

# Aptinol

## The Science of Green

Another in Dr. Hugh Smith's Client Education Series

### Back to Eden

#### Plants for Healing

In the book of Genesis we are told that the first gift to man were seed bearing plants and trees good for food.<sup>1</sup> Adam and Eve were to care for the plants in the garden.<sup>2</sup> We can only speculate why God made this their first job. Was early man a vegetarian only to become omnivorous after the “fall?” Was man learning the value of plants for his ancestors? Was he leaving a legacy for those caught in the toxic world after the “fall?” Did Adam and Eve cultivate plants simply for the enjoyment of God?

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What we *do* know is that for thousands of years plants have been used medicinally. Hippocrates said it best; “Let your food be medicine and your medicine food.” Since the advent of modern medicine however, plants and herbs have been relegated to the world of fairy-tales and quackery. The conundrum for many physicians is that well over 70% of pharmaceuticals are synthesized from plants even though, as we are so often told, there is no evidence that herbs and plants have any value as medicines. Minerals too, are only bio-available to humans when they are plant synthesized.

Over 50 years ago, Dr. Jacque Masquelier discovered a little understood Canadian Indian “healing herb” ... pinebark extract (more commonly known today by Dr. Masquelier's trademarked product, Pycnogenol).<sup>3</sup> Most important to us is that he also discovered that *all* plants have some form of proanthensols, oligomers or oligomeric proanthocyanidins (PROANTHENOLS).

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<sup>1</sup> Genesis 1:11

<sup>2</sup> Genesis 2:15

<sup>3</sup> Jacques Masquelier of the University of Bordeaux, France, first studied proanthensols in depth after reading of explorer Jacques Cartier's 1534 expedition up the St. Lawrence River, in which Cartier's crew, trapped in ice flows and dying of scurvy, survived after Native Americans gave them a tea brewed from the bark and needles of the native pine. Masquelier later postulated the pine constituents contained vitamin C

When these are concentrated, they are 20 times more powerful than vitamin C and 50 times more powerful than vitamin E. Today medical science has finally accepted the importance of pinebark and grapeseed extracts. They simply renamed it Resveratrol and promoting it as an anti-aging compound.

In the late Forties, at roughly the same time as Masquelier, several Soviet scientists discovered that plants also contained some other astonishing factors... adaptogens (a term coined by Russian scientist Nikolas Lazarov). Again, almost every plant and herb contains some form of adaptogen. These were kept a highly guarded secret because the Soviets used these adaptogens with their soldiers and *especially* their athletes and chess players. Why?

Among other things, adaptogens and proanthensols help the body recover from stress faster. We'll cover these in detail later on. What we now know is that the plant kingdom provides us the essence of creation and that proanthensols and adaptogens may be viewed interchangeably.

### **The Stress Factor**

Of the four causes of disease (chemicals, radiation, diet and stress) stress is the one factor with which we all live and is a primary cause of major disease and chronic conditions affecting hormone levels, cardiovascular disease, stress fractures, osteoporosis, premature aging, ad infinitum. Stress produces free radicals which can precede chronic disease and premature aging.

While we have managed to survive by our wits, adapting our environment to suit our needs, in some ways it may be our downfall. We have lost some of our ability to adapt to the environment and the everyday problems associated with stress.

Stress, of course, is a factor with anyone who is involved in sports, running, exercise programs, etc. not to mention everyday stress created by our high tech society. The ability to fight free radicals and cortisol levels are paramount.

Runners are aware of the importance of stretching before a run and cooling off for 30 minutes after. What they often do not understand is that as we age, the body has more difficulty coping with adrenal stress and the high associated cortisol can push them over the edge with something as simple as a bathroom visit after a long run.

Many of our clients participate in athletics. We always recommend Aptinol as a supplement to reduce free radicals and stress associated levels of cortisol.

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and flavonoids that aided in the crew's recovery. Today, dietary intake of proanthensols varies from tens to hundreds of milligrams per day, depending on geographical and seasonal dietary differences.

## Super Oxide Dismutase (SOD)

The human immune system is subjected to hundreds of stressors over time. As the immune system is called upon to track down and kill pathogens, macrophages kick out huge amounts of hydrogen peroxidase. The body normally sweeps up this peroxidase and keeps the body free of these free radical producers.

As time goes on however, the ability of the body to clean these up reduces and free radicals become more pronounced. SOD, unlike proanthensols is an enzyme that catalyzes or breaks down these free radical producers. Simply stated, SOD outcompetes damaging reactions of superoxide, thus protecting the cell from superoxide toxicity.

Superoxide is one of the main reactive oxygen species in the cell and as such, SOD serves a key antioxidant role. The physiological importance of SODs is illustrated by the severe pathologies evident in mice genetically engineered to lack these enzymes. Mice lacking SOD2 die several days after birth, amidst massive oxidative stress.<sup>4</sup>

Mice lacking SOD1 develop a wide range of pathologies, including hepatocellular carcinoma,<sup>5</sup> an acceleration of age-related muscle mass loss,<sup>6</sup> an earlier incidence of cataracts and a reduced lifespan. Mice lacking SOD3 do not show any obvious defects and exhibit a normal lifespan, though they are more sensitive to hyperoxic injury.<sup>7</sup> Knockout mice of any SOD enzyme are more sensitive to the lethal effects of superoxide generating drugs, such as paraquat and diquat, pesticides that have become ubiquitous in modern agriculture.

## Adaptogens

Cereal Secale is at the heart of Aptinol, containing the largest proportion of this extract than proanthensols. Technically all plants contain adaptogens *and* proanthensols. The secret is finding the adaptogen that contains the highest amount of adaptogens in a given

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<sup>4</sup> Li Y, Huang TT, Carlson EJ, Melov S, Ursell PC, Olson JL, Noble LJ, Yoshimura MP, Berger C, Chan PH, Wallace DC, Epstein CJ (December 1995). "Dilated cardiomyopathy and neonatal lethality in mutant mice lacking manganese superoxide dismutase". *Nat. Genet.* **11** (4): 376–81. [doi:10.1038/ng1295-376](https://doi.org/10.1038/ng1295-376). [PMID 7493016](https://pubmed.ncbi.nlm.nih.gov/7493016/).

<sup>5</sup> Elchuri S, Oberley TD, Qi W, Eisenstein RS, Jackson Roberts L, Van Remmen H, Epstein CJ, Huang TT (January 2005). "CuZnSOD deficiency leads to persistent and widespread oxidative damage and hepatocarcinogenesis later in life". *Oncogene* **24** (3): 367–80. [doi:10.1038/sj.onc.1208207](https://doi.org/10.1038/sj.onc.1208207). [PMID 15531919](https://pubmed.ncbi.nlm.nih.gov/15531919/).

<sup>6</sup> Muller FL, Song W, Liu Y, Chaudhuri A, Pieke-Dahl S, Strong R, Huang TT, Epstein CJ, Roberts LJ, Csete M, Faulkner JA, Van Remmen H (June 2006). "Absence of CuZn superoxide dismutase leads to elevated oxidative stress and acceleration of age-dependent skeletal muscle atrophy". *Free Radic. Biol. Med.* **40** (11): 1993–2004. [doi:10.1016/j.freeradbiomed.2006.01.036](https://doi.org/10.1016/j.freeradbiomed.2006.01.036). [PMID 16716900](https://pubmed.ncbi.nlm.nih.gov/16716900/)

<sup>7</sup> Sentman ML, Granström M, Jakobson H, Reaume A, Basu S, Marklund SL (March 2006). "Phenotypes of mice lacking extracellular superoxide dismutase and copper- and zinc-containing superoxide dismutase". *J. Biol. Chem.* **281** (11): 6904–9. [doi:10.1074/jbc.M510764200](https://doi.org/10.1074/jbc.M510764200). [PMID 16377630](https://pubmed.ncbi.nlm.nih.gov/16377630/)

combination that will fulfill the ultimate goal of the final blend. Additionally, adaptogens must meet several requirements.

Adaptogens must be:

1. totally non-toxic,
2. non-habit forming,
3. normalize the system,
4. possess a wide range non-specific therapeutic influences.

Herman Aldercreutz, renowned professor of clinical chemistry at Helsinki University, asserts that mortality rates from bowel and breast cancer in Finland fell significantly during periods of high rye consumption. We chose rye grass extract because it contains high amounts of beta-1,3 glucan, phytoestrogens, genestein, Co enzyme Q10 and squalene.

Beta 1,3 glucan is a molecule that bonds to receptor sites on macrophages. Macrophages are important immune cells (reduced for hours after heavy exercise, exposure to chemicals, sugars, radiation or poor diet). Beta 1,3 glucan has been shown to increase nonspecific immunity to infectious diseases including cancer. The Armed Forces Radiobiology Research Institute in Bethesda, Maryland, confirmed that beta 1,3 glucan protects against the adverse effects of radiation.

Furthermore, beta 1,3 glucan can increase the production of:

1. cytokines. They are the “air raid sirens” to other cells in the immune response system of the body. Cytokines are transported in a very similar fashion as hormones...through the blood.
2. Interleukins – these are the sign posts for cytokines and equip the cytokines with an identifiable amino acid sequence and act on macrophages.

Interleukin-1. These are macrophages or immune cells that are hormone like messengers. Among other things, they stimulate other special immune cells to reproduce. They can mediate inflammatory reactions caused by trauma, injury or an activated immune response. These are, in a very real sense, the mobilizers that gives the body the energy to fight disease.

Interleukin-2. These cells help macrophages recognize enemy cells and govern the expansion and growth and reactivate certain lymphocytes.

3. Interferons. These are anti-viral cells. Virus infected cells secrete interferons, which bind to non-infected cells and trigger enzymes to break down viral RNA, creating a virus resistant cell. Not only do they increase immunity, but we believe that interferons can make cells identify and destroy viruses and tumor cell growth.

Synthesized Interferons have been used since the 1990's to treat multiple sclerosis and Hepatitis C. However, this synthesized interferon has serious side effects. Rye Grass Extract (Cereal Secale) has none of the side effects of the chemical version and can be taken without prescription and is as potent as the pharmaceuticals.

### **Phytoestrogens**

Phytoestrogens are a significant family of plant compounds that have been shown to possess estrogenic and antiestrogenic capabilities. They contain isoflavones, which are weak estrogen-like constituents that act as adaptogens.

If, for example, you have too much estrogen, these compounds help block the estrogen receptor sites, effectively blocking estrogen uptake. On the other hand, if there is not enough estrogen, adaptogens fill the gap in the receptor sites.<sup>8</sup>

Most individuals, men and women, are overloaded with estrogen. Estrogen is emitted from pesticides, herbicides, disposable diapers, plastics, gasoline exhaust, non-organic protein sources (beef, chicken, fish, etc.) and pretty much any modern high tech application.

Phytoestrogens, as adaptogens, help rescue the body from this overload from our toxic environment.

### **Genestein**

Genestein (another phytoestrogen) has appeared in numerous peer reviewed studies and medical journals. Genestein may primarily influence human prostate cancer development by reducing tumor growth.<sup>9</sup>

Isoflavones (genestein) may improve endothelial functioning and attenuate events leading to both lesion and thrombus formation.<sup>10</sup>

Heightened cardiovascular risk associated with menopause can be reduced with isoflavones.<sup>11</sup>

Isoflavones may contribute to the chemo preventive potentials against human cancers.<sup>12</sup>

Dietary isoflavones such as genestein reduce plasma cholesterol and atherosclerosis in test animals. Potential mechanisms include cholesterol lowering, inhibition of lipoprotein oxidation, and inhibition of cell proliferation.<sup>13</sup>

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<sup>8</sup> Journal of Clinical Endocrinology & Metabolism 1998; July;83(7):2223-35

<sup>9</sup> Japanese Journal of Clinical Oncology 1998; Jun;28(6):360-3

<sup>10</sup> Nutritional Reviews 1998; Aug;56(8):231-5

<sup>11</sup> Arteriosclerosis, Thrombosis, & Vascular Biology 1997; Dec;17:3392-8

<sup>12</sup> Nutrition and Cancer 1997; 29(1):77-82

<sup>13</sup> Journal of Nutrition 1998; Jun;128(6):954-9

## Coenzyme Q10

Coenzyme Q10 (CoQ10) is an energy promoting agent and antioxidant, made by the human body and obtained by our diet, mainly in oily fishes, organ meats and whole grains. It works with other enzymes as a “coenzyme factor.”

It has been reported that myocardial function can be improved by the oral administration of CoQ10.<sup>14</sup>

The objectives of this study were to assess the CoQ10 levels in women experiencing a normal pregnancy, in those women experiencing spontaneous abortion, and in those women with threatened abortion. The researchers found a statistically significant difference between the CoQ10 values in those with normal pregnancies and those women who had problems.<sup>15</sup>

CoQ10 can exert a potent antioxidant effect at concentrations considerably lower than that of vitamin E.<sup>16</sup>

Normal total serum calcium concentration was obtained in patients with hypercalcemia (too much calcium) with CoQ10 therapy, while the replacement of CoQ10 with placebo led to hypercalcemia (too little calcium). The mechanism of action of CoQ10 is difficult to explain. The researchers speculate that the capacity of producing an active form of vitamin D in certain cells was restored by CoQ10 therapy. (Effective calcium metabolism is dependent on vitamin D).<sup>17</sup>

Improved cardiovascular morbidity and mortality have been observed in several clinical studies of dietary supplementation with CoQ10.<sup>18</sup>

In sperm cells, the majority of CoQ10 is concentrated in the part of the sperm that provides the energy for movement and all other energy-dependent processes of the sperm. In fact, these processes are dependent on the availability of CoQ10. Based on these facts, the researchers conclude that the administration of CoQ10 may result in improvement in sperm functions in selective patients.<sup>19</sup>

Improved cardiovascular morbidity and mortality have been observed in several clinical studies of dietary supplementation with CoQ10.<sup>20</sup>

CoQ10 helps to stabilize vitamin C, both within and without the cell.<sup>21</sup>

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<sup>14</sup> Europa Journal of Nuclear Medicine 1997;Jun;24(6):629-34

<sup>15</sup> Fetal Diagnosis Therapy 1996;Jul-Aug;11(4):264-70

<sup>16</sup> Molecular Aspects of Medicine 1997;18 Suppl:S105-12

<sup>17</sup> Neuromuscular Disorders 1996;Jan;6(1):49-53

<sup>18</sup> Cardiovascular Pharmacology 1996;Aug;28(2):175-81

<sup>19</sup> Molecular Aspects of Medicine 1997;18 Suppl():S213

<sup>20</sup> Journal of Cardiovascular Pharmacology 1997;Jan;29(1):16-22

This is the first report demonstrating the therapeutic usefulness of CoQ10 on certain cases of diabetes.<sup>22</sup>

### **Squalene**

Squalene is more often recognized as a component of shark liver oil, although it is also found in olive oil and some plants such as rye. Squalene is not only heart protective in its unoxidized fresh state but acts as an anti-angiogenic with cancer tumors. (Cancer must produce its own blood supply through the process of angiogenesis. Squalene, in several clinical trials, has been observed to cut off the supply of blood to tumors).

A squalene diet significantly decreased lung cancer by 70 percent in test animals. In those fed a diet containing 2 percent squalene for only 3 weeks, it was shown that the squalene could effectively inhibit substances leading to lung cancer.<sup>23</sup>

It is proposed that the high squalene content of olive oil, as compared to other human foods, is a major factor in the cancer risk-reducing effect of olive oil. Experiments suggest a tumor-inhibiting role for squalene.<sup>24</sup>

The present findings suggest the safe use of squalene in lipid-lowering therapy.<sup>25</sup>

Combination therapy of a cholesterol-lowering drug with squalene significantly reduced total cholesterol and LDL cholesterol and increased HDL cholesterol to a greater extent than the drug.<sup>26</sup>

### **Proanthenols**

We now move on to the “secondary” components of Aptinol; proanthenols. These are obtained in high concentrations from grapeseed extract (*vitis vinefera*), pinebark extract (*pinus strobus*) and quercetin. All three act as anti-oxidants 20 times more effective than vitamin C and 50 times more effective than vitamin E.

Proanthenols are especially good at neutralizing the hydroxyl radical, the superoxide radical, singlet oxygen, and the dangerous chemical peroxyxynitrate. What makes peroxyxynitrate so dangerous is that it reacts with anything; fats, proteins, DNA, etc. It doesn't really matter what... peroxyxynitrate reacts!

Excessive nitric oxide production is associated with arthritis, diabetes, stroke, septic shock, chronic inflammation and atherosclerosis. The damage it does can easily lead to gene mutations, which replicate themselves as the beginnings of cancer.

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<sup>21</sup> Journal of Bioenergy 1997;Jun29(3):251-7

<sup>22</sup> Diabetologia 1998;May;41(5):584-8

<sup>23</sup> Carcinogenesis 1998;Apr;19(4):703-6

<sup>24</sup> Cancer Epidemiology Biomarkers Prevention 1997;Dec;6(12):1101-3

<sup>25</sup> Journal of Lipid Research 1997;Aug;38(8):1639-48

<sup>26</sup> Journal of Clinical Pharmacology 1996;May;36(5):422-7

The good news is that proanthens are exceptional at neutralizing peroxynitrate. It also reduces the amount of superoxide available that makes peroxynitrate and helps to regulate nitric oxide production so it remains in balance. That means your immune system works better, your joints hurt less and your blood flows better, all because of one single substance. Other antioxidants may help, but researchers have noticed such broad based activities are *only* available in proanthens.

The potent antioxidative properties of proanthens account for their therapeutic benefit in disease states characterized by oxidative stress. Proanthens also demonstrate potent, concentration-dependent, free radical scavenging ability.<sup>27</sup>

Researchers discovered that even when the immune system was barely working, proanthens brought it back. Research in this direction may be very significant for those interested in autoimmune diseases.

### **THE SUPERNUTRIENT THAT FIGHTS AGING AND DISEASE**

At an annual meeting of scientists involved in proanthol research, several studies were presented to substantiate claims that proanthens combat aging and heart disease. David F. Fitzpatrick, associate professor of pharmacology and therapeutics at the University of South Florida College of Medicine in Tampa, reported that the supplement can prevent damage to blood vessels and a decrease in blood clotting, both of which are linked to heart disease. Another study found that proanthens unique combination of natural vitamin-like compounds known as flavonoids, inhibit excessive metabolizing of nitric oxide, a process that has been linked to inflammation, arthritis and Alzheimer's. What's more, research conducted on mice at the University of Arizona at Tucson showed that proanthens stimulate immune activity and delays such age-related changes as hair loss and skin damage. Studies have shown that proanthens are non-toxic and have no known drug interactions making proanthens adaptogenic, as well.

Since proanthens are an antioxidant, research shows they fight cholesterol by discouraging deposits from forming on artery walls. Proanthol's anti-inflammatory activity may help relieve inflammatory conditions, including arthritis, allergies, bronchitis and asthma. Proanthens also correct dangerous blood clotting tendencies that trigger heart attacks and strokes. Dr. Ronald Watson, a researcher at the University of Arizona, recently confirmed that proanthens normalize platelet aggregation, a disorder that in which the "sticky" platelets tend to form blood clots. He showed that when people smoked, their platelets clump together in a tendency to form clots. But, about 20 minutes after taking proanthens, their platelets returned to normal.

Medical studies conducted at the University of Illinois demonstrate that proanthens antioxidant and anti-inflammatory effects have the ability to inhibit all three phases of the cancer process: initiation, promotion, and progression.

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<sup>27</sup> Bagchi D, Garg A, Krohn RL, et al. Oxygen free radical scavenging abilities of vitamins C and E, and a grape seed proanthocyanidin extract in vitro. Res Commun Mol Pathol Pharmacol 1997;95:179-189.



Scientists at the University of Arizona discovered that proanthensols help build resistance to cancer by as much as 40 to 50 percent by boosting the body's first line of cancer defense, known as natural killer cells (NK cells).

Dr. Packer has focused much of his attention on the relationship between proanthensols and nitrous oxide (NO), a free radical produced in the body. Within the body, NO is a double edged immunity sword, made by the body to regulate the muscle tone of blood vessels and employed as a weapon to kill pathogens, the micro-organisms that cause disease. The body's overproduction of NO, on the other hand, can result in chronic, damaging inflammation, the root cause of 1 in 3 cancers. "Proanthensols says Dr. Packer, have a biphasic effect on NO. It both quenches NO when this substance threatens to become a damaging free radical and it inhibits a gene that might otherwise foster enzymes that can lead to NO overproduction."

Preliminary studies have also shown that proanthensols are also effective against Alzheimer's disease. Cell culture studies have shown that proanthensols can inhibit beta-amyloid accumulation also called amyloid-beta-protein, a peptide that accumulates in the form of plaques in the central nervous system. These plaques are a characteristic feature of Alzheimer's disease. Beta-amyloid is directly toxic to nerve cells causing a breaking of membranes.

Dr. D. Schubert of the Salk Institute of Biological Sciences of San Diego accumulated brain cell cultures taken from Alzheimer's patients to which beta-amyloid has been added. In those cultures, proanthensols prevented the toxic protein present in Alzheimer's patients from accumulating.

Somewhat more impressive are reports from patients having Newman-Pick's disease, an ailment closely related to Alzheimer's. These patients reported significant improvement following proanthensol supplementation. Proanthensols possess antioxidant, antimutagenic, anticarcinogenic, anti-inflammatory, adaptogenic and antiviral properties.

### **Antioxidant**

The potent antioxidative properties of proanthensols account for their therapeutic benefit in disease states characterized by oxidative stress. Proanthensols also demonstrate potent, concentration-dependent, free radical scavenging ability.<sup>28</sup> Studies in mice show proanthensols inhibit chemically-induced lipid peroxidation, DNA fragmentation, and subsequent apoptosis (indicators of oxidative tissue damage) in a dose-dependent manner in hepatic and brain tissue. Human studies also demonstrate an antioxidative mechanism as evidenced by decreased lipid peroxidation of LDL cholesterol and increased free-radical trapping capacity after consumption of red wine containing proanthensols.<sup>29</sup>

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<sup>28</sup> Natella F, Belevi F, Gentili V, et al. Grape seed proanthocyanidins prevent plasma postprandial oxidative stress in humans. *J Agric Food Chem* 2002;50:7720-7725.

<sup>29</sup> Serafini M, Maiani G, Ferro-Luzzi A. Alcohol-free red wine enhances plasma antioxidant capacity in humans. *J Nutr* 1998; 128:1003-1007.

Proanthoenols appear to have an affinity for vascular tissue and strongly inhibit several enzymes involved in degradation of collagen, elastin, and hyaluronic acid, the main structural components of the extravascular matrix.<sup>30</sup> These effects are perhaps attributable to trapping reactive oxygen species and preventing oxidative injury to vascular endothelium. In vitro studies have also found proanthoenols increase resistance of cell membranes to injury and degradation.<sup>31</sup>

Proanthocyanidins possess endothelium-dependent relaxing (EDR) activity in blood vessels by increasing nitric oxide production, and stimulate vascular endothelial growth factor, a signaling factor involved in initiation of wound healing. Proanthoenols may also protect the microvasculature of the retina and increase visual acuity, possibly by increasing the rate of rhodopsin regeneration.<sup>32</sup> In a rabbit model of ischemia/reperfusion, proanthoenols beneficial effects were attributed to binding of copper and iron liberated from myocardial tissue, thereby reducing their oxidative effects.<sup>33</sup> The positive effects of proanthoenols on microcirculation are also attributed to their inhibition of LDL oxidation<sup>34</sup> and decreased incidence of foam cells, markers of early stage atherosclerosis.<sup>35</sup> Grape seed proanthocyanidins may have a vitamin E-sparing effect.<sup>36</sup>

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<sup>30</sup> Maffei Facino R, Carini M, Aldini G, et al. Free radicals scavenging action and anti-enzyme activities of procyanidines from *Vitis vinifera*. A mechanism for their capillary protective action. *Arzneimittelforschung* 1994;44:592-601.

<sup>31</sup> Gavignet C, Groult N, Godeau G, et al. Effect of procyanidolic oligomers on cultured mesenchymal cells. I. Effect on attachment, proliferation and detachment of cells. *Pathol Biol (Paris)* 1989;37:746-753. [Article in French]

Robert AM, Groult N, Six C, Robert L. The effect of procyanidolic oligomers on mesenchymal cells in culture. II. Attachment of elastic fibers to the cells. *Pathol Biol (Paris)* 1990;38:601-607. [Article in French]

<sup>32</sup> Corbe C, Boissin JP, Siou A. Light vision and chorioretinal circulation. Study of the effect of procyanidolic oligomers (Endotelon). *J Fr Ophtalmol* 1988;11:453-460. [Article in French] Boissin JP, Corbe C, Siou A. Chorioretinal circulation and dazzling: use of procyanidol oligomers (Endotelon). *Bull Soc Ophtalmol Fr* 1988;88:173-174, 177-179. [Article in French] Boissin JP, Corbe C, Siou A. Chorioretinal circulation and dazzling: use of procyanidol oligomers (Endotelon). *Bull Soc Ophtalmol Fr* 1988;88:173-174, 177-179. [Article in French]

<sup>33</sup> Maffei Facino R, Carini M, Aldini G, et al. Procyanidines from *Vitis vinifera* seeds protect rabbit heart from ischemia/reperfusion injury: antioxidant intervention and/or iron and copper sequestering ability. *Planta Med* 1996;62:495-502.

<sup>34</sup> Preuss HG, Wallerstedt N, Talpur S, et al. Effects of niacin-bound chromium and grape seed proanthocyanidin extract on the lipid profile of hypercholesterolemic subjects: a pilot study. *J Med* 2000;31:227-246.

<sup>35</sup> Vinson JA, Tuefel K, Wu N. Red wine, dealcoholized red wine, and especially grape juice inhibit atherosclerosis in a hamster model. *Atherosclerosis* 2001;156:67-72.

<sup>36</sup> Maffei Facino R, Carini M, Aldini G, et al. Sparing effect of procyanidins from *Vitis vinifera* on vitamin E: in vitro studies. *Planta Med* 1998;64:343-347.

### **Anti-inflammatory**

Proanthoenols from pine bark decrease symptoms of chronic inflammation. In vitro studies demonstrate anti-inflammatory effects may be due to inhibition of peroxide generation by macrophages.<sup>37</sup>) In addition, animal studies demonstrate proanthoenols from grape seed significantly inhibit formation of proinflammatory cytokines, interleukin 1-beta, and tumor necrosis factor-alpha.<sup>38</sup>

### **Antimutagenic/Anticarcinogenic**

Proanthoenols possess natural antimutagenic properties when exposed to certain strains of bacteria.<sup>39</sup> Although the exact mechanism is not known, an in vitro study found proanthoenols exhibit selective cytotoxicity for certain cancerous cell lines, while remaining non-toxic to normal human gastric mucosal cells and macrophages.<sup>40</sup> An in vitro study in a mouse skin tumor model demonstrated proanthoenols' inhibition of two markers of tumor promotion.<sup>41</sup>

### **Antimicrobial Effects**

Flavonoids and associated polyphenols, particularly proanthoenols, elicit an inhibitory effect on human immunodeficiency virus (HIV). A possible mechanism may be inhibition of gene expression regulating virus binding to cell receptors on normal lymphocytes, thus preventing infection.<sup>42</sup>

### **Vascular Conditions: Peripheral Vascular Insufficiency/Lymphedema**

Because of affinity of proanthoenols for vascular tissue, the basal membrane of the skin, and gastrointestinal mucosa, the preponderance of research has focused on conditions affecting these tissues. Europeans use proanthoenols to treat various vascular disorders, including varicose veins, venous insufficiency, capillary fragility, and retinopathies.

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<sup>37</sup> Bayeta E, Lau B. Pycnogenol inhibits generation of inflammatory mediators in macrophages. *Nutr Res* 2000;20:249-259. Blazso G, Gabor M, Rohdewald P. Antiinflammatory activities of procyanidin-containing extracts from *Pinus pinaster* Ait. after oral and cutaneous application. *Pharmazie* 1997;52:380-382.

<sup>38</sup> Li WG, Zhang XY, Wu YJ, Tian X. Antiinflammatory effect and mechanism of proanthocyanidins from grape seeds. *Acta Pharmacol Sin* 2001;22:1117-1120.

<sup>39</sup> Liviero L, Puglisi P. Antimutagenic activity of procyanidins from *Vitis vinifera*. *Fitoterapia* 1994;65:203-209.

<sup>40</sup> Ye X, Krohn RL, Liu W, et al. The cytotoxic effects of a novel IH636 grape seed proanthocyanidin extract on cultured human cancer cells. *Mol Cell Biochem* 1999;196:99-108.

<sup>41</sup> Bomser JA, Singletary KW, Wallig MA, Smith MA. Inhibition of TPA-induced tumor promotion in CD-1 mouse epidermis by a polyphenolic fraction from grape seeds. *Cancer Lett* 1999;135:151-157.

<sup>42</sup> Nair MP, Kandaswami C, Mahajan S, et al. Grape seed extract proanthocyanidins downregulate HIV-1 entry coreceptors, CCR2b, CCR3, and CCR5 gene expression by normal peripheral blood mononuclear cells. *Biol Res* 2002;35:421-431.

Several clinical trials have confirmed the beneficial effects of proanthocyanols use in treating vascular disorders.<sup>43</sup>

A double-blind study of 50 patients with chronic venous insufficiency manifesting as varicose veins revealed 150 mg proanthocyanidins daily for one month had a more rapid and lasting effect on symptom alleviation than 450 mg daily of diosmin (a flavonoid known for its therapeutic efficacy in vascular insufficiency).<sup>44</sup>

A double-blind, placebo-controlled study of 92 patients with peripheral venous insufficiency demonstrated improved venous function at a dose of 300 mg proanthocyanols daily for 28 days. Sixty-nine patients reported 50-percent reduction in clinical parameter scores for pain, paresthesias, nocturnal cramps, and edema. Seventy-five percent of patients felt the treatment was effective, compared to 41 percent of the placebo group.<sup>45</sup>

The use of grape seed proanthocyanols in patients with venous and lymphatic edema was examined in a multicenter study of 165 patients with premenstrual symptoms, including breast tenderness, abdominal swelling, and pelvic pain. Sixty percent of patients reported improvement in, or cessation of, symptoms after initial treatment; when treatment duration doubled, that number increased to 78 percent.<sup>46</sup>

A double-blind, randomized, placebo-controlled study of 63 patients undergoing treatment for lymphedema resulting from breast cancer surgery found six months of proanthocyanols (600 mg daily) was superior to placebo in improving pain, skin tension, and arm and shoulder movements.<sup>47</sup>

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<sup>43</sup> Delacroix P. Double-blind study on Endotelon in chronic venous insufficiency. *Rev Med (Paris)* 1981;1793:27-28. Thebaut JF, Thebaut P, Vin F. Study of Endotelon in functional manifestations of peripheral venous insufficiency. Results of a double-blind study on 92 patients. *Gaz Med (Montr)* 1985;92:12. Amsellem M, Masson JM, Negui B, et al. Endotelon in the treatment of venolymphatic problems in premenstrual syndrome, a multicentered study on 165 patients. *Tempo Med* 1987;November:282. [Article in French] Pecking A. Oligomeric proanthocyanidins (Endotelon[R]) in the treatment of post therapeutic lymphoedema of the upper limbs. *Association de Lymphologie de Lange Francaise Hospital Saint-Louis, Paris* 1989;69-73. [Article in French]

<sup>44</sup> Delacroix P. Double-blind study on Endotelon in chronic venous insufficiency. *Rev Med (Paris)* 1981;1793:27-28.

<sup>45</sup> Thebaut JF, Thebaut P, Vin F. Study of Endotelon in functional manifestations of peripheral venous insufficiency. Results of a double-blind study on 92 patients. *Gaz Med (Montr)* 1985;92:12.

<sup>46</sup> Amsellem M, Masson JM, Negui B, et al. Endotelon in the treatment of venolymphatic problems in premenstrual syndrome, a multicentered study on 165 patients. *Tempo Med* 1987;November:282. [Article in French]

<sup>47</sup> Pecking A. Oligomeric proanthocyanidins (Endotelon[R]) in the treatment of post therapeutic lymphoedema of the upper limbs. *Association de Lymphologie de Lange Francaise Hospital Saint-Louis, Paris* 1989;69-73. [Article in French]

## Skin Conditions

Skin conditions secondary to excessive exposure to ultraviolet rays (UVR) benefit from oral administration of proanthocyanidins. Twenty-one volunteer subjects were given 1.10 mg/kg proanthocyanidins daily for four weeks followed by 1.66 mg/kg Proanthocyanidins daily for a second four-week period. UV sensitivity, expressed as minimal erythema dose (MED), was measured twice prior to PROANTHOCYANIDINS supplementation to establish a baseline, and again at the end of each four-week period. The UVR dose required to induce minimal erythema increased significantly (in a dose-dependent manner) in subjects supplemented with proanthocyanidins.<sup>48</sup> Proanthocyanidin supplementation at the higher dose resulted in nearly twice the mean baseline MED. Activation of nuclear factor-kappaB is believed to play a key role in UVR-induced erythema.<sup>49</sup>

Melasma is a skin condition characterized by hyperpigmentation of the face and neck and is attributed to UV radiation, genetic factors, pregnancy, and various phototoxic drugs. Proanthocyanidins from pine bark have been shown to be beneficial in treating melasma in women.<sup>50</sup>

## Cardiovascular Disease

One explanation for the "French Paradox"--relatively low rates of cardiovascular disease in France despite a diet of rich foods--is that proanthocyanidins in red wine offer protection by reducing LDL oxidation, inhibiting cyclooxygenase and lipoxygenase in platelets and macrophages, and decreasing thrombotic events.<sup>51</sup> Epidemiological studies support this theory, indicating red wine consumption reduces the incidence of coronary heart disease.<sup>52</sup>

Several clinical trials have examined the effect of proanthocyanidins in red wine on lipid peroxidation and cardiovascular disease. In a two-week study of 17 healthy men, nine consumed 400 ml red wine daily with meals, while the remaining eight men consumed the same amount of white wine. Red wine consumption resulted in a 20-percent reduction of lipid peroxidation in plasma, while increased lipid peroxidation was observed in the men who drank white wine, suggesting phenolic substances present in red wine may be responsible for the observed antioxidant effects. Red wine polyphenols also significantly

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<sup>48</sup> Saliou C, Rimbach G, Moini H, et al. Solar ultraviolet-induced erythema in human skin and nuclear factor-kappa-B-dependent gene expression in keratinocytes are modulated by a French maritime pine bark extract. *Free Radic Biol Med* 2001;30:154-160.

<sup>49</sup> Fisher GJ, Datta SC, Talwar HS, et al. Molecular basis of sun-induced premature skin ageing and retinoid antagonism. *Nature* 1996;379:335-339

<sup>50</sup> Ni Z, Mu Y, Gulati O. Treatment of melasma with pycnogenol. *Phytother Res* 2002;16:567-571.

<sup>51</sup> Frankel EN, Kanner J, German JB, et al. Inhibition of oxidation of human low-density lipoprotein by phenolic substances in red wine. *Lancet* 1993;341:454-457.

<sup>52</sup> Das DK, Sato M, Ray PS, et al. Cardioprotection of red wine: role of polyphenolic antioxidants. *Drugs Exp Clin Res* 1999;25:115-120. Sato M, Maulik N, Das DK. Cardioprotection with alcohol: role of both alcohol and polyphenolic antioxidants. *Ann N Y Acad Sci* 2002;957:122-135.

increase plasma high-density lipoprotein (HDL) cholesterol and plasma apolipoprotein A-I concentrations in humans.<sup>53</sup>

Natella et al investigated the effect of grape seed proanthensols on plasma postprandial oxidative stress. Eight healthy volunteers consumed a lipid-rich test meal with or without proanthensols. Proanthensol supplementation resulted in decreased lipid peroxidation, increased plasma antioxidant levels, and improved resistance of LDL to oxidation.<sup>54</sup> A larger, randomized, double-blind, placebo-controlled study of 40 hypercholesterolemic patients examined the effects of supplementation of niacin-bound chromium, grape seed extract, or a combination on total cholesterol, LDL, and autoantibodies to oxidized LDL. Grape seed extract administration did not result in statistically significant improvement in total cholesterol or LDL levels compared to placebo; however, the chromium/ grape seed extract combination resulted in significant improvements in both parameters, superior to results with either substance alone. The group receiving grape seed extract alone demonstrated a greater than 50-percent decrease in autoantibodies to oxidized LDL.<sup>55</sup>

### **Retinopathies/Ophthalmologic Conditions**

Numerous clinical trials in France support the protective benefit of proanthensols on retinal health. In a randomized, double-blind, placebo-controlled study, 75 patients experiencing visual stress from video-display units were given either a proanthensol extract from grape seed, a *Vaccinium myrtillus* (bilberry) extract, or placebo. Dosage in all groups was 100 mg three times daily for 60 days. Assessments at trial conclusion showed subjects given either Proanthensols or bilberry had significant improvement in contrast sensitivity and subjective visual disturbances, compared to placebo. Subjects in the proanthensol group showed improvement superior to those in the bilberry group.<sup>56</sup>

In additional studies of patients without retinal or ophthalmologic pathologies, proanthocyanidins administered at 150-300 mg daily for 30-60 days improved visual acuity, contrast sensitivity in patients with ocular stress due to video display unit use, and visual performance after glare exposure.<sup>57</sup> In another study 91 patients with bilateral myopia and associated ocular disorders demonstrated 100 mg proanthensols given three times daily for 30 days improved retinal sensitivity during dark adaptation in 72 of the patients (79%). Subjective improvement was even greater, with 90 percent of patients

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<sup>53</sup> Lavy A, Fuhrman B, Markel A, et al. Effect of dietary supplementation of red or white wine on human blood chemistry, hematology and coagulation: favorable effect of red wine on plasma high-density lipoprotein. *Ann Nutr Metab* 1994;38:287-294.

<sup>54</sup> Natella F, Belelli F, Gentili V, et al. Grape seed proanthocyanidins prevent plasma postprandial oxidative stress in humans. *J Agric Food Chem* 2002;50:7720-7725.

<sup>55</sup> Preuss HG, Wallerstedt N, Talpur S, et al. Effects of niacin-bound chromium and grape seed proanthocyanidin extract on the lipid profile of hypercholesterolemic subjects: a pilot study. *J Med* 2000;31:227-246.

<sup>56</sup> Fusi L, Czimeg F, Pesce F, et al. Effects of procyanidolic oligomers from *Vitis vinifera* in subjects working at video-display units. *Ann Ophthalmol Clin Ocul* 1990;116:575.

<sup>57</sup> Corbe C, Boissin JP, Siou A. Light vision and chorioretinal circulation. Study of the effect of procyanidolic oligomers (Endotelon). *J Fr Ophtalmol* 1988;11:453-460. [Article in French] Boissin JP, Corbe C, Siou A. Chorioretinal circulation and dazzling: use of procyanidol oligomers (Endotelon). *Bull Soc Ophtalmol Fr* 1988;88:173-174, 177-179. [Article in French]

reporting symptom improvement.<sup>58</sup> In the case of retinopathy, a review of 26 case studies reveals Proanthens significantly improved vascular lesions, micro aneurisms, and exudates associated with diabetic retinopathy.<sup>59</sup>

### **Cancer**

Proanthens incubated with several human cancer cell lines (breast, lung, and gastric) revealed a selective cytotoxicity for the cancerous cells, but not normal gastric mucosal cells or macrophages. It is postulated that in addition to selective cytotoxicity, Proanthens may up-regulate certain apoptosispromoter genes and down-regulate apoptosis-inhibitor genes in cancerous cells.<sup>60</sup>

An in vitro study explored the chemo preventive effects of a proanthanol extract on cultured, non-malignant human Chang liver cells treated with the chemotherapeutic agents idarubicin or 4-hydroxyperoxycyclophosphamide; both agents induce apoptosis in normal cells. Incubation of either chemotherapeutic agent with non-malignant Chang liver cells resulted in growth inhibition significantly reversed with addition of proanthanol extract.<sup>61</sup> This suggests proanthens could be helpful adjuncts in managing the cytotoxicity of chemotherapeutic agents to normal human cells.

### **HIV Infection**

Grape seed proanthocyanidins elicit an inhibitory effect on HIV infection in vitro. Recent research indicates chemokine receptors 3 and 5 expression on Th-2 lymphocytes is a prerequisite for HIV infection of the central nervous system.<sup>62</sup> A proanthanol extract incubated with immunocompetent peripheral blood mononuclear cells (PBMC) resulted in a significant dose-dependent suppression of HIV-chemokine co-receptor gene expression (chemokine receptors 2b, 3, and 5) in normal PBMC. This inhibition may prevent binding of the HIV virus to cell receptor sites on normal white blood cells, thereby preventing infection.<sup>63</sup>

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<sup>58</sup> Moriconi S, Bellezza PG. Clinical study on the activity of procyanidolic oligomers of *Vitis vinifera* on retinal sensitivity in myopic patients. *Ann Ottalmol Clin Ocul* 1988;114:585-594.

<sup>59</sup> Froantin M. Procyanidolic oligomers in the treatment of capillary fragility and retinopathy in diabetics. *Med Int* 1981;16:432-434. [Article in French]

<sup>60</sup> Ye X, Krohn RL, Liu W, et al. The cytotoxic effects of a novel IH636 grape seed proanthocyanidin extract on cultured human cancer cells. *Mol Cell Biochem* 1999;196:99-108.

<sup>61</sup> Joshi SS, Kuszynski CA, Bagchi M, Bagchi D. Chemopreventive effects of grape seed proanthocyanidin extract on Chang liver cells. *Toxicology* 2000;155:83-90.

<sup>62</sup> He J, Chen Y, Farzan M, et al. CCR3 and CCR5 are co-receptors for HIV-1 infection of microglia. *Nature* 1997;385:645-649.

<sup>63</sup> Nair MP, Kandaswami C, Mahajan S, et al. Grape seed extract proanthocyanidins downregulate HIV-1 entry coreceptors, CCR2b, CCR3, and CCR5 gene expression by normal peripheral blood mononuclear cells. *Biol Res* 2002;35:421-431.

## Wound Healing

Nitric oxide stimulates collagen synthesis and subsequent healing at wound sites.<sup>64</sup> In addition, the induction of vascular endothelial growth factor (VEGF) is a crucial step in the reepithelialization phase of skin repair.<sup>65</sup> Extracts of grape seed proanthocyanidins appear to stimulate the expression of VEGF in cultured keratinocytes, making proanthocyanidins a potential therapeutic tool in dermal wound healing.<sup>66</sup>

## Insulin Resistance

Preliminary research in animals indicates proanthocyanidins may have potential in the treatment of insulin resistance. A short-term study in rats revealed grape seed extract decreased circulating insulin levels and systolic blood pressure. A one-year study also revealed significantly lower glycosylated hemoglobin levels in animals receiving a combination of grape seed extract, niacin-bound chromium, and a zinc methionine complex, compared to controls, although the effects of the single ingredients were not evaluated.<sup>67</sup>

## Protection from Drug Toxicity

Animal studies indicate proanthocyanidin administration is beneficial in preventing hepatic and renal toxicity in instances of acetaminophen and other drug poisonings. This protection may be attributable to detoxification of cytotoxic free radicals or facilitation of DNA repair.<sup>68</sup> A study in rats with experimentally-induced myoglobinuric acute renal failure

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<sup>64</sup> Witte MB, Thornton FJ, Efron DT, Barbul A. Enhancement of fibroblast collagen synthesis by nitric oxide. *Nitric Oxide* 2000;4:572-582. Stallmeyer B, Kampfer H, Kolb N, et al. The function of nitric oxide in wound repair: inhibition of inducible nitric oxide-synthase severely inhibits wound reepithelialization. *J Invest Dermatol* 1999;113:1090-1098.

<sup>65</sup> Frank S, Stallmeyer B, Kampfer H, et al. Nitric oxide triggers enhanced induction of vascular endothelial growth factor expression in cultured keratinocytes (HaCaT) and during cutaneous wound repair. *FASEB J* 1999;13:2002-2014. Most D, Efron DT, Shi HP, et al. Characterization of incisional wound healing in inducible nitric oxide synthase knockout mice. *Surgery* 2002;132:866-876.

<sup>66</sup> Khanna S, Roy S, Bagchi D, et al. Upregulation of oxidant-induced VEGF expression in cultured keratinocytes by a grape seed proanthocyanidin extract. *Free Radic Biol Med* 2001;31:38-42. Khanna S, Venojarvi M, Roy S, et al. Dermal wound healing properties of redox-active grape seed proanthocyanidins. *Free Radic Biol Med* 2002;33:1089-1096.

<sup>67</sup> Preuss HG. Effects of glucose/insulin perturbation on aging and chronic disorders of aging; the evidence. *J Am Coll Nutr* 1997;16:397-403. Preuss HG, Bagchi D, Bagchi M. Protective effects of a novel niacin-bound chromium complex and a grape seed proanthocyanidin extract on advancing age and various aspects of syndrome X. *Ann N Y Acad Sci* 2002;957:250-259.

<sup>68</sup> Ray SD, Patel D, Wong V, Bagchi D. In vivo protection of DNA damage associated apoptotic and necrotic cell deaths during acetaminophen-induced nephrotoxicity, amiodarone-induced lung toxicity, and doxorubicin-induced cardiotoxicity by a novel IH636 grape seed proanthocyanidin extract. *Res Commun Mol Pathol Pharmacol* 2000;107:137-166. Bagchi D, Ray SD, Patel D, Bagchi M. Protection against drug- and chemical-induced multiorgan toxicity by a novel IH636 grape seed proanthocyanidin extract. *Drugs Exp Clin Res* 2001;27:3-15.



showed proanthanol administration to be of benefit in reducing blood urea nitrogen and serum creatinine; histological improvement was also noted.<sup>69</sup>

### **Pancreatitis**

A daily dose of 200-300 mg of a grape seed extract was given to three patients with chronic pancreatitis, characterized by epigastric pain with radiation to the back. All three patients reported a significant reduction in pain severity and frequency of painful episodes, and two of three patients reported a significant reduction in use of narcotic analgesics. The third patient, vomiting almost daily, reported resolution of vomiting after taking the proanthanol extract. All three patients reported a return of symptoms upon cessation of treatment.<sup>70</sup>

### **Systemic Lupus Erythematosus**

In a pilot study of 11 patients with systemic lupus erythematosus (SLE), six were given a proanthanol extract (120 mg daily for 30 days, then 60 mg daily for 30 days) in addition to usual medications; the other five patients received placebo with their usual medications. Patients in the treatment group showed reductions in spontaneous lymphocyte apoptosis, T-lymphocyte activation, reduced generation of reactive oxygen species, lower erythrocyte sedimentation rates, and a decrease in the SLE disease activity index compared to the placebo group. The mechanism may be attributable to proanthanol's antioxidant effect, resulting in reduced inflammatory activity.<sup>71</sup>

### **Asthma**

In a pilot study of 26 patients with varying degrees of asthma severity, an proanthanol dosage of 1 mg/lb/day for four weeks, at which time patients in the treatment group were crossed over to the placebo group for another four weeks, resulted in statistically significant improvements in forced expiratory volume (FEV1), forced vital capacity (FVC), and the FEV1/FVC ratios. A significant reduction in serum leukotriene levels was also observed in patients receiving proanthanols when compared to control and baseline values, and patients in the proanthanol group reported significant improvements in asthma symptom scores.<sup>72</sup>

### **Drug Interactions**

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<sup>69</sup> Stefanovic V, Savic V, Vlahovic P, et al. Reversal of experimental myoglobinuric acute renal failure with bioflavonoids from seeds of grape. *Ren Fail* 2000;22:255-266.

<sup>70</sup> Banerjee B, Bagchi D. Beneficial effects of a novel IH636 grape seed proanthocyanidin extract in the treatment of chronic pancreatitis. *Digestion* 2001;63:203-206.

<sup>71</sup> Stefanescu M, Matache C, Onu A, et al. Pycnogenol efficacy in the treatment of systemic lupus erythematosus patients. *Phytother Res* 2001;15:698-704.

<sup>72</sup> Hosseini S, Pishnamazi S, Sadrzadeh SM, et al. Pycnogenol[R] in the management of asthma. *J Med Food* 2001;4:201-209.

There are no known interactions between proanthanol/adaptogen extracts and other medications; however, data from in vitro and human studies indicate proanthanols have an inhibitory effect on platelet aggregation similar to aspirin.<sup>73</sup> Therefore, caution is suggested in patients taking anticoagulant medication.

### **Dosage**

We usually recommend a start-up dosage of 3 mgs. per pound of body weight although we do recommend using higher dosages for critical conditions. We also recommend beginning with a “bulk-up” dosage of 2-3x normal for two weeks and reducing to “normal dosage” after. Therefore, 1 cap per day is considered “normal” while 1 cap 3x daily is a good start up regimen.

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<sup>73</sup> Putter M, Grotemeyer KH, Wurthwein G, et al. Inhibition of smoking-induced platelet aggregation by aspirin and pycnogenol. *Thromb Res* 1999;95:155-161. Yamakoshi J, Saito M, Kataoka S, Kikuchi M. Safety evaluation of proanthocyanidin-rich extract from grape seeds. *Food Chem Toxicol* 2002;40:599-607.