# Phytonutrients & Nutritional Interventions
## *to*
## Support Cardiovascular Health & Wellness


*presented by*

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**INTRODUCTION**

Cardiovascular diseases (CVD) continue to remain the leading cause of morbidity and mortality in the developed world, with coronary heart disease (CHD) being rated as the number one killer, in the United States (AHA, 2008). Over the years, research has established the link between dietary fats (lipids), lipid transport and metabolism in the body, atherosclerosis (the progressive narrowing of the arteries over time), and cardiovascular disease.

Lipids present in the blood and tissues of the body include cholesterol, cholesterol esters, triglycerides, and phospholipids. Since lipids are insoluble in blood (plasma), they must be transported to and from the cells by special carrier molecules, the lipoproteins. Abnormal lipoprotein or lipid metabolism may induce hyperlipidemia, or "high cholesterol" and hypertriglyceridemia known to be etiological factors in cardiovascular disease. Dyslipidemias are defined as disorders of lipoprotein metabolism, including lipoprotein overproduction or deficiency. These disorders are generally manifested as elevated plasma levels of total cholesterol, low-density lipoprotein (LDL) cholesterol and triglyceride concentrations; and a decrease in the plasma high-density lipoprotein (HDL) cholesterol concentration. A condition characterized by small, dense LDL particles, elevated triglycerides, and low HDL, termed the "atherogenic triad", is characteristic of atherogenic dyslipidemia, often found in people with diabetes, metabolic syndrome and CHD (Chase, S.L, 2002).

High levels of low-density lipoprotein cholesterol (LDL-C) are particularly correlated with atherosclerosis and cardiovascular disease, based on evidence from clinical studies and epidemiological analysis. Multiple risk factors include cigarette smoking, hypertension, diabetes, and a low level of high-density lipoprotein cholesterol (HDL-C). Establishing healthy dietary and lifestyle practices is the first step in the intervention of CHD. Drug therapy is the regimen normally used for those that do not respond to lifestyle interventions, and for those facing a high short-term risk for heart disease.

Most therapeutic approaches target reducing LDL. However, studies in animal models show that over-expression of apolipoprotein (apo) A-1, the major HDL lipoprotein, inhibits progression and induces regression of atherosclerosis. Therefore HDL is an important target for therapeutic intervention, and low HDL-C levels are a modifiable risk factor for cardiovascular disease. Clinical studies in recent years revealed that increased HDL-C levels are associated with reduced risk of ischemic stroke in the elderly, and among different racial or ethnic groups (Sacco, SR et al., 2001). These data add to the evidence relating lipids to incidence of stroke, and support HDL-C as an important modifiable stroke risk factor. The mechanism by which HDL cholesterol inhibits atherosclerosis is not as yet completely clear.

The National Institutes of Health in the United States established a public health initiative, the National Cholesterol Education Program (NCEP) in 1985. As part of this effort, the NCEP Adult Treatment Panel I (NCEP-ATP I) developed its first set of guidelines, in 1988, establishing clear goals for patients with lipid abnormalities. These initial recommendations were revised in 1993; with more emphasis on HDL levels, healthy body weight, and physical activity.

A third set of guidelines, was released in May 2001, (III Report of the NCEP) reflecting changes in calculating coronary risk and in the management of hypercholesterolemia. These changes were necessitated by the fact that earlier guidelines, though fairly aggressive, did not cover the entire group of individuals at risk of CHD. Based on these new guidelines, the number of patients with cholesterol levels that can be classified as abnormal has now tripled. The guidelines recommend complete lipoprotein profile (total, LDL, HDL, triglycerides) as preferred screening for assessing CHD risk status. LDL remains a primary target of cholesterol-lowering therapy, along with increased emphasis on optimal HDL levels. Diabetics without CHD have been added to the at-risk group and patients with metabolic syndrome (insulin resistance) are advised intensive therapeutic lifestyle changes. The panel presented a

revised classification of dyslipidemias and also recommended, and outlined dietary and therapeutic measures, along with thresholds for the initiation of pharmacological therapy. Natural approaches, such as the use of plant sterols/stanols as a therapeutic dietary option to lower LDL cholesterol levels formed part of these recommendations.

As NCEP guidelines have been changed to include a global measure for CHD risk, risk status and treatment measures adopted for some patients, may be different as compared to the earlier guidelines. Essential approaches to combat a leading killer disease through helping patients achieve the new target levels include continued educational efforts, improvements in clinical practice, as well as effective and safe therapeutic agents, supported by adequate lifestyle and dietary interventions.

**LIPOPROTEINS, DYSLIPIDEMIAS, AND CVD RISK** (ENAS, EA, 1999)

The six major classes of plasma lipoproteins are:

- ***Chylomicrons***: that transport dietary cholesterol and triglycerides to muscles and other tissues.
- ***Very low-density lipoproteins*** (VLDL): Particles synthesized by the liver that transport triglycerides to muscles and to fat tissue.
- ***Intermediate density lipoproteins (IDL)***: Particles formed when the triglyceride portion of the VLDLs are removed. IDLs are either converted to LDLs or directly taken up by the liver.
- ***Low-density lipoproteins (LDL)***: Particles that are the primary plasma carriers of cholesterol. LDL is also known as the "bad cholesterol" because excess LDL cholesterol in the blood with other substances can form atherosclerotic plaques
- ***High-density lipoproteins (HDL)***: HDL is known as the "good cholesterol" because it mediates the removal of cellular cholesterol carrying it away to the liver for subsequent excretion A high HDL level is associated with a lower risk for coronary heart disease (CHD).
- ***Lipoprotein (a) (Lp(a))***: Particle similar in composition to LDL with an additional apoprotein, apo(a), covalently linked to apo B. Lp(a) is called the "deadly cholesterol" reported to be 10 times more dangerous than low-density lipoprotein (LDL) and 15 times more potent than total cholesterol. Factors influencing Lp(a) levels include race, ethnicity, and genetics. Compared to LDL, Lp(a) preferentially deposits in the human atherosclerotic tissues, restricting blood flow and encouraging clots.

**RISK LEVELS FOR HEART DISEASE**

Ever since Fredrickson and Lees proposed a system for phenotyping hyperlipo-proteinemia in 1965, clinical laboratories use electrophoresis to determine the risk level for coronary heart disease. Lipoproteins can be electrophoretically separated into alpha (HDL), pre-beta (VLDL), and beta (LDL) lipoproteins, with a distinct chylomicron band sometimes visible. Most HDL-C is carried by alpha-lipoproteins, most LDL-C is trans-ported by beta lipoproteins and most endogenous triglyceride is carried by pre-beta lipo-proteins. Thus in most cases, beta is increased with high LDL cholesterol levels, and pre-beta is increased with high endogenous triglyceride levels, indicating increased risk for cardiovascular disease.

C-reactive protein originally discovered in the serum of pneumonia patients and so named because it binds to a polysaccharide in pneumococcal cell walls, is an acute phase reactant used as an index of inflammation in clinical laboratory testing. This protein is produced by the liver in response to acute inflammatory conditions. Both C-reactive protein and low-density lipoprotein (LDL) cholesterol levels are elevated in persons at risk for cardiovascular events. Recent studies suggest that blood levels of myeloperoxidase (MPO) are elevated as well (Renliang, Z. et al., 2001).

In recent years, medical opinion considers inflammation of atherosclerotic plaques, and the subsequent formation of blood clots on the surface of these plaques, as critical events that lead to most atherosclerosis induced cardiovascular events. A clinical study revealed that hsCRP (high sensitivity C-reactive protein) test appeared to correlate more closely with already established cardiovascular disease risk factors than did the LDL test alone (Ridker, PM et al, 2001).

**CURRENT THERAPEUTIC AGENTS**

The role of therapy is to enable the patient to achieve target blood lipid and lipoprotein levels based on the ATP III guidelines. Drugs are administered if lifestyle and dietary approaches alone do not suffice. A therapeutic or nutraceutical agent essentially serves to modulate lipid absorption or affects lipid or lipoprotein metabolism, at different points in the metabolic pathway. An overview of therapeutic and dietary agents that are currently available to address lipid lowering is presented here.

***Statins:***

Most current therapeutic approaches seek to lower LDL-C. The discovery of statins was a major milestone in lipid lowering therapy. Statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, the rate limiting enzyme that catalyzes the conversion of HMG CoA to mevalonate in the liver cells. Mevalonate is the precursor molecule for cholesterol, Coenzymes Q and squalene (an intermediate in cholesterol synthesis). The decrease in cholesterol intracellular level induces a higher surface expression of LDL receptors which consequently increases the clearance of plasma LDL cholesterol. Intermediate-density lipoproteins and very low-density lipoprotein (VLDL) remnants are removed as well, contributing to lowering triglyceride-rich lipoprotein levels (Anon., 2002).

Statins are the most powerful drugs for lowering LDL, facilitating dose-related reductions in LDL ranging from 20-60%. Fluvastatin is reported to be the least potent, (Anon. 2002) decreasing LDL levels by only 22-36% at the maximum recommended dosage. The new member, Rosuvastatin is reported to be the most potent, reducing LDL levels by up to 65% (in a dose range of 20-80 mg/day), in clinical studies.( Olsson AG, et al., 2001; Paoletti R, et al., 2001). Statins also have moderate effects on HDL, raising levels by approximately 5%, and decrease triglyceride concentrations to a maximum of about 30%. (Vega GL,et al.,1990; Broyles FE, et al. ,1995) Statins show remarkable efficacy in reducing major coronary events and mortality rates in patients with CHD (Scandinavian Simvastatin Survival Study Group, 1994).

Unfortunately, the mechanism of action of statins through inhibition of the mevalonate pathway inhibits the biosynthesis of vital biochemical products of this loop, including coenzyme Q10 (CoQ10). In humans, CoQ10 or ubiquinone (2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzoquinone), is a major participant in electron transfer during oxidative phosphorylation in the mitochondria, a potent antioxidant and free radical scavenger, and a membrane stabilizer that preserves cellular integrity. These functions are particularly relevant to cardiovascular health, leading to the logical conclusion that patients on long-term statin therapy should receive supplemental $CoQ_{10}$ (Bliznakov, EG., 2002).

Statins in general are well tolerated with a low risk of adverse drug reactions (< 0.1%) and few drug-drug interactions. According to literature reports, myalgia and myopathy occur in 2% and 0.5% of patients, respectively, with less than 0.1% of cases progressing into rhabdomyolysis, which may be associated with acute renal failure. Myopathy appears to affect 0.1-0.3% of patients treated with lovastatin, atorvastatin, or simvastatin and less than 0.1% treated with pravastatin and fluvastatin. The risk is higher with cerivastatin, which was withdrawn from the market in August 2001 after reports of 31 deaths from rhabdomyolysis, most often in elderly patients who were also taking fibrates. The U.S. Food and Drug Administration (FDA) labeling information recommends liver function testing before and 12 weeks after starting statin therapy (Chad R. Worz, et al. 2003).

***Other lipid-lowering agents:***

Besides statins, other current lipid-altering agents that lower LDL-C primarily through increased hepatic LDL receptor activity include, bile acid sequestrants/resins and cholesterol absorption inhibitors such as ezetimibe. Natural approaches such as plant stanols/sterols, polyphenols, as well as phytonutrients such as oat bran, psyllium and soy proteins are also reported to lower LDL-C (Bays, H, et al., 2003).

Fibrates (including bezafibrate, gemfibrozil and fenofibrate) are a group of lipid lowering drugs that have been in existence for over 40 years. They are usually used in patients with mixed or combined hyperlipidemia and hypertriglyceridemias. Fibrates are reported to decrease plasma triglycerides by decreasing their hepatic synthesis and increasing their catabolism. They decrease the triglyceride-VLDL synthesis through enhancing beta-oxidation of fatty acids in the liver and increase the plasma triglyceride catabolism by inducing lipoprotein lipase gene transcription and decreasing the apoC-III gene transcription. Fibrates are reported to increase high density-lipoprotein (HDL)-cholesterol by increasing apoA-I and apoA-II gene transcription (Knopp RH, 1999).

Other current agents that are proven to beneficially affect lipid metabolism include nicotinic acid (niacin), acipimox, high-dose fish oils, antioxidants and policosanol. Drug combinations (fixed-dose) such as extended-release niacin/lovastatin are available, and current and future lipid-altering drugs may include anti-obesity agents which could favorably affect lipid levels, as well (Duriez P., 2003).

Historically, niacin was avoided in patients with diabetes due to its potential to increase blood glucose levels. Two recent studies, however, suggest that lipid-modifying dosages of niacin can be given safely to patients with diabetes and that the drug may be considered an alternative to statins or fibrates in those in whom these agents are not tolerated or who have high triglyceride or low HDL levels despite therapy. Niacin potentially improves all components of the atherogenic triad, often present in patients with diabetes (Chad R. Worz, et al. 2003).

**PHYTONUTRIENT & DIETARY APPROACHES TO MAINTAINING CARDIOVASCULAR HEALTH AND WELLNESS**

The American Heart Association recommends a daily intake of 20–35 g of dietary fiber/day for healthy adults. However, reports suggest that the average American diet only supplies about 15.6 g of dietary fiber/ day. Soluble or viscous fibers reduce LDL cholesterol levels to some extent, while insoluble fiber may decrease cardiovascular disease risk. A wide range of natural fibers ingredients are available for supplementation. Natural sources include fenugreek, psyllium, whole grains (such as oat bran) and fruit (such as berries) sources. One study examined the association between dietary fiber and serum concentration of C-reactive protein (CRP), and found that dietary fiber intake was inversely associated with serum CRP concentration. (Ajani, UA et al, 2004). Adequate levels of magnesium are also critical to cardiovascular health and wellness (Champagne CM, 2008).

Health claims approved by the FDA in labeling the benefits of functional food products, to support cardiovascular health include:

- ✓ Diets low in saturated fat and cholesterol and high in fruits, vegetables, and grain products that contain fiber "may" or "might" reduce the risk of heart disease; "may" or "might" reduce the risk of heart disease
- ✓ Daily dietary intake levels of soluble fiber sources that have been associated with reduced risk coronary heart disease are: (a) 3 g or more per day of [beta]-glucan soluble fiber from either whole oats or barley, or a combination of whole oats and barley. (b) 7 g or more per day of soluble fiber from psyllium seed husk.

- ✓ The daily dietary intake level of soy protein that has been associated with reduced risk of coronary heart disease is 25 grams (g) or more per day of soy protein.
- ✓ Scientific evidence demonstrates that diets that include plant sterol/stanol esters may reduce the risk of CHD.
- ✓ Diets low in sodium "may" or "might" reduce the risk of high blood pressure;

*Qualified health claims* permitted for dietary supplements/functional foods to support cardiovascular health that may appear on labels, with appropriate disclaimers mandated by the FDA pertain to:

- ✓ Nuts & Heart Disease
- ✓ Walnuts & Heart Disease
- ✓ Omega-3 Fatty Acids & Heart Disease
- ✓ Monounsaturated Fatty Acids From Olive Oil, and Coronary Heart Disease
- ✓ B Vitamins & Vascular Disease

Plant sterols/stanols, (Jenkins, DJ et al., 2003) polyphenols, natural antioxidant herbal extracts such as curcuminoids from turmeric (Soni KB, et al., 1992), viscous fiber such as oat bran (Berg, A. et al., 2003), saponin-rich seed extracts from fenugreek (Gupta, A. et al., 2001), and seed proteins such as soy protein (Wagner, JD et al., 2003) have been shown to be beneficial in lipid lowering. Natural actives that support the management of a healthy body weight and composition, and normal blood pressure levels are also included in formulations for cardiovascular health and wellness. Recent research has shown that many of these actives work at the molecular level in the body and favorably influence cardiovascular health.

In a landmark study reported in 2002, (Urizar, NL, et al., 2002) US researchers unraveled the potential mechanism of action of guggulsterones, the biologically active components of the resin of guggul (*Commiphora mukul*) used in traditional Ayurvedic medicine

to treat inflammation, arthritis, cardiovascular conditions and obesity. Guggulsterone-rich extract of guggul is thought to have beneficial effects on blood lipid levels due to antioxidant action on oxidized LDL, improvement of insulin sensitivity reduction in blood glucose levels, reduction in lipoprotein (a) (Lp(a)) levels and increased fecal excretion of bile acids and cholesterol from the intestine. Guggulsterones were shown to be antagonist ligands for the bile acid receptor FXR, which is an important regulator of cholesterol homeostasis in the body. Scientific studies on guggul began almost 40 years ago when an Indian researcher, G.V. Satyavati was intrigued by the strong parallels between modern concepts on the etiology of atherosclerosis and obesity, and descriptions in the Sushruta Samhita written in the 5th to 4th century B.C.

Cardiovascular disease is currently seen as a process where multiple lipid fractions, not only LDL, play an important role. The most recent considerations in therapy of high cholesterol include indices of inflammation, C-reactive protein (hsCRP), levels of uric acid and lipoprotein(a). In clinical studies, Gugulipid®[1] was shown to significantly benefit the combination of factors. (Badmaev, V et al, 2003).

Policosanol (Gouni-Berthold I, et al, 2002) is a natural mixture of higher aliphatic alcohols, found in plant waxes. Sugarcane wax is the common source. The components of policosanol include 1-octacosanol, 1-dotriacontanol, 1-tetracosanol, 1-tetratriacontanol, 1-hexacosanol, 1-heptacosanol and 1-nonacosanol. This mixture of alcohols is clinically proven to be effective in maintaining normal cholesterol levels.

*In vitro* studies, studies on animal models and clinical studies published in literature reveal that Policosanol beneficially affects cholesterol metabolism. In clinical studies, Policosanol was shown to be effective in lowering both total cholesterol and LDL-C and increase the levels of HDL-C. Other beneficial effects include inhibition of platelet aggregation, which in turn is helpful in maintaining cardiovascular health. A comparative study with the commonly used Lovastatin on subjects suffering from intermittent claudication revealed the superior benefits of policosanol.

Effects on cholesterol metabolism and antioxidant effects that prevent the oxidation of LDL cholesterol are reported to be responsible for its healthful effects of policosanol. In vitro studies

[1] A trademark of Sabinsa Corporation

revealed that policosanol may inhibit cholesterol synthesis in the liver but direct inhibition of the hydroxy-methylglutaryl-coenzyme A reductase (which is the mechanism of action of statins) is unlikely. Animal studies suggest that LDL break down may be enhanced, but the precise mechanism of action has not as yet been completely elucidated.

At doses of 10 to 20 mg per day, policosanol was found to lower total cholesterol by 17% to 21% and low-density lipoprotein (LDL) cholesterol by 21% to 29% and raise high-density lipoprotein cholesterol by 8% to 15%. Daily doses of 10 mg of policosanol were shown to be equally effective in lowering total or LDL cholesterol as the same dose of simvastatin or pravastatin, although it did not affect triglyceride levels. Policosanol was found to effectively lower platelet aggregation with efficacy comparable to aspirin at a dose level of 20 mg, with a combination of Policosanol and aspirin being more efficacious (Arruzazabala ML, et al., 1997) at dosages of up to 20mg per day, policosanol is reported to be safe and well tolerated, even in long-term studies (Gouni-Berthold I, et al, 2002). Most of the successful studies were done with policosanol from Cuban sugarcane. However, a recent study done with policosanol obtained from sugarcane grown in India revealed significant benefits in lipid lowering in human subjects of South Asian origin (Majeed, M et al, 2007).

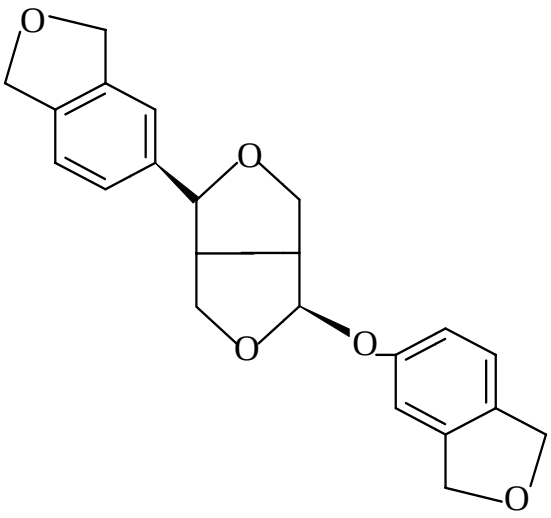
Spices such as turmeric and ginger provide natural compounds that support cardiovascular health and wellness. Curcuminoids, the yellow pigment in turmeric roots benefit cardiovascular health in several ways. Providing antioxidant (bioprotectant) support, anti-inflammatory support, anti-platelet aggregation support and positively influence lipid metabolism, (Majeed, M et al, 1995), increasing HDL-C levels while lowering LDL-C levels and triglyceride levels (Soni KB et al, 1992).

The active constituents of ginger, gingerols, and shogaols are effective antioxidant and anti-inflammatory compounds. Ginger extract has also been shown to lower LDL-C, and have anti-platelet aggregation and vasodilatory effects. Aqueous ginger extract was recently shown to lower elevated blood pressure levels. The authors of this study postulate that the hypotensive action occurs through a dual inhibitory effect mediated via stimulation of muscarinic receptors and blockade of calcium ion channels (Ghayur, MN et al, 2005; Thomson, M et al; 2002).

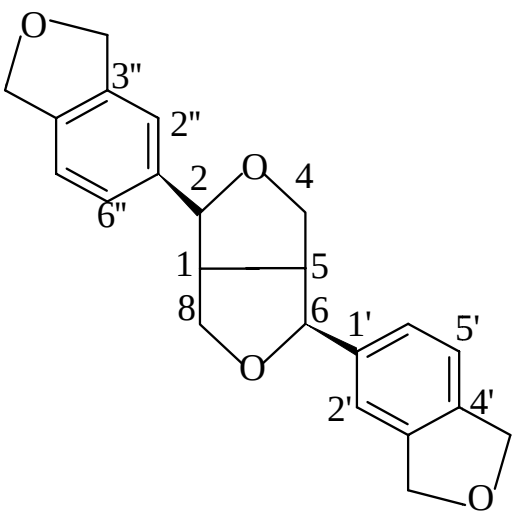
With reference to oils and fats, Scientists are now of the opinion that just as there is "good" cholesterol, there are also good saturated fats. Nearly two thirds of the saturated fat in coconut oil

are Medium Chain Triglycerides (MCTs) ($C_8$ to $C_{14}$). A 30 day clinical study revealed significant beneficial effects of MCT (in the form of functional oil), as compared to LCT (as olive oil) on body composition, energy expenditure, energy intake and subjective appetite (Papamadjaris, JA et al., 2000).

The lignan compound sesamin and its derivative sesamolin are the major biologically active constituents in sesame seed oil that enhance the oxidative stability of the oil. Sesamin is reported to inhibit the micellar solubility of cholesterol and liver microsomal HMG CoA reductase activity. Sesamin and sesamolin significantly decreased the concentration of serum total cholesterol and very low density lipoprotein (VLDL) in laboratory studies. Sesamin with vitamin E significantly suppressed age related elevation in blood pressure and showed vasodilatory effects in animal models (Hirose N., et al., 1991; Sawada R.U., et al., 1995; Noguchi T., et al., 2004).




**Sesamin**




**Sesamolin**

**PERSONALIZED NUTRITION AND CARDIOVASCULAR HEALTH**

A study on individuals with exceptional longevity, and their offspring revealed that these individuals have significantly larger HDL and LDL particle sizes. This phenotype is associated with a lower prevalence of hypertension, cardiovascular disease, the metabolic syndrome, and increased homozygosity for the I405V variant in CETP. These findings suggest that lipoprotein particle sizes are heritable, and encourage a healthy aging phenotype (Barzilai N et al., 2001). In recent years, the hypothesis that peroxidation of LDL may be an initial step in the atherosclerotic process and the discovery of the body's inherent antioxidant enzyme, paraoxanase, principally associated with HDL has triggered a whole new area of research. (Canales, A., 2003) Perhaps it would be possible to beneficially manipulate the induction and activity of this enzyme through dietary and lifestyle approaches.

The citrus flavonoids, naringin and naringenin, were found to significantly lower the expression levels of vascular cell adhesion molecule-1 (VCAM-1) and monocyte chemotactic protein-1 (MCP-1), with potential applications in the prevention of atherosclerosis. (Lee CH et al., 2001) Similarly, MMP-8 (matrix-metalloprotein 8) a collagenase enzyme expressed in atherosclerotic plaques is postulated to be a likely target for the treatment of cardiovascular disease. Phytonutrients that inhibit the expression of this enzyme would therefore be potentially useful in preventing cardiovascular problems.

From this perspective, genomic tools would enable individualized approaches to a healthy heart through lifestyle, nutritional and phytonutrient interventions, in the years to come.

**CONCLUSIONS**

This white paper presents a summary of some of the nutritional and phytonutrient interventions to support heart health. Several other natural actives and nutrients from traditional medicine are available for use in dietary supplements. A comprehensive approach to support healthy blood sugar, blood lipid and blood pressure levels that includes a healthy diet, exercise and lifestyle measures, in combination with supplemental nutrients, would be most conducive to cardiovascular health and wellness. Contact Sabinsa Corporation for further information on “heart healthy” natural ingredients and formulation guidelines.

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