

THE HEALTH
BENEFITS OF
M e g a N a t u r a l G o l d TM

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THE FRENCH PARADOX:

DO WINE COMPONENTS PROTECT AGAINST HEART DISEASE?

These days we are hearing a lot about the potential benefits accruing from red wine consumption. The popular press also carries stories on the beneficial constituents of red wine. People in Southern France consume more fatty foods in comparison to those in North America. And yet, they suffer less from heart diseases than people in North America or in the Northern regions of Europe do. This incompatibility of a diet rich in fatty foods with a decreased risk of heart diseases bears the name "The French Paradox". France and Italy are the two major wine-producing European countries. People in Southern France drink red wine regularly along with their meal. For a long time, people held that the alcohol in the red wine was the protective factor against heart diseases and would explain the French Paradox. However, recently there is an increasing interest in the potential role of non-alcoholic substances found in red wine in the protection against heart diseases. In particular, scientists have increasingly turned their attention toward a family of natural substances called "polyphenols", which are only found in plants and are abundant in grapes. In particular, one could clearly attribute the potential beneficial effects associated with red wine consumption to the increased intake of chemical substances originating from the red grape skin and seed grouped as polyphenols. The question arises as to how these compounds can protect against the onset of heart diseases. The answer lies in their intrinsic biochemical properties. Scientists consider that the modification of fats such as cholesterol in the blood vessels is a prime factor in the initiation of heart disease. One such modification is oxidation. Grape and wine polyphenols possess the capacity to retard this process of oxidation by acting as antioxidants. Another critical factor involved in the healthy functioning of blood vessels is the control of blood pressure and the avoidance of blood clots, which affect blood flow in the vessels. Polyphenols possess the capacity to relax the smooth muscles of these blood vessels. This could be important in reducing blood pressure and the risk of clotting.

GRAPE AND WINE POLYPHENOLS AND HEART DISEASE PREVENTION

Cholesterol is a basic ingredient of the body essential to our well being. Our bodies manufacture it from the diet (fatty acids), guaranteeing that we always have a readily available supply. Since cholesterol is a fat it does not mix with water. Blood helps to transport cholesterol through the body. Cholesterol wraps itself in layers of proteins, forming lipoproteins.

Lipoproteins surround cholesterol and prevent it from coming into contact with water. These are microscopic particles containing cholesterol and they travel to different organs of the body. Low density lipoproteins (LDL) carry cholesterol to the body's cells, where they can be stored, incorporated into the covering of the cell membranes or utilized to make vitamin D or other important substances like hormones.

Cholesterol and other fats undergo changes in the body. One such modification is LDL oxidation, and this is believed to be involved in the development of heart disease. These modified fats accumulate in the arteries and the deposition causes the formation of fatty streaks. Further deposition leads to the formation of fatty plaques. Plaque forms as more and more cholesterol is deposited at the site of the fatty streak. Consequently, the artery wall becomes thick and irregular. This condition is known as atherosclerosis. As the buildup grows, the artery narrows and blood flow to the heart muscle reduces. The reduced blood flow affects the availability of oxygen and nutrients to the heart. When blood flow is reduced or completely blocked, some of the cells in the heart muscle tend to suffocate and die. Thus complications of atherosclerosis lead to the development of heart disease.

A simple plaque turns into a complicated one when blood clots develop. If the covering of the plaque tears heavy bleeding occurs. This causes a local clot, which can clog the artery and markedly cut off flow of blood to the heart muscle, and lead to heart attack.

High blood pressure or hypertension can also cause damage to the arteries, damage that can accelerate the formation of fatty plaques in the walls of the blood vessels, as seen in the process of atherosclerosis. Blood pressure can increase the risk of clotting.

One particular modification of cholesterol in the LDL is its damage brought about by the addition of oxygen. This process is known as oxidation and it

impairs the integrity of the LDL. The oxidation of LDL is implicated in the development of atherosclerosis. The deposition of oxidized LDL and other modified fats appear to set a stage for the initiation of heart disease. In trying to find a clue to the French paradox, scientists at the University of California at Davis (UC Davis) reported in 1993 that wine and grape polyphenols could very effectively protect against the oxidation of cholesterol in the low-density lipoprotein particles. This protection against oxidation is known as antioxidant activity. British researchers demonstrated in 1990 that common polyphenols found in tea, wine and fruits blocked the oxidation of LDL induced by blood vessel-associated cells known as macrophages. This was the first report on the protective effect of polyphenols against LDL oxidation. Subsequent studies published in 1992 by scientists from the U.K. and France further highlighted this remarkable action of polyphenols. The UC Davis researchers also showed that polyphenols extracted from grape seeds possessed very high antioxidant capacity in protecting against LDL oxidation. This capacity far exceeded that of vitamins C and E, known dietary antioxidants. Polyphenols can also function in various other ways in preventing heart diseases.

The LDL oxidation products are also implicated in the consequent formation of certain substances that can cause the activation of blood cells known as platelets. This activation process leads to aggregation, which again leads to blood clots, artery blockage and thrombosis. These processes are linked. Oxidation of LDL can promote platelet activation. On the other hand, activated platelets can increase the susceptibility of LDL to oxidation.

Antioxidants help protect against the oxidation of LDL. They may also protect against heart disease by reducing the tendency for clots to form. When the levels of blood antioxidants are low, the excessive oxidation of LDL cannot be efficiently controlled. Flavonoid (polyphenol) compounds in red wine appear to contribute positively to the antioxidant pool of the blood and to impair LDL oxidation and the modification of fats. Polyphenols found in grapes and wine along with other antioxidants found in the body could offer greater protection against LDL oxidation and the initiation of heart disease.

POLYPHENOLS AND BLOOD VESSEL RELAXATION

The cells lining the walls of the arteries (blood vessels) respond to blood vessel relaxing agents, which cause relaxation of these smooth muscle cells. Certain drugs can cause such an effect. Interestingly red wine and polyphenols found in MegaNatural Gold™ grape seed extract also possess this capacity. This action could be an important factor in reducing blood pressure and interfering with the development of atherosclerosis, and could, in part, explain the French Paradox. Atherosclerosis is believed to be caused by an injury to the cells, lining the vessels. Oxidized LDL, blood pressure, and toxic substances stress hormones (for example, adrenaline) or other agents can cause this. This particular effect of these antioxidants, namely stimulation of the relaxation of blood vessels may be distinct from their protection against LDL oxidation.

Dr. Tissa Kappagoda and colleagues of the division of cardiovascular medicine, at the University of California, Davis, have demonstrated that constituents present in MegaNatural Gold™ grape seed extracts relax isolated blood vessels from rabbits, thereby documenting the potential benefit of the extract in increasing blood flow in blood vessels. Compounds present in MegaNatural Gold™ relax the isolated vessels by a pathway in which nitric oxide production is implicated. The lining of the arteries, known as the endothelium, releases nitric oxide which causes the blood vessels to relax and widen, thus contributing to enhanced blood flow and better regulation of blood pressure. Oligomeric proanthocyanidins found in MegaNatural Gold™ appeared to be the key active substances that cause the relaxation of the isolated blood vessels. The novel findings revealed that only the oligomers possessed blood vessel relaxing activity. MegaNatural Gold™ possesses highly bioactive special components of these flavonoids in a unique composition with consistent proportions of the different chemical constituents.

The above research findings have far reaching implications in light of the nitric oxide studies of the Nobel Prize winners, Robert F. Furchgott, Louis J. Ignarro, and Ferid Murad. The three pharmacologists won the 1998 Nobel Prize for medicine for discover-

ing that the nitric oxide produced by the body acts as a signal, influencing blood vessels to dilate which, in turn, lowers blood pressure. This property is deemed significant for the prevention and treatment of heart diseases.

The identification of naturally occurring blood vessel relaxing flavonoids, such as those found in MegaNatural Gold™ that can modulate the production of nitric oxide in body cells is an exciting prospect. The UC Davis scientists are conducting further studies on MegaNatural Gold™ to delineate clearly its mechanism of action and to identify the most active polyphenol fractions responsible for this action.

FREE RADICALS, ANTIOXIDANTS AND POLYPHENOLS

The cells in our bodies use oxygen as a fuel to transform food into energy, a process known as oxidation. During these transformations oxygen is converted to water. During this conversion, unstable and highly reactive products are formed from oxygen, known as oxygen free radicals and oxidants. Besides oxygen, other chemical substances also generate such highly unstable intermediates (free radicals). Radiation from the sun, air pollution, charcoal broiled foods, pollution, pesticides, cigarette smoking, cancer drugs, alcohol, etc., can also cause free radical and oxidant production. One well-known example of free radical damage is the oxidation of LDL from the blood. Oxygen free radicals initiate this oxidation and the degradation products of LDL oxidation are implicated in heart disease, as alluded to above.

Although free radicals are necessary for normal functions in the body, their uncontrolled production can be harmful. These products accompanying tissue injury are implicated in inflammatory and immune disorders and the increased risk of a wide range of disorders such as heart diseases, cancer, cataracts, diabetes among other degenerative diseases of aging. Antioxidants present in body cells that are present in the as well as those found in the diet possess the capacity to blunt free radicals and to control the

overwhelming accumulation of oxidation products. Increasing evidence points out that polyphenols present in grapes and other sources are highly potent antioxidants. Their antioxidative capacity far exceeds that of common antioxidants such as vitamins C and E.

GRAPE SEED POLYPHENOLS

The polyphenol compounds present in the grape can be broadly divided into four categories: phenolic acids, the highly colored pigments or colored anthocyanins which are flavonoids, simple flavonoids, complex flavonoids known as proanthocyanidins or condensed tannins. The term “polyphenols” generally refers to the above groups of compounds. The anthocyanins are the major coloring matter of red grapes and red wine. Red wine is made by crushing the berries and allowing the skins, seeds and sometimes even the grape stems to ferment together with the pulp and juice for a period of time, a process that creates a mixture rich in antioxidant compounds.

Grape seeds contain large amounts of flavonoid substances and may substantially contribute to juice or wine polyphenol pool depending upon the severity of processing and/or fermentation time on the skins and seeds. The berry’s total extractable phenols are present in only about 10% or less in the pulp with the remaining two-thirds in the seeds and one-third in the skin. The seeds are an important source of polyphenols in grape products, particularly red wines. The seeds have the highest content of phenol substances (about 5-8% by weight).

The polyphenol compounds of grape seed are essentially flavonoids. These are complex chemical substances and belong to a group of flavonoids known as proanthocyanidins. These complex substances known as proanthocyanidins exist as monomers (single residues), oligomers (two or more residues), and polymers (multiple residues). The grape seed polyphenols are generally referred to as OPC. The acronym, OPC, connotes oligomeric proanthocyanidins (oligomers of proanthocyanidi-

dins), which constitute a class of flavonoid compounds distributed throughout the plant kingdom. The term “oligomeric” simply means multiple units. In general, polymers consist of many single copies of monomers linked in chains. The building blocks of the chains are monomers, which are “single residue” subunits. One would end up with monomers that are the smallest units or “residues” that remain on breaking down polymers by chemical means.

Proanthocyanidins containing two monomers, i.e., two individual subunits interlinked (or bonded) chemically and thus condensed to make a two-unit moiety is a dimer. Substances containing three condensed monomers are trimers. Condensed substances containing two or more units, dimers, trimers, etc. are oligomers of proanthocyanidins or oligomeric proanthocyanidins (OPC). Polymers contain a large number of individual monomers bound together. The following diagrammatic representation would give an idea about these condensed units.

Monomer	O (single-unit)
Dimer	O-O (two-unit)
Trimer	O-O-O (three-unit)
Tetramer	O-O-O-O (four-unit)
Pentamer	O-O-O-O-O (five-unit)
Polymer	O-O-O-O-O-O-O-O-O-O-O-O-O (Repeated, Multiple-units)

The proanthocyanidins were previously known as vegetable tannins or “condensed” tannins in reference to the fact that they consist of several basic units or residue subunits chemically bonded together. They are widely distributed in food plants as constituents of various fruits, fruit skins, and seeds, nuts, leaves. Along with other flavonoids such as the pigments, anthocyanins, the proanthocyanidins (OPC) make a significant contribution to the ripening process of fruits, to the taste and flavor of foodstuffs and beverages, fruits and juices, and to the aging of wines and beers. They influence our enjoyment of juices and beverages such as teas, cocoas, ciders, beers and wines and a variety of fruits (e.g., apples, different kinds of berries, and grapes).

FLAVONOIDS AND OPC

The complex flavonoids found in the grape seed constitute a class known as “flavanols” under the group of flavonoids. The flavonoids are almost ubiquitously distributed in the food plants. More than 4,000 chemically unique flavonoids have been identified in plants (i.e., in fruits, cereals, legumes, vegetables, nuts, seeds, herbs, spices, stems, flowers as well as in beverages such as tea, cocoa, beer and wine). Many experimental studies using cells or animals suggest that flavonoids could help protect against the following conditions: inflammation, asthma, allergies and immune disorders, microorganisms (infection), liver diseases, parasites (worms, helminthes), blood clotting and stroke (thrombosis), blood pressure, chronic diseases such as heart diseases, diabetes, etc., arthritis, cancer induction, toxic chemicals (including cancer-causing chemicals), hormonal disorders, and viruses. No other class of chemicals exhibits such an extraordinary range of diverse actions in mammalian cells.

Recent human studies showed that consumption of flavonoid-rich foods was significantly associated with reduction in coronary artery disease in elders in

the Netherlands. The individuals with the lowest flavonoid intake had the highest incidence of heart disease.

Flavonoids are the most potent natural antioxidants known in test systems (laboratory studies). They are several fold more active than are dietary antioxidants, vitamins C and E.

Plant flavonoids were once considered as vitamins, classified as “vitamin P”. However, the vitamin designation was subsequently abolished. A later description for flavonoids was “semi-essential nutrients”. One can discern their potential health-promoting activities from an increasing number of scientific studies with experimental systems, such as animal and human cells, and laboratory animals. Several decades after the abolition of the vitamin P designation, the nutritional and health impact of flavonoids now continues to attract continuing attention. The French researchers consider that proanthocyanidins (OPC) such as those found in the grape seed can fulfill the role of vitamin P in performing functions complementary to that of vitamin C. Grape flavonoids and polyphenols offer greater promise in this regard as natural disease preventatives and health promoting agents.

MegaNatural Gold™

DISTINCT FEATURES AND ADVANTAGES

Polyphenolics, Inc. employs a proprietary process to produce a grape seed product with a consistent composition of monomers, oligomers and polymers in order to provide key health benefits such as antioxidant action (LDL oxidation inhibition), blood vessel relaxation, and increased elimination of cholesterol and fats from the body.

REMARKABLY SAFE

Product safety studies showed the MegaNatural Gold™ grape seed extract to be remarkably non-toxic. Laboratory mice fed MegaNatural Gold™ up to 1.5 grams per kilogram of body weight developed no adverse symptoms. There was no effect on their survival. This is an exceedingly high dosage.

OUTSTANDING ANTIOXIDANT ACTION

MegaNatural Gold™ is superior in protecting the oxidation of LDL from human blood. Researchers at the University of California at Davis evaluated the antioxidant function of MegaNatural Gold™ in protecting LDL from oxidation. They isolated LDL from human blood and subjected them to oxidation in test tubes. They measured the degradation of LDL caused by oxidation by determining the specific degradation products formed from LDL by highly precise and sensitive methods. MegaNatural Gold™ added to the LDL was highly effective in protecting LDL against oxidation. The protective effect of MegaNatural Gold™ was 2 to 3 times higher than that of vitamins C and E. MegaNatural Gold™ was also significantly more active than other commercially available grape seed extracts.

BLOOD VESSEL RELAXATION (VASODILATION)

Recent studies of researchers at UC Davis document the potential benefit of MegaNatural Gold™ grape seed extract in increasing blood flow (circulation) in blood vessels (arteries), which are essentially smooth muscles. Blood vessels constantly contract and relax, a phenomenon caused by substances produced in the body. For instance, the substance noradrenaline (a stress hormone) in the body causes contraction of the blood vessels, and the contracted blood vessel in turn has to relax, so that blood can flow smoothly through the vessels. Cells underlining the vessels produce substances that relax these vessels. The UC Davis researchers separated blood vessels (the large

artery namely, aorta, carrying blood from the heart to various parts of the body) from rabbits, sectioned them into rings and put them in a dish, and maintained them in the laboratory. They contracted these rings by adding noradrenaline. Subsequently, they added MegaNatural Gold™ grape seed extracts to these contracted rings and found the rings to relax to a very significant degree. This study suggests that MegaNatural Gold™ extracts are able to stimulate substances from blood vessels capable of relaxing the vessels. These extracts are, therefore, potential stimulators of blood flow. The relaxation of these smooth muscles is important in reducing blood pressure.

INCREASED FAT AND CHOLESTEROL ELIMINATION

Independent studies showed that consumption of grape seed tannins (polymers of proanthocyanidins) reduced total blood cholesterol and LDL cholesterol in high cholesterol fed rats. There was a significant rise in the level of HDL, a beneficial form of cholesterol. There was also a diminution in the content of certain LDL, known as VLDL, the modification of which is believed to be involved in developing atherosclerosis. Dietary administration of grape seed monomers and polymers had different effects. The consumption of polymers resulted in the elimination of large amounts of cholesterol and other fats in the feces, indicating thereby that the polymers substantially decreased the intestinal absorption of dietary cholesterol. Grape seed (proanthocyanidin) polymers or tannins thus appear to increase the elimination of cholesterol and fat from the body, thus mitigating the effect of high cholesterol in the onset of heart diseases. MegaNatural Gold™ possesses a consistent proportion of monomers, oligomers, and polymers of proanthocyanidins, thus making it suitable for interference with cholesterol absorption, in addition to rendering it effective as an antioxidant and a blood vessel relaxation stimulant.