



AMERICAN BOTANICAL COUNCIL  
PROPRIETARY BOTANICAL INGREDIENT

SCIENTIFIC AND CLINICAL  
M O N O G R A P H

FOR

PYCNOGENOL®

(French Maritime Pine Bark Extract)

*Pinus pinaster* Aiton subsp. *atlantica*

[Fam. Pinaceae]



# Clinical Overview

## PYCNOGENOL®

(French Maritime Pine Bark Extract)  
*Pinus pinaster* Aiton subsp. *atlantica*  
[Fam. Pinaceae]

### OVERVIEW

This Clinical Overview is based on the full monograph covering the published scientific and clinical research on Pycnogenol®, a patented, proprietary extract made exclusively from French maritime pine bark (*Pinus pinaster*, manufactured by Horphag Research, Geneva, Switzerland). Pycnogenol extract is standardized to contain 70 ± 5% procyanidins in compliance with USP 28, compounds known for relatively significant antioxidant and anti-inflammatory activity, among other actions. Pycnogenol was ranked among the top 30 selling herbal dietary supplements in the United States in mainstream retail outlets (food, drug, and mass market stores) in 2008 in terms of dollar sales and had a total sales increase of nearly 34% over the previous year.

### PRIMARY USE

**Cardiovascular Health:** Although there are many potential uses for Pycnogenol, the most well-studied use is for improving vascular health as a result of improved endothelial function and venous insufficiency. Controlled clinical trials have been published that demonstrate symptomatic improvement of blood circulation, blood pressure and platelet function normalization, and venous insufficiency. However, more studies with larger numbers of participants are needed to further establish these findings.

### OTHER POTENTIAL USES

Controlled clinical trials have been published for the following indications: thrombosis, diabetes and its complications, hypertension and its complications, asthma, attention deficit hyperactivity disorder (ADHD), gynecology (endometriosis and dysmenorrhea), and osteoarthritis. None of these indications are supported by more than 1 or 2 well-designed published clinical trials.

Other potential uses with weaker research support include erectile dysfunction, retinopathy, gingivitis, melasma, and cramps and muscular pain.

### PHARMACOLOGICAL ACTIONS

Pharmacological studies employing *in vitro*, animal, and human models have found that Pycnogenol has potent antioxidant activity, anti-inflammatory actions, improves endothelial function (produces vasodilation), reduces platelet aggregation, reduces alpha-glucosidase activity and blood glucose levels, promotes wound healing, alters neurotransmitter levels in children with ADHD, and improves reproductive health by improving sperm morphology and function.

### DOSAGE AND DURATION OF ADMINISTRATION

The following doses were used in the clinical trials reported in the table in the full monograph. [Note: Some of the doses are based on single studies or uncontrolled studies.]

ADHD: 1 mg/kg of body weight/day  
Asthma: 1 mg/lb of body weight/day  
Cholesterol/dyslipidemia: 120-150 mg/day

Chronic Venous Insufficiency: 150-360 mg/day  
Diabetes: 50-200 mg/day  
Dysmenorrhea: 30-60 mg/day  
Endometriosis: 60 mg/day  
Erectile dysfunction: 120 mg/day  
Hypertension: 100-200 mg/day  
Melasma: 75 mg/day  
Muscle cramps: 200 mg/day  
Osteoarthritis: 100-150 mg/day  
Perimenopause: 200 mg/day  
Platelet function: 25-200 mg/day  
Retinopathy: 20-160 mg/day

In the clinical trials the most common duration of use was 2-3 months; however, long-term use may be justified. There is no evidence from actual product use over several decades by millions of people that might warrant a limitation, and based on the published chemistry and pharmacology of Pycnogenol there are no data suggesting a limitation on duration of use. There are no long-term safety studies.

### MANUFACTURER DOSE RECOMMENDATIONS:

According to the manufacturer, the dosage of Pycnogenol will depend on the nature of the desired health benefit. For example, the dose required for preventative effects is different from dose aimed at improving acute or chronic health problems.

As an antioxidant, Pycnogenol may be effective at any dose. The manufacturer states that in order to have measurable physiologic effects related to prevention of oxidative tissue damage the daily intake should be at least 20 mg.

When used as a preventative measure for cardiovascular health, 25 mg/day is recommended. Higher doses ranging from 50 to 100 mg are recommended for cardiovascular health risks such as hypertension, blood hyper-coagulation, and impaired blood circulation.

When using Pycnogenol for anti-edema effects, such as in venous insufficiency, the manufacturer recommends 50 mg/day. For more advanced stages the daily dosage should be higher, in the range of 100-150 mg for a limited period of time such as up to 4 weeks. Once edema and symptoms have improved, a daily maintenance dosage of 50 mg may be considered.

For lowering blood glucose in patients with diabetes the manufacturer recommends taking 50 mg once or twice daily.

Anti-inflammatory effects can be achieved with Pycnogenol doses ≥ 30 mg/day.

For dysmenorrhea, 30 mg once or twice daily is recommended.

For osteoarthritis or asthma, 100 mg/day is recommended.

### CONTRAINDICATIONS AND PRECAUTIONS

There are no known contraindications for Pycnogenol.

**Pregnancy and Lactation:** As a general precaution, Pycnogenol should not be taken during the first 3 months of pregnancy. This precaution is based on general principles and a lack of any published data on pregnant women using Pycnogenol in the first trimester.

# Clinical Overview

Safety trials have demonstrated absence of mutagenic and teratogenic effects, no perinatal toxicity, and no negative effects on fertility.

## ADVERSE EFFECTS

Pycnogenol has been affirmed GRAS (generally recognized as safe) for use in conventional foods, based on the evaluation of clinical safety and pre-clinical toxicology data by an independent panel of toxicology experts contracted by the manufacturer in what is known as a GRAS self-affirmation process.

The safety of Pycnogenol is based on data obtained from 70 clinical studies (n =5723) including both healthy subjects and patients with a particular dysfunction or pathology. The mean daily Pycnogenol dose was 80 mg (range 30-450 mg/day, n = 4665). The global frequency rate of adverse effects (AEs) is 2.4%. However, in healthy subjects, the incidence rate of AEs is 0.19% (based on 2116 subjects in 31 clinical studies). An evaluation of the clinical studies revealed that the occurrence of AEs is unrelated to the dose or duration of use.

From what can be gleaned from the clinical trials, it appears that gastrointestinal (GI) discomfort is the most frequently occurring AE. This may be attributed to the astringent nature of Pycnogenol. The GI effects did not occur when Pycnogenol was taken with or after meals. Dizziness, headache, and nausea are the next most frequently reported AEs. Acne, diarrhea, and dysfunctional bleeding are the most frequent AEs in studies of women with premenstrual syndrome or dysmenorrhea. The majority of AEs observed were mild.

Analysis of clinical safety data obtained from 4 clinical studies (n =185) evaluating Pycnogenol's effect on blood pressure and heart rate in normo-tensive people did not reveal any significant changes on systolic or diastolic blood pressure or heart rate.

Post-marketing surveillance (spontaneous AE reporting) carried out between 2002 and 2005 in Europe and Asia revealed 6 case reports of AEs despite millions of Pycnogenol doses sold. There were 3 cases of urticaria, 1 case of headache, 1 case of nausea, and 1 case of eczema and diarrhea. According to the manufacturer, urticaria is a rare allergic reaction that could be due to the color component of the tablet.

There have been no reports of serious AEs in any clinical study or from commercial use of Pycnogenol since it was initially introduced into the market in Europe around 1970.

## DRUG INTERACTIONS

Pycnogenol has been consumed by adult and elderly patients taking concomitant therapies. No information from spontaneous reporting is available on any interactions resulting from simultaneous intake of other drugs with Pycnogenol. Other interactions with alcohol consumption or nutrition habits have not been reported. Pycnogenol does not affect INR (International Normalization Ratio, a measurement of bleeding tendency) in patients taking aspirin. No other drug interaction studies have been performed with Pycnogenol.

## CLINICAL REVIEW

As of June 2008 there are a total of 33 published human clinical trials on Pycnogenol as a monopreparation that have been published in English or translated to English. Due to space considerations, the authors and editors of the full Pycnogenol monograph decided to

review only selected studies; however, most appear in the Published Clinical Studies Table. Studies included in the text of the Clinical Review section of the full monograph met the following criteria: human trial, any indication, any dose of Pycnogenol, English language or English translation, and any publication year. Exclusion criteria were: pilot study, no control group, untreated control group, or any other significant methodological limitation. Seventeen clinical trials met these criteria and are reviewed in the text in the full monograph. They evaluate chronic venous insufficiency and its complications, thrombosis, diabetes and its complications, hypertension and its complications, asthma, ADHD, gynecology (endometriosis and dysmenorrhea), and osteoarthritis.

To summarize the clinical findings, Pycnogenol may help decrease edema formation in the lower legs, such as in people with chronic venous insufficiency. Pycnogenol improves endothelial function resulting in improved blood circulation, lowered blood pressure in hypertension, and normalization of platelet coagulability. Pycnogenol has been shown to improve glycemic control in patients with type 2 diabetes and to improve treatment of diabetic ulcers. Preliminary studies suggest that Pycnogenol may be beneficial for children with ADHD and may be a useful adjunct therapy for patients with asthma. Pycnogenol may help reduce pain associated with menstrual disorders. Several clinical studies report that Pycnogenol may improve subjective symptoms of knee osteoarthritis.

# PYCNOGENOL® Consumer/Patient Information Sheet

(French Maritime Pine Bark Extract) *Pinus pinaster* Aiton subsp. *atlantica* [Fam. Pinaceae]

## OVERVIEW

Pycnogenol® is a proprietary product made exclusively from French maritime pine bark extract (*Pinus pinaster*). It is manufactured by Horphag Research, Geneva, Switzerland. Pycnogenol was ranked among the 30 top-selling herbal dietary supplements in the United States in mainstream retail outlets (food, drug, and mass market stores) in 2008.

## USES

Although there may be many potential uses for Pycnogenol, the most well-studied use is to treat chronic venous insufficiency, a condition defined by poor drainage of blood from veins resulting in swelling or skin problems. Five controlled clinical trials have been published that show improved symptoms. However, larger and more rigorous studies are warranted to confirm these findings. Controlled human clinical trials have been published suggesting the following potential uses: thrombosis (blood clot), diabetes and its complications, hypertension (high blood pressure) and its complications, asthma, attention deficit hyperactivity disorder (ADHD), gynecology (endometriosis [premenstrual pain caused by endometrial tissue in places other than the uterus] and dysmenorrhea [painful menstruation]), and osteoarthritis. These indications only have 1-2 well-designed published clinical trials that support the findings. Preliminary clinical trials have been conducted in the following areas, but more trials are needed to support these potential uses: erectile dysfunction, retinopathy (a diseased condition of the retina in the eye), gingivitis (infection of oral gums), melasma (a dark discoloration of skin), and cramps and muscular pain.

## DOSAGE AND DURATION OF USE

The following doses were used in the clinical trials reported in the table of clinical trials in the full monograph by the American Botanical Council. It should be noted that some of the doses are based on single studies and/or uncontrolled studies.

- ADHD: 1 mg/kg (2.2 lbs) of body weight/day
- Asthma: 1 mg/lb of body weight/day
- Cholesterol/dyslipidemia: 120-150 mg/day
- Chronic Venous Insufficiency: 150-360 mg/day
- Diabetes: 50-200 mg/day
- Dysmenorrhea: 30-60 mg/day
- Endometriosis: 60 mg/day
- Erectile dysfunction: 120 mg/day
- Hypertension: 100-200 mg/day
- Melasma: 75 mg/day
- Muscle cramps: 200 mg/day
- Osteoarthritis: 100-150 mg/day
- Perimenopause: 200 mg/day
- Platelet function: 25-200 mg/day
- Retinopathy: 20-160 mg/day

In the clinical trials the most common duration of use was 2-3 months; however, long-term use may be justified. Based on the published chemistry, pharmacology, and toxicology of Pycnogenol, there are no data suggesting a limitation on duration of use and there is no evidence from actual product use over several decades by millions of people that might warrant a limitation.

### Manufacturer dose recommendations:

According to the manufacturer, the dosage of Pycnogenol will depend on the nature of the desired health benefit. For example, the dose required for preventative effects is different from the dose aimed at improving acute or chronic health

problems.

As an antioxidant, Pycnogenol may be effective at any dose. The manufacturer states that in order to have measurable physiologic effects related to prevention of oxidative tissue damage, the daily intake should be at least 20 mg.

When used as a preventative measure for cardiovascular health, 25 mg/day is recommended. Higher doses ranging from 50 to 100 mg are recommended for cardiovascular health risks such as hypertension, blood hyper-coagulation, and impaired blood circulation.

When using Pycnogenol for anti-edema (anti-swelling) effects, such as in venous insufficiency, the manufacturer recommends 50 mg/day. For more advanced stages the daily dosage should be higher, in the range of 100-150 mg for a limited period of time such as up to 4 weeks. Once edema and symptoms have improved, a daily maintenance dosage of 50 mg may be considered.

For lowering blood glucose in patients with diabetes the manufacturer recommends taking 50 mg once or twice daily.

Anti-inflammatory effects can be achieved with Pycnogenol doses ≥ 30 mg/day.

For dysmenorrhea, 30 mg once or twice daily is recommended.

For osteoarthritis or asthma, 100 mg/day is recommended.

## CONTRAINDICATIONS AND PRECAUTIONS

There are no known contraindications for Pycnogenol.

**Pregnancy and Lactation:** As a general precaution, Pycnogenol should not be taken during the first 3 months of pregnancy.

## ADVERSE EFFECTS

The safety of Pycnogenol is based on data obtained from 70 human clinical studies on a total of 5723 people, including both healthy subjects and patients. The overall frequency rate of adverse side effects is very low (2.4%). In healthy subjects, the incidence rate is even lower (0.19%). An evaluation of the clinical studies revealed that the occurrence of adverse effects is unrelated to the level of the dose or duration of use.

From what can be gleaned from the clinical trials, it appears that gastrointestinal (GI) discomfort is the most frequently occurring adverse effect (AE). The GI effects may be avoided by taking Pycnogenol with or after meals. Dizziness, headache, and nausea are the next most frequently reported AEs. Acne, diarrhea, and dysfunctional bleeding are the most frequent AEs in studies of women with premenstrual syndrome or dysmenorrhea. The majority of AEs observed were mild.

Analysis of clinical safety data obtained from 4 clinical studies on a total of 185 people evaluating Pycnogenol's effect on blood pressure and heart rate did not reveal any significant changes on systolic or diastolic blood pressure or heart rate.

There have been no reports of serious AEs in any clinical study or from commercial use since it was initially introduced into the market in Europe around 1970.

## DRUG INTERACTIONS

Pycnogenol has been consumed by adult and elderly patients taking conventional pharmaceutical medications at the same time. No information from spontaneous reporting is available on any interactions resulting from simultaneous intake of conventional medicines with Pycnogenol. Other interactions with alcohol consumption or food intake have not been reported. Pycnogenol does not affect INR (bleeding tendency) in patients taking aspirin. No other drug interaction studies have been reported.



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As with all medications and dietary supplements, please inform your healthcare provider of all herbs and medications you are taking. Interactions may occur between medications and herbs or even among different herbs when taken at the same time. Treat your herbal supplement with care by taking it as directed, storing it as advised on the label, and keeping it out of the reach of children and pets. Consult your healthcare provider with any questions. The information contained on this sheet has been excerpted from the full Scientific and Clinical Monograph on Pycnogenol®. ABC is an independent member-based educational organization focusing on the medicinal use of herbs. For more information visit the ABC website at [www.herbalgram.org](http://www.herbalgram.org).

# PROPRIETARY BOTANICAL INGREDIENT SCIENTIFIC AND CLINICAL MONOGRAPH

## PYCNOGENOL®

(French Maritime Pine Bark Extract)  
*Pinus pinaster* Aiton subsp. *atlantica*  
[Fam. Pinaceae]

By Heather Oliff, PhD

### PUBLISHER'S NOTE

The preparation and publication of this literature review and monograph on this proprietary botanical ingredient has been conducted by the American Botanical Council (ABC) for educational purposes only. This publication reflects the state of the scientific and clinical literature on this specific commercial plant-based ingredient up to a reasonable period of time prior to the initial publication (and/or any subsequent revisions). This publication has been peer reviewed for its accuracy by experts qualified in their formal training to assess the literature in various scientific disciplines and/or clinical medicine related to the information included in this document.

This publication should not be interpreted as a promotion or endorsement by the authors or ABC of the specific ingredient or any product containing the ingredient or of the commercial companies affiliated with their manufacture, importation, marketing, or sale. ABC has long recognized that the pharmacological and clinical literature on specific categories of herbs and other botanically-derived ingredients used in conventional foods, dietary supplements, and/or medicinal preparations are often based on one or several leading proprietary commercial nutritional or phyto-medicinal preparations and, as such, this publication reflects and acknowledges the existence of such literature as having been conducted on one or more leading products in a particular category.

The American Botanical Council is an independent, nonprofit research and education organization, tax-exempt under section 501(c)(3) of the Internal Revenue Service code, dedicated to the rational and responsible use of herbs, medicinal plants, phytomedicines, teas, essential oils, and related plant-based ingredients.

### OVERVIEW

French maritime pine bark extract, sold under the trade name Pycnogenol® (manufactured by Horphag Research, Geneva, Switzerland) was ranked among the 30 top-selling herbal dietary supplements in the United States in mainstream retail outlets (food, drug, and mass market stores) in 2008 and had a total sales increase of nearly 34% over the previous year.<sup>1</sup>

Pycnogenol is prepared from the bark of French maritime pine trees (*P. pinaster*) by a standardized process. The trees are cultivated as a monoculture exclusively in a narrow area in Southwest France (Landes de Gascogne). The multi-layered thick outer bark is harvested from 30-year-old cultivated trees grown for timber for furniture. The timber production generates far more bark as by-product than required for extraction of Pycnogenol. The forest is the largest found in Europe with 2.5 million acres. The cut trees are replaced by seedlings and the entire process is completely sustainable. The process is controlled by the French government and the majority of the forest is a National Park.

Recent research suggests significant antioxidant activity for Pycnogenol, based primarily on its procyanidin content. Currently, Pycnogenol is used primarily for cardiovascular health, including chronic venous insufficiency.<sup>2</sup> Pycnogenol has been shown to improve glycemic control in patients with type 2 diabetes and to improve treatment of diabetic ulcers.<sup>3,4</sup> Preliminary studies demonstrate that Pycnogenol may be beneficial for children with attention deficit hyperactivity disorder and may be a useful adjunct therapy for patients with asthma.<sup>5-7</sup> Pycnogenol may help reduce pain associated with menstrual disorders.<sup>8,9</sup> Several clinical studies report that Pycnogenol can improve subjective symptoms of osteoarthritis of the knee.<sup>10-12</sup>

### DESCRIPTION

French maritime pine bark extract is made by extraction of the outer bark of *Pinus pinaster* Ait. subsp. *atlantica*. The French subspecies *atlantica* of *P. pinaster* differs from the Iberian (Spanish) and

Moroccan subspecies by its resistance against salt<sup>13</sup> and in the profile of its phytochemical constituents.<sup>14</sup>

The fresh bark is powdered and extracted with ethanol and water in patented equipment allowing an automated continuous process.<sup>15</sup> After purification of the raw extract, the aqueous solution of the extracted constituents is spray-dried. The resulting fine brownish powder is stable if stored in a dry, dark environment. The extract is standardized to contain  $70 \pm 5\%$  procyanidins, which consist of condensed catechin and epicatechin.

### PRIMARY USE

**Cardiovascular health:** Although there are many uses for Pycnogenol, the most well-studied use is for improvement of endothelial function and venous insufficiency. Controlled clinical trials have been published that demonstrate symptomatic improvement of blood circulation, blood pressure and platelet function normalization, and venous insufficiency.<sup>11-23</sup> However, more studies with larger numbers of participants are needed to further establish these findings.

### OTHER POTENTIAL USES

Controlled clinical trials have been published for the following potential uses: thrombosis, diabetes and its complications, hypertension and its complications, asthma, attention deficit hyperactivity disorder (ADHD), gynecologic disorders (endometriosis and dysmenorrhea), and osteoarthritis. These indications have only 1-2 well-designed published clinical trials that support positive findings suggesting efficacy for each use and warrant further clinical research to support such use.

Other potential uses that require better-designed studies to more fully substantiate the applications of Pycnogenol include erectile dysfunction, retinopathy, gingivitis, melasma (a dark pigmentation of the skin), and muscular cramps and muscular pain.

## DOSAGE AND DURATION OF ADMINISTRATION

### Daily dose in clinical trials:

The following doses were used in the clinical trials reported in the Table of Clinical Trials on Pycnogenol. Note: Some of the doses are based on single studies or uncontrolled studies.

ADHD: 1 mg/kg of body weight/day  
Asthma: 1 mg/pound of body weight/day  
Cholesterol/dyslipidemia: 120-150 mg/day  
Chronic venous insufficiency: 150-360 mg/day  
Diabetes: 50-200 mg/day  
Dysmenorrhea: 30-60 mg/day  
Endometriosis: 60 mg/day  
Erectile dysfunction: 120 mg/day  
Hypertension: 100-200 mg/day  
Melasma: 75 mg/day  
Muscle cramps: 200 mg/day  
Osteoarthritis: 100-150 mg/day  
Perimenopause: 200 mg/day  
Platelet function: 25-200 mg/day  
Retinopathy: 20-160 mg/day

In the clinical trials the most common duration of use was 2-3 months; however, long-term use may be warranted. Based on the published chemistry and pharmacology of Pycnogenol, there are no data suggesting a limitation on duration of use and there is no evidence from actual product use over several decades by millions of people that might warrant a limitation.

### Manufacturer dose recommendations:

According to the manufacturer, the dosage of Pycnogenol will depend on the nature of the desired health benefit. For example, the dose required for preventative effects is different from a dose aimed at improving acute or chronic health problems.

As an antioxidant, Pycnogenol may be effective at any dosage ranges. The manufacturer states that in order to have measurable physiologic effects related to prevention of oxidative tissue damage the daily intake should be at least 20 mg.

When used as a preventative measure for cardiovascular health, 25 mg/day is recommended. Higher doses ranging from 50 to 100 mg are recommended for heart health risks such as hypertension, blood hyper-coagulation, and impaired blood circulation.

When using Pycnogenol for anti-edema effects, such as in venous insufficiency, the manufacturer recommends 50 mg/day. For more advanced stages the daily dosage should be higher, in the range of 100-150 mg for a limited period of time such as up to 4 weeks. Once edema and symptoms have improved a daily maintenance dosage of 50 mg may be considered.

For lowering blood glucose in patients with diabetes the manufacturer recommends taking 50 mg once or twice daily.

Anti-inflammatory effects can be achieved with Pycnogenol doses  $\geq$  30 mg/day.

For dysmenorrhea 30 mg once or twice daily is recommended.

For osteoarthritis or asthma, 100 mg/day is recommended.

## CHEMISTRY

Pycnogenol extract is made from fresh bark, which is powdered and extracted with water and ethanol in a patented process.<sup>15</sup> The result is a very fine, brown-colored, water-soluble powder. Pycno-

genol contains condensed proanthocyanidins\* consisting mainly of procyanidins and phenolic acids. The total amount of procyanidins is standardized to  $70 \pm 5\%$ .<sup>24</sup> Pycnogenol meets the specifications for Maritime Pine Extract detailed in the *US Pharmacopeia*.<sup>25</sup>

The proanthocyanidins are biopolymers consisting of units of the procyanidins catechin and epicatechin, with chain lengths ranging from 2 to 12 monomeric units. The more common dimers, B1 and B3, have been identified as consisting of epicatechin-catechin and catechin-catechin units linked with a C4-C8 bond. Less common are dimers B6 and B7, which are catechin-catechin and epicatechin-epicatechin units linked with a C4-C6 bond. A trimer C2, consisting of catechin-epicatechin-catechin has also been identified. Catechin, epicatechin, and taxifolin represent the "monomeric" procyanidins, of which catechin is the most common.<sup>15</sup>

The phenolic acids in Pycnogenol are derivatives of benzoic acid (p-hydroxybenzoic acid, protocatechic acid, gallic acid, vanillic acid) or cinnamic acid (caffeic acid, ferulic acid, p-cumaric acid). The phenolic acids are found in free form and as glucosides or glucose esters.<sup>24</sup>

Free glucose is present in small amounts, and other sugars including arabinose, rhamnose and xylose are detected following glycolysis.<sup>26</sup>

Inorganic substances include calcium, potassium and iron with traces of manganese, zinc and copper.<sup>15</sup>

## PHARMACOLOGICAL ACTIONS/MECHANISM OF ACTION

### Antioxidant – Anti-inflammatory Activity

#### In vitro

Pycnogenol has potent antioxidant activity, which has been reported in several in vitro studies. Studies show that (1) Pycnogenol can scavenge both hydroxyl radicals and superoxide anions,<sup>27</sup> (2) Pycnogenol can extend the lifetime and increase the antioxidant function of the ascorbate radical (vitamin C),<sup>28</sup> and (3) Pycnogenol can increase the activity of other internal antioxidant systems, namely superoxide dismutase, glutathione peroxidase, and catalase.<sup>29</sup>

Lipids, proteins, and DNA are targets for oxidative damage. Studies have shown that Pycnogenol can prevent oxidative damage to lipids,<sup>30-32</sup> proteins,<sup>33,34</sup> and breakage of plasmid DNA.<sup>31</sup>

Single Pycnogenol components and their metabolites also have antioxidant activity. Catechin inhibits superoxide activity in vitro with effectiveness similar to ascorbic acid.<sup>35</sup> Interestingly, a metabolite of catechin that is generated in humans after oral consumption,  $\delta$ -(3,4-dihydroxyphenyl)- $\gamma$ -valerolactone (M1) was found to be significantly more active than catechin or ascorbic acid.<sup>35</sup>

Reactive oxygen species (ROS) not only directly cause cell injury and can initiate a degenerative process, they can also act as signals for other processes, such as pro-inflammatory pathways involving nuclear-factor-kappaB (NF- $\kappa$ B) activation. In vitro Pycnogenol blocked NF- $\kappa$ B activation in macrophages, which in consequence inhibited expression of the pro-inflammatory cytokine IL-1.<sup>36</sup> Expression of adhesion molecules by endothelial cells is likewise under the control of NF- $\kappa$ B. Adhesion molecules are involved in leukocyte recruitment to inflammatory sites but also contribute to development of vascular disorders. Treatment of endothelial cells with Pycnogenol prior to stimulation with TNF-alpha inhibited activation of NF- $\kappa$ B and limited induction of vascular

\* Pycnogenol is standardized to contain  $70 \pm 5\%$  procyanidins. Procyanidins represent a sub-category of proanthocyanidins. Proanthocyanidin is the "family name" for different condensed flavan-3-ols species: procyanidins, prodelpinidins and propelargonidins, and various other species. Some flavonoids, such as from grape seed, contain prodelpinidins together with procyanidins and, therefore, they are referred to as containing proanthocyanidins, which is correct and easier to communicate than specifying the individual subspecies.

cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1).<sup>37</sup> In vitro experiments with human keratinocytes revealed that Pycnogenol down-regulated activity of 2 genes (calgranulin A and B), which are upregulated in inflammatory skin conditions.<sup>38</sup> In another experiment, pretreatment with Pycnogenol inhibited gamma-interferon- ( $\gamma$ -IFN) induced adherence of T-cells to keratinocytes. The mechanism involved appears to be inhibition of  $\gamma$ -IFN-induced expression of ICAM-1.<sup>39</sup>

ROS are associated with pro-inflammatory conditions through the stimulation of matrix metalloproteinases (MMP's). MMP's are a family of enzymes that cause lysis of connective tissue proteins. MMP-1 (collagenase 1) and MMP-9 (gelatinase B) are upregulated in arthritis, and they contribute to cartilage degradation in rheumatic diseases. MMP-1 also contributes to the aging effect of ultraviolet (UV) light of the skin and MMP-9 also plays a role in asthma. In pulmonary fibrosis, MMP-2 (gelatinase A) is also involved. Pycnogenol had an inhibitory effect on the activity of MMP-1, MMP-9 and MMP-2 and further inhibited their secretion from stimulated human macrophages.<sup>40</sup> In addition, the metabolites of catechin, M1 and M2 ( $\delta$ -(3-methoxy-4-hydroxyphenyl)- $\gamma$ -valerolactone), were significantly more potent for inhibition of MMP's 1, 2, and 9 in vitro than the parent molecules in Pycnogenol extract.<sup>40</sup>

In cell culture, Pycnogenol inhibited expression of the proinflammatory cytokine IL-1.<sup>36</sup>

In inflammation the expression of inducible nitric oxide synthase (iNOS) leads to excess nitric oxide (NO) production and Pycnogenol was shown to inhibit this process.<sup>41</sup> In vitro experiments showed that Pycnogenol treatment of stimulated macrophages decreased cellular generation of NO via scavenging ROS and NO, inhibition of iNOS, and inhibition of iNOS-mRNA expression by blocking NF- $\kappa$ B activation. The authors conclude that based on this experiment and others Pycnogenol may be useful during periods of inflammation.<sup>41</sup>

### Animal

Pycnogenol has antiinflammatory and wound-healing effects on the skin in vivo. In one set of experiments, extracts of *P. pinaster* (Pycnogenol was not mentioned specifically as the study material) containing varying amounts of oligomeric procyanidins, administered orally (100 mg/kg for 10 days), inhibited croton oil-induced ear edema in mice and compound 48/80-induced hind paw edema in rats.<sup>42</sup> Effectiveness was correlated with increasing concentrations of procyanidins. In an experiment evaluating antiinflammatory effects, extracts at concentrations of 0.1–3% in a gel were applied topically to the shaved back of rats and the extracts dose-dependently inhibited UV radiation-induced capillary permeability.<sup>42</sup>

Wound-healing time was examined in a controlled experiment in rats.<sup>43</sup> The healing time was measured as the number of days required for 50% of the scabs to separate spontaneously from a wound. Control animals required 15.4 days to heal and Pycnogenol (at concentrations of 1, 2, and 5%) shortened this time by 1.6 days, 2.8 days and 3.3 days ( $p < 0.05$ ,  $p < 0.01$ , and  $p < 0.01$ ; respectively). Pycnogenol gel also dose-dependently reduced the scar diameter.<sup>43</sup>

### Human – ex-vivo

Cyclooxygenase-1 and 2 (COX-1, -2) are enzymes that produce a cascade of chemical mediators including prostaglandins, which mediate the inflammatory response. Blood plasma taken from 5 healthy volunteers who had taken 200 mg Pycnogenol for 5 days showed inhibition of COX-1 and COX-2 ex vivo, but not significantly.<sup>44</sup> However a single dose of 300 mg Pycnogenol given to 10 healthy subjects produced serum samples showing significantly inhibited COX-1 ( $p < 0.02$ ) and COX-2 ( $p < 0.002$ ). According to

the authors, this activity is consistent with the inhibition of platelet aggregation and the anti-inflammatory effects observed clinically.<sup>44</sup>

In another ex-vivo experiment, plasma samples from 7 healthy volunteers given 200 mg/day Pycnogenol for 5 days reduced LPS-induced release of MMP-9 from human monocytes by 25% ( $p < 0.01$ ).<sup>40</sup> MMP-9 induction and release are initiated by NF- $\kappa$ B activation. Plasma samples also inhibited NF- $\kappa$ B nuclear translocation by 15.5% ( $p < 0.05$ ). The correlation between the two was positive (Spearman rank correlation coefficient  $r = 0.6$ ). These results are consistent with anti-inflammatory effects observed clinically.<sup>40</sup>

### Human

The effect of Pycnogenol on plasma antioxidant capacity was tested in 25 healthy subjects (10 males, 15 females; mean age  $30 \pm 8$  years) given 150 mg/day Pycnogenol for 6 weeks followed by a 4-week washout period.<sup>45</sup> As an indication that Pycnogenol was absorbed, plasma polyphenol levels increased significantly after 3 weeks of supplementation ( $p < 0.05$ ). The antioxidant potential of the plasma, as measured using the ORAC (oxygen radical absorption capacity) assay, increased by 40% over baseline ( $p < 0.05$ ), returning to baseline after the washout period. There was no significant change in plasma lipid peroxidation as measured using the FOX assay or in LDL-cholesterol oxidation as measured by an increase in lag phase. The authors conclude that Pycnogenol significantly increased the antioxidant capacity of plasma.<sup>45</sup>

An open-label study explored the effectiveness of 2 doses of Pycnogenol on UV light-induced erythema in a model simulating sunburn.<sup>46</sup> Twenty-two fair skinned volunteers ( $n = 3$  men,  $n = 19$  women, mean age 23.6 years) were given oral Pycnogenol 1.10 mg/kg for 4 weeks and the dose was increased to 1.66 mg/kg Pycnogenol for the second 4 weeks. The minimal amount of UV light required to induce erythema, known as MED, was measured at baseline and after 4 and 8 weeks. The MED increased dose-dependently, with the 1.66 mg/kg dose inducing an approximately 2-fold increase in MED compared with baseline ( $p < 0.05$ ).<sup>46</sup>

### Cardiovascular

#### In vitro

Endothelial cells line the inner wall of blood vessels, and endothelial cell damage is an important factor in cardiovascular disease. In an in vitro experiment Pycnogenol protected cultured endothelial cells from oxidative injury induced by *t*-butyl hydroperoxide.<sup>47</sup> Pycnogenol enhanced clearance of hydrogen peroxide and oxygen radicals in endothelial cells treated with hypoxanthine, xanthine oxidase, or hydrogen peroxide. Pycnogenol also increased the activities of the following intracellular antioxidant enzyme systems in these cells: glutathione (GSH) peroxidase, GSH disulfide reductase, superoxide dismutase (SOD), and catalase.<sup>48</sup>

Pycnogenol protected endothelial cells from glutathione depletion caused by co-culture with activated macrophages.<sup>49</sup> It also protected endothelial cells from reduction of  $\alpha$ -tocopherol levels caused by reactive nitrogen species (e.g., NO or peroxynitrite) generated by activated macrophages or direct administration of peroxynitrite.<sup>41</sup>

#### Animal

The endothelium-dependent relaxation facilitated by NO represents an important component of vascular function. Pycnogenol was demonstrated in experiments with isolated rat aorta to dose-dependently release constriction of smooth muscle initiated by pretreatment with epinephrine and norepinephrine. The vasorelaxation was shown to result from stimulation of endothelial NO synthase (eNOS) in presence of Pycnogenol.<sup>50</sup>

Pycnogenol caused a significant decrease in blood pressure in rats administered cumulative doses above 4 mg/kg intravenously.

In vitro studies suggest that this effect is mediated via inhibition of angiotensin converting enzyme (ACE).<sup>51</sup>

A mouse model of heart failure was created in elderly mice by treating them with an inhibitor of NO synthase (L-NAME).<sup>52</sup> Supplementing these mice with 30 mg/kg Pycnogenol orally for 4 weeks significantly reduced hypertension and cardiac hypertrophy ( $p < .05$ ). The gene expression pattern and activity of MMP-9 (which is involved in cardiac hypertrophy) was significantly decreased by Pycnogenol treatment ( $p < 0.001$ ). The authors propose that Pycnogenol may help limit cardiac remodeling (hypertrophy) in patients with heart failure.<sup>52</sup>

#### Human

Pycnogenol-enhanced endothelium-dependent vasodilation was evaluated in a randomized, double-blind, placebo-controlled study in healthy volunteers.<sup>53</sup> Forearm blood flow responses to acetylcholine and sodium nitroprusside—both endothelium-independent vasodilators—were measured in 16 healthy young men before and after 2 weeks administration of Pycnogenol (180 mg/day) or placebo. Those taking Pycnogenol had an augmented response to acetylcholine compared with baseline ( $p < 0.05$ ), while there was no change in the placebo group. There was no difference between groups in response to sodium nitroprusside. Administration of N<sup>G</sup>-monomethyl-L-arginine (L-NMMA), a NO synthase inhibitor, abolished the Pycnogenol-induced acetylcholine response. The authors suggest that Pycnogenol augments endothelium-dependent vasodilation by increasing NO production.<sup>53</sup>

Cigarette smoking increases the risk for coronary heart disease by increasing blood pressure and increasing the tendency for blood to clot. Pycnogenol reduced the effects of smoking on platelet reactivity in 2 studies.<sup>54</sup> In one study of 23 German heavy smokers (smoking  $\geq 15$  cigarettes per day), 100 mg Pycnogenol was as effective as 500 mg aspirin in completely inhibiting smoking-induced platelet aggregation 2 hours after smoking.<sup>54</sup> However, in 16 American heavy smokers treated with 125 mg Pycnogenol or 500 mg aspirin, the smoking-induced platelet aggregation was only partially reduced.<sup>54</sup> Pycnogenol had no effect on blood pressure or heart rate. Pycnogenol was shown to dose-dependently lower platelet activity 2 hours after a single intake of Pycnogenol starting from 25 mg up to 200 mg. The effect on platelets was statistically significant from a single intake of 100 mg ( $p < 0.01$ ). The benefits from a single dosage of 200 mg Pycnogenol persisted for 6 days.<sup>54</sup>

To evaluate the chronic effects of Pycnogenol on platelet aggregation, the same research group conducted an open-label study with 4 heavy smokers (15 cigarettes per day for  $\geq 5$  years) and 16 non-smokers.<sup>55</sup> Both groups received 200 mg/day Pycnogenol for 8 weeks. At study end, Pycnogenol taken 3 hours prior to the first cigarette significantly reduced platelet reactivity index ( $p < 0.002$ ) to the level of non-smokers. At baseline smokers also presented with elevated serum thromboxane levels which, after treatment, were reduced to the levels of non-smokers.<sup>55</sup>

The effects of Pycnogenol on microcirculation and platelet function were investigated in patients with coronary artery disease in a double-blind, placebo-controlled study ( $n = 27$  men and  $n = 24$  women; 45-75 years).<sup>56</sup> Patients were given Pycnogenol at 150 mg in 3 divided dosages for 4 weeks, which improved fingernail microcirculation by 53.8%. Myocardial ischemia was improved by 16% in Pycnogenol-treated patients compared with 11% in placebo-treated patients as judged by ECG ( $p$ -values not reported). A marker for platelet activation, platelet granule membrane protein of 140 Da (GMP-140), increased in the blood of all patients over time, although this increase was significantly less in the Pycnogenol group than in the placebo group ( $p < 0.01$ ). In addition, ex-vivo aggregation of platelets induced by ADP was significantly reduced in the

treatment group compared with the placebo group ( $p < 0.05$ ).<sup>56</sup>

Plasma lipid levels were measured in an open-label study with 25 healthy volunteers given Pycnogenol 150 mg/day for 6 weeks, followed by a 4-week washout period.<sup>45</sup> Compared with baseline measurements, LDL-cholesterol decreased significantly (7%,  $p < 0.05$ ), an effect that was reversed after the 4-week washout. HDL-cholesterol levels increased significantly (10.4%,  $p < 0.05$ ), and this effect was not reversed after the washout period. There was no significant change in total cholesterol or triglycerides.<sup>45</sup>

## Diabetes and Complications

#### In vitro

In vitro experiments with alpha-glucosidase were conducted to determine how Pycnogenol clinically-reduces blood sugar in type 2 diabetics.<sup>57</sup> Alpha-glucosidase is an enzyme secreted in the duodenum that hydrolyses glucose residues from polysaccharides (starches). Inhibition of the enzyme diminishes absorption of glucose and reduces the post prandial blood glucose peaks. The activity of Pycnogenol was compared to acarbose, a prescription alpha-glucosidase inhibitor. Pycnogenol was found to be a potent inhibitor of alpha-glucosidase, more potent than acarbose (IC<sub>50</sub> 5.3  $\mu\text{g/mL}$  and 1 mg/mL, respectively).<sup>57</sup>

#### Animal

Pycnogenol's effect on diabetes was evaluated in 2 in vivo studies. Healthy rats and rats with streptozotocin-induced diabetes were treated with 10 mg/kg Pycnogenol intraperitoneally (IP) for 14 days. Pycnogenol significantly reduced blood glucose levels in diabetic rats by 28% ( $p < 0.05$ ), but not to normal levels.<sup>58</sup> In contrast, another study treated streptozotocin-induced diabetic rats with Pycnogenol 5 mg/kg orally for 8 weeks and found no significant reduction in blood sugar.<sup>59</sup> However, it is noteworthy that the streptozotocin rat model represents type 1 diabetes.

A study evaluating diabetes-related eye disorders treated normal and streptozotocin-induced diabetic rats with a low-carbohydrate diet plus Pycnogenol (10 mg/kg, IP for 14 days). The combination treatment reduced the risk of diabetic retinopathy and cataract formation.<sup>60</sup>

## Attention Deficit-Hyperactivity Disorder (ADHD)

#### Human

Attention deficit-hyperactivity disorder (ADHD) may involve a dysregulation of catecholamine (e.g. dopamine, epinephrine and norepinephrine).<sup>61</sup> Urinary catecholamine concentrations were measured in 57 children ( $n = 47$  boys,  $n = 10$  girls; ages 6-14 years) with ADHD and in 17 healthy children ( $n = 8$  boys,  $n = 9$  girls; mean age 11.5 years). Children with ADHD had significantly higher levels of epinephrine and norepinephrine in their urine compared with healthy children ( $p < 0.001$  and  $p = 0.007$ , respectively). Concentrations of urinary dopamine were similar in both groups.<sup>61</sup> The children with ADHD were then entered into a randomized, double-blind, placebo-controlled study.<sup>61</sup> The children were treated with 1 mg/kg Pycnogenol or placebo for one month. There was a significant decrease in dopamine levels in the Pycnogenol group compared with baseline ( $p < 0.05$ ). There were non-significant decreases in epinephrine and norepinephrine in the Pycnogenol group compared with baseline. The differences between the Pycnogenol and placebo groups did not reach statistical significance.<sup>61</sup>

Catecholamine metabolism may be a source of free radical formation (superoxide radicals and hydrogen peroxide).<sup>62</sup> These free radicals could cause oxidative damage to DNA, lipids and proteins. Total damage to DNA was measured in 58 children ( $n = 47$  boys,  $n = 11$  girls; ages 6-14 years) with ADHD and in 56 healthy chil-



dren (mean age 11.5 years). Children with ADHD had significantly higher levels of total damage when compared with healthy children ( $p < 0.001$ ).<sup>62</sup> Children with ADHD ( $n = 50$  boys,  $n = 11$  girls; 6-14 years old) were then entered into a randomized, double-blind, placebo-controlled study.<sup>62</sup> The children were treated with 1 mg/kg Pycnogenol or placebo for 1 month. Levels of 8-oxo-7,8-dihydroguanine (8-oxoG) were measured as an indication of oxidative DNA damage. Treatment with Pycnogenol reduced levels of 8-oxoG compared with baseline and placebo controls ( $p = 0.012$  and  $p = 0.014$ , respectively). After a one-month washout period, levels of 8-oxoG returned to baseline.<sup>62</sup> The total antioxidant status (TAS) non-significantly increased following treatment with Pycnogenol. The decrease in DNA damage and increase in TAS correlated with an improvement in inattention score ( $p = 0.0045$  and  $p < 0.035$ , respectively).<sup>62</sup>

Another study evaluated the effect of Pycnogenol on the levels of oxidative stress in children with ADHD.<sup>63</sup> A randomized, double-blind, placebo-controlled study measured the levels of reduced glutathione (GSH) and oxidized glutathione (GSSG) in 43 children ( $n = 34$  boys,  $n = 9$  girls, ages 6-14 years) with ADHD. The children were treated with 1 mg/kg Pycnogenol or placebo for one month. In the group given Pycnogenol, GSH increased ( $p = 0.054$ ), as did the ratio of GSH to GSSG. There was no change in the placebo group.<sup>63</sup> The authors conclude that treatment with Pycnogenol tended to normalize catecholamine levels in children with ADHD and resulted in decreased hyperactivity and diminished oxidative stress.

## Reproduction

### Human

Reactive oxygen species (ROS) are thought to damage sperm through lipid peroxidation, resulting in altered sperm plasma membrane integrity and functional impairment. The effect of 200 mg/day Pycnogenol for 90 days was evaluated in subfertile men ( $n = 19$ ) in an open-label study.<sup>64</sup> Subfertility was defined as precapacitation (early sperm structural changes), postcapacitation and/or reduced capacity of the sperm to bind to mannose receptors. Semen samples were analyzed before and after treatment. Pycnogenol produced a 38% improvement in sperm morphology and a 19% increase in a mannose binding assay ( $p = 0.001$  and  $p < 0.005$ , respectively). As mannose residues on the oocyte are thought to interact with a sperm surface enzyme prior to fertilization, this result suggests that treatment with Pycnogenol may improve the fertility status of some men. Treatment did not affect sperm count.<sup>64</sup>

### Pharmacokinetics

#### In vitro

Pycnogenol can be absorbed through human skin. Transdermal bioavailability was tested following topical application of a 5% w/v solution of Pycnogenol in polyethylene glycol to human skin from 10 cadavers.<sup>65</sup> Consistently detected in the collection fluid were gallic acid, protocatechuic acid, catechin, p-hydroxybenzoic acid, vanillin, and an unidentifiable compound. Taxifolin was also detected, but only in perfusates from 3 of the 10 donors.<sup>65</sup>

#### Human

Metabolites of compounds in Pycnogenol were identified in the urine of a human volunteer following oral administration of 5.28 and 1.06 g of Pycnogenol extract.<sup>66</sup> Ferulic acid and taxifolin were identified as conjugates of glucuronide or sulfate, with peak urinary excretion 2–3 hours after intake. Two metabolites (M1 and M2) were identified and their chemical structure elucidated, both being identified as metabolic conjugates.<sup>66</sup>

Pycnogenol pharmacokinetics were measured following oral administration of single and multiple doses.<sup>67</sup> Eleven volunteers ( $n$

$= 5$  women,  $n = 6$  men) on a 24-hour flavonoid-free diet received a single dose of 300 mg Pycnogenol and blood samples were collected over 14 hours. After the single dose, 15 compounds were detected in the plasma, 10 of which were unknown. The known compounds were catechin, caffeic acid, ferulic acid, taxifolin, and metabolite M1. Four compounds had a  $t_{\max}$  (time of maximal observed plasma concentration) of up to 5 hours: catechin, caffeic acid, ferulic acid, and one unknown compound. Three compounds had a  $t_{\max}$  between 5 and 10 hours: taxifolin and 2 unknown compounds. There were also 3 compounds with  $t_{\max}$  of approximately 10 hours: M1 and 2 unknown compounds. The  $C_{\max}$  (maximal observed plasma concentration) for catechin was measured at 107 ng/mL, taxifolin at 33 ng/mL, caffeic acid at 17 ng/mL, ferulic acid at 15 ng/mL, and M1 at 4 ng/mL. In another experiment, 5 volunteers ( $n = 4$  women,  $n = 1$  man) were treated with 200 mg Pycnogenol for 5 days.<sup>67</sup> Plasma samples were taken 4 hours after the last dose. Steady states appeared to have been reached for catechin, ferulic acid, caffeic acid, M1, and four of the unknown compounds. Plasma levels of taxifolin were below the limits of detection.<sup>67</sup>

The same study reported that many compounds were present as conjugates of sulfate and/or glucuronic acid, indicating Phase II metabolism. The degree of conjugation varied with the individual volunteer and the individual compound. The mean degree of conjugation was 56.5% for catechin and 69.4% for caffeic acid.<sup>67</sup> The authors conclude that many of the Pycnogenol constituents are bioavailable to humans following oral ingestion and that these compounds can be metabolized. The plasma concentrations of known compounds were within the nanomolar range, both after single and multiple dosing.<sup>67</sup>

## CONTRAINDICATIONS AND PRECAUTIONS

There are no known contraindications for Pycnogenol.

### Pregnancy and Lactation

As a general precaution, Pycnogenol should not be taken during the first 3 months of pregnancy. This precaution is based on general principles and a lack of any published data on pregnant women using Pycnogenol in the first trimester. Toxicological studies demonstrated absence of mutagenic and teratogenic effects, no perinatal toxicity, and no negative effects on fertility.<sup>15</sup>

## ADVERSE EFFECTS/SAFETY DATA

### Pre-clinical Toxicology

The toxicity of Pycnogenol is regarded as very low. The acute toxicity is low after oral administration in mice, rats, and guinea pigs.<sup>68</sup> The representative  $LD_{50}$  values are 2.3, 4.2, and 2.0 g/kg, respectively.<sup>68</sup>

In chronic toxicity tests, oral application of up to 2000 mg/kg/day in rats did not produce clinically meaningful changes in blood status, body weight, or food consumption. Also, the rats exhibited normal behavior.<sup>68</sup>

The level of mutagenicity of Pycnogenol was tested with the Ames test, the micronucleus assay in mouse bone marrow cells in vivo, and with the chromosome aberration assay in human lymphocytes in vitro.<sup>68</sup> The results suggest that Pycnogenol is non-mutagenic.<sup>68</sup>

## HUMAN SAFETY DATA

Pycnogenol is affirmed GRAS (generally recognized as safe) for use in conventional foods based on the evaluation of clinical safety and pre-clinical toxicology data by an independent panel of toxicology experts.

The safety of Pycnogenol is based on data obtained from 70 clinical studies (published and unpublished), which include total

5723 participants up to October 26, 2006. There are 38 double-blind, placebo-controlled, comparative studies and 5 crossover studies with a total of 3350 participants. There are 32 open-label or open-comparative studies and 2 bioavailability studies with a total of 1315 participants. The populations are comprised of both healthy subjects and patients with a dysfunction or pathology. The mean daily Pycnogenol dose was 80 mg (range 30–450 mg/day, n = 4665). The global frequency rate of adverse effects (AEs) is 2.4%.<sup>69</sup> However, in healthy subjects, the incidence rate is 0.19% (based on 2116 subjects in 31 clinical studies).<sup>69</sup> An evaluation of the clinical studies suggest that the occurrence of AEs is unrelated to the dose or duration of use.<sup>69</sup>

From what can be gleaned from the clinical trials (published and unpublished) it appears that gastrointestinal (GI) discomfort is the most frequently occurring treatment-related AE. This may be attributed to the astringent nature of Pycnogenol. The GI effects did not occur when Pycnogenol was taken with or after meals.<sup>69</sup> Dizziness, headache, and nausea are the next most frequently reported treatment-related AEs. Acne, diarrhea, and dysfunctional bleeding are the most frequent AEs in studies of women with premenstrual syndrome or dysmenorrhea.<sup>70, 71</sup> The majority of AEs observed were mild.<sup>69</sup>

Analysis of clinical safety data obtained from 4 clinical studies (n =185) evaluating Pycnogenol's effect on blood pressure and heart rate did not reveal any significant changes on systolic or diastolic blood pressure or heart rate.<sup>54, 72-74</sup>

Post-marketing surveillance (spontaneous AE reporting) carried out between 2002 and 2005 in Europe and Asia revealed 6 case reports despite millions of Pycnogenol doses sold.<sup>75</sup> There were 3 cases of urticaria, 1 case of headache, 1 case of nausea, and 1 case of eczema and diarrhea. According to the manufacturer, urticaria is a rare allergic reaction that could be due to the color component of the tablet.<sup>75</sup>

There have been no reports of serious AEs in any clinical study or from commercial sales of what the manufacturer estimates are possibly billions of doses, in recognition of the widespread use of Pycnogenol since it was initially introduced into the market in Europe around 1970.

## DRUG INTERACTIONS

Pycnogenol has been consumed by adult and elderly patients taking concomitant pharmacological therapies. No information from spontaneous reporting is available on any interactions resulting from simultaneous intake of other drugs with Pycnogenol. Other interactions with alcohol consumption or food have not been reported. Pycnogenol does not affect INR (International Normalization Ratio, a measure of bleeding tendency) in patients taking aspirin.<sup>76</sup>

## REGULATORY STATUS IN VARIOUS COUNTRIES

**ASIA:** Food supplement, food ingredient, or health food status in India, Indonesia, Hong Kong, Korea, Malaysia, Philippines, Singapore, Taiwan, and Thailand.

**AUSTRALIA:** Complementary medicine in the Therapeutic Goods Administration listings.

**CANADA:** Natural Health Product (NHP) decision pending from Natural Health Products Directorate.

**CHINA:** Health food.

**EGYPT:** Medical nutrient (food supplement).

**JAPAN:** Food supplement, cosmetic ingredient.

**LATIN AMERICA:** Over-the-counter (OTC) medicine in Colombia, Venezuela, and Chile.

**RUSSIA:** Food supplement, food ingredient.

**SWITZERLAND:** Non-prescription herbal drug (under category D) for venous disorders.

**EUROPEAN UNION:** Food supplement in many EU countries (Austria, Belgium, Czech-Republic, Finland, France, Italy, Latvia, Netherlands, Poland, Romania, Slovak Republic, and United Kingdom). The labeling advice in the UK reads "For adults only; not to be used by children or pregnant women." This advice is consistent with the labeling of other food supplements in the UK. Registered as an herbal medicine in Greece for venous insufficiency and edema.

**USA:** Dietary supplement through notification under DSHEA 1994.

## PATENTS

**United States Patent** (5,720,956, issued February 24, 1998) Rohdewald P. Method of controlling the reactivity of human blood platelets by oral administration of the extract of the maritime pine (Pycnogenol).

**United States Patent** (6,372,266, issued April 16, 2002) Suzuki N, Kohama T. Medicinal composition for treating dysmenorrhea and endometriosis—industrial use.

**United States Patent** (20040115285 A1, issued June 17, 2004): Rohdewald P. Method of normalizing glucose levels in blood of patients with diabetes mellitus by oral administration of proanthocyanidins containing plant extracts.

**United States Patent** (20060194746, A1, issued August 31, 2006): Rohdewald P. Method and composition to inhibit infections with *Helicobacter pylori* by intake of procyanidins from type B and C.

**United States Patent** (20060293258, A1, issued December 28, 2006): Rohdewald P. Method and composition to treat skin ulcers.

**United States Patent** (20070014883, A1, issued January 18, 2007): Rohdewald P. Method for treating osteoarthritis.

**United States Patent** (20070059392, A1, issued March 15, 2007): Rohdewald P. COX inhibitor.

**United States Patent** (20070269541, A1, issued November 22, 2007): Rohdewald P. Method and compositions for relieving menopausal and perimenopausal symptoms.

There are no issued international patents as of April 2008.

## CLINICAL REVIEW

As of June 2008 there are a total of 33 published human clinical trials on Pycnogenol as a monopreparation that have been published in English or translated to English. Due to space considerations for this publication, the authors and editors decided not to review all of these studies in the text below; however, most appear in the Published Clinical Studies Table. Studies included in the review met the following criteria: human trial, any indication, any dose of Pycnogenol, English language or English translation, and any publication year. For space considerations in this review, the editor decided on the following exclusion criteria: pilot study, no control group, untreated control group, or any other significant methodological limitation. Seventeen clinical trials met these criteria and are reviewed below. Five studies meeting these criteria evaluated Pycnogenol for chronic venous insufficiency and its complications. Only 1 or 2 studies met the criteria for the following indications: thrombosis, diabetes and its complications, hypertension and its complications, asthma, ADHD, gynecology (endometriosis and dysmenorrhea), and osteoarthritis.

### Chronic Venous Insufficiency (CVI) and its Complications

**Cesarone, et al, 2006.**<sup>19</sup> A prospective, randomized, controlled study was conducted with patients with chronic venous insufficiency (CVI) and a history of venous ulcerations. Patients (age range: 40–61 years) were treated daily for 8 weeks with either 150

mg Pycnogenol (n = 24), 300 mg Pycnogenol (n = 20), or 1,000 mg Daflon® (this combination of 450 mg diosmin and 50 mg hesperidin is used to treat CVI, manufacturer not reported) (n = 42). After 8 weeks of treatment both doses of Pycnogenol resulted in a significantly greater improvement in CVI signs, symptoms, and microcirculatory parameters (resting flux, rate of ankle swelling, edema, subjective symptoms, partial pressure of oxygen [PO<sub>2</sub>] and partial pressure of carbon dioxide [PCO<sub>2</sub>]) compared with baseline (p < 0.05 for all parameters, except edema p < 0.001) and Daflon (p < 0.05 for all parameters). The lower dose of Pycnogenol decreased edema by 64% compared to baseline, whereas Daflon lowered edema by 32% compared to baseline. The higher dose of Pycnogenol was more effective than the lower dose at reducing edema (p-value not reported) however, other parameters were not further improved compared to 150 mg treatment. Pycnogenol was well-tolerated and there were no side-effects reported. The authors concluded that Pycnogenol was effective at treating CVI and venous microangiopathy in a short time without unwanted effects.

The limitation of this study is that previous studies have suggested that 1,000 mg of Daflon may be too low to have important microcirculatory effects.<sup>19</sup>

**Koch, 2002.**<sup>20</sup> A randomized, open-label, comparative study was conducted with patients (age range: 34-71 years) who have CVI. Patients (n = 40) were randomized to receive either 360 mg of Pycnogenol (Pygnoforton®, Plantorgan, Bad Zwischenahn, Germany) or 600 mg of standardized dried horse chestnut seed (*Aesculus hippocastanum* L.) extract (100 mg aescin/day; Venostasin® retard, Klinge Pharma GmbH, Munich, Germany) daily for 4 weeks. Compared with 4-weeks of horse chestnut seed extract (HCSE), Pycnogenol produced a significantly greater decrease in heaviness, cramps, and night-time swelling (edema) of both legs (p < 0.05). Pycnogenol significantly reduced lower leg edema from baseline (right lower leg circumference: baseline 46.9 cm, 4 weeks 46.2 cm, p < 0.01; left lower leg circumference: baseline 47.9 cm, 4 weeks 46.9 cm, p < 0.01). Pycnogenol was well-tolerated. Pycnogenol-treated patients also had significant reductions in total cholesterol by 19.7% and LDL-cholesterol by 13% compared with baseline (p < 0.001), while HDL-cholesterol remained unchanged.

The dose of HCSE used in this study was found to be efficacious in many randomized controlled studies.<sup>77</sup> The limitations of this study may include the lack of blinding and a placebo group; however, a strength of the study is the direct comparison with one of the leading horse chestnut extracts, recognized in Europe as an effective medication for treating symptoms of CVI.

**Petrassi, et al, 2000.**<sup>22</sup> This was a 2-part study. Part 1 was a randomized, double-blind, placebo-controlled study (n = 20) and Part 2 was an open-label study (n = 20). In Part 1, patients (mean age: 42.2 years) with CVI symptoms of heaviness and subcutaneous swelling were treated with 300 mg of Pycnogenol or placebo daily for 2 months. Heaviness and swelling significantly declined in Pycnogenol-treated patients compared with placebo-treated patients (p < 0.05) and compared with baseline (p < 0.01). By day 60 there was a 60% decline in heaviness and a 74% decline in swelling in the Pycnogenol-treated patients. The physicians rated Pycnogenol as significantly more effective than placebo. Pycnogenol was rated “good” to “very good” in all of the evaluated patients (n = 24) and placebo was rated as moderate in 7 patients and good in 1 patient (n = 8 evaluated). (Note: the n is different for this parameter because the values are expressed as the number of evaluated patients for this endpoint.) There was no effect on evening edema, localized or

diffuse leg pain, night cramps, or paresthesia (skin tingling). Pycnogenol was well-tolerated. Similar findings were apparent in Part 2 of the study, in patients (mean age: 44.9 years) treated with open-label Pycnogenol (300 mg daily for 2 months).

In addition to the small sample size, another limitation of this study was that most of the measures were subjective rather than objective. The only objective measure was orthostatic venous pressure, but there was no significant difference between Pycnogenol and placebo treatment on leg venous pressure. There was a significant reduction in venous pressure compared with baseline in Pycnogenol-treated patients and it is possible that larger group sizes would yield a statistical change from placebo treatment.

**Arcangeli, et al, 2000.**<sup>16</sup> A randomized, double-blind, placebo-controlled study was conducted in patients (age range: 30-70 years) with clinically evident CVI attributed to deep vein thrombosis or idiopathic venous-lymphatic deficiency. Patients were treated with 300 mg Pycnogenol (n = 20) or placebo (n = 20) daily for 2 months. Patients were not taking any other medications including diuretics and analgesics. Pycnogenol-treated patients had a significant reduction in heaviness, swelling, and pain compared with placebo at day 30 (p < 0.01, p < 0.01, p < 0.05; respectively) and day 60 (p < 0.01, p < 0.01, p < 0.05; respectively). At study end, Pycnogenol-treated patients reported a 54% reduction in heaviness, a 64% reduction in swelling, and a 64% reduction in pain compared with a reduction of 3%, 7%, and 18%, respectively, in placebo-treated patients (p < 0.01, p < 0.01, p < 0.05; respectively). In both groups there was no apparent change in the venous blood flow, as measured by Doppler ultrasound. No adverse effects were reported. Results of hematology and blood chemistry did not differ between groups. Physicians judged Pycnogenol efficacy to be moderate to very good in 19 of 20 patients. They also judged the placebo to be ineffective in 16 out of 20 patients.

This study was a well-conducted study; however, it could have benefited from a larger sample size and used a quantitative measure of efficacy. For example, the researchers could have measured swelling rather than relying on a subjective assessment.

**Schmidtke & Schoop, 1995.**<sup>23</sup> A randomized, double-blind, placebo-controlled trial was conducted in patients (age not reported) with venous circulation problems in their legs. The patients (n = 40) were randomized to receive either 360 mg/day Pycnogenol (Pygenol®, Duomed AG, 9533 Kirchberg, Switzerland) or placebo. After 6 days of treatment, patients treated with Pycnogenol had a significantly lower leg volume increase after changing from supine position to sitting over a period of 2 hours than placebo-treated patients (p < 0.001) (Note: data values not reported here because the data were presented in a bar graph.) Leg volume was measured by water displacement of feet and ankles rested in a plexiglas volumometer. Approximately 50% of the patients rated Pycnogenol as “very good” or “good” and approximately 30% reported that Pycnogenol had no effect. No adverse effects were reported. The authors conclude that in patients with venous insufficiency, Pycnogenol should be used as a supplement to compression treatment.

A limitation of this study is that the Pycnogenol group had much greater leg volumes at baseline than the placebo group. Therefore, accurate between-group comparisons cannot be made. It is possible that the Pycnogenol-treated patients had greater improvements than the placebo-treated patients because they had more severe symptoms. Patient-rated efficacy may have been higher if the treatment duration were longer.

## CVI Summary

All 5 studies reported subjective improvements in symptoms of CVI in patients treated with Pycnogenol. Three studies quantitatively measured leg swelling and all showed an improvement in Pycnogenol-treated patients. Nonetheless, more studies with larger numbers of participants are warranted for more adequate confirmation of the efficacy of Pycnogenol for CVI.

### Thrombosis

**Belcaro, et al, 2004.**<sup>78</sup> A double-blind, placebo-controlled, randomized trial was conducted in airline passengers (age not reported) traveling on a long-flight (7-12 hours) who had moderate-to-high risk for thrombosis. Participants traveled on several different flights. They (n = 198) received either placebo or 200 mg Pycnogenol 2-3 hours prior to the flight, followed by another intake of placebo or 200 mg Pycnogenol 6 hours later during the flight, followed by another dose of placebo or 100 mg Pycnogenol the next day upon arrival, (total of 500 mg Pycnogenol). Deep vein thrombosis (DVT) or superficial vein thrombosis were detected by ultrasonography before departure and again within 120 minutes after arrival at destination. Significantly fewer superficial vein thrombosis events were reported in the Pycnogenol group compared to placebo (0 vs. 4;  $p < 0.05$ ). None of the Pycnogenol-treated participants experienced a DVT, while there was one DVT in the placebo group. No adverse effects were experienced.

All participants viewed an education video that explained methods of venous thrombosis prevention, such as mild exercise, avoiding baggage between seats, and drinking water regularly. However, the researchers did not report the participants' use of preventive measures. The impact of the preventative measures on study outcome is not known.

### Diabetes and its Complications

**Liu, et al, 2004.**<sup>4</sup> A double-blind, placebo-controlled, randomized, multi-center study was conducted in men and women (aged 45-66 years) with type 2 diabetes mellitus. Patients (n=77) were treated with 100 mg/day Pycnogenol or placebo for 12 weeks. Patients continued their antidiabetic medication (sulfonylurea, biguanide, and acarbose) during the study, but vitamin and mineral supplementation were not allowed. Median plasma glucose had a maximum reduction after 8 weeks of treatment (-1.96 mmol/L), which persisted until study completion. Pycnogenol significantly decreased plasma glucose more than placebo at all time intervals (2 weeks: -0.92 vs. -0.34 mmol/L, 4 weeks: -1.51 vs. -0.88 mmol/L, 6 weeks: -1.81 vs. -1.15 mmol/L, 8 weeks: -1.97 vs. -1.24 mmol/L, respectively;  $p < 0.01$  for all values). Hemoglobin A<sub>1c</sub> values significantly decreased after one month of treatment compared with placebo (-0.32 vs. -0.07 mmol/L, respectively;  $p < 0.01$ ), but the difference was not maintained. Median plasma endothelin-1 (a metabolite of vasoconstrictor prostacyclin) concentrations significantly decreased in the Pycnogenol group compared with the placebo group over the entire treatment period (1 month: -11.20 vs. -1.82 mmol/L, 2 months: -20.93 vs. -2.68 mmol/L, and 3 months: -21.42 vs. -4.03 mmol/L, respectively;  $p < 0.01$  for all values). Median plasma 6-keto-prostaglandin F<sub>1 $\alpha$</sub>  (a vasodilator) significantly increased in the Pycnogenol group compared with the placebo group (1 month: 10.53 vs. 3.32 mmol/L, 2 months: 13.47 vs. 5.58 mmol/L, 3 months: 12.70 vs. 6.03 mmol/L;  $p < 0.01$  for all values). There was no effect on heart rate, ECG, BUN, creatinine, and electrolytes. Adverse events were mild, transient, and reported by both groups. The dosage used in the trial is based on previous studies that found maximum lowering of fasting and postprandial glucose, hemoglobin A<sub>1c</sub> and endothelin-1 with doses between 100 and 200 mg of Pycnogenol, with no further decrease at 300 mg/day.<sup>4</sup> A notable finding is that Pycnogenol does not affect insulin

secretion. This study suggests that Pycnogenol may improve glycemic control in type 2 diabetics.

**Belcaro, et al, 2006.**<sup>3</sup> A randomized, controlled study was conducted in patients with diabetes (type not specified) who were taking insulin (mean age: 54 years) and had diabetic ulcers (mean ulcerated area was 44 mm<sup>2</sup>). Patients (n = 30) received standard ulcer care and one of 4 treatments for 6 weeks: (1) 150 mg/day oral Pycnogenol plus 100 mg topical Pycnogenol powder from capsules placed on the ulcerated skin (no vehicle was used), (2) 150 mg/day oral Pycnogenol, (3) 100 mg topical Pycnogenol powder, or (4) no Pycnogenol. After treatment, the ulcerated area was significantly smaller in the patients with combined oral and topical treatment than in those who received only the standard care (11 vs. 34 mm<sup>2</sup>, respectively;  $p < 0.01$ ). Oral only and topical only treatment were less effective, but significantly better than control (30, 27, and 34 mm<sup>2</sup>, respectively;  $p < 0.05$ ). Combination treatment with oral and topical Pycnogenol was the most effective (11 mm<sup>2</sup>,  $p < 0.01$ ). On average, 86% of ulcers completely healed in subjects treated with Pycnogenol compared with 61% treated with standard care ( $p < 0.05$ ). Compared with standard care, the combination treatment significantly improved blood microcirculation to the skin (measured by Laser Doppler) and improved transcutaneous respiration with partial oxygen pressure increasing (48 vs. 58 mmHg, respectively;  $p < 0.05$ ) and pCO<sub>2</sub> decreasing (29.8 vs 27 mmHg, respectively). No AEs were reported.

Although the sample size per groups was small in this clinical trial, the results suggest that using Pycnogenol both orally and topically may be an effective treatment for diabetic ulcers.

### Diabetes Summary

Two studies in diabetic patients suggest that Pycnogenol may improve glycemic control in type 2 diabetes. One study suggests that Pycnogenol taken in addition to standard oral anti-diabetic medication further improves glycemic control. Another trial demonstrated Pycnogenol may be an effective treatment for diabetic ulcers and that oral intake together with topical application is more effective than oral use only. The findings warrant confirmation in a larger study.

### Hypertension and Complications

**Liu, et al, 2004.**<sup>21</sup> A randomized, double-blind, placebo-controlled, parallel-group study was conducted to assess whether Pycnogenol could help reduce the dose of the antihypertensive drug nifedipine used by patients being treated for hypertension. Patients stopped current antihypertensive therapy for 2 weeks prior to starting the study. Baseline pretreatment blood pressure levels (BP) were not reported. They were treated with nifedipine (Shanghai Pharmaceuticals Co, Ltd.) plus placebo or plus 100 mg Pycnogenol for 12 weeks. All patients (n = 58, mean age: 57 years) were started with 20 mg of sustained release nifedipine and the dose was adjusted up or down in 5 mg increments in 2 week intervals until stable BP was reached (systolic/diastolic values not reported). At study end, 57% (16/28) had normal BP (systolic/diastolic values not reported) when treated with 10 mg nifedipine and 100 mg Pycnogenol. In contrast, only 13% (4/30) attained normal BP when treated with 10 mg nifedipine plus placebo. Supplementation with Pycnogenol significantly reduced the dose of nifedipine needed to reduce BP compared with placebo ( $p < 0.001$ ). Pycnogenol-treated patients had a significantly greater increase in plasma 6-keto-prostaglandin F<sub>1 $\alpha$</sub>  (metabolite of vasodilator prostacyclin) values than placebo treatment (12% vs 8% increase, respectively;  $p < 0.05$ ), which shows a significant improvement in endothelial function. Adverse events (gastrointestinal disturbances, nausea, dizziness, headache, and sleepiness) were mild

and transient, and reported by both groups of patients.

The authors conclude that the nifedipine-sparing effect may not seem important when based solely on BP improvement; however, Pycnogenol may have a general beneficial effect on the endothelium.

**Belcaro, et al, 2006.**<sup>17</sup> A placebo-controlled, single-blinded trial was conducted to evaluate the efficacy of Pycnogenol for the prevention of antihypertensive treatment-induced edema. Patients (n = 53, mean age: 48 years) taking ACE inhibitors or nifedipine for at least 4 months to treat essential hypertension and presenting with ankle or foot edema were treated with 150 mg/day Pycnogenol or placebo for 8 weeks. All participants had diet and salt restrictions for at least 6 months. Antihypertensive treatment was maintained throughout the study. Capillary filtration was measured by strain-gauge plethysmography, which measured the size increase or decrease of tissue (= edema) at the level of the foot. Compared with placebo, Pycnogenol treatment significantly reduced capillary filtration in patients treated with ACE inhibitors (2.44 vs. 1.56 mL/min/100 cm<sup>3</sup> of tissue, respectively; p < 0.05) or nifedipine (2.48 vs. 1.61 mL/min/100 cm<sup>3</sup> of tissue, respectively; p < 0.05). No Pycnogenol-induced AEs were reported.

The study demonstrates that Pycnogenol may help patients with a common side-effect of long-term antihypertensive treatment: edema. However, the study was single-blinded and treatment duration was short.

#### Hypertension Summary

Additional rigorous studies are needed to evaluate the effect of Pycnogenol on hypertension and its complications.

#### Asthma

**Lau, et al, 2004.**<sup>7</sup> A randomized, double-blind, placebo-controlled trial was conducted in children (aged 6-18 years) with mild to moderate asthma (mild intermittent, mild persistent, and moderate persistent). Patients (n = 60) received either Pycnogenol, 1 mg/lb body weight per day, in two divided doses, or placebo for 3 months. Pycnogenol treatment resulted in a steady and significant (p < 0.01) increase in peak expiratory flow and placebo treatment produced a slight increase in flow compared with baseline. Compared with baseline, after 3 months treatment with Pycnogenol, peak expiratory flow increased from 70% to 87% of predicted normal value according to gender, age, and height (p < 0.01). Symptoms also significantly decreased monthly in Pycnogenol-treated patients (p < 0.001 compared with baseline) but not placebo-treated patients. The mean number of puffs of rescue medicine (albuterol inhaler) significantly declined in Pycnogenol-treated patients (p < 0.001 compared with baseline) but not in placebo-treated patients. At study end Pycnogenol-treated patients used on average 0.22 puffs per day versus 2.57 puffs at baseline (p < 0.001). Urinary leukotrienes significantly decreased in Pycnogenol-treated patients (baseline: 1300 pg/mL, 3 months: 800 pg/mL, p < 0.001) but not in placebo-treated patients. No AEs were reported.

The authors conclude that Pycnogenol is efficacious as an adjunct therapy for management of mild-to-moderate childhood asthma. However, the study lacked a statistical comparison between Pycnogenol-treated patients and placebo-treated patients.

**Hosseini, et al, 2001.**<sup>6</sup> A randomized, double-blind, placebo-controlled, crossover study was conducted in patients (aged 18-60 years) with asthma. Patients (n = 22 completed) received 1 mg/lb/day, maximum 200 mg/day, Pycnogenol or placebo for 4 weeks. Then the patients were crossed-over to the alternate treatment. There was no washout period. Compared with baseline, Pycno-

genol-treatment significantly increased the 1 second forced expiratory volume (FEV<sub>1</sub>) from 59% to 70% (p = 0.0008), while placebo increased it from 59% to 63% (p = 0.46). The difference between the treatment groups did not reach statistical significance (p = 0.06). However, when assessing the ratio of FEV<sub>1</sub>/forced vital capacity there was a significant difference between Pycnogenol and baseline (73% and 63%, respectively; p < 0.0001) and Pycnogenol and placebo (73% and 65%, respectively; p = 0.003). Serum cysteinyl-leukotrienes significantly declined in Pycnogenol-treated patients compared with baseline and placebo (baseline: 1044 pg/mL, Pycnogenol: 844 pg/mL, placebo: 1017 pg/mL; p < 0.001). One patient reported gastrointestinal disturbances, which were transient.

According to the authors, airway obstruction is considered reversed when treatment produces a 15% or greater increase in FEV<sub>1</sub>. In this study the average increase was only 11%. Pycnogenol may demonstrate better clinical efficacy as an adjunct therapy. Treatment duration was only 4 weeks and longer treatment might have resulted in improved respiration.

#### Asthma Summary

Much of the statistical analysis of these 2 trials results from comparison to baseline and lacks comparison within group. The results are preliminary and larger studies are needed to determine clinical relevance.

#### Attention Deficit Hyperactivity Disorder (ADHD)

**Trebaticka, et al, 2006.**<sup>5</sup> A randomized, double-blind, placebo-controlled trial was conducted in boys and girls (aged 6-14 years) who had clinically diagnosed ADHD for at least 6 months. Patients were treated with 1 mg/kg body weight/day Pycnogenol (n = 44) or placebo (n = 17) for 1 month. Patients were not supplemented with any other drug or vitamins E or C during the study. Standard questionnaires were used by teachers, parents, and doctors to rate performance. On the Child Attention Problem rating scale the teachers reported a significant improvement in hyperactivity and inattention compared with baseline (p < 0.01) and placebo (p < 0.05). After a one-month washout the scores returned to baseline. With the Conner's Teacher Rating Scale only the inattention score was significantly different to placebo (p < 0.05), whereas the hyperactivity score did not reach statistical significance. The Conner's Parent Rating Scale showed improvements of inattention and hyperactivity score, which did not reach statistical significance. Psychologist assessment of visual-motoric coordination and concentration revealed a significant improvement compared with baseline (p = 0.019) and placebo (p = 0.05). No serious adverse side effects were reported. One Pycnogenol-treated patient had moderate gastric discomfort and another had "a rise of slowness." There were no changes in standard blood chemistry parameters, suggesting good tolerance.

Pycnogenol was effective according to 2 of the 4 standard assessments. The authors state that the findings should be confirmed in studies with a greater number of patients.

#### Gynecology

##### Endometriosis

**Kohama, et al, 2007.**<sup>8</sup> A randomized, open-label, comparative study was conducted in women who had undergone conservative operations for endometriosis within the previous 6 months but still had recurrent moderate to severe dysmenorrhea or other pelvic pain or disorders. Patients (aged 21-39 years) were treated with 60 mg/day Pycnogenol for 48 weeks (n = 32) or gonadotropin releasing hormone antagonist Gn-RHa therapy as an injected leuporelin acetate depot (Wyeth Medica Ireland, Kildare, Ireland), 3.75 mg intracutaneously, 6 times every 4 weeks, for 24 weeks (n

= 26). Patients were provided with a rubric to score their symptoms. Treatment with Pycnogenol slowly but steadily reduced all of the symptom scores from severe to moderate: menstrual pain ( $p < 0.001$ ), pelvic pain ( $p = \text{NS}$ ), pelvic tenderness ( $p < 0.05$ ), and pelvic induration ( $p < 0.01$ ). Gn-RHa also reduced all of the scores, but did so more quickly and lowered the scores significantly more than Pycnogenol. However, patients treated with Gn-RHa had a recurrence of symptoms following discontinuation of treatment. GnRHa suppressed menstruation during treatment and lowered estrogen levels dramatically. Pycnogenol treatment did not lead to these adverse effects. The serum marker CA-125 for endometriosis decreased in both groups, which is indicative for possible decreased endometrioma size. Pycnogenol-related AEs were mild and transient and included dysfunctional uterine bleeding, epigastric pain, increase in menstrual bleeding, and acne.

Pycnogenol may be a therapeutic option for endometriosis. Patients will need to be made aware that Pycnogenol works slower and does not reduce symptoms as much as standard Gn-RHa therapy. A larger placebo-controlled trial would be desirable to assess the effects of Pycnogenol in longer treatment duration.

### Dysmenorrhea

**Suzuki, 2008.**<sup>9</sup> A randomized, double-blind, placebo-controlled multicenter study was conducted with women (aged 18-48 years) diagnosed with dysmenorrhea. Participants were observed for 2 menstrual cycles to obtain baseline information. They then took 60 mg/day Pycnogenol ( $n = 49$ ) or placebo ( $n = 56$ ) throughout a period of time covering 2 menstrual cycles. One more menstrual cycle was observed following cessation of the treatment. Menstrual pain decreased more in the Pycnogenol group than in the placebo group, but the difference was not statistically significant ( $P$  values were not reported). Compared with placebo, Pycnogenol treatment reduced the quantity of NSAID analgesics (type not reported) used by patients with dysmenorrhea (4.4 vs. 2.6 pills, respectively) and the number of days during which analgesic medication was required for dysmenorrhea (1.7 vs. 1.2 days, in placebo and control groups, respectively). These effects persisted after Pycnogenol treatment ceased ( $p < 0.05$ ). The number of days during which analgesic medication was required for dysmenorrhea decreased from 2.1 days to 1.3 days at the end of the study period. The quality-of-life assessment (SF-36), physical component summary, and mental component summary revealed no significant differences between groups. However, the bodily pain score was significantly different between groups at the end of Pycnogenol treatment ( $p < 0.05$ ). The authors state that Pycnogenol treatment was safe.

The authors conclude that Pycnogenol has an analgesic sparing effect and may be useful as an adjunct to standard treatment. The authors did not discuss whether the effects were clinically meaningful.

### Osteoarthritis

**Belcaro, et al, 2007.**<sup>10</sup> A randomized, double-blind, placebo-controlled trial was conducted in patients (mean age: 48 years) with primary osteoarthritis (OA) grade I or II in one or both knees, as diagnosed by x-ray. The patients also had mild to moderate pain not adequately controlled by anti-inflammatory drugs. They were treated with 100 mg per day oral Pycnogenol ( $n = 77$ ) or placebo ( $n = 79$ ) for 3 months. The WOMAC (Western Ontario and McMaster Universities) index, with 25 parameters, was used to monitor the course of the disease. The global WOMAC score showed a 50% decrease from baseline in OA symptoms in Pycnogenol-treated patients (baseline score: 79.2, 3-month score: 34.6;  $p < 0.05$ ), which was significantly better than placebo-treatment (Pycnogenol 3-month score: 34.6, placebo 3-month score: 69.5;  $p < 0.05$ ). Pycno-

genol treatment resulted in a significant mean increase in muscular/walking performance compared with placebo (198 m vs. 88 m, respectively;  $p < 0.05$ ). At the end of treatment, 79% of Pycnogenol-treated patients and 1% of placebo-treated patients had a decrease in edema. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) was significantly reduced by 58% during Pycnogenol treatment versus 1% with placebo treatment ( $p < 0.05$ ).

The study appears to be well-designed and executed. Apparently, side-effects were recorded by patients, but were not reported in the publication. Future studies should also include radiological measures to determine whether joint-space narrowing is affected by Pycnogenol treatment.

**Farid, et al, 2007.**<sup>12</sup> A randomized, double-blind, placebo-controlled, parallel-group trial was conducted in patients (aged 25-65 years) with primary knee OA grade I or II and pain. Patients were treated with 150 mg per day oral Pycnogenol ( $n = 19$ ) or placebo ( $n = 18$ ) for 3 months. After 1 month of supplementation there were no significant differences between Pycnogenol and placebo treatment on the WOMAC scores. A significant improvement was evident at 2 months, but at 3 months Pycnogenol supplementation resulted in "relevant improvement" of the WOMAC composite index and the subscales (except stiffness) compared with placebo ( $p < 0.001$ ). Compared with baseline, there was a significant reduction of 43% in pain ( $p < 0.01$ ), 35% in stiffness ( $p < 0.05$ ), 52% in physical dysfunction ( $p < 0.01$ ), and 49% in composite score ( $p < 0.01$ ) with Pycnogenol treatment and no significant changes from baseline with placebo. Pycnogenol treatment resulted in a significant decrease in the use of pain medicine compared with placebo ( $p < 0.001$ ). Adverse events were not reported.

Even though the study was underpowered, the findings were highly significant based on the  $p$ -value after 3 months treatment, which was  $p < 0.001$ . The study could have benefited from additional objective measures such as performance-based functional measures. Functional measures would confirm that the findings were both clinically and statistically significant.

**Cisár, et al, 2008.**<sup>11</sup> A randomized, double-blind, placebo-controlled trial was conducted in patients (aged 25-65 years) with primary knee OA grade I or II and pain. Patients were treated with 150 mg per day oral Pycnogenol ( $n = 50$ ) or placebo ( $n = 50$ ) for 3 months. Compared with baseline, pain and the WOMAC score characterizing ability to perform daily activities significantly improved overtime in Pycnogenol-treated patients ( $p < 0.01$ ), but the improvement was not significantly different from placebo. Compared with placebo, stiffness was significantly improved with Pycnogenol at 2 and 3 months ( $p < 0.05$ ). The overall WOMAC score in the Pycnogenol group was significantly different from placebo at 6, 8 and 12 weeks ( $p < 0.05$ ), but failed to reach significance at week 10. The study evaluated symptoms again after 3 weeks since cessation of treatment and no relapse occurred in the Pycnogenol group. Analgesic consumption during the third month of treatment with Pycnogenol decreased in 38% of patients, whereas it increased in 10% of patients given placebo. Pycnogenol was well-tolerated. None of the analyzed biochemical parameters raised or decreased beyond the range of physiologic levels after 3 months treatment with Pycnogenol or placebo.

The study design was nearly identical to the design of Farid et al, but had a larger group size.

### Osteoarthritis Summary

All 3 studies reported subjective improvements in symptoms of knee OA in patients treated with Pycnogenol. Together the data indicate that the clinical response is delayed and efficacy may not

be apparent until 6-8 weeks after initiating treatment. It is worthy of note that none of the studies evaluated the use of Pycnogenol in lieu of conventional therapies but rather as an adjunct therapy. Also lacking in these studies are any radiological measures. Conventional therapies for OA have many unwanted side effects and the benefit of Pycnogenol may be that it is well tolerated and reduces the need for NSAID analgesics.

## MANUFACTURER INFORMATION

**Manufacturer:** Horphag Research, UK Ltd. Administrative office: Avenue Louis-Casai 71, 1216 Cointrin, Geneva, Switzerland. Web site: [www.pycnogenol.com](http://www.pycnogenol.com).

Importer and distributor in the United States: Natural Health Science, Inc., 5 Marine View Plaza, Ste. 403, Hoboken, NJ 07030. Web site: [www.pycnogenol.com](http://www.pycnogenol.com).

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## CONFLICT OF INTEREST DISCLOSURE

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**Table: Selected Clinical Trials on Pycnogenol®**

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results
<b>Chronic Venous Insufficiency, Edema, and Complications</b>						
Cesarone et al., 2006	Chronic venous insufficiency	R, C n=86 with CVI (48 men, 38 women; age 40-61 years)	8 weeks	150 mg/day Pycnogenol® (3 capsules/day), 300mg/day Pycnogenol (6 capsules/day), 1000 mg/day Daflon® (2 tablets/day)	50 mg Pycnogenol® capsules; 500 mg Daflon® tablets (Servier, France)	Compared with baseline and Daflon, after 8 weeks treatment both doses of Pycnogenol resulted in significantly greater improvement in CVI signs, symptoms, and microcirculatory parameters (resting flux, rate of ankle swelling, edema, subjective symptoms).
Koch, 2002	Chronic venous insufficiency	R, OL, C, Cm n=40 with CVI (7 men, 33 women; age 34-71 years)	4 weeks	360 mg Pycnogenol (3 tablets 3x/day); 600 mg horse chestnut seed extract (2 capsules/day)	40 mg Pycnogenol tablets; 300 mg Venostasin® capsules	Compared with horse chestnut extract, Pycnogenol produced significantly greater decrease in heaviness, cramps, and night-time swelling (edema) of both legs (p<0.05). Pycnogenol significantly reduced lower leg edema from baseline (p<0.01).
Petrassi et al., 2000	Chronic venous insufficiency	R, DB, PC n=20 with CVI (3 men, 17 women; mean age: 42.2 years) OL n=20 (3 men, 17 women; mean age 44.9 years) (Two-part study)	2 months for each study part	300 mg (1 capsule 3x/day)	100 mg capsules	Heaviness and swelling significantly declined in Pycnogenol-treated patients compared with placebo-treated patients (p<0.05) and compared with baseline. By day 60 there was a 60% decline in heaviness and a 74% decline in swelling in Pycnogenol-treated patients. Similar findings were apparent in patients treated with open-label Pycnogenol.
Arcangeli, 2000	Chronic venous insufficiency	R, DB, PC n=40 with CVI (13 men, 27 women; age 30-74 years)	2 months	300 mg (1 capsule 3x/day)	100 mg capsules	Pycnogenol-treated patients had significant reduction in heaviness, swelling, and pain compared with placebo at day 30 (p<0.01, p<0.01, p<0.05; respectively) and day 60 (p<0.01, p<0.01, p<0.05; respectively). At study end, Pycnogenol-treated patients reported 54% reduction in heaviness, 64% reduction in swelling, and 64% reduction in pain compared with reduction of 3%, 7%, and 18%, respectively, in placebo-treated patients (p<0.01, p<0.01, p<0.05; respectively). In both groups there was no apparent change in venous blood flow, measured via Doppler ultrasound.
Schmidtke & Schoop, 1995	Hydrostatic edema of lower limbs	R, DB, PC n=40 with venous circulation problems in their legs (22 men, 18 women; age not reported)	6 days	360 mg/day (no compression therapy during study)	20 mg tablets	After 6 days of treatment, patients treated with Pycnogenol had lower-leg volume (measured after lying down and 2 hours sitting) that was significantly lower than lower-leg volume of placebo-treated patients (p<0.001).

**Table: Selected Clinical Trials on Pycnogenol® Continued**

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results
<b>Chronic Venous Insufficiency, Edema, and Complications</b>						
Belcaro et al., 2005	Venous ulcers	PC n=18 with severe CVI causing ulcerations (10 men, 8 women; mean age 56.6 years)	6 weeks	150 mg/day (3 capsules/day); 150 mg/day (3 capsules/day) and topical local application of 100 mg Pycnogenol powder covered with dressing and reapplied every 2 days. Standard compression stockings supplied for all patients.	50 mg capsules	Starting with 2 weeks treatment, oral local Pycnogenol decreased ulcer size more efficiently than oral treatment alone (p<0.05) or oral placebo (p<0.05). At 6 weeks, transcutaneous respiration (pO <sub>2</sub> & pCO <sub>2</sub> ) was significantly improved with local and/or oral treatment (p<0.05).
Cesarone et al., 2005	Travel-related edema in asymptomatic subjects	R, DB, PC n=211 with mild-to-moderate thrombotic risk (mean age 45 years, gender NR)	2 days	200 mg 2-3 hours before flight (2 capsules); 200 mg 6 hours later (2 capsules), 100 mg the following day (1 capsule)	100 mg capsules	After the flight, edema score was increased by 18% in Pycnogenol-treated group and 58% in placebo-treated group (p<0.05). Ankle circumference increased by 6% in the Pycnogenol group and 11% in the placebo group (p<0.05). Rate of ankle swelling increased 36% in Pycnogenol group and 91% in placebo group (p<0.05).
Cesarone et al., 2006	Venous microangiopathy	OL, C n=39 with severe, chronic CVI (21 patients treated with Pycnogenol: 11 men, 10 women; age 42-60 years) (untreated group NR)	8 weeks	150 mg/day (3 capsules/day); untreated controls. Compression stocking not used.	50 mg capsules	Blood microcirculation was lowered and capillary filtration edema decreased significantly after 2 weeks treatment compared with baseline (p<0.05) and after 8 weeks compared with untreated control group (p<0.05).
Riccioni et al., 2004	Venous insufficiency	OL, C, Cm n=70 with CVI (22 men, 48 women; mean age 47.5 years)	60 days	940 mg/day troxerutin with 40 mg/day Pycnogenol (2 sachet/day); 1200 mg troxerutin (2 tablets 2x/day)	Sachets with 470 mg troxerutin + 20 mg Pycnogenol powder as instant drink (Flebil Plus sachet 490 mg). Troxerutin 300 mg tablets (Flebil 300 mg tablets)	After 60 days there was complete absence of nocturnal cramps, itching, and pain in 96% patients taking troxerutin/Pycnogenol (p<0.001). 80% troxerutin-treated patients reported complete symptom recovery (p<0.005). 3 months after discontinuation 88% patients previously on Pycnogenol/troxerutin and 50% of patients who had taken troxerutin remained symptom free.
<b>Thrombosis</b>						
Belcaro et al., 2004	Venous thrombosis	R, DB, PC n=198 with moderate-to-high risk for deep venous thrombosis or superficial vein thrombosis (age and gender NR)	2 days	200 mg 2-3 hours before flight (2 capsules); 200 mg 6 hours later (2 capsules), 100 mg the following day (1 capsule)	100 mg capsules	Significantly fewer superficial vein thrombosis events were reported in Pycnogenol group compared with placebo (0 vs. 4; p<0.05). None of the Pycnogenol-treated participants had deep vein thrombosis (DVT), while 1 patient in placebo group had DVT. There was significantly lower rate of events in treatment group compared with placebo (0% vs. 5.15%, respectively; p<0.025).

**Table: Selected Clinical Trials on Pycnogenol® Continued**

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results
<b>Diabetes and Complications</b>						
Liu et al., 2004	Type 2 Diabetes	R, DB, PC n=77 with type 2 diabetes (44 men, 23 women; age 45-66 years)	12 weeks	100 mg/day (2 tablets/day); Patients continued their antidiabetic medication	50 mg tablets	Median plasma glucose had maximum reduction after 8 weeks treatment (-1.96 mmol/L), which was maintained through rest of trial. Pycnogenol significantly decreased plasma glucose greater than did placebo at all time intervals (p<0.01). HbA <sub>1c</sub> was lowered (p<0.01); significance only until 1 month. Plasma endothelin-1 decreased and prostacyclin metabolites increased significantly compared with placebo (p<0.01).
Belcaro et al., 2006	Diabetic ulcers	R, OL, C n=30 with diabetic ulcers (14 men, 16 women; mean age 54 years)	6 weeks	(1) 150 mg/day oral Pycnogenol (3 capsules/day) plus 100 mg topical Pycnogenol powder from capsules placed on ulcerated skin; (2) 150 mg/day oral Pycnogenol, (3) 100 mg topical Pycnogenol powder, or (4) no Pycnogenol (standard care).	50 mg capsules	Oral and/or local treatment was significantly more effective than standard compression treatment for reducing ulcer size (p<0.01). Combination therapy was more effective than local or oral therapy alone. Transcutaneous respiration (pO <sub>2</sub> and pCO <sub>2</sub> ), blood micro-circulation and micro-vascular response (laser-doppler) were significantly improved with oral or oral plus topical treatment compared with baseline (p<0.05).
Cesarone et al., 2006	Diabetic micro-angiopathy	OL, C n=60 with severe microangiopathy (34 men, 26 women; age 55-68 years)	4 weeks	150 mg/day (3 capsules/day); diabetic treatment was continued.	50 mg capsules	Microcirculation at rest, venoarteriolar response (both evaluated by laser Doppler), and ankle swelling were significantly improved compared with baseline and (p<0.05) & untreated control group (p<0.05).
Liu et al., 2004	Type 2 Diabetes	O, n=30 with type 2 diabetes (18 men, 12 women; age 28-64 years)	12 weeks	50, 100, 200 and 300 mg/day. Each dosage for 3 weeks.	50 mg tablets	There was dose-dependent lowering of fasting and post-prandial blood glucose and hemoglobin A <sub>1c</sub> . Significant post-prandial blood glucose lowering beginning at 50 mg (p<0.05). Fasting blood glucose was lowered significantly from 100 mg (p<0.05). Maximum effect with 200 mg Pycnogenol.
<b>Hypertension and Complications</b>						
Belcaro et al., 2006	Antihypertensive treatment-induced edema	PC n=53 with edema after treatment with ACE inhibitors or the calcium antagonist nifedipine (29 men, 24 women; mean age 47.7 years)	8 weeks	150 mg/day (3 capsules/day)	50 mg capsules	There was significant lowering of abnormal capillary filtration in patients medicated with nifedipine or ACE inhibitors compared with baseline (p<0.05). No significant effect with placebo.

**Table: Selected Clinical Trials on Pycnogenol® Continued**

Author /Year	Subject	Design	Duration	Dosage	Preparation	Results
<b>Hypertension and Complications</b>						
Hosseini et al., 2001	Mild hypertension	R, DB, PC, CO n=11 with systolic pressure:140-159 mmHg and/or diastolic pressure: 90-99 mmHg (7 men, 4 women; mean age 50 years)	16 weeks	200 mg/day (2 capsules 2x/day)	50 mg capsules	Systolic blood pressure (BP) decreased from mean of 140 mmHg to 133 mmHg after 8 weeks of Pycnogenol treatment. The decrease was significantly lower than placebo treatment (p<0.05). Pycnogenol was less effective in patients with BP less than 140 mmHg. Decrease of diastolic BP did not reach significance. Thromboxane levels decreased (p<0.05).
Liu et al., 2004	Assess whether Pycnogenol can reduce dose of nifedipine used to treat hypertension	R, DB, PC n=58 with hypertension (33 men, 25 women; mean age 57 years)	12 weeks	100 mg/day Pycnogenol (2 tablets/day); ≥20 mg of sustained release nifedipine (dose adjusted in 5 mg increments until stable BP reached).	50 mg tablets	Supplementation with Pycnogenol significantly reduced dose of nifedipine needed to reduce BP compared with placebo (p<0.001). Pycnogenol-treated patients had significantly greater increase in 6-keto-prostaglandin F1a values than placebo treatment (12% vs 8% increase, respectively, p<0.05), which shows significant improvement in endothelial function.
<b>Asthma</b>						
Hosseini et al., 2001	Asthma	R, DB, PC, CO n=22 with asthma (10 men, 12 women; age 18-60 years)	8 weeks	1 mg/lb/day, maximum 200 mg/day	20 mg capsules	Lung function (FEV <sub>1</sub> /FVC) was significantly improved compared with placebo (p=0.003). Leukotriene levels significantly decreased compared with placebo (p<0.001).
Lau et al., 2004	Childhood asthma	R, DB, PC n=60 with asthma (35 boys, 25 girls; age 6-18 years)	3 months	1 mg/lb/day in 2 divided dosages	20 mg tablets	Lung function (peak expiratory flow), asthma symptom score, frequency of albuterol usage (rescue medication) and urinary leukotriene levels were significantly improved beginning from 1 month treatment compared with baseline (p<0.001). All parameters further improved after 2 and 3 months treatment.
<b>ADHD</b>						
Trebaticka et al., 2006	Childhood ADHD	R, DB, PC n=61 children with clinically diagnosed ADHD for at least 6 months (50 boys, 11 girls; age 6-14 years)	1 month, followed by 1 month wash-out	1 mg/kg body weight/day	20 mg tablets	Pycnogenol was effective according to 2 of 4 ADHD assessments. On Child Attention Problem rating scale, teachers reported significant improvement in hyperactivity and inattention compared with baseline (p<0.01) and placebo (p<0.05). After 1-month wash-out the scores returned to baseline. With Conner's Teacher Rating Scale, improvement was not significantly different from baseline. ADHD symptoms as evaluated by parents did not significantly decline compared with baseline and placebo. Psychologist assessment of visual-motoric coordination and concentration revealed significant improvement compared with baseline (p<0.019) and placebo (p<0.05).

**Table: Selected Clinical Trials on Pycnogenol® Continued**

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results
<b>Gynecology</b>						
Suzuki et al., 2008	Dysmenorrhea	R, DB, PC n=116 women with symptoms of menstrual pain (age 18-48 years)	4 menstrual cycles	60 mg/day for 2 menstrual cycles	30 mg capsules	Menstrual pain decreased more in Pycnogenol group than in placebo group. Compared with placebo, Pycnogenol treatment reduced quantity of analgesics used by patients with dysmenorrhea (4.4 vs. 2.6 pills, respectively) and number of days with dysmenorrhea (1.7 vs. 1.2 days, respectively). These effects persisted after Pycnogenol treatment ceased ( $p < 0.05$ ). The quality-of-life assessment (SF-36) physical component summary and mental component summary revealed no significant differences between groups, except for bodily pain score ( $p < 0.05$ Pycnogenol vs placebo).
Kohama et al., 2007	Endometriosis	R, OL, Cm n=58 women who had undergone conservative operations for endometriosis within previous 6 months but still had recurrent moderate to severe dysmenorrhea or other pelvic pain or disorders (age 21-38 years)	48 weeks Pycnogenol; 24 weeks Leuprorelin followed by 24 weeks wash-out	60 mg/day Pycnogenol (1 capsule 2x/day); Gn-RHa therapy as an injected leuprorelin acetate depot, 3.75 mg intracutaneously, 6 times every 4 weeks, for 24 weeks	30 mg Pycnogenol capsules; Leuprorelin 3.75 mg injections	Treatment with Pycnogenol slowly reduced all symptom scores from severe to moderate: menstrual pain ( $p < 0.001$ ), pelvic pain, pelvic tenderness ( $p < 0.05$ ), and pelvic induration ( $p < 0.01$ ). Gn-RHa also reduced all scores, but did so more quickly and lowered the scores significantly more than Pycnogenol. However, patients treated with Gn-RHa had recurrence of symptoms following discontinuation. GnRHa suppressed menstruation during treatment and lowered estrogen levels; Pycnogenol did not. The serum marker CA-125 for endometriosis decreased in both groups.
Kohama et al., 2006	Pain in pregnancy	OL, C n=140 women in 3rd trimester pregnancy with lower back, hip, pelvic, or calf pain (mean age 28.9 years)	Throughout 3rd trimester pregnancy until delivery	30 mg/day (1 tablet/day); no treatment in control group	30 mg tablets	There was significant improvement of pain scores after 2 and 6 weeks, related to hip joint pain, lower back pain, inguinal pain, pain due to varices, and calf cramps ( $p < 0.01$ compared to baseline). There were no significant effects in untreated control group.
Yang et al., 2007	Climacteric syndrome in perimenopause	R, DB, PC n=200 perimenopausal women (who had no menstrual cycles for 3-11 months and then normal cycles reappeared) (mean age 46.9 years)	6 months	200 mg (1 capsule 2x/day)	100 mg capsules	Compared with baseline and placebo, Pycnogenol-treated patients had significant improvement in severity and frequency of climacteric symptoms: somatic problems, depression, vasomotor problems, memory/concentration, attractiveness, anxiety, sexual behavior, sleep, menstrual problems ( $p < 0.01$ for all). Improvement was evident at 1 month.

**Table: Selected Clinical Trials on Pycnogenol® Continued**

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results
<b>Gynecology</b>						
Kohama et al., 2004	Dysmenorrhea	OL 47 women with symptoms of dysmenorrhea (age 21-45 years)	3 complete menstrual cycles; 64 days	60 mg/day (1 capsule in morning and evening)	30 mg capsules	Compared with baseline, abdominal pain scores declined after Pycnogenol intake (cycle 1: $p < 0.05$ , cycle 2: $p < 0.01$ ). Back pain score significantly declined only after Pycnogenol was taken over 2 menstrual cycles ( $p < 0.01$ ). There was no significant change in number of days with abdominal pain.
<b>Osteoarthritis</b>						
Belcaro et al., 2008	Osteoarthritis	R, DB, PC n=156 with primary osteoarthritis grade I or II in one or both knees (78 men, 78 women; mean age 48 years)	3 months	100 mg/day (2 tablets/day)	50 mg tablets	The global WOMAC score showed a 50% decrease from baseline in osteoarthritis symptoms in Pycnogenol-treated patients ( $p < 0.05$ ), which was significantly better than placebo-treatment ( $p < 0.05$ ). Pycnogenol treatment resulted in significant mean increase in muscular/walking performance compared with placebo ( $p < 0.05$ ). At end of treatment, 79% of Pycnogenol-treated patients and 1% of placebo-treated patients had decrease in edema.
Farid et al., 2007	Osteoarthritis	R, DB, PC, PG n=38 with primary knee osteoarthritis grade I or II and pain (3 men, 35 women; age 25-65 years)	3 months	150 mg/day (1 tablet 3x/day)	50 mg tablets	At 3 months there was "relevant" and significant reduction in pain (43% reduction), stiffness (35% reduction), physical function (52% reduction), and composite score (49% reduction) with Pycnogenol treatment and no significant changes with placebo. Pycnogenol treatment resulted in significant decrease in use of pain medicine compared with placebo ( $p < 0.001$ ).
Cisar et al., 2008	Osteoarthritis	R, DB, PC n=100 with primary knee osteoarthritis grade I or II and pain (32 men, 68 women; mean age 54 years)	3 months	150 mg/day (1 tablet 3x/day)	50 mg tablets	Pain and the WOMAC score characterizing ability to perform daily activities were not significantly different from placebo. However, overall WOMAC score was significantly different between treatments at 1.5, 2, and 3 months ( $p < 0.05$ for all). Compared with placebo, stiffness was significantly improved with Pycnogenol at 2 ( $p < 0.05$ ) and 3 months ( $p < 0.05$ ). Use of analgesics was decreased by 38% in Pycnogenol group and by 8% in placebo group.

**Table: Selected Clinical Trials on Pycnogenol® Continued**

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results
<b>Retinopathy</b>						
Spadea & Balestrazzi, 2001	Retinal vascular disorders	R, DB, PC n=40 with vascular disorders of the retina secondary to atherosclerosis, diabetes, hypertension, or thrombosis of central retinal vein (male/female ratio and age unclear)	2 months	150 mg (1 tablet 3x/day)	50 mg capsules	Pycnogenol slowed down deterioration of visual acuity compared with placebo (p<0.05). [Note: after commencing the study the authors added 20 additional patients treated with open-label Pycnogenol for 3 months. They combined much of the data, which is not methodologically appropriate.]
<b>Gingivitis</b>						
Kimbrough et al., 2002	Gingival bleeding and dental plaque	DB, PC, R n=40 dental students (20 men, 20 women, age 22-35 years)	2 weeks	30 mg (6 chewing gums daily)	5 mg chewing gums	Pycnogenol gum produced a significant lowering of gingival bleeding compared with baseline (p<0.05) and did not alter plaque formation. Trident® gum (placebo) did not alter gum bleeding and increased plaque formation compared with baseline (p<0.05).
<b>Melasma</b>						
Ni et al., 2002	Hyperpigmentation (melasma)	OL n=30 women with melasma for a mean of 8 years (mean age 41 years)	30 days	75 mg (1 tablet 3x/day)	25 mg tablets	Pigmentary intensity and size of affected skin were significantly reduced (p<0.001).
<b>Cramps and Muscular Pain</b>						
Vinciguerra et al., 2006	Muscle cramps and pain	<u>Part 1:</u> OL n=66 (22 normal subjects with cramps ≥ 4x/week, 21 patients with venous disease and cramps 4-6x/week, 23 athletes with frequent cramps during exercise) <u>Part 2:</u> DB, PC n=47 (25 patients with intermittent claudication, 22 patients with diabetic microangiopathy, mean age 60 yrs)	4 weeks, 1 week wash-out	200 mg/day (2 x50 mg capsules or 1 100 mg capsules 2x/day)	50 mg capsules or 100 mg capsules	Frequency of cramps and muscle pain score decreased significantly after 4 weeks treatment and after 1 week discontinuation in athletes, normal subjects and subjects with venous problems (p<0.05 for all). Frequency of cramps and muscle pain score decreased significantly (p<0.05) in subjects with intermittent claudication and diabetic microangiopathy after 4 weeks treatment and 1 week discontinuation compared with baseline. There was no effect in placebo-treated patients.

CVI: chronic venous insufficiency, Cm: comparative, C: controlled, DB: double-blind, DVT: deep vein thrombosis, OL: open-label, PC: placebo-controlled, PG: parallel group, R: randomized, WOMAC (Western Ontario and McMaster Universities) index.

# AMERICAN BOTANICAL COUNCIL

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*Provide education using science-based and traditional information to promote responsible use of herbal medicine.*



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