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 (*Pinus pinaster* subsp., *atlantica*, Pinaceae) bark, manufactured by Horphag Research (Geneva, Switzerland). Pycnogenol is standardized to contain 70 ± 5% procyanidins in compliance with the *United States Pharmacopeia* (USP); its compounds are known for significant antioxidant and anti-inflammatory activities, among other actions. In terms of dollar sales, Pycnogenol was ranked among the 100 top-selling herbal dietary supplements in the United States in mainstream retail outlets (food, drug, and mass-market stores) and top 50 in the natural channel (health food stores) from 2013-2015. In 2017, Pycnogenol ranked 117th in the US mainstream retail channel and 63rd in the natural channel. Pycnogenol is one of the most extensively researched herbal supplement preparations in terms of both clinical studies and its underlying biological activity.

PRIMARY USE

Cardiovascular Health: Although there are many uses for Pycnogenol, the most extensively studied use is for cardiovascular health. Regarding improvement of endothelial function and chronic venous insufficiency (CVI), 7 controlled clinical trials have been published that demonstrate symptomatic improvement of blood circulation, blood pressure (BP) normalization, platelet function normalization, and venous insufficiency. In addition, 5 clinical trials have demonstrated the efficacy of Pycnogenol for hypertension and its complications. One study looked at the benefits of Pycnogenol on coronary artery disease and showed that the preparation improved endothelial function. All of these studies have shown a benefit, but studies with larger numbers of participants are needed to further substantiate these findings.

OTHER POTENTIAL USES

Controlled clinical trials have been published for the following potential uses: thrombosis, diabetes and its complications, asthma, attention deficit hyperactivity disorder (ADHD), gynecology (endometriosis, dysmenorrhea, pregnancy-associated pain, and menopause transition), osteoarthritis (OA), acute and postpartum hemorrhoids, and cognition. These indications have been evaluated in 1 to 5 well-designed, published clinical trials. The studies have 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), ultraviolet (UV) light-induced erythema (sunburn), skin elasticity and hydration, muscle cramps and pain, postthrombotic syndrome, diabetic microangiopathy, metabolic syndrome, allergic rhinitis, common cold, psoriasis, chemotherapy/radiotherapy side effects, and tinnitus.

PHARMACOLOGICAL ACTIONS

Pharmacological studies employing in vitro, animal, and/or human models have found that Pycnogenol has potent antioxidant and anti-inflammatory activities; improves endothelial function (relieves vasoconstriction); reduces platelet aggregation; reduces α-glucosidase activity and blood glucose levels; improves diabetes-related BP, neuropathy, cardiomyopathy, and liver damage; promotes wound healing; alters messenger RNA (mRNA)/gene expression to improve skin hydration and elasticity; protects against sunburn; alters neurotransmitter levels in children with ADHD; improves measures of cognition; reduces neuroinflammation, neurodegeneration, and behavioral impairments associated with Parkinson's disease; reduces the loss of presynaptic and postsynaptic proteins in traumatic brain injury; alters mast cell-mediated responses; protects against nephrotoxicity; inhibits growth of cancer cells; suppresses bone loss post menopause; 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 Table 2 in the full monograph. [Note: Some of the doses are based on a single study and/or uncontrolled studies.]

ADHD: 100 mg/day or 1 mg/kg of body weight/day
Allergic rhinitis: 100 mg/day
Asthma: 100 mg/day or 1 mg/lb of body weight/day
Chemotherapy/radiotherapy side effects: 150 mg/day
Cholesterol/dyslipidemia: 120-150 mg/day
Cognition: 100-150 mg/day
Common cold: 100 mg/day
Coronary artery disease: 200 mg/day
CVI: 150-360 mg/day
Diabetes: 50-200 mg/day oral or 100 mg topical Pycnogenol powder
Dysmenorrhea: 60 mg/day
Endometriosis: 60 mg/day
Erectile dysfunction: 120 mg/day
Gingivitis: 30 mg/day
Hemorrhoids (acute): 150-300 mg/day oral plus topical 0.5% Pycnogenol cream
Hemorrhoids (postpartum): 150 mg/day
Hypertension: 100-200 mg/day
Melasma: 75 mg/day
Menopause transition: 60-200 mg/day
Metabolic syndrome: 150 mg/day
Muscle cramps: 200 mg/day
OA: 100-150 mg/day
Platelet function: 100-200 mg/day
Pregnancy-associated pain: 30 mg/day
Psoriasis: 150 mg/day
Retinopathy: 40-200 mg/day
Skin elasticity and hydration: 75 mg/day

Sunburn: 1.10-1.66 mg/kg of body weight/day
Thrombosis: 100-200 mg/day
Tinnitus: 150 mg/day

In the clinical trials, the most common duration of use was 2 to 3 months; however, longer-term use may be justified. There is no evidence from actual product use by millions of people that might warrant a limitation, and based on the published chemistry, pharmacology, and toxicology of Pycnogenol, there are no data suggesting a limitation on duration of use. Long-term safety studies would be a useful addition to the overall safety profile of Pycnogenol.

MANUFACTURER DOSE RECOMMENDATIONS

According to the manufacturer, the dosage of Pycnogenol will depend on the nature of the desired health benefits. For example, the dose required for preventative effects may be different from the dose used for improving acute or chronic health problems.

As an antioxidant, Pycnogenol may be effective at any dose. However, the manufacturer states that in order to have measurable physiological 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 hypercoagulation, 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 of venous insufficiency, the daily dosage should be in the range of 100 to 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 levels in patients with diabetes, the manufacturer recommends taking 50 mg once or twice daily.

Anti-inflammatory effects can be achieved with Pycnogenol doses of at least 30 mg/day.

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

For OA, asthma, and ADHD, 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 or second trimester. Safety trials have demonstrated an absence of mutagenic and teratogenic effects, no perinatal toxicity, and no negative effects on fertility.

Children: As a general precaution, children younger than 6 years old should not use Pycnogenol because appropriate dosing has not been confirmed.

ADVERSE EFFECTS

Pycnogenol has been affirmed GRAS (Generally Recognized As Safe) for use in conventional foods, based on the evaluation of clinical safety and preclinical 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 91 human clinical studies with a total of 6845 people, including both healthy participants and patients with a particular dysfunction or pathology. Oral Pycnogenol daily doses range from 30 to 450 mg/day, with doses between 30 and 200 mg/day being the most commonly evaluated. The global frequency rate of adverse effects (AEs) is 2.4%. However, in healthy participants, the global incidence rate of AEs is 0.1%. An evaluation of the clinical studies revealed that the occurrence of AEs is unrelated to the dose or duration of use.

Gastrointestinal (GI) discomfort is the most frequently occurring treatment-related AE reported in clinical trials. This may be attributed to the astringent nature of Pycnogenol, which may irritate the stomach of sensitive individuals. GI effects did not occur when Pycnogenol was taken with or after meals. According to the manufacturer, GI effects can be prevented when Pycnogenol is taken with food or after a meal. 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. The majority of AEs observed were mild.

Pycnogenol at a dose of 60 mg/day for 12 weeks did not alter hormone levels (insulin-like growth factor 1 [IGF-1], IGF-binding protein 3 [IGFBP-3], estradiol [E2], follicle-stimulating hormone [FSH], and dehydroepiandrosterone [DHEA] sulfate) in women.

Pycnogenol at a dose of 150 mg/day for 6 months did not alter liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and γ-glutamyltransferase [GGT]), alkaline phosphatase (ALP), C-reactive protein (CRP), serum creatinine, or blood parameters (blood cell count, fibrinogen, international normalized ratio [INR] for prothrombin time, and hematocrit) in patients with metabolic syndrome.

Postmarketing surveillance (spontaneous AE reporting) carried out between 2002 and March 28, 2013, in Europe, Asia, Africa, Canada, and the United States revealed 24 case reports, despite millions of Pycnogenol doses sold. The following incidents were reported (participants may have reported more than 1 AE): urticaria (n = 3), headache (n = 3), nausea (n = 2), diarrhea (n = 2), gastric pain (n = 5), gas (n = 1), eczema (n = 1), nontraumatic nose bleed (n = 1), painful joints (n = 1), dizziness (n = 1), bruising (n = 1), mouth ulcers (n = 1), urine colored (n = 1), and rash (n = 1). According to the manufacturer, urticaria is a rare allergic reaction that could be due to the color component of the tablet. Also, according to the manufacturer, gastric discomfort could occur when Pycnogenol is taken on an empty stomach, especially first thing in the morning.

There have been no reports of serious AEs in any clinical study or from commercial use of Pycnogenol since it was 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 intake have not been reported. Pycnogenol does not affect INR (a measurement of bleeding tendency) or platelet function in patients taking aspirin. No drug interaction studies have been performed with Pycnogenol. There were no adverse drug-herb interactions reported in a study that evaluated 28 patients with stable coronary artery disease treated with both optimal standard therapy and 200 mg/day Pycnogenol

for 8 weeks. Standard therapy included aspirin, statins, angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers, β-blockers, diuretics, calcium antagonists, clopidogrel, ezetimibe, oral antidiabetics, phenprocoumon, and α-antagonists.

CLINICAL REVIEW

As of December 2015, a total of 63 published human clinical efficacy trials on Pycnogenol as a monopreparation have been published in English or translated into English. Due to space considerations, the author and editors of the full Pycnogenol monograph decided to review only selected studies; however, all 63 studies appear in Table 2. 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/preliminary study, no control group, and any other significant methodological limitation. Thirty-seven clinical trials met these criteria and are reviewed in the text of the full monograph. These studies evaluated Pycnogenol for the following indications: CVI and its complications, thrombosis, diabetes and its complications, hypertension and its complications, coronary artery disease, asthma, ADHD, gynecology (endometriosis, dysmenorrhea, pregnancy-associated pain, and menopause transition), OA, acute hemorrhoids, and cognition.

To summarize the clinical findings, Pycnogenol may help decrease edema formation in the lower legs, such as in patients with CVI. Pycnogenol improves endothelial function, resulting in improved blood circulation, lowered BP in hypertension, and normalization of platelet coagulability. Pycnogenol may also protect kidney function in patients with hypertension. Pycnogenol has been shown to improve glycemic control in patients with type 2 diabetes, to improve treatment of diabetic ulcers, and to treat diabetic microangiopathy with edema when patients are unable to wear compression stockings. Preliminary studies suggest that Pycnogenol may be beneficial for children with ADHD and may be a useful adjunct therapy for patients with asthma or allergic asthma. Pycnogenol may help reduce pain associated with menstrual disorders and pregnancy and climacteric symptoms associated with menopause. Pycnogenol has been shown to decrease the signs and symptoms of acute external hemorrhoids. Working memory may be improved in healthy elderly people taking Pycnogenol. Several clinical studies report that Pycnogenol may improve subjective symptoms of knee OA. Other potential uses that require better-designed studies to more fully substantiate the applications of Pycnogenol include erectile dysfunction, retinopathy, gingivitis, melasma (discoloration of the skin), UV light-induced erythema (sunburn), skin elasticity and hydration, muscle cramps and pain, postthrombotic syndrome, diabetic microangiopathy, metabolic syndrome, allergic rhinitis, common cold, psoriasis, chemotherapy/radiotherapy side effects, and tinnitus.