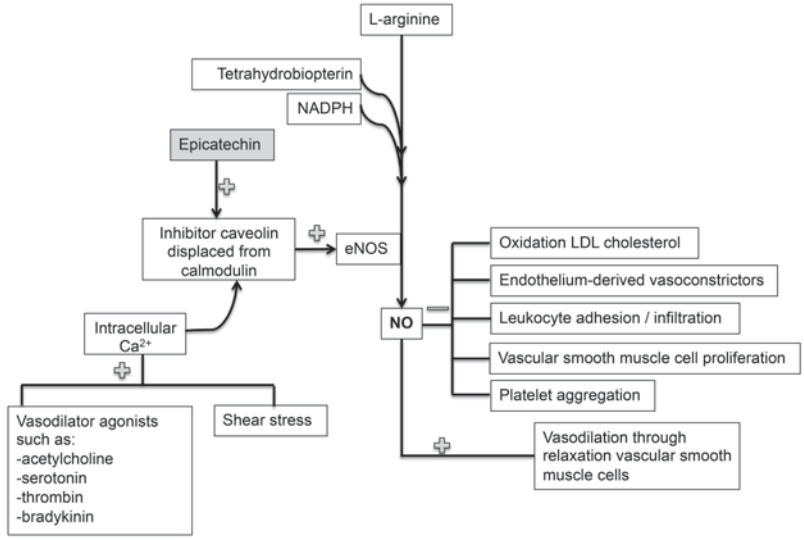

Fig. 22.8 Effects of NO on endothelial function and the possible role of epicatechin in this process. *eNOS* endothelial nitric oxide synthase, *NO* nitric oxide, *NADPH* nicotinamide adenine dinucleotide phosphate, *LDL* low-density lipoprotein. (Based on ref. [23])

ing PGE_2 synthesis has a beneficial effect on platelet aggregation. Finally, the ability of NO to prevent leukocyte adhesion to the endothelium, the reduction of LDL oxidation, and the inhibition of vascular smooth muscle cell proliferation may contribute to the anti-atherosclerotic effects of NO production.

Trans-resveratrol

A recently published article showed an acute, dose-dependent, FMD-improving effect of resveratrol [26]. Here, resveratrol was given to 19 overweight or obese men or postmenopausal women who were borderline hypertensive (systolic blood pressure between 130 and 160 mmHg or diastolic pressure between 85 and 100 mmHg), but did not receive any treatment. Subjects received six capsules containing in total 30, 90, or 270 mg *trans*-resveratrol. The study had a double-blind, randomized crossover design and subjects were asked to consume the indicated doses and a placebo at weekly intervals.

Several in vitro and animal studies have shown that resveratrol may stimulate eNOS and improve NO bioactivity [27]. Except for the effects of resveratrol on NO production, the compound is also thought to exert positive effects on endothelial dysfunction by inhibiting NFκB, leading to lower cytokine production and less vascular inflammation [27]. Furthermore, platelet aggregation might be prevented by resveratrol through prevention of eNOS acetylation and sirtuin type 1 activation.

Polyphenol Metabolism

Flavonoids

Flavonoids, except for catechins, are present in the diet as β-glycosides. Flavonoid glycosides, but not glucosides, are thought to pass the small intestine, followed by hydrolysis to aglycones by enterobacteria in the cecum and colon [28]. Absorption of flavonoid aglycones in the large intestine is facilitated through their lipophilicity by passage across the phospholipid bilayer of the cellular membranes. After entering the circulation, the flavonoid aglycones are further metabolized in the liver (*O*-methylation,

glucuronidation, and/or sulfation). Part of the metabolites will be excreted in the bile, followed by a return to the intestinal lumen, where they might either be reabsorbed by intestinal cells or excreted into feces. Glucosides are thought to be absorbed from the small intestine, which leads to higher plasma values because of the higher absorption efficiency. Catechins are present in foods as aglycones or esterified with gallic acid. Both forms are absorbed from the small intestine.

Bioavailability of flavonol glycosides differs among the separate classes. Time to reach plasma peak concentrations vary between less than 0.5 and 9 h, with the highest bioavailability of quercetin glucosides from onions [29]. Flavonols that are particularly present in cocoa, (epi)-catechin and procyanidin, reach a peak concentration after 2 h [30].

Trans-resveratrol

After oral administration, *trans*-resveratrol is mainly absorbed in the duodenum and, to a lesser extent, the jejunum. After that, metabolic conversion via intestinal and hepatic conjugation starts. Both intestinal subcellular fractions and liver cells are capable of glucuronidation and sulfation of resveratrol, although glucuronidation prevails over sulfation in the liver. This results in low plasma levels of free resveratrol, whereas the major metabolites (*trans*-)resveratrol-3-*O*-sulfate, (*trans*-)resveratrol-3-*O*-glucuronide, and (*trans*-)resveratrol-4'-*O*-glucuronide are mainly found in plasma after resveratrol intake.

A second resveratrol and resveratrol-metabolite peak is observed 6 h after resveratrol intake. This is explained by enterohepatic recirculation of conjugated resveratrol metabolites. During this process, resveratrol is metabolized in the liver and its conjugates are excreted in the bile. This is followed by reabsorption of the conjugates in the small intestine and subsequent return to the liver or excretion via feces (Fig. 22.9).

Resveratrol absorption is at least 70%, and the compound and its metabolites are mainly excreted via urine. The absorption is delayed when resveratrol is taken with foods, especially with a high-fat meal.

Dosing Regimen and Adverse Effects

A recent scientific opinion by the European Food Safety Authority (EFSA) stated that 200 mg of cocoa flavanols should be consumed daily in order to "maintain endothelium-dependent vasodilation, which contributes to normal blood flow" [31]. This amount of flavanols can be consumed through 10 g of high-flavanol dark chocolate. For the other components discussed in this chapter, no effective doses have been formulated by health authorities.

Conclusions

Scientific interest in the relation between polyphenol intake and cardiovascular health has considerably grown during the past decades. Polyphenols can be found in numerous products of which flavonoids from cocoa, the stilbene *trans*-resveratrol from black grapes, green tea catechins, and soy isoflavones have been most widely studied.

Green tea catechins were shown to improve the serum lipid profile by decreasing total cholesterol and LDL cholesterol. Isolated soy isoflavones did not affect serum lipoprotein concentrations, whereas soy protein containing intact isoflavones may have a beneficial effect on the lipid profile. Consumption of cocoa products or dark chocolate for 2 weeks showed a significant decrease in LDL cholesterol. This effect was not found after 4–12 weeks consumption of these products, which raises questions on the clinical usefulness of this finding. HDL cholesterol showed an increase in longer-term studies. Next to this, beneficial effects of flavonoids from cocoa on FMD were reported, which underlines the positive role of these compounds in cardiovascular risk reduction. *Trans*-resveratrol does not affect serum lipid and lipoprotein concentration, but may improve vascular health. However, more studies are needed to substantiate these findings. Several mechanisms underlying these effects of the various polyphenols have been proposed, but an unambiguous explanation cannot be given yet.

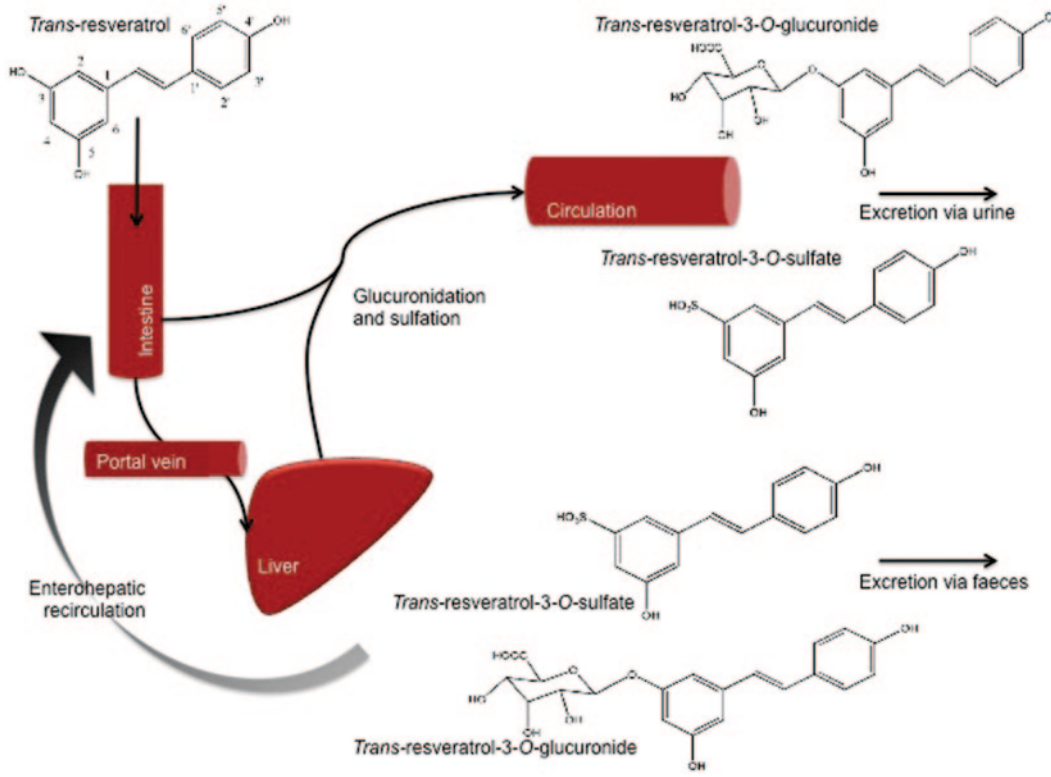

Fig. 22.9 *Trans*-resveratrol is absorbed in the intestine, followed by glucuronidation and sulfation by liver and intestinal subcellular fractions, which results (among others) in the formation of *trans*-resveratrol-3-*O*-glucuronide and *trans*-resveratrol-3-*O*-sulfate. These conjugates can be excreted via urine or undergo enterohepatic recirculation. During this process, *trans*-resveratrol conjugates are returned to the liver via the bile duct, intestines, and portal vein and can either be excreted via feces or reenter the circulation and excreted via urine

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