

## REPORT

### The Disease-Fighting Power of Polyphenols

By Laurie Barclay, MD



Compelling new evidence reveals that a powerful way to protect aging arteries is to consume more plant polyphenols.

Published studies show how polyphenol compounds help improve endothelial function, which is a critical factor in preventing atherosclerosis. Polyphenols have also been shown to inhibit the abnormal platelet aggregation that cause most sudden heart attacks and strokes, while fighting inflammation and supporting healthy blood lipids.

Of particular interest are polyphenols derived from green tea, cocoa, apples, and black chokeberry—all of which may complement each other in bolstering the body's defenses against ailments such as cancer, allergies, and cognitive decline. Here, we'll explore the importance of how consuming diverse polyphenols can help safeguard one's health against common ailments that plague aging adults.

#### POLYPHENOLS: HEALING COMPOUNDS FROM NATURE'S PHARMACY

Throughout history, wellness enthusiasts have celebrated the medicinal potential of plants, looking to these botanical allies to promote vitality and restore good health. Modern science has borne out these theories, showing that edible plants are to be valued not only for their high vitamin and fiber content but also for their rich store of polyphenols—antioxidant compounds that give plants some of their color, flavor, and healing qualities.

Polyphenols are found not only in fruits and vegetables such as the blueberry, but also in cocoa, tea, and the exotic fruit known as the chokeberry. A number of studies show that consuming polyphenols from a variety of sources may be more healthful than limiting ourselves to plants foods typically found in the Western diet.

"Polyphenols are... a kind of chemical that may protect against some common health problems and possibly certain effects of aging," Dalia Akramiene, a physiologist at Kaunas University of Medicine in Lithuania, told Life Extension. "Polyphenols protect cells and body chemicals against damage caused by free radicals—reactive atoms that contribute to tissue damage in the body. For example, when low-density lipoprotein (LDL) cholesterol is oxidized, it can become glued to arteries and cause coronary heart disease."



In a Finnish study of 1,380 middle-aged men, high intake of flavonoids, or polyphenols, was linked to healthier carotid arteries with less obstruction from atherosclerosis.<sup>1</sup> A large French study showed that people over 65 years of age who consumed a flavonoid-rich diet had less cognitive decline over a 10-year period.<sup>2</sup> Polyphenols from different plants may work synergistically when consumed together, with benefits from the combination equaling more than the sum of the parts.

The 1st International Conference on Polyphenols and Health, held in 2005, reviewed impressive evidence strongly supporting a role for polyphenols in preventing degenerative diseases, especially cardiovascular disorders and cancer.<sup>3</sup> Polyphenols are the most abundant antioxidants in the diet, and they promote health by a variety of mechanisms.

"Polyphenols can also block the action of enzymes that cancers need for growth and they can deactivate substances that promote the growth of cancers," Dr. Akramiene said. "Increased consumption of polyphenols has been associated with a reduced risk of cardiovascular disease, and possibly cancer and stroke."

#### COCOA: "FOOD OF THE GODS"

In Aztec culture, cocoa was so highly prized for its medicinal and stimulant value, as well as for its taste, that botanist Linnaeus termed it *Theobroma cacao*, or “food of the gods.” Unlike modern-day hot chocolate, Aztec cocoa was served without sugar and milk, which today add calories and saturated fat to an otherwise healthful libation.

Polyphenols in cocoa occur in higher concentration than in any other food, and have antioxidant activity much greater than that of broccoli or red wine. In fact, dark chocolate has about 10 times the antioxidant power of spinach as measured by the ORAC test (oxygen radical absorbance capacity). The catechins and procyanidins in cocoa also appear to lower the risk of cancer and heart disease.<sup>4</sup>



“Evidence derived from epidemiological surveys, retrospective studies, and follow-up studies as well as from experimental data, shows that cocoa reduces blood pressure, improves insulin sensitivity, and may slightly ameliorate the lipid profile,” Claudio Ferri, MD, a full professor of internal medicine at University of L’Aquila in Italy, told Life Extension. “All of the above must be considered for the insertion of cocoa in a healthy diet. Cocoa is not a junk food; it [is] a healthy and tasteful food; nevertheless, its high caloric content must be taken into consideration and its ingestion must be accompanied by careful reduction of calories from other sources.”

In a study by Dr. Ferri’s group,<sup>5</sup> 15 healthy volunteers were randomly assigned to eat either a 100-gram dark chocolate bar rich in polyphenols, or a 90-gram white chocolate bar, which does not contain polyphenols, every day for 15 days. After eating no cocoa or chocolate for a week, the volunteers then switched to the other type of chocolate. Compared with white chocolate, the dark chocolate was associated with lower blood pressure and with improvements in insulin resistance and insulin sensitivity, which are important markers for diabetes.

Of even greater clinical importance, Dr. Ferri’s group did a similar study in patients with high blood pressure and found that dark chocolate, but not white chocolate, decreased blood pressure and serum low-density lipoprotein (LDL) while improving blood flow and insulin sensitivity.<sup>6</sup> Studies by other researchers suggest that cocoa proanthocyanidins prevent elevation of blood glucose levels in diabetic obese mice.<sup>7</sup>

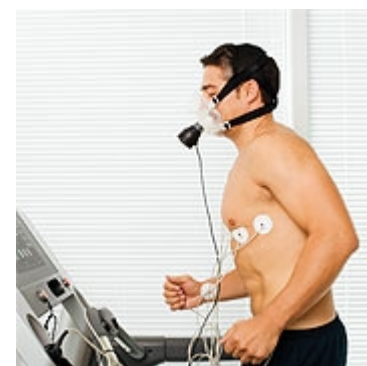
Astoundingly, even small amounts of dark chocolate polyphenols, 30 mg a day or the amount found in a quarter bar of premium dark chocolate, may protect against high blood pressure, according to an 18-week study published this year in JAMA, the flagship publication of the American Medical Association.<sup>8</sup> In individuals with mildly elevated blood pressure (130/85 to 139/89 mmHg), those receiving dark chocolate had a small decrease in average blood pressure, by 2.9 mmHg systolic and 1.9 mmHg diastolic. The percentage of this group classified as hypertensive also decreased from 86% to 68%. The group receiving white chocolate had no significant changes.

Although these blood pressure changes may seem small, they could translate to lower rates of stroke and heart attack and improved survival. When the investigators pooled information from their own and other published studies, they found compelling evidence that cocoa helped lower blood pressure.<sup>9</sup> Some studies showed a dose-response effect, with greater improvements accompanying intake of larger amounts of dark chocolate polyphenols.<sup>9,10</sup>

In a Japanese study, individuals with high cholesterol had improvements in beneficial high-density lipoprotein (HDL), which protects against cardiovascular disease and atherosclerosis, as well as reduction in detrimental LDL when consuming a cocoa drink daily for four weeks.<sup>11</sup>

Similar findings hail from another Japanese study,<sup>12</sup> with an 11.4% increase in HDL after only three weeks of consuming dark chocolate, and a 13.7% increase in the group receiving dark chocolate enriched with cocoa polyphenols. The group consuming white chocolate did not have these improvements in HDL, confirming that the benefit could be attributed to cocoa polyphenols, which are absent from white chocolate.

Cesar G. Fraga, PhD, a research professor of nutrition at the University of California at Davis, told Life Extension about several lines of evidence suggesting that the polyphenols found in cocoa, particularly epicatechin, could improve human health. Population studies in the Netherlands, home of renowned Dutch chocolate, show that eating chocolate is linked to improved survival and fewer deaths from cardiovascular disease.



“Cocoa consumption, especially cocoa containing high levels of polyphenols, protects vascular function and consequently can affect vascular disorders,” Dr. Fraga said. “Cocoa containing high levels of polyphenols can decrease blood pressure, [and] cocoa products decrease platelet aggregation and blood markers of inflammation. The regulation of nitric oxide present in the vasculature is currently the most accepted mechanism in which cocoa polyphenols can be involved.”

## WHAT YOU NEED TO KNOW: DISEASE-FIGHTING POWER OF POLYPHENOLS

- Polyphenols found in fruits and vegetables are potent antioxidants, particularly those in cocoa, green tea, chokeberry, and apples.
- Polyphenols also have beneficial effects on the endothelial lining of blood vessels by increasing the availability of nitric oxide, and by preventing the lipid oxidation underlying atherosclerosis.
- The typical Western diet lacks sufficient amounts and variety of plant polyphenols to be of optimal benefit.
- Polyphenols from different plants may work synergistically to protect against cardiovascular disease, cancer, diabetes, endothelial dysfunction, and other chronic diseases, without any known side effects.

Atherosclerosis, which clogs the arteries, ultimately resulting in heart attack or stroke, is aided and abetted by two culprits: abnormal platelet activation and endothelial dysfunction. Without platelets clumping together, we could bleed to death from a small cut, but when this normal function becomes overactivated, dangerous blood clots can ensue.

Overactivation of platelet aggregation may result from inflammation of the endothelium (the thin layer of cells lining blood vessels). Endothelial cells normally produce nitric oxide, which exerts a range of protective effects by controlling elasticity of the blood vessel wall, allowing the heart to contract normally, protecting blood vessels against injury, and helping prevent atherosclerosis.<sup>13-15</sup> Depletion of endothelial nitric oxide with aging results in stiffening and blockage of arteries, which, if left unchecked, can cause heart attack and stroke.<sup>16-18</sup>



Polyphenols have been shown to positively influence nitric oxide production. Smokers are particularly prone to nitric oxide depletion in the endothelium, which may partly explain their increased cardiovascular risk. Smokers given a cocoa drink rich in polyphenols have improved levels of nitric oxide as well as improved blood flow.<sup>19</sup> Even a single dose of a cocoa drink rich in flavanols transiently improves nitric oxide bioavailability in the blood and significantly reverses endothelial dysfunction.<sup>20</sup>

In the JAMA study described above, consumption of dark chocolate polyphenols, but not white chocolate, resulted in sustained improvement in nitric oxide-related blood markers of endothelial function.<sup>8</sup>

Cocoa polyphenols' ability to regulate nitric oxide activity in the blood vessels might have benefits that extend beyond cardiovascular disease, since nitric oxide regulation is also important in other tissues. Although extensive clinical and population-based studies have not yet been done to determine the effects of cocoa polyphenols on other diseases, Dr. Fraga said they may help protect

the body against cancer, diabetes, and degenerative brain disorders such as Alzheimer's disease.

One common thread tying all these conditions together is inflammation, which interferes with cell and tissue function. Cocoa polyphenols tend to reduce inflammation by regulating proinflammatory mediators and controlling processes that oxidize LDL in the development of atherosclerosis.<sup>21</sup>

"Acute inflammation is evident and therapeutically treated; however, chronic inflammation is less evident and can silently accompany the individual for years, as in diabetes," Dr. Fraga said. "This 'silent' inflammation could be targeted and ameliorated with diet. If the actions of cocoa polyphenols, as well as of the same polyphenols contained in other foods, are confirmed—and I consider that we are on the right track—the incorporation of reasonable amounts of cocoa products could be part of a healthy diet."

### TEA POLYPHENOLS MAY COMBAT HEART DISEASE AND CANCER

"Several cell culture, animal, and human studies have shown that tea polyphenols could be beneficial to human health," Arpita Basu, PhD, an assistant professor of nutritional sciences at Oklahoma State University in Stillwater, told Life Extension. "Research has focused mostly on green tea, and its active compound, epigallocatechin gallate [EGCG], which has been shown to possess anti-obesity, antihypertensive, antidiabetic, antioxidant, anti-inflammatory, and antimutagenic [anticancer] effects."

Second only to water, tea is the world's most consumed beverage, although it is less popular in the Western diet. Green, oolong, black, and white teas come from the tropical evergreen *Camellia sinensis*.<sup>22</sup> Because oolong and black teas undergo more

extensive processing before they are marketed, green tea and white (non-fermented) tea retain more polyphenols in their intact form. Tea polyphenols break down at high temperatures, so freshly brewed tea contains a higher amount of polyphenols per serving than do canned or bottled tea drinks.



“Polyphenols in tea have emerged as potential chemopreventive candidates for cancer treatment,” Yogeshwer Shukla, head of the proteomics laboratory, Industrial Toxicology Research Centre in Lucknow, India, told Life Extension. “Epidemiological studies have described the beneficial effects of tea polyphenols on the reduction of the risk of chronic diseases, including cancer. Other [benefits] include increase in metabolic rate, antidiabetes effects, a boost to the immune system and mental alertness, and lowering stress hormone levels.”

Mechanisms underlying these health benefits of tea polyphenols may include antioxidant activity, and effects on enzymes that metabolize drugs and that are involved in regulation of cell growth and reproduction. Many of these effects lead to anti-tumor properties and to cardiovascular benefits, thereby potentially reducing the risk of heart disease and cancer.<sup>22-24</sup> In Southeast Asia, where daily tea drinking is the norm, drinking more tea is linked to lower incidence of heart attack and other cardiovascular events.<sup>25</sup>

In adult smokers, daily supplementation with green tea alleviates the oxidative damage associated with smoking and reduces C-reactive protein, a marker of inflammation.<sup>25</sup> In individuals with high cholesterol, tea drinking may also curb the rise in blood lipids seen after eating.<sup>25</sup>

“Green tea extracts or EGCG supplementation has also been shown to reduce body fat and waist circumference in healthy overweight adults,” Dr. Basu said. “Tea supplementation containing a mixture of theaflavins [black tea], green tea catechins, and other tea polyphenols were shown to reduce total and LDL cholesterol in men and women with hypercholesterolemia [high blood lipids].”

A recent study of more than 40,000 adults in Japan<sup>26</sup> showed that drinking more green tea was linked to lower death rates from all causes and from cardiovascular disease in particular over 11 years of follow-up. Although polyphenols in black tea have also been associated with decreased risk of cardiovascular disease, the effects of green tea catechins are more pronounced.

“Due to the ability of green tea catechins to reach the human brain, they have also been correlated with a reduced risk of neurodegenerative diseases, such as Alzheimer’s and Parkinson’s diseases,” Dr. Basu said. “Since the underlying cause of most chronic diseases like cardiovascular disease, type 2 diabetes, cancer, and neurodegenerative disorders [includes] oxidative stress and inflammation, tea polyphenols can benefit overall human health by reducing these risk factors.”

Tea polyphenols, particularly green tea catechins, are potent antioxidants and fight inflammation, DNA damage, and LDL oxidation.<sup>27</sup> They are therefore well equipped to counteract the oxidative damage and inflammation associated with aging, smoking, consuming a high-fat diet, obesity and lack of physical exercise, high blood pressure, and high blood sugar.

In cellular studies and animal experiments, green tea has been shown to reduce LDL oxidation and lower cholesterol absorption from the diet.<sup>27-29</sup> It also causes blood vessel relaxation, which lowers blood pressure, and prevents overgrowth of smooth muscle cells in blood vessel walls, which can otherwise narrow the blood vessel, reducing blood flow and increasing blood pressure. Through these actions, green tea seems to protect against cardiovascular disease and death.

“Tea polyphenols are now regarded as ‘extra-nutritional’ compounds in a healthy diet with distinct cardioprotective health benefits,” Dr. Basu said. “Green tea consumption, three to four cups a day, is part of the traditional diet in Asian countries like China and Japan and accounts for most of the health benefits associated with tea consumption in those countries. On the basis of current information, consuming two to three cups of freshly brewed green tea is a healthy dietary choice.”

Dr. Basu recommends additional research on tea polyphenol intake in adults with chronic diseases related to oxidative stress and inflammation. Her group is now comparing the effects of daily intake of four cups of freshly prepared green tea, four cups of water (control), or the equivalent amount of EGCG supplement (500 mg) in pre-diabetic adults.

“This is a novel study and will prove whether...green tea polyphenols could be effective in lowering the risk factors associated with the development of type 2 diabetes and its related cardiovascular complications,” Dr. Basu said. “Comparative studies among white, green, and black tea will further show which one is the most effective and whether a combination therapy leads to better outcomes versus a single source.” Dr. Shukla added that studies in humans are difficult to interpret because tea consumption may be associated with socioeconomic and lifestyle factors that obscure the results. Methods of tea preparation and intake must be clearly defined.

“Effective intervention studies, better understanding of the fundamental mechanism(s) of action of the tea constituents and their

bioavailability are needed to more effectively determine the efficacy of tea constituents as preventive agents for human cancer,” Dr. Shukla said. “Although considerable accumulating information provides a compelling body of evidence for the preventive potential of tea against cancer, naturally occurring tea polyphenols have yet to be evaluated in clinical intervention in human trials.”

## **CHOKEBERRY (ARONIA): RICH IN POLYPHENOLS, ANTIOXIDANTS**

Like the blueberry, the black chokeberry (*Aronia melanocarpa*) is high in anthocyanins and antioxidant activity.<sup>30</sup> Compared with the cranberry, it contains more than five times the amount of flavonoids and anthocyanins. Although native to eastern North America, the chokeberry has become popular in Eastern Europe and Russia because of its health-promoting potential.

“*Aronia melanocarpa* fruits are one of the richest plant sources of phenolic substances, mainly anthocyanins,” Stefka Valcheva-Kuzmanova, MD, PhD, chief assistant professor of medicobiological sciences at the Medical University in Varna, Bulgaria, told Life Extension. “*Aronia melanocarpa* fruit juice and anthocyanins derived from the fruits have been intensively studied during the last 15 years. Most of the effects of *Aronia melanocarpa* anthocyanins are due to their high antioxidative activity.”

In animal studies, Dr. Valcheva-Kuzmanova’s group has shown that *Aronia* protects the liver from chemical poisoning, and the stomach lining from ulcers caused by the nonsteroidal anti-inflammatory drug indomethacin.<sup>31</sup> *Aronia* also acts as an anti-inflammatory substance to prevent swelling caused by release of the allergic mediators histamine and serotonin.<sup>32</sup>

Even more exciting, *Aronia* lowers harmful cholesterol levels in rats fed a high-fat diet,<sup>33</sup> and prevents dangerous swings in blood sugar in experimental diabetes.<sup>34</sup> In the laboratory, *Aronia* fruit juice slows growth of virulent *Staphylococcus aureus* and *Escherichia coli* bacteria and of influenza virus type A.<sup>35</sup> In contrast to antibiotics and other drugs, there is currently no evidence for “any unwanted and toxic effects of *Aronia melanocarpa* fruits, juice, and extracts,” Dr. Valcheva-Kuzmanova explained.

Other studies have shown that *Aronia* tends to prevent harmful mutations in cell cultures, to regulate immune function of human white blood cell cultures and in patients with breast cancer, and to suppress the growth of human colon cancer cells.<sup>31</sup> Athletes consuming chokeberry juice have less oxidative damage to red blood cells during vigorous exercise.<sup>36</sup>

Bringing these findings to the arena of human disease prevention, a placebo-controlled study showed that patients treated with statins following a heart attack had reduced levels of inflammatory markers when they ingested chokeberry extract.<sup>37</sup> Even more amazingly, they had reductions in systolic and diastolic blood pressure of 11 and 7 mmHg, respectively.

“In view of the fact that chokeberry flavonoids reduce the severity of inflammation, regardless of statins, they can be used clinically for secondary prevention of ischemic heart disease,” the authors concluded.



## **AN APPLE A DAY KEEPS THE DOCTOR AWAY**

Based on the high procyanidin content of apples, which also contain a unique polyphenol known as phloridzin, modern science is now confirming the truth of this old adage. Yoko Akazome, PhD, chief researcher at the Fundamental Research Laboratory in Asahi Breweries, Ltd. in Japan, shared with Life Extension some of his recent research on apple polyphenols.

In healthy volunteers, apple polyphenols not only lower blood cholesterol, but also inhibit triglyceride absorption,<sup>38-40</sup> without any apparent ill-effects.<sup>41</sup> Animal studies confirm the anti-obesity effect of apple polyphenols via beneficial effects on fat metabolism and insulin sensitivity.<sup>42-44</sup>

By combating high cholesterol and obesity, apple polyphenols are a good defense against heart disease and diabetes. A randomized, placebo-controlled study in 71 moderately overweight volunteers showed that those taking an apple polyphenol capsule for 12 weeks had reduction in central body fat covering the abdominal organs and improvements in fat metabolism, with no adverse effects.<sup>45</sup>

In addition, apple polyphenols have the potential to reduce allergic conditions<sup>46</sup> by blocking the release of histamine (an irritating substance causing inflammation and itching) from the mast cells that mediate allergic reactions.<sup>47-49</sup>

Even better news is that these anti-allergic effects in the laboratory translate into clinical improvements in patients with atopic dermatitis, an allergic skin condition;<sup>50,51</sup> and in persistent allergic rhinitis, or

hayfever, based on the results of a rigorous, placebo-controlled study.<sup>49</sup> Even in high doses, apple polyphenols have no toxic effects.<sup>50</sup>

Studies by other groups show that the anti-inflammatory and antioxidant qualities of apple polyphenols have a wide range of other health benefits, including protection of colon cells against free-radical damage that could cause cancer,<sup>52</sup> prevention of bone loss in an experimental model of menopausal osteoporosis,<sup>53</sup> decreased lipid oxidation, and cholesterol reduction.<sup>54</sup> Population studies have linked increased consumption of apples with lower risk of some cancers, cardiovascular disease, asthma, and diabetes.<sup>54</sup>

## VARIETY IS THE ELIXIR OF LIFE

As shown above, nature's bounty of polyphenols have beneficial effects that combat free-radical damage and other degenerative processes, thereby potentially lowering the risk of cardiovascular disease, endothelial dysfunction, high blood pressure, diabetes, cancer, and allergic conditions.

In the Western world, not only is our aging population more vulnerable to these conditions, but our diet makes it less likely that we will consume a healthy range of polyphenols in sufficient quantities to be of optimal benefit. The vital nutrients in cocoa, green tea, chokeberry, and apples, may work together so that the sum is greater than the whole of its parts in protecting our bodies from the ravages of disease and aging. Unlike statins, antihypertensives, and other drugs widely used to prevent and treat chronic disease, plant polyphenols have no known adverse effects. •

If you have any questions on the scientific content of this article, please call a Life Extension Health Advisor at 1-800-226-2370.

---

## References

---

1. Mursu J, Nurmi T, Tuomainen TP, et al. The intake of flavonoids and carotid atherosclerosis: the Kuopio Ischaemic Heart Disease Risk Factor Study. *Br J Nutr.* 2007 Oct;98(4):814-8.
2. Letenneur L, Proust-Lima C, Le GA, Dartigues JF, Barberger-Gateau P. Flavonoid intake and cognitive decline over a 10-year period. *Am J Epidemiol.* 2007 Jun 15;165(12):1364-71.
3. Scalbert A, Johnson IT, Saltmarsh M. Polyphenols: antioxidants and beyond. *Am J Clin Nutr.* 2005 Jan;81(1 Suppl):215S-7S.
4. Weisburger JH. Chemopreventive effects of cocoa polyphenols on chronic diseases. *Exp Biol Med (Maywood).* 2001 Nov;226(10):891-7.
5. 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 Mar;81(3):611-4.
6. Grassi D, Necozione S, Lippi C, et al. Cocoa reduces blood pressure and insulin resistance and improves endothelium-dependent vasodilation in hypertensives. *Hypertension.* 2005 Aug;46(2):398-405.
7. Tomaru M, Takano H, Osakabe N, et al. Dietary supplementation with cacao liquor proanthocyanidins prevents elevation of blood glucose levels in diabetic obese mice. *Nutrition.* 2007 Apr;23(4):351-5.
8. Taubert D, Roesen R, Lehmann C, Jung N, Schomig E. Effects of low habitual cocoa intake on blood pressure and bioactive nitric oxide: a randomized controlled trial. *JAMA.* 2007 Jul 4;298(1):49-60.
9. Taubert D, Roesen R, Schomig E. Effect of cocoa and tea intake on blood pressure: a meta-analysis. *Arch Intern Med.* 2007 Apr 9;167(7):626-34.
10. Wang JF, Schramm DD, Holt RR, et al. A dose-response effect from chocolate consumption on plasma epicatechin and oxidative damage. *J Nutr.* 2000 Aug;130(8S Suppl):2115S-9S.
11. Baba S, Natsume M, Yasuda A, et al. Plasma LDL and HDL cholesterol and oxidized LDL concentrations are altered in normo- and hypercholesterolemic humans after intake of different levels of cocoa powder. *J Nutr.* 2007 Jun;137(6):1436-41.
12. Mursu J, Voutilainen S, Nurmi T, et al. Dark chocolate consumption increases HDL cholesterol concentration and chocolate fatty acids may inhibit lipid peroxidation in healthy humans. *Free Radic Biol Med.* 2004 Nov 1;37(9):1351-9.

13. Shaul PW. Endothelial nitric oxide synthase, caveolae and the development of atherosclerosis. *J Physiol.* 2003 Feb 15;547 (Pt 1):21-33.
14. Shaw CA, Taylor EL, Megson IL, Rossi AG. Nitric oxide and the resolution of inflammation: implications for atherosclerosis. *Mem Inst Oswaldo Cruz.* 2005 Mar;100 Suppl 1:67-71.
15. Takimoto E, Champion HC, Li M, et al. Oxidant stress from nitric oxide synthase-3 uncoupling stimulates cardiac pathologic remodeling from chronic pressure load. *J Clin Invest.* 2005 May;115(5):1221-31.
16. Rubio AR, Morales-Segura MA. Nitric oxide, an iceberg in cardiovascular physiology: far beyond vessel tone control. *Arch Med Res.* 2004 Jan;35(1):1-11.
17. Sugawara J, Komine H, Hayashi K, et al. Effect of systemic nitric oxide synthase inhibition on arterial stiffness in humans. *Hypertens Res.* 2007 May;30(5):411-5.
18. Taddei S, Virdis A, Ghiadoni L, et al. Age-related reduction of NO availability and oxidative stress in humans. *Hypertension.* 2001 Aug;38(2):274-9.
19. Heiss C, Kleinbongard P, Dejam A, et al. Acute consumption of flavanol-rich cocoa and the reversal of endothelial dysfunction in smokers. *J Am Coll Cardiol.* 2005 Oct 4;46(7):1276-83.
20. Heiss C, Dejam A, Kleinbongard P, et al. Vascular effects of cocoa rich in flavan-3-ols. *JAMA.* 2003 Aug 27;290(8):1030-1.
21. Sies H, Schewe T, Heiss C, Kelm M. Cocoa polyphenols and inflammatory mediators. *Am J Clin Nutr.* 2005 Jan;81(1 Suppl):304S-12S.
22. Shukla Y. Tea and cancer chemoprevention: a comprehensive review. *Asian Pac J Cancer Prev.* 2007 Apr;8(2):155-66.
23. Khan N, Mukhtar H. Tea polyphenols for health promotion. *Life Sci.* 2007 Jul 26;81(7):519-33.
24. Shankar S, Ganapathy S, Srivastava RK. Green tea polyphenols: biology and therapeutic implications in cancer. *Front Biosci.* 2007;12:4881-9.
25. Basu A, Lucas EA. Mechanisms and effects of green tea on cardiovascular health. *Nutr Rev.* 2007 Aug;65(8 Pt 1):361-75.
26. Kuriyama S, Shimazu T, Ohmori K, et al. Green tea consumption and mortality due to cardiovascular disease, cancer, and all causes in Japan: the Ohsaki study. *JAMA.* 2006 Sep 13;296(10):1255-65.
27. Tipoe GL, Leung TM, Hung MW, Fung ML. Green tea polyphenols as an anti-oxidant and anti-inflammatory agent for cardiovascular protection. *Cardiovasc Hematol Disord Drug Targets.* 2007 Jun;7(2):135-44.
28. Wang S, Noh K, Koo SI. Epigallocatechin gallate and caffeine differentially inhibit the intestinal absorption of cholesterol and fat in ovariectomized rats. *J Nutr.* 2006;136(11):2791-6.
29. Koo SI, Noh SK. Green tea as inhibitor of the intestinal absorption of lipids: potential mechanism for its lipid-lowering effect. *J Nutr Biochem.* 2007;18(3):179-83.
30. Valcheva-Kuzmanova S, Gadjeva V, Ivanova D, Belcheva A. Antioxidant activity of Aronia melanocarpa fruit juice in vitro. *Acta Alimentaria.* 2007;36(4):425-28.
31. Valcheva-Kuzmanova SV, Belcheva A. Current knowledge of Aronia melanocarpa as a medicinal plant. *Folia Med (Plovdiv).* 2006;48(2):11-7.
32. Borissova P, Valcheva S, Belcheva A. Antiinflammatory effect of flavonoids in the natural juice from Aronia melanocarpa, rutin and rutin-magnesium complex on an experimental model of inflammation induced by histamine and serotonin. *Acta Physiol Pharmacol Bulg.* 1994;20(1):25-30.
33. Valcheva-Kuzmanova S, Kuzmanov K, Tsanova-Savova S, et al. Lipid-lowering effects of Aronia melanocarpa fruit juice in rats fed cholesterol-containing diets. *J Food Biochem.* 2007;31:589-602.

34. Valcheva-Kuzmanova S, Russev V, Bojkova K, Belcheva A. Hypoglycemic and hypolipidemic effects of Aronia melanocarpa fruit juice in streptozotocin-induced diabetic rats. *Methods Find Exp Clin Pharmacol*. 2007 Mar;29(2):101-5.
35. Valcheva-Kuzmanova S, Russev V, Bojkova K, Belcheva A. Study of natural Aronia melanocarpa fruit juice for antibacterial and antiviral activity. *Scr Sci Med*. 2003;35:21-3.
36. Pilaczynska-Szczesniak L, Skarpanska-Steinborn A, Deskur E, Basta P, Horoszkiewicz-Hassan M. The influence of chokeberry juice supplementation on the reduction of oxidative stress resulting from an incremental rowing ergometer exercise. *Int J Sport Nutr Exerc Metab*. 2005 Feb;15(1):48-58.
37. Naruszewicz M, Laniewska I, Millo B, Dłuniewski M. Combination therapy of statin with flavonoids rich extract from chokeberry fruits enhanced reduction in cardiovascular risk markers in patients after myocardial infraction (MI). *Atherosclerosis*. 2007 Oct;194(2):e179-4.
38. Akazome Y, Kanda T, Ikeda M, Shimasaki H. Serum cholesterol-lowering effect of apple polyphenols in healthy subjects. *J Oleo Sci*. 2005;54:143.
39. Sugiyama H, Akazome Y, Shoji T, et al. Oligomeric procyanidins in apple polyphenol are main active components for inhibition of pancreatic lipase and triglyceride absorption. *J Agric Food Chem*. 2007 May 30;55(11):4604-9.
40. Ogino Y, Osada K, Nakamura S, et al. Absorption of dietary cholesterol oxidation products and their downstream metabolic effects are reduced by dietary apple polyphenols. *Lipids*. 2007 Mar;42(2):151-61.
41. Akazome Y, Kanda T, Ohtake Y, et al. Evaluation of safety of excessive intake and efficacy of long term intake of beverage containing polyphenols derived from apples. *Jpn Pharmacol Ther*. 2005;33(9):893-911.
42. Ohta Y, Sami M, Kanda T, Saito K, Osada K, Kato H. Gene expression analysis of the anti-obesity effect by apple polyphenols in rats fed a high fat diet or a normal diet. *J Oleo Sci*. 2006;55(6):305-14.
43. Ohta Y, Funayama M, Seino H, et al. Apple polyphenol improves lipid metabolism and insulin independence in obese rats. *Nippon Shokuhin Kagaku Kogaku Kaishi*. 2007;54(6):287-94.
44. Osada K, Suzuki T, Kawakami Y, et al. Dose-dependent hypocholesterolemic actions of dietary apple polyphenol in rats fed cholesterol. *Lipids*. 2006 Feb;41(2):133-9.
45. Nagasako-Akazome Y, Kanda T, Ohtake Y, Shimasaki H, Kobayashi T. Apple polyphenols influence cholesterol metabolism in healthy subjects with relatively high body mass index. *J Oleo Sci*. 2007;56(8):417-28.
46. Akiyama H, Sakushima J, Taniuchi S, et al. Antiallergic effect of apple polyphenols on the allergic model mouse. *Biol Pharm Bull*. 2000 Nov;23(11):1370-3.
47. Kanda T, Akiyama H, Yanagida A, et al. Inhibitory effects of apple polyphenol on induced histamine release from RBL-2H3 cells and rat mast cells. *Biosci Biotechnol Biochem*. 1998 Jul;62(7):1284-9.
48. Tokura T, Nakano N, Ito T, et al. Inhibitory effect of polyphenol-enriched apple extracts on mast cell degranulation in vitro targeting the binding between IgE and FcepsilonRI. *Biosci Biotechnol Biochem*. 2005 Oct;69(10):1974-7.
49. Enomoto T, Nagasako-Akazome Y, Kanda T, Ikeda M, Dake Y. Clinical effects of apply polyphenols on persistent allergic rhinitis: A randomized double-blind placebo-controlled parallel arm study. *J Investig Allergol Clin Immunol*. 2006;16(5):283-9.
50. Akazome Y. Characteristics and physiological functions of polyphenols from apples. *Biofactors*. 2004;22(1-4):311-4.
51. Kojima T, Akiyama H, Sasai M, et al. Anti-allergic effect of apple polyphenol on patients with atopic dermatitis: A pilot study. *Allergol Int*. 2000;49(1):69-73.
52. Schaefer S, Baum M, Eisenbrand G, Janzowski C. Modulation of oxidative cell damage by reconstituted mixtures of phenolic apple juice extracts in human colon cell lines. *Mol Nutr Food Res*. 2006 Apr;50(4-5):413-7.
53. Puel C, Quintin A, Mathey J, et al. Prevention of bone loss by phloridzin, an apple polyphenol, in ovariectomized rats under inflammation conditions. *Calcif Tissue Int*. 2005 Nov;77(5):311-8.

These statements have not been evaluated by the FDA. These products are not intended to diagnose, treat, cure or prevent any disease. The information provided on this site is for informational purposes only and is not intended as a substitute for advice from your physician or other health care professional or any information contained on or in any product label or packaging. You should not use the information on this site for diagnosis or treatment of any health problem or for prescription of any medication or other treatment. You should consult with a healthcare professional before starting any diet, exercise or supplementation program, before taking any medication, or if you have or suspect you might have a health problem. You should not stop taking any medication without first consulting your physician.