Cardiovascular Disease

Phytochemical and Nutritional Prevention and Treatment

Chris D. Meletis, N.D.

Estimates from the year 2000 reveal that approximately 61,800,000 Americans had one or more forms of cardiovascular disease (CVD). These CVDs include hypertension, stroke, and coronary heart disease, including angina pectoris and myocardial infarction.[1] Individually, 50,000,000 people had hypertension; 7,600,000 suffered from acute myocardial infarction; 6,600,000 people experienced angina pectoris; and 4,700,000 people had cerebral vascular accidents.

CVD killed 945,836 people in 2000, comprising 39.4 percent of all deaths, and 150,000 of these deaths occurred in people under age 65. Coronary heart disease (CHD) caused the most deaths in people suffering from CVD, taking the lives of 515,204 people in 2000. Approximately 250,000 people die each year from sudden myocardial infarction, without ever being hospitalized.[11] Internationally, 16.6 million people die from CVD throughout the world each year and, in 2001, CVD contributed to nearly one third of global deaths.[2]

Cardiovascular diseases represent one of the greatest health concerns in modern history. Not limited in prevalence to the United States, diseases of the cardiovascular system affect people across the world, mainly in modernized countries.

The American Heart Association (AHA) identifies increasing age, male gender, and heredity as uncontrollable risk factors for heart disease, and tobacco smoking, high blood cholesterol, high blood pressure, physical inactivity, obesity/overweight, and diabetes as modifiable risk factors for heart disease. Other negative risk factors identified by the AHA as contributory to heart disease include stress levels and responses, sex hormones, birth control pills, and excessive alcohol intake.[3] Despite the acknowledgment of this problem, and intense educational efforts in this country to make people aware of CVD, large numbers of people are continually diagnosed each year in this country and the rest of the world.

New insights into CVD reveal foci for testing and prevention, other than standard lipid profiles. Testing for homocysteine, C-reactive protein (CRP), and fibrinogen place new emphasis on cardiovascular risk parameters while research into naturally derived medicines provides viable preventative and treatment options for CVD.

Lipid Levels

The standard lipid panel provides information about plasma concentrations of total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and very low-density lipoprotein (VLDL) cholesterol. However, a patient who scores within the "average" ranges for these parameters, should take little comfort because being average, in this case, means a greater than 50-percent likelihood of dying of heart disease.

According to the recommendations of the National Cholesterol Education Program, these laboratory tests provide useful parameters for evaluating risk status for coronary heart disease (CHD). Both individual and stand-alone values and comparison ratios between individual components of the lipid panel provide information for classifying patients into low, medium, and high-risk categories. With regard to risk, so-called "normal" levels are derived from groups of patients with no obvious evidence of CVD and this, in itself, is inaccurate because such patients may have preclinical CVD and therefore do not reflect a true "no-risk" population.

Cholesterol levels undergo considerable variation among individuals, with day-to-day values fluctuating by as much as 15 percent, while an 8-percent difference can be identified within the same day. Even positional changes can alter these values; recumbency can decrease cholesterol values by 15 percent.[4] Although cholesterol is no longer considered to be such a significant culprit in CVD as much as in the past, great emphasis is still directed at reducing cholesterol blood levels.

Alternative and complementary (ACM) practitioners utilize the lipid panel in much the same way as standard medical practitioners but ACM practitioners utilize natural-based medicines with minimal side-effects that are effective for lowering cholesterol, LDL, and VLDL while elevating HDL over time. In addition ACM practitioners have a larger arsenal for treating and preventing heart disease, which provides even greater benefit when combined with traditional statin drug therapy. The following plant-derived medicines are used to treat suboptimal cholesterol, HDL, LDL, VLDL, and triglyceride levels.

Myrrh

Also known as gugulipid, *Commiphora mukul* is the standardized extract of the myrrh tree, native to India. This botanical medicine contains two main active compounds: Z-guggulsterone and E-guggulsterone, both of which lower total cholesterol and triglyceride and raise HDL cholesterol.[5] These phytosteroids act as antagonist ligands for the bile acid receptor farnesoid X receptor, an important regulator of cholesterol homeostasis.[6]

More specifically, this regulation involves increasing the liver's metabolism of LDL cholesterol.[7] Gugulipid, administered two times per day, containing a standardized dose of 50 mg of gugul-

sterones per day, for 24 weeks to 31 patients was found to reduce total cholesterol by 11.7 percent, LDL by 12.5 percent, triglycerides by 12 percent, and total cholesterol/high density lipoprotein (HDL) cholesterol ratio by 11.1 percent.[8] HDL cholesterol itself was not affected in this study.

In a multicenter clinical trial, 205 patients took 500 mg of gugulipid, two times per day. On average, cholesterol levels fell 11 percent, while triglycerides decreased by 16.8 percent, and HDL levels increased by 60 percent in cases that responded to the gugul therapy.[9] Purified gugulipid is without side-effects, and is considered to be safe to use in pregnancy while crude gugul extracts have been associated with skin rashes (when applied topically) and diarrhea.[10]

Garlic

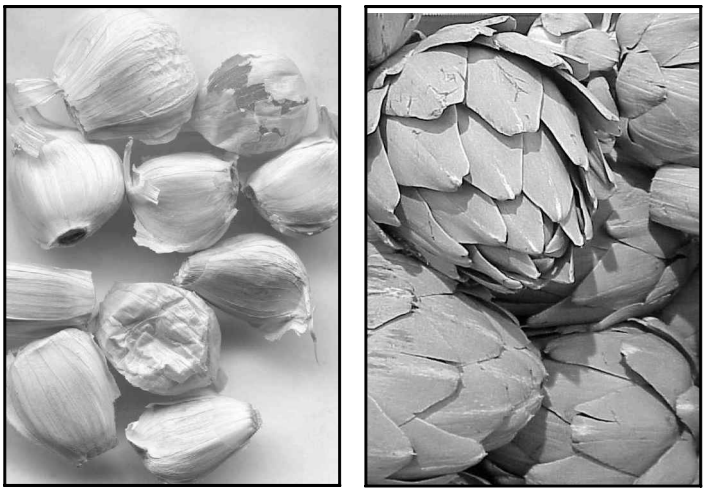
Garlic (*Allium sativum*) and its derivatives are popularly known as effective preventives and treatment options for atherosclerosis, hyperlipidemia, thrombosis, hypertension, diabetes, and other metabolic diseases, with numerous clinical trials demonstrating its efficacy for treating these conditions.[11] The pharmacologic effects of garlic are attributed to allicin, ajoene, and other organosulfur constituents in the herb.[12] Efficacy of garlic compounds is determined by the ability of the product to produce allicin, the keystone constituent that yields the production of other active garlic components.

The hypocholesterolemic properties of garlic are not well-understood and the mechanism of action is not entirely clear at this time. A large portion of the research on garlic has yielded positive results, showing that garlic can modestly improve total cholesterol, LDL, and triglyceride levels.[13] Garlic preparations, used from 4 to 25, weeks will typically lower serum cholesterol by 4–12 percent, while conventional statin drugs lower serum cholesterol by 17–32 percent.[14]

One recent comprehensive study of hydrophilic and hydrophobic compounds of garlic elucidated the inhibitory potency of individual water- and lipid-soluble garlic compounds effects on cholesterol synthesis. Results from this study demonstrated that the cholesterol-lowering effects of garlic extract result mainly from inhibition of hepatic cholesterol synthesis of mainly water-soluble sulfur compounds.[15]

Another study probed further by examining the inhibitory effects at potential sites in the cholesterol biosynthetic pathway. Fresh garlic extract and 16 different water- and lipid-soluble garlic derivatives were studied in relation to purified recombinant human squalene monoxygenase. Squalene monoxygenase catalyzes the second step in the downstream pathway of cholesterol biosynthesis and is considered to be the rate-limiting step in this process. The results of this study indicated squalene monooxygenase as one of the target enzymes through which garlic inhibits cholesterol biosynthesis.[16]

In another study oriented toward establishing the cholesterol-lowering effects of garlic, rat hepatocytes were utilized to determine the effects of garlic preparations (petroleum ether, methanol, and water-extractable fractions from fresh garlic) on $^{[1\text{-}14C]}$acetate and $^{[2\text{-}3H]}$glycerol incorporation into cholesterol, fatty acids, and glycerol lipids. The study results suggested that garlic lowers cholesterol by mitigating hepatic cholesteogenesis while the triglyceride-lowering effect of garlic results from inhibition of fatty-acid synthesis.[17]



Left: *Allium sativum* (garlic); right: *Cynara scolymus* (artichoke).

Garlic and garlic extracts provide a highly cost-effective therapy for hypercholesterolemia, with minimal side-effects, with the most often reported ones being malodourous breath and body odor.

Artichoke

The extract of artichoke (*Cynara scolymus*) has the ability to reduce total serum cholesterol and LDL and to improve the LDL/HDL ratio.[18] New methods of action are continually being explained. While one study suggested a different method of action from the well-known one of lowering cholesterol by increasing its excretion in bile (and listed chemical contents that were thought to be responsible), another study suggested that inhibiting gastric emptying may lower cholesterol. Because of botanical medicines' ability to work via several different biochemical pathways to achieve the same result, the newer research covered in this article does not negate the idea that artichoke acts as a chalogogue.

The results of a study to determine the lipid-lowering effects of artichoke suggest that this occurs via an indirect modulation of hydroxymethylglutaryl-CoA-reductase activity.[19]

Furthermore, this study investigated many of artichoke's main active constituents and revealed that cynaroside and, more specifically, its aglycone luteolin were most responsible for inhibition, while chlorogenic acid was less effective and caffeic acid, cynarin, and dicaffeoylquinic acids exerted little hypocholesterolemic influences.

A methanol-derived extract from artichoke leaves was able to suppress triglyceride elevation in mice who were fed large amounts of olive oil; these active compounds were determined to be both sesquiterpenes (cynaropicrin, aguerin B, and grosheimin) and three newly discovered sesquiterpene glycosides (cynarascolosides A, B, and C).[20] Inhibition of gastric emptying was also shown to contribute to the antihyperlipidemic activity in this study. The side-effects of this plant are minimal, with flatulence being the

Natural Treatments for Preventing or Managing Coronary Heart Disease

- *Gugulipid extract*—standardized to 25 mg of guggulsterone per 500-mg tablet, three times per day
- *Fish oils (EPA + DHA)*—2–3 g per day
- *Garlic*—4000 µg of allicin per day
- *Artichoke*—500 mg of a standardized extract per day
- *Curcumin*—200–400 mg, three times per day, in between meals
- *Bromelain*—standardized to 1800–2000 milk-clotting units or gelatin-digesting units, 500 mg, three times per day, in between meals
- *B vitamins*—B_6: 10 mg per day; B_{12}: 400 µg per day; and folate: 1 mg per day
- *Vitamin E (mixed tocopherols)*—800 international units per day

EPA eicosapentaenoic acid; DHA = docosahexaenoic acid.

most-often reported consequence.[21] No other internal side-effects are mentioned in the literature but one external one—allergic contact dermatitis—did occur; this was attributed to cynaropicrin.[22]

The body of research for artichoke is fairly small at this time; however, it contains positive support for use of this plant as a reliable lipid-lowering agent.

Curcumin

A yellow pigment compound derived from the spice turmeric (*Curcuma longa*), curcumin and its structurally related compounds (curcuminoids) produce several pharmacologic effects, including anti-inflammatory, antioxidative, hypocholesterolemic, and anticarcinogenic activities. Precise mechanisms for the above actions have not been elucidated fully.

Curcuminoids are thought to exert a lipid-lowering effect, possibly as a result of alterations in fatty-acid metabolism.[23] Wistar rats who were fed a high-fat diet for 4 weeks, then placed on a diet containing curcumin (5 g/kg of body weight) had decreased serum levels of cholesterol and triglycerides, with increases in apolipoprotein A. This effect remained for an additional 2 weeks post-diet alteration.[24] There are several studies demonstrating similar effects on animal lipid models but human studies are infrequent. Based on these models, however, curcumin may be a useful tool helping to prevent or manage atherosclerotic diseases.

Markers of Inflammation

C-Reactive Protein and Fibrinogen

CRP, an emerging marker of CHD risk, is a nonspecific acute-phase reactant protein for which the concentration in serum becomes increased in response to inflammatory stimuli. High values are noted in early bacterial infections, active rheumatoid disease, Crohn's disease, and acute myocardial infarction, and following trauma. In patients with ischemic chest pain, elevated CRP is associated with a negative prognosis upon hospital admission. In seemingly healthy individuals, elevated CRP indicates an increased risk of atherosclerotic disease and reflects a chronic inflammatory process of the cardiovascular system.

In particular, high-sensitivity CRP (hsCRP) is considered to be a promising marker of CHD and is interrelated with risk factors such as age, obesity, tobacco use, blood pressure, and dyslipidemia.[25] An elevated CRP level is normally treated with aspirin prophylaxis and hyperlipidemia medications, or "statins." While obesity is, itself, a well-known risk factor for CHD, lowering CRP via lowering body fat will decrease CRP and CHD. In particular, high-sensitivity hsCRP is considered to be a promising marker for CHD and is interrelated with obesity and other risk factors such as age, tobacco use, blood pressure, and dyslipidemia.[1,25]

This being said, complementary and alternative practitioners view CRP as yet another risk factor for CVD in patients that do not manifest the other pathologies that cause elevated CRP. Because current medical opinion does not place CRP decidedly as a definitive cause of CVD, this marker can only be looked upon as a potential warning sign for future disease.

Fibrinogen

Fibrinogen is independently, consistently, and vigorously associated with risk of CVD, based on multiple prospective epidemiologic studies and clinical observations.[26] The reasons for elevation of fibrinogen in CVD are not well-elucidated yet; however it has been speculated that cellular components involved in the atherosclerotic process produce cytokines that belie an acute-phase reaction, leading to increased fibrinogen levels. The role of fibrinogen in the etiology of CVD is yet to be determined. Even so, fibrinogen is an important cardiovascular disease marker.

With the knowledge that CRP and fibrinogen are signatures of inflammatory processes in the body, ACM practitioners use these markers as a sign that the body is creating inflammatory processes in the cardiovascular system and treatments are geared toward lowering levels of these markers in the body. The inflammatory process is considered to be the premier etiologic event that initiates the development and propagation of the atherosclerotic process.[27] Elevated CRP and fibrinogen levels are indirectly treated with an overall anti-inflammatory approach, involving diet, supplementation, and botanical medicines.

Treatments for Inflammation

Fish Oils

The anti-inflammatory effects of fish oils and fish oil supplementation have been widely studied with positive findings for managing chronic inflammatory diseases, such as asthma, rheumatoid arthritis, dermatologic diseases, and antioxidant therapy. In addition, this research has demonstrated the effectiveness of fish oils on CRP levels.

A study involving 269 patients evaluated baseline levels of CRP, granulocyte membrane content of n-3 polyunsaturated fatty acids derived from fish, and angiographic findings. Subjects with lower CRP levels had significantly higher contents of docosahexaenoic acid (DHA) in granulocytes than subjects with higher CRP levels. The study hypothesized that, based on the inverse correlation between CRP and DHA, an anti-inflammatory effect of DHA suggests a novel mechanism by which fish consumption may decrease the risk of coronary artery disease.[28]

A vegetarian diet, or a diet supplemented with fish oils, provides improvement in patients with chronic inflammatory diseases, leading these oils to be useful for treating patients who have elevated CRP levels. Investigators studied the effects of an anti-inflammatory diet providing less than 90 mg of arachidonic acid (AA) per day and 30 mg of fish oil per kg of body weight on fatty-acid composition of erythrocyte lipids, eicosanoids, and inflammatory cytokines. Compared to baseline measurements, the treated subjects' erythrocyte lipids contained higher amounts of eicosapentaenoic acid (EPA) and had decreased formation of leukotriene B4, 11-dehydrothromboxane B(2), and prostaglandin metabolites.[29]

A diet low in AA supplemented with EPA can decrease physiologic markers of inflammation, providing a basis for treatment in patients with elevated inflammatory cardiovascular markers such as CRP.

Vitamin E

α-Tocopherol is another widely researched adjunctive therapy, with various effects throughout the body and on inflammatory diseases. A powerful antioxidant with several anti-atherogenic effects, much attention has been focused on vitamin E lately in the prevention and treatment of cardiovascular disease. Vitamin E exerts beneficial effects on LDL oxidation, proinflammatory cytokines, and CRP levels.[30]

Providing patients with 1200 international units (IU) per day of α-tocopherol significantly lowered interleukin-6 and hsCRP levels in a 5-month study.[31] Other studies have shown a direct dose–response effect of up to 1200 IU of vitamin E on anti-inflammatory effects and inhibition of CRP.[32]

In another study, 1200 IU of vitamin E reduced elevated CRP levels by 33 percent in control subjects who were nondiabetic and by 25 percent in patients with type 2 diabetes after 3 months of supplementation.[31] A similar trial with 800 IU of vitamin E reduced CRP levels by 48 percent in 4 weeks.[33] Supplementation with α-tocopherol is considered to be therapeutically safe, even at 1200 IU.[34] The evidence on the efficacy of α-tocopherol for treating CRP is impressive and use of this supplement is clearly warranted.

Garlic

In addition to lowering lipid levels, garlic shows promise for treating platelet-function discrepancies related to CVD. An aged extract of garlic was shown to exert inhibitory effects on platelet aggregation and adhesion to fibrinogen at all levels of supplementation in the course of one study.[35] In a different study, platelet adhesion to fibrinogen was decreased by approximately 30 percent compared to placebo in subjects whose blood was studied in a laminar-flow chamber.[36] Because of this herb's platelet inhibitory capabilities, its use for treating elevated fibrinogen makes garlic even more useful for prevention or treatment of CVD.

Bromelain

Bromelain includes a grouping of sulfhydryl proteolytic enzymes obtained from the pineapple plant (*Ananas comosus*). Bromelain is typically derived from either the fruit or stem of the plant, with most commercial sources being derived from the stem. In addition to a proteolytic portion, bromelain contains peroxidase, acid phosphatase, and protease inhibitors. It is interesting to note that the purified proteolytic fraction has been shown to be physiologically inactive whereas whole bromelain extract inhibits platelet aggregation, fibrinolytic activity, anti-inflammatory activity, and cytokine modulation as well as producing mucolytic effects and cardiovascular and circulatory improvements.[37]

The fibrinolytic activity of bromelain is thought to be the result of the conversion of plasminogen to plasmin, limiting the coagulation cascade by degrading fibrin.[38] Bromelain acts as a more efficient fibrinolytic in vitro compared to in vivo, possibly because of the antiprotease compounds found in plasma.[37] Bromelain produces dose-dependent decrease in serum fibrinogen, and at higher concentrations, prothrombin and activated partial thromboplastin time are prolonged.[39]

Homocysteine

Associated with increased risk of cardiovascular disease, elevated plasma levels of the amino acid homocysteine are affected by genetic, physiologic, and nutritional factors. Increased homocysteine levels are considered to be, collectively, an independent predictor for atherosclerosis and thromboembolism and are correlated with significant risk of coronary artery disease, myocardial infarction, peripheral vascular occlusive disease, cerebral vascular occlusive disease, and retinal vascular disease.[40] The association between homocysteinemia and CVD is causal, because an increase in plasma homocysteine precedes the onset of cardiovascular disease.[41] Desirable plasma levels are below 10 μmol/L. The plasma concentration ranges for mild, moderate, and severe homocysteinemia are, respectively 15–25; 25–50; and 50–500 μmol/L.

B Vitamins

Nutritional factors that can mitigate elevated homocysteine levels include vitamins B_{12}, B_6, B_2, and folic acid; the presence of these vitamins has been found to be inversely related to plasma homocysteine concentration, thus, combination therapy with these vitamins is an effective way to reduce homocysteine levels.[42] In addition to supplementation, patients are encouraged to consume green leafy vegetables and fruits, all food items that are rich in B vitamins and folate.

Homocysteinemia is a standard laboratory value that is treated similarly by both allopathic and naturopathic physicians, if not more vigorously by naturopathic physicians as a result of their particular view of nutritional status as a generalized health predictor.

Patients with homocysteinemia and known coronary artery disease are encouraged to take 1 mg per day of folic acid, 400 μg per day vitamin of vitamin B_{12}, and 10 mg per day vitamin of vitamin B_6 but the side-effects of this therapy are relatively unknown.[43] In addition, treatment of homocysteinemia also includes a low-methionine diet because homocysteine is an intermediate product of methionine metabolism in the body. Foods that are rich in methionine include cheddar cheese, eggs, chicken, and beef.

Conclusions

Phytochemical treatments for CVDs offer good methods for reducing unfavorable blood-related cardiovascular risk factors. Prevention, probably the best medicine for this grouping of diseases, is a major hurdle for medical practitioners of various types. Natural-based medicines may be used both prior to and following actual clinical diagnosis of heart disease and, with newer cardiovascular risk factors being identified and validated, nutritional treatments can play a major role in reducing these risk factors. □

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Chris D. Meletis, N.D., is a naturopathic doctor in private practice in Portland, Oregon.

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