NUTRI NEWS
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Autumn 2004

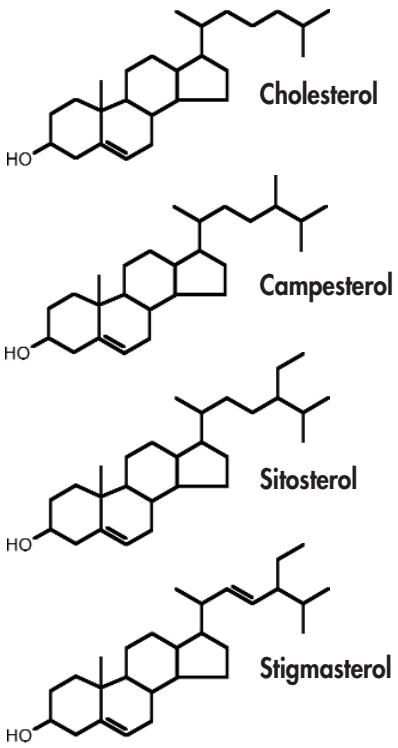
Emerging New Ingredients for Cardiovascular Health

Polymethoxylated Flavones, Plant Sterols and Pomegranate

Natalie Shamitko and Andrew Halpner, Ph.D.

According to the most recent statistics from the American Heart Association, 105 million Americans have total blood cholesterol of ≥ 200 mg/dL. Over the past 15 years, guidelines for what constitutes healthy cholesterol levels have continued to trend downward. The third report of the National Cholesterol Education Program (NCEP), Adult Treatment Panel III (ATP III), recommended that LDL-reduction should be a target of lipid lowering therapy and classified total cholesterol of < 200 mg/dL as desirable. The ATP III also classified an LDL-cholesterol of < 100 mg/dL and an HDL-cholesterol of < 40 as low. As recently as July 2004 additional recommendations for intensive lipid modifying treatment for high risk patients was endorsed by the National Heart Lung and Blood Institute, the American College of Cardiology, and the American Heart Association. These recommendations update the 2001 ATP III report and set lower treatment goals for LDL-cholesterol as well as support the use of lipid-lowering treatment beginning at lower thresholds. While this report continues to stress the importance of lifestyle modifications including nutrition, physical activity and weight control, it set new cholesterol goals for those at increased risk. Although an LDL-cholesterol of < 100 mg/dL is still considered an optimal goal, these updated recommendations advocate treating to < 70 mg/dL for individuals considered to be at very high risk. Since dietary modification and an increase in exercise are often unable to achieve these recommended reductions, many patients are increasingly forced to turn to drug therapy. In fact the use of statins (a class of lipid-lowering drugs that inhibit HMG-CoA, a key enzyme in the pathway of cholesterol synthesis) has risen dramatically. In 1998, annual statin drugs sales totaled just over $4 billion. In 2003, statin drug sales topped $13 billion. While these drugs can be effective at achieving significant reductions in cholesterol, concern over potential side effects including exercise intolerance, muscle weakness, and muscle pain has been growing. As a result, finding natural, scientifically supported products that are effective at modulating lipid levels and are without significant side effects is always welcome.

Figure 1
Molecular Comparison Between Cholesterol and Common Plant Sterols



A number of natural products that effectively target heart health have recently begun to receive increased attention in the dietary supplement marketplace. Products such as plant sterols, polymethoxylated flavones, tocotrienols, and pomegranate have been the focus of clinical studies investigating their potential cardioprotective properties.

Phytosterols

For over 50 years, plant sterols (also known as phytosterols) and their esters have been studied for a number of reasons including their effects on blood cholesterol in

humans. Extensive clinical data in animals and humans indicate that these naturally occurring lipid-soluble compounds can play important roles in the maintenance of healthy cholesterol levels. Plant sterols and stanols can be found in vegetables, fruits, legumes, grains and oils, with some of the most common plant sterols being campesterol, sitosterol and stigmasterol *(Fig. 1)*. As can be seen from their structure, these compounds are chemically similar to cholesterol; however, slight structural differences such as an ethyl group (sitosterol) or methyl group (campesterol) in the side chain differentiate them from cholesterol. Since plant sterols cannot be manufactured in the body, they must be obtained from the diet. Unfortunately, the typical Western diet does not supply enough sterols or stanols to result in significant alterations in blood lipids.

It is well understood that cholesterol plays numerous critical roles in the body, from hormone synthesis to helping maintain proper membrane function. Cholesterol can either be derived from the diet or can be synthesized endogenously in the liver. Dietary cholesterol interacts with bile acids and lipases and is ultimately absorbed across the intestinal mucosa where it is packaged into chylomicrons whereupon it makes its way in to the lymphatic system, the liver and ultimately to the systemic circulation. As part of its many functions, the liver also secretes cholesterol into the intestinal tract where it can either be reabsorbed or excreted from the body. One mechanism by which plant sterols appear to function is by competing with cholesterol at the level of the enterocyte. Since the molecular structure of phytosterols is similar to cholesterol, phytosterols can compete with cholesterol for absorption from the gastrointestinal tract. Specifically, plant sterols can displace cholesterol from intestinal micelles, thus inhibiting the absorption of dietary and biliary cholesterol in the gut. Dietary cholesterol, much of which is esterified, is first hydrolyzed in the gastrointestinal tract. The resulting free cholesterol can then be absorbed through mixed micelles, which are combinations of free cholesterol, mono and diacylglycerols, fatty acids, phospholipids and bile salts. This absorption through mixed micelles has recently thought to be due to existing cholesterol transporters in the intestinal mucosa, though earlier evidence indicated it may be due to passive diffusion. Nonetheless, plant sterols, which are more hydrophobic than cholesterol, may displace cholesterol from the mixed micelles, leading to a reduction of micellar cholesterol absorption. A second mechanism by which plant sterols may function to lower cholesterol is by altering the ability of acyl-coenzyme A cholesterol acyltransferase (ACAT) to esterify cholesterol in the enterocyte. A portion of the free cholesterol that has been absorbed in to the enterocyte must be re-esterified prior to being packaged in to chylomicrons. This re-esterification is performed by the ACAT enzyme. If this re-esterification is inhibited, ultimately, the amount of LDL produced by the liver may be reduced.

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Results of Phytosterol consumption

Clinical studies have demonstrated that supplemental phytosterols can lower total cholesterol an average of 6 - 10%, and LDL-cholesterol 8 - 15%. Additionally, studies show that use of supplemental phytosterols in combination with statins may provide additional reductions in blood cholesterol. For example, the combination of statins and phytosterols lowered blood cholesterol by 39%, with sterols contributing 7% of the overall reduction. Importantly, phytosterols do not appear to cause a statistically significant decrease in HDL cholesterol.

A brief overview of a number of the phytosterol studies is given below:

- In a randomized, controlled, single-blind study, 22 hypercholesterolaemic subjects were given a phytosterol enriched breakfast cereal, breads and margarine-like spreads to consume on a daily basis.

After 12 weeks, subjects experienced a 13.6% reduction in median LDL cholesterol from the consumption of 2.4 g of sterol esters/day.

- A study in healthy volunteers evaluated the safety and efficacy of phytosterol-enriched spreads. This 12 month randomized, double-blind placebo-controlled study found that consumption of 1.6 g/day of phytosterols lowered total and LDL-cholesterol by 4 and 6%, respectively, and demonstrated that consumption of these phytosterols is both efficacious and safe for long term use.
- A study involving 38 children between the ages of 7 and 12 years with familial hypercholesterolemia consumed either a margarine type spread (placebo) or phytosterol-containing spread with 1.6 g of phytosterols for 8 weeks. Reductions in total cholesterol of 7.4% and LDL-cholesterol levels by 10.2% were observed. Triglycerides and HDL were unaffected in this study.

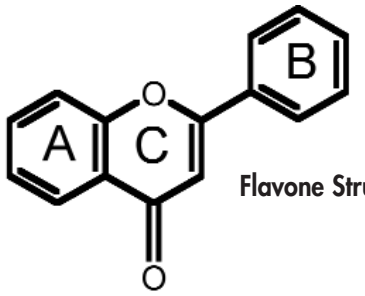
The safety of phytosterols has also been confirmed by their achieving GRAS (Generally Recognized as Safe) status in the late 1990s. In 2000 the FDA approved the use of cardiovascular disease reduction claims for certain foods that contain plant sterols and stanols. Recently, the FDA has acknowledged extensions of these health claims to include a wider variety of foods including dietary supplements. The result has been an increase in the number of dietary supplements that now contain phytosterols.

Polymethoxylated Flavones

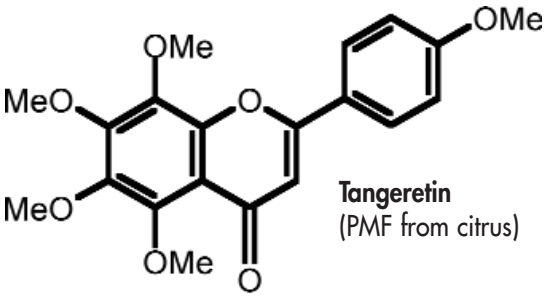
Flavonoids are a large class of phytochemicals that have powerful antioxidant properties and play important roles in the support of both circulatory and immune health. While the benefits of flavonoids as a general class of compounds have been known for years, more recently a specific class of flavonoids called polymethoxylated flavones (also known as PMFs) have been receiving greater attention for their ability to lower cholesterol in both animal and human studies. The term polymethoxylated flavones is derived from the fact that these compounds consist of a flavone backbone to which additional methyl groups have been added *(Fig. 2)*. Typical PMFs are compounds such as nobiletin, tangeritin and sinensetin, and can be found in concentrated amounts in the peel of citrus fruits, including oranges and tangerines. In vitro, as well as animal and in vivo human studies have demonstrated that PMFs possess potent cholesterol-lowering properties. Studies in human hepatoma HepG2 cells (a model used to study hepatic regulation of apolipoprotein B-containing lipoproteins including VLDL and LDL), involving nobiletin and tangeritin demonstrated the ability of these compounds to inhibit apo B secretion. The ability of these two compounds to inhibit apo B

Figure 2

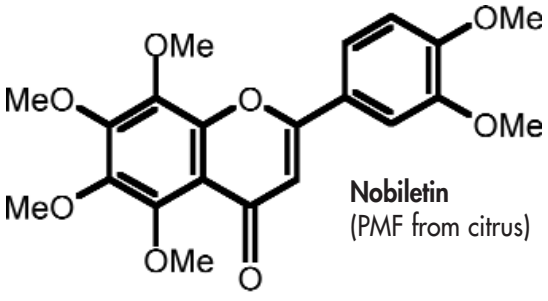
Molecular Stucture of Flavones and Polymethoxylated Flavones (PMFs)



Flavone Structure



Tangeretin
(PMF from citrus)



Nobiletin
(PMF from citrus)

secretion was stronger than other flavonoids such as hesperetin and naringenin, which have also be studied for their ability to decrease apo B. In a recent study involving hamsters fed a hypercholesterolemic diet, the addition of 1% PMFs significantly reduced total serum cholesterol 27%, VLDL + LDL cholesterol by 40%, and triglycerides by 44%. No toxic effects of PMFs were observed. It is thought that PMF metabolites in the liver may be responsible in part for the hypolipidemic effects.

There appear to be at least 2 mechanisms of action by which PMFs or their metabolites can function to lower cholesterol.

- As mentioned above, PMFs have been shown in cell culture studies to decrease apo B secretion. This lipoprotein is a structural protein needed for the endogenous synthesis of LDL cholesterol. Consequently, by reducing the production of this lipoprotein PMFs may influence the hepatic production of LDL-cholesterol.
- Cell culture studies also demonstrate that PMFs decrease the activity of the enzyme diacylglycerol acetyl transferase (DGAT), which is involved in the endogenous synthesis of triglycerides. This may explain the significant triglyceride-lowering effects of a patented extract containing PMFs that has been studied in humans.

Tocotrienols

Tocotrienols comprise one half of the vitamin E family that includes the better-known tocopherols, and can be found in various foods, most prominently in rice bran and palm oil. Like tocopherols, tocotrienols function as powerful antioxidants, and in certain systems there is evidence that tocotrienols may even possess greater antioxidant activity compared with tocopherols. While structurally similar, tocotrienols contain double bonds on their isoprenoid side chains, whereas tocopherols do not *(Fig. 3)*. In addition to their antioxidant function, tocotrienols

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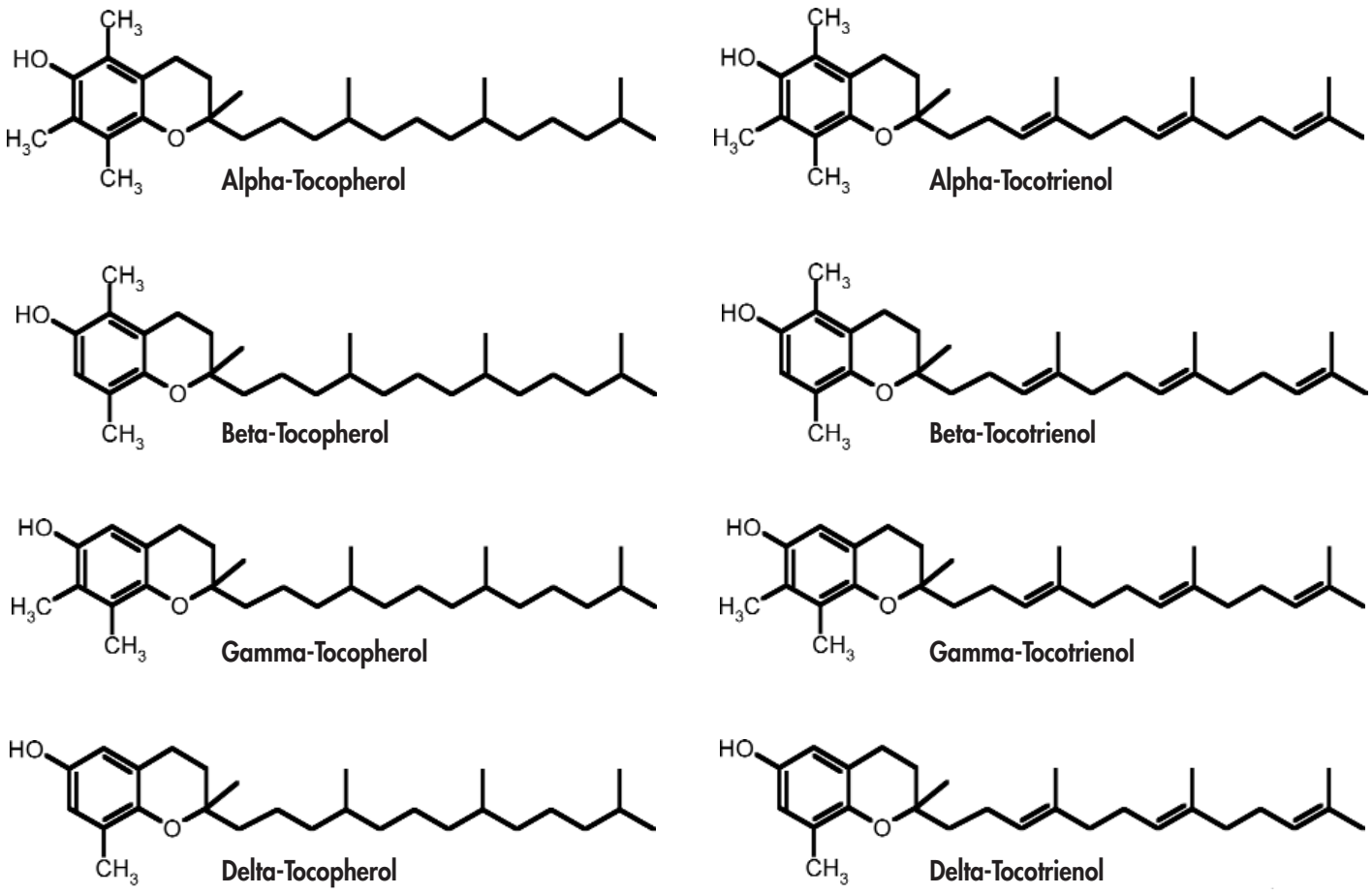
Figure 3

Eight Isomers of Vitamin E



OPCs: One Powerful Compound for Cardiovascular Health

Dr. Ronald Klatz and Dr. Bob Goldman

OPCs (Oligomeric Proanthocyanidin Complex) are among today's most potent and most promising antioxidant nutrients. Proanthocyanidins are a specific category of flavonoids, which only are produced by plants to defend them against invasions from funguses, toxins, and environmental stress. "Oligomeric" proanthocyanidins are particularly important to human health because the complex molecular structure makes them very active and potent antioxidants.

OPCs are most plentiful in food sources including red wine, blueberry, cranberry (red bilberry), lingonberry, barley, and other foods. As a nutritional supplement, OPCs are extracted from botanical sources including grape seed (*Vitis vinefera*), white pine (P*inus maritima*, *Pinus pinaster*), and other plants. The earliest described use of OPCs to cure disease dates back to the 1534, when the crew of French explorer Jacques Cartier's winter expedition of North America was rescued from near-death by a Native American concoction of pine bark and needles. A substantial body of scientific literature now supports the value of OPCs in human health; most notably, OPCs have been shown to exert a beneficial effect in helping to combat various aspects of cardiovascular disease.

OPCs inhibit atherosclerosis in different ways. Dr. Halpern and colleagues from Superior Institute for Health Sciences (Portugal) found that red wine extract prevents platelet aggregation by relaxing arterial tissue. In a study by Dr. Fremont and team from Laboratoire de Nutrition et Sécurité Alimentaire (France), a red wine extract containing 50% proanthocyanidins prevented oxidation of LDL in pigs. A group led by Dr. Auger from the Laboratoire Genie Biologique et Sciences des Aliments (France) determined that red wine extract reduced levels of cholesterol, triglycerides, and apolipoprotein B (the protein component of LDL), while increasing the activity of an antioxidant enzyme produced by the liver by a remarkable 67%.

In a study involving rabbits that were fed a high-cholesterol atherosclerotic diet, Dr. Yamokoshi and colleagues from Kikkoman Corporation (Japan) found that the rabbits that also received grape seed extract avoided a ten-fold increase in their levels of peroxides (a marker of oxidation) that occurred in rabbits that did not receive the grape seed supplement. Dr. Yamokoshi's work deteremined that the OPCs present in grape seed extract trapped the reactive oxygen species (ROS) before it could cause oxidation of LDL.

Dr. Rong and team from Loma Linda University (California USA) found that bathing cells from arteries in a solution of pine bark extract protected them from oxidative damage.

Atherosclerosis can lead to a condition known as ischemic reperfusion injury, a condition that OPCs have been found to ameliorate. In 2002, Dr. Pataki and colleagues from the University of Debrecen (Hungary) published results of a study in which they fed grape seed extract to rats for three weeks, then initiated ischemic reperfusion. They found that the incidence of arrhythmia was reduced by 50-70% (depending on the dose of grape seed extract), as compared to rats that were not fed the extract before ischemia. Additionally, the rats treated with a higher dose of grape seed extract recovered heart blood flow and pressure better than their untreated counterparts. Most notably, Dr. Pataki observed that free radical activity was reduced by 75% in the rats fed grape seed extract than those not fed it.

In another study of grape seed extract, Dr. Sato and colleagues from University of Connecticut (USA) determined that the OPCs present in grape seed extract significantly inhibited the formation of reactive oxygen species, and also reduced the death of heart cells after ischemic reperfusion. This group of researchers had previously determined that grape seed extract OPCs were able to scavenge free radicals, thereby reducing the level of oxidative stress in the ischemic reperfusion state. Dr. Sato also has conducted evaluations that determined similar benefits of red wine OPCs for ischemic reperfusion injury. In 2002, Dr. Sato's group found that red wine extract improves postischemic heart function while reducing the signal that prompts for heart cell death. Previously, Dr. Sato and team had also determined that the amount of oxidative by-products in ischemic reperfusion is reduced by red wine extract.

OPCs have been shown to have a therapeutic effect in cardiovascular conditions including atherosclerosis (hardening of the arteries), by preventing changes to LDL cholesterol that promote artery clogging; and ischemic reperfusion injury, by maintaining regular heart beat and reducing heart cell death. As a result, we can consider nutritional supplementation with OPCs as an important way in which we can harvest nature's anti-aging bounty. For an in-depth review of the multitude of potential therapeutic benefits of OPC supplementation in cobatting modern-day killer diseases and protecting cells from head-to-toe, we invite you to read

Continued on the following page

OPCs – Continued from page 5

The New Anti-Aging Revolution, available from the American Academy of Anti-Aging Medicine (A4M), the world's leading non-profit medical organization dedicated to the advancement of technology to detect, prevent, and treat aging related disease and to promote research into methods to retard and optimize the human aging process. Call A4M at 773-528-4333 to order this life-changing book.

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Dr. Ronald Klatz and Dr. Bob Goldman are physicians and co-founders of the anti-aging medical movement and of the American Academy of Anti-Aging Medicine (A4M; Chicago, IL USA; www.worldhealth.net), a non-profit medical organization dedicated to the advancement of technology to detect, prevent, and treat aging related disease and to promote research into methods to retard and optimize the human aging process. A4M is also dedicated to educating physicians, scientists, and members of the public on anti-aging issues.

Emerging Ingredients – Continued from page 4

have demonstrated the ability to reduce cholesterol synthesis by inhibiting the hepatic enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA), a rate-limiting enzyme in cholesterol biosynthesis. This finding has resulted in research investigating the ability of tocotrienols to effect cholesterol levels as well as other cardiovascular health parameters. Studies have shown that subjects with carotid atherosclerosis who consumed tocotrienols for 2 years had a reduction in amount of cholesterol-laden plaque in their carotid arteries compared with those who received a placebo.

PMFs + Tocotrienols = Sytrinol™

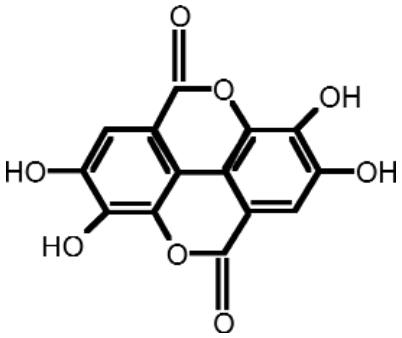
Intriguing data are now emerging from a new patented blend of PMFs and tocotrienols called Sytrinol™. Three human clinical studies investigating the effect of Sytrinol on blood lipids have yielded impressive results. In the first study, 10 subjects having an average total cholesterol >230 mg/dl, LDL-cholesterol > 155 mg/dl and total triglycerides of between 100 and 307 mg/dl received 300 mg of Sytrinol for 4 weeks. Compared with baseline values, total cholesterol decreased by 24%, LDL-cholesterol decreased by 19% and triglycerides dropped by 24%. These results were confirmed in a second study also involving 10 hypercholesterolemic subjects in whom similar reductions in lipid parameters were observed. A 21% reduction in apo B levels was also observed in this study, supporting the notion that polymethoxylated flavones inhibit apo B secretion. Given the success of the first two studies, a placebo-controlled, randomized, 3-phase, cross-over study involving 120 hypercholesterolemic subjects was initiated. During phase one subjects received either 300 mg/day of Sytrinol or a placebo for 12 weeks. Blood was drawn at baseline, 4, 8 and 12 weeks. The second phase of the study consisted of a 4 week washout period, followed by phase 3 in which the subjects were crossed over, so that those that received the placebo in phase 1 would then receive the active treatment. After 12 weeks, compared with baseline values, subjects receiving Sytrinol experienced statistically significant average reductions for total cholesterol, LDL-cholesterol and triglycerides of 27, 25, and 30%, respectively. No significant changes were reported in the placebo group. HDL-cholesterol was not significantly altered in either group. As of the time of this publication, the data from the first two human trials have been submitted for publication, and the third trial is now in its third phase. In all 3 studies, Sytrinol was well tolerated and there were no differences in adverse effects between the treatment and placebo groups. The strength of these results may be attributable to the unique combination of mechanisms of action by which Sytrinol is thought to work; inhibition of apo B secretion, inhibition of triglyceride synthesis, and inhibition of cholesterol synthesis.

Pomegranate

Another interesting natural product that is receiving increased attention for its potential role in helping to maintain cardiovascular health is the pomegranate. In

addition to the fact that the fruit tastes delicious and is fun to eat, pomegranates contain a wide array of beneficial polyphenolic compounds including anthocyanins, catechins, tannins, and ellagic and gallic acids *(Fig. 4)*. Supplementation with pomegranate juice in animal studies has been shown to reduce macrophage lipid accumulation, cellular cholesterol accumulation as well as reduce the development of atherosclerosis. Recent human research has also reported the effect of supplementation with pomegranate juice in those with carotid artery stenosis. A report out of Israel earlier this year showed that after 1 year of pomegranate juice consumption, subjects with severe atherosclerosis experienced up to a 30% reduction in intima-media thickness compared with an increase in intima-thickness of 9% in the placebo group. The resistance of LDL to oxidation, as well as serum paraoxonase 1 activity was also increased after 1 year in the group receiving the pomegranate juice. Serum paraoxonase 1 (PON 1) is an enzyme associated with HDL-cholesterol that can reduce certain lipid peroxides found in arterial cells as well as lipoproteins. PON 1 has been shown to be reduced in those with diabetes and cardiovascular disease. Consequently, increases in paraoxonase activity is believed to be a beneficial outcome with respect to cardiovascular health. While the mechanisms of action and specific compounds responsible for these actions are not well understood, the combination of potent antioxidants present in pomegranates may in part be responsible for the findings. As more people look for alternatives to statin drugs, exciting natural products that help to lower cholesterol and help maintain cardiovascular health are quickly becoming a reality. Coupled with other nutrients that are well-known for their cardioprotective properties such as CoQ10, B vitamins, and omega-3 fatty acids, the addition of pomegranate, polymethoxylated flavones and plant sterols offer strong new weapons to help maintain optimal heart health.

Figure 4
Molecular Structure of Ellagic Acid



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