

Chocolate/cocoa and human health: a review

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ABSTRACT

Chocolate/cocoa has been known for its good taste and proposed health effects for centuries. Earlier, chocolate used to be criticised for its fat content and its consumption was a sin rather than a remedy, associated with acne, caries, obesity, high blood pressure, coronary artery disease and diabetes. Therefore, many physicians tended to warn patients about the potential health hazards of consuming large amounts of chocolate. However, the recent discovery of biologically active phenolic compounds in cocoa has changed this perception and stimulated research on its effects in ageing, oxidative stress, blood pressure regulation, and atherosclerosis. Today, chocolate is lauded for its tremendous antioxidant potential. However, in many studies, contradictory results and concerns about methodological issues have made it hard for health professionals and the public to understand the available evidence on chocolate's effects on health. The purpose of this review is to interpret research done in the last decade on the benefits and risks of chocolate consumption.

KEYWORDS

Chocolate, cocoa, *Theobroma cacao*, polyphenols, flavonoids

INTRODUCTION

Chocolate came to Europe in the 16th century. Since then, the modern chocolate industry has developed, and cocoa seeds are now processed in different ways. Chocolate is the most commonly craved food in the world.¹ Initially it was thought of as a luxury item, but now it is considered to be a medicine.

HISTORY OF CHOCOLATE

Chocolate originated from Mexico where the Mayas, Incas, and Aztecs cultivated the cacao tree. At first, it was seen

as an aphrodisiac, accessible only for the affluent and rich. Later on, because of its high price, chocolate was replaced by coffee and tea as the main drink. However, ultimately, chocolate did become a favourite confection in most developed countries including Europe and North America. Nowadays cocoa is grown mainly in West Africa, Indonesia, and Sri Lanka.

In the past, due to its health effects, it was considered the drink of Gods,² an association that gave rise to the scientific name of the cocoa tree, *Theobroma cacao*, from the Greek words theo (God) and broma (drink). This attribution was given to the tree by a Swedish naturalist Carl Von Linné (1707–1778). In fact, this name is symbolic of the social, religious, and economic importance of chocolate in both New and Old World cultures.

The tree and its dried seeds prior to processing are called 'cacao' in American English; after processing, i.e. roasting and grinding, the term 'cocoa' is used. 'Chocolate' is the food prepared from roasted cacao seeds.

CHEMICAL COMPOUNDS IN CHOCOLATE THAT MAY AFFECT HUMAN HEALTH

The nutritional qualities of chocolate have been acknowledged by several authors and some people have called it a complete food. Important chemicals found in chocolate are as follows.

Fats

The fat predominantly found in dark chocolate is cocoa butter³ which contains approximately 33% oleic acid (monounsaturated), 25% palmitic acid (saturated), and 33% stearic acid (saturated).⁴ Oleic acid has a positive effect on lipid levels.⁵ Saturated fats adversely increase the total cholesterol and low-density lipoprotein levels.⁶ However, regardless of being one of the saturated fats, stearic acid may not have any effect on lipid levels,^{7,8} or it

may increase lipid levels.⁹ The reason of this discrepancy regarding stearic acid may be the different nature of cocoa-derived stearic acid, from animal derived sources; or less absorption of stearic acid.^{10,11} However, few studies have negated this possibility.^{12,13}

Antioxidants

Cocoa contains large concentrations of flavonoids, epicatechin, catechin, and procyanidins.¹⁴ Cocoa has the maximum levels of flavonoids, greater than even tea and wine.¹⁵ Dark chocolate contains considerably higher amounts of flavonoids than milk chocolate.¹⁶ Moreover, the biological effects of flavonoids may also be greater in dark chocolate because the milk in milk chocolate may slow down the intestinal absorption of flavonoids.¹⁷ Finally, chocolate is also rich in procyanidin flavonoids, comparable with levels in procyanidin-rich apples.¹⁸

Nitrogenous compounds

The nitrogenous compounds of cacao include both proteins and the methylxanthines theobromine and caffeine. They are central nervous system stimulants, diuretics, and smooth muscle relaxants.

Minerals and other properties

Cocoa mass also contains minerals such as potassium, phosphorus, copper, iron, zinc, and magnesium¹⁹ which potentiate the health benefits of chocolate. Chocolate also contains valeric acid which acts as a stress reducer despite the presence of the stimulants caffeine and theobromine in the chocolate.²⁰

EPIDEMIOLOGICAL EVIDENCE ABOUT HEALTH EFFECTS OF CHOCOLATE

Epidemiological evidence about beneficial effects of chocolate came from the Kuna Indian population of the islands of Panama. This population is characterised by a low prevalence of atherosclerosis, type 2 diabetes, and hypertension. The 'secret' behind this is the daily intake of homemade cocoa drink by indigenous Kuna Indians. These traits disappear after migration to urban areas on mainland Panama and subsequent changes in diet (i.e. consumption of much less cocoa, which is commercially processed), hence negating the genetic nature of the traits.²¹

Further epidemiological evidence has come from a longitudinal study looking at the lifestyle and cardiovascular risk in a cohort of older men.²² This study found cocoa intake to be inversely related to blood pressure. Even after multivariate adjustment, mean systolic blood pressure was 3.8 mmHg lower in the highest cocoa intake group compared with the lowest intake group. In

a perspective analysis, higher cocoa intake was associated with a reduction in cardiovascular and all-cause mortality.²³ These studies show that chocolate may not only be bad for us; some forms of chocolate may actually be good for us.

POTENTIAL HEALTH BENEFITS OF CHOCOLATE CONSUMPTION

Interestingly, regular cocoa ingestion is claimed to be inversely associated with the risk of cardiovascular disease. The past decade has seen an increasing interest in potential anti-pathogenic properties of cocoa. Although still debated, a range of potential mechanisms through which cocoa might exert its beneficial effects on health have been proposed. Some of them are discussed here.

Cocoa and cardiovascular diseases

Numerous studies have suggested beneficial effects of cocoa in cardiovascular diseases (CVD). Most recently, Zomer *et al.*, have concluded that the daily consumption of dark chocolate could be an effective cardiovascular preventive strategy in patients with metabolic disease.²⁴ The potential mechanisms involved in these beneficial effects of cocoa are as follows.

Rich source of antioxidants

Oxidative stress and reduced antioxidant defences play a pivotal role in the pathogenesis of atherosclerosis. Chocolate is the third highest daily source of antioxidants for Americans.²⁵ Antioxidants found in chocolate have been shown to inhibit plasma lipid oxidation.²⁶ However, there is a study negating the direct antioxidant potential of chocolate, documenting that the large increase in plasma total antioxidative capacity observed after the consumption of flavonol-rich food is most likely not due to flavonols but probably is a consequence of the increased uric acid levels resulting from fructose metabolism.²⁷

Blood pressure lowering effects

A large-scale, longer duration study in the Netherlands recruited men aged 65-84 years. The subjects were asked about their dietary intake when they enrolled in the study and again at five-year intervals. Over the next 15 years, men who consumed cocoa regularly had significantly lower blood pressure than those who did not.²² Consumption of dark chocolate bars for 15 days has been reported to reduce systolic blood pressure in healthy subjects²⁸ as well as in young²⁹ and elderly³⁰ hypertensive patients.

The exact mechanism behind antihypertensive effects of chocolate is not known but this may involve increased nitric oxide (NO) bioavailability, flavonol-induced inhibition of angiotensin converting enzyme,³¹ and stearic acid-based reduction of diastolic blood pressure.³²

Contrary to that, a few studies showed no effect on blood pressure with chocolate/cocoa ingestion.^{33,34} Van den Bogaard *et al.* in fact put in question the blood pressure lowering effects of cocoa. They concluded from their randomised controlled trial that natural cocoa drinks did not significantly change either 24-hour ambulatory or central systolic blood pressure.³⁵ Alonso also found no association between chocolate consumption and incidence of hypertension in a Cohort study.³⁶ The reason for these inconsistencies may relate to a number of factors, including the study design. Since these studies were performed in a rather small number of normotensive individuals and with a lower chocolate intake for a shorter period, an antihypertensive effect may have been missed as a consequence of their study design. Moreover, use of different dietary intake questionnaires and food consumption tables, differences in the levels and the types of chocolates/cocoa studied and differences in the populations investigated, might also account for inconsistencies. Most of the studies supporting antihypertensive effects of chocolate used chocolate bars, whereas the negative studies used cocoa drinks. Perhaps the chocolate matrix is necessary for the antihypertensive effect, acting either directly or synergistically with flavonols.

Effects on blood vessels and nitric oxide

Numerous studies have reported that cocoa causes significant vasodilatation by increasing serum NO levels³⁷ and endothelial NO bioavailability.³⁸ The underlying molecular mechanism is the ability of flavonols to increase the NO in the endothelial cells via their capacity to activate vascular endothelial NO synthase³⁹ and their antioxidant actions which lead to diminished inactivation of NO by free radicals through inhibition of NADPH oxidase.³³

Inhibits platelet activation

Platelet dysfunction is another characteristic feature of atherosclerotic lesions. Cocoa has aspirin-like effects on platelet function,⁴⁰ and the joint effects of the cocoa and aspirin are additive in nature, suggesting improved clot prevention afforded by cocoa.⁴¹ Chocolate has a dual effect on platelets. It not only decreases platelet aggregation⁴² but also reduces platelet adhesion.⁴³

Consumption of chocolate with high procyanidin content significantly lowered the levels of leukotrienes and increased the levels of prostacyclin when compared with a group consuming a low-procyanidin chocolate.⁴⁴

Antidiabetic effects

Numerous approaches have been tried to improve insulin sensitivity in diabetics.⁴⁵ Insulin sensitivity partially relies on NO bioavailability in endothelial cells.⁴⁶ Hence flavonol may reduce insulin resistance by ameliorating

NO bioavailability. A reduction in insulin resistance and an increase in insulin sensitivity were observed after ingestion of flavonol-rich chocolate in healthy subjects²⁸ and hypertensive patients.²⁹ Another study demonstrated a positive impact on glucose and insulin responses to an oral glucose tolerance test, in hypertensive adults with impaired glucose tolerance following flavonol-rich chocolate ingestion.⁴⁷

Antistress effects

There are several bioactive compounds in chocolate that promote alertness.⁴⁸ A study in Switzerland also confirmed that chocolate alleviates stress. Following 14 days of dark chocolate ingestion, stress parameters in the adults exhibiting high anxiety profiles became comparable with the low-stress subjects.⁴²

Chocolate affects stress levels by prompting serotonin production which is a calming neurotransmitter.^{49,50}

Anti-obese effects

Obesity is one of the major risk factors in the development of CVD. In a study an identical high fat diet, with or without cocoa, was fed to rats for three weeks. Cocoa consumption led to a significant decrease in total body weight, mesenteric white adipose tissue weight and serum triglycerides. When DNA analysis was carried out on liver and mesenteric fat tissue samples, the results showed a reduction in expression of various genes associated with fatty acid transport and synthesis in liver and mesenteric fat and increased expression of genes associated with thermogenesis.⁵¹

Effects on the neurons

A recent study of young, healthy subjects using magnetic resonance imaging found that cocoa intake results in increased cerebral blood flow,⁵² suggesting that cocoa might play a role in treatment of cerebral conditions such as dementia and stroke. Nurk *et al.* also reported better cognitive performance with chocolate intake.⁵³ Larsson *et al.*, investigated the association between chocolate consumption and risk of stroke in men and concluded that daily chocolate consumption reduces the likelihood of a stroke attack.⁵⁴ Walters *et al.*, showed that chocolate acutely improves cerebral blood flow.⁵⁵

Antitumour effects

A few *in vitro* studies suggest that cocoa inhibits the growth of cancerous cells.^{56,57} The exact anticancer mechanisms are not clearly understood at this stage. On the other hand, some studies suggest that excess chocolate intake makes a person more prone to develop cancers.^{58,59} Further preclinical and clinical trials are needed to investigate the mechanisms involved in cocoa actions and to justify cocoa's usage as a therapy for the prevention and treatment of cancer.



Anti-inflammatory effects

Chocolate inhibits lipoxygenase pathways, by directly binding to the active sites of the enzymes lipoxygenases.⁶⁰

Cocoa and exercise recovery

It has been documented that chocolate supplementation before exercise results in rapid recovery of post-exercise physiological and metabolic changes. Plasma glucose levels of subjects increased significantly at 15 minutes after chocolate intake and stayed at moderately high levels until 30 minutes after an hour's running when compared with the glucose levels of placebo supplemented group.⁶¹

POTENTIAL HEALTH RISKS OF CHOCOLATE CONSUMPTION

Surprisingly, literature on adverse effects produced by chocolate is scarce when compared with the plenty of studies touting the benefits of chocolate. Chocolate is believed to cause heartburn because of one of its constituents – theobromine, which relaxes the oesophageal sphincter muscle – hence permitting stomach acidic contents to enter into the oesophagus.⁶² A few studies have documented allergic reactions with chocolate in children.^{63,64}

COULD CHOCOLATE BE A NOVEL THERAPY FOR TREATMENT OF HEALTH DISORDERS?

There appears to be some scientific evidence to justify eating a moderate amount (approximately 2 oz) of dark chocolate daily. However, the major criticism against the consumption of chocolate for therapeutic benefit is the high amount of sugar and triglycerides that needs to be consumed to reach what has been demonstrated to be a potentially therapeutic dose and a person must then compensate for the additional calories by increasing the amount of daily exercise or reducing caloric intake of other fats, sweets, or carbohydrates to prevent obesity and the metabolic and cardiovascular risks related to it.

The current evidence suggests that the beneficial effects of chocolate are attributed mainly to its flavonol content, especially epicatechin. Hence, direct dietary supplementation with flavonol instead of whole chocolate consumption deserves further study.

CONCLUDING REMARKS

The majority of studies claiming the benefits of chocolate are small-scale, sponsored/carried out by the chocolate manufacturers whose personal interests cannot be ignored. This warrants due consideration in implications of the results as there may be potential for research bias.⁶⁵ Additional large-scale observational and/or interventional studies from non-biased sources are needed before clinicians can absolutely recommend 'a chocolate a day' to their patients.

In addition, the products used in controlled studies often contain much higher polyphenol contents than most of the commercially available products.^{22,66} Since flavonols exhibit a bitter taste, manufacturers have established processing techniques for cocoa which eliminate the bitterness together with flavonoids.⁶⁷ As much as 90% of the flavonoids may be lost due to cocoa processing.⁶⁸ Thus, it needs to be established whether the consumption of products with lower polyphenol content are associated with any health benefits in humans.

Conflict of interests: none.

REFERENCES

1. Weingarten HP, Elston D. Food cravings in a college population. *Appetite*. 1991;17:167-75.
2. Dillinger TL, Barriga P, Escarcega S, Jimenez M, Salazar Lowe D, Grivetti LE. Food of the gods: cure for humanity? A cultural history of the medicinal and ritual use of chocolate. *J Nutr*. 2000;130:2057S-72S.

3. Kris-Etherton PM, Mustad V, Derr J. Effects of dietary stearic acid on plasma lipids and thrombosis. *Nutr Today*. 1993;28:30-8.
4. USDA National Nutrient Database <http://www.nal.usda.gov/>
5. American Dietetic Association. Chocolate: facts and fiction. Nutrition fact sheet. Chicago, Ill: American Dietetic Association Foundation; 2000.
6. Hu FB, Manson JE, Willett WC: Types of dietary fat and risk of coronary heart disease: a critical review. *J Am Coll Nutr*. 2001;20:5-19.
7. Mensink RP, Zock PL, Kester AD, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. *Am J Clin Nutr*. 2003;77:1146-55.
8. Kris-Etherton PM, Yu S. Individual fatty acid effects on plasma lipids and lipoproteins: human studies. *Am J Clin Nutr*. 1997;65(Suppl):1628S-44S.
9. Thijssen MA, Mensink RP: Small differences in the effects of stearic acid, oleic acid, and linoleic acid on the serum lipoprotein profile of humans. *Am J Clin Nutr*. 2005;82:510-6.
10. Jones AE, Stolinski M, Smith RD, Murphy JL, Wootton SA. Effect of fatty acid chain length and saturation on the gastrointestinal handling and metabolic disposal of dietary fatty acids in women. *Br J Nutr*. 1999;81:37-43.
11. Baer DJ, Judd JT, Kris-Etherton PM, Zhao G, Emken EA. Stearic acid absorption and its metabolizable energy value are minimally lower than those of other fatty acids in healthy men fed mixed diets. *J Nutr*. 2003;133:4129-34.
12. Bonanome A, Grundy SM. Intestinal absorption of stearic acid after consumption of high fat meals in humans. *J Nutr*. 1989;119:1556-60.
13. Emken EA, Adlof RO, Rohwedder WK, Gulley RM. Influence of linoleic acid on desaturation and uptake of deuterium labeled palmitic and stearic acids in humans. *Biochim Biophys Acta*. 1993;1170:173-81.
14. Natsume M, Osakabe N, Yamagishi M, et al, Analyses of polyphenols in cacao liquor, cocoa, and chocolate by normal-phase and reversed phase HPLC. *Biosci Biotechnol Biochem*. 2000;64:2581-7.
15. Lee KW, Kim YJ, Lee HJ, Lee CY. Cocoa has more phenolic phytochemicals and a higher antioxidant capacity than teas and red wine. *J Agric Food Chem*. 2003;51:7292-5.
16. Vinson JA, Proch J, Zubik L: Phenol antioxidant quantity and quality in foods: cocoa, dark chocolate, and milk chocolate. *J Agric Food Chem*. 1999;47:4821-4.
17. Serafini M, Bugianesi R, Maiani G, Valtuena S, De Santis S, Crozier A. Plasma antioxidants from chocolate. *Nature*. 2003;424:1013.
18. Hammerstone JF, Lazarus SA, Schmitz HH: Procyanidin content and variation in some commonly consumed foods. *J Nutr*. 2000;130(8S Suppl):2086S-92S.
19. Ashton J, Ashton S. Why chocolate is a health food. In: *A Chocolate a Day: Keeps the Doctor Away*. New York, NY: Thomas Dunne Books/St. Martin's Press; 2003:39-52.
20. Ashton J, Ashton S. The best food for mood. In: *A Chocolate a Day: Keeps the Doctor Away*. New York, NY: Thomas Dunne Books/St. Martin's Press; 2003:26-38.
21. McCullough ML, Chevaux K, Jackson L, et al, Hypertension, the Kuna, and the epidemiology of flavanols. *J Cardiovasc Pharmacol*. 2006;47:5103-9.
22. Buijsse B, Feskens EJM, Kok FJ, Kromhout D. Cocoa intake, blood pressure, and cardiovascular mortality: the Zutphen elderly study. *Arch Intern Med*. 2006;166:411-7.
23. Janszky I, Mukamal KJ, Ljung R, Ahnve S, Ahlbom A, Hallqvist J. Chocolate consumption and mortality following a first acute myocardial infarction: The Stockholm Heart Epidemiology Program. *J Int Med*. 2009;266:248-357.
24. Zomer E, Owen A, Magliano DJ, Liew D, Reid CM. The effectiveness and cost effectiveness of dark chocolate consumption as prevention therapy in people at high risk of cardiovascular disease: best case scenario analysis using a Markov model. *BMJ*. 2012; 344:e3657.
25. Vinson JA, Proch J, Bose P, et al, Chocolate is a powerful ex vivo and in vivo antioxidant, an anti-atherosclerotic agent in an animal model, and significant contributor to antioxidants in European and American diets. *J Agric Food Chem*. 2006;54:8071-6.
26. Wiswedel I, Hirsch D, Kropf S, et al, Flavanol-rich cocoa drink lowers plasma F(2)-isoprostane concentrations in humans. *Free Radic Biol Med*. 2004;37:411-21.
27. Lotito SB, Frei B. Consumption of flavonoid-rich foods and increased plasma antioxidant capacity in humans: cause, consequence, or epiphenomenon? *Free Radic Biol Med*. 2006;41:1727-46.
28. Grassi D, Lippi C, Necozione S, Desideri G, Ferri C. Short-term administration of dark chocolate is followed by a significant increase in insulin sensitivity and a decrease in blood pressure in healthy persons. *Am J Clin Nutr*. 2005;81:611-4.
29. Grassi D, Necozione S, Lippi C, et al, Cocoa reduces blood pressure and insulin resistance and improves endothelium-dependent vasodilation in hypertensives. *Hypertension*. 2005;46:398-405.
30. Taubert D, Berkels R, Roesen R, Klaus W. Chocolate and blood pressure in elderly individuals with isolated systolic hypertension. *JAMA*. 2003;290:1029-30.
31. Actis-Goretta L, Ottaviani JI, Fraga CG. Inhibition of angiotensin converting enzyme activity by flavanol-rich foods. *J Agric Food Chem*. 2006;54:229-34.
32. Simon JA, Fong J, Bernert JT Jr. Serum fatty acids and blood pressure. *Hypertension*. 1996;27:303-7.
33. Fisher ND, Hughes M, Gerhard-Herman M, Hollenberg NK. Flavanol-rich cocoa induces nitric-oxide-dependent vasodilation in healthy humans. *J Hypertens*. 2003;21:2281-6.
34. Engler MB, Engler MM, Chen CY, et al, Flavanoid-rich dark chocolate improves endothelial function and increases plasma epicatechin concentrations in healthy adults. *J Am Coll Nutr*. 2004;23:197-203.
35. van den Bogaard B, Draijer R, Westerhof BE, van den Meiracker AH, van Montfrans GA, van den Born BJ. Effects on peripheral and central blood pressure of cocoa with natural or high-dose theobromine: a randomized, double-blind crossover trial. *Hypertension*. 2010;56:839-46.
36. Alonso A, de la Fuente C, Beunza JJ, Sanchez-Villegas A, Martinez-Gonzalez MA. Chocolate consumption and incidence of hypertension. *Hypertension*. 2005;46:e21- e22.
37. 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 U S A*. 2006;103:1024-9.
38. Fisher ND, Hollenberg NK. Aging and vascular responses to flavanol-rich cocoa. *J Hypertens*. 2006;24:1575-80.
39. Karim M, McCormick K, Kappagoda CT. Effects of cocoa extracts on endothelium-dependent relaxation. *J Nutr*. 2000;130:S2105-8.
40. Pearson DA, Paglieroni TG, Rein D, et al, The effects of flavanol-rich cocoa and aspirin on ex vivo platelet function. *Thromb Res*. 2002;106:191-7.
41. Rein D, Paglieroni TG, Wun T, et al, Cocoa inhibits platelet activation and function. *Am J Clin Nutr*. 2000;72:30-5.
42. Martin FJ, Rezzi S, Pere-Trepal E, et al., Metabolic Effects of Dark Chocolate Consumption on Energy, Gut Microbiota, and Stress-Related Metabolism in Free-Living Subjects. *J. Proteome Res*. 2009;8:5568-79.
43. Hermann F, Spieker LE, Ruschitzka F, et al, Dark chocolate improves endothelial and platelet function. *Heart*. 2006;92:119-20.
44. Schramm DD, Wang JF, Holt RR, et al, Chocolate procyanidins decrease the leukotriene-prostacyclin ratio in humans and human aortic endothelial cells. *Am J Clin Nutr*. 2001;73:36-40.
45. Ryan DH, Diabetes Prevention Program Research Group. Diet and exercise in the prevention of diabetes. *Int J Clin Pract*. 2003;134:28-35.
46. Konopatskaya O, Whatmore JL, Tooke JE, Shore AC. Insulin and lysophosphatidylcholine synergistically stimulate NO-dependent cGMP production in human endothelial cells. *Diabet Med*. 2003;20:838-45.
47. Grassi D, Desideri G, Necozione S, et al, Blood Pressure Is Reduced and Insulin Sensitivity Increased in Glucose-Intolerant, Hypertensive Subjects after 15 Days of Consuming High-Polyphenol Dark Chocolate. *J. Nutr*. 2008; 138:1671-6.
48. Zurer, P. Chocolate may mimic marijuana in brain. *Chem Eng News*. 1996;74:31-2.

49. Walcutt DL, Chocolate and Mood Disorders. PsychCentral; 2009. Available at: <http://psychcentral.com/blog/archives/2009/04/27/chocolate-and-mood-disorders/>. Accessed on October 18, 2012.
50. Benton D, Donohoe RT. The effects of nutrients on mood. *Public Health Nutr.* 1999;2:403-9.
51. Matsui N, Ito R, Nishimura E, et al, Ingested cocoa can prevent high fat diet induced obesity by regulating the expression of genes for fatty acid metabolism. *Nutrition.* 2005;21:594-601.
52. Francis ST, Head K, Morris PG, Macdonald IA. The effect of flavanol-rich cocoa on the fMRI response to a cognitive task in healthy young people. *J Cardiovasc Pharmacol.* 2006; 47(suppl 2):S221-3.
53. Nurk E, Refsum H, Drevon CA, et al, Intake of Flavonoid-Rich Wine, Tea, and Chocolate by Elderly Men and Women Is Associated with Better Cognitive Test Performance. *J. Nutr.* 2009;139:120-7.
54. Larsson SC, Virtamo J, Wolk A. Chocolate consumption and risk of stroke A prospective cohort of men and meta-analysis. *Neurology WNL.ob013e31826aacfa*; published ahead of print, 29 August 2012
55. Walters MR, Williamson C, Lunn K, Munteanu K. Acute effects of chocolate ingestion on cerebral vasculature. http://www.neurology.org/content/early/2012/08/29/WNL.ob013e31826aacfa.abstract/reply#neurology_el_55876
56. Carnesecchi S, Schneider Y, Lazarus SA, Coehlo D, Gosse F, Raul F. Flavanols and procyanidins of cocoa and chocolate inhibit growth and polyamine biosynthesis of human colonic cancer cells. *Cancer Lett.* 2002;175:147-55.
57. Kozikowski AP, Tuckmantel W, Bottcher G, Romanczyk LJ Jr. Studies in polyphenol chemistry and bioactivity. 4.(1) Synthesis of trimeric, tetrameric, pentameric, and higher oligomeric epicatechin-derived procyanidins having all-4beta,8-interflavan connectivity and their inhibition of cancer cell growth through cell cycle arrest. *J Org Chem.* 2003;68:1641-58.
58. Richardson S, Gerber M, Cenee S. The role of fat, animal protein and some vitamin consumption in breast cancer: a case control study in southern France. *Int J Cancer.* 1991;48:1-9.
59. Boutron-Ruault MC, Senesse P, Faivre J, Chatelain N, Belghiti C, Meance S. Foods as risk factors for colorectal cancer: a case-control study in Burgundy (France). *Eur J Cancer Prev.* 1999;8:229-35.
60. Schewe T, Kuhn H, Sies H. Flavonoids of cocoa inhibit recombinant human 5- ipoxygenase. *J Nutr.* 2002;132:1825-9.
61. Chen JD, Ai H, Shi JD, Wu YZ, Chen ZM. Effect of a chocolate bar supplementation on moderate exercise recovery of recreational runners. *Biomed Environ Sci.* 1996;9:247-55.
62. Murphy DW, Castell DO. Chocolate and heartburn, evidence of increased esophageal acid exposure after chocolate ingestion. *Am J Gastroentrol.* 1988;83:633-6.
63. Steinman HA, Potter PC. The precipitation of symptoms by common foods in children with a topic dermatitis. *Allergy Proc.* 1994;15:203-10.
64. Businco L, Falconieri P, Bellioni-Businco B, Bahna SL. Severe food-induced vasculitis in two children. *Pediatr Allergy Immunol.* 2002;13:68-71.
65. Cooper KA, Donovan JL, Waterhouse AL, Williamson G. Cocoa and health. A decade of research. *Br J Nutr.* 2008;99:1-11.
66. Mullen W, Borges G, Donovan JL, et al, Milk decreases urinary excretion but not plasma pharmacokinetics of cocoa flavan-3-ol metabolites in humans. *Am J Clin Nutr.* 2009;89:1784-91.
67. Hollenberg NK, Fisher ND. Is it the dark in dark chocolate? *Circulation.* 2007;116:2360-2.
68. Mehrinfar R, Frishman WH. Flavanol rich cocoa. A cardioprotective nutraceutical. *Cardiol Rev.* 2008;16:109-15.