Paladini AC, Marder M, Viola H, et al. Flavonoids and the central nervous system: from forgotten factors to potent anxiolytic compounds. *J Pharm Pharmacol.* 1999; 51:519-526.

Salgueriro JB, Ardenghi P, Dias M, et al. Anxiolytic natural and synthetic flavonoid ligands of the central benzodiazepine receptor have no effect on memory tasks in rats. *Pharmacol Biochem Behav.* 1997; 58:887-891.

Walle UK, Galijatovic A, Walle T. Transport of the flavonoid chrysin and its conjugated metabolites by the human intestinal cell line Caco-2. *Biochem Pharmacol.* 1999; 58:431-438.

Cocoa Flavonoids

DESCRIPTION

Cocoa and chocolate are products derived from cacao beans, the seeds of the *Theobroma cacao* tree. Polyphenols comprise about 12 to 18% of the dry weight of cacao beans. About 60% of the polyphenols are in the form of procyanidins (also known as leucocyanidins).

Procyanidins in cocoa and chocolate are mainly homodimers and homotrimers of (-)-epicatechin or heterodimers of (-)-epicatechin and (+)-catechin. (-)-Epicatechin and (+)-catechin belong to the flavan-3-ol class of flavonoids. Procyanidins containing up to 10 subunits (decamers) are found in fresh cacao beans and in dark chocolate. These are also called oligomeric procyanidins.

In addition to containing (-)-epicatechin, (+)-catechin and procyanidins, cocoa and chocolate contain other flavonoids, including other catechins and the flavanol quercetin and its glycosides. Collectively, these flavonoids are known as cocoa flavonoids or cocoa polyphenols.

Interestingly, the Mayans and Aztecs used cacao beans for the preparation of various remedies. The cocoa flavonoids appear to have potent antioxidant activity and may eventually turn out to have health-promoting benefits.

ACTIONS AND PHARMACOLOGY

ACTIONS

Cocoa flavonoids have antioxidant activity. They also may have anti-inflammatory and immunomodulatory activities.

MECHANISM OF ACTION

Cocoa flavonoids have been demonstrated to scavenge reactive oxygen and reactive nitrogen species. They may also chelate metals, such as ferrous cations, which participate in reactive oxygen species-generating reactions. Further, there is some evidence that the larger procyanidin oligomers have greater antioxidant potential.

Cocoa flavonoids have been shown to inhibit the oxidation of LDL. The oxidation of LDL is thought to be a crucial event in the pathogenesis of atherosclerosis.

Some of the cocoa flavonoids appear to reduce the expression of phytohemagglutinin-induced interleukin 2 (IL-2) mRNA, as well as the expression of interleukin 1beta (IL-1B), in peripheral blood mononuclear cells (PBMC).

Reduction of IL-2 and IL-1beta in PBMC could account, in part, for possible anti-inflammatory and immunomodulatory activities of cocoa flavonoids. The mechanism of these actions could again be due to the antioxidant action of cocoa flavonoids. Reactive oxygen species can activate nuclear transcription factor-Kappa B (NF-Kappa B). NF-Kappa B, in turn, may stimulate the production of such pro-inflammatory factors as IL-2 and IL-1 beta.

PHARMACOKINETICS

Little is known about the pharmacokinetics of cocoa polyphenols in humans. It appears that they do, at least partially, get absorbed. However, the extent of absorption appears to vary widely, not only among the different cocoa flavonoids, but also among subjects.

It also appears that the cocoa flavonoids undergo extensive glucuronidation, sulfation and methylation following and/or during absorption.

INDICATIONS AND USAGE

Cocoa flavonoids have been shown, in some mostly small, preliminary studies, to have possible benefit in blood pressure and in heart health generally.

RESEARCH SUMMARY

The cocoa bean is a rich source of polyphenols that exhibit significant antioxidant activity *in vitro.* These polyphenols are found in cocoa, baking chocolate and milk chocolate, among other foods. In one *in vitro* study, all three of these showed some ability to inhibit oxidation of LDL-cholesterol. Cocoa was the most potent of the three in this respect. In the decade since cocoa polyphenols have been investigated, some further small studies have demonstrated some benefits in humans, including lower platelet aggregation in one study and increased HDL-cholesterol in another.

In a few studies, improved insulin sensitivity was noted and blood pressure was improved. In a recent review of studies conducted over the past decade, the authors questioned the value of many of these studies since so many of them were small, poorly controlled and utilized healthy, well-nourished subjects. They also questioned whether observed effects were from cocoa polyphenols or from some other components in the agents used, such as caffeine or magnesium, or from synergistic effects of several components with cocoa. They noted that the majority of the studies were industry-

funded and designed, but also observed that since they were published in peer-reviewed journals the industry factor should not invalidate them. They called for more and better-designed studies in the future and suggested that endpoints other than just vascular endpoints be investigated. And, they concluded, "The *bona fide* health effects of cocoa polyphenols will not be answered short of a large-scale epidemiological study or long-term intervention." At present, they stated, there is insufficient data to know whether cocoa has any real public health benefit.

The review authors provided this checklist, which they propose for future planning of cocoa and chocolate trials:

1. Where possible, conduct randomized, controlled, cross-over, multi-dose trials.

2. Use well-defined cocoa or chocolate (if possible, for industry to allow similar cocoa/chocolate to be available for independent researchers for future studies/repeating work).

3. Ensure bioavailability of the active component from its matrix.

4. Use an appropriate control of no-polyphenol chocolate.

5. Recruit volunteers with at least one non-optimal biomarker or disease risk factor.

6. Use a dose of cocoa or chocolate that can readily be incorporated into the daily diet, giving appropriate dietary advice to volunteers on balancing energy.

7. Measure composition, including the polyphenol profile of the cocoa or chocolate before and after the trial (check for stability on storage or batch variations).

8. Ensure the final publication contains the analytical results along with the appropriate description of analytical methodology.

9. Carefully assess the biological relevance of the chosen biomarker, with special attention to antioxidant biomarkers.

10. Strive for transparency by registering human trials, before they start, with a recognized database, eg, www.clinicaltrials.gov.

11. Attempt to publish null or negative results, to enable balancing of the literature and preventing needless duplication of work. Challenge journals if papers are rejected on this basis.

In one recent study involving a cohort of elderly men, cocoa intake was inversely associated with blood pressure and 15-year cardiovascular and all-cause mortality. The data used were derived from 470 elderly men participating in the Zutphen Elderly Study who were free of chronic diseases at baseline. Blood pressure was measured at baseline and at five-year intervals.

Another recent study found that supplementing diet in 34 elderly males with flavonol-rich cocoa increased cerebral blood flow velocity in the middle cerebral artery in these subjects, compared with controls. This, the researchers said, suggested some possible role for cocoa products in cerebrovascular ischemic syndromes, including dementia and stroke. Far more research will be needed, however, to establish clinical significance.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

Cocoa polyphenols are contraindicated in those who are hypersensitive to any component of a cocoa polyphenol-containing product.

OVERDOSAGE

There are no reports of overdosage.

DOSAGE AND ADMINISTRATION

Chocolate bars and beverage mixtures that are rich in cocoa flavanols are available. Dark chocolate is generally higher in cocoa flavanols than milk chocolate. This is because the flavanols come from the cocoa liquor and milk chocolate generally contains less cocoa liquor than dark chocolate. White chocolate contains no cocoa liquor and hence no flavanols at all.

No dosage recommendations at this time.

LITERATURE

Aron PM, Kennedy JA. Flavan-3-ols: nature, occurrence and biological activity. *Mol Nutr Food Res.* 2008;52(1):79-104.

Arteel GE, Sies H. Protection against peroxynitrite by cocoa polyphenol oligomers. *FEBS Left.* 1999;462:167-170.

Arts ICW, Hollman PCH, Kromhout D. Chocolate as a source of tea flavonoids. *Lancet.* 1999;354:488.

Balzer J, Rassaf T, Heiss C, et al. 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(22):2141-2149.

Buijsse B, Feskens EJ, Kok FJ, et al. Cocoa intake, blood pressure, and cardiovascular mortality: the Zutphen Elderly Study. *Arch Intern Med.* 2006;166(4):411-417.

Cooper KA, Donovan JL, Waterhouse AL, et al. Cocoa and health: a decade of research. *Br J Nutr.* 2008;99(1):1-11.

Ding EL, Hutfless SM, Ding X, et al. Chocolate and prevention of cardiovascular disease: a systematic review. *Nutr Metab* (Lond). 2006;3:2.

Engler MB, Engler MM. The emerging role of flavonoid-rich cocoa and chocolate in cardiovascular health and disease. *Nutr Rev.* 2006;64(3):109-118.

Erdman JW Jr, Carson L, Kwik-Uribe C, et al. Effects of cocoa flavanols on risk factors for cardiovascular disease. *Asia Pac J Clin Nutr.* 2008;17 Suppl 1:284-287.

Fisher ND, Hughes M, Gerhard-Herman M, et al. Flavanol-rich cocoa induces nitric-oxide-dependent vasodilation in healthy humans. *J Hypertens.* 2003;21(12):2281-2286.

Hammerstone JF, Lazarus SA, Mitchell AE, et al. Identification of procyanidins in cocoa (*Theobroma Cacao*) and chocolate using high-performance liquid chromatography/mass spectrometry. *J Agric Food Chem.* 1999;47:490-496.

Heiss C, Schroeter H, Balzer J, et al. Endothelial function, nitric oxide, and cocoa flavanols. *J Cardiovasc Pharmacol.* 2006;47 Suppl 2:S128-135; discussion S172-176.

Holt RR, Actis-Goretta L, Momma TY, et al. Dietary flavanols and platelet reactivity. *J Cardiovasc Pharmacol.* 2006;47 Suppl 2:S187-196; discussion S206-209.

Keen CL, Holt RR, Oteiza PI, et al. Cocoa antioxidants and cardiovascular health. *Am J Clin Nutr.* 2005;81(1 Suppl):298S-303S.

Kwik-Uribe C, Bektash RM. Cocoa flavanols—measurement, bioavailability and bioactivity. *Asia Pac J Clin Nutr.* 2008;17 Suppl 1:280-283.

Lazarus SA, Hammerstone JF, Schmitz HA. Chocolate contains additional flavonoids not found in tea. *Lancet.* 1999;354:1825.

Mao TK, Powell J, Van de Water J, et al. The effect of cocoa procyanidins on the transcription and secretion of interleukin 1beta in peripheral blood mononuclear cells. *Life Sci.* 2000;66:1377-1386.

Mao TK, Powell JJ, Van de Water J, et al. The influence of cocoa procyanidins on the transcription of interleukin-2 in peripheral blood mononuclear cells. *Int J Immunotherapy.* 1999;15:23-29.

Mehrinfar R, Frishman WH. Flavanol-rich cocoa: a cardioprotective nutraceutical. *Cardiol Rev.* 2008;16(3):109-115.

Sanbongi C, Suzuki N, Sakane T. Polyphenols in chocolate, which have antioxidant activity, modulate immune function in humans *in vitro*. *Cell Immunol.* 1997;177:129-136.

Schroeter H, Heiss C, Balzer J, et al. (-)-Epicatechin mediates beneficial effects of flavanol-rich cocoa on vascular function in humans. *Proc Natl Acad Sci USA.* 2006;103(4):1024-1029.

Selmi C, Mao TK, Keen CL, et al. The anti-inflammatory properties of cocoa flavanols. *J Cardiovasc Pharmacol.* 2006;47 Suppl 2:S163-171; discussion S172-176.

Sorond FA, Lipsitz LA, Hollenberg NK, et al. Cerebral blood flow response to flavanol-rich cocoa in healthy elderly humans. *Neuropsychiatr Dis Treat.* 2008;4(2):433-440.

Taubert D, Roesen R, Lehmann C, et al. Effects of low habitual cocoa intake on blood pressure and bioactive nitric oxide: a randomized controlled trial. *JAMA.* 2007;298(1):49-60.

Vinson JA, Proch J, Zubik L. Phenol antioxidant quantity and quality in foods: cocoa, dark chocolate and milk chocolate. *J Agric Food Chem.* 1999;47:4821-4824.

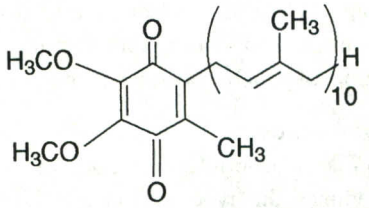
Coenzyme Q10 (CoQ10)

DESCRIPTION

Coenzyme Q_{10} or CoQ_{10} belongs to a family of substances called ubiquinones. Ubiquinones, also known as coenzymes Q and mitoquinones, are lipophilic, water-insoluble substances involved in electron transport and energy production in mitochondria. The basic structure of ubiquinones consists of a benzoquinone "head" and a terpinoid "tail." The "head" structure participates in the redox activity of the electron transport chain. The major difference among the various coenzymes Q is in the number of isoprenoid units (5-carbon structures) in the "tail." Coenzymes Q contain one to 12 isoprenoid units in the "tail"; 10 isoprenoid units are common in animals.

Coenzymes Q occur in the majority of aerobic organisms, from bacteria to plants and animals. Two numbering systems exist for designation of the number of isoprenoid units in the terpinoid "tail": coenzyme Qn and coenzyme Q(x). N refers to the number of isoprenoid side chains, and x refers to the number of carbons in the terpinoid "tail" and can be any multiple of five. Thus, coenzyme Q_{10} refers to a coenzyme Q having 10 isoprenoid units in the "tail." Since each isoprenoid unit has five carbons, coenzyme Q_{10} can also be designated coenzyme Q(50). The structures of coenzymes Q are analogous to those of vitamin K2.

Coenzyme Q_{10} is also known as Coenzyme Q(5O), CoQ_{10}, CoQ(50), ubiquinone (50), ubiquinol— 10 and ubidecarerone. Chemically, CoQ_{10} is known as 2, 3-dimethyoxy-5-methyl-6-decaprenyl-1,4-benzoquinone, and its structural formula is:



CoEnzyme Q_{10}

It is a solid wax-like substance. CoQ_{10} is the predominant form in humans, and CoQ_9 is the predominant form in rats.

Supplemental CoQ_{10} is typically derived from tobacco leaf extracts and fermented sugar cane and beets.

ACTIONS AND PHARMACOLOGY

ACTIONS

Supplemental CoQ_{10} may have cardioprotective, cytoprotective and neuroprotective activities.