# H-ONE: HEART DISEASE PREVENTION

1) Lifestyle and dietary strategies can help you avoid a host of diseases, but they are probably most effective in preventing heart disease. Recent research confirms that certain nutrients, specially **resveratrol, grape seed extracts, B vitamins** can provide **many heart-healthy benefits**.

## 2) What it is

What most people consider heart disease is really atherosclerosis- a buildup of fatty deposits(called plaque)within the walls of the arteries. As plaque grows, it hinders the flow of blood that carries oxygen and nutrients throughout the body. The tiny arteries that thread through the heart and nourish it with blood are particularly susceptible to plaque accumulation. If any of them become blocked, a heart attack can occur.

## 3) What causes it

The primary cause of atherosclerosis is high blood cholesterol levels. LDL("bad")cholesterol sticks to artery walls, and this accumulation eventually leads to plaque growth. High blood pressure, smoking, a sedentary lifestyle, obesity, and stress can also contribute to plaque buildup, as well as reduce the ability of the arteries to widen and constrict as necessary. In their younger years , men are at higher risk for heart disease than women, because estrogen may have a heart-protective effect. After menopause, however, women are as susceptible to heart disease as men.

## 4) Symptoms

In the early stages, heart disease has no symptoms. Warning signs include high blood cholesterol levels and high blood pressure.
In advanced stages, chest, arm, or jaw pain (especially after physical activity), palpitations, and shortness of breath.

## 5) When to take H-One, super anti-oxidants

If you have any symptoms of heart disease.
If you suffer unexplained dizziness, weakness, or faintness.
If you have skipped or extra heartbeats or other irregularities with any frequency.
If you have squeezing or crushing chest pain, accompanied by light-headness, nausea, or shortness of breath- this may be a sign of a heart attack.

## 6) H-One contains (A) **resveratrol**, (B) **grape seed extract**, (C) **B vitamins**.

## 7) Preventing Heart Disease of Grape Seed Extract

If there is a health villain which is well-known to Americans, it is cholesterol.
The media reminds us almost daily that fat and cholesterol are dangerous to health.
Any blood cholesterol reading above 200 mg/dL is considered to be in the undesirable range. And yet, again, we have the "French Paradox" in which the average Frenchman registers higher blood cholesterol levels than does his American counterpart, eats more saturated fat, smokes more, and yet suffers only

about 40% of our heart disease death rate. Clearly, then, something more than mere cholesterol levels are involved in the development of cardiovascular disease.

Chronic heart disease (coronary artery disease) is associated with modifications in fatty acid metabolism and excessive lipid peroxidation of low density lipoproteins (LDL). The LDL oxidation theory implicates this oxidation in the development of atherosclerotic plaques. These oxidation products are also implicated in the consequent formation of thromboxane, which leads first to enhanced platelet aggregation, then to artery blockage and to thrombosis. The accumulation of lipid oxidation products from LDL can be attributed to the low levels of plasma antioxidants. Dietary antioxidants such as OPC and other flavonoids along with antioxidants found in the body (endogenous antioxidants) may offer protection against LDL oxidation.

Even when wine extract containing OPCs (anthocyanins,etc.), were diluted 1000 times, their activity in inhibiting the oxidation of isolated human LDL far exceeded that of the vitamins C and E. OPCs can protect against oxidation in ways which otherwise would require vitamins C and E together, at perhaps 50 times the concentration of OPCs. This is not just due, perhaps, to grape seeds. Red wine also contains very potent antioxidant flavonoids coming from the grape skin, and white wine, properly prepared, can also exert significant protection from the same source.

The protective influence of wine components could be due to a hemostatic effect, the consequences of which could be decreased platelet reactivity and a diminution in the occurrence of atherosclerotic lesions. Nevertheless, an honest assessment must point out that studies in this area report controversial findings. A recent study of human volunteers concluded that the observed positive effect of red wine on hemostasis seems to be due to alcohol and not the nonalcoholic fraction in the red wine.

Both white and red wines have been reported to increase the levels of healthful HDL cholesterol(high density lipoprotein); red wine also raised triglyceride and total
cholesterol concentrations. The favorable effects of wines on plasma lipid and lipoprotein concentrations were suggested to be due to their alcohol content. Dealcoholized red wines were shown to inhibit the aggregation of platelets isolated from human subjects. However, there were no advantages found with red wine in volunteers who consumed red wine for four weeks, and the authors concluded that, *in vivo,*ethanol is the dominant anti-aggregatory factor.

In two studies, the protective role of red wine on atherosclerosis and coronary artery disease has been attributed to a polyphenol, trans-resveratrol, a stilbene. When polyphenolic constituents isolated from red, white and a white wine that was in contact with the grape skin before fermentation were added at the same concentration (in gallic acid equivalents), all of them showed antioxidant effects on isolated LDL. The last category of compounds had much higher antioxidant activity. If white wine is fermented in contact with the grape skin, it could gain higher antioxidant activity. White and red wines are consumed in Mediterranean countries. The lack of effect of white wine polyphenols on LDL oxidation in earlier studies was apparently due to low levels of these compounds present in the extracts inasmuch as quantitatively similar extracts of white and red wine were not used. (In assessing this information, it must be kept in mind that white wines seldom are fermented in a way which includes much contact with the grape skins.) In yet another study, healthy volunteers received either red or white wine in a randomized double-blind trial. The susceptibility of LDL isolated from these individuals to copper ion-induced oxidation was not altered; the potential plasma lipid peroxidation was estimated by assessing the concentrations of relative protective antioxidants, whereas in the earlier studies, total plasma lipid peroxidation was determined *in vitro* by measuring degradation products of lipid peroxidation. These incompatible results arise from contrasting testing methods, and it is still accurate to say that a reduction

in lipid peroxidation degradation products indicates that something significant is being accomplished through the consumption of the wine polyphenols.

In any event, the quality of antioxidant compounds present in the wine (and grape extracts) appears to be important, rather than merely the quantity of polyphenols present.

The importance of polyphenolic compounds can also be inferred from studies with teas. The incidence of atherosclerosis has been reported as extremely low in China,

where tea is consumed exclusively. Tea contains OPCs linked to gallates, as are found in grape seed. It is striking how tea consumption leads to rapidly increased plasma antioxidant activity in human volunteers. Tea catechin gallates have been detected in human plasma.

In addition to the presumed free radical-mediated damage, blood pressure can also contribute to arterial damage. One of the interesting observations about OPCs is their potential to lower blood pressure in animal studies. This was described above with regard to extracts of the Japanese persimmon, and similar results have been gathered with grape seed extracts. After administration of the most active of these fractions to rabbits, grape seed extracts had a slight (20%) modifying effect on blood pressure, presumed to be due to protein binding, a nonspecific effect. *In vitro* studies showed that grape seed extract had a positive effect on the tone of vascular smooth muscle in aortic rings isolated from rabbits. This is important for dilation of blood vessels.

8) Cardioprotective Properties of Resveratrol
Inhibits LDL oxidation and platelet aggrgation
Reduces serum cholesterol and triglyceride levels
Induces vasorelaxing effects
Inhibits tissue factor expression in vascular cells
Reduces myocardial infarction and ischemia-reperfusion injury
Stimulates endogenous adenosine release and protects against chronic ischemia

**Resveratrol** induces leukotriene production in human neutrophils by inhibiting 5-lipoxygenase and 15-lipoxygenase, enzymes involved in the metabolism of arachidonic acid to leukotrienes. These effects are independent of resveratrol's free-radical scavenging ability, since other more powerful antioxidants did not have the same effect. Leukotrienes are powerful mediators of inflammatory reactions and are thought to be involved in the cellular processes that contribute to atherosclerosis.

At a concentration of 10 mcM, resveratrol reduced thromboxane A2 production in human blood platelet cells by approximately 60%. Thromboxane A2 is a powerful eicosanoid produced from arachidonic acid and is involved in the propagation of blood platelet aggregation. Neither quercetin nor any of the other wine phenolics or antioxidants tested had any effect at this concentration.

**Resveratrol** inhibited adenosine diphosphate(ADP)- and thrombin-induced platelet aggregation of healthy human blood plasma in a dose-dependent manner. The IC50 concentrations were rather high, but were still three orders of magnitude lower than that of ethanol, even though the antiplatelet activity of athanol has been advanced as one of the mechanisms involved in protection against cardiovascular disease.

**Resveratrol** demonstrated an inhibitory effect on platelet aggregation due to its influence on arachidonate metabolism. Resveratrol lowered platelet aggregation of healthy human blood plasma by 50.3% at a concentration of 3.45 mcg per liter.

Red wine containing 1.2 milligrams per liter of natural *trans*-resveratrol and 3.6 grams per liter of polyphenols diluted 1,000-fold (final resveratrol concentration: 1.2 mcg per liter) inhibited platelet aggregation by 41.9%. By adding resveratrol to wine up to a concentration of 1.2 mcg per liter, inhibition was raised to 78.5%. These results suggest that the antiaggregating activity of resveratrol is related to its concentration in wine.

One hundred mcg per one milliliter *trans*-resveratrol also lowered serotonin release from "aspirinated" platelets activated by thrombin or cathepsin G. This suggests that *trans*-resveratrol does not primarily interfere with the formation of prostaglandins and thromboxane in platelets, and that its inhibitory effect may be added to that of aspirin.

In rats fed a high cholesterol diet, resveratrol inhibited cholesterol and triglyceride liver deposition, lowered serum triglyceride and low-density lipoprotein(LDL) cholesterol levels, reduced the atherogenic index (total cholesterol: high-density lipoprotein (HDL) cholesterol), and decreased the rate of hepatic triglyceride synthesis from (14C)-palmitate.

**Resveratrol** promoted both direct and indirect vasorelaxing effects on arterial vessels of rats by nitric oxide-mediated and non-nitric oxide-mediated mechanisms. At a concentration of 3 x 10(-5)M, resveratrol caused vasorelaxation that was reversed by a 1 x 10(-6)M concentration of nitric oxide synthetase inhibitor. At a higher concentration of 6 x 10(-5)M, resveratrol induced vasorelaxation that could not be reversed by nitric oxide synthetase inhibitor. This indicates that resveratrol acts directly on vascular smooth muscle cells.

Peroxidation of LDL cholesterol obtained from two healthy volunteers by 81% and 70% was inhibited upon the addition of 10 mcg per liter of resveratrol. By contrast, 10 mcg per liter of alpha-tocopherol (natural vitamin E0-which has been associated with a reduced risk of heart disease-had a much lower antioxidant potency than resveratrol, and inhibited LDL chloesterol oxidation by only 40% and 19%.

**Resveratrol** increased plasma and LDL polyphenols and enhanced antioxidant activity as judged by decreased plasma total peroxides, increased lag time, and decreased LDL lipid peroxides and lipid peroxidation in the copper-catalyzed peroxidation of LDL conjugated dienes.

Protykin, a natural extract of *trans*-resveratrol(20%) derived from the dried rhizome of *Polygonum cuspidatum,* demonstrated excellent *in vitro* peroxyl radical(generated by 2.2-azobis(2-amidinopropane) dihydrochloride) and hydroxyl radical (in a 7-OH-coumarin-3-carboxylic acid model) scavenging abilities; and provided significant cardioprotection *in vivo*. Myocardial protection of protykin was assessed *in vivo* to determine whether protykin could preserve the heart during ischemic arrest. In an *in vivo* ischemia-reperfusion model, three weeks of protykin supplementation to rats significantly improved postischemic left ventricular functions (dp, dp/dtmax) and aortic flow. It also reduced myocardial infarction (determined by TTC staining) and reduced malondialdehyde formation (a presumptive marker of oxidative stress) in the coronary effluent. Thus the researchers demonstrated that protykin offers dramatic cardioprotection, presumably by virtue of its potent free radical scavenging ability.

Polyphenolic compounds are known to possess antioxidant, anti-atherogenic, antithrombotic, and platelet antiaggregating activities. Very recently they have been shown to stimulate the release of adenosine, an endogenous nucleo-side. Adenosine is considered to be one of the mediators-perhaps the only mediator-of the most important spontaneous organic protection against chronic ischemia, a phenomenon known as "ischemic preconditioning." Following oral administration of a single dose of resveratrol(1.5 milligrams per kilogram of body weight) to ten healthy human volunteers, plasma adenosine levels increased

progressively and reached a peak 30 minutes after ingestion and then successfully decreased to the starting values at 120 minutes.

# (A) RESVERATROL

## Cardio-Protective Properties of RESVERATROL

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- **Reduces** serum cholesterol and triglyceride levels
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- **Inhibits** tissue factor expression in vascular cells
- **Reduces** myocardial infarction and ischemia-reperfusion injury
- **Stimulates** endogenous adenosine release and protects against chronic ischemia

**Resveratrol** induces leukotriene production in human neutrophils by inhibiting 5-lipoxygenase and 15-lipoxygenase, enzymes involved in the meabolism of arachidonic acid to leukotrienes (IC50 of 22.4 and 8.7 uM, respectively). These effects are independent of resveratrol's free-radical scavenging ability, since other more powerful antioxidants did not have the same effect. Leukotrienes are powerful mediators of inflammatory reactions and are thought to be involved in the cellular processes that contribute to atherosclerosis.

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## THE FRENCH PARADOX AND CORONARY HEART DISEASE

A resurgence of interest has recently been focused on the roles of wine, and therefore resveratrol, in the diet based on the phenomenon called "the French paradox." Early epidemiological studies indicated that in most developed countries, high dietary intakes of saturated fat, cholesterol, total fat, and total caloric intake correlate positively with mortality from heart disease. However, more recent and larger studies suggest the high-fat theory is not a major factor in heart disease. Epidemiological studies are difficult to interpret and they can sometimes be used as proof of an idea, when, in fact, all that can be obtained from them is a trend, but never direct proof.

However, St. Leger and his colleagues conducted an epidemiological study in 1979 that demonstrated a significant reduction in mortality from coronary heart disease with higher consumption of wine. French people are known to consume foods high in saturated fats and cholesterol, yet they have a low mortality rate from coronary heart disease. The discovery that the saturated fat intake in France is similar to that of other developed countries, while French mortality from coronary heart disease is only one-third the average of such countries, has become known as the French paradox. There are probably other important environmental factors that contribute to this paradox, such as total calrorie intake, exercise, or sugar intake, but wine consumption was the basis of this study.

The major risk factors of coronary heart diseases are high levels of LDL (low-density lipoprotein) in blood, hypertension (high blood pressure), obesity, smoking, and a sedentary lifestyle. The main causes of death from coronary heart disease are myocardial infarction (heart attack), increased thrombogenic activity (blood clots), and atherosclerosis.

Coronary heart disease may be defined as "atherosclerosis of the coronary arteries." Atherosclerosis causes cerebrovascular and cardiovascular disease, leading to ischemic stroke and myocardial infarction, respectively, and causes more than 40 percent of all deaths in Western civilization. Atherosclerosis is a disease that results in abnormally thickened regions of the vascular wall. These regions, called plaques, are characterized by typical proliferations of modified smooth muscle cells and deposits of large quantities of cholesterol in the form of "foam cells" just beneath the endothelium. As plaque development narrows arteries, decreased blood supply may cause damage to the heart or brain. Because the plaque is an abnormal surface, a clot may form on it and eventually block the artery, causing either a heart attack or stroke.

A clot is a web of threadlike fibrin molecules that forms a patch over the break in the blood vessel. Clots are dissolved naturally by plasmin, an enzyme formed from the plasma protein plasminogen. Tissue type plasminogen activator is capable of converting plasmin to plasminogen.

Arteriosclerosis is another type of mechanism that leads to narrowing of the arteries, but in this case the arteries become brittle and they are narrowed by calcification, without the presence of significant amounts of fats and cholesterol. This fact suggests that protection from wine, and therefore from resveratrol, is more important in reducing the oxidation of cholesterol than in reducing its amount in the blood.

## (B) GRAPE SEED EXTRACT

With antioxidant properties many times more powerful than vitamin C or vitamin E, grape seed extract is a heart-smart and cancer-smart botanical. It also has the power to improve vascular health and increase your well-being in myriad ways.

This extract from the tiny seeds of red grapes is a flavonoid and one of Europe's leading natural treatments. Plant substances with potent anti-oxidant potential, flavonoids protect the cells from damage by unstable oxygen molecules called free radicals. Grape seed extract contains procyanidolic oligomers (PCOs), also called proanthocyanidins. PCOs are believed to play an important role in preventing heart disease and cancer.

Grape seed extract exerts a powerful, positive influence on blood vessels. Not coincidentally, the active substances in this extract, PCOs, are key ingredients in one of the drugs most frequently prescribed for blood vessel (vascular) disorders in Western Europe.

Because it is both oil-and water-soluble, grape seed extract can penetrate all types of cell membranes, delivering antioxidant protection throughout the body. Moreover, it is one of the few substances that can cross the blood-brain barrier, which means it may protect brain cells from free-radical damage.

Major Benefits: With its powerful ability to enhance the health of blood vessels, grape seed extract may both reduce the risk of heart attack and stroke and also strengthen fragile or weak capillaries and increase blood flow, particularly to the extremities. For this reason, many experts find it a beneficial supplement for almost any type of vascular insufficiency, as well as for conditions that are associated with poor vascular function, including diabetes, varicose veins, numbness and tingling in the arms and legs, and even painful leg cramps.

## (C) B VITAMINS

While certain fats are certainly associated with high risk of heart disease, and while high cholesterol certainly increases the risk of arterial damage, there is a new story unfolding about the heart- a story whose discoveries may help us truly cut the risk of America's number one killer as well as a host of other conditions.

One and a half million heart attacks strike Americans each year, and half a million people die of heart disease annually. Cardiac disease will continue to ring out its death toll until we accept the whole truth, which is that high cholesterol alone is not the root of heart disease. In fact, many people die from heart attacks and coronary artery disease with normal or low cholesterol levels.

Meanwhile, a special derivative of an amino acid called homocysteine lurks in the shadows, letting cholesterol take the blame as it stealthily sabotages our arteries. Homocysteine is derived from an amino acid called methionine. Methionine is found in many foods, like garlic, onions, legumes, fish, eggs, and meat. A process called transsulfuration turns methionine into homocysteine.

Physicians who practice natural therapies are not the only ones taking note of homocysteine's dangers: A 1997 study in the *New England Journal of Medicine,* one of the most respecteed journals in traditional medicine, confirms that increased plasma levels of homocysteine confer an independent risk of vascular disease. This means that even if you are a healthy person with normal cholesterol levels, no family history of illness, and good eating habits, high levels of homocysteine in your body can predispose you to heart disease. And this predisposition to heart risk is powerfully increased if you smoke or have hypertension.

As a pathologist at Havard Medical School, Kilmer McCully made a series of intriguing observations about homocysteine and our hearts. Two children had died of a genetic disorder called homocystinuria, which is commonly associated with elevated homocysteine levels. Strangely, autopsies showed that these youngsters had a severe degree of arteriosclerosis, or hardened arteries- a condition normally seen only in much older individuals.

McCully hypothesized that this arterial damage was caused by excess homocysteine and might also occur in other people who had elevated levels of the amino acid but not the genetic disorder. This was such a radical departure from the accepted cholesterol theory of heart disease that it got him thrown out of Havard. He ended up working at a small veteran's hospital in Rhode Island.

# Getting to the Heart of Homocysteine

Homocysteine is created from-and related to-several quite innocuous compounds, like the amino acid methionine. It can be changed in two directions: it can use vitamin B6 to change into two other important amino acids, cysteine and taurine, or it can use vitamin B12 and folic acid to return back to its methionine form. In a normal, healthy body, homocysteine is just a brief intermediate step between methionine, cysteine, and taurine.

But in as many as one in four victims of heart disease, that step is not so brief. If our levels of vitamin B6, B12, or folic acid are low, then homocysteine cannot be transformed back into these safe substances, and it accumulates to dangerous amounts. Some inviduals may have a genetic predisposition to elevated homocysteine levels and may need extra B vitamins.

Homocysteine causes damage to the lining of the arteries and any low density lipoprotein(LDL) cholesterol that might be found there. And this is why LDL cholesterol-often known as "bad" cholesterol-is to harmful: not because it is the root of coronary artery disease, but because, when oxidized, it causes free radical damage and makes arterial disease worse. Homocysteine may well be the root of much coronary artery disease. Think of homocysteine as the creator of potholes in the walls of the arteries; and when fat or cholesterol surround these potholes, they clumsily plug up the hole, further aggrevating the damage.

The current mainstream treatment for heart disease includes coronary bypass surgery, literally a chest-splitting procedure; angioplasty, which inflates your vulnerable arteries like baloons to deflect cholesterol plaques; and numerous potent medications with various side effects.

Although the big news is that homocysteine, and not just cholesterol, is a major independent risk factor for cardiovascular disease, there are many other ways that this amino acid exerts its harmful effects. Heart disease is just the first.

Heart Disease: An amazing number of conclusive studies clearly demonstrate that high levels of homocysteine can increase your risk of heart disease, including myocardial infarctions and coronary artery disease. A recent report in the journal *Arteriosclerosis, Thrombosis, and vascular biology* stated that for every 10 percent increase in homocysteine levels, heart disease risk increases by the same amount. Similary, a study in *JAMA* showed that, of 1,500 men and women, the ones in the top 20 percent of homocysteine levels had double the risk of heart disease. However, in 1998, a study in the journal *circulation* showed homocysteine levels were not found to be an independent risk factor coronary heart disease. More research will be necessary.