

Natural Products Used in the Management of Hyperlipidemia

By: William Sparks, BS

Hyperlipidemia is associated with an increased risk of the development of cardiovascular disease. High cholesterol is a condition of unhealthy levels of cholesterol in the blood. High cholesterol is also called dyslipidemia, lipid disorder and hyperlipidemia. The human body obtains cholesterol in two ways: up to 80% of the cholesterol is produced in the body by the liver, the remainder of the cholesterol is obtained from the diet in the form of animal products, such as meats, fish, poultry, eggs, butter, whole milk, and cheeses. Plant foods do not contain cholesterol.

There is not an accepted level of cholesterol in the human body that is necessarily considered safe. The safety of levels of cholesterol in humans will depend on other individual risk factors such as antioxidants levels, genetic history, toxic chemicals exposure, stress, lack of exercise, tobacco use, and other cardiovascular risk factors such as altered blood pressure or established coronary heart disease. Total cholesterol levels of less than 200 mg/dl are considered desirable. High risk levels are considered above 240 mg/dl.¹ At least 20% of the US population has high blood cholesterol. Nearly 105 million U.S. adults have total blood cholesterol values above 200 mg/dl. 37 million adults have levels above 240 mg/dl. As compared with those who have a cholesterol value of less than 200 mg/dl, the group with more than 240 mg/dl cholesterol has twice the risk of developing cardiovascular disease.

Management of hyperlipidemia begins with a dietary program that eliminates a high saturated fat diet and replaces it with a low fat diet. A diet containing less than 30% calories from fat is considered a low fat diet. Such a low fat diet should contain 10% of calories from polyunsaturated fatty acids. Trans fats and hydrogenated fats need to be eliminated also from the diet. The use of monounsaturated and polyunsaturated fats instead of saturated fats can help to lower blood cholesterol levels. These "healing" fats are available in vegetable oils and fish oils. Patients with cardiovascular disease should be placed on a low fat, low protein, high complex carbohydrate diet, eliminating salt and refined carbohydrate foods.²

Serum cholesterol values are generally reported as HDL (high density lipoprotein, or "good" cholesterol) and LDL (low density lipoprotein, or "bad" cholesterol). The importance of lowering cholesterol to desirable levels is made evident by the Helsinki Heart Study.³ Lowering LDL cholesterol levels by 11% with an increase of HDL by 11% was associated with a 34% reduction in coronary heart disease end points of definite heart attack and/or heart disease. Specific nutritional supplements have been found to lower serum cholesterol. The use of nutritional supplements maybe of value in aiding patients to lower their cholesterol levels to desirable levels. Supplementation can modify the production of cholesterol in the liver by reacting with hepatic enzymes, increase cholesterol excretion by the bile, and inhibit cholesterol uptake from the intestine.

Pantethine

Pantethine is natural compound that is a stable disulfide form of pantetheine, a precursor of coenzyme A. Pantethine is the coenzymatic form of vitamin B5 (pantothenic acid) and cysteamine. Pantothenic acid exhibits no lipid-altering properties. Cysteamine has been shown to react with hepatic enzymes such as HMG-Co reductase, fatty acid synthetase and acetyl-CoA carboxylase. Pantethine has been used as a lipid lowering agent in Asia and Europe for over thirty years. The exact mechanism by which pantethine exhibits normalizing parameters associated with dyslipidemia⁴ is not known. Pantethine may increase levels of coenzyme A. Increased levels of coenzyme A can increase the beta oxidation of fatty acids directly. Pantethine's metabolite cysteamine may decrease the hepatic synthesis of cholesterol by inhibiting HMG-Co reductase.

Susan First⁵ presented the clinical findings of pantethine in a study done at the University of Minnesota Medical School. The patients in the study were generally healthy, un-medicated adults. The study was double-blind, randomized, placebo controlled and cross-over. Each patient was given placebo, 600 mg and 900 mg pantethine for 6 weeks. Under these conditions pantethine reduced LDL-c by 10-15%, fasted triglycerides by 20-25% and increased HDL-c by 15-20%. Participants were also required to maintain all other lifestyle habits (i.e.; exercise and alcohol intake) throughout the study. Liver function, platelet counts, white blood cell counts and all other parameters were unchanged by any of the treatment doses. No side effects were reported by the patients. The study concluded that pantethine appears to be a safe, effective, and affordable lipid-altering therapy for those individuals who have not attained their lipid goals. Similar studies using pantethine have shown a progressive decrease in serum cholesterol (LDL) and an increase in HDL.^{6,7} Depending upon the type of dyslipidemia results using pantethine may vary.⁴

Delta tocotrienol

Natural vitamin E includes two groups of similar fat soluble compounds, the tocopherols and the tocotrienols. Each group consists of four separate isomers alpha, beta, delta and gamma. Both the tocopherol and tocotrienol groups have an aromatic chromanol ring and differ in their side chains. The tocopherol compounds have a phytol side chain and the tocotrienols have an unsaturated side chain with three double bonds in the tail of the molecule. The name tocotrienol refers to the three (tri) double bonds found on the tail. The term "toco" is obtained from the Greek word for child birth "tokos". In 1922 vitamin E was originally identified by Dr. Herbert Evans and Katherine Bishop in green leafy vegetables.⁸ In a series of experiments they isolated vitamin E from germ oil and identified it as a fertility factor in rats. Each individual isomer of vitamin E was assigned a unit of biological activity based upon the increased fertility in a rat that has been depleted of vitamin E. Using this assay method alpha tocopherol has the highest unit of activity. Labeling laws require that vitamin E be labeled in terms of its biological activity based upon the fertility assay.

Tocopherols have a side tail that allows the molecule to anchor itself in the membrane of cells. The tocotrienol side chain allows the molecule to move more in the membranes and cells. Based upon this tocotrienols are able to hunt down free radicals across a much larger area. This is why tocotrienols are reported to be a more effective as antioxidants when compared

to tocopherols. Unlike tocopherols, tocotrienols have been shown to reduce DNA damage in human studies.⁹ Free radicals attack molecules such as DNA resulting in DNA damage. The accumulation of damaged DNA contributes to a variety of disorders associated with the aging process. Based upon its lipophilicity, vitamin E is considered to be the major chain breaking antioxidant preventing the propagation of oxidative stress, especially in biological membranes.¹⁰

Qureshi¹¹ published in 2001 that novel tocotrienols of rice bran were able to inhibit the progression of atherosclerotic lesions in mice. Animals were fed a high fat diet and were either supplemented with alpha tocopherol, a tocotrienol rich fraction from rice bran or didesmethyl tocotrienol (d-P(25)-T3). The atherosclerotic lesions were decreased 23% by the alpha tocopherol, 36% by the tocotrienol rich fraction and 57% by d-P(25)-T3. d-P(25)-T3 is a delta, gamma tocotrienol rich fraction and does not contain tocopherols.

Quershi had originally shown in 1986 that tocotrienols isolated from barley were able to effectively lower serum cholesterol levels in a variety of animal models. Plant oils such as palm, rice bran, oat and barley contain mainly tocotrienols. Common cereals such as corn, wheat, soybean and peanut primarily contain vitamin E as tocopherols. Quershi had shown¹² in 1986 that tocotrienols from barley inhibited HMG-CoA reductase, the first rate limiting enzyme in the biosynthetic pathway for cholesterol synthesis. Alpha tocopherol was found to inhibit the tocotrienol's ability to suppress HMG-CoA reductase activity. In animal models Quershi¹³ showed that tocotrienols could not lower serum cholesterol in animals that were also given alpha tocopherol.

Delta and gamma tocotrienol were found to possess the greatest ability to inhibit cholesterol synthesis. Isolating delta and gamma tocotrienols from rice or palm oil has generally proved too costly to provide those natural products as materials for dietary usage free of tocopherols. Rice oil is composed of 50% tocotrienol and 50% tocopherol, palm oil contains about 75% tocotrienol and 25% tocopherol. These oils were the first to be used as dietary forms of tocotrienols and contained tocopherols. The benefits of providing a full spectrum vitamin E complex that included all 8 vitamin E molecules appeared much better than providing alpha tocopherol alone. The transport protein for vitamin E in humans selectively prefers alpha tocopherol. It should be noted that serum concentrations of alpha tocopherol are associated with a decreased chronic disease risk.¹⁴ 93% of the men and women in the United States do not consume the recommended daily amount of dietary vitamin E (12 mg proposed by the Food and Nutrition Board). Traber¹⁵ estimates that a vitamin E intake of 15 mg per day would yield optimal serum concentrations of alpha tocopherol which are associated with a decrease in chronic diseases. These chronic diseases include ischemic or hemorrhagic stroke, respiratory disease and certain forms of cancers.

The quest to obtain a delta/gamma tocotrienol rich fraction that was void of tocopherol was finally obtained when Dr. Barrie Tan discovered that Annatto contained 100% tocotrienol without tocopherol. Tan has reported that small daily doses (75-100 mg) of delta/gamma tocotrienols from annatto reduce total cholesterol, LDL and triglycerides by 15-20%. Unlike other HMG-CoA reductase inhibitors, tocotrienols do not inhibit the synthesis of coenzyme Q10. Working with Dr. Tan, Dr. William Judy has found that tocotrienols actually increase

up to 25% CoQ10 levels.¹⁶ Dr. Judy worked very closely with Dr. Karl Folkers who was generally considered the world's leading authority on coenzyme Q10.

Some studies have reported that tocotrienols supplements do not improve cardiovascular risk factors in men and women with hypercholesterolemia.¹⁷ Schaffer¹⁸ has reviewed those findings and concludes that alpha tocopherol concentrations greater than 20% in tocotrienol rich supplements may attenuate the cholesterol lowering potential of tocotrienols. Qureshi was able to show a dose dependent suppression of serum cholesterol by the tocotrienol rich fraction (25-200 mg/day) of rice bran in hypercholesterolemic humans following the American Heart Association Step-1 diet.¹⁹

Phytosterols

Phytosterols are structurally similar to cholesterol and have been shown to reduce the intestinal absorption of cholesterol by 30-40%.²⁰ Phytosterols do not affect plasma concentrations of other lipids such as HDL- cholesterol or triglycerides. Plant sterols are commonly found in foods such as fruits, legumes, nuts, grains and cooking oils. In plants phytosterols are essential components of plant membranes.²¹ The most common plant sterols are sitosterol, campesterol and stigmasterol. In the late 1990s plant sterols were granted GRAS (generally recognized as safe) status.

The intestine absorbs cholesterol from dietary and biliary (liver) sources. The average diet contains 300 mg to 400 mg of cholesterol per day. Via the bile, the liver secretes an average of 1,000 mg of cholesterol per day of which 60 % is reabsorbed.²¹ Plant sterols may act by blocking the absorption of cholesterol in the digestive tract.

Labeling law allows products to carry a health claim for plant sterols: "Foods containing at least 0.4 grams per serving of vegetable oil sterols, eaten twice a day with meals for a daily intake of at least 0.8 grams, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease".²² This level represents the lowest effective cholesterol lowering dose from published literature.

Sterols can lower serum cholesterol even in patients using agents to inhibit the production of cholesterol by the liver. One study found that statins reduced LDL by 32% and added phytosterols further reduced LDL cholesterol by 7%.²³ Dozens of clinical trials have shown that plant sterols can lower total cholesterol by an average of 6 to 10% and LDL cholesterol by 8 to 15%. Results for cholesterol reduction with phytosterols are generally observed between one and three months. Plant sterols are a safe, natural and highly effective intervention for the reduction of cholesterol reduction of cardiovascular disease risk.

Although the structure of cholesterol and plant sterols is very similar, few sterols are actually absorbed. As the intake of sterols increases, the percent of absorbed sterols decreases. Sterols are eliminated faster through the bile than cholesterol. Sterol blood levels are about 100 fold less than cholesterol blood levels.

Green Tea Extract

Aside from water, tea is the most consumed beverage in the world. Green tea is made from the dried leaves of *Camellia sinensis*. Green tea contains a high content of polyphenolic flavonoids, mainly catechins. In green tea epigallocatechin gallate (EGCG) is the most abundant catechin (44-55%). Green tea is traditionally consumed at an average of three

cups per day with a total polyphenol intake from green tea of 240 to 320 milligrams per day. The potential protective health effects from the catechins have been attributed to antioxidant, antithrombogenic and antiinflammatory properties.

Green tea consumption has been associated with a reduced mortality due to all causes and due to cardiovascular disease (CVD).²⁴ The Ohsaki study followed individuals for up to 11 years and was initiated in 1994 with over 40,000 individuals. In women, compared with those who consumed less than one cup per day, those who consumed 5 or more cups per day had a 31% lower risk of CVD. Imai^{25,26} investigated the association between the consumption of green tea and various serum markers in a Japanese population of 1,371 men aged over 40 years. Increased consumption of green tea was associated with decreased serum concentrations of total cholesterol (P for trend < 0.001), triglyceride, increased proportion of high density lipoprotein cholesterol, decreased level of very low lipoprotein cholesterol and decreased the atherogenic index. Imai concluded that green tea may act protectively against CVD.

Green tea extract has been shown to scavenge nitric oxide and superoxides. Studies have shown that green tea catechins can reduce LDL oxidation *in vitro*. Consumption of a single dose of green tea induces a significant rise in plasma antioxidant activity *in vivo*.²⁷ Plasma antioxidant levels peak about one hour after consuming tea. Green tea polyphenols are able to recycle vitamin E as an antioxidant. Polyphenolic green tea compounds have been shown, *in vitro*, to protect DNA from oxidative damage.^{28,29}

EGCG possesses the most potent antioxidative activity of the green tea polyphenols. EGCG is very well absorbed from the intestinal tract. Plasma levels peak 5 hours after ingestion and remain in the plasma for up to 24 hours.³⁰

Both short term and long term tea consumption improve endothelium-dependant flow mediated dilation in patients with endothelial dysfunction.³¹ The normal endothelium regulates vascular tone, platelet activity, leukocyte adhesion and vascular smooth muscle proliferation. Endothelial functions may be impaired in atherosclerosis. Oxidative stress increases endothelial dysfunction. Green tea consumption increases the antioxidant capacity of the plasma and decreases oxidative stress. Green tea flavonoids can accumulate in tissues. EGCG also increases endothelial nitric oxide activity dose dependently.³² Nitric oxide release from the endothelial results in vasodilation. Impaired vasodilation is associated with the progression of CVD.

Widlansky³³ examined the effects of EGCG on endothelial function in a double blind, placebo controlled, crossover designed study in patients with coronary artery disease. EGCG was given at 150 mg twice per day. The primary end point was the effect of treatment on brachial artery flow-mediated dilation. EGCG improved endothelial function in patients with endothelial dysfunction.

Green tea extracts have a cholesterol lowering effect. Green tea catechins have been shown in animal models.³⁴ to decrease the solubility of cholesterol in micelles, thereby reducing the intestinal absorption of cholesterol. Green tea catechins have been shown to increase the fecal excretion of total fatty acids as well as bile acids.³⁵ Unno³⁶ investigated whether tea catechins could modulate postprandial lipaemia using human subjects. Subjects consumed a test meal along with green tea extracts. Moderate (224 mg/dose) and high doses (674 mg/

dose) reduced plasma triglycerides by 15.1% and 28.7% respectively. Unno suggested that one of the possible mechanism of the inhibition maybe that green tea extracts exhibit an ability to inhibit pancreatic lipases. Individual catechins such as EGCG exert strong inhibitory effects of digestive lipases, *in vitro*.

EGCG is a known inhibitor of the enzyme catechol-O-methyltransferase, which degrades noradrenaline. This reduction in noradrenalin degradation could potentially prolong adrenergic drive and exert a regulatory effect on sympathetic activation.³⁷ EGCG is also an inhibitor of xanthine oxidase an enzyme that produces the purine uric acid.³⁸ Xanthine oxidase inhibition has been shown to improve endothelial vasodilation in hypercholesterolemic, but not hypertensive individuals.³⁹

Polymeric Proanthocyanidins

Polymeric procyanidins have been shown to increase endothelial nitric oxide synthase to a greater extent than monomers in aortic endothelial cells⁴⁰ *in vitro*. Preparations of extracts from the seed coats of lentils contain a rich mixture of condensed tannins (procyanidins). A standardized extract from lentils is trademarked under the name Phytolens and is patented.⁴¹ Grape seed extracts also contain polymeric proanthocyanidins.

Natural products can be used safe and effectively for the early management of hyperlipidemia. Dietary changes and exercise should be employed first in the management of this condition. Natural products such as pantethine and delta tocotrienols can be used to reduce the production of cholesterol in the liver. Natural products such as plant sterols and green tea extract can be used to prevent the absorption of cholesterol from the intestinal tract. Green tea appears to stimulate the biliary elimination of cholesterol from the liver.

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