Catechins as Potential Mediators of Cardiovascular Health

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Abstract—The impact of diet on cardiovascular disease has become an increasingly relevant topic as ongoing epidemiological evidence continues to demonstrate clear associations with disease burden and mortality. Certain diets, such as those high in sodium and saturated fat, are associated with cardiovascular disease states, while other diets can be cardioprotective. However, there is limited knowledge on how the micro- and macronutrients within such cardioprotective diets afford their benefits. One such micronutrient is the catechin class, which are naturally occurring compounds in plant foods, such as teas, cocoa, wine, pears, and apples. Recent evidence reveals that catechins may be a key mediator in cardiovascular health via mechanisms of blood pressure reduction, flow-mediated vasodilation, and atherosclerosis attenuation. This review evaluates the current literature on the interplay between catechins and cardiovascular disease, which may have important implications for nutrition counseling and pharmaceutical drug development.

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Key Words: atherosclerosis ■ blood pressure ■ cardiovascular disease ■ catechin ■ coronary artery ■ epicatechin ■ hypertension ■ platelet ■ thrombosis

In recent years, there has been a growing interest in the relationship between diet and cardiovascular health. Certain diets, such as those high in sodium and saturated fat, are known to be associated with cardiovascular disease states, such as hypertension and atherosclerosis.[1] Current guidelines, including those endorsed by the American Health Association, emphasize heart-healthy diets such as the DASH diet (Dietary Approaches to Stop Hypertension) and the Mediterranean diet, which both incorporate ample consumption of fruits, vegetables, low-fat dairy and lean meats.[2–5] These diets are beneficial for both disease and mortality reduction.[6–8] The Mediterranean diet, for example, is associated with a 50% lower incidence of all-cause mortality and cardiovascular-specific mortality.[9] However, there is limited literature that identifies how individual micro- and macronutrients within these diets contribute to disease and mortality reduction. One such micronutrient is the catechin class, which is a type of flavanoid found in common plant foods, such as legumes, teas, cocoa, grapes, apples, pears, and several other fruit.[10] Epidemiological studies have shown that populations consuming high quantities of catechins have a decreased incidence of coronary artery disease.[11] The cardioprotective effects of catechins are manifold and include reductions in systemic blood pressure, atherosclerosis, platelet activation, and thrombus formation. This review highlights the current literature on the relationship between catechins and cardiovascular health, which may prove to have implications for nutrition counseling, as well as pharmaceutical development.

The Catechin Class

The catechins are a class of flavanoids found naturally in plant-based foods, such as cocoa, tea, fruits, and legumes.[12] Chocolate and apples contain the largest amount of procyanins, which are oligomeric compounds formed by catechins.[13,14] After consumption, catechins are absorbed in the small intestine and thereafter undergo end-product modification, including glucoronidation, sulphation, and methylation, in the liver.[15] The specific catechins subtypes most commonly cited as cardioprotective are (+)-catechin and (−)-epicatechin.[16]

Systemic Blood Pressure

There is a substantial body of evidence demonstrating the beneficial effects of catechin consumption on blood pressure. Overall, it seems that human consumption of catechins, particularly via cocoa, reduces blood pressure and improves flow-mediated vasodilation (FMD).[17] A recent Cochrane Review meta-analysis of 20 randomized controlled trials including 856 subjects found that cocoa consumption was associated with a mean reduction in systolic blood pressure by 2.77 mm Hg (P=0.005) and diastolic blood pressure by 2.20 mm Hg (P=0.006).[18] In another meta-analysis by Ellinger et al,[19] a nonlinear regression model incorporating data from 16 randomized controlled trials and 391 subjects revealed that there is an inverse relationship between catechin consumption and systemic blood pressure. Namely, at roughly 25 mg of epicatechin, which is the amount that can be found in 25 to 30 g of commercial cocoa, there is a

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Nonstandard Abbreviations and Acronyms	
ApoE	apolipoprotein E
FMD	flow-mediated vasodilation

reduction in systolic blood pressure by roughly 4.1 mm Hg (95% confidence interval [CI], −4.6 to −3.6 mm Hg) and diastolic blood pressure by roughly 2 mm Hg (95% CI, −2.4 to −1.5 mm Hg).[19] One of the largest single center studies was that of Buijsse et al,[20] which followed blood pressure, cardiovascular disease, and chocolate consumption in a 19 357 German male cohort over 8 years. Those who consumed the top quartile of chocolate had a lower mean systolic blood pressure by 1.0 mm Hg (95% CI, 1.6–0.4 mm Hg) and a lower mean diastolic blood pressure by 0.9 mm Hg (95% CI, 1.3–0.5 mm Hg) compared with the bottom quartile of chocolate consumers.[20] Further, after controlling for cardiometabolic variables, the relative risk of myocardial infarction and stroke in the top quartile of chocolate consumers versus the bottom quartile was 0.61 (95% CI, 0.44–0.87; P=0.014), suggesting significant differences in cardiovascular outcomes based on chocolate consumption. Other smaller trials have surfaced supporting the inverse relationship between catechin consumption and systemic blood pressure reduction. Table 1 summarizes these trials. Taubert et al[21] found that in 13 subjects with normal blood pressure, consumption of chocolate for 14 days was associated with a 5.1 mm Hg (P<0.001) mean decrease in systolic blood pressure and a 1.6 mm Hg (P=0.002) mean decrease in diastolic blood pressure. Similarly, Grassi et al[25] found that in 19 hypertensive subjects randomly assigned to 15 days of flavanol-rich or flavanol-free chocolate, those who consumed flavanol-rich chocolate experienced a significant reduction in systolic and diastolic blood pressure by 3.82 and 3.92 mm Hg, respectively. Although these studies represent relatively small populations, they reflect a general trend in blood pressure reduction with consumption of foods containing sufficient amounts of catechins. Other studies, however, have demonstrated that catechins may not decrease blood pressure, but rather have a neutral effect. Dower et al[31] randomized 37 healthy patients to either 100 mg/d of (−)-epicatechin or placebo for 4 weeks and found no difference in systemic blood pressure. Similarly, in a study that involved 40 hypertensive subjects randomized to either a flavanol-rich drink (roughly 900 mg flavanol/d) or placebo for 2 weeks, there was no significant difference found in blood pressure.[27]

One significant criticism of the current literature is that the majority of studies do not report current antihypertensive medication use or specifically exclude patients taking antihypertensive medications. As such, it remains unclear if there are potential interactions between antihypertensive medications and catechin consumption. Additionally, a major concern with the current evidence is the lack of control for alternative compounds found within catechin-rich foods, which may affect blood pressure. Finally, an increased consumption of catechin-rich foods, particularly chocolate, may be accompanied by increased sugar intake, which may worsen glycemic control in diabetics. Commercialized chocolate also contains high amounts of saturated fat, which has previously been associated, albeit controversially, with increased cardiovascular mortality.[34]

FMD, Peripheral Vasodilation, and Coronary Vasodilation

FMD, or the endothelial-driven vasodilatory response to transient ischemia, also seems to be influenced by catechin consumption (Table 2). Nitric oxide–mediated vasodilatation is a normal physiological response in healthy subjects but can become diminished or dampened in those with coronary artery disease or atherosclerosis.[38] Impaired FMD has also been identified as an independent predictor of future cardiovascular events.[39] Balzer et al[36] found that consumption of flavanol-enriched cocoa is associated with a dose-dependent increase in FMD. Ten subjects who consumed increasing amounts of flavanol concentrations, which contained mostly (−)-epicatechin, had a significant increase in FMD ≤6 hours after ingestion. Forty-one subjects were also randomized to drink either a control concentration or a high-dose flavanol (963 mg/d) concentration, and at the 30-day mark, those who consumed high-dose flavanol concentrations continued to have a sustained dose-dependent response in FMD, suggesting the absence of attenuation over time. Schroeter et al[40] demonstrated that subjects who consumed pure (−)-epicatechin or flavanol-rich cocoa experienced similar changes in FMD, suggesting the key role of (−)-epicatechin in particular. Finally, Engler et al[35] found similar results in a cohort of 21 patients randomized to high or low flavonoid concentrations. The mechanisms involved in catechin-induced FMD are indeed mediated by novel nitric oxide production. Numerous rat and human models have previously validated this relationship using in vivo nitric oxide assays.[41–43] Further, in a study by Fisher et al[44] involving 27 human subjects, peripheral vasodilation after consumption of flavanol-rich cocoa was reversed with a nitric oxide synthase inhibitor, confirming that the mechanism of flavanol-induced vasodilation is nitric oxide dependent. In this study, FMD was assessed via pulse wave amplitudes obtained using a plethysmographic device on the index finger of subjects both before and after 5 minutes of radial artery occlusion. After 4 days of flavanol-rich cocoa consumption containing roughly 0.070 mg/g epicatechin and 0.082 mg/g catechin, pulse wave amplitudes had increased by 29% (7.3±0.7 to 9.4±1.0 μL; P=0.01). Further, on the fifth day when patients were given an additional dose of cocoa followed by an infusion with L-arginine methyl ester, a potent nitric oxide synthase inhibitor, pulse wave amplitudes decreased by 36% (12.5±2.5 bμL after cocoa to 8.0±0.7 μL after L-arginine methyl ester; P=0.004). Another study demonstrated that the effects of high flavanol cocoa on FMD are preserved with chronic administration.[37] Davison et al[37] followed 49 subjects randomized to either high-flavanol cocoa (902 mg of flavanols daily) or low-flavanol cocoa (35 mg of flavanols daily). Subjects had a baseline body mass index of 33.5 mg/m^2 and blood pressure of 123/76 mm Hg. FMD was assessed through ultrasonographic measurement

Table 1. Major Clinical Studies Evaluating the Effect of Catechin Consumption on Systemic Blood Pressure

Author	No of Subjects, N	Mean Age, y	Mean BMI, kg/m^2	Male, %	Vehicle for Catechin	Blood Pressure Preintervention, mm Hg	Blood Pressure Postintervention, mm Hg	Mean Change in Systolic BP, mm Hg	Mean Change in Diastolic BP, mm Hg
Taubert et al[21]	13	55–64	21.9–26.2	46.2	100-g dark chocolate for 14 days	Not available	Not available	–5.1 (P<0.001)	–1.8 (P=0.002)
Fraga et al[22]	28	18	24.1	100	105-g milk chocolate for 14 days	123 (±3)/72 (±2)	117 (±2)/67 (±2)	–6.0 (P=0.06)	–5.0 (P=0.01)
Grassi et al[23]	20	43.7	25.4	50	100-g dark chocolate for 15 days	135.5 (±5.8)/88.0 (±4.1)	123.6 (±6.3)/79.6 (±5.4)	–11.9 (P<0.0001)	–8.4 (P<0.0001)
Taubert et al[24]	44	63.4	24	45.5	6.3-g dark chocolate for 18 wk	147.7 (±7.1)/86.4 (±4.1)	144.8/84.5	–2.9 (P<0.001)	–1.9 (P<0.001)
Grassi et al[25]	19	44.8	26.5	57.9	100-g dark chocolate for 15 days	134.6 (±4.4)/86.8 (±3.7)	130.1 (±5.0)/82.6 (±5.4)	–4.52 (P<0.05)	–4.17 (P<0.05)
Al-Faris[26]	89	21.3	22	0	100-g dark chocolate for 15 days	115.9 (±12.6)/73 (±9.9)	107.5 (±8.6)/67.7 (±9.7)	–8.4 (P<0.05)	–5.3 (P<0.05)
Muniyappa et al[27]	20	51	33.2	40	Cocoa drink (900 mg flavanol) for 14 days	141 (±3)/91 (±3)	139 (±2)/88(± 2)	–1.0 (P=0.74)	+1.0 (P=0.48)
Bogdanski et al[28]	56	49.2	32.5	46	379-mg green tea extract for 3 mo	145 (±10)/88 (±4)	141 (±8)/84 (±3)	–4.0 (P=0.004)	–4.0 (P<0.001)
Petyaev et al[29]	29	54	28.4	40	30-g dark chocolate for 28 days	135.5/84.5	128/80.5	–6.5 (P<0.05)	–4.0 (P<0.05)
Rostami et al[30]	60	51	33.2	40	25-g dark chocolate for 8 wk	137 (±10.6)/85.2 (±8.6)	131 (±11.2)/79.2 (±8.9)	–5.93 (P=0.004)	–6.4 (P=0.002)
Dower et al[31]	37	66.4	27	67.6	100-g (–)-epicatechin for 4 wk	129.3 (±14.1)/74.8 (±9.8)	Not available	–0.51 (P=0.84)	–0.06 (P=0.96)
Draijer et al[32]	60	57.6	26.3	55	800-mg polyphenols from grape-wine extract for 4 wk	Not available	Not available	–3.0 (P<0.05)	–1.9 (P<0.05)
Nogueira et al[33]	20	41.1	33.6	0	1500-mg green tea extract for 4 wk	Not available	Not available	–3.61 (P<0.05)	–1.61 (P=0.18)

Most studies were compared with either placebo or low-flavanol controls. BMI indicates body mass index; and BP, blood pressure.

of the diameter of the brachial artery before and after sphygmomanometric compression of the forearm. Compared with the low-flavanol group, high-flavanol cocoa increased FMD by 2.4% (P<0.01) 2 hours after initial consumption and by 1.6% (P<0.01) after 12 weeks.

The role of increasing FMD may also prove to be beneficial in disease states subject to low-flow ischemia, such as peripheral artery disease. In a small study by Loffredo et al,[45] 20 patients with confirmed peripheral artery disease were randomized to receive either 40 g of dark chocolate or 40 g of milk chocolate. Those who received dark chocolate, which was associated with significantly higher serum epicatechin levels, experienced a significant increase in maximal walking distance (+11%; P<0.001), maximal walking time (+15%; P<0.001), and serum nitric oxide (+57%; P<0.001). However, those who received milk chocolate did not experience any significant changes in these parameters.

Furthermore, the question of whether catechin consumption has any effect on coronary vasodilation is of particular importance in the management of coronary artery disease. Flammer et al[46] found that in heart-transplant patients who underwent routine coronary angiograms, ingestion of 40 g of flavanol-rich chocolate compared with control chocolate resulted in a significant increase in coronary artery diameter (2.36±0.51 to 2.51±0.59 mm; P<0.01). In this study, subjects underwent coronary angiograms both before and 2 hours after consumption of either 40 g of dark chocolate (0.27 mg/g catechin and 0.9 mg/g epicatechin) or control chocolate (flavanoid free). Each angiogram included imaging at rest and after immersion of the subject's hand in ice water for 2 minutes. Interestingly, after cold-water immersion, subjects who consumed cocoa experienced coronary vasodilation (+4.5%±11.4%), whereas controls experienced coronary vasoconstriction (–4.3%±11.7%; P=0.018). This finding may have implications in cases of coronary vasospasm; however, as only acute ingestion of cocoa was studied, it is unclear if the same effects can be extrapolated to chronic consumption. Some studies, however, have demonstrated a neutral effect of catechins on FMD. In a study involving 40 hypertensive subjects randomized to either a flavanol-rich drink (roughly 900 mg flavanol/d) or placebo for 2 weeks, there was no significant difference in FMD found.[27]

Atherosclerosis

The majority of studies assessing the effect of catechin consumption on atherosclerosis are based on animal models and epidemiological studies. One of the largest studies is a prospective cohort study that surveyed 34 492 postmenopausal

Table 2. Major Clinical Studies Evaluating the Effect of Catechin Consumption on Flow-Mediated Dilation

Author	No of Subjects, N	Mean Age, y	Mean BMI, kg/m^2	Male, %	Vehicle for Catechin	FMD (%) Preintervention	FMD (%) Postintervention, mm Hg	Mean Change in FMD, %
Engler et al[35]	21	31.8	23.2	52.4	120-g flavonoid-rich dark chocolate for 14 days	10.2 (±1.3)	Not available	+1.33 (P=0.024)
Grassi et al[23]	20	43.7	25.4	50	100-g dark chocolate for 15 days	7.4 (±1.4%)	8.9 (±1.4)	+1.5 (P<0.05)
Balzer et al[36]	41	63.1	32.1	61.9	Cocoa (963 mg flavanol) for 30 days	3.3 (±1.1)	4.3 (±1.2)	+5.5 (P<0.001)
Davison et al[37]	49	45.3	33.5	36.7	Cocoa (902 mg flavanol) for 12 wk	4.3	Not available	+2.4 (P<0.01)
Draijer et al[32]	60	57.6	26.3	55	800-mg polyphenols from grape-wine extract for 4 wk	4.8 (±0.3)	4.9 (± 0.3) ±	+0.10 (P>0.05)

Additional studies with variations on FMD measurement process not included. FMD indicates flow-mediated dilation.

women between ages 55 and 69 over the span of 13 years and showed that there is an inverse relationship between consumption of foods rich in (+)-catechins and (−)-epicatechins and deaths from coronary artery disease.[16] Even after multivariate adjustment for diabetes mellitus, body mass index, blood pressure, physical activity, pack-years of smoking, estrogen replacement therapy, and micronutrient consumption, including whole grains and polyunsaturated fatty acids, the inverse relationship remained. Those who consumed the highest quantities of (+)-catechins and (−)-epicatechins had a 0.76 relative risk of death from coronary artery disease. Reis et al[47] studied a smaller cohort of 5115 subjects over 20 years and found that tea consumption was associated with a nonsignificant inverse relationship with coronary artery calcification scores. Janszky et al[48] found that in a cohort of 1169 subjects followed for 8 years after their first myocardial infarction, those who had the highest frequency of chocolate consumption had a strong inverse association with subsequent cardiovascular-specific mortality. In fact, when compared with those who never consumed chocolate, those who consumed chocolate 2 or more times per week had a multivariable-adjusted hazard ratio for cardiac mortality of 0.34 (95% CI, 0.17–0.70; P=0.01).

Rodent models have offered the majority of evidence on the mechanisms by which catechins may mitigate atherosclerosis. Hayek et al[49] found that in 40 apolipoprotein E (ApoE)–deficient mice who were fed catechin-rich water at 50 µg/d versus placebo for 6 weeks, atherosclerotic aortic arch lesion areas were 39% smaller (P<0.05) in the catechin group compared with the placebo group. Further, catechin-treated mice had a 31% reduction in low-density lipoprotein cellular uptake and a reduced susceptibility to oxidation. In another rodent study, ApoE-deficient mice were fed an atherogenic diet with or without catechin-rich tea extract, which contained 584 mg/g (−)-epigallocetechin-gallate, 117 mg/g (−)-epigallocatechin, 66 mg/g (−)-epicatechin, 16 mg/g (+)-gallocatechingallate, and 5 mg/g (−)-epicatechingallate. Over a 14-week period, ApoE-deficient mice consumed an average of 3.2 mg/d of tea extract and experienced a significant attenuation in the amount of atherosclerosis in their entire aortic area by 23% compared with controls (P<0.01). Further, tea-treated mice had reductions in their aortic weight by 23% (P<0.001) and cholesterol content by 27% (P=0.01) compared with the controls.[50] These results were further expanded on by Morrison et al,[51] who assessed the effect of pure (−)-epicatechin extracts on female-only ApoE2-leiden mice. In the study, the mice were fed a Western-type diet with supplemental 1% cholesterol for 4 weeks and then given either (−)-epicatechin or control for 16 additional weeks. Both groups were continued on a high-cholesterol diet. After 20 weeks, epicatechin-treated mice consumed roughly 110±11 mg/kg body weight of epicatechin per day and experienced a 27% attenuation in atherosclerotic lesion area compared with control mice not supplemented with epicatechin. The mechanism of atherosclerotic attenuation did not seem to involve prevention of dyslipidemia because epicatechin-treated mice had no significant differences in total cholesterol levels of lipoprotein profiles.[51] In another study by Auclair et al,[52] male apoE-deficient mice who were fed a high-catechin diet for 6 weeks at doses of 0.02% of total meal, which equates to roughly 100 mg/d in human intake, had a 32% reduction of the mean atherosclerotic lesion area as compared with a control group not supplemented with catechins (P<0.01). Further, catechin-treated mice demonstrated downregulation of numerous atherogenic genes, including the gene that encodes for lipoprotein lipase. Lipoprotein lipase is a rate-limiting enzyme that breaks down circulating triglycerides from chylomicrons and very low–density lipoproteins into free fatty acids and low-density lipoproteins. Other genes involved in the direct cascade of atherogenesis, such as *SCARA5*, *FABP4*, *CD34*, and *Selpl*, were also significantly downregulated. These studies highlight the inverse relationship between catechin consumptions and both in situ atherosclerosis and coronary artery events.

Antiplatelet and Antithrombotic Effects

Catechin consumption also seems to have an inverse relationship with platelet aggregation and subsequent thrombus formation, although this relationship is less defined. Pearson et al examined the effect of cocoa on ex vivo platelet function in 16 healthy adults and found that flavanol-rich cocoa effectively inhibited epinephrine-stimulated platelet activation.[53] In

the study, subjects consumed 81 mg aspirin, aspirin plus cocoa (containing 897 mg epicatechin), and cocoa alone on 3 different crossover days, separated by 14 days when aspirin was consumed. Platelet activation was assessed 2 hours and 6 hours after consumption using ex vivo assays for PAC-1 (procaspace-activating compound), which binds to GPIIb/IIIa, and P-selection, a marker for activated platelets. Cocoa consumption significantly reduced GpIIb/IIIa expression 2 hours after consumption (P=0.005); however, it had no effect on P-selection expression. Platelet function was also assessed using an analyzer that measured collagen–epinephrine and collagen–ADP platelet plug formation under shear stress. The authors found that cocoa significantly reduced both CEPI (collagen and epinephrine)-stimulated closure times at 6 hours and CADP (collagen and adenosine disphosphate)-stimulated closure times at 2 hours. Overall, these results suggest a significant reduction in platelet activation and function after catechin consumption. However, other studies have shown less promising results on the relationship between catechin consumption and platelet aggregation. Duffy et al[54] analyzed platelet aggregation studies in 49 subjects with confirmed coronary artery disease who consumed either 900 mL of black tea or water daily. Tea concentration contained roughly 13 mg/dL of total catechins. After 8 weeks, there was no significant difference in ex vivo platelet aggregation between the 2 groups using either ADP (adenosine disphosphate)-induced or TRAP (thrombin receptor agonist peptide)-induced assays. However, notably in this study, all subjects were taking high dose aspirin as part of their coronary artery disease regimen, so it is not entirely clear if tea consumption would have demonstrated an effect in the absence of aspirin.

Conclusions

There is a large body of evidence that supports the numerous cardioprotective effects of catechin consumption, namely, a reduction in systemic blood pressure, increase in FMD, and an attenuation of atherosclerosis, platelet activation, and thrombosis formation. Blood pressure reduction is the most validated association, particularly with use of dark chocolate at 100 g daily. These findings suggest that catechins may be one of the key mediators of cardiovascular health in previously established heart-healthy diets, such as the DASH diet or the Mediterranean diet. Overall, there does not seem to be significant adverse effects to excess catechin consumption aside from an overabundance of concomitant macronutrients in catechin-rich foods, such as the sugar or saturated fat content found in chocolate. Nonetheless, many questions remain unanswered regarding the effects of catechins. It is unclear whether trials that exhibited statistical significance will translate to clinical significance with respect to reducing long-term cardiovascular outcomes. Further, a chief criticism of the current literature is that catechin-containing food is frequently used as a surrogate for catechins, which may be confounded by the presence of alternative components within the food items. Future efforts should focus on placebo-controlled trials involving pure catechin derivatives and a patient population with preexisting cardiovascular disease. At present, several larger trials are currently underway, such as the COCOA-BP trial (Chocolate Consumption And Blood Pressure) and the FLAVASCULAR study (The Effects of Apple Derived Flavanols on Cardiovascular Disease Risk), which both seek to evaluate the effect of catechin-rich food on systemic blood pressure.[55,56] The potential implications of such research would be particularly meaningful for future pharmaceutical drug development should larger scale trials corroborate the current medical literature.

Disclosures

None.

References

1. American Heart Association Nutrition Committee; Lichtenstein AH, Appel LJ, Brands M, et al. Diet and lifestyle recommendations revision 2006: A scientific statement from the American Heart Association Nutrition Committee. *Circulation*. 2006;114:82–96.
2. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, Windhauser MM, Lin PH, Karanja N. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med*. 1997;336:1117–1124. doi: 10.1056/NEJM199704173361601.
3. Eckel RH, Jakicic JM, Ard JD, et al.; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25 suppl 2):S76–S99. doi: 10.1161/01.cir.0000437740.48606.d1.
4. Sacks FM, Obarzanek E, Windhauser MM, Svetkey LP, Vollmer WM, McCullough M, Karanja N, Lin PH, Steele P, Proschan MA. Rationale and design of the Dietary Approaches to Stop Hypertension trial (DASH). A multicenter controlled-feeding study of dietary patterns to lower blood pressure. *Ann Epidemiol*. 1995;5:108–118.
5. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Miller ER 3rd, Simons-Morton DG, Karanja N, Lin PH; DASH-Sodium Collaborative Research Group. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med*. 2001;344:3–10. doi: 10.1056/NEJM200101043440101.
6. Parikh A, Lipsitz SR, Natarajan S. Association between a DASH-like diet and mortality in adults with hypertension: findings from a population-based follow-up study. *Am J Hypertens*. 2009;22:409–416. doi: 10.1038/ajh.2009.10.
7. Levitan EB, Wolk A, Mittleman MA. Consistency with the DASH diet and incidence of heart failure. *Arch Intern Med*. 2009;169:851–857. doi: 10.1001/archinternmed.2009.56.
8. Reedy J, Krebs-Smith SM, Miller PE, Liese AD, Kahle LL, Park Y, Subar AF. Higher diet quality is associated with decreased risk of all-cause, cardiovascular disease, and cancer mortality among older adults. *J Nutr*. 2014;144:881–889. doi: 10.3945/jn.113.189407.
9. Knoops KT, de Groot LC, Kromhout D, Perrin AE, Moreiras-Varela O, Menotti A, van Staveren WA. Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: the HALE project. *JAMA*. 2004;292:1433–1439. doi: 10.1001/jama.292.12.1433.
10. Donovan JL, Bell JR, Kasim-Karakas S, German JB, Walzem RL, Hansen RJ, Waterhouse AL. Catechin is present as metabolites in human plasma after consumption of red wine. *J Nutr*. 1999;129:1662–1668.
11. Arts IC, Hollman PC, Feskens EJ, Bueno de Mesquita HB, Kromhout D. Catechin intake might explain the inverse relation between tea consumption and ischemic heart disease: the Zutphen Elderly Study. *Am J Clin Nutr*. 2001;74:227–232.
12. Kwik-Uribe C, Bektash RM. Cocoa flavanols - measurement, bioavailability and bioactivity. *Asia Pac J Clin Nutr*. 2008;17(suppl 1):280–283.
13. Hammerstone JF, Lazarus SA, Schmitz HH. Procyanidin content and variation in some commonly consumed foods. *J Nutr*. 2000;130(8S suppl):2086S–2092S.
14. Holt RR, Lazarus SA, Sullards MC, Zhu QY, Schramm DD, Hammerstone JF, Fraga CG, Schmitz HH, Keen CL. Procyanidin dimer B2 [epicatechin-(4beta-8)-epicatechin] in human plasma after the consumption of a flavanol-rich cocoa. *Am J Clin Nutr*. 2002;76:798–804.
15. Ottaviani JI, Momma TY, Kuhnle GK, Keen CL, Schroeter H. Structurally related (-)-epicatechin metabolites in humans: assessment using de novo chemically synthesized authentic standards. *Free Radic Biol Med*. 2012;52:1403–1412. doi: 10.1016/j.freeradbiomed.2011.12.010.

16. Arts IC, Jacobs DR Jr, Harnack LJ, Gross M, Folsom AR. Dietary catechins in relation to coronary heart disease death among postmenopausal women. *Epidemiology*. 2001;12:668–675.
17. Ried K, Sullivan T, Fakler P, Frank OR, Stocks NP. Does chocolate reduce blood pressure? A meta-analysis. *BMC Med*. 2010;8:39. doi: 10.1186/1741-7015-8-39.
18. Ried K, Sullivan TR, Fakler P, Frank OR, Stocks NP. Effect of cocoa on blood pressure. *Cochrane Database Syst Rev*. 2012;8:CD008893.
19. Ellinger S, Reusch A, Stehle P, Helfrich HP. Epicatechin ingested via cocoa products reduces blood pressure in humans: a nonlinear regression model with a Bayesian approach. *Am J Clin Nutr*. 2012;95:1365–1377. doi: 10.3945/ajcn.111.029330.
20. Buijsse B, Weikert C, Drogan D, Bergmann M, Boeing H. Chocolate consumption in relation to blood pressure and risk of cardiovascular disease in German adults. *Eur Heart J*. 2010;31:1616–1623. doi: 10.1093/eurheartj/ehq068.
21. Taubert D, Berkels R, Roesen R, Klaus W. Chocolate and blood pressure in elderly individuals with isolated systolic hypertension. *JAMA*. 2003;290:1029–1030. doi: 10.1001/jama.290.8.1029.
22. Fraga CG, Actis-Goretta L, Ottaviani JI, Carrasquedo F, Lotito SB, Lazarus S, Schmitz HH, Keen CL. Regular consumption of a flavanol-rich chocolate can improve oxidant stress in young soccer players. *Clin Dev Immunol*. 2005;12:11–17.
23. Grassi D, Necozione S, Lippi C, Croce G, Valeri L, Pasqualetti P, Desideri G, Blumberg JB, Ferri C. Cocoa reduces blood pressure and insulin resistance and improves endothelium-dependent vasodilation in hypertensives. *Hypertension*. 2005;46:398–405. doi: 10.1161/01.HYP.0000174990.46027.70.
24. Taubert D, Roesen R, Lehmann C, Jung N, Schömig E. Effects of low habitual cocoa intake on blood pressure and bioactive nitric oxide: a randomized controlled trial. *JAMA*. 2007;298:49–60. doi: 10.1001/jama.298.1.49.
25. Grassi D, Desideri G, Necozione S, Lippi C, Casale R, Properzi G, Blumberg JB, Ferri C. Blood pressure is reduced and insulin sensitivity increased in glucose-intolerant, hypertensive subjects after 15 days of consuming high-polyphenol dark chocolate. *J Nutr*. 2008;138:1671–1676.
26. Al-Faris NA. Short-term consumption of a dark chocolate containing flavanols is followed by a significant decrease in normotensive population. *Pakistan Journal of Nutrition*. 2008;7:773–781.
27. Muniyappa R, Hall G, Kolodziej TL, Karne RJ, Crandon SK, Quon MJ. Cocoa consumption for 2 wk enhances insulin-mediated vasodilatation without improving blood pressure or insulin resistance in essential hypertension. *Am J Clin Nutr*. 2008;88:1685–1696. doi: 10.3945/ajcn.2008.26457.
28. Bogdanski P, Suliburska J, Szulinska M, Stepien M, Pupek-Musialik D, Jablecka A. Green tea extract reduces blood pressure, inflammatory biomarkers, and oxidative stress and improves parameters associated with insulin resistance in obese, hypertensive patients. *Nutr Res*. 2012;32:421–427. doi: 10.1016/j.nutres.2012.05.007.
29. Petyaev IM, Dovgalevsky PY, Chalyk NE, Klochkov V, Kyle NH. Reduction in blood pressure and serum lipids by lycosome formulation of dark chocolate and lycopene in prehypertension. *Food Sci Nutr*. 2014;2:744–750. doi: 10.1002/fsn3.169.
30. Rostami A, Khalili M, Haghighat N, Eghtesadi S, Shidfar F, Heidari I, Ebrahimpour-Koujan S, Eghtesadi M. High-cocoa polyphenol-rich chocolate improves blood pressure in patients with diabetes and hypertension. *ARYA Atheroscler*. 2015;11:21–29.
31. Dower JI, Geleijnse JM, Gijsbers L, Schalkwijk C, Kromhout D, Hollman PC. Supplementation of the Pure Flavonoids Epicatechin and Quercetin Affects Some Biomarkers of Endothelial Dysfunction and Inflammation in (Pre)Hypertensive Adults: A Randomized Double-Blind, Placebo-Controlled, Crossover Trial. *J Nutr*. 2015;145:1459–1463. doi: 10.3945/jn.115.211888.
32. Draijer R, de Graaf Y, Slettenaar M, de Groot E, Wright CI. Consumption of a polyphenol-rich grape-wine extract lowers ambulatory blood pressure in mildly hypertensive subjects. *Nutrients*. 2015;7:3138–3153. doi: 10.3390/nu7053138.
33. Nogueira LP, Nogueira Neto JF, Klein MR, Sanjuliani AF. Short-term effects of green tea on blood pressure, endothelial function, and metabolic profile in obese prehypertensive women: A crossover randomized clinical trial. *J Am Coll Nutr*. 2016;31:1–8.
34. Blekkenhorst LC, Prince RL, Hodgson JM, Lim WH, Zhu K, Devine A, Thompson PL, Lewis JR. Dietary saturated fat intake and atherosclerotic vascular disease mortality in elderly women: a prospective cohort study. *Am J Clin Nutr*. 2015;101:1263–1268. doi: 10.3945/ajcn.114.102392.
35. Engler MB, Engler MM, Chen CY, Malloy MJ, Browne A, Chiu EY, Kwak HK, Milbury P, Paul SM, Blumberg J, Mietus-Snyder ML. Flavonoid-rich dark chocolate improves endothelial function and increases plasma epicatechin concentrations in healthy adults. *J Am Coll Nutr*. 2004;23:197–204.
36. Balzer J, Rassaf T, Heiss C, Kleinbongard P, Lauer T, Merx M, Heussen N, Gross HB, Keen CL, Schroeter H, Kelm M. Sustained benefits in vascular function through flavanol-containing cocoa in medicated diabetic patients a double-masked, randomized, controlled trial. *J Am Coll Cardiol*. 2008;51:2141–2149. doi: 10.1016/j.jacc.2008.01.059.
37. Davison K, Coates AM, Buckley JD, Howe PR. Effect of cocoa flavanols and exercise on cardiometabolic risk factors in overweight and obese subjects. *Int J Obes (Lond)*. 2008;32:1289–1296. doi: 10.1038/ijo.2008.66.
38. Moens AL, Goovaerts I, Claeys MJ, Vrints CJ. Flow-mediated vasodilation: a diagnostic instrument, or an experimental tool? *Chest*. 2005;127:2254–2263. doi: 10.1378/chest.127.6.2254.
39. Inaba Y, Chen JA, Bergmann SR. Prediction of future cardiovascular outcomes by flow-mediated vasodilatation of brachial artery: a meta-analysis. *Int J Cardiovasc Imaging*. 2010;26:631–640. doi: 10.1007/s10554-010-9616-1.
40. Schroeter H, Heiss C, Balzer J, Kleinbongard P, Keen CL, Hollenberg NK, Sies H, Kwik-Uribe C, Schmitz HH, Kelm M. (-)-Epicatechin mediates beneficial effects of flavanol-rich cocoa on vascular function in humans. *Proc Natl Acad Sci U S A*. 2006;103:1024–1029. doi: 10.1073/pnas.0510168103.
41. Benito S, Lopez D, Sáiz MP, Buxaderas S, Sánchez J, Puig-Parellada P, Mitjavila MT. A flavonoid-rich diet increases nitric oxide production in rat aorta. *Br J Pharmacol*. 2002;135:910–916. doi: 10.1038/sj.bjp.0704534.
42. Ramirez-Sanchez I, Maya L, Ceballos G, Villarreal F. (-)-Epicatechin induces calcium and translocation independent eNOS activation in arterial endothelial cells. *Am J Physiol Cell Physiol*. 2011;300:C880–C887. doi: 10.1152/ajpcell.00406.2010.
43. Ramirez-Sanchez I, Maya L, Ceballos G, Villarreal F. (-)-epicatechin activation of endothelial cell endothelial nitric oxide synthase, nitric oxide, and related signaling pathways. *Hypertension*. 2010;55:1398–1405. doi: 10.1161/HYPERTENSIONAHA.109.147892.
44. Fisher ND, Hughes M, Gerhard-Herman M, Hollenberg NK. Flavanol-rich cocoa induces nitric-oxide-dependent vasodilation in healthy humans. *J Hypertens*. 2003;21:2281–2286. doi: 10.1097/01.hjh.0000084783.15238.eb.
45. Loffredo L, Perri L, Catasca E, Pignatelli P, Brancorsini M, Nocella C, De Falco E, Bartimoccia S, Frati G, Carnevale R, Violi F. Dark chocolate acutely improves walking autonomy in patients with peripheral artery disease. *J Am Heart Assoc*. 2014;3:e001072.
46. Flammer AJ, Hermann F, Sudano I, Spieker L, Hermann M, Cooper KA, Serafini M, Lüscher TF, Ruschitzka F, Noll G, Corti R. Dark chocolate improves coronary vasomotion and reduces platelet reactivity. *Circulation*. 2007;116:2376–2382. doi: 10.1161/CIRCULATIONAHA.107.713867.
47. Reis JP, Loria CM, Steffen LM, Zhou X, van Horn L, Siscovick DS, Jacobs DR Jr, Carr JJ. Coffee, decaffeinated coffee, caffeine, and tea consumption in young adulthood and atherosclerosis later in life: the CARDIA study. *Arterioscler Thromb Vasc Biol*. 2010;30:2059–2066. doi: 10.1161/ATVBAHA.110.208280.
48. Janszky I, Mukamal KJ, Ljung R, Ahnve S, Ahlbom A, Hallqvist J. Chocolate consumption and mortality following a first acute myocardial infarction: the Stockholm Heart Epidemiology Program. *J Intern Med*. 2009;266:248–257.
49. Hayek T, Fuhrman B, Vaya J, Rosenblat M, Belinky P, Coleman R, Elis A, Aviram M. Reduced progression of atherosclerosis in apolipoprotein E-deficient mice following consumption of red wine, or its polyphenols quercetin or catechin, is associated with reduced susceptibility of LDL to oxidation and aggregation. *Arterioscler Thromb Vasc Biol*. 1997;17:2744–2752.
50. Miura Y, Chiba T, Tomita I, Koizumi H, Miura S, Umegaki K, Hara Y, Ikeda M, Tomita T. Tea catechins prevent the development of atherosclerosis in apoprotein E-deficient mice. *J Nutr*. 2001;131:27–32.
51. Morrison M, van der Heijden R, Heeringa P, Kaijzel E, Verschuren L, Blomhoff R, Kooistra T, Kleemann R. Epicatechin attenuates atherosclerosis and exerts anti-inflammatory effects on diet-induced human-CRP and NFκB in vivo. *Atherosclerosis*. 2014;233:149–156. doi: 10.1016/j.atherosclerosis.2013.12.027.
52. Auclair S, Milenkovic D, Besson C, Chauvet S, Gueux E, Morand C, Mazur A, Scalbert A. Catechin reduces atherosclerotic lesion development in apo E-deficient mice: a transcriptomic study. *Atherosclerosis*. 2009;204:e21–e27. doi: 10.1016/j.atherosclerosis.2008.12.007.

53. Pearson DA, Paglieroni TG, Rein D, Wun T, Schramm DD, Wang JF, Holt RR, Gosselin R, Schmitz HH, Keen CL. The effects of flavanol-rich cocoa and aspirin on ex vivo platelet function. *Thromb Res*. 2002;106:191–197.
54. Duffy SJ, Vita JA, Holbrook M, Swerdloff PL, Keaney JF Jr. Effect of acute and chronic tea consumption on platelet aggregation in patients with coronary artery disease. *Arterioscler Thromb Vasc Biol*. 2001;21:1084–1089.
55. ChOcolate COnsumption and blood pressure (COCOA-BP): A wearable devices pilot trial (COCOA-BP). 2017. Available from https://clinicaltrials.gov/ct2/show/NCT02764203.
56. The effects of apple derived flavanols on cardiovascular disease risk (FLAVASCULAR study) (FLAVASCULAR). 2017. Available from https://clinicaltrials.gov/ct2/show/NCT02013856.

Highlights

- Catechins are flavonoids found in common plant foods, such as cocoa, tea, apples, and legumes.
- Diets that are rich in catechins may play a role in cardiovascular disease and mortality reduction.
- Catechins are associated with reductions in systemic blood pressure, thrombosis, and platelet activity.
- Catechins are associated with improvement in flow-mediated vasodilation, coronary artery vasodilation, and peripheral vasodilation.

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