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File: ■ Cocoa (*Theobroma cacao*)
■ Health Benefits
■ Mechanisms of Action

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RE: Review of Cocoa and Human Health

Ellam S, Williamson G. Cocoa and human health. *Annu Rev Nutr*. 2013;33:105-128.

Cocoa (*Theobroma cacao*) is a dry, non-fat, powdered substance that is derived from the plant's seeds and used in many food products. Chocolate is a popular cocoa confectionary, which consists of cocoa liquor (cocoa powder and cocoa butter), as well as other variable ingredients (e.g., sugar and milk). Due to the popularity of cocoa, there is an interest in its health effects. In this review, the authors describe the potential active components, mechanisms, and health benefits of cocoa.

Bioactive Chemical Constituents
Many of the health benefits of cocoa are attributed to flavonoids, a class of polyphenolic compounds that include the subgroup flavan-3-ols. Cocoa mostly consists of flavan-3-ols, such as the monomers epicatechin and catechin, as well as B-type proanthocyanidins (polymers or oligomers of monomeric flavan-3-ols). These compounds can be lost in food processing by fermentation, roasting, or alkali treatment, and account for the variability in many cocoa products. Theobromine is an alkaloid and another constituent of cocoa products (2.5% dry weight of cocoa). Theobromine is not degraded by processing techniques and has high bioavailability. Moreover, cocoa is also a good source of magnesium. A 40 g sample of 70% dark chocolate contributes to roughly 10% of the recommended daily allowance (300-400 mg/day for adults).

Bioavailability of Flavonoids and Theobromine
Flavan-3-ols are stable in the stomach and are able to reach the small intestine intact. Epicatechin and proanthocyanidins are largely unaffected in the small intestine, potentially due to the presence of proteins or other food constituents. Epicatechin absorbs efficiently in the small intestine, resides in conjugated forms at maximal concentrations in the blood for 3-4 hours, and is excreted into the urine. The food matrix also has an effect on the rate and amount of absorption; however, intact proanthocyanidins are poorly absorbed. Flavonoids that are not absorbed reach the colon. Mounting evidence suggests that these compounds are broken down into smaller metabolites by microorganisms in the colon, and are eventually absorbed and excreted into the urine.

Theobromine is highly absorbed in the small intestine. Modified (main metabolite is 7-methylxanthine) and unmodified theobromine is found in the urine and a small amount of theobromine is found in the feces. The maximal concentration of theobromine in the blood is found at 2 hours. In addition, the half-life of theobromine from a gelatin capsule or solution is 7.2 and 10 hours, respectively.

Human Intervention and Epidemiological Studies
The main outcomes from 28 human intervention studies (between 2000 and 2007) for mostly healthy subjects consuming a cocoa beverage or a dark chocolate bar include improved endothelial function, decreased susceptibility of low-density lipoprotein (LDL) to oxidation, inhibition of platelet aggregation/activation, and decreased levels of F2-isoprostanes. Human trials conducted since 2007 also found that cocoa consumption affected blood pressure, cholesterol, oxidative parameters, glucose/insulin levels, platelet function, brain blood flow/cognitive function, inflammation, and the skin; however, variations in time and dosage make it difficult to interpret all these studies together.

On the other hand, epidemiological studies with men and women have indicated that long-term consumption of cocoa products reduced cardiovascular mortality. Based on epidemiological studies, it can be inferred that 50-100 g/week of chocolate may reduce the risk of cardiovascular disease (CVD); however, these studies did not evaluate what type of chocolate (e.g., dark, milk) was the most effective. Some studies suggest that cocoa may have more benefits when combined with other ingredients (nuts, fiber, etc.). Some epidemiological studies also indicated increased intake of flavan-3-ols and proanthocyanidins was associated with a reduced risk of CVD, although this effect was not linear and was reversed in the highest intake groups.

Potential Mechanisms
Many of the studies on the health effects of cocoa consumption report improvements in endothelial function. In particular, animal studies suggest that cocoa intake increases nitric oxide (NO) and thereby reduces arterial dilation and blood pressure. Moreover, increased NO production from epicatechin intake is hypothesized to involve the phosphatidylinositol 3-kinase pathway that leads to vasodilation. Epicatechin was also shown to induce endothelial NO synthase (eNOS) in vitro. Endothelial cells treated with a proanthocyanidin-rich cocoa extract produced less endothelin-1 (vascular constrictor) than control cells. Epicatechin also reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and arginase activity, which increases NO levels. The vasodilation and anti-platelet properties of NO may explain how cocoa intake reduces the risk of CVD.

Cocoa products may also reduce inflammation and oxidative stress, which may lower CVD risk. Several studies have indicated that cocoa consumption in healthy subjects is associated with a significant reduction in the inflammatory marker serum C-reactive protein (CRP); however, no significant changes were observed in patients with hypertension, hypercholesterolemia, or type 2 diabetes. This may be because it is still not clear if CRP is linked to the development of the disease or is a consequence of the disease.

Improved lipid profiles have been associated with cocoa consumption. Because dyslipidemia is a risk factor for CVD, this may at least partially explain how cocoa intake reduces CVD risk. Although animal studies support these effects, this has not been

linked with clinical outcomes. Studies have shown that cognitive function may also be improved by cocoa consumption as a result of increased blood flow to the brain and the nervous system.

Based on the multitude of studies that have evaluated human cocoa consumption, there is strong evidence that cocoa intake has beneficial effects on the cardiovascular system and that these effects are probably linked with increased NO and vasodilation. Cocoa flavan-3-ols may contribute to these effects, but other cocoa compounds may also play a role in these effects. The authors suggest more long-term studies are needed and that the effects of sugar and other chocolate ingredients should be evaluated in addition to cocoa itself. As technology improves, it may become possible to better evaluate the complete chemistry of cocoa products, their synergistic mechanisms, and their health effects.

—Laura M. Bystrom, *PhD*