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Cocoa Consumption, Cocoa Flavonoids, and Effects on Cardiovascular Risk Factors: An Evidence-Based Review

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Abstract There has been considerable interest in the health effects of cocoa products. Cocoa flavonoids have especially been associated with cardiovascular disease (CVD) risk factors. We summarize the effects of total flavonoid and cocoa flavonoid consumption on CVD endpoints in observational studies and intermediate risk factors in experimental designs. From an evidence-based review, there is strong evidence that high cocoa intake lowers blood pressure, improves vascular endothelial function, and potentially increases insulin sensitivity. However, evidence does not support effects on blood lipids and body weight. Total flavonoid intake, and potentially cocoa flavonoid intake, is associated with coronary heart disease mortality in observational studies; however, there is conflicting evidence regarding the dose at which cocoa flavonoids are beneficial. Moreover, because chocolate is often nutritionally energy dense and with added sugar, considerations must be given to caloric balance and body weight. Overall, combining the multiple lines of evidence from experimental and observational studies on the effects of cocoa flavonoids and cocoa intake on cardiovascular risk factors, there is rather strong evidence supporting and demonstrating that cocoa consumption improves several important cardiovascular risk factors and likely reduces the risk of CVD, although more research is needed to further examine etiological mechanisms, demonstrate efficacy on hard clinical CVD endpoints in large-scale randomized trials, as well as carefully estimate attributable disease burden. More importantly, as intake of cocoa is inextricably linked with increased calories in chocolate consumption, further careful risk-benefit analysis is needed to assess whether consuming cocoa in the form of energy-dense chocolate products may yield a net benefit on cardiovascular risks.

Keywords Cocoa · Chocolate · Flavonoids · Coronary heart disease · Blood pressure · Lipids · Body mass index · Weight · Cardiovascular disease · Stroke · Review · Procyanidins · Catechins · Epicatechins

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Introduction

Flavonoids are a family of several bioactive substances that include flavones, flavonols, anthocyanins, and flavanols such as proantocyanidins, catechins, and epicatechins. Tea, fruits, and vegetables are rich in flavonoids, but flavonoids are notably abundant in the cocoa solids of the cocoa bean. In recent years, there has been

a growing interest in high-flavonoid dark chocolate, fueled by emerging evidence for health benefits of flavonoids. Although a past literature review of total flavonoid consumption identified the potential benefits on cardiovascular disease (CVD) [1], the precise mechanisms of benefits for CVD risk are controversial. Therefore, this evidence-based review focuses on the direct benefits of cocoa and cocoa flavonoids on CVD and potential mechanisms influencing CVD risk.

Nutritional Constituents of Chocolate and Cocoa

The Aztecs and Mayans believed the cocoa tree to be of divine origin, and cocoa to be the "food of the gods" [2]. The original chocolate consumed by the Aztec was a thick, bitter, unsweetened drink, with fat contributing to almost 50% of total content by weight [3]. Adulterations of this original beverage occurred when cocoa was introduced in the 16th century in Europe, together with sugar, tea, and coffee [3]. Sugar and starches were added to mask its bitter taste.

Modern manufacturing of chocolate involves fermentation of the cocoa beans from the *Theobroma cacoa* followed by drying. This substance is then separated into fat-free cocoa powder and cocoa butter, which are added together in varying proportions to create different chocolate products. Cocoa butter accounts for 50% to 57% of the dry weight of cocoa beans, and the main fats are stearic acid (35%), palmitic acid (25%), and oleic acid (35%). Unsweetened cocoa powder contains 82% non-fat cocoa solids, dark chocolate 23%, and milk chocolate 6% [4]. Because the issue of saturated fat content and stearic acids in chocolate has been previously reviewed [1], this article focuses on the flavonoids of cocoa and effects of overall cocoa and chocolate consumption.

Cocoa and Flavonoid Consumption

Flavonoids as a group are a diverse class of polyphenolic antioxidants (Fig. 1), and are thought to be the primary constituent of cocoa that possesses potential health benefits. Cocoa is predominantly rich in three types of flavonoids: procyanidins, catechins, and epicatechins [2]. However, there are many foods besides cocoa that are also rich in these compounds, as well as others in the flavonoid class.

Chocolate and Cocoa Flavonoid Content

Although chocolate bars are primarily consumed in smaller quantities, they represent the main food source of cocoa flavonoids. Chocolate is especially rich in catechin, epicatechin, and procyanidin, containing an average of 41.50 mg/100 g of epicatechin and 11.99 mg/100 g of catechin [5]. However, modern manufacturing of chocolate may induce losses of more than 80% of the original flavonoids from the cocoa beans [6]. Therefore, flavonoid content of chocolate products may vary depending on the proportion of cocoa solids. Total catechin content of chocolate varies from 46.0 to 61.0 mg/100 g in dark chocolate and 15.3 to 16.3 mg/100 g in milk chocolate [7]. Procyanidin content in commercially available chocolates varies between 9 mg/100 g and 400 mg/100 g [8]. However, a concern is that a 50-g serving of dark chocolate also provides 250 kcal, which is a concern for potential weight gain [5]. In contrast, green tea contains no energy, but provides 8.47 mg/100 g of epicatechin and 2.73 mg/100 g of catechin in addition to flavan-3-ols [5].

This review is divided into sections on observational studies with CVD endpoints and randomized controlled

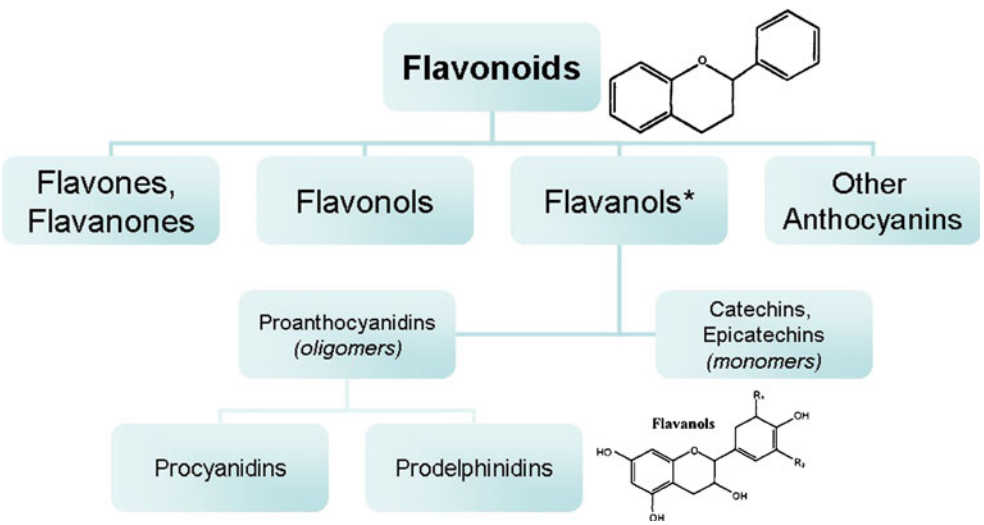

Fig. 1 Flavonoids are a diverse class of polyphenolic antioxidants and are thought to be the primary constituent of cocoa that pos sesses potential health benefits. *Asterisk* indicates that flavanol is the predominate class of flavo noid found in cocoa and chocolate

trials on intermediate CVD risk factors. We begin with the latter, covering different etiologic pathway risk factors.

Effect of Cocoa Flavonoids on Cardiovascular Intermediate Risk Factors in Experimental Trials

Although no long-term trial of cocoa or chocolate yet exists to evaluate hard clinical CVD endpoints, such as myocardial infarction (MI) or stroke, a sizeable body of short-term experimental trials exists to demonstrate effects on intermediate endpoints on various CVD etiology pathways. Notably, short-term randomized clinical trials suggest that flavonoids in chocolate may affect cardiovascular risk through effects on blood pressure (BP), endothelial function, nitric oxide (NO), anti-platelet and anti-inflammatory effects, blood lipids, and insulin resistance [9•].

Blood Pressure

There is strong evidence that high-flavonoid cocoa supplementation lowers systolic (SBP) and diastolic blood pressure (DBP). Four meta-analyses have evaluated the effect of high-flavonoid cocoa products on BP from randomized controlled trials and found strong evidence for a protective association [10–13•]. Changes in mean SBP ranged from −3.2 to −5.88 mmHg and changes in DBP ranged from −2.0 to −3.30 mmHg. The most recent meta-analysis of 21 trials on BP change revealed that dark chocolate (50–70% cocoa), compared to cocoa-free controls, or high-flavanol cocoa compared to low-flavanol cocoa, lowered BP (−3.2 mmHg SBP, −2.0 mmHg DBP). The effects were consistent across flavonoid dose, quality, and duration of trials as well as population demographics; reductions were most notable observed among hypertensive patients (−5 mmHg). These reductions in BP, possibly through effects on angiotensin-I-converting enzyme inhibitor and enhancing NO synthase activity [14–16], are quite pronounced in magnitude of BP reduction and likely of clinical and public health importance. Indeed, a 3- to 5-mm Hg reduction in SBP would yield significant decreases in overall population-wide CVD and mortality burden [17]. Indeed, a recent 3-cohort-pooled prospective study found that two cocoa-rich flavonoids, catechin and epicatechin, was notably associated with lower risk of developing hypertension [18].

Endothelial Function

Short-term cocoa supplementation increased flow-mediated dilation (FMD) in several trials. Eight randomized controlled trials (339 subjects) reported FMD after short-term (15 days to 12 weeks) supplementation with high-flavonoid cocoa among primarily hypertensive or high-risk patients (with history of obesity, diabetes, hypercholesterolemia, or coronary artery disease) [19–25•, 26]. The majority of these trials reported an increased FMD among the treatment arm [19–23, 25•, 26], and improved vascular dilation was observed in primarily high-risk populations [20–25•, 26], although one study even found effects in healthy subjects as well [19]. However, brachial artery FMD systemic arterial compliance was not affected by a flavonol-rich cocoa supplementation [27], and the effect on FMD was lower when sugar was added to the cocoa products [25•, 26–28]. Also for vasodilation, it has been found that cocoa consistently induces NO-dependent vasodilation in the finger or forearm circulation of healthy subjects [15, 19, 29] and in subjects with previous cardiovascular risk factors [20, 22, 30–32], again favorable for vascular function.

Overall, there is a consistent and very strong body of evidence from randomized trials that indicates cocoa flavonoids improve vascular health via reduction of BP and improvement of endothelial function.

Lipid Concentrations

There is conflicting evidence for the effects of high-flavonoid cocoa supplementation on blood lipids. A meta-analysis of five studies, including both short- and long-term clinical trials, found no association between cocoa supplementation and high-density lipoprotein (HDL) or low-density lipoprotein (LDL) cholesterol [12]. A more recent meta-analysis of eight short-term randomized controlled trials (15 days to 12 weeks), with a total of 215 participants, reported a decrease in LDL cholesterol by 5.87 mg/dL (95% CI, −11.13 to −0.61) and a marginal decrease in total cholesterol by 5.82 mg/dL (95% CI, −12.39 to 0.76) [33]. However, there was a large amount of heterogeneity and the association was not observed among high-quality studies. These findings were also limited to low doses of cocoa among participants with cardiovascular risk factors. No difference was observed for triglycerides and HDL cholesterol. In summary, the evidence does not support the effects of cocoa flavonoids on blood lipids.

Insulin Sensitivity

Although few experimental studies have been conducted, preliminary evidence suggests that cocoa flavonoids are associated with insulin sensitivity. Four published randomized controlled trials have evaluated the effect of high-flavonoid cocoa supplementation on Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) and Quantitative Insulin-Sensitivity Check Index (QUICKI) [20, 23, 24, 26]. All studies observed a decrease in HOMA-IR and an increase in QUICKI compared to controls, among both healthy and hypertensive populations. In the three studies that measured Insulin

Sensitivity Index (ISI) scores, an increase in ISI score was found, which corresponds to improved insulin sensitivity [20, 24, 34]. Although preliminary evidence from a few randomized controlled trials suggests beneficial effects of cocoa flavonoids on insulin sensitivity, additional large randomized controlled trials are warranted to evaluate this potential effect.

Other Mechanisms

Other pathophysiologic pathways have been proposed by which cocoa flavonoids may affect CVD risk. Daily consumption of cocoa beverages led to significant reductions in platelet activation markers and primary platelet aggregation among healthy volunteers [35]. An in vitro study also suggests immunoregulatory effects of an enriched polyphenol fraction purified from cacao liquor [36]. Additionally, cocoa procyandins may reduce the inflammatory effects of various cytokines (eg, interleukin-5, tumor necrosis factor-α, transforming growth factor-β) [37–41].

Observational Studies on Flavonoids and Cardiovascular Disease

Although flavonoids are a diverse polyphenol class, it is important for etiologic compatibility and robustness to examine cocoa flavonoids in the overall context of total flavonoids on CVD risk. Observational evidence exists for associations between flavonoids from fruits, vegetables, tea, and cocoa consumption and CVD endpoints. Several cross-sectional and prospective cohort studies have found inverse associations between total or specific flavonoid intake and mortality.

First, total flavonoid consumption varies widely between countries. High flavonoid intakes are found in Japan and Australia: among 516 Japanese women, average flavonoid intake was 1,597 μmol/day (380 mg/day), as estimated by 24-hour weighted dietary records. The main sources of flavonoids were tea, onions, grapefruit, and tofu [42]. In a study of 13,858 Australians, total flavonoid consumption was 454 mg/day in adults, with the most important sources being tea (76% of intake) and oranges [43]. Lower flavonoid intakes of approximately 200 mg/day were reported in Europe and the United States. In the UK and Ireland, total daily flavonoid intake was 182 mg and 177 mg (estimated from Food and Agriculture Organization [FAO] Food Balance Sheets), respectively [44]. In a study among 2007 Finnish adults, total flavonoid intake was 207 mg/day, mostly from fruit consumption [45]. In the United States, flavonoid intake was 189.7 mg/day and tea was the major contributor to intake (83% of intake) [46].

Total Flavonoid Intake and Coronary Heart Disease Mortality

The most consistent finding is the association between total flavonoid intake with CVD mortality. A meta-analysis of prospective cohort studies found a combined risk ratio of 0.80 (95% CI, 0.69–0.93) for higher dietary flavonoid intake and coronary heart disease (CHD) [47]. Eight observational studies have found lower risk of CVD mortality for high intakes compared with low intakes of flavonoids [48–57]. Because of the observational nature of these studies, residual confounding by other lifestyle factors may explain part of the association with CVD. For example, in the Zutphen Elderly Study, smoking, lower social economic status, and lower intake of fruits and vegetables were associated with lower intake of flavonoids [58]. Furthermore, it is also of note that total flavonoids include flavones, flavonols, and anthocyanins, which are not present in cocoa. Thus, caution should first be taken when interpreting these findings for cocoa per se.

However, among these cohort studies, one study among Welsh men found no association between flavonoid intake and CHD mortality, possibly because of a high background intake of milk with tea. High milk consumption might affect intestinal flavonoid absorption [59, 60]; however, this mechanism has been debated [60–63]. In the study by Mink et al. [57], other major flavonoid-rich foods were bran, apples, pears, red wine, grapefruit, and strawberries, although it is of note that flavonoids from chocolate alone were independently associated with reduced CVD risk. Main sources in the study by Knekt et al. [56] were onions and apples, which together contributed to 64% of the total intake, and other sources were fruits, berries, sweetened juices and jams (mainly from berries), and vegetables. In the study by Yochum et al. [54], tea, apples, and broccoli were the major contributors to flavonoid intake. In the Zutphen Elderly Study, chocolate accounted for only 3% of catechin intake, whereas black tea accounted for 87% and could be interpreted as perhaps a major factor behind the inverse association with ischemic heart disease [48]. Nevertheless, the Zutphen Elderly Study, in a later report on cocoa [64], found that cocoa intake was, itself, also strongly associated with lower mortality (see later section on cocoa observational studies).

Total Flavonoid Intake and Stroke

There is no evidence for an association between total flavonoid intake and stroke. Most prospective studies found no association between total flavonoid intake and risk of stroke [52, 53, 65]. Only one small study found a significantly lower risk of stroke with higher total flavonoid intake [66]. However, these studies were again for total flavonoids and not cocoa or cocoa flavonoids per se.

Observational Studies of Cocoa Consumption, Cocoa Flavonoids, and Cardiovascular Endpoints

We also examined studies on cocoa intake and cardiovascular disease outcomes. Seven observational studies have looked at associations with cocoa intake specifically. In the prospective Zutphen Elderly Study, a very detailed study of a comprehensive range of dietary items related to cocoa, the highest tertile of cocoa intake (mean, 4.18 g/day) found both significantly lower BP levels (−3.7 mmHg) as well as a remarkable adjusted relative risk of 0.50 (95% CI, 0.32–0.78; P=0.004 for trend) for cardiovascular mortality and 0.53 (95% CI, 0.39–0.72; P<0.001) for all-cause mortality compared to the lowest tertile (exclusively those with 0 g/day) [64]. Moreover, in a prospective cohort study of 31,823 Swedish women, Mostofsky et al. [67•] found inverse associations between chocolate intake and heart failure only among elderly women consuming one to three servings of chocolate per month or one to two servings per week; rate ratios were 0.74 (95% CI, 0.58–0.95) and 0.68 (95% CI, 0.50–0.93), respectively. However, in this study, a curvilinear relationship of no association was found for higher servings: rate ratios were 1.09 (95% CI, 0.74–1.62) for those consuming three to six servings per week and 1.23 (95% CI, 0.73–2.08) for those consuming more than 1 serving per day [67•]. The authors suggested a possible J-shaped dose–response curve, where CVD benefits only occur with moderate chocolate intake. One possibility is that the attenuation of benefits with higher consumption may be in part due to excess weight or caloric intake, especially given that the majority of chocolate consumed in Sweden during this time period was milk chocolate (~30% cocoa solids), which again may or may not have negative interaction in inhibiting effects of flavonoids [60–62]. Nevertheless, the possibility of a J-shaped relationship should not be entirely dismissed, as it was also seen in the Harvard Alumni Health study, which found moderate consumption of chocolate (and candy) associated with lower all-cause mortality (relative risk 0.73; 95% CI, 0.60–0.89), but only in moderation, as a trend toward higher risk was observed in ranges of upper intakes [68].

In the National Heart, Lung, and Blood Institute (NHLBI) Family Heart Study, chocolate consumption was associated with a reduced odds of CHD. In this cross-sectional design study, the odds ratio was 0.43 (95% CI, 0.28–0.67) for chocolate consumption of more than 5 times a week compared to no intake [69]. A reduced risk of both MI and stroke was also observed among a cohort of German adults; relative risk of both outcomes was 0.61 (95% CI, 0.44–0.87), although the inverse association was stronger for stroke [70]. Lower blood pressure only explained 12% of this reduction in risk. Furthermore, chocolate consumption was weakly associated with a decrease in total mortality and nonfatal outcomes among Swedish patients with a previous MI [71]. Conversely, in the Nurses' Health Study (NHS), chocolate consumption was not associated with CHD incidence [72], although chocolate intake was not well defined in the NHS cohort, unlike in the earlier Zutphen Elderly Study (ZES), which comprehensively assessed cocoa intake using diet records and larger battery of cocoa food items [64]. This method leads to substantially less measurement error, and consequently a strong inverse association was reported for cocoa and mortality in ZES.

These observational studies for cocoa and chocolate consumption overall indicate a strong body of evidence that supports a general trend for an inverse association between not only total flavonoid intake, but also cocoa intake and CVD. However, residual confounding may still be present and causality is still uncertain without larger long-term trials with hard clinical endpoints. When combined with the body of evidence from short-term randomized trial evidence on intermediate CVD risk factors, multiple lines of evidence suggest that cocoa has likely beneficial effects. Nevertheless, future large-scale randomized trials of cocoa and chocolate consumption and hard clinical CVD endpoints would be highly welcome to clarify effectiveness of an intervention.

Chocolate and Body Weight

Although cocoa flavonoids are associated with lower risk of CVD, consumption of chocolate products particularly dense in energy may be a concern. Average commercially available chocolate consumption is approximately 5.5 kg per person per year, varying between 1.02 and 10.14 kg per person per year across countries [73].

On average, a typical chocolate bar contains 500 kcal per 100 g of product and might tip the energy balance toward excessive calorie consumption, increasing the risk of obesity followed by hypertension, dyslipidemia, and diabetes. Indeed, cocoa has been added as an ingredient in snacks and candy such as chocolate bars, and more recently in regularly eaten foodstuffs such as breakfast cereals (United States) and sandwich toppings (The Netherlands). Moreover, chocolate is viewed as something people claim to crave and need [74]. Competing with the potential benefits of cocoa flavonoids on vascular function, a 50-g serving of dark chocolate provides 250 kcal and added sugar makes up almost half of the weight of dark chocolate, with typical fat content around 30% [5]. Indeed, the direct daily consumption of a 50-g serving of dark chocolate may potentially add up to 91,250 kcal each year. However, it is not clear whether other foods are isocalorically replaced by chocolate, and by how much isocaloric replacement of chocolate intake occurs, which would thereby mitigate the excess calorie estimate. Moreover, dark chocolate also contains the most cocoa flavonoids,

and the balance of risks and benefits is yet undetermined. To our knowledge, no experimental studies were designed to assess the effects of chocolate consumption on weight as the primary outcome. Nevertheless, in one trial, consumption of 41 g of chocolate for 6 weeks did not cause weight gain [75].

Added sugar in chocolate is also a concern. Approximately half of the content of an average dark chocolate bar is sugar, providing almost 200 cal of added sugar in the diet for a 100-g chocolate bar. The American Heart Association recommends no more than 100 cal of sugar for women per day, and 150 cal for men, equivalent to one serving of chocolate [76•]. Aside from the controversial status of sugar, it should be noted that the beneficial effects of chocolate on FMD are also reduced when sugar is added to cocoa products [25•, 28].

However, these concerns have not stopped certain researchers from recommending 100 g/day of dark chocolate, as part of a supposedly cardiopreventive "polymeal" dietary pattern [77] (although the seriousness of the recommendation has been questioned given the Christmas holiday publication timing). Ultimately, eating chocolate to increase intake of flavonoids may also be challenging. Indeed, it has been reported in one study that 50% of participants given a chocolate treatment found it difficult to consume 50 g of dark chocolate every day, and 20% considered it an unacceptable long-term treatment option. In contrast, all participants found it easy and acceptable to take a capsule each day for blood pressure [78]. Regarding real-world efficacy, again, no studies have been done to assess whether chocolate consumption replaces consumption of nutrient-dense, low-caloric foods. Therefore, considerations of chocolate consumption, in addition to the potentially beneficial cocoa flavonoid constituents, must also be viewed in the light of its caloric content, body weight implications, degree of isocaloric replacement, and the quality and nutrition of the foods it would displace.

Conclusions

Combining the multiple lines of evidence from experimental and observational studies on the effects of cocoa flavonoids and cocoa intake on cardiovascular risk factors shows there is rather strong evidence supporting and demonstrating that cocoa consumption improves several important cardiovascular risk factors and likely reduces the risk of CVD, although more research is needed to further examine etiologic mechanisms, demonstrate efficacy on hard clinical CVD endpoints in large-scale randomized trials, as well as carefully estimate attributable disease burden. More importantly, as intake of cocoa is inextricably linked with increased calories in chocolate consumption, further careful risk-benefit analysis is needed to assess whether consuming cocoa in the form of energy-dense chocolate products may yield a net benefit on cardiovascular risks.

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