The Benefit of Pycnogenol’s Anti-Oxidant Affect on Health
A Literature Review

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ABSTRACT

OBJECTIVE

(1) To identify the possible health benefits of the pine bark extract Pinus maritima (pycnogenol). (2) To discuss cited research related to pycnogenol, oxidants, and antioxidants. (3) To provide the reader with a general understanding of the effects of oxidative damage and the benefits of antioxidants.

BASIC PROCEDURES

Literature review articles were taken from the database PUBMED. Articles chosen were those used in a clinically oriented environment and pertaining to retrospective studies, peer-reviewed literature reviews and controlled studies.

Additional information was taken from a booklet entitled “All About Pycnogenol” from the Avery Publishing Group.

MAIN FINDINGS

Antioxidants are substances found in foods, vitamins, and supplements which attack unpaired electrons (free radicals), thus decreasing the incidence of oxidative damage to the body.

Pycnogenol, an extract from the pine bark Pinus maritima, has recently gained popularity as an antioxidant. It has been studied on a limited basis for its action against the damaging effects oxidants have on the body and for its benefit as a nutritional supplement. Along with its antioxidant affect, pycnogenol is also reported to reduce inflammation and edema, protect vascular endothelial cells, and aid the immune system.

CONCLUSIONS

Current scientific literature suggests that pycnogenol provides exceptional antioxidant support against a myriad of conditions resulting from oxidative damage. Briefly, these conditions include cancer, diabetes, atherosclerosis, and premature aging.

Since this supplement has only been researched on a limited basis, the full spectrum of its benefits cannot be determined. Thus, further research must be conducted in order to assess its full potential benefit.

KEY WORDS

Pycnogenol, pinus maritima, antioxidants, procyanadins, free radicals, reactive oxygen, and reactive nitrogen species.

INTRODUCTION

Antioxidants are fast becoming one of the most popular items among health care providers and those individuals concerned with health and wellness. The concepts of free radicals, oxidative damage, and the aging process are becoming familiar ones among lay people, and the subjects of much controversy.

The phrase “oxidative stress” relates to the phenomenon by which there is an overload of oxidants, in particular, the reactive oxygen species (ROS) in the body. These oxidants, which can occur via pollutants, radiation, oxidized foods, ischemia, and via the body’s normal production of free radicals, are known to damage the function of the cell, and may be involved in the genesis of a multitude of health conditions.

Another important concept is that of free radicals. In 1956, a researcher by the name of D. Harman brought this concept to the attention of the scientific community, calling it the free radical theory of aging. This theory postulates that aerobic organisms contribute to the formation of these free radicals, primarily again, the ROS, which appear to be the culprits for many age related diseases. The formation of these free radicals occurs when atoms that are grouped together (called radicals) are disrupted by various reactions. If, during this process an electron is pulled away from the molecular structure of an atom, a “free radical” is formed. This free radical, now unstable, will attract another electron from another molecule, making itself stable, but forming another free radical. This process can go on repetitively, possibly causing permanent damage to many molecules.

Since body cells normally produce free radicals during normal metabolic function (primarily the superoxide and hydrogen peroxide species), they have been equipped with their own antioxidants to combat their effects. Superoxide dismutase (SOD) will destroy superoxide and glutathione peroxidase will destroy the peroxide. Certain cells within the body undergo numerous enzymatic reactions in order to produce these natural antioxidants, but the cells can only
undergo a certain number of cycles before the protein matrix of the cell becomes damaged. Radicals can be formed after these enzymes are destroyed, and they can create free radical oxidation in other parts of the cell.

Antioxidants are the prime scavengers of free radicals. They seek these free radicals out and pair the unmatched electron, thus making them stable. Antioxidants are found in various foods including whole grain cereals, fruits and vegetables, and certain water and fat-soluble vitamins and botanical supplements.

Pycnogenol is a natural plant bioflavonoid (phytochemical) and procyanidin supplement made from the bark of the European coastal pine, *Pinus maritima*. It is found exclusively in the Landes Forest in southwest France. Dr. Jacques Masquelier, of the University of Bordeaux in France, studied the use of this particular species of pine bark in 1966 and is responsible for the name pycnogenol. Bioflavonoids, also known as flavanoids, are a class of beneficial compounds found in various plants. Procyanidins are the class of bioflavonoids to which pycnogenol belongs. Presently, there are approximately 250 procyanidins in nature. *Pinus maritima* (Pycnogenol) is currently being promoted and marketed as a powerful anti-oxidant and free radical scavenger. It is touted as being 50 times more powerful than Vitamin E. Others that fall within the class of anti-oxidants are Vitamins C (ascorbic acid) and E (alpha tocopherol), and beta carotene. It has been postulated that pycnogenol is 20 times more potent than vitamin C as a free radical scavenger.

Anti-oxidants are substances that can have potential positive health effects by neutralizing oxygen free radicals, which are highly active and damaging atoms produced by various environmental and chemical substances. These free radicals, if left unmanaged by the body, can lead to a host of detrimental conditions associated with the aging process. Anti-oxidants are also protective against cytotoxic (cell damaging) agents, including the neurotransmitter glutamate. Although this is an important substance that the body requires, excess amounts can lead to various neurological disorders.

In general, the use of pine bark therapeutically dates back to as early as the 4th century B.C. when the great physician, and teacher Hippocrates mentioned its use against inflammatory disease. Pharmacist H. Miner, in 1479, considered the use of pine bark helpful for wound healing and it was suggested to be useful in the treatment of scurvy and skin disorders. Pine bark was also used for food and as a beverage by the early Native Americans. The particular species of European pine bark, pycnogenol has recently been used in the treatment of Attention Deficit Hyperactive Disorder (ADHD) as well. Pycnogenol (*Pinus maritima*) exists specifically in the Landes de Forest in France because of the climate conditions, which allows it to be distinctly characteristic from other species of pine bark.

Pycnogenol contains various plant compounds, which are protective against many age-related, and free radical induced, diseases such as atherosclerosis, cerebral ischemia, Alzheimer’s disease, Parkinson’s disease, arthritis, and other various forms of cardiovascular and cerebrovascular diseases. Pycnogenol is purported to aid the immune system, protect vascular endothelial cells, and reduce inflammation and edema. An anti-aggregatory affect has also been noted. Included in pycnogenol’s composition are the transitional metals iron, copper, and zinc, as well as a surprisingly high content of calcium. Pycnogenol is highly water-soluble and has a high bioavailability, meaning that the body readily utilizes the various compounds contained in the substance. It is also relatively free of toxicity. What is unique about this substance is that the compounds found in pycnogenol are very consistent, which make it a highly stable supplement when compared to others, such as grape seed extract, which makes pycnogenol reliable when determining its effectiveness via experimental therapeutic studies.

The focus of this literature review will be to examine the literature to ascertain the potential therapeutic benefit and clinical relevance of pycnogenol utilizing cited research articles as the basis for the author’s conclusion.

**REVIEW OF LITERATURE**

The anti-oxidant effect of pycnogenol has been linked to the prevention of lipid peroxidation, particularly the low-density lipoprotein (LDL) that can aid in the prevention of atherosclerosis, heart disease, and stroke. In the oxidation process, damage to the endothelial cells by free radical oxidants can trigger the formation of atherogenesis. A mild hypotensive effect of pycnogenol has also been noted via inhibition of the angiotensin-converting enzyme (ACE). The compounds that are responsible for these noted effects appear to have a protective quality, and consist of catechin, taxifolin, procyanidines, phenolic acids and their glucose esters or glucosides. The pharmacognosy of these compounds is not within the scope of this review.

The four main therapeutic properties of these procyanidin bioflavonoids include free radical scavenging, collagen binding, inhibition of pro-inflammatory enzymes, and the inhibition of histamine release via mast cell degranulation. These are processes which occur naturally on a daily basis in every individual and can have an effect on aging by preventing oxidative damage to DNA, proteins, and other macromolecules which have been shown to accumulate with age.
During the body’s natural inflammatory response, the principal inflammatory cell, the macrophage produces a massive amount of oxidants. The primary oxidant being the reactive oxygen species (ROS), such as hydrogen peroxide, superoxide anion, and the reactive nitrogen species (RNS), such as nitric oxide (NO). These oxidants have been linked to diseases such as cancer, diabetes, and atherosclerosis, and may contribute to ischemia, and the aging process.1,12,14,15 The reactive oxygen species, if left unattended, can cause significant damage to lipids, proteins, carbohydrates, and nucleic acid cells.9 The pro-oxide environment that is produced triggers cell responses that lead to endothelial cell dysfunction. Macrophages not only interact with endothelial cells, but with smooth muscle cells and lymphocytes as well. This is an important interaction because of the production of the ROS and RNS oxidant species that are generated during this inflammatory process.22 Pycnogenol has been reported to enhance the antioxidant capacity of cultured endothelial cells by specifically increasing enzyme expression and by protecting them from organic peroxide induced oxidative stress. Pycnogenol has been further shown to scavenge both ROS and RNS species, as well as to modulate NO metabolism in the activated macrophage.9

A study in 1997 compared the anti-oxidant affects and free radical scavenging capability of pycnogenol, and 5B scymnl, which is an active component of deep sea shark liver oil that is found in the bile of sharks and rays. This bile product has been used by the Japanese population for many years as a folk remedy for scalds, burns, and acne. This study actually found that the 5B scymnl, taken from two species of dogfish sharks, had a much better overall protective effect as an OH scavenger when compared to pycnogenol, but the study did note similar effects of pycnogenol as well.9 Neither the age, nor the geographical location of the sharks used in this study was disclosed.

Another anti-oxidant, alpha tocopherol (Vitamin E) has also been shown to have a protective effect against cardiovascular diseases. A study performed at the University of California, Berkley, was able to demonstrate via an ESR spectrometer, that not only was alpha tocopherol effective in this protective manner, but that pycnogenol was actually able to protect the action of this vitamin. The study focused on pycnogenol’s ability to scavenge the RNS (reactive nitrogen species) generated by activated RAW 264.7 macrophage.17 This RNS has a damaging affect on the endothelial cell. Alpha tocopherol can mitigate this damage because it helps to maintain endothelial cell function.

The benefits of pycnogenol have also been found in the stimulation of lipolysis (fat breakdown). An in vitro study, conducted in 1999 in Nagoya Japan, didn’t necessarily suggest that pycnogenol be utilized as an anti obesity supplement, but noted that its use, on a cellular level, caused lipolysis to occur primarily in small droplets. The study found these results by first converting preadipocytes to adipocytes with insulin. Then either 2 x 10-6m of epinephrine or 50 micrograms/ml of pycnogenol was added to the medium. The study then compared the size of the droplets. Although the authors did not specifically note the type of insulin utilized (bovine or human), the results of the study did indicate that pycnogenol may be useful in the prevention of obesity.23 Another apparent flaw here is the influence of exposing insulin to an aerobic environment. The authors apparently took human insulin and via dropper, added it to a medium. This would have a deleterious effect on the experiment’s outcome and the validity of the study since pycnogenol must be ingested.

It has been demonstrated that pycnogenol modulates the depressed immune response (improving both T and B cell function), and hemopoetic function associated with aging in retro-virus infected or ethanol-fed mice. Here, it reduced the elevated levels of both interleukin 6 and interleukin 10, which are key inflammatory markers in the body. Pycnogenol has also been shown to increase the cytotoxicity of natural killer cells.19 A study performed in 1998 on 7 month old mice demonstrated that feeding pycnogenol at 5mg/kg and 10mg/kg of body weight for a two month period significantly enhanced the proliferation of T cells and B cells, stimulated by the reagents concanavalin (ConA) and lipopolysaccharide (LPS) respectively in senile-prone (SAMP) mice.19 This study did not specifically address the methods used to sacrifice the mice, nor did it indicate whether the spleens were removed using aseptic techniques.

Another protective effect of pycnogenol was demonstrated in a study that involved smokers.24 The short-term effects of smoking include increased heart rate, blood pressure, and platelet aggregation, which can lead to thrombus formation. The long-term effects include various respiratory and cardiovascular disorders, and the possibility of cancer formation. A study was performed on 29 male and 11 female smokers between the ages of 20 and 64 to compare the protective effects of pycnogenol to aspirin. In this study, the subjects were separated into two groups and in random order were given doses of pycnogenol (100-150mg), and aspirin (500mg). This study found that pycnogenol was protective against platelet reactivity, which is the ratio of non-aggregated platelets to the total number of platelets measured. Bleeding time, as determined by breaking the skin of the earlobe with a lancet, however, was effected more so by aspirin than by pycnogenol. This study appeared flawed in that it did not state the number of years the volunteers smoked. This could have had an effect on the health status of the individual. The study demonstrated the vascular hazards associated with both long and short
term smoking, including platelet aggregation, and the benefits that pycnogenol affords.

Another study performed by the same group of researchers, looked at the effects of pycnogenol on liver and lung microsomes in 6 and 20-month-old rats. This study focused on the tobacco specific nitrosamine, 4-(methylamino)-1(3-pyridyl)-1-butanone (NNK), in the presence of pycnogenol. NNK has potential mutagenic and carcinogenic capabilities, which can be found in tobacco smoke. In this study, pycnogenol interrupted the major pathway of NNK metabolism in the rat lung microsomes, demonstrating that it may afford “some” protection against the dangerous mutagenic and carcinogenic effects of NNK.

A similar study looking at the detrimental affects of NNK on lung and liver microsomes was performed at the Loma Linda University School of Medicine, in Loma Linda, CA. This study also utilized 6 and 20-month-old rats, but in this experiment the rats were given 5mg of pycnogenol/kg intragastrically. After asphyxiation and acclimation for an undetermined amount of time, the liver and lungs were removed and then analyzed by looking at the amount of un-metabolized NNK. The results of this study conclusively demonstrated that pycnogenol had a significant overall inhibition of NNK metabolism, primarily in the lung microsomes. The benefit indicated by this study was a lowered risk for lung tumorgenesis.

An in-vivo and in-vitro study conducted in 1995 looked at the inhibition effect (the vasopressive response) of angiotensin converting enzyme (ACE), and the hypotensive affect of procyandin, utilizing rabbit lung and rats. ACE catalyzes the conversion of angiotensin I to the vasoactive peptide, angiotensin II, which is concentrated in the proximal tubules of the kidney. This study, without specifically defining the method of ACE extraction, took samples from rabbit lungs and examined it after incubation in an extract of pine bark. The blood pressure of rats was then determined via a carotid cannula after intravenous injection of a pine bark extract to assess the hypotensive effects. The results of the study conclusively demonstrated that the oligomeric procyandins found in pine bark have a hypotensive effect and an inhibitory effect on ACE in a non-competitive manner, but the investigators speculate that the results would only be moderate in human’s.

During the body’s natural inflammatory process, special cells known as polymorphonuclear neutrophils and macrophages are sent to the site of injury. During this process, these cells, which contain proteolytic enzymes including elastase-type proteases, engulf phagocytic material to aid the healing process. Natural inhibitors normally control these enzymes, but there are several conditions that may block this inhibitory effect, thus allowing degradation (elastolysis) of the connective tissue macromolecule elastin, to occur.

An in-vivo and in-vitro study conducted in France in 1983 looked at the binding capability of pycnogenol to elastin to determine its efficacy in decreasing the rate of elastase degradation. During this study, procyandin oligomers (PCO’s) and elastase was injected intradermally into rabbits. Elastase was extracted from calf ligamentum nuchae by an undefined technique known as “hot alkali technique”. The results of the study showed that PCO injected into elastin fibers had a protective affect against proteolytic elastase degradation.

PROCEDURES

Databases searched

For this literature review, the database PUBMED was utilized. The reason for this choice was that this database is a highly respected and medically oriented site and that it is also readily available via the Internet. It is also frequently updated to provide the reader with the most recent and concise information on various medical conditions. The majority of the searches were conducted in the library of the University of Bridgeport, Bridgeport, CT.

Since pycnogenol appears to be relatively new to the research community, there was no limit used as to the years for the database searches. This option provided the literature review with the most up to date information available.

The two MeSH (Medical Subject Headings) terms used for this review were pycnogenol and antioxidants. The two terms were not combined. The heading of “antioxidants” alone was quite overwhelming; therefore only those articles that were the subject of free radicals and dietary antioxidants were chosen. The term “free radicals” also provided numerous articles, therefore, the choice of which articles to use became one in which the information provided was relevant to this literature review. The articles chosen provided information regarding the genesis of free radicals. The articles also provided an insight as to some of the health related consequences of free radical formation and how antioxidant use impacts the neutralization of these radicals.

When searching using only “pycnogenol”, any article that was available was evaluated. Journal articles from respected peer-reviewed sources such as the Journal of American College of Nutrition, Free Radical Biological Medicine, Anticancer Research, and Biochemical Pharmacology were prioritized, however, a few selected others were also used.
ANALYSIS OF DATA

As stated previously, PUBMED inquiries were utilized for this review. There were 31 articles on pycnogenol. Using the original index MeSH term pycnogenol and antioxidants, 31 and 47,436 articles, respectively, were produced. In essence, any article that was produced by the term pycnogenol was analyzed. Initially, the abstracts were looked at to determine if the study was worthy of inclusion for this review. The articles chosen for inclusion in this review were those that dealt with general information regarding antioxidants, and those used in experimental situations where pycnogenol was looked at in various testing situations. After this review, 24 articles were deemed worthy for inclusion. More specifically, the effects and/or comparison of pycnogenol in human or animal studies were looked at. The main objective was determining if this supplement had any therapeutic value according to the research conducted.

The MeSH term antioxidants produced an unsurprisingly large amount of articles. It would have been impossible to screen all of these articles to determine which ones would be appropriate for use. Specifically, the effects of antioxidants in the diet, the general effects that oxidative damage has on the body, and the benefit one could achieve utilizing antioxidant supplementation were evaluated. After following these criteria, 6 articles were chosen. Since the main focus of this study was not of antioxidants, but the effects of the antioxidant pycnogenol, only 6 articles were chosen to briefly inform the reader of the basics of oxidative stress and antioxidant therapy.

SUMMARY AND CONCLUSIONS

The formation of free radicals, or oxidants, occurs during many situations, including those caused by exposure to environmental and chemical substances, and by normal body metabolism. Free radicals have been associated with a myriad of adverse health conditions including age related diseases, such as atherosclerosis, Alzheimer’s and Parkinson’s disease, and arthritis, to name a few.

The main free radicals are the reactive oxygen species (ROS) and the reactive nitrogen species (RNS). The damage that these oxidants produce occurs in lipids, proteins, carbohydrates, and nucleic acids cells.

The body is equipped with natural antioxidants, which include superoxide dismutase (S.O.D.), and glutathione peroxidase. These antioxidants are produced by the body after a series of enzymatic reactions occur. These enzymatic reactions, although necessary in the production of the antioxidants, may themselves deteriorate after several of the enzymatic cycles to create free radicals. The interruption of this vicious cycle may be accomplished with the use of added antioxidant supplementation.

Antioxidants are the single most important scavengers of the unpaired electron free radical. Antioxidants are found in vegetables, fruits, and supplements. Pycnogenol, a certain species of the European pine bark, Pinus maritima, appears to be a superior form of antioxidant supplementation. Pycnogenol demonstrated consistent superior benefits in a wide array of testing situations. This particular form of pine bark dates back to the 4th century, and was also used by the early Native Americans as food and a beverage.

Pycnogenol’s benefit goes beyond its antioxidant ability, and its ability to aid in the prevention of lipid peroxidation. It can act as a mild hypotensive agent, modulate depressed immune responses, reduce inflammation and edema, and even stimulate lipolysis on a cellular level. Interestingly, pycnogenol is reported to contain a high amount of calcium. Although the use of pycnogenol for calcium deficiency was not looked at in this review, one could theorize that a benefit may be seen in a deficiency situation, and could be the focus of further investigation.

Although there were notable flaws in many of the studies used for this review, the outcome of these studies certainly seemed favorable overall. Since the majority of these studies were conducted on animals, primarily rabbits and rats, one could speculate that these effects would be seen in humans as well, however, actual human trials would be necessary to confirm this.

As this is a relatively new subject in antioxidant research, further studies must be conducted to completely ascertain the full range of potential therapeutic benefits of supplemental pycnogenol.

REFERENCES


