Cocoa and chocolate have recently been found to be rich plant-derived sources of antioxidant flavonoids with beneficial cardiovascular properties. These favorable physiological effects include: antioxidant activity, vasodilation and blood pressure reduction, inhibition of platelet activity, and decreased inflammation. Increasing evidence from experimental and clinical studies using cocoa-derived products and chocolate suggest an important role for these high-flavanol-containing foods in heart and vascular protection.

Key words: cardiovascular, chocolate, cocoa, flavonoid, flavanol

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INTRODUCTION

Evidence based on epidemiological studies suggests that flavonoid-rich diets high in fruits and/or vegetables reduce the risk of coronary heart disease.1-3 Recent studies also report reduced cardiovascular risk and events associated with the consumption of foods rich in flavonoids.4,5 A meta-analysis of seven prospective cohort studies with 105,000 individuals indicates that high dietary intake of flavonoids from a small number of fruits and vegetables, tea, and red wine is inversely associated with coronary heart disease risk.6 Dietary flavonoids and their potential role in the prevention of cardiovascular disease have gained recent scientific and medical interest due to their antioxidant properties: their ability to scavenge reactive oxygen species (ROS) and reactive nitrogen species.7,8 Oxidative stress due to excess production of free radicals or ROS is associated with a number of cardiovascular risk factors such as hypertension, dyslipidemias, diabetes, and smoking. Cellular DNA, proteins, and lips are susceptible to ROS attack, which can result in damage to cell membranes and organelles. Mitogenicity and apoptosis of vascular cells is enhanced, and increased expression and activation of redox-sensitive genes occurs. Tissue damage and pathophysiological processes, including endothelial dysfunction and atherosclerosis, eventually ensue.9 Oxidative modification of low-density lipoproteins (LDL) due to oxidative stress is believed to be a major contributing factor in atherosclerosis. The antioxidant properties of flavonoids represent one of many diverse beneficial effects that these polyphenolic compounds may exert in cardiovascular disease. The direct antioxidant-quenching theory of flavonoids is now being supplanted by other physiological theories, including their effects on cellular redox regulation, signal transduction, and modulation of other enzyme and genomic systems.

Flavonoids, a subclass of polyphenols, are ubiquitous micronutrients derived from plants, primarily fruits and vegetables. There are more than 5000 flavonoids and six major flavonoid categories: flavanols, flavanones, flavones, isoflavones, flavonols, and anthocyanidins.10 The various subclasses are listed below and include typical foods or beverages with a substantial content of flavonoids:

- Flavanols (catechin, epicatechin): chocolate, tea, red wine, beans, apricot, cherry, grape, peach, blackberry, apple;
- Flavanones (hesperetin, naringenin, eriodictyol): citrus fruits and juices;
- Flavones: (apigenin, luteolin): parsley, celery;
- Isoflavones: (daidzein, genistein): soy products;
- Flavonols: (quercetin, kaempferol, myricetin): onions, kale, broccoli, tomato, blueberry, apples, tea, red wine; and
- Anthocyanidins (cyanidin, pelargonidin, peonidin, delphinidin, malvidin): blueberry, black grape, cherry, blackberry, black currant, rhubarb, strawberry, red wine, plum, red cabbage.11,12
The antioxidant properties of flavonoids are related to their structure, two aromatic rings (an A-ring and a B-ring) on the ends bound by an oxygenated heterocycle in the middle (C-ring), which promote free radical scavenging. Specifically, the presence of the catechol or dihydroxylated B-ring allows rapid donation of hydrogen (electron) for stabilization of radical species. This is considered the most important structural feature defining the “classical” antioxidant nature of flavonoids. Structure-activity studies also show that flavonoids inhibit key enzymes such as NAD(P)H-oxidase (a major source of endogenous free radicals), tyrosine kinase, and protein kinase based on varied hydroxylation/methylation patterns.

The number of hydroxyl groups on the B-ring and the oxo group at the 4 position of the C-ring are also important in the suppression of cyclooxygenase-2 (COX-2), an inducible enzyme that is upregulated during inflammation and certain tumor formations. Due to this structural feature, flavanols have been found to have more suppressive activity on COX-2 than flavonols. It is apparent that some functions of flavonoids are dependent on structure. While the antioxidant properties require two hydroxyl groups on the B-ring (with no carbonyl group at C4 or unsaturation of the C-ring), the anti-proliferative effects of flavonoids in many cancer studies require the additional presence of a carbonyl group at C4 or unsaturation of the C-ring. Catechins and epicatechins, based on their catechol or dihydroxylated B-ring, appear to have a relatively restricted diversity in physiological activity. Flavonoids, depending on their structure, may also affect pathways in a cell- or tissue-specific manner depending on their structure.

Recent reviews also suggest that flavonoids exert non-antioxidant mechanisms that may confer protection such as binding to receptors, modulation of cellular signaling (i.e., protein and lipid kinase pathways), and gene expression. For example, flavonoids of the catechin family, major constituents of red wine, have been found to mediate the inhibitory effects of red wine on β-platelet-derived growth factor (PDGF) receptor signaling, PDGF-dependent proliferation, and migration of vascular smooth muscle cells. PDGF is a potent mitogenic and chemotactic factor and one of many inflammatory components that contribute to atherogenesis. Interestingly, the findings of this study are believed to provide a molecular explanation for the “French paradox” in that the French have a high consumption of red wine and one of the lowest incidences of coronary heart disease despite a diet with a high fat content.

Cocoa and chocolate contain both a high quantity and quality of antioxidant flavonoids, even exceeding black and green tea and red wine. Cocoa and chocolate, especially dark chocolate, have only recently been identified as rich sources of flavonoids due to advances in technology and analytical methods used in the detection of complex flavonoids. The high antioxidant capacity of cocoa and chocolate are attributed to their significant amount of procyanidins, the oligomeric form of the flavanol monomeric units, (–)-epicatechin and (+)-catechin. These monomers, mainly (–)-epicatechin, provide most of the total procyanidin content in chocolate; however, dimers (two monomer units) and up to 10 monomer units are also present. The amount of flavonoids in chocolate is not only dependent on the cacao bean, but also on the processing steps involved in chocolate’s manufacture. For example, excess heat and alkalinization (“Dutch” processing) can significantly reduce the amount of flavonoids. Typically, dark chocolate contains two to three times as many cocoa flavonoids as milk chocolate.

The antioxidant capacities of foods and beverages measured by current methodology, i.e., oxygen radical absorbance capacity (ORAC) assay with fluorescein, Trolox equivalent antioxidant capacity (TEAC), total radical-trapping antioxidant parameter (TRAP), ferric-reducing ability of plasma (FRAP), may not reflect in vivo antioxidant effects. The measurement of antioxidant capacity, which reflects the concentrated polyphenolic content of the food or beverage, is also not comparable among the different methods. Measurement of both the lipophilic and hydrophilic fractions in a given sample are needed to obtain an accurate total ORAC value.

Other factors such as processing, plant genetics, season, and growing conditions may also alter the phenolic content and, thus, the antioxidant capacity of foods. Therefore, the content of flavonoids in various foods and beverages and their respective antioxidant properties may be dependent on a number of factors. Careful evaluation of these factors and the methodology used for measurements are important. With these considerations, flavonoids, specifically, the flavanols catechin and epicatechin, may be beneficial in cardiovascular health and disease based on their antioxidant properties, anti-proliferative effects, and other emerging physiologically relevant mechanisms.

HISTORY

The cacao tree, Theobroma cacao or “food of the gods,” was first cultivated in 250–900 AD by the ancient Maya civilization in the Mesoamerican (Mexico to Central American) region. A typical football-shaped fruit pod of the cacao (pronounced “kah-kow”) tree contains approximately 25 to 75 cocoa beans. The Aztec elite civilization in the 12th to 16th centuries drank chocolate derived from the cocoa beans in combination
with spices as a nourishing staple beverage. Both Maya and Aztec royal and religious events had offerings of chocolate to the Aztec god Quetzalcoatl, who by legend brought heavenly cacao down to earth. The beans were also used as currency and for medicinal purposes to fight fatigue and gastrointestinal distress.22,23

Following the Spanish conquest of Mexico by Hernán Cortés, the cocoa beans were brought back to Spain in 1528. Over the next 100 years, chocolate swept across Europe as a fad. Cane sugar, vanilla, cinnamon, and aniseed were added to the bitter chocolate drink instead of the peppers and other native herbs used by the Aztecs. Sweet, hot chocolate had arrived. In France, only the royal courts were allowed to drink chocolate due to its status. In 1657, the first chocolate house opened in London. Chocolate was not readily available in the United States until the mid-1800s due to the high duties on imports of cocoa beans and sugar. It was during World War I that chocolate was provided as rations to US servicemen in Europe.22,23 Interestingly, the chocolate was found to be resistant to spoilage, which is now believed to be due to the natural antioxidant flavonoids it contains.

### ANTIOXIDANT ACTIVITY

Decreased susceptibility of LDL oxidation has recently been ascribed to the cocoa flavonoids.24-27 The antioxidant capacity and diminished production of oxidative products in plasma is related to increased concentrations of the cocoa and chocolate flavonoid (−)-epicatechin.28,29 A study on the plasma kinetics of epicatechin showed significant increases in epicatechin 2 hours after chocolate consumption. Plasma epicatechin levels reach 0.7 μmol/L following acute ingestion of 80 g of dark chocolate (164 mg of epicatechin)30 and 0.2 μmol/L with a 2-week daily consumption of 46 g (46 mg of epicatechin) dark chocolate.31,32

### Table 1. Effects of Cocoa and Chocolate on Oxidation

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type</th>
<th>Subjects</th>
<th>Antioxidant Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang et al., 200029</td>
<td>Dark chocolate, single dose (27 g, 53 g, or 80 g)</td>
<td>Healthy adults (N = 20)</td>
<td>Weak +</td>
</tr>
<tr>
<td>Rein et al., 200052</td>
<td>Dark chocolate, single dose (80 g)</td>
<td>Healthy adults (N = 10)</td>
<td>+</td>
</tr>
<tr>
<td>Wan et al., 200126</td>
<td>Cocoa powder (22 g) plus dark chocolate (16 g/d) for 4 weeks</td>
<td>Healthy adults (N = 23)</td>
<td>+</td>
</tr>
<tr>
<td>Osakabe et al., 200125</td>
<td>Cocoa powder (36 g/d) for 2 weeks</td>
<td>Healthy adults (N = 15)</td>
<td>+ LDL oxidizability, − ORAC antioxidant capacity, − urinary F₂ Isoprostanes</td>
</tr>
<tr>
<td>Mathur et al., 200227</td>
<td>Dark chocolate (36 g/d) plus Cocoa powder (30 g/d) for 6 weeks</td>
<td>Healthy adults (N = 25)</td>
<td>+</td>
</tr>
<tr>
<td>Steinberg et al., 200224</td>
<td>Cocoa powder, single dose (37.5 g)</td>
<td>Healthy adults (N = 6)</td>
<td>+</td>
</tr>
<tr>
<td>Serafini et al., 200335</td>
<td>Dark chocolate, single dose (100 g, 100 g with 200 mL milk, or 200 g milk chocolate)</td>
<td>Healthy adults (N = 12)</td>
<td>+, −, −</td>
</tr>
<tr>
<td>Murphy et al., 200349</td>
<td>Cocoa tablets (6/d) for 28 days</td>
<td>Healthy adults (N = 32)</td>
<td>−</td>
</tr>
<tr>
<td>Engler et al., 200331 and</td>
<td>Dark chocolate (46 g/d) for 2 weeks</td>
<td>Healthy adults (N = 21)</td>
<td>−</td>
</tr>
<tr>
<td>Engler et al., 200432</td>
<td>Dark chocolate or high-polyphenol dark chocolate (75 g/d) for 3 weeks</td>
<td>Healthy adults (N = 45)</td>
<td>−</td>
</tr>
<tr>
<td>Wiswedel et al., 200466</td>
<td>Cocoa drink, single dose (100 mL)</td>
<td>Healthy adults (N = 20)</td>
<td>+</td>
</tr>
<tr>
<td>Kurosawa et al., 200567</td>
<td>Cacao liquor-supplemented diet 1% (w/w), 1–4 months</td>
<td>Healthy adults (N = 15)</td>
<td>+</td>
</tr>
<tr>
<td>Fraga et al., 200568</td>
<td>Flavanol-containing milk chocolate (105 g) for 2 weeks</td>
<td>Healthy adults (N = 28)</td>
<td>+</td>
</tr>
<tr>
<td>Vlachopoulos et al., 200569</td>
<td>Dark chocolate, single dose (100 g)</td>
<td>Healthy adults (N = 17)</td>
<td>+</td>
</tr>
</tbody>
</table>
centrations following cocoa or chocolate consumption were found.

These changes are in agreement with a recent study examining the effect of epicatechin and polyphenolic cocoa extract in human caco-2 cells using functional genomic analysis. Differential expression of the MRP1, MAPKK1, STAT1, and FTH1 genes that are involved in the cellular response to oxidative stress are consistent with the antioxidant properties of cocoa flavonoids. Multiple signal transduction pathways, including those influencing the antioxidant responsive elements in the promoter region of the respective genes, may also be affected by many phytochemical antioxidants. This effect on gene expression may result in the induction of phase II metabolic enzymes involved in the detoxification of carcinogens.

In the studies cited with negative findings related to improvement in oxidative measurements, this may be attributed to a number of factors including variability in the subjects’ baseline epicatechin concentrations and/or the percent increase in these levels seen after consumption. This may be due in part to differences in baseline diets or in the detection sensitivity of low concentrations of plasma epicatechin. Moreover, the human health effects seen with flavonoids may ultimately depend on both their concentration in cells and tissues and on an individual’s genetic makeup. These may also contribute to the null observations seen with oxidative stress biomarkers in some human studies with dietary flavonoids. It is interesting that the presence of milk with chocolate consumption was found to diminish the increase in both total antioxidant capacity and epicatechin concentrations, but others have found no such milk-related connection under similar conditions.

**VASODILATION**

Endothelial dysfunction is recognized as an early event in the development of atherosclerosis, and is associated with decreased bioavailability of the vasodilator nitric oxide. Current evidence suggests that the consumption of cocoa and chocolate, rich in flavonoids, may provide protective vascular effects. In isolated rabbit aortic rings, cocoa extracts were shown to induce endothelium-dependent relaxation and to activate endothelial nitric oxide synthase. Oligomeric forms of the monomeric units (−)-epicatechin and (+)-catechin, such as tetramers and higher, were associated with these effects. Additionally, a favorable balance in eicosanoid synthesis has been reported in cultured human aortic endothelial cells exposed to cocoa flavanols and in human plasma samples from subjects 2 hours following the consumption of high-flavanol chocolate (37 g). A decrease in the plasma leukotriene-prostacyclin ratio was also found, which would result in more vasodilation, less platelet aggregation, and an anti-inflammatory profile. A significant rise in plasma epicatechin was also noted at the 2-hour time point following chocolate consumption.

Other recent studies (Table 2) in healthy subjects following 4 days to 2 weeks of daily consumption of a

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type</th>
<th>Cocoa Flavanoids Amount</th>
<th>Model</th>
<th>Endothelium-Dependent Relaxation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karim et al., 2000²⁷</td>
<td>Cocoa extracts (10⁻⁷ to 10⁻⁵ mol/L)</td>
<td>—</td>
<td>Isolated rabbit aorta</td>
<td>+</td>
</tr>
<tr>
<td>Fisher et al., 2003³⁹</td>
<td>Cocoa beverage (230 mL/d) for 4 days</td>
<td>821 mg/d</td>
<td>Healthy adults (N = 27) fingertip peripheral artery tonometry</td>
<td>+</td>
</tr>
<tr>
<td>Heiss et al., 2003⁴¹</td>
<td>Cocoa beverage (100 mL/d) for 2 days</td>
<td>176 mg/d</td>
<td>Adults with one cardiovascular risk factor or history of CAD (N = 26) brachial artery</td>
<td>+</td>
</tr>
<tr>
<td>Engler et al., 2003³¹ and Engler et al., 2004³²</td>
<td>Dark chocolate bars (46 g/d) for 2 weeks</td>
<td>259 mg/d</td>
<td>Healthy adults (N = 21) brachial artery</td>
<td>+</td>
</tr>
<tr>
<td>Vlachopoulos et al., 2005⁶⁶</td>
<td>Dark chocolate, single dose (100 g)</td>
<td>2.62 g</td>
<td>Healthy adults (N = 17) brachial artery</td>
<td>+</td>
</tr>
<tr>
<td>Grassi et al., 2005⁴²</td>
<td>Dark chocolate bars (100 g) for 15 days</td>
<td>88 mg/d</td>
<td>Hypertensive adults (N = 20) brachial artery</td>
<td>+</td>
</tr>
</tbody>
</table>
cocoa beverage or flavonoid-rich dark chocolate bar reported increased vasodilation or improvement in endothelial function.31,32,39,40 Participants who had at least one cardiovascular risk factor, including hypertension, hyperlipidemia, diabetes, smoking, or history of coronary artery disease demonstrated a reversal of endothelial dysfunction with just a single dose of a cocoa beverage.41 An increase in nitric oxide bioactivity was seen in this study,41 and further increases in vasodilation were reversed with the nitric oxide synthase inhibitor N\textsuperscript{G}–nitro-L-arginine methyl ester (L-NAME), given intravenously in the study by Fisher et al.39 The improvement in endothelial function was substantiated in a recent investigation with hypertensive individuals who consumed 100 g of dark chocolate for 15 days.42 It was found that dark chocolate consumption also improved insulin sensitivity in both healthy and hypertensive individuals.40,42 Plasma epicatechin concentrations were also significantly increased following cocoa or chocolate consumption in several of these studies.

The cardioprotective mechanisms, including vasodilation, of the major flavanols found in cocoa and chocolate, epicatechin and catechin, are shown in Figure 1. These mechanisms may be related to increases in plasma epicatechin or catechin concentrations that signal the release of vasoactive substances from the endothelium, including nitric oxide and prostacyclin. Epicatechin has been shown to preferentially inhibit nitric oxide-related nitration and oxidation reactions without affecting nitric oxide synthesis and cyclic GMP signaling.43 This effect is also depicted in Figure 1. Overproduction of reactive nitrogen species associated with inflammatory conditions such as atherosclerosis and coronary artery disease may be mitigated with epicatechin or catechin as selective inhibitors of nitric oxide-related oxidation and nitration reactions.

The above vascular studies also provide evidence for increased nitric oxide synthesis and beneficial changes in the eicosanoid ratio. Epicatechin in particular has been recently found to protect the integrity of endothelial cells by scavenging free radicals and by maintaining endothelial nitric oxide synthase.44 Moreover, several of the studies31,32,39,41,42 measured endothelium-dependent, flow-mediated dilation, which reflects an increase in flow and shear stress after reactive hyperemia, and is mediated by endothelium-derived nitric oxide and possibly prostanooids derived from the endothelium.45 When considered together with the increased expression and/or activity of endothelial nitric oxide synthase seen with long-term exposure to epicatechin and related polyphenols, this

Figure 1. In the endothelial cells, nitric oxide (NO\textsuperscript{+}) is synthesized from L-arginine by the enzyme nitric oxide synthase. NO\textsuperscript{+} then diffuses into the vascular smooth muscle cells and activates the enzyme soluble guanylyl cyclase (sGC). Guanosine 3',5'-cyclic monophosphate (cGMP) is formed from GTP, resulting in vasodilation. Epicatechin and catechin may signal the release of NO\textsuperscript{+} and inhibit NO-related nitration and oxidation reactions that generate the reactive nitrogen species (RNS) nitrosonium (NO\textsuperscript{+}), nitroxyl anion (NO\textsuperscript{-}), and peroxynitrite (ONOO\textsuperscript{-}). These reactive species may be linked to NO\textsuperscript{+} overproduction in inflammatory diseases such as coronary artery disease. Formation of peroxynitrite (ONOO\textsuperscript{-}) due to superoxide anions (O\textsubscript{2}\textsuperscript{-}) reacting with NO\textsuperscript{+} leads to endothelial dysfunction and decreased vasodilation. This deleterious process may be inhibited by epicatechin and catechin.
research provides a molecular basis for the cardioprotective effects of high epicatechin/catechin-containing foods and drinks.43

BLOOD PRESSURE EFFECTS

In healthy subjects, the effects of cocoa and chocolate on blood pressure have been negative,28,32,39,46 with the exception of two recent studies.40,68 Two randomized, crossover trials in untreated hypertensives have also shown a blood pressure lowering effect following 14 to 15 days of consumption of 100 g of dark chocolate.42,47 A recent report suggests that cocoa flavanols may lower blood pressure by acting as an angiotensin I converting enzyme inhibitor, which also has antioxidant properties and can modulate nitric oxide production.48

PLATELET FUNCTION EFFECTS

A suppressive effect on platelet reactivity and platelet-related primary hemostasis has been demonstrated in many studies even after a single chocolate dose (Table 3).49-53 The anti-platelet effects of cocoa and chocolate may be due to increased production of nitric oxide, which not only causes vasodilation, as previously discussed, but also inhibits platelet aggregation. Increased plasma epicatechin concentrations were reported in the studies by Pearson et al.50 and Murphy et al.,49 and may signal increased nitric oxide synthesis in both the endothelial cells and platelets. Increased production of prostacyclin, an inhibitor of platelet aggregation, has also been proposed as a possible mechanism.54 These platelet inhibitory effects by cocoa and chocolate may be beneficial due to the pathophysiological role of platelets in atherosclerosis and thrombotic events.

INFLAMMATION AND IMMUNE FUNCTION EFFECTS

It is now widely accepted that atherosclerosis is a chronic inflammatory disease.55 Inflammation and increased oxidative stress promote endothelial dysfunction and atherogenesis.56 Nitric oxide normally inhibits nuclear transcription factor (NFκB), which binds to the promoter regions of genes coding for pro-inflammatory proteins such as cytokines and adhesion molecules. In endothelial dysfunction, which is manifested by decreased bioavailability of nitric oxide, this inhibition is lost. Excess intracellular ROS in oxidative stress also activates NFκB. Cocoa flavonoids may prevent activation of NFκB and subsequent cytokine transcription by diminishing intracellular ROS.

In experimental studies, the expression of the pro-inflammatory cytokines interleukin-β (IL-1β) and interleukin-2 (IL-2) is modulated by cocoa flavonoids. Specifically, IL-1β expression in phytohemagglutinin-stimulated peripheral blood mononuclear cells is reduced by purified monomer to tetramer cocoa flavonoids and IL-2 mRNA expression of and secretion by T-cells have also been shown to be inhibited with cocoa treatment.57,58 Cocoa flavonoids (epicatechin, catechin, dimeric procyanidins) are also incorporated into Jurkat T-cells with pretreatment, which inhibits phorbol miristate acetate (PMA)-induced NFκB activation.59 This finding suggests that the immune response can be

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type</th>
<th>Cocoa Flavonoids Amount</th>
<th>Subjects</th>
<th>Platelet Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rein et al., 2000</td>
<td>Cocoa beverage, single dose (300 mL)</td>
<td>897 mg</td>
<td>Healthy adults (N = 10)</td>
<td>Decreased platelet activation</td>
</tr>
<tr>
<td>Rein et al., 2000</td>
<td>Cocoa beverage, single dose (300 mL)</td>
<td>897 mg</td>
<td>Healthy adults (N = 30)</td>
<td>Decreased platelet activation and microparticle formation; aspirin-like effect on primary hemostasis</td>
</tr>
<tr>
<td>Pearson et al., 2002</td>
<td>Cocoa beverage, single dose (300 mL)</td>
<td>897 mg</td>
<td>Healthy adults (N = 16)</td>
<td>Decreased platelet activation and induced platelet plug formation</td>
</tr>
<tr>
<td>Holt et al., 2002</td>
<td>Semisweet chocolate chips, single dose (25 g)</td>
<td>220 mg</td>
<td>Healthy adults (N = 18)</td>
<td>Decreased platelet-related primary hemostasis</td>
</tr>
<tr>
<td>Murphy et al., 2003</td>
<td>Cocoa tablets (6/d) for 28 days</td>
<td>234 mg</td>
<td>Healthy adults (N = 32)</td>
<td>Decreased platelet activation and induced aggregation</td>
</tr>
<tr>
<td>Innes et al., 2003</td>
<td>Dark chocolate, single dose (100 g)</td>
<td>—</td>
<td>Healthy adults (N = 30)</td>
<td>Decreased platelet-induced aggregation</td>
</tr>
</tbody>
</table>
regulated by cocoa flavonoids, in part by modulating the oxidant-responsive transcription factor NFκB.

Cocoa-derived dimers have recently been found to protect Jurkat T-cells from oxidation and to increase plasma membrane fluidity. They also maintain the membrane integrity by preventing leakage of small molecules from vesicles. The increase in membrane fluidity may be linked with functional changes in membrane-associated receptors and enzymes as well as ion transport. Mathur et al. recently reported that cocoa products have no effect on markers of inflammation (whole-blood cytokines, IL-1β, IL-6, TNF-α, high-sensitivity C-reactive proteins, and P-selectin). The healthy subjects in this study consumed the cocoa and chocolate supplementation (651 mg of cocoa flavonoids) for 6 weeks. Epicatechin was not detected in the subjects’ plasma, and the lack of effect on inflammatory markers was attributed to the short half-life of cocoa flavonoids. It is known that epicatechin peaks in the plasma at 2 hours after cocoa or chocolate consumption and is cleared approximately 8 hours later.

CONCLUSION

The investigations on the antioxidant, vasodilatory, blood-pressure lowering, anti-platelet, and anti-inflammatory effects of cocoa and chocolate provide exciting new evidence into the potential cardiovascular benefits of flavonoid-rich foods. Balance and moderation are also important in a healthy diet and must be considered for foods such as chocolate, which is also high in calories and fat. Interestingly, the fat in chocolate (cocoa butter) contains approximately 35% oleic acid, the monounsaturated fat found in olive oil, and 60% saturated fat (35% stearic acid, 25% palmitic acid). Palmitic acid has cholesterol-raising effects; however, it is believed to be offset by the neutral cholesterol effects of stearic acid and the slightly cholesterol-lowering effect of oleic acid. Stearic acid can also be readily converted to oleic acid.

Short-term and long-term clinical studies of chocolate supplementation have shown neutral or favorable changes in cholesterol levels. In fact, daily consumption of the “polymeal,” a combined meal of seven food components, including dark chocolate, wine, fish, fruits, vegetables, garlic, and almonds, was recently proposed as a strategy to reduce cardiovascular disease events by 76% and increase total life expectancy by 4.8 to 6.6 years. It is clear that nutritional therapy with flavonoid-rich foods, especially those that raise plasma epicatechin concentrations, may prove beneficial in reducing or preventing oxidative stress and endothelial dysfunction. As illustrated in Figure 2, the cocoa flavonoids may inhibit both pathophysiological processes that lead to atherosclerosis and eventual cardiovascular events.

Based on the existing literature, it would be practical to advise consumption of a wide range of flavonoid-rich foods and beverages, especially those that contain substantial amounts of the same flavonoids (flavanols) found in cocoa and dark chocolate. These include: green and black tea (especially Ceylon), red wine, cherries (sweet), apples, purple grapes, blackberries, raspberries, and broad beans. Other common fruits and vegetables with a high total antioxidant capacity (calculated by summing the lipophilic and hydrophilic ORAC values) per serving (ranked highest to lowest) include: blueberry,

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**Figure 2.** Possible inhibitory effects of cocoa flavonoids on oxidative stress and endothelial dysfunction.
cranberry, artichoke (cooked), blackberry, prunes, raspberry, strawberry, Red Delicious and Granny Smith apples (with peel), pecans, sweet cherries, plums, and russet potatoes (cooked). These foods represent plentiful sources of flavonoids and, in moderation with a healthy and active lifestyle, small amounts of dark chocolate may also be good for your heart.

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