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File: ■ Cocoa (*Theobroma cacao*)
■ Cardiovascular Disease
■ Polyphenolic Antioxidants
■ Flavanols and Nitric Oxide Metabolism

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RE: A Comprehensive Review of Cocoa and Its Health Benefits, History, and Nutritional Profile

Katz DL, Doughty K, Ali A. Cocoa and chocolate in human health and disease. *Antioxid Redox Signal.* 2011 Jun 13; [Epub ahead of print]. doi:10.1089/ars.2010.3697.

This invited review provides a comprehensive, well-written look at the current research on the health benefits of cocoa (*Theobroma cacao*), in addition to its history, economics, nutritional breakdown, and epidemiology.

Cocoa is considered an indulgent confection, but in its origins, cocoa was best known for its medicinal properties, with over 100 different uses recorded between the 16th and 20th centuries. Today, cocoa consumption ranges from 0.12 kg/person/year in China to 11.85 kg/person/year in Ireland, with the US in the middle of this range at 5.18 kg/person/year. In 2006-2007, over 1.2 million tons of cocoa were produced in the largest producing country of Cote d'Ivoire (Ivory Coast).

Processing consists of grounding, roasting, shelling, and fermenting the cocoa beans (nibs), which makes a thick paste called cocoa liquor; the amount of cocoa liquor is what is measured to arrive at the percent cacao (which also includes the cocoa butter added back into the product) listed on food packaging. When combined with cocoa butter (the fat component of the nibs) and sugar, it makes dark chocolate, and milk chocolate when milk is also added. White chocolate is made using only the cocoa butter from nibs, with added sweeteners and dairy ingredients. Nibs also contain fiber (most of which is lost with processing) and minerals such as magnesium, copper, and iron (providing a significant portion of the RDA). The cocoa butter consists of the monosaturated fatty acid oleic acid (as in olive oil) and saturated fatty acids palmitic acid and stearic acid, the latter of which does not elevate serum lipids as do other saturated fatty acids.

Cocoa also contains large amounts of polyphenols (a single serving delivers more phenolic antioxidants than most foods), in particular a sub-class called flavanols, or flavan-3-ols. These are responsible for the bitter, astringent taste of dark chocolate. The main flavanols are the monomers catechin and epicatechin, with polymers called

procyanidins or condensed tannins also being present. Flavanols consist of two carbon rings and a benzene ring; this tricyclic structure gives rise to its antioxidant properties. Cocoa also contains the methylxanthines theobromine and caffeine. A table details all of the numerous flavonoids and other phenolics found in cocoa.

Independent of their antioxidant nature, cocoa acts in the body by elevating the nitric oxide (NO). NO acts as a vasodilator and also prevents leukocyte adhesion and migration, smooth muscle cell proliferation, and platelet adhesion and aggregation. Low NO is associated with atherosclerosis and increased cardiovascular risk. Epicatechin has been shown to increase the bioavailability of NO, and while the mechanism of this is still only partially understood, it is clear that cocoa's benefits are more substantially related to an NO mechanism than an antioxidant mechanism.

In the last ten years, several epidemiological studies have been conducted in patients with cardiovascular disease, diabetes, and no disease. Those eating the highest levels of chocolate had significantly lower rates of all-cause mortality, cardiac death, cardiovascular disease, heart failure, myocardial infarction, stroke, and diabetes. One of the ways that cocoa polyphenols are thought to modulate the risk of cardiovascular problems is by downregulating inflammatory mediators that exacerbate their development.

A large number of intervention trials have been conducted on the effect of cocoa on cardiovascular health. Proper function of the vascular endothelium is an important factor in the development of cardiovascular disease. It is modulated by NO. Seventeen human clinical studies consisting of long-term and acute studies and conducted with either healthy, smoking, or cardiovascular disease populations have demonstrated that cocoa or dark chocolate significantly improved flow-mediated dilation (FMD), a measure of the health and flexibility of vessels. Amounts tested ranged from to 176-917 mg total flavanols/day. The authors discuss each of the studies in detail.

Platelets also contribute to cardiovascular health, and NO plays a role in their proper functioning as well. In a systematic review of 25 intervention studies looking at the effects of polyphenol-rich foods on platelet function, cocoa was noted as the only food with consistently positive findings of inhibiting platelet activity. The authors describe six studies using cocoa in particular and conclude that the evidence supporting a positive effect is strong and most likely due to the action of the flavanols.

Studies assessing the effect of cocoa on blood lipids are also reviewed, including a meta-analysis of eight trials. The authors conclude that the data are limited and inconclusive, but that at worst chocolate has a neutral effect on lowering of serum cholesterol. Studies testing effects on oxidation of low density lipoprotein cholesterol (LDL) do suggest that cocoa may play an important role in reducing this oxidation.

The effect of cocoa on blood pressure has also been studied. Most of the trials have shown that cocoa does lower blood pressure, though there are a number of conflicting studies and epicatechin intake varied greatly. The mechanism involved is thought to be due to NO and possibly inhibition of angiotensin converting enzyme (ACE).

Overall, the authors conclude that the beneficial effects on cardiovascular activity are strong, despite the fact that some of the trials have small populations. Most studies are

randomized, double-blind, placebo-controlled, and crossover, and reported significant differences. All of the trials discussed and their effects are catalogued in a table.

Another area of investigation has been on reducing insulin resistance. The benefit may be a result of either the antioxidant or NO elevating properties of cocoa. Only a few human studies have been conducted with mixed results, but the authors contend that there are plausible mechanisms for a benefit and encouraging data from animal work, and additional human research should be pursued.

Understanding the effects of cocoa on immune function is also limited by the lack of human studies, though work in animals and in vitro systems gives reason to believe there could be positive effects. Of particular interest are effects on prevention of cancer, and preliminary work has focused on effects on scavenging of free radicals, inhibition of apoptosis and mutagenesis, and modulation of expression of genes that could affect carcinogenesis.

With regard to neuroprotection, there is promising preliminary evidence for decreased neuroinflammation (as in Parkinson's disease), improved cerebral blood flow (important in memory function and in preventing dementia and stroke), and protection of neurons (a factor in stroke and Alzheimer's disease). Clinical trials will be necessary to further clarify these effects.

For skin, the antioxidant properties of cocoa may help prevent erythema due to UV exposure and improve microcirculation when cocoa is ingested.

Obesity may also benefit from cocoa and chocolate; when ingested in small amounts, they do not cause weight gain. The NO increasing effects help to improve uptake of glucose and inhibit fat synthesis. It has also been shown that just the smell of chocolate can suppress the appetite. The authors state that there is reason to believe that cocoa may induce favorable metabolic changes and weight loss, though human studies have not tested this hypothesis.

The psychological effects of chocolate on mood, cravings, and cognitive function have also been investigated. The craving for chocolate, particularly by women, and particularly during the perimenopausal period, is probably due to cultural rather than physiological factors. Depressed mood was shown to increase the craving for chocolate, but the reasons were unclear. A number of studies point to the sensory experience of eating chocolate being the most critical factor in cravings. Improvements in mood and cognitive ability may relate to the caffeine and theobromine content of cocoa. Studies testing effects on cognitive ability have had mixed results.

The bioavailablity of cocoa has been well studied but is not extensively covered in this review. Dose response testing has shown that serum epicatechin levels reach a peak 2 hours post-consumption.

Food processing affects the level of flavanols remaining in the finished product and levels are widely variable between types of products (milk, dark, white chocolate, cocoa) and even within categories. The process called "dutching," which is performed on cocoa nibs and sometimes on the cocoa powder, substantially reduces the levels of flavanols in the finished product. (Note: Ingredient lists will often use the term "processed with alkali"

to refer to the dutching process.) Addition of other ingredients such as milk, sugar, and fat may affect the bioavailability of flavanols, though data have been ambiguous.

The potential detrimental effects of cocoa and chocolate have also been explored. While there is a perception that chocolate can cause acne and migraine headache, this has not borne out in studies. Chocolate is also named as an aggravator of gastroesophageal reflux disease, though studies have not rigorously tested this. Over-indulgence in chocolate can cause weight gain.

The authors end by saying that contrary to the trend in finding one active ingredient and one mechanism for the benefits of a food, they believe that cocoa as a whole is the active ingredient and that many mechanisms of action are at play in the recorded benefits. They point out a number of avenues for further research by the many different types of scientists investigating cocoa. One practical question the authors point out that still remains to be answered is: "How much of what kind of chocolate is ideal for overall health?" Other unanswered questions include: Who stands to most benefit? Who is at greatest risk with its regular use? They conclude that there is a strong body of evidence accumulating for a net health benefit of routine chocolate consumption, even as the weight gain possibility and food processing uncertainties must be remembered.

—Risa Schulman, PhD

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