Tea, Chocolate and Coffee

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Polyphenols

- A large family of natural compounds widely distributed in plant foods.
- Polyphenols have specific health-promoting actions, and it is generally recognized that they can reduce the risk factors for many types of chronic diseases.

Polyphenols

- The largest and best studied polyphenols are the flavonoids, which include several thousand compounds, among them the flavonols, flavones, catechins, flavanones, anthocyanidins, and isoflavonoids.
- Important dietary sources of polyphenols in Western societies are onions (flavonols); cocoa, tea, apples, and red wine (flavonols and catechins); citrus fruit (flavanones); berries and cherries (anthocyanidins); and soy (isoflavones).

- **Drinking a daily cup of tea will surely starve the apothecary**

--Chinese Proverb

Proceedings of the Third International Scientific Symposium on Tea and Human Health: Role of Flavonoids in the Diet

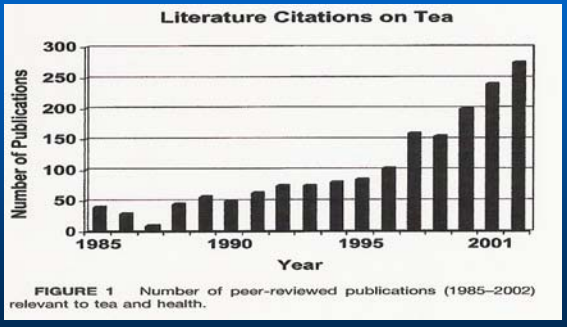


FIGURE 1 Number of peer-reviewed publications (1985–2002) relevant to tea and health.

Blumberg, J. Nutr. 133: 3244S- 3246S, 2003

- Camellia sinensis is an evergreen plant that grows mainly in tropical climates.
- However, some varieties can also tolerate marine climates and are cultivated as far north as Cornwall on the UK mainland and Seattle in the US.

Processing of tea

- Tea is traditionally classified based on producing technique:
- White tea: Unwilted and unoxidized
- Green tea: Wilted and unoxidized
- Oolong: Wilted, bruised, and partially oxidized
- Black tea: Wilted, crushed, and fully oxidized

Catechins are polyphenols and tea has a large concentration of catechins.

Green Tea

- Major polyphenols in green tea are catechins.
- There are 4 major green tea catechins:
  - Epigallocatechin-3-gallate (EGCG)
  - Epicatechin-3-gallate
  - Epigallocatechin
  - Epicatechin
- It's antioxidant activity is reported to be 100X stronger than vitamin C and 25X stronger than vitamin E in protecting DNA from mutations associated with oxidative damage.

Mechanism of action of tea on health

Action of tea polyphenols	Consequence
Potent antioxidant activity	Lower risk of heart disease; ↓ LDL oxidation, ↓ lipid peroxidation, ↓ oxidation of DNA and inhibition of carcionogenesis.
Selectively induce Phase I and Phase II metabolic enzymes	Detoxification of carcinogens
Inhibit cell proliferation rates	Decreased growth of abnormal cells and neoplasms
Improved composition of intestinal bacterial flora	Undesirable components of flora replaced by beneficial bacteria.
Prevents angiogenesis	Reduce blood vessel growth (↓ metastasis)

Catechins / EGCG Green Tea

- **Antioxidant (↓ LDL oxidation, ↓ lipid peroxidation, and ↓ DNA oxidation)**
- **↓ cholesterol levels**
- **↓ platelet aggregation**
- **↓ cancer risk in lungs, stomach, breast, colon cancers-** detoxification of carcinogens (phase I and phase II)
- **↑ thermogenesis (fat oxidation & energy expenditure)**
- **Anti-inflammatory (skin disorders, arthritis)**

NUTRITION

Applied nutritional investigation

Standardized capsule of *Camellia sinensis* lowers cardiovascular risk factors in a randomized, double-blind, placebo-controlled study

Meri P. Nantz, B.S.*, Cheryl A. Rowe, Ph.D.*, Jack F. Bukowski, M.D.†,‡, and Susan S. Percival, Ph.D.†,§

Daily supplements of extracts from green tea (*Camellia sinensis*) was effective for decreasing, in as quickly as 3 weeks, blood pressure, LDL cholesterol, oxidative stress, and a marker of chronic inflammation, all independent cardiovascular risk factors.

Mechanisms by which tea may confer its cardiovascular protective properties

- Inhibition of oxidized LDL cholesterol
- Attenuation of the inflammatory process in atherosclerosis
- Reduction in thrombosis
- Promotion of the normal endothelial function
- Blocking of adhesion molecules
- Reduction in plasma total and LDL cholesterol (LDL-C)

Tea flavonoids gain recognition as powerful weapon against disease

- **People who drink five cups of tea daily are not only likely to improve their cholesterol levels but may also protect against damage from smoking**

• **Journal of Nutrition, (2003) vol 133, no 10**

Effect of Increased Tea Consumption on Oxidative DNA Damage among Smokers: A Randomized Controlled Study[1,2]

Iman A. Hakim,*†3 Robin B. Harris,*† Sylvia Brown,*† H-H. Sherry Chow,† Sheila Wiseman,** Sanjiv Agarwal‡ and Wendy Talbot*

*Mel and Enid Zuckerman Arizona College of Public Health, University of Arizona, Tucson, AZ 85724; †Arizona Cancer Center, Tucson, AZ 85724; **Unilever Health Institute, Vlaardingen, The Netherlands; and ‡Unilever Bestfoods North America, Englewood Cliff, NJ 07632

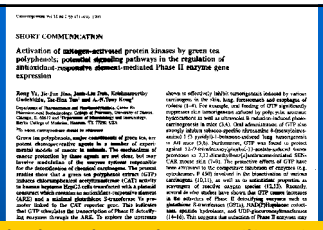
ABSTRACT Tea drinking has been associated with decreased occurrence of cancer and heart disease. One potential mechanism for these findings is the strong antioxidant effect of tea polyphenols. A phase II randomized controlled tea intervention trial was designed to study the effect of high consumption (4 cups/d) of decaffeinated green or black tea on oxidative DNA damage as measured by urinary 8-hydroxydeoxyguanosine (8-OHdG) among smokers over a 4-mo period. A total of 143 heavy smokers, aged 18–79 y, were randomized to drink either green or black tea or water. Levels of plasma and urinary catechins and urinary 8-OHdG were measured monthly. A total of 133 of 143 smokers completed the 4-mo

"These data suggest that regular green tea drinking might protect smokers from oxidative damages and could reduce cancer risk or other diseases caused by free radicals associated with smoking.

J. Nutr. 133: 3303S-3309S, 2003

Foods provide key nutrients that support these detoxification pathways

- Indoles, phytochemicals found in broccoli, cauliflower and other cruciferous vegetables, and green tea catechins markedly enhance phase I pathways.
- Dithioilthiones and isothiocynates; liminoids, phytochemicals in citrus, organosulfuric compounds found in the allium family vegetables (garlic, onions, shallots, and leeks), green tea catechins and curcumin increase phase II enzymes, including Glutathione S Transferase which blocks carcinogens from damaging cellular DNA.



SHORT COMMUNICATION

Activation of mitogen-activated protein kinases by green tea polyphenols: potential signaling pathways in the regulation of antioxidant-responsive element-mediated Phase II enzyme gene expression

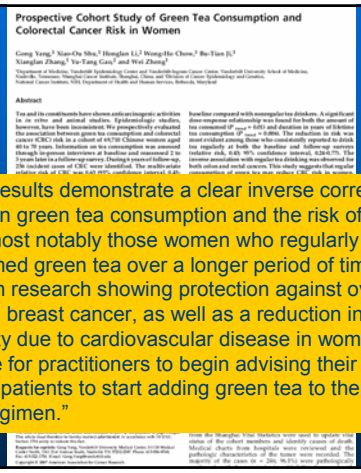
"Green tea polyphenols, major constituents of green tea, are potent chemopreventive agents in a number of experimental models of cancer in animals…This indicates that GTP stimulates the transcription of Phase II detoxifying enzymes through the antioxidant responsive element (ARE)."

Yu R, *et al. Carcinogenesis* 1997;18(2):451-56.

Nakachi (1998) found that the consumption of 5 or more cups of green tea per day was associated with decreased recurrence of stage I and II breast cancer in Japanese women.

Nakachi, et al (as cited in Hasler, 1998).

- Epidemiological studies on Japanese women report that those who drink 2-3 cups or more of green tea a day have a lower incidence of cancer (or develop the disease at a later date).
- The custom of drinking green tea with meals in Japan may be one reason for the low cancer rates. The Japanese smoke nearly twice as many cigarettes as Americans, yet they have approx. half the incidence of lung cancer.
- In vitro showed inhibitory effect on the growth of mammary cell cancer. Prevents angiogenesis (blood vessel growth).



Prospective Cohort Study of Green Tea Consumption and Colorectal Cancer Risk in Women

Gong Yang,[1] Xiao-Ou Shu,[1] Honglan Li,[2] Wong-Ho Chow,[3] Bu-Tian Ji,[1] Xianglan Zhang,[1] Yu-Tang Gao,[2] and Wei Zheng[1]

Abstract

Tea and its constituents have shown anticarcinogenic activities in in vitro and animal studies. Epidemiologic studies, however, have been inconsistent. We prospectively evaluated the association between green tea consumption and colorectal cancer risk among 69,710 women, a cohort study conducted in 40 to 70 years. Information on tea consumption was assessed through in-person interviews at baseline and reassessed 2 to 3 years later in a follow-up survey. During 6 years of follow-up, 256 incident cases of CRC were identified. The multivariate relative risk of CRC was 0.63 (95% confidence interval, 0.45-

baseline compared with nonregular tea drinkers. A significant dose-response relationship was found for both the amount of tea consumed ($P_{trend} = 0.01$) and duration in years of lifetime tea consumption ($P_{trend} = 0.006$). The reduction in risk was most evident for those women who reported drinking green tea consistently at both the baseline and follow-up surveys (relative risk, 0.43; 95% confidence interval, 0.24-0.77). The inverse association with regular tea drinking was observed for both colon and rectal cancers. This study suggests that regular consumption of green tea may reduce CRC risk in women.

From the Shanghai Vital Statistics were used to update vital status of the cohort members and identify causes of death. Medical charts from hospitals were reviewed and pathologic characteristics of the tumors were recorded. The majority of the cases (n = 256, 96.5%) were pathologically

✶The results demonstrate a clear inverse correlation between green tea consumption and the risk of CRC-most notably those women who regularly consumed green tea over a longer period of time.
✶ "With research showing protection against ovarian cancer, breast cancer, as well as a reduction in mortality due to cardiovascular disease in women, it's time for practitioners to begin advising their female patients to start adding green tea to their daily regimen."

Green Tea Prevents Colorectal Cancer in Women

- **Key Findings:** The multivariate relative risk of colorectal cancer (CRC) was 0.63 (95% confidence interval, 0.45-0.88) for women who reported drinking green tea regularly at baseline compared with non-regular tea drinkers.
- A significant dose-response relationship was found for both the amount of green tea consumed (p trend = 0.001) and the duration in years of lifetime tea consumption (p trend = 0.006).
- Compared with non-drinkers, each 1.67 g increase (approximately equal to the amount of tea in one tea bag) in daily green tea consumption was associated with a 10% reduction in CRC risk (RR, 0.90; CI: 0.80-1.00).
- Additional 5-year consumption of green tea was also associated with a 10% reduction in CRC risk (RR, 0.90; 95% CI: 0.83-0.97) after fully adjusting for potential confounding variables (e.g. cigarette smoking, alcohol consumption, exercise).
- The reduction in risk was most evident for those women who reported to drink tea regularly at both baseline and during follow-up surveys (RR, 0.43; 95% CI: 0.24-0.77).

For a long time, it was believed that these cancer-fighting polyphenols could only be obtained from GREEN tea, not BLACK. Stoner, G.D. & Mukhtar, H. (1995)

However, recent research has shown that both GREEN and BLACK tea can inhibit lung cancer in animal experiments.

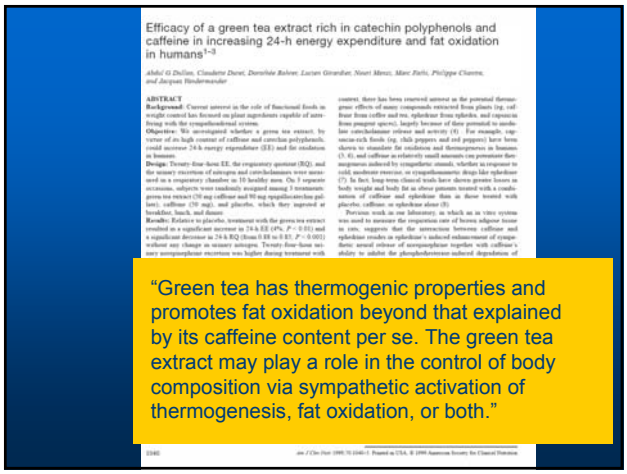
Yang, et al (1998)

- Recent studies indicate the compounds contained in black tea – theaflavins and thearubigens - do more than contribute to its dark color and distinctive flavor. They also provide health benefits originally attributed solely to green tea.

Tea shown to fight infection

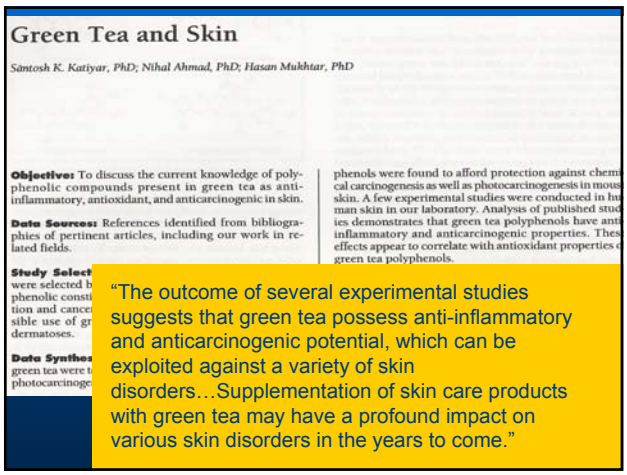
- Drinking tea appears to prime the immune system to fight infection and chronic disease.
- Subjects who drank five to six small cups of black tea daily for two weeks were better able to fight off bacterial infections
- Gamma delta T cells act to prevent and reduce the effects of disease. Previous experiments have shown that exposing these cells to ethylamine, produced when the tea ingredient L-theanine is broken down in the liver, boosted the abilities of the cells to fight infections.
- The researchers also carried out in vivo studies on people who either drank about 20 ounces of tea a day for two weeks, or consumed coffee instead. The tea drinkers' gamma delta T cells produced a wealth of anti-bacterial chemicals when exposed to bacteria.
- In contrast, people who drank coffee during the study produced no disease-fighting proteins in response to bacteria.

Proceedings of the National Academy of Sciences 2003;10.1073/pnas.1035603100



Efficacy of a green tea extract rich in catechin polyphenols and caffeine in increasing 24-h energy expenditure and fat oxidation in humans[1–3]

"Green tea has thermogenic properties and promotes fat oxidation beyond that explained by its caffeine content per se. The green tea extract may play a role in the control of body composition via sympathetic activation of thermogenesis, fat oxidation, or both."



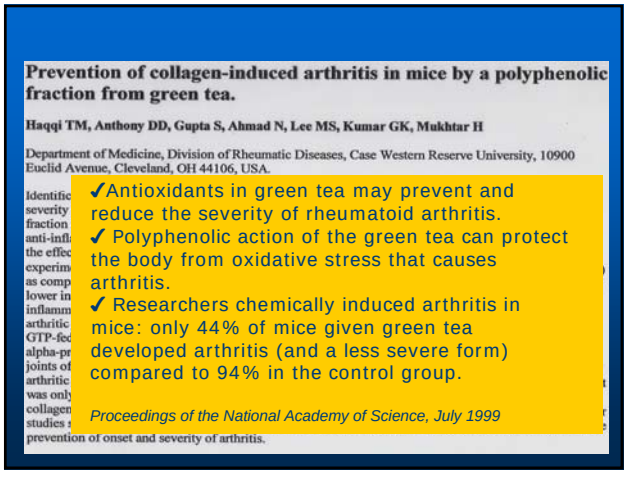
Green Tea and Skin

Santosh K. Katiyar, PhD; Nihal Ahmad, PhD; Hasan Mukhtar, PhD

Objective: To discuss the current knowledge of polyphenolic compounds present in green tea as anti-inflammatory, antioxidant, and anticarcinogenic in skin.

Data Sources: References identified from bibliographies of pertinent articles, including our work in related fields.

"The outcome of several experimental studies suggests that green tea possess anti-inflammatory and anticarcinogenic potential, which can be exploited against a variety of skin disorders…Supplementation of skin care products with green tea may have a profound impact on various skin disorders in the years to come."



Prevention of collagen-induced arthritis in mice by a polyphenolic fraction from green tea.

Haqqi TM, Anthony DD, Gupta S, Ahmad N, Lee MS, Kumar GK, Mukhtar H

Department of Medicine, Division of Rheumatic Diseases, Case Western Reserve University, 10900 Euclid Avenue, Cleveland, OH 44106, USA.

✓Antioxidants in green tea may prevent and reduce the severity of rheumatoid arthritis.
✓ Polyphenolic action of the green tea can protect the body from oxidative stress that causes arthritis.
✓ Researchers chemically induced arthritis in mice: only 44% of mice given green tea developed arthritis (and a less severe form) compared to 94% in the control group.

Proceedings of the National Academy of Science, July 1999

1: Eur J Clin Nutr. 1998 May;52(5):356-9.

Bioavailability of catechins from tea: the effect of milk.

van het Hof KH, Kivits GA, Weststrate JA, Tijburg LB.

Unilever Research Vlaardingen, The Netherlands.

OBJECTIVES: To assess the blood concentration of catechins following green or black tea ingestion and the effect of addition of milk to black tea. DESIGN: Twelve volunteers received a single dose of green tea, black tea and black tea with milk in a randomized cross-over design with one-week intervals. Blood samples were drawn before and up to eight hours after tea consumption. SETTING: The study was performed at the Unilever Research Vlaardingen in The Netherlands. SUBJECTS: Twelve healthy adult volunteers (7 females, 5 males) participated in the study. They were recruited among employees of Unilever Research Vlaardingen. INTERVENTIONS: Green tea, black tea and black tea with semi-skimmed milk (3 g tea solids each). RESULTS: Consumption of green tea (0.9 g total catechins) or black tea (0.3 g total catechins) resulted in a rapid increase of catechin levels in blood with an average maximum change from baseline (CVM) of 0.46 micromol/l (13%) after ingestion of green tea and 0.10 micromol/l (13%) in case of black tea. These maximum changes were reached after (mean (s.e.m.)) t=2.3 h (0.2) and t=2.2 h (0.2) for green and black tea respectively. Blood levels rapidly declined with an elimination rate (mean (CVM)) of t1/2=4.8 h (5%) for green tea and t1/2=6.9 h (8%) for black tea. Addition of milk to black tea (100 ml in 600 ml) did not significantly affect the blood catechin levels (areas under the curves (mean (CVM) of 0.53 h. micromol/l (11%) vs 0.60 h. micromol/l (9%) for black tea and black tea with milk respectively. CONCLUSION: Catechins from green tea and black tea are rapidly absorbed and milk does not impair the bioavailability of tea catechins.

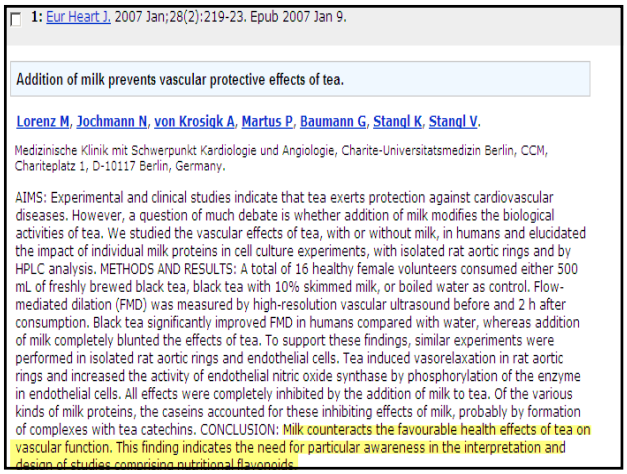
1: Eur J Clin Nutr. 2000 Jan;54(1):87-92.

A single dose of tea with or without milk increases plasma antioxidant activity in humans.

Leenen R, Roodenburg AJ, Tijburg LB, Wiseman SA.

Unilever Nutrition Centre, Unilever Research Vlaardingen, PO Box 114, 3130 AC Vlaardingen, The Netherlands.

OBJECTIVE: To investigate the effect of black and green tea consumption, with and without milk, on the plasma antioxidant activity in humans. DESIGN: In a complete cross-over design, 21 healthy volunteers (10 male, 11 female) received a single dose of black tea, green tea (2 g tea solids in 300 ml water) or water with or without milk. Blood samples were obtained at baseline and at several time points up to 2 h post-tea drinking. Plasma was analysed for total catechins and antioxidant activity, using the ferric reducing ability of plasma (FRAP) assay. RESULTS: Consumption of black tea resulted in a significant increase in plasma antioxidant activity reaching maximal levels at about 60 min. A larger increase was observed after consumption of green tea. As anticipated from the higher catechin concentration in green tea, the rise in plasma total catechins was significantly higher after consumption of green tea when compared to black tea. Addition of milk to black or green tea did not affect the observed increases in plasma antioxidant activity. CONCLUSIONS: Consumption of a single dose of black or green tea induces a significant rise in plasma antioxidant activity in vivo. Addition of milk to tea does not abolish this increase. Whether the observed increases in plasma antioxidant activity after a single dose of tea prevent in vivo oxidative damage remains to be established.
European Journal of Clinical Nutrition (2000) 54, 87-92



1: Eur Heart J. 2007 Jan;28(2):219-23. Epub 2007 Jan 9.

Addition of milk prevents vascular protective effects of tea.

Lorenz M, Jochmann N, von Krosigk A, Martus P, Baumann G, Stangl K, Stangl V.

Medizinische Klinik mit Schwerpunkt Kardiologie und Angiologie, Charite-Universitatsmedizin Berlin, CCM, Chariteplatz 1, D-10117 Berlin, Germany.

AIMS: Experimental and clinical studies indicate that tea exerts protection against cardiovascular diseases. However, a question of much debate is whether addition of milk modifies the biological activities of tea. We studied the vascular effects of tea, with or without milk, in humans and elucidated the impact of individual milk proteins in cell culture experiments, with isolated rat aortic rings and by HPLC analysis. METHODS AND RESULTS: A total of 16 healthy female volunteers consumed either 500 mL of freshly brewed black tea, black tea with 10% skimmed milk, or boiled water as control. Flow-mediated dilation (FMD) was measured by high-resolution vascular ultrasound before and 2 h after consumption. Black tea significantly improved FMD in humans compared with water, whereas addition of milk completely blunted the effects of tea. To support these findings, similar experiments were performed in isolated rat aortic rings and endothelial cells. Tea induced vasorelaxation in rat aortic rings and increased the activity of endothelial nitric oxide synthase by phosphorylation of the enzyme in endothelial cells. All effects were completely inhibited by the addition of milk to tea. Of the various kinds of milk proteins, the caseins accounted for these inhibiting effects of milk, probably by formation of complexes with tea catechins. CONCLUSION: Milk counteracts the favourable health effects of tea on vascular function. This finding indicates the need for particular awareness in the interpretation and design of studies comprising nutritional flavonoids.

- Adding milk does not seem to affect antioxidant status of tea, however, it may inhibit nitric oxide synthesis and thereby reduce vascular relaxation.

Cocoa

- A natural antioxidant
- Traditionally used in Mexico and parts of Latin America for medicinal purposes
- Theobroma cacao plant used to make chocolate
- Recent studies find cocoa to be cardioprotective improve blood flow to the heart muscle.

Chocolate Polyphenols

Cocoa is rich in antioxidant flavonoids called flavanols, which include procyanidins, epicatechins, and catechins.

Chocolate Polyphenols

- Antioxidant
- ↓ blood platelet aggregation
- ↑ flexibility of blood vessels and ↑ blood flow (↑ production of nitric oxide).
- ↓ moderately high BP
- ↓ LDL oxidation

- High concentration of polyphenol compounds called flavanols, including epicatechin and catechin.
- Cocoa flavanols improve endothelial function by enhancing nitric oxide bioactivity which helps dilate the blood vessels, increasing blood flow, reducing blood clot formation, and reducing blood pressure. Flavanols can also reduce LDL oxidation which may prevent buildup of artherosclerotic plaque in the artery walls.

Chocolate: Food as Medicine/Medicine as Food

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Department of Nutrition and Internal Medicine, University of California at Davis, Davis, California

Key words: chocolate, flavonoids, antioxidants, procyanidins, epicatechin, cardiovascular disease

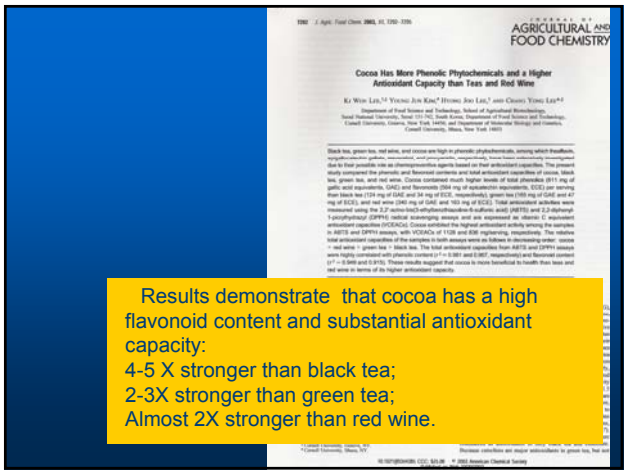
Key teaching points:

- Cocoa and chocolate products have the highest concentration of flavonoids among commonly consumed foods
- The predominant flavonoids are catechin and epicatechin, which are found in polymers
- These flavonoids have potent antioxidant effects in vitro and in vivo, and exert antioxidant vitamins
- Cocoa-derived polyphenols also inhibit platelet reactivity
- Multiple mechanisms are described by which phytochemicals from cocoa may exert healthful effects

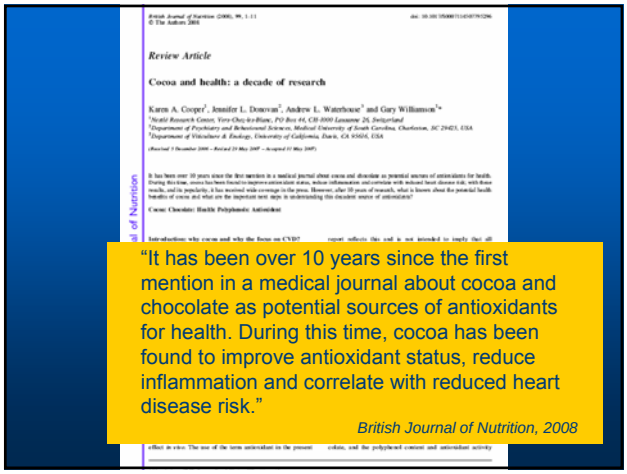
Journal of the American College of Nutrition, Vol. 20, No. 5, 436S–439S (2001)
Published by the American College of Nutrition

- Preliminary clinical studies, with participants consuming flavanol-rich cocoas and chocolates, have resulted in a number of positive effects relating to cardiovascular health, including decreased blood pressure and improved blood flow through the vessels.
- In fact, a recent clinical study simultaneously compared low-dose aspirin and a flavanol-rich cocoa beverage, and found reductions in platelet "stickiness," which may improve blood flow, with both.

- *In vitro* studies found that the flavanols in chocolate may decrease the oxidation of Low Density Lipoproteins (LDL), or "bad" cholesterol. When LDLs become oxidized, they promote the build up of plaque along the lining of blood vessels, which can reduce blood flow and supports the development of high blood pressure and atherosclerosis.
- Additional *in vitro* studies found that flavanols may reduce platelet aggregation. Platelet aggregation is when blood components become "sticky" and adhere to the lining of the blood vessel. Platelet aggregation may be a risk factor for cardiovascular disease and is thought to lead to high blood pressure and other forms of heart disease.
- A diet containing about an ounce of chocolate a day increases good cholesterol and prevents bad cholesterol from oxidizing.



Results demonstrate that cocoa has a high flavonoid content and substantial antioxidant capacity:
4-5 X stronger than black tea;
2-3X stronger than green tea;
Almost 2X stronger than red wine.



"It has been over 10 years since the first mention in a medical journal about cocoa and chocolate as potential sources of antioxidants for health. During this time, cocoa has been found to improve antioxidant status, reduce inflammation and correlate with reduced heart disease risk."

British Journal of Nutrition, 2008

Table 1. Human intervention trials with cocoa

	Intervention	Polyphenol content	Control	Subjects	Main outcomes	Industry-funded	Reference
1	Semi-sweet chocolate baking bits (one dose of a, 27 g; b, 53 g; c, 80 g)	Total procyanidins (epicatechin): (a) 186 mg (46 mg); (b) 365 mg (90 mg); (c) 551 mg (136 mg)	No chocolate	20 healthy adults (20–56 years)	Dose-dependent increase in plasma epicatechin. Non-significant trend for an increase in plasma antioxidant activity and a decrease in TBARS	Partially	Wang *et al.*[14]
2	18·75 g procyanidin-rich cocoa powder in 330 ml water (one dose)	897 mg epicatechin and total procyanidins	Caffeine and sucrose hot drink or water	30 healthy adults (24–50 years), 10 per group	Suppression of platelet activation. Aspirin-like effect on primary haemostasis 6 h after consumption	Authors from industry, not stated outright	Rein *et al.*[14]
3	105 g (of which 80 g chocolate) semi-sweet baking bits (one dose)	557 mg total procyanidins (of which 137 mg epicatechin)	Vanilla milk chips (isoenergetic)	10 healthy adults (26–49 years) + 3 healthy adults (28–36 years) consuming control	12-fold increase in plasma epicatechin 2 h later, increase in plasma total antioxidant activity and decrease in TBARS	Partially	Rein *et al.*[15]
4	12 g cocoa powder × 3/d for 2 weeks	2610 mg total polyphenols/d (of which 244 mg epicatechin)	Sugar	15 healthy men, 9 in active group (32·5 ± 6·4 years)	Increase in LDL oxidation lag time, no change in plasma lipids or antioxidants. Higher excretion of epicatechin/metabolites in urine	Authors from industry, not stated outright	Osakabe *et al.*[40]
5	22 g cocoa powder and 16 g dark chocolate/d for 4 weeks	466 mg procyanidins/d (of which 111 mg monomers)	Average American diet	23 healthy adults (21–62 years)	Increase in LDL oxidation lag time, increase in serum antioxidant capacity, increase in HDL cholesterol	No but industrial authors	Wan *et al.*[46]
6	18·75 g cocoa powder in 300 ml water with sugar, with and without aspirin (one dose)	897 mg epicatechin and procyanidins	81 mg aspirin	16 healthy adults (22–49 years)	After 6 h, cocoa inhibited epinephrine-stimulated platelet activation and function	Partially	Pearson *et al.*[42]
7	36·9 g dark chocolate and 30·95 g cocoa powder in a drink/d for 6 weeks	651 mg total procyanidins/d (chocolate = 108 mg/d; cocoa = 463 mg/d)	None	25 healthy adults (20–60 years)	LDL oxidisability was lower, but no effect on inflammation markers, or plasma antioxidant capacity	Partially	Mathur *et al.*[43]
8	25 g semi-sweet chocolate chips (one dose)	220 mg flavanols and procyanidins	None	18 healthy adults	Increase in plasma epicatechin after 2 h with concurrent increase in prostacyclin–leukotriene ratio. Reduction in platelet-related haemostasis	Partially	Holt *et al.*[34]
9	100 g dark chocolate/d for 14 d	500 mg/d total polyphenols	90 g white chocolate	13 elderly adults (55–64 years with mild hypertension)	Lower systolic and diastolic blood pressure	No	Taubert *et al.*[44]
10	Cocoa flavanol/procyanidin tablets for 28 d	234 mg flavanols and procyanidins/d (6 × 39 mg tablets/d)	Placebo tablets	13 healthy adults (active 40 y ± 9), 15 healthy adults (control 47.4 years ± 4)	Lower platelet aggregation and P-selectin expression, higher plasma ascorbic acid, no change in oxidation/antioxidant status markers. Increase in plasma epicatechin and catechin	Partially	Murphy *et al.*[45]
11	High polyphenol cocoa drink 4 × 230 ml/d for 4 d	821 mg/d total flavanols (epicatechin, catechin and related oligomers)	Low flavanol cocoa drink	27 healthy adults (19–72 years)	Improved peripheral vasodilation after 4 d, large acute response after 90 min	Partially	Fisher *et al.*[60]
12	100 ml high cocoa polyphenol drink (one dose)	176 mg total (70 mg monomers, 106 mg procyanidins)	Low flavanol cocoa drink	20 adults (all with 1 CHD risk factor) (41 years ± 14) (77 % were smokers)	NO bioactivity and arterial FMD increased	Partially	Heiss *et al.*[57]

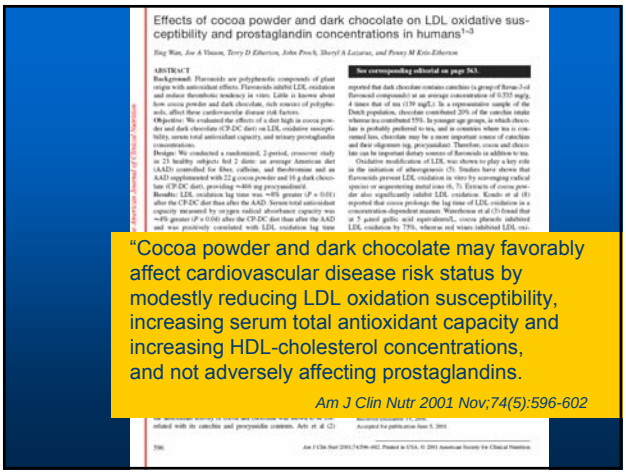
Table 1. *Continued*

	Intervention	Polyphenol content	Control	Subjects	Main outcomes	Industry-funded	Reference
13	100 g dark chocolate (with and without 200 ml milk) (one dose)	Polyphenols not stated but FRAP values were 1474 μmol FE/100 g)	200 g milk chocolate (FRAP 78·3 μmol FE/100 g)	12 healthy adults (25–35 years)	Dark chocolate increased plasma antioxidant capacity and epicatechin. Consuming milk with it reduced these effects. Milk chocolate had less effect than both these treatments	No	Serafini *et al.*[61]
14	75 g dark chocolate or high phenolic dark chocolate for 3 weeks	Dark = 274 mg/d (114 mg/d epicatechin). High = 418 mg/d (170 mg/d epicatechin)	75 g white chocolate	45 healthy adults (19–49 years)	Both dark chocolates increased HDL cholesterol and lipid peroxidation decreased (but also with white chocolate control). No change in plasma antioxidant capacity	Partially	Mursu *et al.*[58]
15	46 g/d high phenolic dark chocolate for 14 d	213 mg/d total procyanidins (of which 46 mg/d epicatechin)	Low phenolic dark chocolate	21 healthy adults (21–55 years)	Improved endothelium-dependent FMD, no change in blood pressure, oxidative markers or blood lipids. Higher plasma epicatechin	No	Engler *et al.*[47]
16	High polyphenol cocoa drink, 100 ml (one dose)	187 mg total monomers and oligomeric procyanidins	Low phenolic cocoa drink	20 healthy males (20–40 years)	F2 isoprostanes improved 2 and 4 h after exercise	No but industrial involvement	Wiswedel *et al.*[54]
17	Dark chocolate, 100 g (one dose)	500 mg total polyphenols	90 g white chocolate	15 healthy adults (34 ± 7·6 years)	Insulin sensitivity higher and insulin resistance lower. Systolic blood pressure lower	No	Grassi *et al.*[55]
18	Flavonoid-rich drink at 0·25, 0·375, 0·5 g/kg body weight) (one dose)	12·2 mg/g monomers, 9·7 mg/g dimers, 28·2 mg/g procyanidins	Bread and water	8 healthy males (26 ± 2 years)	Reduction in the rate of free radical-induced haemolysis	Partially	Zhu *et al.*[48]
19	105 g/d milk chocolate for 14 d	168 mg/d flavanols (of which 39 mg monomers and 126 mg polymers)	Cocoa butter chocolate	28 healthy males (18–20 years) under exercise stress	Decrease in diastolic and mean blood pressure, plasma cholesterol, LDL, malondialdehyde, urate and lactate dehydrogenase activity, increase in vitamin E–cholesterol ratio. No change in plasma epicatechin but samples were fasting	No but industrial involvement (via authorship)	Fraga *et al.*[59]
20	100 g dark chocolate (one dose)	2·62 g (of which 0·54 g monomers and dimers, 0·76 g trimer-heptamers)	Sham chewing and water	17 healthy adults (24–32 years)	Increase in resting and hyperaemic brachial artery diameter. Increase in FMD at 60 min. Aortic augmentation index decreased. No significant change in malondialdehyde, and total antioxidant capacity and pulse wave velocity	No	Vlachopoulos *et al.*[37]
21	100 g/d dark chocolate for 15 d	88 mg/d flavanols (22 mg catechin, 66 mg epicatechin)	90 g white chocolate	20 never-treated adults with essential hypertension (44 ± 8 years)	Insulin sensitivity improved, lower systolic and diastolic blood pressure and LDL, and improved FMD	No	Grassi *et al.*[75]
22	High polyphenol cocoa drink, 100 ml (one dose)	176–195 mg flavanols (70–74 mg monomers, 20–22 mg epicatechin, 106–111 mg procyanidins)	Low phenolic cocoa drink	11 adult smokers (average 31 years)	Increased circulating NO. FMD, both correlated to increases in flavanol metabolites. Effects were reversed with NG-monomethyl-l-arginine to prove link to NO	Yes	Heiss *et al.*[56]

Table 1. *Continued*

	Intervention	Polyphenol content	Control	Subjects	Main outcomes	Industry-funded	Reference
23	300 ml high polyphenol cocoa drink (one dose)	917 mg flavanols (19 % epicatechin)	300 ml low polyphenol cocoa drink	16 healthy males (25–32 years)	Acute elevations in levels of circulating NO species, an enhanced FMD response of conduit arteries, and an augmented microcirculation	Partially	Schroeter *et al.*[38]
24	40 g dark chocolate (one dose)	Not stated but same brand as used for Vlachopoulos *et al.*[37]	White chocolate	20 male smokers (age not given)	Improved FMD after 2 h lasting for 8 h. Reduction in platelet function. Increased plasma total antioxidant status	No	Hermann *et al.*[8]
25	High polyphenol cocoa drink 4 × 230 ml/d for 4–6 d	Per 100 ml, 9·2 mg epicatechin, 10·7 mg catechin and 69·3 mg flavanol oligomers (821 mg/d)	None	15 young (<50 years) and 19 older (>50 years)	NO synthesis after cocoa was suppressed in older volunteers. FMD was enhanced in both groups but more in older group. Pulse wave amplitude enhanced in both groups, with acute rises with cocoa ingestion, more robustly in older subjects. No change in BP	Partially	Fisher & Hollenberg[76]
26	22 g cocoa powder and 16 g dark chocolate (in a muffin)	111 mg monomers and 466 procyanidins	Cocoa butter equivalent in muffin	4 (30–49 years) normolipidaemic subjects (pilot trial)	Dark chocolate increased resistance of LDL and VLDL to oxidation whilst cocoa butter alone decreased resistance. Noted after examination of dietary data that chocolate is third highest contributor of antioxidants to the American diet	No	Vinson *et al.*[10]
27	41 g/d of high polyphenol dark chocolate either with or without almonds 60 g/d for 6 weeks plus dietary advice	Not stated	No intervention except same dietary advice	49 women with cholesterol 4·1–7·6 mmol/l (22–65 years)	Dark chocolate decreased TAG by 21 %, 19 % when eaten with almonds, 13 % with almonds alone and 11 % with no intervention. Circulating intercellular adhesion molecule with dark chocolate alone	No. Industry supplied chocolate only	Kurlandsky & Stote[77]
28	High flavanol cocoa drink 100 ml × 3/d for 1 week	Per 100 ml, 59 mg epicatechin, 15 mg catechin and 232 mg flavanol oligomers (918 mg/d procyanidins)	Low phenolic cocoa drink	6 male smokers with smoking-related endothelial dysfunction (11 total) (22–32 years)	Daily continual FMD increases at baseline (fasted) and a sustained FMD augmentation at 2 h post-ingestion. A dose-dependent effect also seen with FMD and nitrate. Biomarkers for oxidative stress unaffected.	Yes	Heiss *et al.*[39]

FE, Ferric equivalents; FMD, flow-mediated dilation; FRAP, ferric-reducing ability of plasma; TRAP, ferric-reducing ability of plasma (or antioxidant potential); TBARS, thiobarbituric acid reactive substances.



Effects of cocoa powder and dark chocolate on LDL oxidative susceptibility and prostaglandin concentrations in humans[1–3]

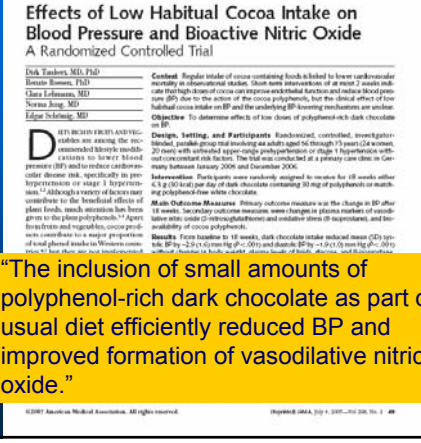
"Cocoa powder and dark chocolate may favorably affect cardiovascular disease risk status by modestly reducing LDL oxidation susceptibility, increasing serum total antioxidant capacity and increasing HDL-cholesterol concentrations, and not adversely affecting prostaglandins.

Am J Clin Nutr 2001 Nov;74(5):596-602

- **Dark chocolate inhibits platelet aggregation in healthy volunteers.**
  Innes AJ, Kennedy G, McLaren M, Bancroft AJ, Belch JJ. *Platelets*. 2003 Aug;14(5):325-7.
- **Vascular effects of cocoa rich in flavan-3-ols**
  Heiss C, Dejam A, Kleinbongard P, Schewe T, Sies H, Kelm M. *JAMA*. 2003 Aug 27;290(8):1030-1
- **Chocolate and blood pressure in elderly individuals with isolated systolic hypertension** **Taubert D, Berkels R, Roesen R, Klaus W.** *JAMA*. 2003 Aug 27;290(8):1029-30

Dietary flavanols and procyanidin oligomers from cocoa (*Theobroma cacao*) inhibit platelet function[1–3]

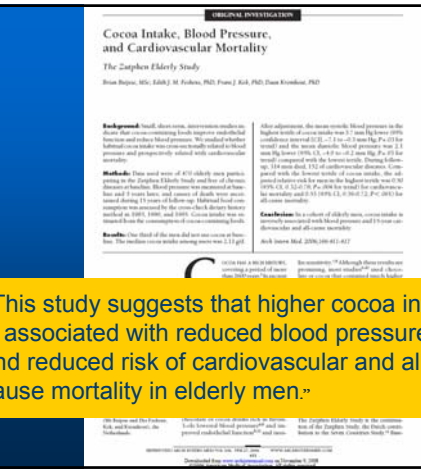
"Researchers found that cocoa flavanol and procyanidin supplementation for 28 d significantly increased plasma epicatechin and catechin concentrations and significantly decreased platelet function. These data support the results of studies that used higher doses of cocoa flavanols and procyanidins." *Am J Clin Nutr. 2003 Jun;77(6):1466-73*



Effects of Low Habitual Cocoa Intake on Blood Pressure and Bioactive Nitric Oxide

A Randomized Controlled Trial

"The inclusion of small amounts of polyphenol-rich dark chocolate as part of a usual diet efficiently reduced BP and improved formation of vasodilative nitric oxide."



Cocoa Intake, Blood Pressure, and Cardiovascular Mortality

The Zutphen Elderly Study

"This study suggests that higher cocoa intake is associated with reduced blood pressure and reduced risk of cardiovascular and all-cause mortality in elderly men."

Cocoa increases blood flow to brain

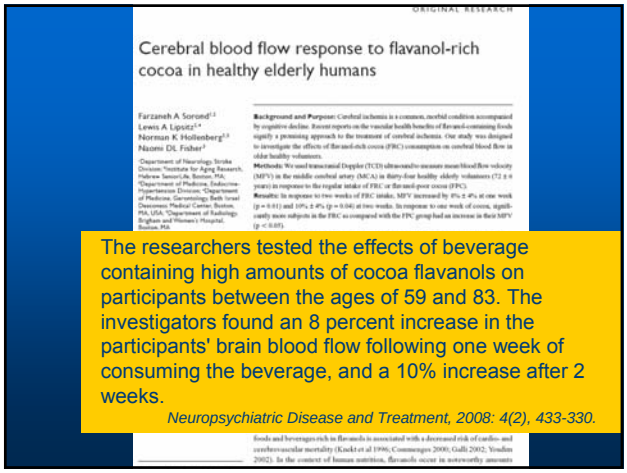
- Cocoa flavonols have been directly linked with improved cerebral blood flow.
- Thirteen men and women (avg age 72) consumed flavonol-rich cocoa and a 21 participants consumed a flavonoid-poor cocoa product.
- Ultrasound methods were used to analyze blood flow to the brain.
- The 13 participants who consumed flavonol-rich cocoa for 2 weeks (900 mg flavanols daily) achieved a 10% increase in cerebral blood flow.

Sorond FA, Lipsitz LA, Hollenberg NK, Fisher NDL. Cerebral blood flow response to flavanol-rich cocoa in healthy elderly humans. Neuropsychiatric Disease and Treatment. 2008;4:433-440.

Cocoa increases blood flow to brain

- Harvard researchers report that cocoa flavanols improve brain flow in older adults. It has been speculated that increasing blood flow to the brain could help reduce cognitive decline in aging individuals. The current finding could be helpful in improving cognitive function among individuals suffering from conditions in which brain flow is impaired, such as stroke and dementia.

Sorond FA, Lipsitz LA, Hollenberg NK, Fisher NDL. Cerebral blood flow response to flavanol-rich cocoa in healthy elderly humans. Neuropsychiatric Disease and Treatment. 2008;4:433-440.



ORIGINAL RESEARCH

Cerebral blood flow response to flavanol-rich cocoa in healthy elderly humans

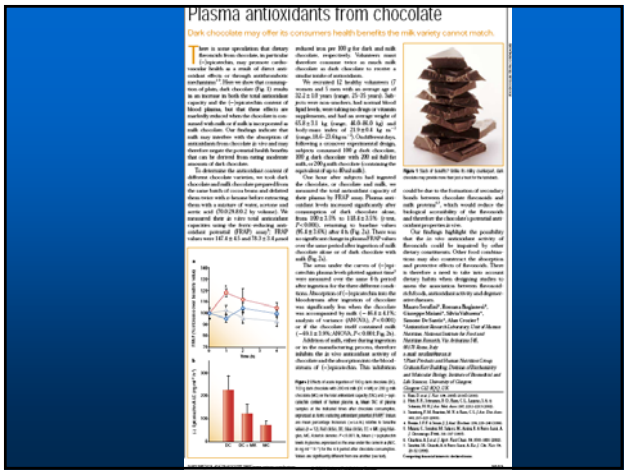
The researchers tested the effects of beverage containing high amounts of cocoa flavanols on participants between the ages of 59 and 83. The investigators found an 8 percent increase in the participants' brain blood flow following one week of consuming the beverage, and a 10% increase after 2 weeks.

Neuropsychiatric Disease and Treatment, 2008: 4(2), 433-330.

Cocoa increases blood flow to brain

Table 2 Nutritional content of the study beverages

	Flavanol-rich cocoa (FRC)	Flavanol-poor cocoa (FPC)
Cocoa flavanols, mg	451.1	18.2
Calories	118.1	117.2
Total fat, g	1.4	1.5
Cholesterol, mg	4.4	4.9
Total carbohydrates, g	17.1	16.5
Dietary fiber, g	3.0	3.9
Sugars, g	9.4	9.2
Protein, g	9.4	9.4
Caffeine, mg	18.3	21.2
Theobromine, mg	336.5	327.4
Sodium, mg	105.1	155.0
Potassium, mg	530.1	644.8
Calcium, mg	243.7	241.2
Iron, mg	1.9	2.9
Phosphorous, mg	280.2	265.4
Magnesium, mg	85.9	78.4
Zinc, mg	1.6	1.6
Copper, mg	0.4	0.4
Manganese, mg	0.6	0.6



Plasma antioxidants from chocolate

Dark chocolate may offer its consumers health benefits the milk variety cannot match.

Plasma antioxidants from chocolate

Dark chocolate may offer its consumers health benefits the milk variety cannot match.

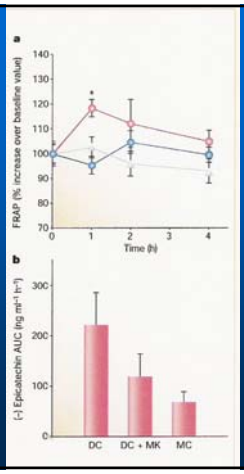
Nature 2003 Aug 28;424(6952): 1013.

Serafini M, Bugianesi R, Maiani G, Valtuena S, De Santis S, Crozier A.

Figure 1 Stack of benefits? Unlike its milky counterpart, dark chocolate may provide more than just a treat for the tastebuds.

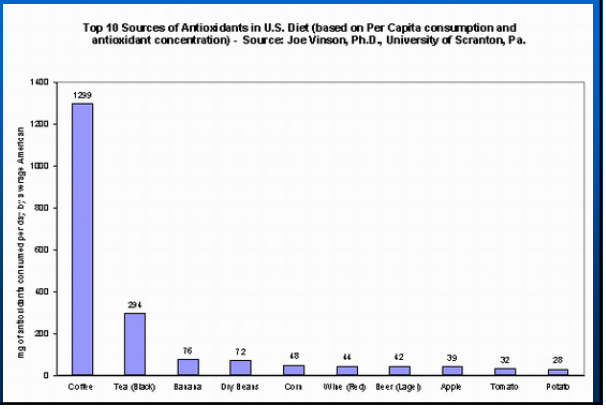
Effects of ingesting 100g dark chocolate (DC), 100 g dark chocolate with 200 ml milk (DC+ MK), or 200 g milk chocolate on total antioxidant capacity and epicatechin content of human plasma.

(red=DC; blue DC+MK; grey=MC. FRAP= ferric-reducing antioxidant potential was used to measure antioxidant capacity. Asterisk = P<0.001)



- **Coffee Is No. 1 Source of Antioxidants** (*Fox News*)
- **That daily cup of coffee can help prevent cancer, researchers find** (*Detroit Free Press*)
- **'Joe' gives free radicals a jolt** (*Newsday*)
- **Grounds for Health** (*San Jose Mercury News*)
- **Study says coffee delivers more health benefits than fruit and veg**(*Scotsman*)
- **What apples? A cup of coffee a day keeps the doctor away** (*Newwindpress.com* – India)
- **Coffee found to be high in health-giving antioxidants** (*The Independent* – UK)

Coffee came out on top, on the combined basis of both antioxidants per serving size and frequency of consumption



- Chlorogenic acid and caffeic acid are strong antioxidants *in vitro*.
- The amount of chlorogenic acid or caffeic acid available to act as an antioxidant *in vivo* will depend on absorption from the gut. It has recently been demonstrated that humans absorb about 33% of ingested chlorogenic acid and about 95% of ingested caffeic acid.
- Coffee beans are one of the richest dietary sources of chlorogenic acid and for many consumers this will be their major dietary source.
- It has been estimated that coffee drinkers might ingest as much as 1 g per day of chlorogenic acid and 500 mg per day of caffeic acid.
- Coffee could supply as much as 70% of the total making it far and away the most important dietary source of this group of antioxidants.

- The roasting of coffee beans dramatically increases their total antioxidant activity. A roasting time of 10 minutes (medium-dark roast) was found to produce coffee with optimal oxygen scavenging and chain breaking activities *in vitro*
- It can be concluded that coffee possesses greater in-vitro antioxidant activity than other beverages, due in part to intrinsic compounds such as chlorogenic acid, in part to compounds formed during roasting such as melanoidins and in part to as yet unidentified compounds.


Consumption of coffee is associated with reduced risk of death attributed to inflammatory and cardiovascular diseases in the Iowa Women's Health Study[1–4]

Lene Frost Andersen, David R Jacobs Jr, Monica H Carlsen, and Rune Blomhoff

ABSTRACT

Consumption of coffee, a major source of dietary antioxidants, may inhibit inflammation and thereby reduce the risk of cardiovascular and other inflammatory diseases in postmenopausal women.

Am J Clin Nutr, 2006, 83: 1039-46.

Coffee May Protect Against Colon Cancer *Journal of Agricultural and Food Chemistry,* Nov. 5, 2003

Researchers say they've found a highly active anti-cancer compound, called methylpyridinium, in coffee that may prevent colon cancer. In studies with animals, this potent antioxidant compound appears to boost the activity of phase II enzymes, which are believed to protect against colon cancer.

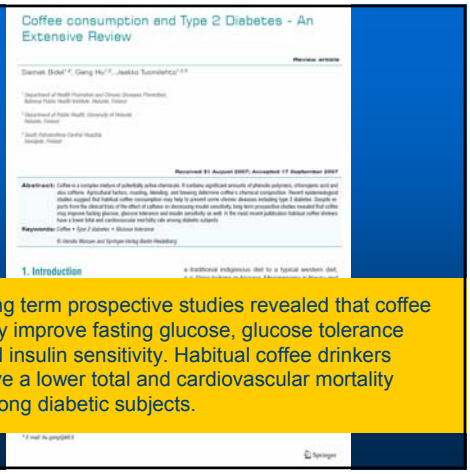
- Espresso-type coffee contains about two to three times more of the anticancer compound than a medium roast coffee.
- Methylpyridinium is found almost exclusively in coffee and coffee products. It's not present in raw coffee beans. It's formed during the roasting process from its chemical precursor, trigonellin.
- The anticancer compound is present in both caffeinated and decaffeinated coffee and is even found in instant coffee.

Journal of Agricultural and Food Chemistry, Nov. 5, 2003

Effects of coffee consumption on glucose tolerance, serum glucose and insulin levels--a cross-sectional analysis

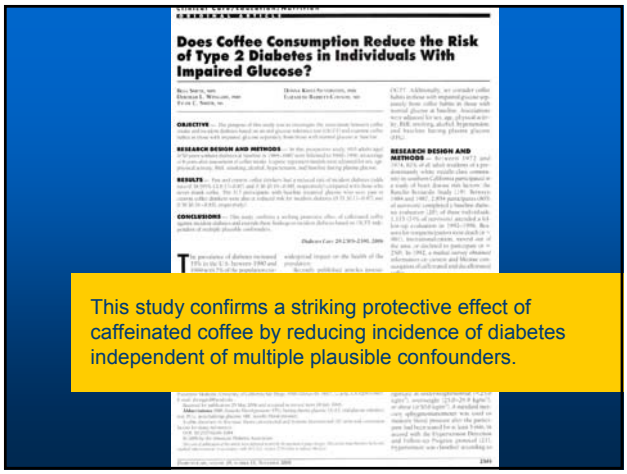
- Coffee consumption showed positive effects on glucose tolerance, and on glucose and insulin levels.
- Coffee consumption was significantly and inversely associated with fasting glucose, two-hour plasma glucose, and fasting insulin, in both men and women.
- Additionally, coffee consumption was significantly and inversely associated with impaired fasting glucose, impaired glucose regulation, and hyperinsulinemia, in both men and women, and inversely associated with isolated impaired glucose tolerance in women.
- Thus, this cross-sectional analysis suggests that the consumption of coffee exerts positive effects on glucose tolerance, and glucose and insulin levels.

Horm Metab Res., 2006; 38(1): 38-43


Coffee consumption and Type 2 Diabetes - An Extensive Review

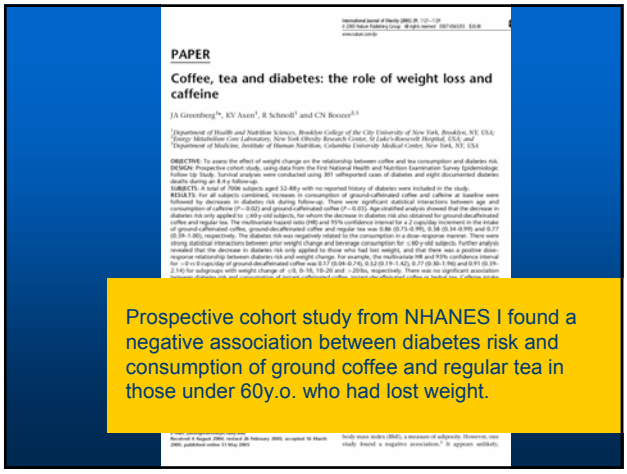
1. Introduction

Long term prospective studies revealed that coffee may improve fasting glucose, glucose tolerance and insulin sensitivity. Habitual coffee drinkers have a lower total and cardiovascular mortality among diabetic subjects.



Does Coffee Consumption Reduce the Risk of Type 2 Diabetes in Individuals With Impaired Glucose?

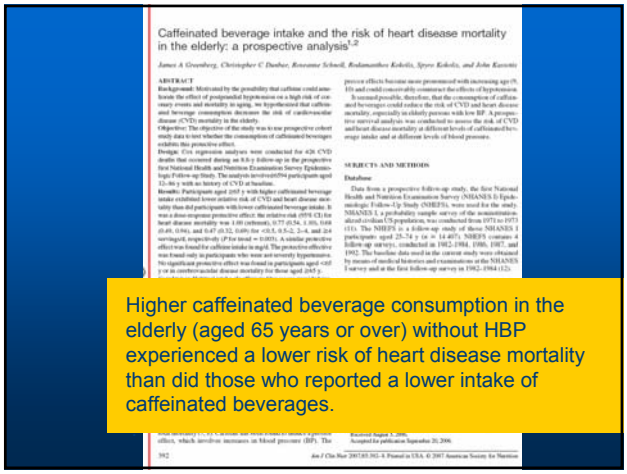
This study confirms a striking protective effect of caffeinated coffee by reducing incidence of diabetes independent of multiple plausible confounders.



PAPER

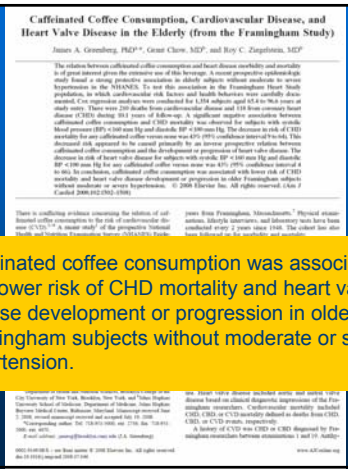
Coffee, tea and diabetes: the role of weight loss and caffeine

Prospective cohort study from NHANES I found a negative association between diabetes risk and consumption of ground coffee and regular tea in those under 60y.o. who had lost weight.



Caffeinated beverage intake and the risk of heart disease mortality in the elderly: a prospective analysis[1,2]

Higher caffeinated beverage consumption in the elderly (aged 65 years or over) without HBP experienced a lower risk of heart disease mortality than did those who reported a lower intake of caffeinated beverages.



Caffeinated Coffee Consumption, Cardiovascular Disease, and Heart Valve Disease in the Elderly (from the Framingham Study)

James A. Greenberg, PhD*, Grant Chow, MD*, and Roy C. Ziegelstein, MD*

Caffeinated coffee consumption was associated with lower risk of CHD mortality and heart valve disease development or progression in older Framingham subjects without moderate or severe hypertension.

Caffeine May Provide Protection from Parkinson's Disease

- As part of a long-term study of the Honolulu Heart Program, a team of researchers examined the relationship between coffee intake and the incidence of Parkinson's disease.
- Researchers studied 8,004 Japanese-American men over a 30 year period. Of these men, 102 developed Parkinson's disease.
- The incidence of Parkinson's disease was found to be lower in those who drank coffee. In fact, the men who drank the most coffee were the *least likely* to get Parkinson's disease. Men who did not drink any coffee were five times more likely to exhibit symptoms of Parkinson's disease than men who drank more than 28 ounces of coffee each day. Consumption of caffeine from other sources such as green tea, black tea, chocolate and soda was also associated with a lower risk of Parkinson's disease
- Caffeine belongs to the **xanthine** chemical group. A naturally occurring xanthine in the brain called adenosine is used as a neurotransmitter at some synapses. When adenosine receptors are blocked, levels of the neurotransmitter dopamine increase. Caffeine may protect against Parkinson's disease by blocking adenosine receptors, thus increasing the amount of dopamine in the brain.