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Cocoa and Cardiovascular Health

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Abstract—Epidemiological data demonstrate that regular dietary intake of plant-derived foods and beverages reduces the risk of coronary heart disease and stroke. Among many ingredients, cocoa might be an important mediator. Indeed, recent research demonstrates a beneficial effect of cocoa on blood pressure, insulin resistance, and vascular and platelet function. Although still debated, a range of potential mechanisms through which cocoa might exert its benefits on cardiovascular health have been proposed, including activation of nitric oxide and antioxidant and antiinflammatory effects. This review summarizes the available data on the cardiovascular effects of cocoa, outlines potential mechanisms involved in the response to cocoa, and highlights the potential clinical implications associated with its consumption. (*Circulation*. 2009;119:1433-1441.)

Key Words: cocoa ■ endothelium ■ hypertension ■ platelets

For centuries, cocoa-rich chocolate has been known not only for its good taste but also for its proposed health effects. Indeed, the Incas considered it the drink of gods, an association that gave rise to the scientific name of the cocoa tree, *Theobroma cacao*, from the Greek words theo (god) and broma (drink). The first hints of cocoa consumption date back to 1600 BC. In Honduras, archeologists uncovered elaborately designed bowls of this period that are believed to have been used by the Aztecs to drink liquid cocoa thousands of years ago.¹ In the 16th century, Aztec Emperor Montezuma was a keen admirer of cocoa, calling it a “divine drink, which builds up resistance and fights fatigue. A cup of this precious drink permits a man to walk for a whole day without food” (Hernán Cortés, 1519). In the language of the Aztecs, this drink was called chocolatl. With the discovery of the New World, cocoa came to Europe in the 16th century.² Since then, the modern chocolate industry has developed, and cocoa seeds are now processed in different ways.

Several supposed health effects of cocoa have been considered, including improved heart function and relief of angina pectoris, stimulation of the nervous system, facilitated digestion, and improved kidney and bowel function. In addition, cocoa has been used to treat anemia, mental fatigue, tuberculosis, fever, gout, kidney stones, and even poor sexual appetite.² In the 19th century, chocolate became a luxury item; hence, its consumption was a sin rather than a remedy. Nowadays, chocolate is associated with caries, obesity, high blood pressure, and diabetes. Therefore, many physicians currently tend to warn patients about the potential health hazards of consuming large amount of chocolate-based nutrients. However, the recent discovery of biologically active

phenolic compounds in cocoa has changed this perception³ and stimulated research on its effects in ageing, blood pressure regulation, and atherosclerosis.

Here, we review the clinically relevant cardiovascular effects of cocoa, focusing on potential mechanisms involved in the response to cocoa and the potential clinical implications associated with its consumption. It is important to strictly differentiate between the natural product *cacao* and the processed product *chocolate*, which refers to the combination of cocoa, sugar, and eventually milk and other ingredients into a solid food product. Many of the health effects of cocoa and its contents discussed here may not be applicable to chocolate.

Epidemiological Evidence

Epidemiological data demonstrate that regular dietary intake of plant-derived foods and beverages reduces the risk of coronary heart disease⁴⁻⁷ and stroke⁸ and is inversely associated with the risk of cardiovascular disease.^{5,7}

First evidence of a similar effect of cocoa was obtained in Kuna Indians, a native population living on islands off the coast of Panama. The Kuna belong to one of the few cultures that are protected against the age-dependent increase in blood pressure and the development of arterial hypertension. Interestingly, the Kunas consume enormous amounts of cocoa daily, sometimes even enriched with salt.⁹ Clinical studies revealed that the Kunas indeed have lower blood pressure values⁹ and no age-dependent decline in kidney function.¹⁰ Moreover, in this native population, mortality resulting from cardiovascular events is markedly lower compared with other Pan-American citizens (9.2±3.1 versus 83.4±0.7 age-adjusted

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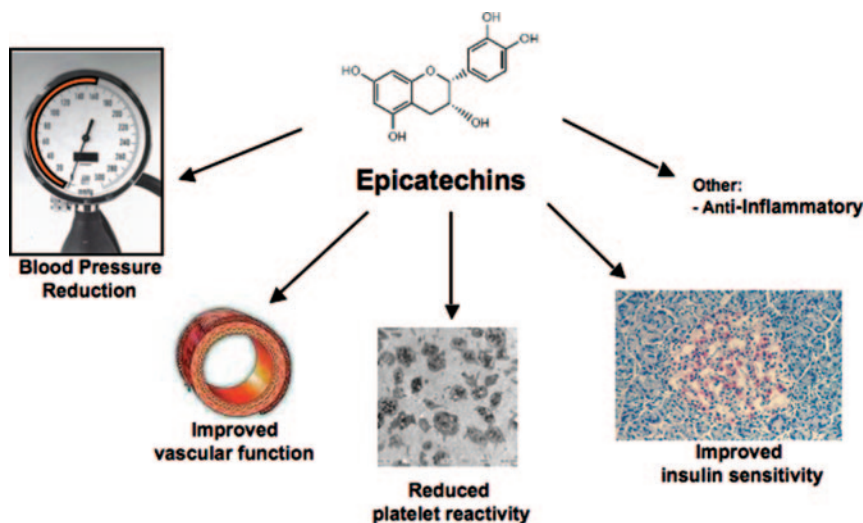


Figure 1. Health-relevant effect of epicatechins.

deaths per 100'000).¹¹ The factors involved are clearly environmental rather than genetic because this protection is lost on migration to urban Panama City, where the home-prepared cocoa is replaced by other food with a lower flavanol content.⁹

A prospective study in 34 489 postmenopausal women with a 16-year follow-up in the Iowa Women's Health Study who were free of cardiovascular disease found that foods rich in flavonoids were associated with a decreased risk of death caused by coronary heart disease. Furthermore, a borderline significant inverse association between chocolate intake and cardiovascular mortality after multivariate adjustment was observed.¹² The Dutch Zutphen Study provided important further data. In a cross-sectional analysis, cocoa intake was inversely related to blood pressure, and in a prospective analysis, intake was associated with a reduction of cardiovascular and all-cause mortality.¹³ Indeed, the Zutphen Elderly Study, involving 470 elderly men free of chronic disease, highlighted the protective effects of cocoa intake. After adjustment for age, body mass index, lifestyle factors, drug use, food, and caloric intake, the risk of cardiovascular mortality for men in the highest tertile of cocoa intake was reduced by 50% compared with the lowest tertile ($P=0.004$). The adjusted relative risk for all-cause mortality was 0.53 (95% CI, 0.39 to 0.72; $P\leq 0.001$).

Cocoa Polyphenols

These epidemiological observations led to the hypothesis that such health benefits might be linked, at least in part, to plant-derived flavonoids, a large subgroup of the heterogeneous group of polyphenols. All flavonoids share a common chemical structure: C6-C3-C6 (Figure 1). Flavonoids can be further distinguished: flavonols, flavones, isoflavones, flavanones, anthocyanidins, and flavanols.¹⁴ Flavanols (also called flavan-3-ols) have attracted particular interest because they can be found in high concentrations in certain fruits and vegetables. In the context of human nutrition, certain teas, grape juice, wine, various berries, and especially cocoa represent noteworthy sources (Table 1). Flavanols occur as the monomers epicatechin and catechin, which are the main flavanols in fruits.¹⁵ These monomers can form links between

C4 and C8, allowing them to assemble as dimers, oligomers, and polymers of catechins, the so-called procyanidins.¹⁶ Procyanidins are also known as condensed tannins, which, through the formation of complexes with salivary proteins, are responsible for the bitterness of cacao.¹⁴

After oral intake of cocoa, both the flavanol content and the total antioxidant capacity in plasma increase. These effects appear to be markedly reduced when cocoa is consumed with milk or if cocoa is ingested as milk chocolate¹⁷; however, this finding is controversial.^{18,19} The highest plasma peak concentrations of flavanols are obtained 2 to 3 hours after ingestion in a dose-dependent manner^{17,20} and are still measurable after 8 hours.²¹ In addition, molecular size matters; ie, the smaller the polyphenol is, the higher the concentration in blood is. However, there is a large interpersonal variation in absorption. Therefore, a single measurement of plasma levels at 2 hours cannot be considered a measurement of bioavailability but rather a check for compliance, limiting the usefulness of this measure.²²

Beside molecular size, there are other important factors modulating the in vivo efficacy of polyphenols that must be considered, eg, their metabolic conversion in intestinal cells, liver, and other tissues; their binding to proteins; their accumulation in cells; and the urinary elimination rate.²³

Table 1. Catechin/Epicatechin Concentrations Found in Food¹⁴

Source	Flavanol Content, mg/kg or mg/L
Chocolate	460–610
Beans	350–550
Apricots	100–250
Cherries	50–220
Peaches	50–140
Blackberries	130
Apples	20–120
Green tea	100–800
Black tea	60–500
Red wine	80–300
Cider	40



Figure 2. The fruit of the theobroma cocoa tree.

Therefore, careful distinction between *in vitro* and *in vivo* effects of flavanols is mandatory. For example, although procyanidins are biologically active *in vitro*, they are hardly absorbed in the intestine and thus are largely inactive *in vivo*.

An important point is that, during the conventional chocolate manufacturing process from fresh cocoa seeds (Figure 2) to the final product, the concentration of flavanols markedly decreases.²⁴ In particular, food processing methods such as fermentation and roasting have a detrimental impact on the final flavanol content of foods. Furthermore, flavanol concentrations may depend on the agricultural origin of the raw cocoa.²⁵ In particular, milk chocolate has the lowest flavanol content compared with cocoa powder and dark chocolate.²⁶

Although still debated, a range of potential mechanisms through which flavanols and cocoa might exert their benefits on cardiovascular health have been proposed (Figure 3): activation of nitric oxide (NO) and antioxidant, antiinflammatory, and antiplatelet effects, which in turn might improve endothelial function, lipid levels, blood pressure, insulin resistance, and eventually clinical outcome.²⁷

Possible Mechanisms of the Protective Effects of Cocoa

Endothelial Function and NO

The endothelium is a continuous, smooth, nonthrombogenic surface of all blood vessels that exhibits a highly selective permeability in its healthy state. It synthesizes and releases a broad range of vasoactive substances. Functional impairment of the vascular endothelium in response to injury occurs long before the development of structural atherosclerotic changes. NO, synthesized by endothelial NO synthase (eNOS) from L-arginine²⁸ in the presence of the cofactor tetrahydrobiopterin, is released from endothelial cells mainly in response to shear stress elicited by the circulating blood or receptor-operated substances such as acetylcholine, bradykinin, or serotonin.²⁹ NO has an *in vivo* half-life of only a few seconds and rapidly crosses biological membranes. After diffusion from endothelial to vascular smooth muscle cells, NO increases intracellular cGMP concentrations and, in turn, induces a relaxation of vascular smooth muscle cells.^{30,31} However, NO not only leads to vasodilation but also prevents leukocyte adhesion and migration, smooth muscle cell proliferation, and platelet adhesion and aggregation. Reduced

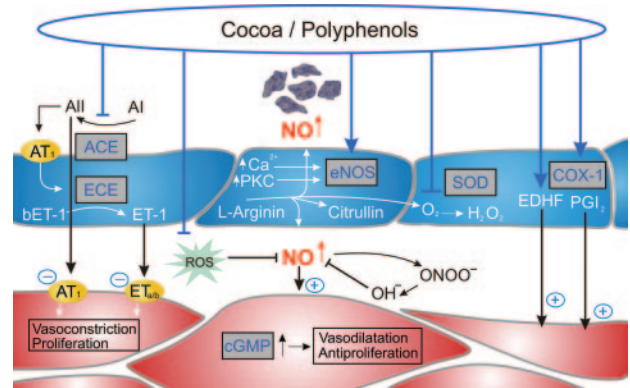


Figure 3. Endothelium-dependent effect of cocoa polyphenols. NO is released from endothelial cells mainly in response to shear stress elicited by the circulating blood or receptor-operated substances such as acetylcholine, bradykinin, or serotonin. NO is synthesized by eNOS from L-arginine in the presence of the cofactor tetrahydrobiopterin. The activation may be due to an increase in Ca^{2+} or a phosphorylation of eNOS by the PI3-kinase/Akt pathway. Cocoa also lowers vascular arginase activity in human endothelial cell *in vitro*, thus augmenting the local levels of L-arginine. Once released, NO increases intracellular cGMP concentrations and, in turn, induces a relaxation of vascular smooth muscle cells. NO not only leads to vasodilation but also prevents leukocyte adhesion and migration, smooth muscle cell proliferation, and platelet adhesion and aggregation. Other NO-mediated mechanisms are discussed. Antioxidant effects may reduce the production of reactive oxidant species, thus contributing to an enhanced endothelial function. Cocoa polyphenols may activate endothelium-derived hyperpolarizing factor (EDHF), increase endothelial prostacyclin release, or inhibit the synthesis of endothelin-1 (ET). Moreover, polyphenols may directly inhibit angiotensin-converting enzyme (ACE). All indicates angiotensin II; AI, angiotensin I; PKC, protein kinase C; SOD, superoxide dismutase; PGI_2 , prostacyclin; ACE, angiotensin-converting enzyme; ECE, endothelin-converting enzyme; AT_1 , angiotensin receptor; ET-1, endothelin 1; bET-1, big endothelin 1; $\text{ET}_{a/b}$, endothelin receptor a and b; cGMP, cyclic guanosine monophosphate; and ROS, reactive oxygen species.

eNOS expression and/or NO bioavailability is associated with endothelial dysfunction and eventually atherosclerotic disease.³² Indeed, endothelial dysfunction is associated with cardiovascular disease. Endothelial dysfunction in the forearm circulation correlates with coronary vascular dysfunction and is predictive of future coronary events.^{33–36}

In patients with coronary artery disease, eating food rich in flavanols, particularly short- and long-term consumption of black tea³⁷ and red wine,^{38,39} mostly improves endothelial function. In healthy smokers, green tea exerts similar effects.⁴⁰ In line with these findings, cocoa induces NO-dependent vasodilation in the rat aorta⁴¹ and in the finger or forearm circulation of healthy humans^{42–44} or patients with cardiovascular risk factors, including diabetes (Table 2).^{45–49}

The underlying mechanisms are still elusive. In cultured endothelial cells^{50,51} and rat aorta,⁵² plant extracts rich in flavonoids increase eNOS activity. Incubation of endothelial cells with flavonoid-rich red wine upregulates eNOS mRNA and protein expression, most likely via stabilization of eNOS mRNA. Furthermore, endothelial cells produce up to 3 times more bioactive NO than control cells under such conditions.⁵³ Cocoa also lowers vascular arginase activity in human endothelial cells *in vitro*, thus

Table 2. Studies Investigating Cocoa and Endothelial Function

Authors	Year	n	Animals/Patients	Duration	Intervention	Outcome
Karim et al ⁴¹	2000	5	Aortic rings from rats	Immediately	Procyanidins derived from cocoa	Endothelium-derived relaxation mediated by activation of NOS
Fisher et al ⁴²	2003	27	Healthy people	5 d	Flavanol-rich cocoa (821 mg/d)	Peripheral vasodilatation, improvement in vasodilator response to ischemia assessed by pulse-wave amplitude on the finger
Engeler et al ⁴³	2004	21	Healthy subjects	2 wk	High-flavonoid chocolate (213 mg procyanidins, 46 mg epicatechin) vs low-flavonoid chocolate	Improvement in flow-mediated vasodilatation of the brachial artery, increase in epicatechin concentrations
Schroeter et al ⁴⁴	2006	16	Healthy subjects, isolated rabbit rings		Drink with high flavanoid content	Improvement in flow-mediated vasodilatation paralleled the appearance of flavanols in plasma; concentrations in plasma enough to mediate ex vivo vasodilatation; pure epicatechins mimic vascular effects of cocoa; high-flavanol diet is associated with high urinary excretion of NO metabolites
Heiss et al ⁴⁵	2003	26	Patients with at least 1 cardiovascular risk factor	2 h (crossover)	Flavanol-rich cocoa drink (100 mL)	Improvement in flow-mediated vasodilatation, increase in levels of nitrosated and nitrosylated species
Hermann et al ⁴⁶	2006	20	Healthy smokers	2 h	40 g commercially available dark chocolate vs white chocolate	Increase in flow-mediated vasodilatation of the brachial artery, improvement in antioxidant status and platelet function
Grassi et al ⁴⁷	2005	20	Patients with untreated essential hypertension	15 d (crossover)	100 g dark chocolate (21.91 mg catechin, 65.97 mg epicatechins) vs flavanol free white chocolate	Increase in flow-mediated vasodilatation of the brachial artery, decrease in blood pressure and LDL cholesterol, increase in insulin sensitivity
Heiss et al ⁴⁸	2005	11	Smokers	2 h (crossover)	100 mL cocoa drink with high (176–18 mg) or low (<11 mg) flavanol content	Increase in flow-mediated vasodilatation and circulating NO pool, increase in flavanol metabolites
Balzer et al ⁴⁹	2008	41	Diabetes	4 wk	Drink with high flavanol content	Improvement in flow-mediated vasodilatation (acute and chronic)
Flammer et al ⁶⁶	2007	22	Heart transplant recipients	2 h	40 g commercially available dark chocolate vs flavanol-free placebo chocolate	Induction of coronary vasodilatation, improvement in coronary endothelial function and platelet function
Grassi et al ⁶⁹	2008	19	Hypertensives, impaired glucose tolerance patients	2 wk	Flavanol-rich dark chocolate	Improvement in flow-mediated vasodilatation, insulin sensitivity, β -cell function, and blood pressure
Shiina et al ¹⁰⁰	2008	39	Healthy subjects	2 wk	45 g commercially available dark chocolate vs white chocolate	Improvement in coronary circulation as measured by coronary velocity flow reserve

augmenting the local levels of L-arginine.⁵⁴ Importantly, cocoa-derived flavanols induce NOS in vitro.⁵⁵

In vivo, in patients with cardiovascular risk factors, including smoking, a cocoa drink high in flavanol content (176 to 185 mg) rapidly enhances the circulating pool of bioactive NO by more than a third and, in turn, augments flow-mediated vasodilation.^{45,48} Moreover, infusion of *N*^G-monomethyl-L-arginine, an inhibitor of NO synthesis, reverses the increase in NO and the augmentation in endothelial function associated with cocoa intake, whereas infusion of ascorbic acid has no effect.⁴⁸ Similarly, in isolated aortic rings, concentrations of flavanols comparable to those occurring in plasma after cocoa intake induce endothelium-dependent

relaxations. Chronic consumption of a high-flavanol diet is associated with a high urinary excretion of NO metabolites, consistent with an augmented NO production or diminished degradation.⁴⁴ Finally, in humans, epicatechins closely mimic the vascular effects of flavanol-rich cocoa, suggesting that they represent the primary mediator of the beneficial effect of cocoa flavanols on vascular function.⁴⁴

At the molecular level, it appears in endothelial cells that the short-term effects of epicatechin are due mainly to diminished inactivation of NO by free radicals through inhibition of NADPH oxidase by epicatechin metabolites, whereas an increased generation of NO as a consequence of higher protein eNOS expression is involved in the long-term

effects.^{23,56} Furthermore, pure epicatechin ingestion not only augments NO bioavailability but also acutely reduces the plasma levels of endothelin-1, a potent endothelium-derived vasoconstrictor in healthy men.⁵⁷

Of interest, drinking a flavonoid-enriched cocoa beverage results in regional changes in cerebral blood flow and an overall increased blood flow to gray matter for up to 3 hours as assessed by functional magnetic resonance imaging.⁵⁸ In addition, in elderly humans, cerebral blood flow velocity in the middle cerebral artery increases, as measured by transcranial Doppler ultrasound,⁵⁹ suggesting that cocoa flavanols may protect against dementia and stroke.

Antioxidant Properties

Besides their direct effects on eNOS expression and activity, cocoa flavanols and procyanidins exert strong antioxidant effects *in vitro*. First evidence came from an experiment in which extracted polyphenols from commercial cocoa delayed low-density lipoprotein (LDL) oxidation.⁶⁰ Other studies showed a reduction in the production of reactive oxygen species in activated leukocytes⁶¹ and an inhibition of ultraviolet-induced DNA oxidation.⁶² In humans, flavanol-rich cocoa counteracts lipid peroxidation and therefore lowers the plasma level of F₂-isoprostanes, markers of *in vivo* lipid peroxidation,⁶³ and plasma levels of oxidized LDL in hypercholesterolemic patients⁶⁴ and increases overall antioxidant capacity.^{16,20} In young healthy smokers, commercially available dark chocolate (74% cocoa), but not white chocolate, markedly improves flow-mediated vasodilation and improves plasma antioxidant status, suggesting that induction of eNOS and, in turn, elevated NO levels and a reduction in the production of reactive oxidant species contribute to the enhanced endothelial function under these conditions.⁴⁶ Indeed, antioxidants may prevent NO transformation into peroxynitrite and protect against vasoconstriction and vascular damage.⁶⁵ Oxidative stress and reduced antioxidant defense play a crucial role in the pathogenesis of atherosclerosis, particularly transplant vasculopathy. We therefore recently assessed in a double-blind, randomized study the effect of flavonoid-rich dark chocolate compared with cocoa-free control chocolate on coronary vasomotion in cardiac transplant recipients. Interestingly, consumption of 40 g dark chocolate induced coronary vasodilation, improved coronary vascular function, and decreased platelet adhesion. These beneficial effects were again paralleled by a reduction in serum oxidative stress as assessed by plasma isoprostanes and were positively related to serum epicatechin concentrations.⁶⁶

However, the antioxidative effects of cocoa have been disputed recently. Indeed, Sies⁶⁷ cautioned that fruits and vegetables contain many macronutrients and micronutrients in addition to flavanols that may directly or through their metabolites affect the total antioxidative capacity of plasma. The large increase in plasma total antioxidative capacity observed after the consumption of flavanol-rich food is probably not due to flavanols but more likely is a consequence of the increased uric acid levels resulting from fructose metabolism.⁶⁸

Platelet Function

Platelet dysfunction is another hallmark of atherosclerotic vascular disease.⁶⁹ Interestingly, in addition to providing antioxidant vitamins, certain fruits and vegetables may also protect against thrombosis because of their high flavanol content.⁷⁰ Several studies have demonstrated platelet inhibitory properties of cocoa.^{71–73} Cocoa reduces ADP/collagen-activated, platelet-related primary hemostasis within hours of ingestion. These effects were explained, at least in part, by a reduction in the ADP-induced expression of the activated conformation of glycoprotein IIb/IIIa surface proteins. Furthermore, similar to low-dose aspirin, *ex vivo* catechin and epicatechin reduce glycoprotein IIb/IIIa expression, thereby exerting antiplatelet effects.⁷² In healthy volunteers, consuming 100 g dark chocolate reduced platelet aggregation, an effect not seen after ingestion of white chocolate or milk chocolate.⁷⁴ Cocoa decreases not only platelet aggregation but also adhesion. In young healthy smokers, dark chocolate reduces platelet adhesion as assessed by a shear stress-dependent platelet test.⁴⁶ Similarly, stearic acid, a saturated fat commonly found in chocolate, reduces mean platelet volume, an index of platelet activation, in humans.^{75,76}

Antihypertensive Effects of Cocoa

Besides the initial observations in Kuna Indians, epidemiological support for the blood pressure-lowering capacity of chocolate comes from the Zutphen Elderly Study. In this cohort of 470 men, cocoa intake was inversely related to blood pressure.¹³ Even after multivariate adjustment, mean systolic blood pressure was 3.8 mm Hg lower in the highest tertile of cocoa intake compared with the lowest tertile. Another study evaluated the association between chocolate consumption and new-onset hypertension in a cohort of university graduates; however, no protection of cocoa was observed.⁷⁷

More evidence on potential antihypertensive properties of cocoa comes from a recently published interventional study that compared the long-term effect of dark compared with white chocolate consumption in patients with prehypertension or stage I hypertension. A small amount of dark chocolate daily (6 g) in the evening significantly reduced mean systolic blood pressure by 2.9±1.6 mm Hg and diastolic blood pressure by 1.9±1.0 mm Hg with no changes in body weight, plasma lipid levels, glucose, and 8-isoprostane.⁷⁸ However, serum levels of S-nitrosoglutathione, which is produced by unstable NO reacting with thiol groups to form a stable product,⁷⁹ were increased in the dark chocolate group. Although preliminary in nature, these changes indicate an increase in NO production as a potential mechanism of the small reduction in blood pressure seen with dark chocolate consumption.⁸⁰

Besides increased eNOS activity, other mechanisms may contribute to the antihypertensive effect of cocoa-rich food. Indeed, either isolated or food-derived flavanols inhibit angiotensin-converting enzyme activity *in vitro*.⁸¹ Whether such angiotensin-converting enzyme inhibition also occurs *in vivo* needs to be evaluated further. Finally, stearic acid or theobromine⁸² may contribute to these effects. Indeed, a cross-sectional linear regression analysis within the Multiple Risk

Factor Intervention Trial found that stearic acid levels are inversely associated with diastolic blood pressure.⁸³

No matter what mechanism is responsible, several independent, albeit small, studies indicate that ingestion of cocoa-rich chocolate has blood pressure-lowering effects. One study reported reductions in systolic and diastolic blood pressures in hypertensive elderly subjects,⁸⁴ and another study noted a decrease in daytime and nighttime blood pressures, as assessed by ambulatory 24-hour measurements, after intake of 100 g flavonoid-rich dark chocolate daily for 2 weeks.⁴⁷ In the latter study, systolic blood pressure decreased after consumption of dark chocolate by 12 mm Hg, whereas white chocolate had no effect. However, other studies showed no effect on blood pressure.^{42,43} Because these studies were performed in a relatively small number of normotensive individuals and with a lower chocolate intake of shorter duration, an antihypertensive effect may have been missed as a result of their study design.⁴²

A recent meta-analysis of randomized controlled studies of cocoa administration (173 subjects; mean duration, 2 weeks) confirmed a significant reduction in pressure: mean systolic and diastolic blood pressures were reduced by 4.7 mm Hg (95% CI, 7.6 to 1.8; $P=0.002$) and 2.8 mm Hg (95% CI, 4.8 to 0.8; $P=0.006$), respectively.⁸⁵ This finding is remarkable in that the blood pressure-lowering effects of currently used antihypertensive drugs are in the same range.

Considering the small number of subjects studied so far and the variable dose of flavanols and/or chocolate used, a large, well-controlled, interventional study appears warranted.

Since the demonstration that treatment of prehypertensive subjects with candesartan reduced the risk of incident hypertension, there has been ongoing discussion about the therapeutic need in this large population.⁸⁶ Therefore, the response to flavanol-rich cocoa in subjects with prehypertensive (Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure VII, 120 to 139 mm Hg) or high-normal (European Society of Cardiology, 130 to 139 mm Hg) blood pressure would be particularly interesting because it could have the potential to delay the onset of hypertension in this population.

Cocoa and Other Antiatherogenic Effects

Insulin Resistance

Insulin sensitivity is partly dependent on insulin-mediated NO release.⁸⁷ Thus, flavanols and dietary antioxidants may decrease insulin resistance by ameliorating NO bioavailability. In line with this concept, Grassi et al^{47,88} reported reduced insulin resistance in patients with essential hypertension after a 15-day diet with 100 g flavonoid-rich chocolate daily. Moreover, in hypertensive patients with impaired glucose tolerance, flavonoid-rich dark chocolate not only reduced blood pressure and improved endothelial function but also ameliorated insulin sensitivity and β -cell function.⁸⁹ Because intravenous infusion of ascorbic acid improves not only flow-mediated dilation but also insulin sensitivity in subjects with impaired glucose tolerance and in smokers,⁹⁰ the antioxidant properties of flavanols might contribute to these beneficial effects of cocoa on insulin sensitivity.

However, because studies with cocoa in diabetics are scarce and because diabetics tend to be obese, recommending cocoa or flavonoid-rich chocolate consumption to such patients should be done cautiously. Nevertheless, experimental evidence in obese diabetic mice suggests that cocoa dose dependently prevents hyperglycemia.⁹¹

Blood Lipids

Cocoa butter, a fat derived from cocoa plants and found predominantly in dark chocolate, contains an average of 33% monounsaturated oleic acid and 33% stearic acid. In general, plant stearic acid neither lowers high-density lipoprotein (HDL) nor increases LDL or total cholesterol.^{92,93} Interestingly, in a study involving young healthy subjects, consumption of a milk chocolate bar (46 g) instead of a high-carbohydrate snack increased HDL cholesterol and decreased plasma triglycerides but did not affect LDL despite an increase in total fat in the diet.⁹⁴ In hypertensive patients, daily consumption of 100 g flavonoid rich chocolate over 2 weeks led to a significant 12% reduction of serum total and LDL cholesterol levels.⁴⁷ Moreover, cocoa appears to inhibit LDL oxidation.⁹⁵ In healthy subjects, daily consumption of 75 g polyphenol-rich dark chocolate over 3 weeks increases HDL cholesterol by up to 14% and inhibits lipid peroxidation.⁹⁶ A recent Japanese study demonstrated that, in hypercholesterolemic patients, flavanol-rich cocoa lowers plasma levels of LDL and oxidized LDL and increases HDL serum concentrations.^{64,97}

Overall, the effects of chocolate and its various components on lipid levels are not conclusive, strongly suggesting that a larger well-controlled study appears mandatory. Importantly, however, despite its high fat content, cocoa itself does not seem to exert untoward effects on lipid metabolism. It must be stressed that many chocolate products contain milk or processed fats, eg, palm oils. The effect of processed chocolate on blood lipids is not known and may indeed be less favorable.

Precautions and Limitations

Although many positive effects of chocolate and its ingredients have been documented in the cardiovascular system, precautions in its use are mandatory. Indeed, the high caloric load of commercially available chocolate (about 500 kcal/100 g) may induce weight gain, a risk factor for hypertension, dyslipidemia, and diabetes. Surprisingly, a study in 49 healthy women showed no weight gain after daily consumption of 41 g chocolate, 60 g almonds, or almonds and chocolate together for 6 weeks.⁹⁸ Thus, weight gain may occur only with higher amounts of daily chocolate and/or its prolonged use. Furthermore, the occasionally high sugar and fat content of commercially available chocolate has to be considered. Because high sugar intake is associated with obesity, caries, and diabetes, cocoa-based products with no or low sugar content are certainly preferred. On the other hand, cocoa itself, unlike chocolate, can be recommended without hesitation because it is low in sugar and fat.

Although further research is required, current evidence suggests that the beneficial effects of cocoa are attributed mainly to its flavanol content, especially epicatechin. There-

fore, direct dietary supplementation with flavanols instead of chocolate consumption deserves further study. Indeed, protocols using epicatechin or other flavanoids specifically are now feasible and should clarify this question. At this point, recommending dietary supplementation with flavanols, similar to vitamins, appears problematic because potential prooxidative effects of large quantities cannot be excluded.⁹⁹

Because of the limitations of the data available so far, future studies should provide detailed information about the chocolate product used; the exact content in polyphenols, especially flavanols; and most importantly, the flavanol plasma concentrations achieved. Furthermore, it has to be taken into account that cocoa contains many other potentially active substances, eg, theobromine or magnesium, substances not discussed in this review.

Finally, to definitively clarify the protective effects of cacao on cardiovascular health, larger studies with a placebo-controlled prospective design focusing initially on surrogate end points such as carotid atherosclerosis and eventually morbidity and mortality are needed.

Conclusions

For many centuries, cocoa has been known for its good taste and its beneficial effects on health. Recent research revealed that cocoa does indeed exert beneficial cardiovascular effects, probably mediated mainly by its polyphenols, a heterogeneous group of molecules found primarily in fruits and vegetables. The beneficial effects of cacao are most likely due to an increased bioavailability of NO. This may explain the improvement in endothelial function, the reduction in platelet function, and the potentially beneficial effects on blood pressure, insulin resistance, and blood lipids.

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Disclosures

Drs Lüscher and Hollenberg have been consultants for MARS Inc. The other authors report no conflicts.

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