AMERICAN BOTANICAL COUNCIL

PROPRIETARY BOTANICAL INGREDIENT

SCIENTIFIC AND CLINICAL MONOGRAPH FOR PYCNOGENOL®

(French Maritime Pine Bark Extract)

Pinus pinaster Aiton subsp. *atlantica*

[Fam. Pinaceae]

Pinus pinaster. Photo ©2019 Horphag

2019 UPDATE

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.

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 (*Pinus pinaster* subsp. *atlantica*, Pinaceae) bark extract. It is manufactured by Horphag Research (Geneva, Switzerland). 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.

USES

Although there may be many potential uses for Pycnogenol, the most extensively studied use is to treat cardiovascular health, especially chronic venous insufficiency (CVI), a condition defined by poor drainage of blood from veins resulting in swelling or skin problems. Seven 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 on the following potential uses: thrombosis (blood clots), diabetes and its complications, hypertension (high blood pressure) and its complications, coronary artery disease, asthma, attention deficit hyperactivity disorder (ADHD), gynecology (endometriosis [premenstrual pain caused by endometrial tissue outside the uterus], dysmenorrhea [painful menstruation], pregnancy-associated pain, and menopause transition), osteoarthritis (OA), acute and postpartum hemorrhoids, and memory. These indications have 1 to 5 well-designed, published clinical trials that support the findings. All of these studies have shown a benefit, but larger studies are needed to confirm 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), 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.

DOSAGE AND DURATION OF USE

The following doses were used in the clinical trials reported in Table 2 in the full monograph by the American Botanical Council. It should be noted that 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: 40-160 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. 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 by millions of people that might warrant a limitation. 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 (anti-swelling) 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.

Children: As a general precaution, children younger than 6 years old should not use Pycnogenol.

ADVERSE EFFECTS

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. The overall frequency rate of adverse effects (AEs) is very low (2.4%). In healthy participants, the incidence rate is even lower (0.1%). An evaluation of the clinical studies revealed that the occurrence of AEs 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 treatment-related AE. According to the manufacturer, GI effects may be avoided by taking Pycnogenol 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.

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 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 international normalized ratio (INR, a measurement of bleeding tendency) in patients taking aspirin. No drug interaction studies have been performed with Pycnogenol.

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. This monograph, which was originally published in 2008, has been revised and updated to include published research up to December 2015. The relevant research/clinical trials have been included regardless of the study outcome (i.e., positive, negative, or neutral). 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 author or ABC of the specific ingredient, any product containing the ingredient, or 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 1 or several leading proprietary commercial nutritional or phytomedicinal preparations. As such, this publication reflects and acknowledges the existence of such literature as having been conducted on 1 or more leading products in a particular category.

ABC is an independent, tax-exempt [under section 501(c)(3) of the Internal Revenue Code], nonprofit research and education organization that is dedicated to the rational and responsible use of herbs, medicinal plants, phytomedicines, teas, essential oils, related plant-based ingredients, and medicinal fungi.

OVERVIEW

French maritime pine (*Pinus pinaster* subsp. *atlantica*, Pinaceae) bark extract is sold under the trade name Pycnogenol® (manufactured by Horphag Research; Geneva, Switzerland). According to data provided by ABC (T. Smith, email communication, August 30, 2017), 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 63d in the US natural retail channel (data provided by the American Botanical Council; T. Smith, email communication, January 8, 2019). Pycnogenol is one of the most extensively researched herbal supplement preparations in terms of both clinical studies and its underlying biological activity.

Pycnogenol is prepared from the bark of French maritime pine trees by a standardized process. The trees are cultivated as a monoculture exclusively in a narrow area in southwestern France (Landes de Gascogne). The multilayered thick outer bark is harvested from 30-year-old cultivated trees grown for timber. The timber production generates far more bark as a byproduct than what is 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.

Research suggests significant antioxidant activity for Pycnogenol, based primarily on its procyanidin content. The available evidence from published clinical trials suggests that Pycnogenol comes close to being a panacea; it is used and has been evaluated for nearly all body systems. Clinical trials have demonstrated efficacy for chronic venous insufficiency (CVI), thrombosis during air travel, deep vein thrombosis (DVT), diabetes, diabetic ulcers, leg edema associated with diabetes, diabetic retinopathy, hypertension, antihypertensive treatment-induced edema, hypertension-associated kidney disease, coronary artery disease, asthma, attention deficit hyperactivity disorder (ADHD), endometriosis, dysmenorrhea, pregnancy-associated pain, menopause transition, osteoarthritis (OA), acute and postpartum hemorrhoids, and cognition. Other potential uses that require better-designed studies to more fully substantiate the applications of Pycnogenol include erectile dysfunction and male reproduction, retinopathy, gingivitis, melasma (a discoloration 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. In addition to the aforementioned conditions evaluated in humans, preclinical research has been conducted on gouty arthritis, sepsis, atherosclerosis, diabetic cardiomyopathy, diabetic neuropathy, diabetes-induced liver damage, Parkinson's disease, traumatic brain injury, osteoporosis, sunburn, inflammatory skin disorders (psoriasis, atopic dermatitis, and lupus erythematosus), hexavalent chromium-induced dermatotoxicity, allergy, allergic asthma, nephrotoxicity, and nonalcoholic steatohepatitis.

DESCRIPTION

French maritime pine bark extract is made by extraction of the outer bark of *P. pinaster* Aiton subsp. *atlantica*. The French subspecies *atlantica* of *P. pinaster* differs from the Iberian (Spanish) and Moroccan subspecies by its resistance against salt[1] and its profile of phytochemical constituents.[2]

Table 1. Abbreviations & Symbols Used in this Monograph

Abbreviation/ Symbol	Full Name
5-LOX	5-lipoxygenase
8-oxoG	8-oxo-7,8-dihydroguanine
ACE	angiotensin converting enzyme
ADHD	attention deficit hyperactivity disorder
ADRP	adipose differentiation-related protein
AEs	adverse effects
ALP	alkaline phosphatase
AMPK	AMP-activated protein kinase
AST	aspartate aminotransferase
ALT	alanine aminotransferase
BMI	body mass index
BP	blood pressure
CaMKII	calcium/calmodulin-dependent protein kinase II
CARR U	Carratelli unit
CAT	catalase
C_{max}	maximal observed plasma concentration
COX-1	cyclooxygenase-1
COX-2	cyclooxygenase-2
CRP	C-reactive protein
Cu/Zn-SOD	copper-zinc superoxide dismutase
CVI	chronic venous insufficiency
DHEA	dehydroepiandrosterone
DNP	dinitrophenyl
E2	estradiol
FEV_1	forced expiratory volume
FSH	follicle-stimulating hormone
GGT	gamma-glutamyl transpeptidase
γ-IFN	gamma-interferon
GI	gastrointestinal
GLUT4	glucose transporter 4
GnRH-a	gonadotropin releasing hormone antagonist
GPx	glutathione peroxidase
GR	glutathione reductase
GRAS	generally recognized as safe
GSH	glutathione
GST	glutathione-S-transferase
H_2O_2	hydrogen peroxide
HbA1c	glycosylated hemoglobin
HDL	high-density lipoprotein
ICAM-1	intercellular adhesion molecule-1
IGF-1	insulin-like growth factor 1
IGFBP-3	IGF binding protein 3
INR	international normalized ratio
iNOS	inducible nitric oxide synthase

Abbreviation/ Symbol	Full Name
IP	intraperitoneally
IQ	intelligence quotient
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
IV	intravenous
LDL	low-density lipoprotein
L-NMMA	NG-monomethyl-L-arginine
LPS	lipopolysaccharide
M1	δ-(3,4-dihydroxy-phenyl)-γ-valerolactone
M2	δ-(3-methoxy-4-hydroxy-phenyl)-γ-valerolactone
MDA	malondialdehyde
MMPs	matrix metalloproteinases
MMP-1	collagenase 1
MMP-2	gelatinase A
MMP-9	gelatinase B
Mn-SOD	manganese superoxide dismutase
NK-κB	nuclear-factor-kappaB
NHP	Natural Health Product
NO	nitric oxide
NSAID	non-steroidal anti-inflammatory drug
OA	osteoarthritis
ORAC	oxygen radical absorption capacity
OTC	over-the-counter
pCO_2	partial pressure of carbon dioxide
PK	pharmacokinetics
PLA2	phospholipase A2
PMNL	polymorphonuclear leukocytes
pO_2	partial pressure of oxygen
ROS	reactive oxygen species
SOD	superoxide dismutase
TBARS	thiobarbituric reactive substances
TLR4	Toll-like receptor 4
t_{max}	time to maximum plasma concentration
USP	*United States Pharmacopoeia*
UV	ultraviolet
VCAM-1	vascular cell adhesion molecule-1
WHQ	women's health questionnaire
WOMAC	Western Ontario and McMaster Universities

The fresh bark is powdered and extracted with 70% ethanol and 30% water in patented equipment allowing an automated continuous process.[3] After purification of the raw extract, the aqueous solution of the extracted constituents is spray-dried. The resulting fine, brownish powder is stable for 3 years if stored in a dry, dark environment. The extract is standardized to contain 70 ± 5% procyanidins, which consist of condensed catechin and epicatechin.[4]

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 venous insufficiency, 7 controlled clinical trials have been published that demonstrate symptomatic improvement of blood circulation, blood pressure (BP) normalization, platelet function normalization, and venous insufficiency.[5-11] In addition, there have been 5 clinical trials demonstrating the efficacy of Pycnogenol for hypertension and its complications.[6,9,12-14] One study looked at the benefits of Pycnogenol on coronary artery disease and showed that the preparation improved endothelial function.[15] All of these studies have shown a benefit; however, the studies had unique patient populations, so each study should be repeated to confirm the findings. In addition, 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, ADHD, gynecology (endometriosis, dysmenorrhea, pregnancy-associated pain, and menopause transition), 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 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.

DOSAGE AND DURATION OF ADMINISTRATION

The following doses were used in the clinical trials reported in Table 2. [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 warranted. 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 by millions of people that might warrant a limitation. 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, intake should be at least 20 mg/day.

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 or asthma, 100 mg/day is recommended.

CHEMISTRY

Pycnogenol extract is made from fresh bark, which is powdered and extracted with 30% water and 70% ethanol in a patented process.[5] The result is a very fine, brown-colored, water-soluble powder. Pycnogenol contains mainly procyanidins and phenolic acids. The total amount of procyanidins is standardized to 70 ± 5%.[4] Pycnogenol meets the specifications for Maritime Pine Extract detailed in the *United States Pharmacopeia* (USP).[16]

The procyanidins are biopolymers consisting of units of catechin

and epicatechin, with chain lengths of 2-12 monomeric units. The more common dimers, B1 and B3, have been identified as consisting of epicatechin-catechin and catechin-catechin units, respectively, linked with a C4-C8 bond. Less common are dimers B6 and B7, which are catechin-catechin and epicatechin-catechin units, respectively, linked with a C4-C6 bond. A trimer, C2, consisting of catechin-epicatechin-catechin, also has been identified. Catechin, epicatechin, and taxifolin represent the "monomeric procyanidins," of which catechin is the most common.[3]

The phenolic acids in Pycnogenol are derivatives of benzoic acid (*p*-hydroxybenzoic acid, protocatechuic acid, gallic acid, and vanillic acid) or cinnamic acid (caffeic acid, ferulic acid, and *p*-coumaric acid). The phenolic acids are found in free form and as glucosides or glucose esters.[4]

Free glucose is present in small amounts, and other sugars including arabinose, rhamnose, and xylose are detected following glycolysis.[17]

Inorganic substances include calcium, potassium, and iron, with traces of manganese, zinc, and copper.[3]

PHARMACOKINETICS

Bioavailability and Excretion

Pycnogenol is orally bioavailable. The pharmacokinetics (PK) of a single and multiple dose of Pycnogenol were evaluated in healthy men and women (aged 18-30 years).[18] In the single-dose study, participants (5 women and 6 men) abstained from consuming dietary flavonoids for 24 hours prior to consuming a single 300-mg dose of Pycnogenol. Blood was drawn at regular intervals over 14 hours. After the single dose, 15 compounds were detected in the plasma, of which 10 were unknown. The known compounds were catechin, caffeic acid, ferulic acid, taxifolin, and metabolite M1 [δ-(3,4-dihydroxy-phenyl)-γ-valerolactone]. After a single dose, Pycnogenol was rapidly absorbed (within 30 minutes) into the blood. The constituents/metabolites were detectable up to 14 hours post dosing, with each constituent having a different t_{max} (time to maximum plasma concentration). Four compounds (catechin, caffeic acid, ferulic acid, and 1 unknown compound) had a t_{max} of up to 5 hours; 3 compounds (taxifolin and 2 unknown compounds) had a t_{max} between 5 and 10 hours; and 3 compounds (M1 and 2 unknown compounds) had a t_{max} of approximately 10 hours. 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 the multiple-dose study, participants (4 women and 1 man) consumed 200 mg Pycnogenol every morning for 5 days. Participants abstained from consuming dietary flavonoids for 24 hours prior to consuming the fifth dose. Blood was drawn 4 hours after dosing on day 5. It was assumed that steady-state plasma concentration of Pycnogenol was reached after 5 days. Steady states appeared to have been reached for catechin, ferulic acid, caffeic acid, M1, and 4 of the unknown compounds. Plasma levels of taxifolin were below the limit of detection. The authors point out that it is possible that the newly uncovered constituents may be responsible for Pycnogenol's various mechanisms of action. [18]

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 participant and the individual compound. The mean degree of conjugation was 56.5% for catechin and 69.4% for caffeic acid.[18] The authors conclude that many of the Pycnogenol constituents are bioavailable in humans following oral ingestion and that these compounds can be metabolized. The plasma concentrations of known compounds were within the nanomolar range, after both single and multiple dosing.[18]

In another study, 11 healthy adults (4 women and 7 men) consuming a diet low in polyphenols for 2 days were treated with 2 doses of 100 mg or a single dose of 200 mg oral Pycnogenol.[19] There was a close association between the dietary intake of Pycnogenol and the urinary excretion of ferulic acid. Ferulic acid was excreted as glucuronide or sulfate derivatives in the urine. The authors conclude that the phenolic components of 100 and 200 mg oral Pycnogenol are absorbed, metabolized, and excreted.[19]

Urinary metabolites following doses of 5.28 g and 1.06 g Pycnogenol were evaluated in 1 participant.[20] Ferulic acid, taxifolin, M1, and δ-(3-methoxy-4-hydroxy-phenyl)-γ-valerolactone (M2) were conjugated as sulfates or glucuronate derivatives and excreted in the urine. Peak ferulic acid and taxifolin urinary excretion occurred 2 to 3 hours after intake, while peak M1 and M2 excretion occurred 8 to 12 hours after intake. The study demonstrates that polymeric procyanidins from Pycnogenol are metabolized in human gastrointestinal (GI) tracts by gut microbiota.[20]

Transdermal Bioavailability

Transdermal bioavailability was evaluated by applying 5% weight/volume Pycnogenol in polyethylene glycol topically to human cadaver skin (n = 10). Six substances (gallic acid, protocatechuic acid, *p*-hydroxybenzoic acid, vanillin, catechin, and an unidentified substance) were absorbed through the skin. The absorption was rapid (30 minutes). Taxifolin also was absorbed, but only in perfusates from 3 of the 10 skin samples. The authors conclude that Pycnogenol can be used for topical application.[21]

Biodistribution

Plasma protein binding can alter PK and pharmacodynamic properties. Hence, the plasma protein binding of Pycnogenol's constituents/metabolites were assessed in vitro. The greatest protein binding was for catechin = taxifolin > procyanidin B1 > ferulic acid > caffeic acid > *p*-coumaric acid > vanillic acid > *p*-hydroxybenzoic acid > gallic acid > protocatechuic acid > M1 > M2.[22] The clinical significance needs to be elucidated. Others have shown that the protein-bound fraction of polyphenols is protected from degradation; in turn, the protein is protected against peroxidation.[23]

M1 is not a constituent of Pycnogenol but rather is generated from catechin units by gut microflora after ingestion. An in vitro human cell culture study revealed that M1 is transported into cells (macrophages, monocytes, and endothelial cells) where it accumulates to levels that could be bioactive.[24] This explains why M1, which is present only in low concentrations in the plasma after Pycnogenol ingestion, could produce a biological effect. In addition, it accumulates in erythrocytes and forms an M1-glutathione adduct.[25]

PHARMACOLOGICAL ACTIONS / MECHANISMS OF ACTION

Antioxidant and Anti-inflammatory Activity

In vitro

Pycnogenol has potent antioxidant activity, which has been reported in several in vitro studies. Studies have shown that Pycnogenol can scavenge both hydroxyl radicals and superoxide anions,[26] extend the lifetime and increase the antioxidant function of the ascorbate radical (vitamin C),[27] and increase the activity of endogenous antioxidant enzymes, namely superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT).[28] Lipids, proteins, and DNA are targets for oxidative damage. Studies have shown that Pycnogenol can prevent oxidative damage to lipids,[29-31]

proteins, [32,33] and breakage of plasmid DNA.[30]

Single Pycnogenol components and their metabolites also have antioxidant activity. Catechin inhibits superoxide activity in vitro with effectiveness similar to ascorbic acid.[34] Interestingly, a metabolite of catechin that is generated in humans after oral consumption, M1, was found to be significantly more active than catechin or ascorbic acid in superoxide scavenging.[34]

M1 concentration-dependently inhibits nitrite production and inducible nitric oxide synthase (iNOS) expression in cell culture with a mouse cell line and human monocytes.[24]

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 proinflammatory pathways involving nuclear factor-kappa B (NF-κB) activation. In vitro, Pycnogenol blocked NF-κB activation in macrophages, which in consequence inhibited expression of the proinflammatory cytokine interleukin (IL)-1.[35] Expression of adhesion molecules by endothelial cells is likewise under the control of NF-κB. 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 tumor necrosis factor-α (TNF-α) inhibited activation of NF-κB and limited induction of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1).[36]

ROS are associated with proinflammatory conditions through the stimulation of matrix metalloproteinases (MMPs). MMPs 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 UV light on the skin, and MMP-9 also plays a role in asthma. In pulmonary fibrosis, MMP-2 (gelatinase A) also is 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.[37] In addition, the metabolites of catechin, M1 and M2, were significantly more potent for inhibition of MMP-1, MMP-2, and MMP-9 in vitro than the parent molecules in Pycnogenol extract [37]

In cell culture of mouse macrophage cell lines, Pycnogenol inhibited expression of the proinflammatory cytokine IL-1. [35]

During inflammation, the expression of iNOS leads to excess nitric oxide (NO) production, and Pycnogenol was shown to inhibit this process.[38] In vitro experiments showed that Pycnogenol decreased cellular generation of NO via scavenging ROS and NO, inhibition of iNOS activity, and inhibition of iNOS-messenger RNA (mRNA) expression by blocking NF-κB activation in stimulated macrophages. The authors conclude that, based on this experiment, Pycnogenol may be useful during inflammation.[38]

In adipocyte cell culture, Pycnogenol inhibited lipid accumulation and ROS production via downregulation of adipogenic gene expression and mRNA expression of pro-oxidant enzymes, respectively.[39]

In a simulation of gouty arthritis in human articular chondrocytes and synovial fibroblasts, Pycnogenol inhibited upregulation of cyclooxygenase-2 (COX-2) and IL-8 and attenuated iNOS gene expression and NO production.[40]

In human lymphocytes, Pycnogenol reduced chromosome breakage and DNA damage induced by hydrogen peroxide (H_2O_2).[41]

Fruit juices enriched with 0.5 g/L Pycnogenol reinforced the antioxidative capacity of the juices, leading to an antiproliferative effect of a colon carcinoma cell line.[42]

Pycnogenol attenuates the release of proinflammatory cytokines and expression of perilipin-2 (adipose differentiation-related protein [ADRP]) in lipopolysaccharide (LPS)-stimulated mice microglia by inhibition of the NF-κB and activator protein-1 (AP-1) pathway.[43]

Animal

Pycnogenol has anti-inflammatory effects on the skin in vivo. Pycnogenol dose-dependently decreased carrageenan-induced paw edema, a model of inflammation ($P < 0.05$).[44]

In a rat model of gouty arthritis, Pycnogenol inhibited acute inflammatory cell infiltration and expression of COX-2 and iNOS in synovial tissue and articular cartilage.[40]

In mice exposed to ozone, oral Pycnogenol reduced the levels of nitrite and reactive nitrogen species, and the levels of the antioxidants Cu/Zn-SOD (copper-zinc superoxide dismutase), Mn-SOD (manganese superoxide dismutase), GPx, and glutathione reductase (GR) were enhanced.[45]

In rats with sepsis, intraperitoneal (IP) injection of Pycnogenol significantly decreased DNA damage and increased capacity of DNA repair in lymphocytes, liver, and kidney cells compared with untreated rats. Also in the rats with sepsis, Pycnogenol treatment inhibited TNF-α secretion, and increased total glutathione (GSH) levels ($P < 0.05$), SOD activity ($P < 0.05$), and GPx activity ($P < 0.05$).[46]

Human (ex vivo)

Cyclooxygenase-1 (COX-1) and COX-2 are enzymes that produce a cascade of chemical mediators, including prostaglandins, which mediate the inflammatory response. Plasma of 5 healthy participants who had taken 200 mg Pycnogenol for 5 days tended to inhibit COX-1 and COX-2 ex vivo, but not significantly.[47] However, a single dose of 300 mg Pycnogenol given to 10 healthy participants produced serum samples showing significant inhibition of COX-1 ($P < 0.02$) and COX-2 ex-vivo ($P < 0.002$). According to the authors, this inhibition is consistent with the inhibition of platelet aggregation and the anti-inflammatory effects observed clinically.[47]

In another ex vivo experiment, plasma samples from 7 healthy participants given 200 mg/day Pycnogenol for 5 days reduced LPS-induced release of MMP-9 from human monocytes by 25% ($P < 0.01$).[37] MMP-9 induction and release are initiated by NF-κB activation. Plasma samples also inhibited NF-κB nuclear translocation by 15.5% ($P < 0.05$). The correlation between the two was positive (Spearman's rank correlation coefficient, $r = 0.6$). These results are consistent with anti-inflammatory effects observed clinically.[37]

A third ex vivo study evaluated the molecular basis of the anti-inflammatory effect of Pycnogenol supplementation by isolating and activating polymorphonuclear leukocytes (PMNL) from the blood of 6 healthy participants given 150 mg/day Pycnogenol for 5 days. Pycnogenol supplementation inhibited 5-lipoxygenase (5-LOX) gene expression, COX-2 gene expression, and phospholipase A2 (PLA2) activity, and reduced leukotriene production.[48] These results further demonstrate the anti-inflammatory properties of Pycnogenol.

Human

The effect of Pycnogenol on plasma antioxidant capacity was tested in 25 healthy participants (10 men and 15 women; mean age, 30 ± 8 years) given 150 mg/day Pycnogenol for 6 weeks, followed by a 4-week washout period.[49] Plasma polyphenol levels increased significantly after 3 weeks of supplementation, indicating that Pycnogenol was absorbed ($P < 0.05$). The antioxidant potential of the plasma, as measured using the oxygen radical absorbance capacity (ORAC) assay, increased by 40% over baseline ($P < 0.05$), returning to baseline at the end of the washout period. There was

no significant change in plasma lipid peroxidation products, as measured using the ferrous oxidation-xylenol orange (FOX) assay, or in ex vivo low-density lipoprotein (LDL) cholesterol oxidation, as measured by an increase in lag phase. The authors conclude that Pycnogenol significantly increased the antioxidant capacity of plasma.[49]

In a randomized, double-blind, placebo-controlled study, the effect of Pycnogenol on DNA repair associated with oxidative damage was evaluated in 54 elderly people (41 women and 13 men; mean age, 54 years) with knee OA.[50] Patients were treated with placebo or 150 mg/day Pycnogenol for 3 months. There was no significant difference between placebo and Pycnogenol treatment on the level of oxidative damage to DNA or DNA repair in the patients' lymphocytes, as measured by levels of 8-oxo-7,8-dihydroguanine (8-oxoG), a marker of oxidative damage to DNA. This finding is particularly interesting because it demonstrates that Pycnogenol had no effect on oxidative damage to DNA in elderly people, whereas another report found that Pycnogenol was effective in children with ADHD.[51] Additional age-related studies are needed to further elucidate this discrepancy.

The anti-inflammatory and antioxidant activities of Pycnogenol were evaluated in patients with elevated C-reactive protein (CRP) and plasma free radicals in a randomized, double-blind, placebo-controlled trial.[52] CRP levels are associated with disease progression in OA. Patients (n = 55; mean age, 52 years) with primary OA grade 1 or 2 in 1 or both knees and mild-to-moderate pain not adequately controlled by anti-inflammatory drugs were treated with 100 mg/day oral Pycnogenol or placebo for 3 months. Pycnogenol reduced CRP levels by 71.3%, plasma free radicals by 29.9%, and fibrinogen by 37.1%; the placebo group had minimal changes. There were significant differences in these 3 biomarkers between groups ($P < 0.05$ for all). The authors conclude that Pycnogenol decreases inflammatory processes in OA.[52]

Oxidative stress and plasma free radicals are increased during and after exercise. Male triathletes (n = 54) were treated with 150 mg/day Pycnogenol during training for 30 days or served as controls. The Pycnogenol group had a significantly smaller increase of oxidative stress ($P < 0.05$) and a faster return to normal values compared with the control group. Post triathlon (1 hour after exercise), plasma free radicals were on average 26.7% lower in the Pycnogenol group compared with the control group ($P < 0.05$). In addition, in normal men and women (n = 147) treated with 100 mg/day Pycnogenol for 8 weeks, the concentration of plasma free radicals significantly decreased compared with the control group following the US Army Physical Fitness Test ($P < 0.05$).[53]

Cigarette smoking is associated with elevated free radicals, increased lipid peroxidation, and depleted levels of plasma antioxidants. The antioxidant potential of Pycnogenol was evaluated in otherwise healthy smokers (n = 155) in an open-label, placebo-controlled study. Participants received either placebo or 50 mg/day Pycnogenol for 8 weeks. The Pycnogenol group had a 38% increase from baseline in the biological antioxidant potential, which was significantly higher than the placebo group ($P < 0.05$). Further, Pycnogenol significantly lowered plasma levels of derivatives of reactive oxygen metabolites (d-ROMs) by 25% compared with baseline, which was significantly lower than the placebo group ($P < 0.05$).[54]

The oxidative stress status of patients with asymptomatic metabolic syndrome (n = 130; 45-55 years of age) was assessed in an open-label, controlled study by quantifying d-ROMs. Patients received diet and weight management programs along with 150 mg/day Pycnogenol for 6 months or without Pycnogenol treatment. Plasma free radicals decreased 34.6% in the Pycnogenol group ($P < 0.05$ vs. baseline) compared with a 13.0% decrease in the control group ($P < 0.022$ vs. Pycnogenol).[55] Reducing the production of ROS is hypothesized to aid in normalization of the metabolic pathways.

Cardiovascular

In vitro

Endothelial cells line the inner walls 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.[56] Pycnogenol enhanced clearance of H_2O_2 and oxygen radicals in endothelial cells treated with hypoxanthine and xanthine oxidase or H_2O_2. Pycnogenol also increased the activities of the following intracellular antioxidant enzyme systems in endothelial cells: GSH, GPx, GR, SOD, and CAT.[57]

Pycnogenol protected endothelial cells from GSH depletion caused by co-culture with activated macrophages.[58] It also protected endothelial cells from reduction of α-tocopherol levels caused by reactive nitrogen species (e.g., NO or peroxynitrite) generated by activated macrophages or direct administration of peroxynitrite.[38]

Toll-like receptor 4 (TLR4)-mediated signals stimulate the expression of ADRP, which is involved in atherosclerosis formation. Pycnogenol inhibited TLR4 stimulation of ADRP.[59] Also, Pycnogenol suppressed ADRP expression by facilitating mRNA degradation.[60]

The endothelium-dependent relaxation facilitated by NO is an important component of vascular function. Pycnogenol dose-dependently relaxed constricted rat aorta smooth muscle via stimulation of endothelial NO synthase.[61]

Animal

Intravenous (IV) Pycnogenol administration significantly decreased BP in rats, which was mediated by inhibition of angiotensin-converting enzyme (ACE).[62]

In a mouse model of heart failure, orally administered Pycnogenol significantly reduced hypertension and cardiac hypertrophy compared with control ($P < 0.05$ for both). The gene expression pattern and activity of MMP-9 (which is involved in cardiac hypertrophy) were significantly decreased by Pycnogenol ($P < 0.001$ for both). The authors propose that Pycnogenol may help limit cardiac remodeling (hypertrophy) in patients with heart failure.[63]

Spontaneously hypertensive rats treated with Pycnogenol had a significant improvement in mesenteric small resistance artery structure and endothelial function, in part due to a normalization of COX-2 and iNOS and reduction of myeloperoxidase activity.[64,65]

In a mouse model of atherosclerosis, mice were fed a high-cholesterol and high-fat diet. Those treated with oral Pycnogenol had a decreased oxidized LDL-induced lipid accumulation in peritoneal macrophages and decreased size of atherosclerotic lesions compared with untreated controls.[66] In addition, Pycnogenol inhibited the LPS-induced upregulation of fatty-acid-binding protein and macrophage scavenger receptor class A through the TLR4 pathway, which supports in vitro reports.[66]

Human

Pycnogenol-enhanced endothelium-dependent vasodilation was evaluated in a randomized, double-blind, placebo-controlled study with healthy participants.[67] Forearm blood flow responses to acetylcholine—an endothelium-dependent vasodilator—and sodium nitroprusside—an endothelium-independent vasodilator—were measured in 16 healthy young men before and after 2 weeks of 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*G-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. [67]

Another randomized, double-blind, placebo-controlled, crossover study was conducted to assess the effect of Pycnogenol on endothelial function.[15] Patients (n = 23; aged 49-73 years; mean age, 63 years) with stable coronary artery disease and receiving optimal standard therapy were treated with 200 mg/day Pycnogenol or placebo for 8 weeks. Flow-mediated dilatation (FMD, a test assessing endothelial function) significantly increased with Pycnogenol treatment compared with placebo treatment ($P < 0.0001$). Concentrations of 15-F_{2t}-isoprostane, an index of lipid peroxidation, significantly decreased after Pycnogenol treatment but not after placebo treatment ($P = 0.012$). The authors conclude that the improvement in endothelial function was related to the ability of the antioxidant properties of Pycnogenol to increase NO availability.[15]

The effect of Pycnogenol on endothelial function was further evaluated in participants with borderline hypertension, hyperglycemia, or hyperlipidemia.[71] In this open-label, pilot study, asymptomatic participants with borderline hypertension (n = 32), borderline hyperglycemia (n = 30), or borderline hyperlipidemia (n = 31) received diet and exercise modification plus 150 mg/day Pycnogenol or diet and exercise modification only (control) for 12 weeks. Untreated normal participants (n = 31) served as a second control group. FMD was measured at the level of the brachial artery. In the Pycnogenol-treated participants, FMD increased from a mean 5.3% to 8.2% at 8 weeks and 8.8% at 12 weeks ($P < 0.05$ vs. baseline for both). No changes in FMD were found in control or normal participants. Skin flux after occlusion was measured at the level of the finger. An increase in flux after occlusion is considered a microcirculatory measure of reactive hyperemia, which is generally decreased in people with endothelial dysfunction. Pycnogenol-treated participants had an increase in flux from a mean 12.4% to 23.3% at 8 weeks ($P < 0.05$ vs. baseline) and 24.7% at 12 weeks ($P < 0.05$ vs. baseline). No effects were observed in control or normal participants. No adverse effects (AEs) were observed during the study period. The Pycnogenol-treated group had significantly normalized BP in participants with borderline hypertension ($P < 0.05$), reduced cholesterol levels in participants with borderline hyperlipidemia ($P < 0.05$), and improved fasting glucose in participants with borderline hyperglycemia ($P < 0.05$). The participants treated with both Pycnogenol and diet/exercise modifications had better improvements than those in the control group. A limitation of this study is that statistical analyses were not conducted comparing Pycnogenol with control.[68]

Cigarette smoking increases the risk for coronary heart disease by increasing BP and increasing the tendency for blood to clot. Pycnogenol reduced the effects of smoking on platelet reactivity in 3 studies.[69] In a study of German heavy smokers (smoking ≥ 15 cigarettes per day) (n = 22), 100 mg Pycnogenol was found to be as effective as 500 mg aspirin in completely inhibiting smoking-induced platelet aggregation 2 hours after smoking.[69] However, in American heavy smokers (n = 16) treated with 125 mg Pycnogenol or 500 mg aspirin, the smoking-induced platelet aggregation was only partially reduced.[69] Pycnogenol had no effect on BP or heart rate. In another group of American heavy smokers (n = 19), Pycnogenol was shown to dose-dependently lower platelet reactivity 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.[69]

The chronic effects of Pycnogenol on platelet aggregation were evaluated in an open-label study with 4 heavy smokers (15 cigarettes per day for ≥ 5 years) and 16 nonsmokers.[70] Both groups received 200 mg/day Pycnogenol for 8 weeks. At study end, Pycnogenol taken 3 hours prior to the first cigarette significantly reduced the platelet reactivity index ($P < 0.002$) to the level of nonsmokers. At baseline, smokers also presented with elevated serum thromboxane levels which, after treatment, were reduced to the levels of nonsmokers.[70]

The effects of Pycnogenol on microcirculation and platelet function were investigated in patients with coronary artery disease in a double-blind, placebo-controlled study (27 men and 24 women; 45-75 years of age).[71] Patients were given 150 mg/day Pycnogenol 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 electrocardiogram (ECG) (P values not reported). A marker for platelet activation, platelet granulometric 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 adenosine diphosphate (ADP) was significantly reduced in the treatment group compared with the placebo group ($P < 0.05$).[71]

Plasma lipid levels were measured in an open-label study with 25 healthy participants given 150 mg/day Pycnogenol for 6 weeks, followed by a 4-week washout period.[49] Compared with baseline measurements, LDL cholesterol decreased significantly by 7% ($P < 0.05$), an effect that was reversed after the 4-week washout period. High-density lipoprotein (HDL) cholesterol levels increased significantly by 10.4% ($P < 0.05$); this effect was not reversed after the washout period. There was no significant change in total cholesterol or triglycerides.[49]

Diabetes and Complications

In vitro

In vitro experiments with α-glucosidase were conducted to determine how Pycnogenol reduces blood sugar in type 2 diabetics.[72] α-Glucosidase is an enzyme secreted in the duodenum that mediates hydrolysis of starches to glucose. Inhibition of the enzyme diminishes absorption of glucose and reduces the postprandial blood glucose peaks. The activity of Pycnogenol was compared to acarbose, a prescription α-glucosidase inhibitor. Pycnogenol was found to be a potent inhibitor of α-glucosidase and more potent than acarbose (half maximal inhibitory concentration [IC_{50}]: 5.3 µg/mL and 1 mg/mL, respectively).[72]

In an in vitro model of diabetic nephropathy, renal tubular cells exposed to high glucose concentrations were protected against apoptosis and morphological changes by Pycnogenol via upregulation of antiapoptotic Bcl-2 protein levels and reduction of proapoptotic Bax protein levels. In addition, Pycnogenol prevented induction of the proinflammatory genes COX-2, iNOS, and NF-κB in the renal tubular cells, and downregulated lipid peroxidation, total reactive species, superoxide, NO, and peroxynitrite.[73]

Animal

Pycnogenol's effect on diabetes was evaluated in a series of in vivo studies that experimentally induced diabetes via streptozotocin.

In the first study, rats were treated with 10 mg/kg IP Pycnogenol for 14 days. Pycnogenol significantly reduced blood glucose levels in diabetic rats by 28% ($P < 0.05$), but not to normal levels.[74] In another study, rats received 10, 20, and 50 mg/kg oral Pycnogenol for 6 weeks, and plasma glucose significantly and dose-dependently decreased 4- to 6-fold ($P < 0.05$).[75] Another study used 5 mg/kg oral Pycnogenol for 8 weeks and found no significant reduction in blood sugar.[76] Preprandial glycemia was significantly decreased by 10, 20, and 50 mg/kg oral Pycnogenol, and postprandial glycemia was significantly decreased by 10 and 20 mg/kg oral Pycnogenol, compared with nontreated diabetic rats.[77]

Diabetes can cause liver damage. In a rat model of type 2 diabetes, streptozotocin-induced diabetic rats received IP injection of Pycnogenol (10 mg/kg/day) or no treatment (control) for 4 weeks, and their livers were evaluated at study end. The control group had a significant increase in glycosylated hemoglobin (HbA1c) ($P < 0.05$) and a significant decrease in hepatic glycogen levels ($P < 0.05$). Pycnogenol treatment reversed these effects. In addition, Pycnogenol treatment significantly decreased the elevated levels of thiobarbituric acid reactive substances (TBARS), malondialdehyde (MDA), and protein carbonyl formation, and restored depleted GSH, glutathione *S*-transferase (GST), CAT, SOD, GPx, and GR activity ($P < 0.05$ for all).[78] Similar results were found in a study using a type 1 diabetes rat model.[79]

A study evaluating diabetes-related eye disorders treated normal and streptozotocin-induced diabetic rats with a low-carbohydrate diet plus Pycnogenol (10 mg/kg body weight, IP) for 14 days. The combination treatment reduced the risk of diabetic retinopathy and cataract formation.[79]

Diabetes can cause high BP. Streptozotocin-induced diabetic rats had an increase in BP, which was dose-dependently reduced by 10, 20, and 50 mg/kg oral Pycnogenol for 6 weeks.[75] In the same rat model, diabetes produced thicker left ventriculi wall, weaker myocardial contraction, decreased coronary flow, and prolonged the heart QT interval. Oral Pycnogenol at a dose of 20 mg/kg/day improved the cardiac effects.[80]

Oral administration of 30 mg/kg/day Pycnogenol for 6 weeks in healthy rats resulted in a significant decrease in blood glucose levels ($P < 0.001$), BP ($P < 0.001$), heart rate ($P < 0.043$), and weight gain ($P < 0.002$), and a significant increase in antioxidant enzymes ($P < 0.001$).[81]

Diabetes can cause diabetic neuropathy, where nerve conduction decreases. In streptozotocin-induced diabetic rats, motor nerve conduction velocity was improved by 10 and 20 mg/kg oral Pycnogenol compared with nontreated diabetic rats.[77]

Diabetes can also cause diabetic cardiomyopathy and endothelial dysfunction. Pycnogenol corrected diabetic cardiac dysfunction in streptozotocin-induced diabetic rats via direct radical scavenging activity as measured via protein expression of ROS.[82] Also, in streptozotocin-induced diabetic rats with cardiac dysfunction, Pycnogenol and metformin (a standard pharmaceutical treatment for diabetes) similarly improved blood glucose levels, vascular reactivity, left ventricular hypertrophy, adenosine monophosphate (AMP)-activated protein kinase (AMPK) expression, glucose transporter type 4 (GLUT4) expression, and calcium/calmodulin-dependent protein kinase II (CaMKII) in the left ventricle of the heart. However, metformin combined with Pycnogenol did not potentiate any of the improvements.[83]

Diabetes can alter Cu/Zn-SOD (SOD-1) and NO synthase in the brain. Pycnogenol significantly increased the synthesis of SOD-1 and restored neuronal NO synthase levels in the cerebral cortex of streptozotocin-induced diabetic rats.[84]

Human

The glucose-lowering effect of Pycnogenol was evaluated in an open-label, dose-finding study of 30 patients with type 2 diabetes. Patients received 50, 100, 200, and 300 mg/day Pycnogenol, each for 3 weeks in succession. There were no washout periods between the changes in dose. Pycnogenol dose-dependently and significantly lowered fasting blood glucose ($P < 0.05$); however, 300 mg was not more effective than 200 mg. HbA1c was significantly decreased by doses of 200 and 300 mg/day ($P < 0.05$ for both), and endothelin-1 was significantly decreased by doses of 100, 200, and 300 mg/day ($P < 0.05$ for all). No change of insulin secretion was noted. The following AEs were reported (all were minor and transitory): dizziness (n = 4), headache (n = 2), gastric discomfort (n = 2), and mouth ulcer (n = 1).[85]

Neurology

Attention Deficit Hyperactivity Disorder (ADHD)

Human

ADHD may involve a dysregulation of catecholamine (e.g., dopamine, epinephrine, and norepinephrine).[86] Urinary catecholamine concentrations were measured in 57 children (47 boys and 10 girls; 6-14 years of age) with ADHD and in 17 healthy children (8 boys and 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.[86] The children with ADHD were then entered into a randomized, double-blind, placebo-controlled study.[86] The children were treated with 1 mg/kg body weight Pycnogenol or placebo for 1 month. There was a significant decrease in dopamine levels in the Pycnogenol group compared with baseline ($P < 0.05$). There were nonsignificant 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.[86]

Catecholamine metabolism may be a source of free radical formation (superoxide radicals and H_2O_2).[51] These free radicals could cause oxidative damage to DNA, lipids, and proteins. Total damage to DNA was measured in 58 children (47 boys and 11 girls; 6-14 years of age) with ADHD and in 56 healthy children (mean age, 11.5 years). Children with ADHD had significantly higher levels of total damage when compared with healthy children ($P < 0.001$).[51] Children with ADHD (50 boys and 11 girls; 6-14 years of age) were then entered into a randomized, double-blind, placebo-controlled study.[51] The children were treated with 1 mg/kg Pycnogenol or placebo for 1 month. Levels of 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 1-month washout period, levels of 8-oxoG returned to baseline.[51] The total antioxidant status (TAS) nonsignificantly 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).[51]

Another study evaluated the effect of Pycnogenol on the levels of oxidative stress in children with ADHD.[87] A randomized, double-blind, placebo-controlled study measured the levels of reduced GSH and oxidized glutathione (GSSG) in 43 children (34 boys and 9 girls; 6-14 years of age) with ADHD. The children were treated with 1 mg/kg Pycnogenol or placebo for 1 month. In the Pycnogenol group, GSH increased ($P = 0.054$), as did the ratio of GSH to GSSG. There was no change in the placebo group.[87] 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.

Cognition

Animal

In rats, Pycnogenol increased nerve growth factor in the hippocampus and cortex, areas of the brain important for learning and memory.[88] Pycnogenol also improved spatial memory impairment.[88] In another study, Pycnogenol attenuated cognitive performance decline in a rat model of oxidative stress-related neurodegeneration (i.e., Alzheimer's disease).[89]

Human

There is a relationship between cognition, brain aging, and oxidative stress. A randomized, double-blind, placebo-controlled, matched-pair-design study was conducted to determine whether Pycnogenol could alter biochemical and cognitive measures.[90] Elderly participants (n = 101; 60-85 years of age; mean age, 67.8 years) without chronic disease received either 150 mg/day Pycnogenol or placebo for 3 months. Participants were matched between groups based on age, sex, body mass index (BMI), premorbid intelligence quotient (IQ), intake of antioxidants, and intake of micronutrients. At 3 months, the Pycnogenol-treated group compared to the placebo-treated matched group performed significantly better on spatial working memory and quality of working memory ($P < 0.05$ for both), and had a significant decrease in plasma F_2-isoprostane concentrations compared with placebo ($P < 0.01$), indicating an antioxidant effect.[90]

Two similarly designed, prospective, pilot, open-label, controlled studies were conducted to evaluate the effect of Pycnogenol on cognitive function, attention, and mental performance. The first study was conducted in healthy professionals with high oxidative stress (as measured by levels of plasma free radicals). Stress can cause mild cognitive impairment. Participants (n = 59; 34 men and 25 women; 35-55 years of age) were treated with 150 mg/day Pycnogenol for 12 weeks or were followed as untreated controls. All participants received a personal plan for sleep, diet, and exercise because improved lifestyle patterns are associated with better professional performance. They were told to avoid caffeine and alcohol before testing. At 12 weeks, the Pycnogenol group had a median 30% decrease in plasma free radicals, which was significantly better than control ($P < 0.05$). Increased oxidative stress can impair cognitive function. Accordingly, the Pycnogenol group performed significantly better than the control group on measures of attention, mental performance, sustained attention, memory, executive functions, mood, and cognitive function ($P < 0.05$ for all, except mood, $P < 0.01$).[91] The second such study was conducted in healthy participants with high oxidative stress (as measured by an epidemiological cardiovascular screening program). Participants (n = 77; 55-70 years of age) were treated with 100 mg/day Pycnogenol for 12 months or were followed as untreated controls. All participants received the same recommendations as in the previous study. Cognitive function was evaluated with the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), daily tasks, visual analog scales, and the Short Blessed Test. Pycnogenol reduced oxidative stress (plasma free radicals) by 28% at 12 months; in contrast, the control group had no decrease in oxidative stress. Accordingly, at 12 months, the Pycnogenol group had significantly improved cognitive function compared with the control group, with a significant increase in attention, mental performance, sustained attention, memory, executive functions, and mood ($P < 0.05$ for all). The IQCODE and daily tasks also improved significantly in the Pycnogenol group compared with control ($P < 0.05$ for both). No AEs were observed.[92]

Parkinson's Disease

Animal

The effect of Pycnogenol on Parkinson's disease was evaluated in 2 studies using a mouse model. One study showed that 20 mg/kg body weight IP Pycnogenol pretreatment before inducing the Parkinson's model significantly protected antioxidant enzyme activity and GSH content; significantly decreased elevated levels of TBARS; and significantly restored the number of dopaminergic D_2 receptors and the level of dopamine and its metabolite in the brain striatum.[93] The other study showed that mice with Parkinson's-like disease injected with Pycnogenol had reduced neuroinflammation, neurodegeneration, and behavioral impairments.[94]

Traumatic Brain Injury

Animal

In a rat model of traumatic brain injury, 100 mg/kg body weight IP Pycnogenol significantly improved levels of protein carbonyls, lipid peroxidation, and protein nitration; significantly reduced the loss of presynaptic and postsynaptic proteins; and significantly reduced the level of proinflammatory cytokines compared to vehicle-treated controls.[95] In another rat model of traumatic brain injury, IV injection of 10 mg/kg body weight Pycnogenol 15 minutes after brain injury preserved synaptic function in the hippocampus 7 and 14 days following injury; saline-treated rats did not have preservation of function.[96]

Reproduction

Human

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.[97] Subfertility was defined as precapacitation (early sperm structural changes), post capacitation, and/or reduced capacity of the sperm to bind to mannose receptors. Semen samples were analyzed before and after treatment. Compared with baseline, 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.[97]

Gynecology/Women's Health

Animal

Oral Pycnogenol for 3 months suppressed bone loss induced by ovariectomy in rats; bone strength and bone density increased. Pycnogenol restored serum osteocalcin and C-terminal telopeptide of type I collagen, thereby decreasing the rate of bone turnover.[98]

In ovariectomized mice, oral Pycnogenol for 3 months reduced the loss of bone density and prevented trabecular structure deterioration compared with untreated control ovariectomized mice.[99]

Human

A randomized, blinded, placebo-controlled trial was conducted in healthy perimenopausal women (n = 70; 41-49 years of age) with symptoms of menopause.[100] Women received either 100 mg/day Pycnogenol or placebo for 8 weeks. Studies show a correlation

between oxidative stress and menopause symptoms. The oxidative stress status of the women was evaluated. At baseline, both treatment groups had elevated oxidative stress, with plasma free radicals exceeding 300 Carratelli units (1 CARR U corresponds to 0.8 mg/L H_2O_2). After 4 and 8 weeks of treatment, the Pycnogenol group had a significant reduction in plasma free radicals as compared with baseline ($P < 0.05$ at 4 weeks; $P < 0.022$ at 8 weeks). This corresponds with Pycnogenol significantly improving the participants' symptoms of menopause. The authors believe that the improvement in symptoms was related in part to an antioxidant effect of Pycnogenol.[100]

Dermatology

In vitro

Activation of the proinflammatory and redox-regulated transcription factor NF-κB may play a role in UV-induced erythema. Pycnogenol added to keratinocyte cell culture inhibited UV-induced NF-κB-dependent gene expression in a concentration-dependent manner.[101] However, NF-κB DNA-binding activity was not prevented, suggesting that Pycnogenol affects the transactivation capacity of NF-κB. Inhibition of NF-κB-dependent gene expression by Pycnogenol may contribute to its mechanism of protecting human skin against solar UV-simulated light-induced erythema.[101]

Pycnogenol may be beneficial for patients with inflammatory skin disorders. Human keratinocytes were treated with Pycnogenol or control in cell culture. Pycnogenol downregulated calgranulin A and calgranulin B genes, which are upregulated in patients with psoriasis and other dermatological disorders.[102] Also, patients with psoriasis, atopic dermatitis, and lupus erythematosus have upregulation of ICAM-1 expression in keratinocytes. A cell culture experiment revealed that Pycnogenol inhibited interferon-γ (IFN-γ)-induced expression of ICAM-1 and adherence of T-cells to keratinocytes.[103]

Pycnogenol suppresses melanin biosynthesis via its antioxidative properties. It suppressed superoxide, NO, peroxynitrite, and hydroxyl radical in a melanoma cell culture.[104]

Animal

Pycnogenol dose-dependently and significantly reduced the incidence and severity of skin irritation and histopathological lesions in a rat model of hexavalent chromium-induced dermatotoxicity ($P < 0.05$ for all). Also, Pycnogenol reduced MDA concentration and increased GST and CAT activities.[105]

Wound healing was examined in 2 experiments in rats. Pycnogenol at concentrations of 1%, 2%, and 5% shortened the time of wound healing by 1.6 days, 2.8 days, and 3.3 days, respectively ($P < 0.05$, $P < 0.01$, and $P < 0.01$, respectively).[106] Pycnogenol gel also dose-dependently reduced scar diameter.[106] Pycnogenol at a concentration of 2% decreased MDA and increased SOD in the wound.[107]

Human

Healthy, nonsmoking postmenopausal women (n = 20; 55-68 years of age) with no history of skin disease were treated with 75 mg/day Pycnogenol for 12 weeks.[108] A 4-mm punch biopsy was obtained from the buttock skin for assessment of gene expression. There was a significant 44% increase in mRNA expression of hyaluronic acid synthase-1, the gene involved in hyaluronic acid (a component of cartilage and skin) synthesis, compared with baseline ($P < 0.001$). Regarding the genes involved in collagen synthesis, there was a nonsignificant 41% increase in COL1A1 gene expression and 29% increase in COL1A2 mRNA expression. The changes in mRNA expression were associated with significant skin biophysical improvements (hydration [$P < 0.05$], elasticity [$P < 0.05$], and fatigue [$P < 0.01$]).[108]

A prospective, open-label, pilot clinical study was conducted in patients (n = 73; 30-45 years of age) with moderate/severe plaque psoriasis. Patients were treated with 150 mg Pycnogenol daily for 12 weeks in addition to standard care or received standard care alone (control). After 12 weeks, both groups had an improvement in the affected body areas; however, the Pycnogenol group had a significantly reduced psoriasis-affected skin area size in all body regions compared with control ($P < 0.05$). Pycnogenol significantly improved erythema compared with baseline, induration compared with baseline and control, and desquamation compared with baseline and control ($P < 0.05$ for all). In addition, both groups had an increase in skin water content; however, the Pycnogenol group had significantly greater skin hydration compared to control ($P < 0.05$). Pycnogenol reduced the need for standard management drugs. The Pycnogenol group, but not control, had significantly reduced oxidative stress at 12 months ($P < 0.05$ compared with baseline), which plays a role in psoriasis as a possible marker of active inflammation. No AEs were observed.[109]

Allergy

In vitro

Pycnogenol dose-dependently reduced histamine release from rat peritoneal mast cells and decreased anti-dinitrophenyl (DNP) immunoglobulin E (IgE)-induced calcium uptake into rat peritoneal mast cells (which is required to perpetuate the allergic reaction).[110]

Animal

Immune system dysfunction was induced in mice via a diet containing only 7.5% of recommended nutrients, and resulted in an abnormal pattern of cytokine secretion, enhanced hepatic lipid peroxidation, low lymphocyte proliferation, and shorter survival time. Oral administration of Pycnogenol restored function of the immune system and prolonged survival time of the mice.[111]

In a rat model of allergy, oral Pycnogenol significantly inhibited anti-DNP IgE-mediated passive cutaneous anaphylaxis.[110] This along with in vitro data[110] demonstrate a potential use of Pycnogenol in mast cell-mediated immediate-type allergies.

The effects of Pycnogenol on allergic asthma were evaluated with a mouse model of ovalbumin-induced allergic asthma. Pycnogenol attenuated airway inflammation, decreased mucus hypersecretion, and decreased levels of ILs and IgE in serum and bronchoalveolar lavage fluid.[112]

Nephrology

Animal

Environmental and occupational exposure to chromium compounds can cause nephrotoxicity. Pycnogenol prevented chromium-induced oxidative stress-mediated nephrotoxicity in rats by ameliorating increases in TBARS, MDA, and protein carbonyl, and decreasing levels of GSH and CAT activity.[113]

Vancomycin treatment can cause nephrotoxicity. Mice were treated with vancomycin, and markers for renal cortical oxidative stress, apoptosis, and autophagy (an intracellular degradation system that delivers cytoplasmic constituents to the lysosome) were induced. Mice receiving Pycnogenol had decreased serum creatinine, blood urea nitrogen (BUN), renal MDA, and immunoexpression of the proapoptotic protein Bax, the autophagic marker protein LC3/B, and iNOS compared with untreated control.[114]

Oxygen free radicals contribute to ischemia-reperfusion-induced oxidative renal damage. Pycnogenol provided renoprotection in rats with ischemia-reperfusion-induced renal injury by decreasing renal GSH, MDA, and myeloperoxidase.[115]

Liver

Animal

Nonalcoholic steatohepatitis is a chronic liver disease. In a rat model of nonalcoholic steatohepatitis, histological liver analysis revealed hepatocytes with macrovesicles of fat and fibrosis. Oral Pycnogenol improved fibrosis and cirrhosis, which would delay the progression of fatty liver to fibrosis. Pycnogenol also significantly reduced liver triglycerides and serum alanine aminotransferase (ALT) levels ($P < 0.05$ for both) more than control.[116]

Carbon tetrachloride was given to rats to induce oxidative stress and hepatotoxicity. Accordingly, carbon tetrachloride induced significantly elevated levels of serum aspartate aminotransferase (AST) and ALT, and produced extensive liver injuries; namely, extensive hepatocellular degeneration/necrosis, fatty changes, inflammatory cell infiltration, congestion, and sinusoidal dilatation. In addition, carbon tetrachloride increased MDA concentration and decreased GSH, CAT, SOD, and GST activities in hepatic tissues. When rats were pretreated with oral Pycnogenol, hepatotoxicity and oxidative damage were prevented.[117]

Oncology

In vitro

Colon carcinoma cells were exposed to fruit juices enriched with 0.5 g/L Pycnogenol or without Pycnogenol. Cells exposed to Pycnogenol had a greater inhibition of cell growth.[42]

In a human cell line of oral squamous cell carcinoma, Pycnogenol decreased cell viability and induced apoptosis.[118]

Pycnogenol selectively induced cell death in a human cell line of fibrosarcoma cells, and caused more apoptosis in the human cell line of fibrosarcoma cells than in the human cell line of fibroblastoma cells. Apoptosis was induced via activation of caspase-3. This indicates that Pycnogenol may have a differential effect on the inhibition of cell growth depending on the cell type.[119]

Pycnogenol inhibited growth of 3 different human leukemia cell lines via caspase-3 activation, which induced apoptosis.[120]

Animal

Cisplatin, used to treat cancer, is limited by ototoxicity. Rats treated with cisplatin plus Pycnogenol were protected against cisplatin-induced cochlear apoptosis. Pycnogenol alone was not ototoxic. Pycnogenol may have a protective role against cisplatin ototoxicity.[121]

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. Toxicological studies demonstrated an absence of mutagenic and teratogenic effects, no perinatal toxicity, and no negative effects on fertility.[3]

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

ADVERSE EFFECTS / SAFETY DATA

Preclinical Toxicology

The toxicity of Pycnogenol is very low. The acute toxicity is low after oral administration in mice, rats, and guinea pigs.[122] The most representative median lethal dose (LD_{50}) value, following the current Organisation for Economic Co-operation and Development (OECD) guidelines (OECD 423[123]), is > 5.0 g/kg body weight in rats.[122]

In chronic toxicity tests (OECD 408[124]), oral application of up to 1000 mg/kg/day in rats did not produce abnormal clinical or behavioral signs, nor any change in body weight, hematology, clinical biochemistry, or food/water consumption. Furthermore, no pathomorphological changes were found.[122]

The level of mutagenicity of Pycnogenol was assessed with the OECD 471[125] bacterial reverse mutation test (Ames test), the micronucleus assay in mouse bone marrow cells in vivo, and the chromosome aberration assay in human lymphocytes in vitro.[122] The results all converge to suggest that Pycnogenol is nonmutagenic.[122]

HUMAN SAFETY DATA

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.[126]

The safety of Pycnogenol is based on data obtained from 91 clinical studies, which include a total of 6845 participants up to January 24, 2014.[127] There are 34 double-blind, placebo-controlled, comparative studies, including 6 crossover studies, with a total of 1976 participants. There are 57 open-label or open, comparative studies with a total of 4869 participants. The populations are comprised of 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.[127] The global frequency rate of AEs is 2.4%. However, in healthy participants, the global incidence rate of AEs is 0.1%.[127] An evaluation of the clinical studies revealed that the occurrence of AEs is unrelated to the dose or duration of use.[128] From what can be gleaned from the clinical trials (published and unpublished), it appears that GI discomfort is the most frequently occurring treatment-related AE. 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.[128] 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.[129,130] The majority of AEs observed were mild.[128]

Analysis of clinical safety data obtained from 6 clinical studies did not reveal any significant changes in systolic or diastolic BP ($n = 287$) or heart rate ($n = 185$) in participants with normal BP or heart rate.[15,69,90,131-133]

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.[133]

Pycnogenol at a dose of 150 mg/day for 6 months did not alter liver enzymes (ALT, AST, and γ-glutamyltransferase [GGT]), alkaline phosphatase (ALP), CRP, serum creatinine, or blood param-

eters (blood cell count, fibrinogen, international normalized ratio [INR] for prothrombin time, and hematocrit) in patients with metabolic syndrome.[55]

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.[134] 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. No drug interaction studies have been performed with Pycnogenol. Pycnogenol does not affect INR (a measure of bleeding tendency) or platelet function in patients taking aspirin.[15,135] One study evaluated patients (n = 28; 49-73 years of age) with stable coronary artery disease treated with both optimal standard therapy and 200 mg/day Pycnogenol for 8 weeks. Standard therapy included aspirin (100% of patients), statins (87%), ACE inhibitors/angiotensin receptor blockers (78%), β-blockers (74%), diuretics (35%), calcium antagonists (17%), clopidogrel (17%), ezetimibe (17%), oral antidiabetics (17%), phenprocoumon (4%), and α-antagonists (4%). There were no adverse drug-herb interactions.[15]

REGULATORY STATUS IN VARIOUS COUNTRIES

ASIA: Food supplement, health supplement, functional food ingredient, cosmetic ingredient, or health food status in Bangladesh, China, Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Taiwan, Thailand, and Vietnam

AUSTRALIA: Health supplement in the Therapeutic Goods Administration listings

CANADA: Natural Health Product (NHP) designation

EGYPT: Medical nutrient (food supplement)

EUROPEAN UNION (EU): Food supplement in many EU countries (Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom, along with Andorra, Monaco, Saint-Marin, and Vatican). The labeling advice in the United Kingdom 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 United Kingdom.

LATIN AMERICA: Over-the-counter (OTC) medicine in Brazil, Chile, Colombia, Ecuador, Peru, and Venezuela

RUSSIA: Food supplement, food ingredient

SOUTH AFRICA: Food supplement

SWITZERLAND: Nonprescription herbal drug (under category D) for venous disorders

UNITED STATES: Dietary supplement through notification under the Dietary Supplement Health and Education Act of 1994 (DSHEA)

PATENTS

United States Patent (6,372,266, issued April 16, 2002). Suzuki N, Kohama T, inventors; Tradepia Co. Ltd. (Saitama, Japan), Horphag Research Limited (St. Peter Port, Guernsey), assignees. Medicinal composition for treating dysmenorrhea and endometriosis—industrial use.

United States Patent (6,565,851, issued May 20, 2003). Rohdewald P, Ferrari V, inventors; Horphag Research Limited (Geneva, Switzerland), assignee. Relieving symptoms of erectile dysfunction with proanthocyanidins.

United States Patent (9,028,890, issued May 12, 2015). Ferrari V, Schonlau F, Burki C, inventors; Horphag Research (IP) Pre Ltd. (Limassol, Cyprus), assignee. Composition for improving sexual wellness.

United States Patent (9,125,925, issued September 8, 2015). Ferrari V, Malandrino S, Burki C, Schoenlau F, inventors; Horphag Research (Luxembourg) Holdings SA (Luxembourg, Luxembourg), Indena S.P.A. (Milan, Italy), assignees. Abnormal intraocular pressure treatment.

United States Patent (9,308,230, issued April 12, 2016). Belcaro G, Burki C, Ferrari V, inventors; HORPHAG RESEARCH IP (Limassol, Cyprus), assignee. Combination of proanthocyanidins and *Centella asiatica* for the treatment of atherosclerosis.

There are patent extensions in Australia, China, Europe, Japan, Mexico, the Russian Federation, Singapore, South Africa, and Taiwan.

CLINICAL REVIEW

As of December 2015, there were a total of 63 published human clinical efficacy trials on Pycnogenol as a monopreparation that have been published in English or translated into English and included in this review. Due to space considerations for this publication, the author and editors decided to review only selected studies in the text below; however, all 63 trials appear in Table 2. Studies included in the review below 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 below. These studies evaluated Pycnogenol for the following indications: CVI and its complications (7 studies), thrombosis (2 studies), diabetes and its complications (4 studies), hypertension and its complications (5 studies), coronary artery disease (1 study), asthma (3 studies), ADHD (1 study), gynecology (endometriosis, dysmenorrhea, pregnancy-associated pain, and menopause transition; 8 studies), OA (3 studies), acute hemorrhoids (1 study), and cognition (2 studies).

Chronic Venous Insufficiency (CVI) and Complications

Belcaro (2015b)[136] A prospective, open-label, comparative study was conducted in patients (n = 166; mean age, 43 years) with symp-

tomatic CVI awaiting surgery. Patients were treated with 100 mg/day Pycnogenol (n = 61), 720 mg/day Antistax® (red vine [grape; *Vitis vinifera* var. *tinctoria*, Vitaceae] leaf extract; Sanofi; Paris, France) (n = 55), or compression stockings only (n = 50) for 8 weeks. After 8 weeks, Pycnogenol resulted in significant improvements in microcirculatory parameters (rate of ankle swelling, resting flux, transcutaneous partial pressure of oxygen [pO_2], and morning ankle circumference) compared with baseline ($P < 0.05$ for all) and compared with compression stockings and Antistax ($P < 0.05$ for all). There was minimal improvement with Antistax. The Pycnogenol group also had significant improvements in CVI signs and symptoms (pain, venous edema, induration, and need for compression) compared with baseline ($P < 0.05$ for all). The compression stockings group had significant improvements in pain and venous edema compared with baseline ($P < 0.05$ for both). Venous edema was decreased 40% in the Pycnogenol group, 30% in the compression stockings group, and 3% in the Antistax group. No AEs were observed.

An advantage of this study is that the Antistax treatment could have worked as a psychological placebo and yet the Pycnogenol outcomes surpassed the Antistax outcomes. Nonetheless, CVI is a chronic condition, and the study results are limited by the 8-week time course. It is important to know how the outcomes of the compression stockings group and Pycnogenol group would compare following a longer treatment duration. These data add to the numerous studies that show a benefit of Pycnogenol compared with stockings.

Cesarone et al. (2010b)[137] A prospective, randomized, open-label, controlled, comparative study was conducted in patients (n = 98; mean age, 48 years) with symptomatic severe CVI plus edema. Patients were randomly assigned to 1 of the following 3 treatment groups: (1) 150 mg/day Pycnogenol (n = 33); (2) elastic stockings only (n = 31); and (3) 150 mg/day Pycnogenol plus elastic stockings (n = 34). After 8 weeks, all 3 groups had significant decreases in the rate of ankle swelling, resting flux, transcutaneous pO_2, and clinical symptom scores. However, Pycnogenol alone was significantly more effective than stockings alone in relieving all parameters ($P < 0.05$ for all), and Pycnogenol plus stockings was the most efficacious group ($P < 0.05$ for all). No AEs were observed, and the compliance and tolerability was very good. The authors conclude that this study corroborates a significant clinical role for Pycnogenol in the management, treatment, and control of CVI, both alone and in combination with compression stockings.

A limitation of the study is that the elastic stockings-only group did not have an oral placebo control. Without this control, it is unclear whether the additional benefit provided by Pycnogenol was due to a placebo effect. Further, the authors did not exclude patients who used stockings previously, so the patients could have entered the study biased (either favoring or doubting the benefit of stockings), which could ultimately affect the study outcomes. Despite these shortcomings, these data adds to the numerous studies that show a benefit of Pycnogenol compared with stockings.

Cesarone et al. (2006a)[7] A prospective, randomized, controlled study was conducted with patients (n = 86; 40-61 years of age) with CVI and a history of venous ulcerations. Patients were treated daily for 8 weeks with either 150 mg Pycnogenol (n = 24), 300 mg Pycnogenol (n = 20), or 1000 mg Daflon® (a combination formula containing 450 mg diosmin and 50 mg hesperidin that is used to treat CVI; Servier; Suresnes, France) (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, pO_2, and partial pressure of carbon dioxide [pCO_2]) compared with baseline ($P < 0.05$ for all, except edema, $P < 0.001$) and Daflon ($P < 0.05$ for all). 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 Pycnogenol. Pycnogenol was well tolerated and there were no AEs reported. The authors conclude 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 1000 mg of Daflon may be too low to have important microcirculatory effects.[7] However, it should be noted that 1000 mg Daflon is the manufacturer's recommended daily dose for treatment of CVI.

Koch (2002)[8] A randomized, open-label, comparative study was conducted in patients (n = 40; aged 34-71 years) with CVI. Patients were randomly assigned to receive either 360 mg Pycnogenol (Pygnoforton®; Plantorgan; Bad Zwischenahn, Germany) or 600 mg standardized dried horse chestnut (*Aesculus hippocastanum*, Sapindaceae) seed extract (HCSE; Venostasin® retard; Klinge Pharma GmbH; Holzkirchen, Germany; corresponding to 100 mg aescin/day) daily for 4 weeks. Compared with 4 weeks of HCSE, Pycnogenol produced a significantly greater decrease in heaviness, cramps, and nighttime swelling (edema) of both legs ($P < 0.05$ for all). Pycnogenol significantly reduced lower leg edema from baseline (right lower leg circumference: 46.9 cm at baseline vs. 46.2 cm at 4 weeks, $P < 0.01$; left lower leg circumference: 47.9 cm at baseline vs. 46.9 cm at 4 weeks, $P < 0.01$). Pycnogenol was well tolerated. Pycnogenol-treated patients also had significant reductions in total cholesterol and LDL cholesterol of 19.7% and 13%, respectively, compared with baseline ($P < 0.001$ for both), while HDL cholesterol remained unchanged.

The dose of HCSE used in this study was found to be efficacious in many randomized, controlled studies.[138] 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 HCSEs, recognized in Europe as an effective medication for treating symptoms of CVI.

Petrassi et al. (2000)[10] This was a 2-part study in patients (n = 40) with CVI. Part 1 was a randomized, double-blind, placebo-controlled study, and Part 2 was an open-label study. In Part 1, patients (n = 20; mean age, 42.2 years) with CVI symptoms of heaviness and subcutaneous swelling were treated with 300 mg Pycnogenol or placebo daily for 2 months. Heaviness and swelling significantly declined in Pycnogenol-treated patients compared with placebo-treated patients ($P < 0.05$ for both) and compared with baseline ($P < 0.01$ for both). 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 values here 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 (n = 20; mean age, 44.9 years) with CVI treated with Pycnogenol (300 mg daily for 2 months) in an open-label study.

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 in 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 (2000)[5] A randomized, double-blind, placebo-controlled study was conducted in patients (n = 40; 30-74 years of age) with clinically evident CVI attributed to DVT 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 significant reductions in heaviness, swelling, and pain compared with placebo at day 30 ($P < 0.01$, $P < 0.01$, and $P < 0.05$, respectively) and day 60 ($P < 0.01$, $P < 0.01$, and $P < 0.05$, 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 reductions of 3%, 7%, and 18%, respectively, in placebo-treated patients ($P < 0.01$, $P < 0.01$, and $P < 0.05$, respectively). In both groups, there was no apparent change in the venous blood flow, as measured by Doppler ultrasound. No AEs were reported. Results of hematology and blood chemistry did not differ between groups. Physicians judged Pycnogenol's efficacy to be moderate to very good in 19 of 20 patients; they judged the placebo to be ineffective in 16 out of 20 patients.

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

Schmidtke & Schoop (1995)[11] A randomized, double-blind, placebo-controlled trial was conducted in patients (n = 40; age not reported) with venous circulation problems in their legs. The patients were randomly assigned to receive either 360 mg/day Pycnogenol (Pygenol®; Horphag Research) 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, compared to placebo-treated patients ($P < 0.001$). [Note: Data values are 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® volumenometer. Approximately 50% of the patients rated Pycnogenol as "very good" or "good," and approximately 30% reported that Pycnogenol had no effect. No AEs 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 than the placebo group at baseline. 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 had been longer.

CVI Summary

All 7 studies reported subjective improvements in symptoms of CVI in patients treated with Pycnogenol. [5,7,8,10,11,136,137] Six studies quantitatively measured leg swelling, and the studies all showed an improvement in Pycnogenol-treated patients. [7,8,10,11,136,137] Nonetheless, additional studies with larger numbers of patients are warranted for more adequate confirmation of the efficacy of Pycnogenol for CVI.

Thrombosis

Belcaro et al. (2004)[139] A double-blind, placebo-controlled, randomized trial was conducted in airline passengers (n = 198; age not reported) traveling on a long flight (7-12 hours) who had a moderate to high risk for thrombosis. Participants traveled on several different flights. They received either placebo or 200 mg Pycnogenol 2 to 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). DVT or superficial vein thrombosis was 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 the placebo group (0 vs. 4, respectively; $P < 0.05$). None of the Pycnogenol-treated participants experienced a DVT, while there was 1 DVT in the placebo group. No AEs were reported.

All participants viewed an educational 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. Since there was only 1 incident of DVT in the study, no conclusions can be drawn on the effect of Pycnogenol on DVT in this airline passenger population.

Errichi BM et al. (2011)[140] An open-label, controlled study was conducted in men and women (n = 156; 35-50 years of age) with a single, major episode of proximal DVT. For 12 months, the patients received either (1) elastic compression stockings; (2) 150 mg/day Pycnogenol; or (3) elastic compression stockings plus 150 mg/day Pycnogenol. All patients received standard anticoagulant treatment for the first 3 months. There were no new incidents of DVT in the Pycnogenol treatment groups, whereas there were 2 new incidents of DVT in the compression stockings-only group. At 6 months, all 3 treatments significantly improved edema, limb volume, and ankle circumference compared with baseline ($P < 0.05$ for all). Both Pycnogenol groups had significantly more improvement than the compression stockings-only group ($P < 0.05$ for both). The Pycnogenol plus stockings group was significantly more effective than Pycnogenol alone ($P < 0.05$). All improvements persisted to 12 months. Pycnogenol was well tolerated. The stockings were less well tolerated because they were too warm on hot days.

This study would have benefited from the addition of a stockings plus placebo group and blinding. Although the measures of efficacy were quantitative rather than qualitative, without blinding it is unknown whether the person taking the measurements was biased.

Thrombosis Summary

Preliminary research indicates that Pycnogenol may be beneficial for preventing DVT. Both clinical studies[139],[140] had limitations that need to be addressed in future studies.

Diabetes and Complications

Liu et al. (2004a)[141] A double-blind, placebo-controlled, randomized, multicenter study was conducted in men and women (n = 77; 45-66 years of age) with type 2 diabetes mellitus. Patients 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 fasting plasma glucose had a maximum reduction after 8 weeks of Pycnogenol 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 mmol/L vs. –0.34 mmol/L, respectively; 4 weeks: –1.51 mmol/L vs. –0.88 mmol/L, respectively; 6 weeks: –1.81 mmol/L vs. –1.15 mmol/L, respectively; and 8 weeks: –1.96 mmol/L vs. –1.24 mmol/L, respectively; $P < 0.01$ for all). HbA1c values significantly decreased after 1 month of Pycnogenol treatment compared with placebo (–0.32% vs. –0.07%, respectively; $P < 0.01$), but the difference was not maintained. Median plasma endothelin-1 (a vasoconstrictor) concentrations significantly decreased in the Pycnogenol group compared with the placebo group over the entire treatment period compared with baseline (1 month: –11.20 mmol/L vs. –1.82 mmol/L, respectively; 2 months: –20.93 mmol/L vs. –2.68 mmol/L, respectively; and 3 months: –21.42 mmol/L vs. –4.03 mmol/L, respectively; $P < 0.01$ for all). Median plasma 6-keto-prostaglandin $F_{1\alpha}$ (a metabolite of the vasodilator prostacyclin) significantly increased in the Pycnogenol group compared with the placebo group (1 month: 10.53 mmol/L vs. 3.32 mmol/L, respectively; 2 months: 13.47 mmol/L vs. 5.58 mmol/L, respectively; and 3 months: 12.70 mmol/L vs. 6.03 mmol/L, respectively; $P < 0.01$ for all). There was no effect on heart rate, ECG, BUN, creatinine, or electrolytes. AEs (dizziness, headache, gastric discomfort, and mouth ulcer) 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, HbA1c, and endothelin-1 with doses between 100 and 200 mg of Pycnogenol, with no further decrease at 300 mg/day.[141] A notable finding is that Pycnogenol does not affect insulin secretion. This study suggests that Pycnogenol may improve glycemic control in patients with type 2 diabetes.

Belcaro et al. (2006b)[142] A randomized, controlled study was conducted in patients (n = 30; mean age, 54 years) with diabetes (type not specified) who were taking insulin and had diabetic ulcers (mean ulcerated area was 44 mm^2). Patients received standard ulcer care and 1 of the following 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) (n = 8); (2) 150 mg/day oral Pycnogenol (n = 6); (3) 100 mg topical Pycnogenol powder (n = 8); and (4) no Pycnogenol (standard ulcer care only [control]) (n = 8). After treatment, the ulcerated area was significantly smaller in the patients who received combined oral and topical Pycnogenol treatment compared to those who received only standard care (11 mm^2 vs. 34 mm^2, respectively; $P < 0.01$). Oral-only and topical-only Pycnogenol treatments were less effective, but were significantly better than control (30 mm^2, 27 mm^2, and 34 mm^2, respectively; $P < 0.05$ and $P < 0.01$, respectively). Combination treatment with oral and topical Pycnogenol was the most effective (11 mm^2; $P < 0.01$ vs. control). On average, 86% of ulcers completely healed in patients treated with Pycnogenol, compared with 61% in patients treated with standard care only ($P < 0.05$). Compared with standard care, the combination treatment significantly improved blood microcirculation to the skin (measured by laser Doppler), with pO_2 increasing (48 mmHg vs. 58 mmHg, respectively; $P < 0.05$) and pCO_2 decreasing (29.8 mmHg vs. 27 mmHg, respectively). No AEs were reported.

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

Cesarone et al. (2006b)[143] A placebo-controlled study was conducted in patients (n = 60; 55-68 years of age; mean age, 59 years) with diabetes (type not specified) who had been taking insulin for at least 3 years, were in stable control, and had severe microangiopathy with edema. Patients received 150 mg/day Pycnogenol (n = 30) or placebo (n = 30) for 4 weeks. All patients continued with their diabetic treatment as initiated before study inclusion. Baseline levels of microangiopathy were comparable between groups. Pycnogenol significantly decreased capillary filtration compared with baseline and control ($P < 0.05$ for both). Accordingly, venoarteriolar response (reflex vasoconstriction when changing from supine to standing position) was significantly increased in the Pycnogenol group compared with baseline and control ($P < 0.05$ for both). Skin flux at rest in the foot was significantly decreased in the Pycnogenol group compared with baseline and control ($P < 0.05$ for both). Edema rapidly responded, with a clinically significant decrease in 5 to 8 days in the Pycnogenol-treated patients with the most severe, visible foot and ankle edema (n = 14). No AEs were observed.

The authors conclude that the results were clinically significant and that Pycnogenol should be used by patients with severe edema when they cannot wear compression stockings (i.e., in the summer). The study should be continued to see what happens when Pycnogenol treatment stops; in other words, to see how long the benefits last. Also, it should be repeated with a larger population to confirm the findings.

Steigerwalt et al. (2009)[144] A randomized, double-blind, placebo-controlled study was conducted to assess whether Pycnogenol could improve early stages of diabetic retinopathy. Patients (n = 46; mean age, 51.5 years) with controlled diabetes mellitus type 2 for at least 4 years and a moderate degree of diabetic retinopathy (macular edema, retinal swellings, minor presence of exudates, and hemorrhages) were treated with 150 mg/day Pycnogenol (n = 24) or placebo (n = 22) for 3 months. The patients were grouped by mild or moderate macular edema. Of the patients with moderate macular edema (n = 21), Pycnogenol treatment significantly improved visual acuity, retinal edema, retinal flow, diastolic flow relative to maximal systolic flow, and retinal thickness, compared with placebo treatment ($P < 0.05$ for all). Of the patients with mild macular edema (n = 25), Pycnogenol treatment significantly improved visual acuity (at 2 months only), retinal edema, retinal flow, and diastolic flow relative to maximal systolic flow, compared with placebo treatment ($P < 0.05$ for all). No AEs were observed.

Although the sample size per group was small in this clinical trial, the results suggest that Pycnogenol may be beneficial for patients with diabetes and early stages of retinopathy. This is particularly interesting since current treatment of eyes with diabetic retinopathy with edema involves surgery. Studies are needed to determine whether Pycnogenol treatment of early diabetic retinopathy stops the progression of the disease so that surgery is not needed.

Diabetes Summary

Two studies in patients with diabetes suggest that Pycnogenol may improve glycemic control in type 2 diabetes. [14,141] One study suggests that Pycnogenol taken in addition to standard oral antidiabetic medication further improves glycemic control.[141]

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.[142] The findings

warrant confirmation in a larger study.

Pycnogenol appears to be a viable option for patients with diabetic microangiopathy with edema when they are unable to wear compression stockings, considering that there is no definitive treatment or prevention of diabetic microangiopathy, and considering that there are 2 small studies that both demonstrate that Pycnogenol helps with leg edema and is well tolerated. [140,143]

Pycnogenol may be beneficial for patients with diabetes and early stages of retinopathy[145]; however, additional research is needed.

Hypertension and Complications

Liu et al. (2004a)[9] 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 (n = 58; mean age, 57 years) being treated for hypertension. Patients stopped current antihypertensive therapy for 2 weeks prior to starting the study. Baseline pretreatment BP levels were not reported. Patients were treated with nifedipine (Shanghai Pharmaceuticals Co., Ltd.; Shanghai, China) plus placebo or plus 100 mg Pycnogenol for 12 weeks. All patients 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 patients) had normal BP (systolic/diastolic values not reported) when treated with 10 mg nifedipine and 100 mg Pycnogenol. In contrast, only 13% (4/30 patients) attained normal BP when treated with 10 mg nifedipine plus placebo. Supplementation with Pycnogenol significantly reduced the dose of nifedipine needed to normalize BP compared with placebo ($P < 0.001$). Pycnogenol-treated patients had a significantly greater increase in plasma 6-keto-prostaglandin $F_{1\alpha}$ (a metabolite of the vasodilator prostacyclin) values than placebo-treated patients (12% vs. 8% increase, respectively; $P < 0.05$), which shows a significant improvement in endothelial function. AEs (GI disturbances, nausea, dizziness, headache, and sleepiness), reported by both groups of patients, were mild and transient.

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. (2006a)[6] 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 patients 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 mL/min/100 cm^3 vs. 1.56 mL/min/100 cm^3 of tissue, respectively; $P < 0.05$) or nifedipine (2.48 mL/min/100 cm^3 vs. 1.61 mL/min/100 cm^3 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, namely, edema. However, the study was single-blinded and treatment duration was short.

Cesarone et al. (2010a)[12] A controlled, open-label trial was conducted to determine the protective effects of Pycnogenol on kidney function when taken as an adjunct treatment with standard ACE-inhibitor hypertension treatment. Patients (n = 55; mean age, 53.5 years) with hypertension who were symptomatic for cardiovascular disease and had altered kidney function were treated with 10 mg/day ramipril (n = 26) or 10 mg/day ramipril plus 150 mg/day Pycnogenol (n = 29) for 6 months. All patients were instructed to live a healthier lifestyle (i.e., diet, exercise, and weight loss). Ramipril was effective for all parameters compared to baseline. Ramipril plus Pycnogenol was significantly more effective than ramipril alone in decreasing diastolic BP ($P < 0.05$), heart rate ($P < 0.05$), serum creatinine ($P < 0.05$), leukocyte count ($P < 0.05$), CRP ($P < 0.05$), and 24-hour urinary albumin excretion ($P = 0.002$), and improving kidney blood flow and perfusion ($P < 0.05$). Pycnogenol was well tolerated.

The data show that Pycnogenol worked with ramipril to further decrease the progression of hypertension-associated kidney disease. The authors conclude that Pycnogenol can protect the kidney, especially since the combination did not lower BP enough to explain the findings. The authors did not report on lifestyle changes. There is the chance that the group taking Pycnogenol had more lifestyle changes. Considering that patients would take ramipril for longer than 6 months, it would be valuable to repeat this study with a longer treatment duration, a larger patient population, and an assessment of lifestyle changes.

Stuard et al. (2010)[13] A controlled, open-label trial was conducted to determine the protective effects of Pycnogenol on kidney function when taken as an adjunct treatment with standard ACE-inhibitor hypertension treatment in patients (n = 58; mean age, 58.5 years) with metabolic syndrome. Patients with hypertension and metabolic syndrome who were not taking any hypoglycemic medications and had altered kidney function were treated with 10 mg/day ramipril (n = 27) or 10 mg/day ramipril plus 150 mg/day Pycnogenol (n = 31) for 6 months. All patients were instructed to live a healthier lifestyle (i.e., diet, exercise, and weight loss). Ramipril plus Pycnogenol was significantly more effective than ramipril alone for decreasing systolic and diastolic BP, fasting glucose, HbA1c (a measurement of plasma glucose concentrations over time), urinary albumin, serum creatinine, CRP, and fibrinogen, and improving kidney blood flow and perfusion ($P < 0.05$ for all). Pycnogenol was well tolerated.

The data show that Pycnogenol worked with ramipril to further decrease the progression of kidney disease in patients with hypertension and metabolic syndrome. The authors conclude that Pycnogenol is effective for better hypertension control than ramipril alone in patients with metabolic syndrome, and the combination provided significant kidney-protective benefits. The authors did not report on lifestyle changes, so there is the chance that the Pycnogenol group had more lifestyle changes. Considering that patients would take ramipril for longer than 6 months, it would be valuable to repeat this study with a longer treatment duration, a larger patient population, and an assessment of lifestyle changes.

Zibadi et al. (2008)[14] A randomized, double-blind, placebo-controlled study was conducted in patients (n = 48; mean age, 59.5 years) with type 2 diabetes and hypertension (treated with ACE inhibitors) to determine whether Pycnogenol would reduce use of antihypertensive medication and reduce cardiovascular risk factors. Patients received 125 mg/day Pycnogenol or placebo for 12 weeks. Patients maintained their current medications. BP was similar between groups at baseline. Significantly more Pycnogenol-treated patients (58.3%) compared with placebo-treated patients (20.8%) were able to reduce their dose of BP medication by 50%

(P < 0.05). Pycnogenol-treated patients compared with placebo-treated patients had significant reductions in plasma endothelin-1 (P < 0.001), mean HbA1c (P < 0.05), fasting plasma glucose (P < 0.0001), LDL cholesterol (P < 0.001), and urinary albumin (P < 0.05, at 8 weeks only). AEs were not reported.

The authors conclude that Pycnogenol treatment improves diabetes control, reduces use of antihypertensive medications, and may favor a reduction in cardiovascular disease risk factors in patients with type 2 diabetes and hypertension. A study with a larger population is warranted to confirm the findings.

Hypertension Summary

Two studies evaluated antihypertensive drug-sparing activity of Pycnogenol. [14,9] One evaluated ACE inhibitors[14] and the other evaluated nifedipine.[9] Both small studies had the same conclusion—that Pycnogenol treatment reduces the antihypertensive drug dose needed for normalizing BP.

The 2 studies that evaluated adjunct Pycnogenol treatment on kidney function had a very similar design, but had slightly different patient populations. [12,13] The conclusion that Pycnogenol protects the kidney is more credible since both studies had similar findings despite the relatively small sample sizes.

One study demonstrated the edema-reducing activity of Pycnogenol in patients with antihypertensive drug-induced edema,[6] and the findings support those reported in other patient populations. [140,143]

Coronary Artery Disease

Enseleit et al. (2012)[15] A randomized, double-blind, placebo-controlled, crossover study was conducted to assess the effect of Pycnogenol on endothelial function. Patients (n = 23; 49-73 years of age; mean age, 63 years) with stable coronary artery disease receiving optimal standard therapy received 200 mg/day Pycnogenol or placebo for 8 weeks. There was a 2-week washout period before the crossover. FMD (a test assessing endothelial function) significantly increased with Pycnogenol treatment compared with placebo treatment (P < 0.0001). Concentrations of 15-F_{2t}-isoprostane, an index of oxidative stress, significantly decreased after Pycnogenol treatment but not after placebo treatment (P = 0.012). There were no significant changes between groups in BP, markers of inflammation, or platelet adhesion.

The authors hypothesize that there was no effect on BP because it was already well controlled by the standard therapy, and higher doses of Pycnogenol may be needed to inhibit platelet function. The authors conclude that Pycnogenol improves endothelial function. The clinical implications need to be confirmed in a large-scale study.

Asthma

Lau et al. (2004)[145] A randomized, double-blind, placebo-controlled trial was conducted in children (n = 60; 6-18 years of age) with mild-to-moderate asthma (mild intermittent, mild persistent, or moderate persistent). Patients received either 1 mg/lb body weight Pycnogenol per day, in 2 divided doses, or placebo for 3 months. Pycnogenol treatment resulted in a steady and significant increase in peak expiratory flow (P < 0.01), and placebo treatment produced a slight increase in flow, compared with baseline. Compared with baseline, after 3 months of treatment with Pycnogenol, peak expiratory flow increased from 70% to 87% of predicted normal value according to sex, age, and height (P < 0.01). Symptoms also significantly decreased monthly in Pycnogenol-treated patients (P < 0.001 vs. baseline) but not in placebo-treated patients. The mean number of puffs of rescue medicine (albuterol inhaler) significantly declined in Pycnogenol-treated patients (P < 0.001 vs. baseline) but not in placebo-treated patients. At study end, Pycnogenol-treated patients used an average of 0.22 puffs per day vs. 2.57 puffs per day at baseline (P < 0.001). Urinary leukotrienes significantly decreased in Pycnogenol-treated patients (1300 pg/mL at baseline vs. 800 pg/mL at 3 months; 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. (2001b)[146] A randomized, double-blind, placebo-controlled, crossover study was conducted in patients (n = 22 who completed the study; 18-60 years of age) with asthma. Patients received 1 mg/lb/day Pycnogenol (maximum 200 mg/day) or placebo for 4 weeks. The patients were then crossed over to the alternate treatment for 4 weeks. There was no washout period. Compared with baseline, Pycnogenol treatment significantly increased the 1-second forced expiratory volume (FEV_1) 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_1/forced vital capacity, there were significant differences 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 (844 pg/mL Pycnogenol vs. 1044 pg/mL at baseline and 1017 pg/mL placebo; P < 0.001 for both). One patient reported GI disturbances, which were transient.

According to the authors, airway obstruction is considered reversed when treatment produces a 15% or greater increase in FEV_1. In this study, the average increase in FEV_1 was only 11%. Pycnogenol may demonstrate better clinical efficacy as an adjunct therapy. Treatment duration was only 4 weeks; longer treatment might have resulted in improved respiration.

Belcaro et al. (2011)[147] An open-label, controlled study was conducted in adults (n = 65 who completed the study; 25-45 years of age) with mild-to-moderate allergic asthma (house dust mite) with Global Initiative for Asthma treatment levels II and III. Patients could choose to be treated for 6 months with 100 mg/day Pycnogenol plus fluticasone propionate steroid inhalation (n = 33 who completed the study) or fluticasone propionate steroid inhalation alone (n = 32 who completed the study). The dose of the steroid treatment was classified in predefined steps associated with daily doses as follows: step 2 was 50 µg 2x/day; step 3 was 100 µg 2x/day; and step 4 was 250 µg 2x/day. For study inclusion, at least step 2 was required. The primary outcome was a change in the dose steps. Eighteen (55%) of the Pycnogenol-treated patients compared with 2 (6.3%) of the steroid-only-treated patients had an improvement in steps; however, the difference was not statistically significant (P = 0.25). In addition, no patients in the Pycnogenol group deteriorated to a higher-dose step, whereas 6 (18.8%) patients in the steroid-only group deteriorated (P < 0.02 between groups). The Pycnogenol group had a significant improvement in the number of days with a peak expiratory flow < 80% compared with the steroid-only group (P < 0.05). Compared with baseline, the Pycnogenol group had significant improvements in nighttime awakenings, dry cough, chest tightness, wheezing, dyspnea, and daytime asthma symptoms (P < 0.05 for all). For comparison, the steroid-only group did not have a significant improvement in any of those parameters. No AEs occurred.

The authors conclude that Pycnogenol can have a corticoid-sparing effect, and Pycnogenol may help make managing symptoms of asthma easier.

Asthma Summary

The 2 earlier studies (published in 2004 and 2001) had some limitations—much of the statistical analysis of these 2 trials was from comparison to baseline, and comparison within group was lacking.[145,146] The results are preliminary and larger studies are needed to determine clinical relevance. However, the study published in 2011 supports the conclusions of the earlier studies and overcomes some of the aforementioned limitations.[147] Taken together, the data from all 3 small studies seem to support using Pycnogenol as an adjunct treatment for asthma. A large randomized, controlled study is needed to confirm the findings and to provide awareness and confidence in using Pycnogenol as adjuvant treatment for asthma.

Attention Deficit Hyperactivity Disorder (ADHD)

Trebatická et al. (2006)[148] A randomized, double-blind, placebo-controlled trial was conducted in boys and girls (n = 61; 6-14 years of age) 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 vitamin E or C during the study. Standard questionnaires were used by teachers, parents, and physicians to rate performance. On the Child Attention Problems rating scale, the teachers reported significant improvements in hyperactivity and inattention compared with baseline ($P < 0.01$ for both) and placebo ($P < 0.05$ for both). After a 1-month washout period, the scores returned to baseline values. On the Conners' Teacher Rating Scale, only the inattention score was significantly different from placebo ($P < 0.05$), whereas the hyperactivity score did not reach statistical significance. The Conners' Parent Rating Scale showed improvements in inattention and hyperactivity scores, but these did not reach statistical significance. Psychologist assessment of visual-motor coordination and concentration revealed significant improvements compared with baseline ($P = 0.019$ for both) and placebo ($P = 0.05$ for both). No serious AEs 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 and a balanced study design.

Gynecology/Women's Health

Endometriosis

Kohama et al. (2007)[149] A randomized, open-label, comparative study was conducted in women (n = 58; 21-39 years of age) 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 were treated with 60 mg/day Pycnogenol for 48 weeks (n = 32) or gonadotropin-releasing hormone agonist (GnRH-a) therapy as injected leuprorelin acetate depot, 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 following symptom scores from severe (at baseline) to moderate: menstrual pain ($P < 0.01$ at all time points), pelvic pain (P value not significant at 4 weeks; $P < 0.01$ at 12, 24, and 48 weeks), pelvic tenderness ($P < 0.05$ at 4 weeks; $P < 0.01$ at 12, 24, and 48 weeks), and pelvic induration ($P < 0.05$ at 4 weeks; $P < 0.01$ at 12, 24, and 48 weeks). GnRH-a therapy also reduced all of the scores, but did so more quickly, and lowered the scores significantly more than Pycnogenol. However, patients treated with GnRH-a had a recurrence of symptoms following discontinuation of treatment. GnRH-a suppressed menstruation during treatment and lowered estrogen levels dramatically. Pycnogenol treatment did not lead to these AEs. The serum marker CA-125 (cancer antigen 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 GnRH-a therapy. A larger, placebo-controlled trial would be desirable to assess the effects of Pycnogenol with a longer treatment duration.

Maia et al. (2014a)[150] A prospective, open, controlled, randomized study evaluated women (n = 45; 22-37 years of age) with diagnosed endometriosis and pelvic pain. Patients were treated for 3 months with either (1) 75 µg/day gestodene and 30 µg/day ethinylestradiol (n = 7); (2) 75 µg/day gestodene, 30 µg/day ethinylestradiol, and 100 mg/day Pycnogenol (n = 14); (3) 3 mg/day drospirenone and 30 µg/day ethinylestradiol (n = 13); or (4) 3 mg/day drospirenone, 30 µg/day ethinylestradiol, and 100 mg/day Pycnogenol (n = 11). Pain scores were determined using a visual analog scale before and after 3 months of treatment. All groups had a significant decrease in pain scores after 3 months of treatment ($P < 0.001$ vs. baseline); however, the reduction was significantly greater in the groups using Pycnogenol ($P < 0.01$ for both) compared with those using oral contraceptives alone. Most patients taking Pycnogenol with an oral contraceptive (56%) had complete resolution of pain; none of the patients taking an oral contraceptive alone had full pain resolution.

These results suggest that Pycnogenol increases the efficacy of oral contraceptives for the treatment of endometriosis-related pain. However, it should be noted that there were only 7 to 14 patients in each group; so, this study should be viewed as preliminary evidence of efficacy, even though the authors do not mark this as a pilot study.

Dysmenorrhea

Suzuki et al. (2008)[151] A randomized, double-blind, placebo-controlled, multicenter study was conducted with women (n = 116; 18-48 years of age) diagnosed with dysmenorrhea. Patients were observed for 2 menstrual cycles to obtain baseline information. They were then treated with 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 value not reported). Compared with placebo, Pycnogenol treatment reduced both the quantity of nonsteroidal anti-inflammatory drug (NSAID) analgesics (type not reported) used by patients with dysmenorrhea (4.4 pills vs. 2.6 pills, respectively) and the number of days during which analgesic medication was required for dysmenorrhea (1.7 days vs. 1.2 days, respectively). These effects persisted after Pycnogenol treatment ceased ($P < 0.05$ for both). The quality-of-life assessment (36-item Short Form Health Survey [SF-36]) and the physical and mental component summaries of the SF-36 revealed no significant differences between groups; however, the bodily pain score was significantly improved Pycnogenol group compared with placebo at end of 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.

Maia et al. (2014b)[152] A prospective, open-label, controlled, randomized study was conducted in women (n = 24; 17-38 years of age; mean age, 29 years) diagnosed with severe dysmenorrhea during the hormone-free period of a 21-day/7-day oral contraceptive regimen. Patients were treated for 3 months with an oral contraceptive combination (60 mg gestodene and 15 µg ethinylestradiol; Adoless®; Farmoquímica S.A.; Rio de Janeiro, Brazil) in a 24-day/4-day regimen alone (n = 13) or the oral contraceptive plus 100 mg/day Pycnogenol (Flebon®; Farmoquímica S.A.) (n = 11). Pain scores were determined using a visual analog scale before and after 3 months of treatment. Both treatments significantly reduced pain by the end of the third cycle; however, the reduction in pain scores was significantly greater in the Pycnogenol combination group compared to the oral contraceptive-only group ($P < 0.0001$ in the abstract; $P = 0.0001$ in the text). Significantly more patients in the Pycnogenol combination group (27%) became pain-free during the hormone-free period; none of the patients in the oral contraceptive-only group became pain-free ($P = 0.04$ for difference).

The authors conclude that a 24-day/4-day oral contraceptive regimen plus 100 mg/day Pycnogenol reduces menstrual pain in patients with severe dysmenorrhea. It should be noted that there were only 11 patients in the group taking Pycnogenol. Therefore, this study should be viewed as preliminary evidence of efficacy, even though the authors do not mark this as a pilot study.

Pregnancy-associated Pain

Kohama & Inoue (2006)[153] An open-label study was conducted in women (n = 140; mean age, 28.9 years) in the third trimester of pregnancy with lower back pain, hip joint pain, inguinal pain, pain due to varices, or calf cramps to assess the effect of Pycnogenol on alleviating pregnancy-associated pain. Women received either 30 mg/day Pycnogenol (n = 80) for 6 weeks or were untreated controls (n = 60). Lower back pain, hip joint pain, inguinal pain, pain due to varices, and calf cramps were significantly reduced after 2 and 6 weeks of Pycnogenol treatment compared with baseline ($P < 0.01$ for all). The untreated control group had no significant improvements. No statistical comparisons between groups were reported. In a subgroup of 28 women who did not respond to 2 weeks of pain treatment with Loxonin or wet compressions, 30 mg/day Pycnogenol significantly improved only lower back pain compared with baseline. No AEs were observed.

The authors conclude that Pycnogenol used in the third trimester of pregnancy is a safe and effective way of alleviating pregnancy-associated pain. The authors state that Pycnogenol should not be used in the first 3 months of pregnancy because safety has not been established during the first or second trimester. Although it appears that Pycnogenol was more effective than no treatment, the authors should have provided the statistical analysis comparing the 2 conditions. They hypothesize that a higher dose of Pycnogenol may have been needed to help the patients who did not respond to treatment.

Menopause Transition

Yang et al. (2007)[154] A randomized, double-blind, placebo-controlled study was conducted in healthy perimenopausal women (n = 200; mean age, 47 years) to evaluate the effect of Pycnogenol on climacteric symptoms. Women received 200 mg/day Pycnogenol or placebo for 6 months. At study start, both groups had similar severity of signs and symptoms. A total of 80 participants in the Pycnogenol group and 75 participants in the placebo group completed all questionnaires and participated in all investigations. None of the participants discontinued the study due to AEs. After 3 and 6 months of treatment, compared with placebo, the Pycnogenol group had significant improvements in somatic symptoms, depression, vasomotor symptoms, memory and concentration, feelings of attractiveness, anxiety, sexual behavior, sleep, and menstrual problems ($P < 0.001$ for all, except for menstrual problems at 3 months, $P < 0.01$). Symptoms were evaluated by the Women's Health Questionnaire (WHQ). Participants in the placebo group had significant improvements in somatic symptoms and memory and concentration compared with baseline ($P < 0.01$ and $P < 0.05$, respectively). The Pycnogenol group had a significant increase in HDL compared with baseline ($P < 0.05$) but not compared with placebo. The Pycnogenol group had a significant decrease in LDL and increase in TAS, compared with baseline ($P < 0.05$ and $P < 0.001$, respectively) and placebo ($P < 0.001$ and $P < 0.01$, respectively). Hence, the Pycnogenol group had an improvement in the LDL/HDL ratio. No AEs were observed.

The authors conclude that supplementation improved the quality of life for perimenopausal women. This study demonstrates that the benefits of Pycnogenol on climacteric symptoms can be safely sustained for up to 6 months. With Pycnogenol, most symptoms changed from always or sometimes occurring to never occurring, while the frequency of occurrence was maintained in the placebo group. This demonstrates a clinically relevant improvement.

Errichi S et al. (2011)[100] A randomized, blinded, placebo-controlled trial was conducted in healthy perimenopausal women (n = 70; 41-49 years of age). Women received either 100 mg/day Pycnogenol or placebo for 8 weeks. All participants were trained on lifestyle changes to limit menopause symptoms. At baseline, both groups had similar severity of signs and symptoms. The following symptoms were significantly improved in the Pycnogenol group compared with the placebo group ($P < 0.05$ for all): hot flashes, bloating, irregular heartbeat, pain feeling like electric shocks, and digestive problems. The following symptoms were significantly improved in the Pycnogenol group compared with baseline ($P < 0.05$ for all): night sweats, irregular periods, loss of libido, vaginal dryness, mood swings, fatigue, hair loss, difficulty concentrating, memory lapses, dizziness, weight gain, brittle nails, depression, anxiety, irritability, panic disorder, breast pain, headaches, joint pain, gum problems, muscle tension, itchy skin, and tingling extremities. The control group did not have any significant change in any of these symptoms. Pycnogenol was well tolerated; there were no AEs and compliance was 98.6%.

The authors conclude that Pycnogenol would be a very good, basic, daily dietary supplement for menopausal women. Although the findings were statistically significant, the authors did not discuss whether the effects were clinically meaningful. Also, the study was relatively short; the benefits of Pycnogenol could have become more profound or conversely, could have returned to baseline. Finally, it is unclear whether the study was double blind. The participants were blinded; if the researchers were not blinded, then the study could be biased. In any event, it is notable that the Pycnogenol-treated participants showed an improvement, while the placebo-treated participants did not.

Kohama & Negami (2013)[133] A randomized, double-blinded, placebo-controlled, parallel-group trial was conducted in healthy perimenopausal women (n = 170; 42-58 years of age). Women

received either 60 mg/day Pycnogenol (n = 79 who completed the study) or placebo (n = 77 who completed the study) for 12 weeks. At baseline, both groups had similar severity and frequency of symptoms. Compared with placebo, Pycnogenol significantly improved vasomotor symptoms (P = 0.036; hot flashes, sweating, cold sensation of the body and limbs, and shortness of breath), insomnia/sleeping problems (P = 0.003; difficulty falling asleep, easily awaking during the night, awakening too early in the morning with the inability to return to sleep, and tired when getting up), and feeling tired and worthless (P = 0.048). There was no significant change in BP, HDL, LDL, triglycerides, total cholesterol, IGF-1, IGFBP-3, E2, FSH, or DHEA sulfate in either group.

The authors conclude that unaltered hormone levels demonstrate the safety of Pycnogenol. Also, this study demonstrated the efficacy of Pycnogenol in improving climacteric complaints at a lower dose than previously evaluated.

Gynecology/Women's Health Summary

Pycnogenol may be a therapeutic option for endometriosis; however, it may work slower and may not be as effective as standard GnRH-a therapy.[149] Also, Pycnogenol may increase the efficacy of oral contraceptive treatment of endometriosis.[150]

Preliminary research indicates that Pycnogenol may be an adjunct treatment for dysmenorrhea.[151,152]

Pycnogenol may be safe and effective in the third trimester of pregnancy as a way of alleviating pregnancy-associated pain.[154] Safety has not been established in the first or second trimester of pregnancy.

The 3 clinical trials evaluating the treatment of Pycnogenol for climacteric symptoms during menopause transition support efficacy.[100,133,154] One well-designed, rigorous study showed that Pycnogenol-treated participants had a clinically relevant improvement in climacteric symptoms, which was maintained over 6 months.[154] However, in 2 additional studies, it is unclear whether the improvements were clinically relevant.[100,133] It would have been valuable if the authors of those 2 studies [100,133] included a questionnaire assessing whether the participants found the improvements beneficial and whether the participants would choose to continue treatment with Pycnogenol.

Osteoarthritis (OA)

Belcaro et al. (2008a)[155] A randomized, double-blind, placebo-controlled trial was conducted in patients (n = 156; mean age, 48 years) with primary OA grade 1 or 2 in 1 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/day oral Pycnogenol (n = 77) or placebo (n = 79) for 3 months. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), with 24 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 (79.2 at baseline vs. 34.6 at 3 months; P < 0.05), which was significantly better than placebo-treated patients (34.6 Pycnogenol at 3 months vs. 69.5 placebo at 3 months; P < 0.05). Pycnogenol 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 NSAIDs was significantly reduced by 58% during Pycnogenol treatment vs. 1% with placebo treatment (P < 0.05).

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

Farid et al. (2007)[156] A randomized, double-blind, placebo-controlled, parallel-group trial was conducted in patients (n = 37; 25-65 years of age; mean age, 48 years) with primary knee OA grade 1 or 2 and pain. Patients were treated with 150 mg/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 treatments in WOMAC scores. A significant improvement was evident at 2 months, but at 3 months, Pycnogenol supplementation resulted in a "relevant improvement" of the WOMAC composite index and the subscales (except stiffness) compared with placebo (P < 0.001 for all). Compared with baseline, there were significant reductions of 43% in pain (P < 0.001), 35% in stiffness (P < 0.05), 52% in physical dysfunction (P < 0.001), and 49% in composite score (P < 0.001) with Pycnogenol treatment; there were no significant changes from baseline with placebo. Pycnogenol treatment resulted in a significant decrease in the use of pain medicine, in both the number of pills and number of days compared with baseline (P < 0.001 for both); in contrast, the placebo treatment resulted in a significant increase compared to baseline in the number of pills (P < 0.05) and number of days (P < 0.001). No AEs were reported for any study participant.

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

Cisár et al. (2008)[157] A randomized, double-blind, placebo-controlled trial was conducted in patients (n = 100; 25-65 years of age; mean age, 54 years) with primary knee OA grade 1 or 2 and pain. Patients were treated with 150 mg/day oral Pycnogenol (n = 50) or placebo (n = 50) for 3 months. Compared with baseline, pain (P < 0.001 in the text; P = 0.001 in figure 1) and the WOMAC score characterizing ability to perform daily activities (P < 0.01 in the text; P = 0.01 in figure 3) significantly improved over time in Pycnogenol-treated patients, but the improvements were not significantly different from placebo. Compared with placebo, stiffness significantly improved with Pycnogenol at 2 and 3 months (P < 0.05 for both). The overall WOMAC score in the Pycnogenol group was significantly different from placebo at 6, 8, and 12 weeks (P < 0.05 for all), but failed to reach significance at week 10. The study evaluated symptoms again 2 weeks after cessation of treatment and no relapse occurred in the Pycnogenol group. Analgesic use over the course 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 of treatment with Pycnogenol or placebo.

The study design was nearly identical to that of Farid et al.,[156] but had a larger group size.

OA Summary

All 3 studies reported subjective improvements in symptoms of knee OA in patients treated with Pycnogenol.[155-157] Together, the data indicate that the clinical response is delayed and efficacy may not be apparent until 6 to 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, and biochemical measures, such as inflammatory cytokine status locally and systemically. 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.

Hemorrhoids (Acute)

Belcaro et al. (2010)[158] A randomized, blinded, placebo-controlled trial was conducted in patients (n = 84; mean age, 49 years) with an acute episode of external hemorrhoids beginning 24 to 48 hours prior to study inclusion. It is unclear whether the study was double blinded or single blinded. Patients were divided into 4 treatment groups. Group 1 (n = 20) was treated with 300 mg/day oral Pycnogenol for 4 days followed by 150 mg/day for 3 days. Group 2 (n = 21) was treated with oral placebo for 7 days. Group 3 (n = 21) was treated with oral Pycnogenol as described for group 1 plus topical 0.5% Pycnogenol cream (the dosage of the cream was not indicated) for 7 days. Group 4 (n = 22) was treated with oral Pycnogenol as described for group 1 plus a sham cream for 7 days. Compared with the placebo group, the 3 Pycnogenol groups had significantly greater decreases in signs/symptoms ($P < 0.05$ for all). The patients treated with oral plus topical Pycnogenol had a significantly faster and better improvement than the other groups ($P < 0.05$ for all). Hemorrhoidal bleeding completely resolved in all patients taking Pycnogenol but was not resolved in the placebo-treated patients. Compared with placebo, the Pycnogenol groups had significant improvements in social quality of life ($P < 0.021$). AEs were not reported.

Pycnogenol appears to be effective for managing acute hemorrhoids. Chronic studies are needed to determine whether Pycnogenol will prevent new attacks. A study is also needed to determine whether topical Pycnogenol without oral Pycnogenol would be beneficial for acute hemorrhoids.

Cognition

Ryan et al. (2008)[90] A randomized, double-blind, placebo-controlled, matched-pair-design study was conducted in elderly participants (n = 101; 60-85 years of age; mean age, 67.8 years) without chronic disease. Participants received either 150 mg/day Pycnogenol (n = 49) or placebo (n = 52) for 3 months. Participants were matched between groups based on age, sex, BMI, premorbid IQ, intake of antioxidants, and intake of micronutrients. At 3 months, the Pycnogenol-treated group compared to the placebo-treated matched group performed significantly better on spatial working memory and quality of working memory ($P < 0.05$ for both). There were no significant improvements for other aspects of cognitive performance, namely, concentration/attention, episodic memory, and psychomotor abilities. The Pycnogenol-treated group had a significant decrease in plasma F_2-isoprostane concentrations compared with placebo ($P < 0.01$), indicating an antioxidant effect. There were no significant differences between groups in hepatic enzymes, cholesterol, triglycerides, HDL, LDL, postprandial glucose, or human growth hormone. AEs were not reported.

Although the participants were matched by intellect, the level of cognitive decline was not reported other than to state that patients with advanced stages of cognitive decline or dementia were excluded from the study. It would have been helpful to know the exact type of study population. The authors acknowledge that the statistical observations were of only moderate size and the study should be repeated with more participants and for a longer duration.

Luzzi et al. (2011)[159] A prospective, open-label, controlled study was conducted to evaluate the effect of Pycnogenol on cognitive function, attention, and mental performance in healthy students (n = 108; 18-27 years of age). Participants were treated with 100 mg/day Pycnogenol for 8 weeks (n = 53) or were followed as untreated controls (n = 55). All participants received a personal plan for sleep, diet, and exercise because improved lifestyle patterns are associated with better exam performance. They were told to avoid caffeine and alcohol before testing. At 8 weeks, the Pycnogenol group had a statistically better improvement in sustained attention compared with baseline and control; improvement in delayed recall of words compared with baseline; improvement in delayed recall of pictures compared with baseline and control; reduction in the latency to correctly respond compared with baseline; improvement in anxiety, alertness, and contentedness compared with baseline and control; improved mental flexibility compared with baseline and control; and improved planning ability compared with baseline and control ($P < 0.05$ for all). Significantly fewer Pycnogenol-treated participants compared with control participants failed the university exam ($P = 0.043$). Safety was not measured.

The authors state that this is the first study evaluating the effect of Pycnogenol on mood in healthy young adults. They conclude that anxiety, alertness, and contentedness were all significantly improved in Pycnogenol-treated participants compared with baseline and control. However, this was an open-label study comparing treatment to no treatment, so it is possible that the improvement was due to a placebo effect. As such, these results should be viewed as preliminary.

Cognition Summary

It is difficult to improve already-normal participants. One study indicates a possible role for Pycnogenol in improving cognitive function, mood, and attention in healthy people; however, the study was not properly controlled.[159] In the other study, elderly participants treated with Pycnogenol had significant improvements in memory; however, it is unclear if these were individuals with cognitive decline.[90] More rigorous studies are needed to evaluate Pycnogenol for cognition.

MANUFACTURER INFORMATION

Manufacturer: Horphag Research; Administrative Office: Avenue Louis-Casaï 71, CH-1216 Cointrin, Geneva, Switzerland. Website: www.pycnogenol.com.

Importer and distributor in the United States: Natural Health Science, Inc., 5 Marine View Plaza, Ste. 403, Hoboken, NJ 07030. Website: www.pycnogenol.com.

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CONFLICT OF INTEREST DISCLOSURE

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Table 2. Selected Clinical Trials on Pycnogenol®

	Author/Year	Subject	Design	Duration	Dosage	Preparation	Results
Chronic Venous Insufficiency (CVI), Edema, and Complications							
1.	Arcangeli, 2000 [1]	CVI	R, DB, PC n=40 with CVI (13 men, 27 women; aged 30-74 years)	2 months	300 mg/day Pycnogenol (1 capsule tid); or placebo.	100-mg capsules	Pycnogenol-treated patients had significant reductions in heaviness, swelling, and pain compared with placebo at day 30 (P<0.01, P<0.01, and P<0.05, respectively) and day 60 (P<0.01, P<0.01, and 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 reductions of 3%, 7%, and 18%, respectively, in placebo-treated patients (P<0.01, P<0.01, and P<0.05, respectively). In both groups, there was no apparent change in venous blood flow, measured via Doppler ultrasound.
2.	Belcaro et al., 2005 [2]	Venous ulcers	PC n=18 with severe CVI causing ulcerations (10 men and 8 women; mean age, 56.6 years)	6 weeks	[1] 150 mg/day Pycnogenol (3 capsules/day); [2]150 mg/day Pycnogenol (3 capsules/day) and topical application of 100 mg Pycnogenol powder covered with dressing and reapplied every 2 days; or [3] placebo. Standard compression stockings were supplied for all patients.	50-mg capsules	Starting at 2 weeks of treatment, oral plus local Pycnogenol treatment decreased ulcer size more efficiently than oral Pycnogenol alone and oral placebo (P<0.05 for both). At 6 weeks, microcirculation (pO2 and pCO2) was significantly improved with local and/or oral treatment (P<0.05 for both).
3.	Belcaro et al., 2017 [3]	Postpartum varicose veins	P, OL, Cm n=133 healthy women with postpartum varicose veins after the second pregnancy (mean age, 31 years)	6 months	100 mg/day Pycnogenol (2 tablets/day); or compression stockings alone.	50-mg capsules	At 6 months, the number of varicose veins and participants with edema were significantly less in the Pycnogenol group compared to the compression stockings group (P<0.05 for both). No participant in the Pycnogenol group had to stop treatment, while 35 out of 69 participants in the control group had to stop using the compression stockings or used them only irregularly.
4.	Belcaro et al., 2015a [4]	CVI	OL, Cm n=166 with symptomatic CVI awaiting surgery (89 men and 77 women; mean age, 43 years)	8 weeks	[1] 100 mg/day Pycnogenol; [2] 720 mg/day Antistax® (red vine [grape; *Vitis vinifera* var. *tinctoria*, Vitaceae] leaf extract; Sanofi; Paris, France) (2 tablets/day); or [3] compression stockings only.	100-mg Pycnogenol capsules; 360-mg Antistax tablets	Pycnogenol significantly improved microcirculatory parameters (rate of ankle swelling, resting flux, transcutaneous pO2, and morning ankle circumference) compared with baseline (P<0.05 for all) and compared-with compression stockings and Antistax (P<0.05 for all).
5.	Cesarone et al., 2005 [5]	Travel-related edema in asymptomatic individuals	R, DB, PC n=211 with mild-to-moderate thrombotic risk (mean age, 45 years; sex NR)	2 days	200 mg Pycnogenol 2-3 hours before flight (2 capsules), 200 mg Pycnogenol 6 hours later (2 capsules), and 100 mg Pycnogenol the following day (1 capsule); or placebo.	100-mg capsules	After the flight, edema score increased by 18% in the Pycnogenol-treated group and by 58% in the placebo-treated group (P<0.05). Ankle circumference increased by 6% in the Pycnogenol group and by 11% in the placebo group (P<0.05). Rate of ankle swelling increased by 36% in the Pycnogenol group and by 91% in the placebo group (P<0.05).

Table 2. Selected Clinical Trials on Pycnogenol® Continued

	Author/Year	Subject	Design	Duration	Dosage	Preparation	Results
6.	Cesarone et al., 2006a [6]	Venous micro-angiopathy	OL, C n=39 with severe CVI (21 patients treated with Pycnogenol [11 men and 10 women; aged 42-60 years; mean age, 53 years]; 18 patients in the untreated control group [age and sex NR])	8 weeks	150 mg/day Pycnogenol (3 capsules/day); or no treatment (control). Compression stockings were not used.	50-mg capsules	Blood microcirculation was improved and capillary filtration and edema decreased significantly after 2 weeks of treatment compared with baseline (P<0.05 for all), and after 8 weeks compared with the control group (P<0.05 for all).
7.	Cesarone et al., 2006b [7]	CVI	R, C n=86 with CVI (48 men, 38 women; aged 40-61 years)	8 weeks	[1] 150 mg/day Pycnogenol (3 capsules/day); [2] 300 mg/day Pycnogenol (6 capsules/day); or [3] 1000 mg/day Daflon® (a combination formula containing 450 mg diosmin and 50 mg hesperidin that is used to treat CVI; Servier; Suresnes, France) (2 tablets/day).	50-mg Pycnogenol capsules; 500-mg Daflon tablets	Compared with baseline and Daflon, after 8 weeks of treatment, both doses of Pycnogenol resulted in significantly greater improvements in CVI signs, symptoms, and microcirculatory parameters (resting flux, rate of ankle swelling, edema, subjective symptoms, pO2, and pCO2) (P<0.05 for all, except edema, P<0.001 vs baseline).
8.	Cesarone et al., 2010a [8]	CVI	R, OL, C, Cm n=98 with CVI and edema (53 men and 45 women; mean age, 48 years)	8 weeks	[1] 150 mg/day Pycnogenol (3 capsules/day); [2] elastic stockings only; or [3] 150 mg/day Pycnogenol plus elastic stockings.	50-mg capsules	Pycnogenol alone was significantly more effective than stockings alone in relieving rate of ankle swelling, resting flux, transcutaneous pO2, and clinical symptom scores (P<0.05 for all); Pycnogenol plus stockings was the most efficacious group (P<0.05 for all).
9.	Koch, 2002 [9]	CVI	R, OL, C, Cm n=40 with CVI (7 men and 33 women; aged 34-71 years)	4 weeks	360 mg Pycnogenol (3 tablets tid); or 600 mg HCSE (Venostasin® retard; Klinge Pharma GmbH; Holzkirchen, Germany; corresponding to 100 mg aescin/day) (2 capsules/day).	40-mg Pycnogenol tablets; 300-mg Venostasin capsules	Compared with HCSE, Pycnogenol produced a significantly greater decrease in heaviness, cramps, and nighttime swelling (edema) of both legs (P<0.05). Pycnogenol significantly reduced lower leg edema from baseline (P<0.01).
10.	Petrassi et al., 2000 [10]	CVI	Part 1: R, DB, PC n=20 with CVI (3 men and 17 women; mean age, 42.2 years) Part 2: OL n=20 with CVI (3 men and 17 women; mean age, 44.9 years)	2 months for each study part	300 mg Pycnogenol (1 capsule tid); or placebo.	100-mg capsules	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 Pycnogenol-treated patients. Similar findings were apparent in patients treated with OL Pycnogenol.
11.	Riccioni et al., 2004 [11]	Venous insufficiency	OL, C, Cm n=70 with CVI (22 men and 48 women; mean age, 47.5 years)	60 days	940 mg/day troxerutin with 40 mg/day Pycnogenol (2 sachets); or 1200 mg troxerutin (2 tablets bid).	Sachets with 470 mg troxerutin plus 20 mg Pycnogenol powder as instant drink (490-mg Flebil® Plus sachets); 300-mg troxerutin tablets (300-mg Flebil tablets) (Bracco; Milan, Italy)	After 60 days, there was complete absence of nocturnal cramps, itching, and pain in 96% of patients taking troxerutin/Pycnogenol (P<0.001); 80% troxerutin-treated patients reported complete symptom recovery (P<0.005). Three months after discontinuation, 88% of patients previously on Pycnogenol/troxerutin and 50% of patients who had taken troxerutin remained symptom free.
12.	Schmidtke & Schoop, 1995 [12]	Hydrostatic edema of lower limbs	R, DB, PC n=40 with venous circulation problems in their legs (22 men and 18 women; age NR)	6 days	360 mg/day Pycnogenol (Pygenol®; Horphag Research; Geneva, Switzerland); or placebo. No compression therapy during the study.	20-mg tablets	After 6 days of treatment, patients treated with Pycnogenol had a significantly lower leg volume (measured after lying down and 2 hours of sitting) compared to that of placebo-treated patients (P<0.001).

Table 2. Selected Clinical Trials on Pycnogenol® Continued

	Author/Year	Subject	Design	Duration	Dosage	Preparation	Results
Thrombosis							
13.	Belcaro et al., 2004 [13]	Venous thrombosis	R, DB, PC n=198 with a moderate to high risk for DVT or superficial vein thrombosis (age and sex NR)	2 days	200 mg Pycnogenol 2-3 hours before flight (2 capsules), 200 mg Pycnogenol 6 hours later (2 capsules), and 100 mg Pycnogenol the following day (1 capsule); or placebo.	100-mg capsules	Significantly fewer superficial vein thrombosis events were reported in the Pycnogenol group compared to the placebo group (0 vs 4, respectively; P<0.05). None of the Pycnogenol-treated participants had a DVT, while 1 participant in the placebo group had a DVT. There was a significantly lower rate of events in the treatment group compared with placebo (0% vs 5.15%, respectively; P<0.025).
14.	Errichi et al., 2011a [14]	Postthrombotic syndrome	OL, C n=156 with a single major episode of proximal DVT (66 men and 90 women; aged 35-50 years)	12 months	[1] Compression stockings; [2] 150 mg/day Pycnogenol (1 tablet tid); or [3] compression stockings plus 150 mg/day Pycnogenol (1 tablet tid).	50-mg tablets	At 6 months, all 3 treatments significantly improved edema, limb volume, and ankle circumference compared with baseline (P<0.05). Both Pycnogenol groups had significantly more improvement than the compression stockings-only group (P<0.05). The Pycnogenol plus stockings group was significantly more effective than Pycnogenol alone (P<0.05). All improvements persisted to 12 months. Pycnogenol was well-tolerated.
15.	Rodriguez et al., 2015 [15]	Nonischemic retinal vein thrombosis	P, OL n=77 with a single episode of retinal vein thrombosis (43 men and 34 women; mean age, 45 years)	9 months	[1] 100 mg/day Pycnogenol plus standard management; [2] 100 mg/day aspirin plus standard management; [3] standard management only.	50-mg capsules	Recurrent retinal vein thrombosis was observed in 17.39% of controls, 15.38% of the aspirin group, and 3.56% of the Pycnogenol group. Pycnogenol was significantly better at reducing the edema score, and resulted in better improvement of visual acuity (P<0.05).
Diabetes and Complications							
16.	Belcaro et al., 2006a [16]	Diabetic ulcers	R, OL, C n=30 with diabetic ulcers (14 men and 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 only). All groups received standard ulcer care.	50-mg capsules	Oral and/or local treatment was significantly more effective than standard compression treatment for reducing ulcer size (P<0.05 and P<0.01, respectively). Combination therapy was more effective than local or oral therapy alone. Microcirculation (pO2 and pCO2) and microvascular response (laser Doppler) were significantly improved with oral or oral plus topical treatment compared with baseline (P<0.05 for both).
17.	Cesarone et al., 2006c [17]	Diabetic microangiopathy	PC n=60 with stable diabetes and severe microangiopathy with edema (34 men and 26 women; aged 55-68 years; mean age, 59 years)	4 weeks	150 mg/day Pycnogenol (3 capsules/day); or placebo. Diabetic treatment was continued.	50-mg capsules	Pycnogenol significantly decreased capillary filtration vs baseline and control (P<0.05 for both). Venoarteriolar response significantly increased with Pycnogenol vs baseline and control (P<0.05 for both). Foot skin flux at rest significantly decreased with Pycnogenol vs baseline and control (P<0.05 for both). There was a clinically significant, rapid (5-8 days) decrease in edema in Pycnogenol-treated patients with the most severe, visible foot and ankle edema (n=14). No AEs were observed.

Table 2. Selected Clinical Trials on Pycnogenol® Continued

	Author/Year	Subject	Design	Duration	Dosage	Preparation	Results
18.	Liu et al., 2004a [18]	Type 2 diabetes	R, DB, PC n=77 with type 2 diabetes (44 men and 23 women; aged 45-66 years)	12 weeks	100 mg/day Pycnogenol (2 tablets/day); or placebo. Patients continued their antidiabetic medication.	50-mg tablets	Median fasting plasma glucose had a maximum reduction after 8 weeks of treatment (−1.97 mmol/L), which was maintained throughout the rest of the trial. Pycnogenol significantly decreased fasting plasma glucose greater than did placebo at all time intervals (P<0.01 for all); HbA1c was lowered (P<0.01) significantly but only until 1 month; and plasma endothelin-1 decreased and prostacyclin metabolites increased significantly compared with placebo (P<0.01 for both).
19.	Liu et al., 2004b [19]	Type 2 diabetes	OL n=30 with type 2 diabetes (18 men and 12 women; aged 28-64 years)	12 weeks	50, 100, 200, and 300 mg/day Pycnogenol (1 tablet/day, 2 tablets/day, 4 tablets/day, 6 tablets/day, respectively). Each dosage for 3 weeks.	50-mg tablets	There was dose-dependent lowering of fasting and postprandial blood glucose and HbA1c. There was significant lowering of postprandial blood glucose beginning at 50 mg (P<0.05). Fasting blood glucose was lowered significantly from 100 mg (P<0.05). Maximum effects were seen with 200 mg Pycnogenol.
20.	Steigerwalt et al., 2009 [20]	Early diabetic retinopathy	R, DB, PC n=46 with controlled diabetes mellitus type 2 for ≥ 4 years and a moderate degree of diabetic retinopathy (29 men and 17 women; mean age, 51.5 years)	3 months	150 mg/day Pycnogenol (1 tablet tid); or placebo.	50-mg tablets	Of the patients with moderate macular edema (n=21), Pycnogenol significantly improved visual acuity, retinal edema, retinal flow, diastolic flow relative to maximal systolic flow, and retinal thickness, compared with placebo (P<0.05 for all). Of the patients with mild macular edema (n=25), Pycnogenol significantly improved visual acuity (at 2 months only), retinal edema, retinal flow, and diastolic flow relative to maximal systolic flow, compared with placebo treatment (P<0.05 for all). No AEs were observed.
Hypertension and Complications							
21.	Belcaro et al., 2006b [21]	Antihypertensive treatment-induced edema	B, PC n=53 with edema after treatment with ACE inhibitors or the calcium antagonist nifedipine (29 men and 24 women; mean age, 47.7 years)	8 weeks	150 mg/day Pycnogenol (3 capsules/day); or placebo.	50-mg capsules	There was significant lowering of abnormal capillary filtration in Pycnogenol-treated patients medicated with nifedipine or ACE inhibitors compared with baseline and placebo (P<0.05 for all). No significant effects were seen with placebo.
22.	Cesarone et al., 2010b [22]	Hypertension-associated kidney disease	OL, C n=55 with hypertension who were symptomatic for cardiovascular disease and had altered kidney function (34 men and 21 women; mean age, 53.5 years)	6 months	10 mg/day ramipril (2 tablets/day); or 10 mg/day ramipril (2 tablets/day) plus 150 mg/day Pycnogenol (3 tablets/day).	50-mg Pycnogenol tablets; 5-mg ramipril	Ramipril was effective for all parameters compared to baseline. Ramipril plus Pycnogenol was significantly more effective than ramipril alone in decreasing diastolic BP (P<0.05), heart rate (P<0.05), serum creatinine (P<0.05), leukocyte count (P<0.05), CRP (P<0.05), and 24-hour urinary albumin excretion (P=0.002), and increasing kidney blood flow and perfusion (P<0.05). Pycnogenol was well-tolerated.

Table 2. Selected Clinical Trials on Pycnogenol® Continued

	Author/Year	Subject	Design	Duration	Dosage	Preparation	Results
23.	Hosseini et al., 2001a [23]	Mild hypertension	R, DB, PC, CO n=11 with systolic BP of 140-159 mmHg and/or diastolic BP of 90-99 mmHg (7 men and 4 women; mean age, 50 years)	16 weeks	200 mg/day Pycnogenol (2 capsules bid); or placebo.	50-mg capsules	Systolic BP decreased from a mean of 140 mmHg to 133 mmHg after 8 weeks of Pycnogenol treatment. The decrease was significantly more than that of placebo treatment (P<0.05). Pycnogenol was less effective in patients with BP < 140 mmHg. Decrease of diastolic BP did not reach significance. Thromboxane levels decreased from baseline with Pycnogenol (P<0.05).
24.	Liu et al., 2004c [24]	Assess whether Pycnogenol can reduce dose of nifedipine used to treat hypertension	R, DB, PC, PG n=58 with hypertension (33 men and 25 women; mean age, 57 years)	12 weeks	100 mg/day Pycnogenol (2 tablets/day); or placebo. All patients were given ≥ 20 mg of sustained-release nifedipine (Shanghai Pharmaceuticals Co., Ltd.; Shanghai, China) (dose adjusted in 5-mg increments until stable BP reached).	50-mg tablets	Supplementation with Pycnogenol significantly reduced the dose of nifedipine needed to normalize BP compared with placebo (P<0.001). Pycnogenol-treated patients had a significantly greater increase in 6-keto-prostaglandin F1α values than placebo-treated patients (12% vs 8% increase, respectively; P<0.05), which shows significant improvement in endothelial function.
25.	Stuard et al., 2010 [25]	Hypertension with metabolic syndrome-associated kidney disease	OL, C n=58 with hypertension, metabolic syndrome, and early kidney function impairment (31 men and 27 women; mean age, 58.5 years)	6 months	10 mg/day ramipril (2 tablets/day); or 10 mg/day ramipril (2 tablets/day) plus 150 mg/day Pycnogenol (3 tablets/day).	50-mg Pycnogenol tablets; 5-mg ramipril tablets	Ramipril plus Pycnogenol was significantly more effective than ramipril alone for decreasing systolic and diastolic BP, fasting glucose, HbA1c, urinary albumin, serum creatinine, CRP, and fibrinogen, and improving kidney blood flow and perfusion (P<0.05 for all). Pycnogenol was well-tolerated.
26.	Zibadi et al., 2008 [26]	Hypertension with non-insulin-dependent type 2 diabetes	R, DB, PC n=48 with non-insulin-dependent type 2 diabetes and hypertension (treated with ACE inhibitors) (27 men and 21 women; mean age, 59.5 years)	12 weeks	125 mg/day Pycnogenol (1 tablet 5x/day); or placebo.	25-mg tablets	Significantly more Pycnogenol-treated patients (58.3%) vs placebo-treated patients (20.8%) reduced their dose of BP medication by 50% (P<0.05). Pycnogenol-treated patients vs placebo-treated patients had significant reductions in plasma endothelin-1 (P<0.001), mean HbA1c (P<0.05), fasting plasma glucose (P<0.0001), LDL cholesterol (P<0.001), and urinary albumin (P<0.05, at 8 weeks only). AEs were NR.
Coronary Artery Disease							
27.	Enseleit et al., 2012 [27]	Endothelial function	DB, PC, CO n=23 with stable coronary artery disease receiving optimal standard therapy (19 men and 4 women; aged 49-73 years)	8 weeks	200 mg/day Pycnogenol; or placebo.	NR	FMD significantly increased with Pycnogenol treatment vs placebo treatment (P<0.0001). 15-F2t-isoprostanes significantly decreased after Pycnogenol treatment but not after placebo treatment (P=0.012). There were no significant changes between groups in BP, markers of inflammation, or platelet adhesion.

Table 2. Selected Clinical Trials on Pycnogenol® Continued

	Author/Year	Subject	Design	Duration	Dosage	Preparation	Results
28.	Hu et al., 2015 [28]	Endothelial function	OL, P n=32 with borderline hypertension, n=30 with borderline hyperglycemia, n=31 with borderline hyperlipidemia, and n=31 untreated controls	12 weeks	[1] 150 mg/day Pycnogenol plus diet and exercise modification; [2] diet and exercise modification only; or [3] no treatment.	NR	With Pycnogenol, FMD and flux increased at 8 and 12 weeks (P<0.05 vs baseline). No effects were found in controls or normal participants; however, there was no significant difference between Pycnogenol and control. Pycnogenol significantly normalized BP in participants with borderline hypertension (P<0.05), reduced cholesterol levels in participants with borderline hyperlipidemia (P<0.05), and improved fasting glucose in participants with borderline hyperglycemia (P<0.05). No AEs were observed during the study period.
Metabolic Syndrome							
29.	Belcaro et al., 2013a [29]	Asymptomatic metabolic syndrome	OL, C n=130 with all 5 risk factors of metabolic syndrome (64 men and 66 women; aged 45-55 years)	6 months	150 mg/day Pycnogenol (3 tablets/day); or no treatment. All patients received diet and weight management programs.	50-mg tablets	There were significant improvements in the Pycnogenol group vs the control group in waist circumference, plasma free radicals, fasting glucose, triglyceride levels, HDL levels, and BP (P<0.05 for all). No AEs were observed. Compliance and tolerability were good. No significant changes were seen in ALT, AST, GGT, ALP, CRP, serum creatinine, blood cell count, fibrinogen, INR for prothrombin time, or hematocrit.
Asthma							
30.	Belcaro et al., 2011 [30]	Allergic asthma	OL, C n=65 with mild-to-moderate allergic asthma (house dust mite) (34 men and 31 women; aged 25-45 years)	6 months	100 mg/day Pycnogenol (1 tablet tid) plus 100-500 µg/day fluticasone propionate steroid inhalation; or 100-500 µg/day fluticasone propionate steroid inhalation only (control).	50-mg tablets	More Pycnogenol-treated patients compared with steroid-only-treated patients had an improvement in steroid dose steps (55% vs 6.3%, respectively; P=0.25). Significantly more of the steroid-only group deteriorated to a higher-dose step vs the Pycnogenol group (18.8% vs 0%, respectively; P<0.02). There was a significant improvement in the number of days with a peak expiratory flow < 80% in the Pycnogenol group vs the steroid-only group (P<0.05). Compared with baseline, the Pycnogenol group had significant improvements in nighttime awakenings, dry cough, chest tightness, wheezing, dyspnea, and daytime asthma symptoms (P<0.05 for all); the steroid-only group had no significant improvement in any of these parameters. No AEs occurred.
31.	Hosseini et al., 2001b [31]	Asthma	R, DB, PC, CO n=22 with asthma (10 men and 12 women; aged 18-60 years)	8 weeks	1 mg/lb/day Pycnogenol (maximum 200 mg/day); or placebo.	20-mg capsules	Lung function (FEV1/forced vital capacity) significantly improved with Pycnogenol compared to placebo (P=0.003). Leukotriene levels significantly decreased with Pycnogenol compared to placebo (P<0.001).
32.	Lau et al., 2004 [32]	Childhood asthma	R, DB, PC n=60 children with asthma (35 boys and 25 girls; aged 6-18 years)	3 months	1 mg/lb/day Pycnogenol in 2 divided doses; or placebo.	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 of Pycnogenol treatment compared with baseline (P<0.001). All parameters further improved after 2 and 3 months of treatment.

Table 2. Selected Clinical Trials on Pycnogenol® Continued

	Author/Year	Subject	Design	Duration	Dosage	Preparation	Results
ADHD							
33.	Trebatická et al., 2006 [33]	Childhood ADHD	R, DB, PC n=61 children with clinically diagnosed ADHD for at least 6 months (50 boys and 11 girls; aged 6-14 years)	1 month, followed by 1-month washout	1 mg/kg/day Pycnogenol; or placebo.	20-mg tablets	Pycnogenol was effective according to 2 of 4 ADHD assessments. On the Child Attention Problems Rating Scale, teachers reported significant improvements in hyperactivity and inattention compared with baseline (P<0.01) and placebo (P<0.05). After a 1-month washout period, the scores returned to baseline values. On the Conners' Teacher Rating Scale, improvement for inattention was significantly different from baseline and placebo, but not for hyperactivity. ADHD symptoms as evaluated by parents did not significantly decline compared with baseline or placebo. Psychologist assessment of visual-motor coordination and concentration revealed significant improvements compared with baseline (P=0.019) and placebo (P=0.05).
Gynecology							
34.	Errichi et al., 2011b [34]	Menopause transition	R, B, PC n=70 healthy perimenopausal women (aged 41-49 years)	8 weeks	100 mg/day Pycnogenol (1 tablet tid); or placebo.	50-mg tablets	The following symptoms were significantly improved in the Pycnogenol group vs the placebo group (P<0.05): hot flashes, bloating, irregular heartbeat, pain feeling like electric shocks, and digestive problems. The following symptoms were significantly improved in the Pycnogenol group vs baseline (P<0.05): night sweats, irregular periods, loss of libido, vaginal dryness, mood swings, fatigue, hair loss, brittle nails, difficulty concentrating, memory lapses, dizziness, weight gain, depression, anxiety, irritability, panic disorder, breast pain, headaches, joint pain, gum problems, muscle tension, itchy skin, and tingling extremities. The control group did not have any significant change in any of these symptoms. There were no AEs.
35.	Kohama & Negami, 2013 [35]	Menopause transition	R, DB, PC, PG n=170 healthy perimenopausal women (aged 42-58 years)	12 weeks	60 mg/day Pycnogenol (1 tablet tid); or placebo.	30-mg tablets	There were significant improvements in the Pycnogenol group vs the placebo group in vasomotor symptoms (P=0.036; hot flashes, sweating, cold sensation of the body and limbs, and shortness of breath), insomnia/sleeping problems (P=0.003; difficulty falling asleep, easily awaking during the night, awakening too early in the morning with the inability to return to sleep, and tired when getting up), and feeling tired and worthless (P=0.048). There were no significant changes in BP, HDL, LDL, triglycerides, total cholesterol, IGF-1, IGFBP-3, E2, FSH, or DHEA sulfate in either group.

Table 2. Selected Clinical Trials on Pycnogenol® Continued

	Author/Year	Subject	Design	Duration	Dosage	Preparation	Results
36.	Maia et al., 2014a [36]	Endometriosis	P, OL, C, R n=45 women with endometriosis and pelvic pain (aged 22-37 years)	3 months	[1] 75 µg/day gestodene and 30 µg/day ethinylestradiol; [2] 75 µg/day gestodene, 30 µg/day ethinylestradiol, and 100 mg/day Pycnogenol; [3] 3 mg/day drospirenone and 30 µg/day ethinylestradiol; or [4] 3 mg/day drospirenone, 30 µg/day ethinylestradiol, and 100 mg/day Pycnogenol.	50 mg Pycnogenol	All groups had a significant decrease in pain scores after 3 months of treatment (P<0.001 vs baseline); however, the reduction was significantly greater in the groups using Pycnogenol (P<0.01 for both). Most patients taking Pycnogenol with an oral contraceptive (56%) had complete resolution of pain.
37.	Maia et al., 2014b [37]	Dysmenorrhea	R, OL, C n=24 women with severe dysmenorrhea and pelvic pain who failed to respond to treatment with 21-day/7-day oral contraceptives (aged 17-38 years; mean age, 29 years)	3 months	Oral contraceptive containing 60 mg gestodene and 15 µg ethinylestradiol in a 24-day/4-day regimen alone or with 100 mg/day Pycnogenol.	Pycnogenol: Flebon® (Farmoquímica S.A.; Rio de Janeiro, Brazil); Oral contraceptive: Adoless® (Farmoquímica S.A.)	Both treatments significantly reduced pain by the end of the third cycle; however, the reduction in pain scores was significantly greater in the Pycnogenol combination group compared to the oral contraceptive-only group (P<0.0001 in the abstract; P=0.0001 in the text). A total of 27% of the patients in the Pycnogenol combination group became pain-free during the hormone-free interval, while none of the patients in the oral contraceptive-only group became pain-free. The number of bleeding days also was lower in the Pycnogenol combination group.
38.	Yang et al., 2007 [38]	Menopause transition	R, DB, PC n=200 healthy 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/day Pycnogenol (1 capsule bid); or placebo.	100-mg capsules	Compared with baseline and placebo, Pycnogenol-treated participants had significant improvements in the severity and frequency of the following climacteric symptoms: somatic problems, depression, vasomotor problems, memory/concentration, feelings of attractiveness, anxiety, sexual behavior, sleep, and menstrual problems (P<0.01 for all). Improvements were evident at 1 month.
39.	Kohama et al., 2004 [39]	Dysmenorrhea	OL n=47 women with symptoms of dysmenorrhea (aged 21-45 years)	3 complete menstrual cycles; 64 days	60 mg/day Pycnogenol (1 capsule bid).	30-mg capsules	Compared with baseline, abdominal pain scores declined after Pycnogenol intake (P<0.05 for cycle 1; P<0.01 for cycle 2). Back pain scores significantly declined only after Pycnogenol was taken over 2 menstrual cycles (P<0.01). There was no significant change in the number of days with abdominal pain.
40.	Suzuki et al., 2008[40]	Dysmenorrhea	R, DB, PC n=116 women with symptoms of menstrual pain (aged 18-48 years)	4 menstrual cycles	60 mg/day Pycnogenol (2 capsules/day); or placebo for 2 menstrual cycles.	30-mg capsules	Menstrual pain decreased more in the Pycnogenol group than in the placebo group. Compared with placebo, Pycnogenol treatment reduced both the quantity of analgesics used by patients with dysmenorrhea (4.4 pills vs 2.6 pills, respectively) and the number of days during which analgesic medication was required for dysmenorrhea (1.7 days vs 1.2 days, respectively). These effects persisted after Pycnogenol treatment ceased (P<0.05 for both). The quality-of-life assessment (SF-36) and the physical and mental component summaries of the SF-36 revealed no significant differences between groups, except for the bodily pain score (P<0.05 for Pycnogenol vs placebo).

Table 2. Selected Clinical Trials on Pycnogenol® Continued

	Author/Year	Subject	Design	Duration	Dosage	Preparation	Results
41.	Kohama et al., 2007 [41]	Endometriosis	R, OL, Cm n=58 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 (aged 21-39 years)	48 weeks Pycnogenol; 24 weeks leuprorelin, followed by 24-week washout	60 mg/day Pycnogenol (1 capsule bid); or GnRH-a therapy as injected leuprorelin acetate depot, 3.75 mg intracutaneously, 6x every 4 weeks for 24 weeks.	30-mg Pycnogenol capsules; 3.75-mg leuprorelin acetate depot injections	Treatment with Pycnogenol slowly reduced all of the following symptom scores from severe (at baseline) to moderate: menstrual pain (P<0.01 at all time points), pelvic pain (P value not significant at 4 weeks; P<0.01 at 12, 24, and 48 weeks), pelvic tenderness (P<0.05 at 4 weeks; P<0.01 at 12, 24, and 48 weeks), and pelvic induration (P<0.05 at 4 weeks; P<0.01 at 12, 24, and 48 weeks). GnRH-a therapy also reduced all scores, but did so more quickly, and lowered the scores significantly more than Pycnogenol. However, patients treated with GnRH-a had a recurrence of symptoms following discontinuation of treatment. GnRH-a suppressed menstruation during treatment and lowered estrogen levels; Pycnogenol did not. The serum marker CA-125 for endometriosis decreased in both groups.
42.	Kohama & Inoue, 2006 [42]	Pain in pregnancy	OL, C n=140 women in the third trimester of pregnancy with lower back, hip, pelvic, or calf pain (mean age, 29.8 years)	Throughout the third trimester of pregnancy until delivery	30 mg/day Pycnogenol (1 tablet/day); or no treatment (control).	30-mg tablets	After 2 and 6 weeks of Pycnogenol treatment, there was significant improvement of pain scores related to hip joint pain, lower back pain, inguinal pain, pain due to varices, and calf cramps (P<0.01 for all vs baseline). There were no significant effects in the untreated control group.
Osteoarthritis (OA)							
43.	Belcaro et al., 2008a [43]	OA	R, DB, PC n=156 with primary OA grade 1 or 2 in 1 or both knees (78 men and 78 women; mean age, 48 years)	3 months	100 mg/day Pycnogenol (2 tablets/day); or placebo.	50-mg tablets	The global WOMAC score showed a 50% decrease from baseline in OA symptoms in Pycnogenol-treated patients (P<0.05), which was significantly better than placebo treatment (P<0.05). Pycnogenol treatment resulted in a significant mean increase in muscular/walking performance compared with placebo (P<0.05). At the end of treatment, 79% of Pycnogenol-treated patients and 1% of placebo-treated patients had a decrease in edema.
44.	Cisar et al., 2008 [44]	OA	R, DB, PC n=100 with primary knee OA grade 1 or 2 and pain (32 men and 68 women; mean age, 54 years)	3 months	150 mg/day Pycnogenol (1 tablet tid); or placebo.	50-mg tablets	For Pycnogenol-treated patients, pain and the WOMAC score characterizing ability to perform daily activities were not significantly different from placebo at inclusion. However, the overall WOMAC score was significantly different between groups at 1.5, 2, and 3 months (P<0.05 for all). Compared with placebo, stiffness significantly improved with Pycnogenol at 2 and 3 months (P<0.05 for both). Use of analgesics was decreased by 38% in the Pycnogenol group and by 8% in the placebo group.

Table 2. Selected Clinical Trials on Pycnogenol® Continued

	Author/Year	Subject	Design	Duration	Dosage	Preparation	Results
45.	Farid et al., 2007 [45]	OA	R, DB, PC, PG n=37 with primary knee OA grade 1 or 2 and pain (3 men and 34 women; aged 25-65 years; mean age, 48 years)	3 months	150 mg/day Pycnogenol (1 tablet tid); or placebo.	50-mg tablets	At 3 months, there were "relevant" and significant reductions in pain (43% reduction), stiffness (35% reduction), physical dysfunction (52% reduction), and composite score (49% reduction) with Pycnogenol treatment; there were no significant changes with placebo. Pycnogenol treatment resulted in a significant decrease in the use of pain medicine, in both the number of pills and number of days compared with baseline (P<0.001 for both).
Erectile Dysfunction							
46.	Ďuračková et al., 2003 [46]	Erectile dysfunction and hypercholesterolemia	R, DB, PC n=21 men with erectile dysfunction (mean age, 46.5 years)	3 months, followed by 1-month washout	120 mg Pycnogenol (2 tablets tid); or placebo.	20-mg tablets	Erectile function score improved from moderate dysfunction to mild dysfunction after 3 months of Pycnogenol treatment. Placebo treatment did not cause an improvement.
Retinopathy							
47.	Spadea & Balestrazzi, 2001 [47]	Retinal vascular disorders	R, DB, PC n=40 with vascular disorders of the retina secondary to atherosclerosis, diabetes, hypertension, or thrombosis of the central retinal vein (age and sex unclear)	2 months	150 mg Pycnogenol (1 tablet tid); or placebo.	50-mg capsules	Pycnogenol slowed deterioration of visual acuity compared with placebo (P<0.05). [Note: After commencing the study, the authors added 20 additional patients treated with OL Pycnogenol for 3 months. They combined much of the data, which is not methodologically appropriate.]
Gingivitis							
48.	Kimbrough et al., 2002 [48]	Gingival bleeding and dental plaque	DB, PC, R n=40 dental students (20 men and 20 women; aged 22-35 years)	2 weeks	30 mg Pycnogenol (6 chewing gums daily); or control chewing gum (Trident® gum; Mondelēz International, Inc.; Deerfield, Illinois).	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 gingival bleeding, and increased plaque formation compared with baseline (P<0.05).
Dermatology							
49.	Belcaro et al., 2014a [49]	Plaque psoriasis	OL, P n=73 with moderate-to-severe plaque psoriasis (47 men and 26 women; aged 30-45 years)	12 weeks	150 mg/day Pycnogenol (1 tablet tid) plus standard care; or standard care alone (control).	50-mg tablets	The Pycnogenol group had a significantly greater decrease in the area of skin affected by psoriasis in all body regions compared with control (P<0.05). Pycnogenol significantly improved erythema, induration, and desquamation (P<0.05 for all). The Pycnogenol group had significantly greater skin hydration compared to control (P<0.05).
50.	Marini et al., 2012 [50]	Skin elasticity and hydration	OL n=20 healthy postmenopausal women (aged 55-68 years)	12 weeks	75 mg/day Pycnogenol (3 capsules/day).	25-mg Pycnogenol capsules	At 6 weeks, but not at 12 weeks, women with dry skin (n=13) had a 21% increase in hydration (P=0.02). At 6 and 12 weeks, all women had a significant increase in skin elasticity (P≤0.02).
51.	Ni et al., 2002 [51]	Hyperpigmentation (melasma)	OL n=30 women with melasma for a mean of 8 years (aged 29-59 years; mean age, 41 years)	30 days	75 mg Pycnogenol (1 tablet tid).	25-mg tablets	Pigmentary intensity and size of affected skin were significantly reduced (P<0.001 for both).

Table 2. Selected Clinical Trials on Pycnogenol® Continued

	Author/Year	Subject	Design	Duration	Dosage	Preparation	Results
52.	Saliou et al., 2001 [52]	UV light-induced erythema (sunburn)	OL n=22 fair-skinned participants (3 men and 19 women; mean age, 23.6 years)	8 weeks (4 weeks/dose)	1.10 mg/kg/day Pycnogenol for 4 weeks and then 1.66 mg/kg/day Pycnogenol for another 4 weeks.	NR	The minimal erythema dose, the dose of UV light required to induce erythema, dose-dependently and significantly increased vs baseline (P<0.05). This indicates Pycnogenol reduced the risk of sunburn.
Refer to diabetes section for study on diabetic ulcers							
Cramps and Muscular Pain							
53.	Vinciguerra et al., 2006 [53]	Muscle cramps and pain	Part 1: OL n=66 (22 normal participants with cramps ≥ 4x/week [11 men and 11 women; mean age, 38.7 years], 21 patients with venous diseases and cramps 4-6x/week [10 men and 11 women; mean age, 47.4 years], and 23 athletes with frequent cramps during exercise [12 men and 11 women; mean age, 28.4 years]) Part 2: DB, PC n=47 (25 patients with intermittent claudication and 22 patients with diabetic microangiopathy; 33 men and 14 women; mean age, 60 years)	4 weeks, followed by 1-week washout	200 mg/day Pycnogenol (two 50-mg capsules or one 100-mg capsule bid); or placebo.	50-mg capsules or 100-mg capsules	Frequency of cramps and muscle pain score decreased significantly after 4 weeks of treatment and after 1 week of discontinuation in athletes, normal participants, and patients with venous problems (P<0.05 for all). Frequency of cramps and muscle pain score decreased significantly in patients with intermittent claudication or diabetic microangiopathy after 4 weeks of treatment and 1 week of discontinuation compared with baseline (P<0.05 for all). There was no effect in placebo-treated patients.
Hemorrhoids							
54.	Belcaro et al., 2010a [54]	Acute hemorrhoids	R, B, PC n=84 with an acute episode of external hemorrhoids (47 men and 37 women; mean age, 49 years)	7 days	[1] 300 mg/day oral Pycnogenol for 4 days (6 tablets/day) followed by 150 mg/day Pycnogenol for 3 days (3 tablets/day); [2] oral placebo for 7 days; [3] oral Pycnogenol as described for [1] plus topical 0.5% Pycnogenol cream (dosage not indicated) for 7 days; or [4] oral Pycnogenol as described for [1] plus a sham cream for 7 days.	50-mg tablets	Compared with the placebo group, the 3 Pycnogenol groups had significantly greater decreases in signs/symptoms (P<0.05). The patients treated with oral plus topical Pycnogenol had a significantly faster and better improvement than the other groups (P<0.05). Hemorrhoidal bleeding completely resolved in all patients taking Pycnogenol but was not resolved in the placebo-treated patients. Compared with placebo, the Pycnogenol groups had significant improvements in social quality of life (P<0.021).
55.	Belcaro et al., 2014b [55]	Postpartum hemorrhoids	OL, C, P n=70 women with third- or fourth-degree hemorrhoids after their second pregnancy (mean age, 32 years)	6 months	4-6 tablets Pycnogenol (1 tablet/12 kg) for 1 week and then 150 mg Pycnogenol (3 tablets, 1 tablet every 8 hours) plus standard best management; or standard best management only (control).	50-mg tablets	In the third-degree hemorrhoid group, 75% of the Pycnogenol group and 56% of the control group were symptom-free at 6 months (P<0.05). In the fourth-degree hemorrhoid group, 70% of the Pycnogenol group and 36% of the control group were symptom-free at 6 months (P<0.05).

Table 2. Selected Clinical Trials on Pycnogenol® Continued

	Author/Year	Subject	Design	Duration	Dosage	Preparation	Results
Allergic Rhinitis							
56.	Wilson et al., 2010 [56]	Allergic rhinitis	R, DB, PC, P n=60 with a positive allergy response to birch pollen (21 men and 39 women; aged 18-65 years)	12 weeks (including 3-4 weeks prior to birch pollen season; n=19) or 14 weeks (including 7-8 weeks prior to birch pollen season; n=41)	100 mg Pycnogenol (1 tablet bid); or placebo.	50-mg tablets	Pycnogenol taken for more than 5 weeks before onset of birch allergy season decreased nasal and ocular symptoms compared with placebo; however, the difference was not statistically significant.
Common Cold							
57.	Belcaro et al., 2013b [57]	Common cold	C, OL, P Part 1: n=73 with first signs of a probable cold (35 men and 38 women; aged 25-70 years). Part 2: n=73 with first signs of a probable cold (35 men and 38 women; aged 25-70 years).	Part 1: Approximately 1 week (varied with duration of symptoms) Part 2: 5 days	Part 1: 100 mg Pycnogenol (1 tablet bid); or no Pycnogenol (control). Part 2: [1] 100 mg Pycnogenol (1 tablet bid) plus 200 mg/day vitamin C; [2] 100 mg Pycnogenol (1 tablet bid) plus 30 mg/day zinc gluconate; or [3] supplement containing 100 mg Pycnogenol, 30 mg zinc gluconate, and 200 mg vitamin C. All treatments were in addition to standard care.	50-mg tablets	Part 1: Days with disease were significantly decreased in the Pycnogenol group compared with control (6.5 days vs 8.2 days, respectively; P<0.05). Part 2: The tricomplex supplement was the most effective treatment at decreasing days with disease, lost days of work, and use of other on-demand treatment. There were no AEs.
Oncology							
58.	Belcaro et al., 2008b [58]	AEs associated with oncologic treatment	P, B, PC [1] n=64 post surgery for solid tumor cancer and scheduled for chemotherapy (32 men and 32 women; mean age, 50.5 years); [2] n=46 post surgery for solid tumor cancer and scheduled for radiotherapy (18 men and 28 women; mean age, 51.5 years)	2 months	150 mg/day Pycnogenol (1 tablet tid), starting the day after the first cycle of chemotherapy/radiotherapy; or placebo.	50-mg tablets	No statistical analyses were conducted. The Pycnogenol group had fewer AEs (especially nausea, vomiting, diarrhea, edema, weakness, mouth/throat soreness and ulceration, dry mouth, and dry eyes) associated with cancer treatment vs placebo.
Tinnitus							
59.	Grossi et al., 2010 [59]	Idiopathic tinnitus	P, C n=82 with mild-to-moderate idiopathic, unilateral tinnitus for ≥ 2 weeks (27 men and 55 women; aged 35-55 years)	4 weeks	[1] 150 mg/day Pycnogenol (1 tablet tid); [2] 100 mg/day Pycnogenol (1 tablet bid); or [3] no treatment (control).	50-mg tablets	Pycnogenol significantly improved diastolic and systolic flow velocity vs baseline (P<0.05), but was not significantly different from control. Pycnogenol significantly improved subjective severity of tinnitus vs control (P<0.05), with the 150-mg dose significantly more effective than the 100-mg dose (P<0.05). The 100-mg and 150-mg dose groups had a significant improvement on the tinnitus scale vs baseline (P<0.05), but not the controls.

Table 2. Selected Clinical Trials on Pycnogenol® Continued

	Author/Year	Subject	Design	Duration	Dosage	Preparation	Results
Cognition							
60.	Belcaro et al., 2014c [60]	Cognitive function, attention, and mental performance	P, OL, C n=59 healthy professionals with high oxidative stress (34 men and 25 women; aged 35-55 years)	12 weeks	150 mg/day Pycnogenol (3 tablets/day); or no treatment (control).	50-mg tablets	The Pycnogenol group performed significantly better than the control group on measures of attention, mental performance, sustained attention, memory, executive functions, mood, and cognitive function (P<0.05 for all, except mood, P<0.01).
61.	Belcaro et al., 2015b [61]	Cognitive function, attention, and mental performance	P, OL, C n=77 healthy participants with high oxidative stress (41 men and 36 women; aged 55-70 years)	12 months	100 mg/day Pycnogenol (2 capsules/day); or no treatment (control).	50-mg capsules	At 12 months, the Pycnogenol group had significant increases in attention, mental performance, sustained attention, memory, executive functions, mood, daily tasks, and the IQCODE compared with control (P<0.05 for all).
62.	Luzzi et al., 2011 [62]	Cognitive function, attention, and mental performance	OL, C n=108 healthy university students with "average" test performance (53 men and 55 women; aged 18-27 years)	8 weeks	100 mg/day Pycnogenol (2 tablets/day); or no treatment (control).	50-mg tablets	Pycnogenol vs untreated control and vs baseline significantly improved sustained attention, items recalled, pattern recognition memory, mental flexibility, planning ability, and mood (P<0.05 for all). Significantly fewer Pycnogenol-treated participants vs control participants failed the university exam (P=0.043).
63.	Ryan et al., 2008 [63]	Cognition	R, DB, PC n=101 elderly participants without chronic disease (46 men and 55 women; aged 60-85 years; mean age, 67.8 years)	3 months	150 mg/day Pycnogenol (bid, divided dose); or placebo.	50-mg tablets	At 3 months, Pycnogenol vs placebo significantly improved spatial working memory and quality of working memory (P<0.05 for both). There were no significant improvements for other aspects of cognitive performance, namely, concentration/attention, episodic memory, and psychomotor abilities. The Pycnogenol group had a significant decrease in plasma F2-isoprostane concentrations compared with placebo (P<0.01). There were no significant differences between groups in hepatic enzymes, cholesterol, triglycerides, HDL, LDL, postprandial glucose, or human growth hormone. AEs were NR.

ACE: angiotensin-converting enzyme; AEs: adverse effects; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; B: blinded; bid: twice daily; BP: blood pressure; C: controlled; CA-125: cancer antigen 125; Cm: comparative; CO: crossover; CRP: C-reactive protein; CVI: chronic venous insufficiency; DB: double blind; DHEA: dehydroepiandrosterone; DVT: deep vein thrombosis; E2: estradiol; FEV1: 1-second forced expiratory volume; FMD: flow-mediated dilatation; FSH: follicle-stimulating hormone; GGT: γ-glutamyltransferase; GnRH-a: gonadotropin-releasing hormone agonist; HbA1c: glycosylated hemoglobin; HCSE: horse chestnut (*Aesculus hippocastanum*, Sapindaceae) seed extract; HDL: high-density lipoprotein; IGF-1: insulin-like growth factor 1; IGFBP-3: IGF-binding protein 3; INR: international normalized ratio; IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly; LDL: low-density lipoprotein; NR: not reported; OA: osteoarthritis; OL: open label; P: pilot; PC: placebo controlled; pCO2: partial pressure of carbon dioxide; PG: parallel group; pO2: partial pressure of oxygen; R: randomized; SF-36: 36-item Short Form Health Survey; tid: 3 times daily; UV: ultraviolet; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

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