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## 1. Review Articles

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- Ref. 346**      A review on the broad applicability of Pycnogenol® for personalized health care, for prevention as well as treatment.  
Strong J  
French maritime pine bark extract (Pycnogenol®) and the use of health supplements in the age of personalized medicine.  
Panminerva Med 53: 1-2, 2011
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- Ref. 326**      A comprehensive review of the composition and pharmacology of Pycnogenol® as well as the published medical research.  
Maimoona A, Naeem I, Saddiqe Z, Jameel K  
A review on biological, nutraceutical and clinical aspects of French maritime pine bark extract.  
J Ethnopharmacol 133: 261-277, 2011
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- Ref. 269**      A clinical overview based on the full monograph covering published scientific and clinical research on Pycnogenol®.  
Oliff H  
Scientific and clinical monograph on Pycnogenol®.  
The American Botanical Council 2009
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- Ref. 266**      A comprehensive review of research on Pycnogenol® in the field of venous insufficiency.  
Gulati OP  
Pycnogenol®: a nutraceutical for venous health.  
Biomedical Reviews 19: 33-43, 2008
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- Ref. 261**      This review article covers the wide range of contributions of Pycnogenol® for diabetic people, such as lowering of blood glucose and helping with a majority of diabetic complications.  
Rohdewald P  
Regulation of diabetes by Pycnogenol®.  
Botanical medicine in clinical practice. (ed.) Watson, R.R., Preedy, V.R.; Wallingford, England, CABI Publishing, Ch. 62: 587-594, 2008
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- Ref. 259**      A comprehensive review of Pycnogenol®'s anti-inflammatory activity and its role for controlling diverse inflammatory disorders.  
Farid R  
Pycnogenol® in the treatment of inflammatory diseases: osteoarthritis, asthma and heart disease.  
Botanical medicine in clinical practice. (ed.) Watson RR, Preedy VR; Wallingford, England, CABI Publishing, chapter 68: 633-640, 2008
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**Ref. 258** A review of the extensive number of studies related to treatment of edema with Pycnogenol® including findings on leg swellings occurring during long haul travelling.  
 Belcaro G, Cesarone MR, Cornelli U, Rohdewald P, Ledda A, Di Renzo A, Stuard, S, Cacchio M, Vinciguerra G, Gizzi G, Pellegrini L, Dugall M, Ricci A, Ruffini I, Fano F  
 Treatment of chronic venous insufficiency and prevention of economy class syndrome.  
 Botanical medicine in clinical practice. (ed.) Watson, R.R., Preedy, V.R.; Wallingford, England, CABI Publishing, Ch. 64: 603-609, 2008

**Ref. 257** Review of Pycnogenol®'s manifold benefits for cardiovascular health.  
 Watson RR, Argüelles MC  
 Pycnogenol® and cardiovascular health.  
 Botanical medicine in clinical practice. (ed.) Watson, R.R., Preedy, V.R.; Wallingford, England, CABI Publishing, Ch. 56: 538-544, 2008

**Ref. 228** Introduction to the pathology of myocarditis and a discussion on mechanisms by which Pycnogenol® may help the heart to recover.  
 Matsumori A  
 Treatment Options in Myocarditis.  
 Herz 32: 452-456, 2007

**Ref. 210** Clinical Pharmacology of Pycnogenol® - A review.  
 Rohdewald P  
 Clinical Pharmacology of Pycnogenol®.  
 Pharma Bio World 5: 79-81, 2006

**Ref. 168** Pycnogenol® as a nutraceutical in cardiovascular health and diabetes.  
 Gulati OP  
 The Nutraceutical Pycnogenol®: Its role in cardiovascular health and blood glucose control.  
 Biomed Rev 16: 49-57, 2005

**Ref. 160** Monograph on Pycnogenol® covering pharmacological activities and clinical benefits.  
 Rohdewald P  
 Pycnogenol®, French Maritime Pine Bark Extract.  
 Encyclopedia of Dietary Supplements; Ed. Marcel Dekker, digital publisher, 545-553, 2005

**Ref. 180** Pycnogenol®'s beneficial effects in blood micro-circulation, dysmenorrheal, stiff shoulder, and pregnancy associated pain.  
 Kohama T  
 Nutritional supplements in clinical practice.  
 Progr Med 24: 1503-1510, 2004



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**Ref. 169**      **Monograph on Safety and efficacy aspects of Pycnogenol®.**  
 Blumenthal M  
 Pycnogenol® (French Maritime Pine Bark Extract) *Pinus Pinaster* Aiton subsp. *atlantica*.  
 The American Botanical Council guide to Herbs, 369-373, 2003

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**Ref. 114**      **Review of the cardiovascular health benefits of Pycnogenol®.**  
 Watson RR  
 Pycnogenol® and cardiovascular health.  
 Evid Based Integr Med 1: 27-32, 2003

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**Ref. 094**      **Summary of beneficial effects of Pycnogenol® for skin care.**  
 Schönlau F  
 The cosmeceutical Pycnogenol®.  
 J Appl Cosmetol 20: 241-246, 2002

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**Ref. 092**      **Summary of five clinical studies describing the effects of Pycnogenol® in patients with diabetic retinopathy.**  
 Schönlau F, Rohdewald P  
 Pycnogenol® for diabetic retinopathy: A review.  
 Int Ophthalmol 24: 161-171, 2002

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**Ref. 085**      **Review article on the pharmacologic activities of Pycnogenol®.**  
 Rohdewald P  
 A review of the French maritime pine bark extract (Pycnogenol®), a herbal medication with a diverse clinical pharmacology.  
 Int J Clin Pharmacol Ther 40: 158-168, 2002

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**Ref. 041**      **A review of the efficacy and safety of Pycnogenol® for treatment of venous disorders.**  
 Gulati OP  
 Pycnogenol® in venous disorders: A review.  
 Eur Bull Drug Res 7: 8-13, 1999

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**Ref. 039**      **The cardiovascular pharmacological profile of Pycnogenol®, with focus on platelet aggregation prevention is reviewed.**  
 Watson R  
 Reduction of cardiovascular disease risk factors by French Maritime Pine Bark Extract.  
 Cardiovasc Rev Rep XX: 326-329, 1999

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- Ref. 038** This article reviews the antioxidant activity of Pycnogenol® and its effects on the immune system and modulation of inducible nitric oxide synthase.  
Virgili F, Kobuchi H, Noda Y, Cossins E, Packer L  
Procyanidins from *Pinus maritima* bark: Antioxidant activity, effects on the immune system and Modulation of Nitrogen Monoxide Metabolism.  
In "Antioxidant Food Supplements in human health", ed. L. Packer, M. Hiramatsu and T. Yoshikawa, published by Academic Press, Chapter 21, pages 323-342, 1999
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- Ref. 034** An introduction to the chemistry, antioxidant activity and biologic properties of Pycnogenol®.  
Packer L, Rimbach G, Virgili F  
Antioxidant activity and biologic properties of a procyanidin-rich extract from pine (*Pinus maritima*) bark, Pycnogenol®.  
*J Free Radic Biol Med* 27: 704-724, 1999
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- Ref. 031** The history of ancient pine bark uses to the present day development of Pycnogenol®.  
Drehlsen G  
From ancient pine bark uses to Pycnogenol®  
In "Antioxidant Food Supplements in human health", ed. L. Packer, M. Hiramatsu and T. Yoshikawa, published by Academic Press, Chapter 20, pages 311-322, 1999
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## 2. Cardiovascular System

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- Ref. 349**      **CLINICAL STUDY: Pycnogenol® taken in addition to heart medications significantly enhances endothelial function in individuals who previously suffered a heart attack.**  
 Enseleit F, Sudano I, Périat D, Winnik S, Wolfrum M, Flammer AJ, Fröhlich GM, Kaiser P, Hirt A, Haile SR, Krasniqi N, Matter CM, Uhlenhut K, Högger P, Neidhart M, Lüscher TF, Ruschitzka F, Noll G  
 Effects of Pycnogenol® on endothelial function in patients with stable coronary artery disease: a double-blind, randomized, placebo-controlled, cross-over study.  
 Eur Heart J 2012 Jan 11. [Epub ahead of print]
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- Ref. 295**      **CLINICAL STUDY: Pycnogenol® reduces the disturbing “ringing” or “hissing” noise sensation in tinnitus patients which is suggested to result from an improved blood flow to the cochlea of the ears.**  
 Grossi MG, Belcaro G, Cesarone MR, Duggall M, Hosoi M, Cacchio M, Ippolito E, Bavera P  
 Improvement in cochlear flow with Pycnogenol® in patients with tinnitus: a pilot evaluation.  
 Panminerva Med 52 (suppl. 1 to No. 2): 63-67, 2010
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- Ref. 294**      **CLINICAL STUDY: Pycnogenol® in synergy with CoQ10 strengthens the heart for higher ejection fraction, lower heart rate and a significant increase of physical capacity.**  
 Belcaro G, Cesarone MR, Dugall M, Hosoi M, Ippolito E, Bavera P, Grossi MG  
 Investigation of Pycnogenol® in combination with coenzymeQ10 in heart failure patients (NYHA II/III).  
 Panminerva Med 52 (suppl. 1 to No. 2): 21-25, 2010
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- Ref. 293**      **CLINICAL STUDY: Pycnogenol® restores compromised kidney function of metabolic syndrome patients as judged by decreased urinary protein and improved blood flow to kidneys.**  
 Stuard S, Belcaro G, Cesarone MR, Ricci A, Cornelli U, Gizzi G  
 Kidney function in metabolic syndrome may be improved with Pycnogenol®.  
 Panminerva Med 52 (suppl. 1 to No. 2): 27-32, 2010
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- Ref. 291**      **Pycnogenol® protects cardiac muscle from damage resulting from diabetes in an animal model.**  
 Klimas J, Kmecova J, Jankyova S, Yaghi D, Priesolova E, Kyselova Z, Musil P, Ochodnický P, Krenek P, Kyselovic J, Matyas S  
 Pycnogenol® improves left ventricular function in streptozotocin-induced diabetic cardiomyopathy in rats.  
 Phytother Res 24: 969-974, 2010
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- Ref. 283**      **CLINICAL STUDY: Pycnogenol® taken as an adjunct to hypertensive medication improves kidney flow and function and further improves blood pressure.**  
Cesarone MR, Belcaro G, Stuard S, Schönlau F, Di Renzo A, Grossi MG, Dugall M, Cornelli U, Cacchio M, Gizzi G, Pellegrini L  
Kidney Flow and Function in Hypertension: Protective Effects of Pycnogenol® in Hypertensive Participants-A Controlled Study.  
J Cardiovasc Pharmacol Ther 15: 41-46, 2010
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- Ref. 281**      **Pycnogenol® protects the kidneys from damage caused by oxidative stress and ischemia in an animal model.**  
Ozer Sehirli A, Sener G, Ercan F  
Protective effects of Pycnogenol® against ischemia reperfusion-induced oxidative renal injury in rats.  
Ren Fail 31: 690-697, 2009
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- Ref. 274**      **Pycnogenol® improves heart function in experimentally induced heart damage in diabetic rats.**  
Klimas J, Kmecova J, Jankyova S, Yaghi D, Priesolova E, Kyselova Z, Musil P, Ochodnický P, Krenek P, Kyselovic J, Matyas S  
Pycnogenol® improves left ventricular function in streptozotocin-induced diabetic cardiomyopathy in rats.  
Phytother Res 24: 969-974, 2010
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- Ref. 257**      **Review of Pycnogenol®'s manifold benefits for cardiovascular health.**  
Watson RR, Argüelles MC  
Pycnogenol® and cardiovascular health.  
Botanical medicine in clinical practice. (ed.) Watson, R.R., Preedy, V.R.; Wallingford, England, CABI Publishing, Ch. 56: 538-544, 2008
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- Ref. 237**      **CLINICAL STUDY: Pycnogenol® given in addition to diabetic and hypertensive medication significantly further improves blood sugar and cardio-vascular risk factors and allows a majority of patients to lower anti-hypertensive medication.**  
Zibadi S, Rohdewald P, Park D, Watson RR  
Reduction of cardiovascular risk factors in subjects with Type 2 Diabetes by Pycnogenol® supplementation.  
Nutr Res 28: 315-320, 2008
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- Ref. 233** Pycnogenol® lowers platelet hyperactivity more effectively than aspirin in a type I diabetes pharmacologic model suggesting a protective effect from thrombosis in diabetes.  
Nocun M, Ulicna O, Muchova J, Durackova Z, Watala C  
French maritime pine bark extract (Pycnogenol®) reduces thromboxane generation in blood from diabetic male rats.  
Biomed Pharmacother 62: 168-172, 2007
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- Ref. 230** CLINICAL STUDY: Pycnogenol® increases endothelium-dependent vasodilation by 42%, by enhancing the synthesis of nitric oxide in young healthy men.  
Nishioka K, Hidaka T, Nakamura S, Umemura T, Jitsuiki D, Soga J, Goto C, Chayama K, Yoshizumi M, Higashi Y  
Pycnogenol®, French Maritime Pine Bark Extract, augments endothelium-dependent vasodilation in humans.  
Hypertens Res 30: 775-780, 2007
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- Ref. 229** Pycnogenol® counteracts viral infection and prevents development of virus-induced heart muscle inflammation.  
Matsumori A, Higuchi H, Shimada M  
French maritime pine bark extract inhibits viral replication and prevents development of viral myocarditis.  
J Card Fail 13: 785-791, 2007
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- Ref. 216** Pycnogenol® prevents heart failure damage in mice.  
Zibadi S, Yu Q, Rohdewald PJ, Larson DF, Watson RR  
Impact of Pycnogenol® on cardiac extracellular matrix remodeling induced by L-NAME administration to old mice.  
Cardiovasc Toxicol 7: 10-18, 2007
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- Ref. 207** Pycnogenol® shows strengthening of heart muscle cells *in vitro*.  
Hasegawa N, Kinoshita H, Mochizuki M  
Pycnogenol® increases the probability of the contraction state in chick embryonic cardiomyocytes, indicating inotropic effects.  
Phytother Res 21: 181-182, 2007
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- Ref. 187** CLINICAL STUDY: Pycnogenol® significantly lowered LDL and increased HDL in 155 menopausal women during a treatment period of 6 months.  
Yang HM, Liao MF, Zhu SY, Liao MN, Rohdewald P  
A randomized, double-blind, placebo-controlled trial on the effect of Pycnogenol® on the climacteric syndrome in peri-menopausal women.  
Acta Obstet Gynecol Scand 86: 978-985, 2007
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- Ref. 200**      **CLINICAL STUDY: Pycnogenol® reduces oedema as side effect from hypotensive medication in hypertensive subjects.**  
 Belcaro G, Cesarone MR, Ricci A, Cornelli U, Rohdewald P, Ledda A, Di Renzo A, Stuard S, Cacchio M, Vinciguerra G, Gizzi G, Pellegrini L, Dugall M, Fano F  
 Control of edema in hypertensive subjects treated with calcium antagonist (Nifedipine) or angiotensin-converting enzyme inhibitors with Pycnogenol®.  
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- Ref. 168**      **Pycnogenol® as a nutraceutical in cardiovascular health and diabetes (Review).**  
 Gulati OP  
 The Nutraceutical Pycnogenol®: its role in cardiovascular health and blood glucose control.  
 Biomed Rev 16: 49-57, 2005
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- Ref. 140**      **Pycnogenol® increases red blood cell membrane fluidity and protects erythrocytes against oxidative stress.**  
 Sionova M, Waczulikova I, Kilanczyk E, Hrcnciarova M, Bryszewska M, Klajnert B, Durackova Z  
 The effect of Pycnogenol® on the erythrocyte membrane fluidity.  
 Gen Physiol Biophys 23: 39-51, 2004
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- Ref. 117**      **CLINICAL STUDY: Pycnogenol® as an adjunct to hypotensive medication with Nifedipine improves endothelial function and allows for lowering the drug dosage.**  
 Liu X, Wei J, Tan F, Zhou S, Würthwein G, Rohdewald P  
 Pycnogenol® French maritime pine bark extract, improves endothelial function of hypertensive patients.  
 Life Sci 74: 855-862, 2004
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- Ref. 114**      **A review of published beneficial effects of Pycnogenol® for cardiovascular health.**  
 Watson RR  
 Pycnogenol® and cardiovascular health.  
 Evid Based Integrative Med 1: 27-32, 2003
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- Ref. 093**      **CLINICAL STUDY: Pycnogenol® supplementation lowered total cholesterol and LDL and increased HDL, resulting in a better atherosclerotic index.**  
 Durackova Z, Trebaticka B, Novotny V, Zitnanova I, Breza J  
 Lipid metabolism and erectile function improvement by Pycnogenol®, extract from the bark of *Pinus pinaster* in patients suffering from erectile Dysfunction - a pilot study  
 Nutr Res 23: 1189-1198, 2003
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**Ref. 090**      **CLINICAL STUDY: Pycnogenol® supplementation improves blood antioxidant capacity, lowers LDL and increases HDL cholesterol in human volunteers.**  
 Devaraj S, Vega-López S, Kaul N, Schönlau F, Rohdewald P, Jialal I  
 Supplementation with a pine bark extract rich in polyphenols increases plasma antioxidant capacity and alters plasma lipoprotein profile.  
 Lipids 37: 931-934, 2002

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**Ref. 079**      **CLINICAL STUDY: Pycnogenol® lowered LDL significantly in patients with chronic venous insufficiency while horse chestnut seed extract had no effect.**  
 Koch R  
 Comparative study of Venostasin® and Pycnogenol® in chronic venous insufficiency.  
 Phytother Res 16: 1-5, 2002

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**Ref. 080**      **CLINICAL STUDY: Pycnogenol® reduces blood pressure in hypertensive patients not taking medication.**  
 Hosseini S, Lee J, Sepulveda RT, Rohdewald P, Watson RR  
 A randomized, double-blind, placebo-controlled, prospective, 16 week crossover study to determine the role of Pycnogenol® in modifying blood pressure in mildly hypertensive patients.  
 Nutr Res 21: 1251-1260, 2001

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**Ref. 053**      **CLINICAL STUDY: Pycnogenol® inhibits smoking-induced increase of thromboxane B<sub>2</sub> levels, which explains the decreased platelet aggregation observed with Pycnogenol® in smokers.**  
 Araghi-Niknam M, Hosseini S, Larson D, Rohdewald P, Watson RR  
 Pine bark extract reduces platelet aggregation.  
 Int Med 2: 73-77, 1999

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**Ref. 043**      **CLINICAL STUDY: Pycnogenol® inhibits platelet aggregation and adhesion and improves blood micro-circulation in heart disease patients.**  
 Wang S, Tan D, Zhao Y, Gao G, Gao X, Hu L  
 The effect of Pycnogenol® on the microcirculation, platelet function and ischemic myocardium in patients with coronary artery diseases.  
 Eur Bull Drug Res 7: 19-25, 1999

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**Ref. 042**      **Pycnogenol® helps to maintain a healthy circulation through vasodilatation, anti platelet aggregation, free radical scavenging and capillary sealing effects. The role of endothelial nitric oxide (NO) is also discussed.**  
 Rohdewald P  
 Reducing the risk for stroke and heart infarction with Pycnogenol®.  
 Eur Bull Drug Res 7: 14-18, 1999

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**Ref. 036**      **CLINICAL STUDY: Pycnogenol® inhibits smoking induced platelet aggregation in dose-dependent manner in humans. The effect lasts for more than 6 days and unlike aspirin does not increase bleeding.**  
Pütter M, Grotemeyer KHM, Würthwein G, Araghi-Niknam M, Watson RR, Hosseini S, Rohdewald P  
Inhibition of smoking-induced platelet aggregation by aspirin and Pycnogenol®.  
Thromb Res 95: 155-161, 1999

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**Ref. 027**      **Pycnogenol® counteracts the constriction of blood vessels. The vaso-relaxant activity of Pycnogenol® is mediated through nitric oxide.**  
Fitzpatrick DF, Bing B, Rohdewald P  
Endothelium-dependent vascular effects of Pycnogenol®.  
J Cardiovasc Pharmacol 32: 509-515, 1998

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**Ref. 017**      **Pycnogenol® inhibits the angiotensin II converting enzyme (ACE) and produces a moderate hypotensive effect in rats.**  
Blazso G, Gaspar R, Gabor M, Rüge H-J, Rohdewald P  
ACE inhibition and hypotensive effect of procyanidinis containing extract from the bark of *Pinus pinaster* Sol.  
Pharm Pharmacol Lett 6: 8-11, 1996

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### 3. Venous Disorders

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- Ref. 337**      **CLINICAL STUDY: Pycnogenol® protects people who suffered deep vein thrombosis from subsequently developing edema and recurring thrombosis over a 12 month investigation period.**  
Errichi BM, Belcaro G, Hosoi M, Cesarone MR, Dugall M, Feragalli B, Bavera P, Hosoi M, Zulli C, Corsi M, Ledda A, Luzzi R, Ricci A  
Prevention of post thrombotic syndrome with Pycnogenol® in a twelve month study.  
Panminerva Med 53: 21-27, 2011
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- Ref. 292**      **CLINICAL STUDY: Pycnogenol® is as effective as compression stockings for relieving signs and symptoms of chronic venous insufficiency.**  
Cesarone MR, Belcaro G, Rohdewald P, Pellegrini L, Ledda A, Vinciguerra G, Ricci A, Ippolito E, Fano F, Dugall M, Cacchio M, Di-Renzo A, Hosoi M, Stuard S, Corsi M  
Improvement of signs and symptoms of chronic venous insufficiency and microangiopathy with Pycnogenol®: A prospective, controlled study.  
Phytomedicine 17: 835-839, 2010
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- Ref. 280**      **CLINICAL STUDY: Pycnogenol® treatment lowers pain and bleeding in acute haemorrhoids and improves recovery.**  
Belcaro G, Cesarone MR, Errichi B, Di Renzo A, Grossi MG, Ricci A, Dugall M, Cornelli U, Cacchio M, Rohdewald P  
Pycnogenol® Treatment of Acute Hemorrhoidal Episodes.  
Phytother Res 24: 438-444, 2010
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- Ref. 258**      **A review of the extensive number of studies related to treatment of edema with Pycnogenol® including findings on leg swellings occurring during long haul travelling.**  
Belcaro G, Cesarone MR, Cornelli U, Rohdewald P, Ledda A, Di Renzo A, Stuard, S, Cacchio M, Vinciguerra G, Gizzi G, Pellegrini L, Dugall M, Ricci A, Ruffini I, Fano F  
Treatment of chronic venous insufficiency and prevention of economy class syndrome.  
Botanical medicine in clinical practice. (ed.) Watson, R.R., Preedy, V.R.; Wallingford, England, CABI Publishing, Ch. 64: 603-609, 2008
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- Ref. 206**      **CLINICAL STUDY: Pycnogenol® provides relief in venous microangiopathy.**  
Cesarone MR, Belcaro G, Rohdewald P, Pellegrini L, Ledda A, Vinciguerra G, Ricci A, Gizzi G, Ippolito E, Fano F, Dugall M, Acerbi G, Cacchio M, Di Renzo A, Hosoi M, Stuard S, Corsi M  
Rapid Relief of Signs/Symptoms in Chronic Venous Microangiopathy With Pycnogenol®: A Prospective, Controlled Study.  
Angiology 57: 569-576, 2006
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**Ref. 200**      **CLINICAL STUDY: Pycnogenol® reduces oedema, a common side effect of chronic treatment with anti-hypertensive medication.**  
 Belcaro G, Cesarone MR, Ricci A, Cornelli U, Rohdewald P, Ledda A, Di Renzo A, Stuard S, Cacchio M, Vinciguerra G, Gizzi G, Pellegrini L, Dugall M, Fano F  
 Control of Edema in Hypertensive Subjects Treated With Calcium Antagonist (Nifedipine) or Angiotensin-Converting Enzyme Inhibitors with Pycnogenol®.  
 Clin Appl Thromb Hemost 12: 440-444, 2006

**Ref. 195**      **CLINICAL STUDY: Pycnogenol® accelerates healing of diabetic ulcers.**  
 Belcaro G, Cesarone MR, Errichi BM, Ledda A, Di Renzo A, Stuard S, Dugall M, Pellegrini L, Gizzi G, Rohdewald P, Ippolito E, Ricci A, Cacchio M, Cipollone G, Ruffini I, Fano F, Hosoi M  
 Diabetic Ulcers: Microcirculatory Improvement and Faster Healing with Pycnogenol®.  
 Clin Appl Thromb Hemost 12: 318-323, 2006

**Ref. 182**      **CLINICAL STUDY: Pycnogenol® demonstrates superior activity versus Daflon® in treatment of chronic venous insufficiency in a comparative clinical study.**  
 Cesarone MR, Belcaro G, Rohdewald P, Pellegrini L, Ledda A, Vinciguerra G, Ricci A, Gizzi G, Ippoliti E, Fano F, Dugall M, Acerbi G, Cacchio M, Di Renzo A, Hosoi M, Stuard S, Corsi M  
 Comparison of Pycnogenol® and Daflon® in Treating Chronic Venous Insufficiency: A Prospective, Controlled Study.  
 Clin Appl Thromb Hemost 12: 205-212, 2006

**Ref. 172**      **CLINICAL STUDY: Ulcers of the lower legs heal faster after oral plus topical application of Pycnogenol®.**  
 Belcaro G, Cesarone MR, Errichi BM, Ledda A, Di Renzo A, Stuard S, Dugall M, Pellegrini L, Rohdewald P, Ippolito E, Ricci A, Cacchio M, Ruffini I, Fano F, Hosoi M  
 Venous Ulcers: Microcirculatory Improvement and Faster Healing with Local Use of Pycnogenol®.  
 Angiology 56: 699-705, 2005

**Ref. 151**      **CLINICAL STUDY: Pycnogenol® effectively counteracts ankle swellings occurring during long-haul travelling in a double-blind, placebo-controlled study.**  
 Cesarone MR, Belcaro G, Rohdewald P, Pellegrini L, Ippolito E, Scoccianti M, Ricci A, Dugall M, Cacchio M, Ruffini I, Fano F, Acerbi G, Vinciguerra MG, Bavera P, Di Renzo A, Errichi BM, Mucci F  
 Prevention of edema in long flights with Pycnogenol®.  
 Clin Appl Thromb Hemost 11: 289-294, 2004



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- Ref. 134**      **CLINICAL STUDY: Pycnogenol® prevents thrombosis and thrombophlebitis on long-haul flights.**  
Belcaro G, Cesarone MR, Rohdewald P, Ricci A, Ippolito E, Dugall M, Griffin M, Ruffini I, Acerbi G, Vinciguerra MG, Bavera P, Di Renzo A, Errichi BM, Cerritelli F  
Prevention of venous thrombosis and thrombophlebitis in long-haul flights with Pycnogenol®.  
Clin Appl Thromb Hemost 10: 373-377, 2004
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- Ref. 112**      **CLINICAL STUDY: Addition of Pycnogenol® to troxerutin significantly enhances the efficacy of chronic venous insufficiency treatment and prolongs symptom relief.**  
Riccioni C, Sarcinella R, Izzo A, Palermo G, Liguori L  
Efficacia della troxerutina associata al Pycnogenol® nel trattamento farmacologico dell'insufficienza venosa.  
Minerva Cardioangiol 52: 43-48, 2004
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- Ref. 116**      **CLINICAL STUDY: Pycnogenol® in combination with nattokinase prevents deep vein thrombosis during long-haul flights.**  
Cesarone MR, Belcaro G, Nicolaidis AN, Ricci A, Geroulakos G, Ippolito E, Brandolini R, Vinciguerra G, Dugall M, Griffin M, Ruffini I, Acerbi G, Corsi M, Riordan N, Stuard S, Bavera P, Di Renzo A, Kenyon J, Errichi BM  
Prevention of venous thrombosis in long-haul flights with Flite Tabs: The Lonflit- Flite randomized controlled trial.  
Angiology 54: 531-539, 2003
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- Ref. 079**      **CLINICAL STUDY: Pycnogenol® demonstrated higher efficacy for treatment of venous insufficiency than horse chestnut seed extract in a clinical trial.**  
Koch R  
Comparative study of Venostasin® and Pycnogenol® in chronic venous insufficiency.  
Phytother Res 16: 1-5, 2002
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- Ref. 067**      **CLINICAL STUDY: Pycnogenol® provides significant symptoms relief from chronic venous insufficiency symptoms.**  
Petrassi C, Mastromarino A, Spartera C  
Pycnogenol® in chronic venous insufficiency.  
Phytomed 7: 383-388, 2000
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- Ref. 066**      **CLINICAL STUDY: Pycnogenol® significantly improves chronic venous insufficiency and relieves disappearance of symptoms of chronic venous insufficiency.**  
Arcangeli P  
Pycnogenol® in chronic venous insufficiency.  
Fitoterapia 71: 236-244, 2000
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- Ref. 041**      Review article: Describes efficacy and safety profile of Pycnogenol® in treating venous disorders in humans. Mechanisms of reducing oedema are also discussed.  
Gulati OP  
Pycnogenol® in venous disorders: A review.  
Eur Bull Drug Res 7: 8-13, 1999
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- Ref. 009**      Pycnogenol® increases the pathologically low capillary wall resistance. Pycnogenol® is shown to be the most potent among other bioflavonoids tested for strengthening capillary walls to decrease capillary filtration.  
Gabor M, Engi E, Sonkodi S  
Die Kapillarwandresistenz und ihre Beeinflussung durch wasserlösliche Flavonderivate bei spontan hypertonen Ratten.  
Phlebologie 22: 178-182, 1993
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- Ref. 334** In pharmacological experiments Pycnogenol® is demonstrated to protect renal cells from glucose damage in a diabetic nephropathy model.  
Kim YJ, Kim YA, Yokozawa T  
Pycnogenol® modulates apoptosis by suppressing oxidative stress and inflammation in high glucose-treated renal tubular cells.  
Food Chem Toxicol 49: 2196-2201, 2011
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- Ref. 308** Pycnogenol® provides antioxidant protective effects to the liver in an animal diabetes model.  
Parveen K, Khan MR, Mujeeb M, Siddiqui WA  
Protective effects of Pycnogenol® on hyperglycemia-induced oxidative damage in the liver of type 2 diabetic rats.  
Chem Biol Interact 186: 219 -227, 2010
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- Ref. 300** Pycnogenol® is shown in an in vitro model to facilitate better glucose uptake by fat cells which suggests anti-diabetic benefits.  
Lee HH, Kim K-J, Lee OH, KJ, Lee BY  
Effect of Pycnogenol® on glucose transport in mature 3T3-L1 adipocytes.  
Phytother Res 24: 1242-1249, 2010
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- Ref. 293** **CLINICAL STUDY: Pycnogenol® improves kidney function of metabolic syndrome patients as judged by lowered urinary albumins and improved kidney perfusion.**  
Stuard S, Belcaro G, Cesarone MR, Ricci A, Cornelli U, Gizzi G  
Kidney function in metabolic syndrome may be improved with Pycnogenol®.  
Panminerva Med 52 (suppl. 1 to No. 2): 27-32, 2010
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- Ref. 288** Pycnogenol® improves endothelial function and blood vessel morphology in an animal model.  
Rezzani R, Porteri E, De Ciuceis, C, Bonomini F, Rodella LF, Paiardi S, Boari GEM, Platto C, Pilu A, Avanzi D, Rizzoni D, Rosei EA  
Effects of melatonin and Pycnogenol® on small artery structure and function in spontaneously hypertensive rats.  
Hypertension 55: 1373-1380, 2010
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- Ref. 271**      **CLINICAL STUDY: Pycnogenol® taken at early stages of diabetic retinopathy may partially restore vision further to strengthening retinal capillaries.**  
Steigerwalt R, Belcaro G, Cesarone MR, Di Renzo A, Grossi MG, Ricci A, Dugall M, Cacchio M, Schönlau F  
Pycnogenol® improves microcirculation, retinal edema, and visual acuity in early diabetic retinopathy.  
J Ocul Pharmacol Ther 25: 537-540, 2009
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- Ref. 261**      **This review article comprises the manifold contributions of Pycnogenol® to people who have diabetes.**  
Rohdewald P  
Regulation of diabetes by Pycnogenol®.  
Botanical medicine in clinical practice. (ed.) Watson, R.R., Preedy, V.R.; Wallingford, England, CABI Publishing, Ch. 62: 587-594, 2008
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- Ref. 237**      **CLINICAL STUDY: Pycnogenol® given in addition to diabetic and hypertensive medication significantly further improves blood sugar and cardio-vascular risk factors and allows a majority of patients to lower anti-hypertensive medication.**  
Zibadi S, Rohdewald P, Park D, Watson RR  
Reduction of cardiovascular risk factors in subjects with Type 2 Diabetes by Pycnogenol® supplementation.  
Nutr Res 28: 315-320, 2008
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- Ref. 233**      **Pycnogenol® lowers platelet hyperactivity more effectively than aspirin in a type I diabetes pharmacologic model suggesting a protective effect from thrombosis in diabetes.**  
Nocun M, Ulicna O, Muchova J, Durackova Z, Watala C  
French maritime pine bark extract (Pycnogenol®) reduces thromboxane generation in blood from diabetic male rats.  
Biomed Pharmacother 62: 168-172, 2007
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- Ref. 209**      **Pycnogenol® inhibits dietary carbohydrate absorption by inhibition of alpha-glucosidase.**  
Schäfer A, Högger P  
Oligomeric procyanidins of French maritime pine bark extract (Pycnogenol®) effectively inhibit alpha-glucosidase.  
Diabetes Res Clin Pract 77: 41-46, 2007
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 Cesarone MR, Belcaro G, Rohdewald P, Pellegrini L, Ledda A, Vinciguerra G, Ricci A, Gizzi G, Ippolito E, Fano F, Dugall M, Cipollone G, Acerbi G, Cacchio M, Del Boccio G, Di Renzo A, Stuard S, Corsi M  
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- Ref. 195**      **CLINICAL STUDY: Pycnogenol® accelerates healing of diabetic ulcers.**  
 Belcaro G, Cesarone MR, Errichi BM, Ledda A, Di Renzo A, Stuard S, Dugall M, Pellegrini L, Gizzi G, Rohdewald P, Ippolito E, Ricci A, Cacchio M, Cipollone G, Ruffini I, Fano F, Hosoi M  
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- Ref. 184**      **Pycnogenol® increases anti-oxidative enzyme concentrations in the retina of rats, suggesting a lower risk for retinopathy and cataract formation.**  
 Kamuren ZT, McPeck CG, Sanders RA, Watkins JB  
 Effects of low-carbohydrate diet and Pycnogenol® treatment on retinal antioxidant enzymes in normal and diabetic rats. J Ocul Pharmacol Ther 22: 10-18, 2006
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- Ref. 156**      **Pycnogenol® either alone or in combination with other antioxidants stimulates antioxidant enzyme activities in the retina of diabetic rats.**  
 Dene BA, Maritime AC, Sanders RA, Watkins JB  
 Effects of Antioxidant Treatment on Normal and Diabetic rat retinal enzyme activities. J Ocul Pharmacol Ther 21: 28-35, 2005
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 Berryman AM, Maritim AC, Sanders RA, Watkins JB  
 Influence of treatment of Diabetic rats with combinations of Pycnogenol®, beta-carotene, and alpha-lipoic acid on parameters of oxidative stress. J Biochem Mol Toxicol 18: 345-352, 2004
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 Liu X, Wei J, Tan F, Zhou S, Würthwein G, Rohdewald P  
 Antidiabetic effect of Pycnogenol® French maritime pine bark extract in patients with diabetes type II. Life Sci, 75: 2505-2513, 2004
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- Ref. 109**      **CLINICAL STUDY:** In a dose-finding study Pycnogenol® lowers glucose levels of type II diabetic patients and improves endothelial function.  
 Liu X, Zhou H-J, Rohdewald P  
 French maritime pine bark extract Pycnogenol® dose-dependently lowers glucose in type II diabetic patients.  
 Diabetes Care 27: 839, 2004
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- Ref. 110**      Pycnogenol® inhibits *in vitro* the Maillard reaction which results in advanced glycation end products (AGE) in diabetes.  
 Zhang TM, Han CH, Han YW, Gong H, Zhang EY, Zhang Y  
 Inhibitory effect of Pycnogenol® on generation of advanced glycation end products *in vitro*.  
 Chin Pharmacol Bull 19: 437-440, 2003
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- Ref. 105**      Pycnogenol® lowers blood glucose and increases intracellular antioxidant defense mechanism in diabetic rats.  
 Maritim A, Dene BA, Sanders RA, Watkins JB  
 Effect of Pycnogenol® treatment on oxidative stress in streptozotocin-induced diabetic rats.  
 J Biochem Mol Toxicol 17: 193-199, 2003
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- Ref. 092**      **CLINICAL STUDY:** The review presents results of five clinical studies with Pycnogenol® showing the efficacy of Pycnogenol® for patients with diabetic retinopathy.  
 Schönlau F, Rohdewald P  
 Pycnogenol® for diabetic retinopathy: A review.  
 Int Ophthalmol 24: 161-171, 2002
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- Ref. 090**      **CLINICAL STUDY:** Pycnogenol® supplementation reduced blood levels of the “bad” cholesterol LDL in human volunteers.  
 Devaraj S, Vega-López S, Kaul N, Schönlau F, Rohdewald P, Jialal, I  
 Supplementation with a pine bark extract rich in polyphenols increases plasma antioxidant capacity and alters plasma lipoprotein profile.  
 Lipids 37: 931-934, 2002
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- Ref. 080**      **CLINICAL STUDY:** Pycnogenol® reduces blood pressure, as shown in a randomized, double-blind, placebo-controlled study performed in mildly hypertensive patients. Furthermore, Pycnogenol® significantly decreases the level of the vasoconstrictor factor (thromboxane) in blood of these patients.  
 Hosseini S, Lee J, Sepulveda RT, Rohdewald P, Watson RR  
 A randomized, double-blind, placebo-controlled, prospective, 16 week crossover study to determine the role of Pycnogenol® in modifying blood pressure in mildly hypertensive patients.  
 Nutr Res 21: 1251-1260, 2001
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## 5. Eye Health

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- Ref. 271**      **CLINICAL STUDY: Pycnogenol® taken at early stages of diabetic retinopathy may partially restore vision further to strengthening retinal capillaries.**  
Steigerwalt R, Belcaro G, Cesarone MR, Di Renzo A, Grossi MG, Ricci A, Dugall M, Cacchio M, Schönlau F  
Pycnogenol® improves microcirculation, retinal edema, and visual acuity in early diabetic retinopathy.  
J Ocul Pharmacol Ther 25: 537-540, 2009
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- Ref. 227**      **Pycnogenol® in combination with Lutein provides synergistic antioxidant activity for protecting retinal lipids from oxidation.**  
Nakanishi-Ueda T, Kamegawa M, Ishigaki S, Tsukahara M, Yano S, Wada K, Yasuhara H  
Inhibitory Effect of Lutein and Pycnogenol® on Lipid Peroxidation in Porcine Retinal Homogenate.  
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Effects of low-carbohydrate diet and Pycnogenol® treatment on retinal antioxidant enzymes in normal and diabetic rats.  
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Dene BA, Maritime AC, Sanders RA, Watkins JB  
Effects of Antioxidant Treatment on Normal and Diabetic rat retinal enzyme activities.  
J Ocul Pharmacol Ther 21: 28-35, 2005
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- Ref. 092**      **CLINICAL STUDY: The review contains results of 5 clinical studies with Pycnogenol® showing the efficacy of Pycnogenol® supplementation for patients with diabetic retinopathy.**  
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Int Ophthalmol 24: 161-171, 2002
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- Ref. 075**      **CLINICAL STUDY: Pycnogenol® shows beneficial effects in retinopathy.**  
Spadea L, Balestrazzi E  
Treatment of vascular retinopathies with Pycnogenol®.  
Phytother Res 15: 219-223, 2001
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**Ref. 051** Pycnogenol® protects the retina against oxidative damage more effectively than any other antioxidant tested. Pycnogenol® shows synergistic antioxidant effectiveness when combined with other antioxidants such as Coenzyme Q<sub>10</sub>.  
Chida M, Suzuki K, Nakanishi-Ueda T, Ueda T, Yasuhara H, Koide R, Armstrong D  
*In vitro* testing of antioxidants and biochemical end-points in bovine retinal tissue.  
Ophthalmic Res 31: 407-415, 1999.

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**Ref. 018** Pycnogenol® protects the retina of the eye against free radicals damage.  
Ueda T, Ueda T, Armstrong D  
Preventive effect of natural and synthetic antioxidants on lipid peroxidation in the mammalian eye.  
Ophthalmic Res 28: 184-192, 1996.

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## 6. Inflammation

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- Ref. 283**      **CLINICAL STUDY: Pycnogenol® significantly lowers the inflammatory marker CRP in hypertensive patients with chronic kidney disease.**  
 Cesarone MR, Belcaro G, Stuard S, Schönlau F, Di Renzo A, Grossi MG, Dugall M, Cornelli U, Cacchio M, Gizzi G, Pellegrini L.  
 Kidney Flow and Function in Hypertension: Protective Effects of Pycnogenol® in Hypertensive Participants--A Controlled Study.  
 J Cardiovasc Pharmacol Ther 15: 41-46, 2010
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- Ref. 272**      **CLINICAL STUDY: Pycnogenol® inhibits the generation of COX-2 and 5-LOX enzymes in pharmacological investigations of inflammatory processes in humans.**  
 Canali R, Comitato R, Schonlau F, Virgili F  
 The anti-inflammatory pharmacology of Pycnogenol® in humans involves COX-2 and 5-LOX mRNA expression in leukocytes.  
 Int Immunopharmacol 9: 1145-1149, 2009
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- Ref. 250**      **CLINICAL STUDY: Pycnogenol® significantly lowers the inflammatory marker CRP in patients with osteoarthritis, thus demonstrating its anti-inflammatory potency.**  
 Belcaro G, Cesarone MR, Errichi S, Zulli C, Errichi BM, Vinciguerra G, Ledda A, Di Renzo A, Stuard S, Dugall M, Pellegrini L, Gizzi G, Ippolito E, Ricci A, Cacchio M, Cipollone G, Ruffini I, Fano F, Hosoi M, Rohdewald P  
 Variations in C-reactive protein, plasma free radicals and fibrinogen values in patients with osteoarthritis treated with Pycnogenol®.  
 Redox Rep 13: 271-276, 2008
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- Ref. 208**      **Pycnogenol® *in vitro* study provides evidence of chemoprevention.**  
 Buz'Zard AR, Lau BHS  
 Pycnogenol® reduces Talc-induced Neoplastic Transformation in Human Ovarian Cell Cultures.  
 Phytother Res 21: 579-586, 2007
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- Ref. 185**      **CLINICAL STUDY: Pycnogenol® inhibits key triggers involved in the initiation of an inflammation in a pharmacological investigation in humans.**  
 Grimm T, Chovanova Z, Muchova J, Sumegova K, Liptakova A, Durackova Z, Högger P  
 Inhibition of NF-kappaB activation and MMP-9 secretion by plasma of human volunteers after ingestion of maritime pine bark extract (Pycnogenol®).  
 J Inflamm 3: 1-6, 2006
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- Ref. 183** Pycnogenol® protects intestinal mucosa against radiotherapy induced damage: histomorphological evidence in rats.  
 Ramos FM, Schönlau F, Novaes PD, Manzi FR, Bóscolo FN, Almeida SM  
 Pycnogenol® protects against ionizing radiation as shown in the intestinal mucosa of rats exposed to X-rays.  
 Phytother Res 20: 676-679, 2006
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- Ref. 176** Pycnogenol® non-selectively inhibits the activity of enzymes involved in pain sensation during inflammation.  
 Schäfer A, Chovanová Z, Muchová J, Sumegová K, Liptáková A, Duracková Z, Högger P  
 Inhibition of COX-1 and COX-2 activity by plasma of human volunteers after ingestion of French maritime pine bark extract (Pycnogenol®).  
 Biomed Pharmacother 60: 5-9, 2005
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- Ref. 154** Pycnogenol® significantly counteracts inflammatory damage of the colon in an experimental animal model.  
 Mochizuki M, Hasegawa N  
 Therapeutic efficacy of Pycnogenol® in experimental inflammatory bowel diseases.  
 Phytother Res 18: 1027-1028, 2004
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- Ref. 107** Matrix metalloproteinases, enzymes involved in connective tissue destruction, are potently inhibited by Pycnogenol® as well as its metabolites found in blood of humans.  
 Grimm T, Schäfer A, Högger P  
 Antioxidant activity and inhibition of matrix metalloproteinases by metabolites of maritime pine bark extract (Pycnogenol®).  
 J Free Radic Biol Med 36: 811-822, 2004
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- Ref. 074** CLINICAL STUDY: Pycnogenol® dose-dependently inhibits UV-induced erythema in humans. This effect was found to be associated to the anti-inflammatory potency of Pycnogenol®.  
 Saliou C, Rimbach G, Moini H, McLaughlin L, Hosseini S, Lee J, Watson RR, Packer L  
 Solar ultraviolet-induced erythema in human skin and nuclear factor-kappa-B-dependent gene expression in keratinocytes are modulated by French maritime pine bark extract.  
 J Free Radic Biol Med 30: 154-160, 2001
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- Ref. 068** Pycnogenol® inhibits several mechanisms related to recruitment of leukocytes to tissue which results in anti-inflammatory activity.  
 Peng Q, Wei Z, Lau BHS  
 Pycnogenol® inhibits tumor necrosis factor- $\alpha$ -induced nuclear factor kappa B activation and adhesion molecule expression in human vascular endothelial cells.  
 Cell Mol Life Sci 57: 834-841, 2000
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**Ref. 019** Pycnogenol® produces anti-inflammatory and anti-oedema effects in two different models. Topical application of Pycnogenol® gel protects the skin against UV radiation.  
Blazso G, Gabor M, Rohdewald P  
Antiinflammatory activities of procyanidin containing extracts from *Pinus pinaster* Ait. after oral and cutaneous application.  
Pharmazie 52: 380-382, 1997

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**Ref. 010** Pycnogenol® scavenges superoxide radicals *in vitro* and inhibits oedema *in vivo*. The anti-inflammatory and free radical scavenging activities are closely correlated.  
Blazso G, Gabor M, Sibbel R, Rohdewald P  
Anti-inflammatory and superoxide radical scavenging activities of a procyanidins containing extract from the bark of *Pinus pinaster* sol. and its fractions.  
Pharmarmacol Lett 3: 217-220, 1994

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## 7. Joint Health

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- Ref. 330**      **Pycnogenol® helps prevent bone demineralization in an osteoporosis animal model.**  
Takano T, Kozai Y, Kawamata R, Wakao H, Sakurai T, Kashima I  
Inhibitory effect of maritime pine bark extract (Pycnogenol®) on deterioration of bone structure in the distal femoral epiphysis of ovariectomized mice.  
Oral Radiol 27: 8-16, 2011
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- Ref. 272**      **CLINICAL STUDY: Pycnogenol® inhibits the generation of COX-2 and 5-LOX enzymes in pharmacological investigations of inflammatory processes in humans.**  
Canali R, Comitato R, Schonlau F, Virgili F  
The anti-inflammatory pharmacology of Pycnogenol® in humans involves COX-2 and 5-LOX mRNA expression in leukocytes.  
Int Immunopharmacol 9: 1145-1149, 2009
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- Ref. 250**      **CLINICAL STUDY: Pycnogenol® significantly lowers the inflammatory marker CRP in patients with osteoarthritis, thus demonstrating its anti-inflammatory potency.**  
Belcaro G, Cesarone MR, Errichi S, Zulli C, Errichi BM, Vinciguerra G, Ledda A, Di Renzo A, Stuard S, Dugall M, Pellegrini L, Gizzi G, Ippolito E, Ricci A, Cacchio M, Cipollone G, Ruffini I, Fano F, Hosoi M, Rohdewald P  
Variations in C-reactive protein, plasma free radicals and fibrinogen values in patients with osteoarthritis treated with Pycnogenol®.  
Redox Rep 13: 271-276, 2008
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- Ref. 249**      **CLINICAL STUDY: Pycnogenol® improves flexibility of osteoarthritic joints, lowers pain and allows patients to decrease their pain medication.**  
Cisar P, Jany R, Waczulikova I, Sumegova K, Muchova J, Vojtassak J, Durackova Z, Lisy M, Rohdewald P  
Effect of pine bark extract (Pycnogenol®) on symptoms of knee osteoarthritis.  
Phytother Res 22: 1087-1092, 2008
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- Ref. 223**      **CLINICAL STUDY: Pycnogenol® improves pain and mobility in osteoarthritis in 156 patients.**  
Belcaro G, Cesarone MR, Errichi S, Zulli C, Errichi BM, Vinciguerra G, Ledda A, Di Renzo A, Stuard S, Dugall M, Pellegrini L, Errichi S, Gizzi G, Ippolito E, Ricci A, Cacchio M, Cipollone G, Ruffini I, Fano F, Hosoi M, Rohdewald P  
Treatment of osteoarthritis with Pycnogenol®. The SVOS (San Valentino Osteo-Arthrosis Study). Evaluation of Signs, Symptoms, Physical Performance and Vascular Aspects.  
Phytother Res 22: 518-523, 2008
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- Ref. 188**      **CLINICAL STUDY: In osteoarthritis Pycnogenol® reduces pain and joint stiffness and decreases the required NSAID medication.**  
Farid R, Mirfeizi Z, Mirheidari M, Rezaieyazdi Z, Mansouri H, Esmaili H, Zibadi S, Rohdewald P, Watson RR  
Pycnogenol® supplementation reduces pain and stiffness and improves physical function in adults with knee osteoarthritis.  
Nutr Res 27: 692-697, 2007
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- Ref. 185**      **CLINICAL STUDY: Pycnogenol® inhibits key triggers involved in the initiation of an inflammation in a pharmacological investigation in humans.**  
Grimm T, Chovanova Z, Muchova J, Sumegova K, Liptakova A, Durackova Z, Högger P  
Inhibition of NF-kappaB activation and MMP-9 secretion by plasma of human volunteers after ingestion of maritime pine bark extract (Pycnogenol®).  
J Inflamm 3: 1-6, 2006
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- Ref. 176**      **Pycnogenol® non-selectively inhibits the activity of enzymes involved in pain sensation during inflammation in humans.**  
Schäfer A, Chovanová Z, Muchová J, Sumegová K, Liptáková A, Duracková Z, Högger P  
Inhibition of COX-1 and COX-2 activity by plasma of human volunteers after ingestion of French maritime pine bark extract (Pycnogenol®).  
Biomed Pharmacother 60: 5-9, 2005
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- Ref. 107**      **Pycnogenol® as well as its metabolites found in blood of humans potently inhibit matrix metalloproteinases, enzymes involved in cartilage destruction.**  
Grimm T, Schäfer A, Högger P  
Antioxidant activity and inhibition of matrix metalloproteinases by metabolites of maritime pine bark extract (Pycnogenol®).  
J Free Radic Biol Med 36: 811-822, 2004
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## 8. Allergy & Asthma

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- Ref. 344**      **CLINICAL STUDY: Pycnogenol® helps to deal with allergic asthma symptoms and allows for lowering medication dosage.**  
Belcaro G, Luzzi R, Cesinaro Di Rocco P, Cesarone MR, Dugall M, Feragalli B, Errichi BM, Ippolito E, Grossi MG, Hosoi M, Errichi S, Cornelli U, Ledda A, Gizzi G  
Pycnogenol® improvements in asthma management.  
Panminerva Med 53: 57-64, 2011
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- Ref. 287**      **CLINICAL STUDY: Pycnogenol® taken prior to the onset of allergen season lowers hay-fever symptoms and pollen-specific antibodies in allergic people.**  
Wilson D, Evans M, Guthrie N, Sharma, P, Baisley J, Schönlau F, Burki C  
A randomized, double blind, placebo controlled exploratory study to evaluate the potential of Pycnogenol® for improving allergic rhinitis symptoms.  
Phytother Res 24: 1115-1119, 2010
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- Ref. 270**      **In animal experiments Pycnogenol® suppressed an immediate immunoglobulin type E mediated allergic response. This suggests that Pycnogenol® would have general anti-allergic effectiveness.**  
Choi YH, Yan GH  
Pycnogenol® inhibits immunoglobulin E-mediated allergic response in mast cells.  
Phytother Res 23: 1691-1695, 2009
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- Ref. 149**      **CLINICAL STUDY: Pycnogenol® improves pulmonary functions and reduces symptoms of asthma in children.**  
Lau BHS, Riesen SK, Truong KP, Lau EW, Rohdewald P, Barreta RA  
Pycnogenol® as an adjunct in the management of childhood Asthma.  
J Asthma 41: 825-832, 2004
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- Ref. 089**      **Pycnogenol® blocks release of histamine from mast cells *in vitro* to the same extent as the antiasthmatic drug DNCG.**  
Sharma SC, Sharma S, Gulati OP  
Pycnogenol® inhibits the release of histamine from mast cells.  
Phytother Res 17: 66-69, 2003
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- Ref. 077**      **CLINICAL STUDY: Pycnogenol® reduces asthma symptoms and improves lung function of asthmatic patients in a placebo-controlled, cross-over study.**  
Hosseini S, Pishnamazi S, Sadrzadeh MH, Farid F, Farid R, Watson RR  
Pycnogenol® in the management of asthma.  
J Med Food 4: 201-209, 2001
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## 9. Fertility & the Reproductive System

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- Ref. 336**      **CLINICAL STUDY: Pycnogenol® significantly contributes to reduce signs and symptoms related to the menopausal transition period.**  
Errichi S, Bottari A, Belcaro G, Cesarone MR, Hosoi M, Cornelli U, Dugall M, Ledda A, Feragalli B  
Supplementation with Pycnogenol® improves signs and symptoms of menopausal transition.  
Panminerva Med 53: 65-70, 2011
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- Ref. 220**      **CLINICAL STUDY: Pycnogenol® significantly lowers menstrual pain and the quantity of required analgesic medication in a multi-center study with four hospitals in Japan.**  
Suzuki N, Uebaba K, Kohama T, Moniwa N, Kanayama N, Koike K  
French Maritime Pine Bark Extract Significantly Lowers the Requirement for Analgesic Medication in Dysmenorrhea. A multicenter, randomized, double-blind, placebo-controlled study.  
J Reprod Med 53: 338-346, 2008
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- Ref. 219**      **CLINICAL STUDY: Pycnogenol® reduces pain from endometriosis, shows less side effects than hormonal treatment and enabled some women to conceive.**  
Kohama T, Herai K, Inoue M  
Effect of French Maritime Pine Bark Extract on endometriosis as compared with Leuprorelin acetate.  
J Reprod Med 52: 703-708, 2007
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- Ref. 187**      **CLINICAL STUDY: Pycnogenol® improves a broad range of climacteric symptoms in a study with 200 menopausal women.**  
Yang H-M, Liao M-F, Zhu SY, Liao M-N, Rohdewald P  
A randomized, double-blind, placebo-controlled trial on the effect of Pycnogenol® on the climacteric syndrome in peri-menopausal women.  
Acta Obstet Gynecol Scand 86: 978-985, 2007
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- Ref. 174**      **CLINICAL STUDY: Pycnogenol® reduces low-back pain in late period of pregnancy.**  
Kohama T, Inoue M  
Pycnogenol® Alleviates Pain Associated with Pregnancy.  
Phytother Res 20: 232-234, 2006
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- Ref. 145**      **CLINICAL STUDY: Pycnogenol® produces analgesic effect in gynaecological disorders such as endometriosis and dysmenorrhea. It reduces menstrual cramps, abdominal pain and tenderness.**  
Kohama T, Suzuki N, Ohno S, Inoue M  
Analgesic efficacy of French maritime pine bark extract in dysmenorrhea. An open clinical trial.  
J Reprod Med 49: 828-832, 2004
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- Ref. 091**      **CLINICAL STUDY:** After treatment with Pycnogenol® increase in functionally normal sperm may allow infertile couples to forgo *in vitro* fertilization.  
Roseff SJ  
Improvement in sperm quality and function with French maritime pine tree bark extract.  
J Reprod Med 47: 821-824, 2002
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- Ref. 046**      **CLINICAL STUDY:** Pycnogenol® improves the morphology of spermatozoa. The percentage of non-deformed sperms in sub-fertile men was increased by 99% after supplementation with Pycnogenol®.  
Roseff S, Gulati R  
Improvement of sperm quality by Pycnogenol®.  
Eur Bull Drug Res 7: 33-36, 1999
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- Ref. 045**      **CLINICAL STUDY:** Pycnogenol® helps in gynaecological disorders such as endometriosis and dysmenorrhea. It reduces menstrual cramps, abdominal pain and tenderness.  
Kohama T, Suzuki N  
The treatment of gynaecological disorders with Pycnogenol®.  
Eur Bull Drug Res 7: 30-32, 1999
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## 10. Sport & Endurance

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- Ref. 230**      **CLINICAL STUDY: Pycnogenol® consumption increases vasodilatation by 42% in young healthy men, which warrants sufficient blood and oxygen supply to performing muscle.**  
Nishioka K, Hidaka T, Nakamura S, Umemura T, Jitsuiki D, Soga J, Goto C, Chayama K, Yoshizumi M, Higashi Y  
Pycnogenol®, French Maritime Pine Bark Extract, augments endothelium-dependent vasodilation in humans.  
Hypertens Res 30: 775-780, 2007
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- Ref. 189**      **CLINICAL STUDY: Pycnogenol® reduces muscular pain and cramps in athletes and in patients with vascular problems or poor blood circulation of the legs.**  
Vinciguerra G, Belcaro G, Cesarone MR, Rohdewald P, Stuard S, Ricci A, Di Renzo A, Hosoi M, Dugall M, Ledda A, Cacchio M, Acerbi G, Fano F  
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Angiology 57: 331-339, 2006
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- Ref. 044**      **CLINICAL STUDY: Pycnogenol® increases exercise endurance in recreational athletes by 21% on a treadmill.**  
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Eur Bull Drug Res 7: 26-29, 1999
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## 11. Cognitive Function

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- Ref. 345**      **CLINICAL STUDY: Pycnogenol® significantly improves memory, cognition, attention and mood in healthy students.**  
Luzzi R, Belcaro G, Zulli C, Cesarone MR, Cornelli U, Dugall M, Hosoi M, Feragalli B  
Pycnogenol® supplementation improves cognitive function, attention and mental performance in students.  
Panminerva Med 53: 75-82, 2011
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- Ref. 241**      **CLINICAL STUDY: Pycnogenol® significantly improves memory in 101 senior citizens with memory deficits and saves their poly-unsaturated fatty acids, such as from neuronal membranes, from oxidative destruction.**  
Ryan J, Croft K, Wesnes K, Stough C  
An examination of the effects of the antioxidant Pycnogenol® on cognitive performance, serum lipid profile, endocrinological and oxidative stress biomarkers in an elderly population.  
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Urinary catecholamines in children with attention deficit hyperactivity disorder (ADHD): modulation by a polyphenolic extract from pine bark (Pycnogenol®).  
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Dvorakova M, Sivonova M, Trebaticka J, Skodacek I, Waczulikova I, Muchova J, Durackova Z  
Research Article: The effect of polyphenolic extract from pine bark, Pycnogenol®, on the level of glutathione in children suffering from attention deficit hyperactivity disorder (ADHD).  
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- Ref. 204**      **CLINICAL STUDY: Pycnogenol® protects DNA against oxidation in children with Attention Deficit Hyperactivity Disorder (ADHD).**  
Chovanova Z, Muchova J, Sivonova M, Dvorakova M, Zitnanova I, Waczulikova I, Trebaticka J, Skodacek I, Durackova Z  
Effect of polyphenolic extract, Pycnogenol®, on the level of 8-oxoguanine in children suffering from attention deficit/hyperactivity disorder.  
Free Radic Res 40: 1003-1010, 2006
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**Ref. 190**      **CLINICAL STUDY:** Pycnogenol® relieves hyperactivity and improves attention in children with ADHD in a double-blind placebo controlled study.  
 Trebaticka J, Kopasova S, Hradecna Z, Cinovsky K, Skodacek I, Suba J, Muchova J, Zitnanova I, Waczulikova I, Rohdewald P, Durackova Z  
 Treatment of ADHD with French maritime pine bark extract, Pycnogenol®.  
 Eur Child Adolesc Psychiatry 15: 329-335, 2006

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 Peng QL, Buz'Zard AR, Lau BHS  
 Pycnogenol® protects neurones from amyloid β peptide-induced apoptosis.  
 Brain Res Mol Brain Res 104: 55-65, 2002

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**Ref. 069**      **Pycnogenol® produces significant reduction in vascular damage caused by β-amyloid protein. β-amyloidosis is one of the neuropathological hallmarks of Alzheimer's disease (AD). This explains the role of Pycnogenol® in reducing the risk of AD.**  
 Liu F, Lau BHS, Peng Q, Shah V  
 Pycnogenol® protects vascular endothelial cells from β-amyloid-induced injury.  
 Biol Pharm Bull 23: 735-737, 2000

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**Ref. 052**      **Pycnogenol® improves learning impairment and loss of memory, common symptoms of the ageing process.**  
 Liu F, Zhang Y, Lau BHS  
 Pycnogenol® improves learning impairment and memory deficit in senescence-accelerated mice.  
 J Anti Aging Med 2: 349-355, 1999

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**Ref. 048**      **CLINICAL STUDY: Pycnogenol® is recommended for treatment of Attention Deficit Disorder.**  
 Hanley JL  
 Attention Deficit Disorder.  
 Impact Communications Inc., Green Bay, WI, USA, 17-19, 1999

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 Heimann SW  
 Pycnogenol® for ADHD?  
 J Am Acad Child Adolesc Psychiatry 38: 357-358, 1999

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## 12. Skin Care

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- Ref. 348**      **CLINICAL STUDY: Pycnogenol® increases women’s skin elasticity and hydration which coincides with significantly elevated collagen and hyaluronic synthesis in their skin.**  
 Marini A, Grether-Beck S, Jaenicke T, Weber M, Burki C, Formann P, Brenden H, Schönlau F, Krutmann J  
 Pycnogenol® Effects on Skin Elasticity and Hydration Coincide with Increased Gene Expressions of Collagen Type I and Hyaluronic Acid Synthase in Women.  
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- Ref. 243**      **Pycnogenol® inhibits pigment formation in skin cells four times more potently than kojic acid, a compound commonly used in skin-whitening products.**  
 Kim YJ, Kang KS, Yokozawa T  
 The anti-melanogenic effect of Pycnogenol® by its anti-oxidative actions.  
 Food and Chemical Toxicol 46: 2466-2471, 2008
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- Ref. 195**      **CLINICAL STUDY: Pycnogenol® accelerates healing of diabetic ulcers in humans.**  
 Belcaro G, Cesarone MR, Errichi BM, Ledda A, Di Renzo A, Stuard S, Dugall M, Pellegrini L, Gizzi G, Rohdewald P, Ippolito E, Ricci A, Cacchio M, Cipollone G, Ruffini I, Fano F, Hosoi M  
 Diabetic Ulcers: Microcirculatory Improvement and Faster Healing with Pycnogenol®.  
 Clin Appl Thromb Hemost 12: 318-323, 2006
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- Ref. 193**      **Oral administration of Pycnogenol® is able to delay and to reduce skin cancer following UV radiation.**  
 Kyriazi M, Yova D, Rallis M, Lima A  
 Cancer chemopreventive effects of Pinus maritima bark extract on ultraviolet radiation and ultraviolet radiation -7,12 dimethylbenz(a) anthracene induced skin carcinogenesis of hairless mice.  
 Cancer Lett 237: 234-241, 2006
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- Ref. 185**      **CLINICAL STUDY: Pycnogenol® inhibits release of enzymes involved in breaking-down collagen and elastin in inflamed skin in humans.**  
 Grimm T, Chovanova Z, Muchova J, Sumegova K, Liptakova A, Durackova Z, Högger P  
 Inhibition of NF-kappaB activation and MMP-9 secretion by plasma of human volunteers after ingestion of maritime pine bark extract (Pycnogenol®).  
 J Inflamm 3: 1-6, 2006
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 Belcaro G, Cesarone MR, Errichi BM, Ledda A, Di Renzo A, Stuard S, Dugall M, Pellegrini L, Rohdewald P, Ippolito E, Ricci A, Cacchio M, Ruffini I, Fano F, Hosoi M  
 Venous Ulcers: Microcirculatory Improvement and Faster Healing with Local Use of Pycnogenol®.  
 Angiology 56: 699-705, 2005

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**Ref. 150**      **Pycnogenol® shows antimicrobial activity at very low concentration.**  
 Torras MAC, Faura CA, Schönlau F, Rohdewald P  
 Anti-microbial activity of Pycnogenol®.  
 Phytother Res 19: 647-648, 2005

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**Ref. 211**      **Beneficial effects of Pycnogenol® in wrinkles - A review article.**  
 Rona C, Vailati F, Berardesca E  
 The cosmetic treatment of wrinkles.  
 J Cosmet Dermatol 3: 26-34, 2004

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**Ref. 137**      **Evidence of percutaneous absorption of Pycnogenol® in human skin.**  
 Sarikaki V, Rallis M, Tanojo H, Panteri I, Dotsikas Y, Loukas YL, Papaioannou G, Demetzos C, Weber S, Moini H, Maibach HI, Packer L  
*In vitro* percutaneous absorption of pine bark extract (Pycnogenol®) in human skin.  
 J Toxicol Cutaneous Ocul Toxicol 23: 149-158, 2004

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**Ref. 133**      **Topically applied Pycnogenol® dose-dependently speeds-up the wound healing process and reduces scar formation.**  
 Blazso G, Gabor M, Schönlau F, Rohdewald P  
 Pycnogenol® accelerates wound healing and reduces scar formation.  
 Phytother Res 18: 579-581, 2004

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**Ref. 132**      **CLINICAL STUDY: Supplementation with Pycnogenol® in combination with vitamins, minerals improves skin smoothness and elasticity in women.**  
 Segger D, Schönlau F  
 Supplementation with Evelle® improves smoothness and elasticity in a double blind, placebo-controlled study with 62 women.  
 J Dermatolog Treat 15: 222-226, 2004

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**Ref. 111**      **Pycnogenol® applied topically after sunburn inhibits photocarcinogenesis.**  
 Sime S, Reeve VE  
 Protection from inflammation, immunosuppression and carcinogenesis induced by UV radiation in mice by topical Pycnogenol®.  
 Photochem Photobiol 79: 193-198, 2004

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**Ref. 107**      **CLINICAL STUDY: The collagen and elastin destroying enzymes are potently inhibited by Pycnogenol® as well as its metabolites prevailing in humans after oral consumption.**  
Grimm T, Schäfer A, Högger P  
Antioxidant activity and inhibition of matrix metalloproteinases by metabolites of maritime pine bark extract (Pycnogenol®).  
J Free Radic Biol Med 36: 811-822, 2004

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**Ref. 094**      **Review summarizing the beneficial effects of Pycnogenol® for skin care.**  
Schönlau F  
The cosmeceutical Pycnogenol®.  
J Appl Cosmetol 20: 241-246, 2002

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**Ref. 081**      **CLINICAL STUDY: Pycnogenol® counteracts skin hyper-pigmentation in women.**  
Ni Z, Mu Y, Gulati O  
Treatment of melasma with Pycnogenol®.  
Phytother Res 16: 567-571, 2002

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**Ref. 074**      **CLINICAL STUDY: Pycnogenol® dose-dependently inhibits UV-induced erythema in humans, demonstrating a potent anti-photoageing effect.**  
Saliou C, Rimbach G, Moini H, McLaughlin L, Hosseini S, Lee J, Watson RR, Packer L  
Solar ultraviolet-induced erythema in human skin and nuclear factor-kappa-B-dependent gene expression in keratinocytes are modulated by French maritime pine bark extract.  
J Free Radic Biol Med 30: 154-160, 2001

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**Ref. 073**      **Pycnogenol® favourably affects the gene expression profile in human keratinocytes, indicating a promising potential for improving inflammatory skin disorders such as psoriasis and dermatoses.**  
Rihn B, Saliou C, Bottin MC, Keith G, Packer L  
From ancient remedies to modern therapeutics: Pine bark uses in skin disorders revisited.  
Phytother Res 15: 76-78, 2001

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**Ref. 057**      **Pycnogenol® inhibits the production of adhesion molecules in human skin cells during inflammation which would contribute to relieving inflammatory skin disorders.**  
Bito T, Roy S, Sen CK, Packer L  
Pine bark extract Pycnogenol® down regulates IFN- $\gamma$  - induced adhesion of T cells to human keratinocytes by inhibiting inducible ICAM-1 expression.  
J Free Radic Biol Med 28: 219-227, 2000

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**Ref. 030** Pycnogenol® prolongs the lifetime of vitamin C which will contribute to higher vitamin C presence in the skin.  
 Cossins E, Lee R, Packer L  
 ESR studies of vitamin C regeneration, order of reactivity of natural source phytochemical preparations.  
 Biochem Mol Biol Int 45: 583-597, 1998

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**Ref. 026** Pycnogenol® protects  $\alpha$ -tocopherol from oxidation and extends its life-time in endothelial cells.  
 Virgili F, Kim D, Packer L  
 Procyanidins extracted from pine bark protect  $\alpha$ -tocopherol in ECV 304 endothelial cells challenged by activated RAW 264.7 macrophages: role of nitric oxide peroxynitrite.  
 FEBS Lett 431: 315-318, 1998

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**Ref. 019** Pycnogenol® produces an anti-oedema effect in two different models. Topical application of Pycnogenol® gel protects the skin against UV radiation.  
 Blazso G, Gabor M, Rohdewald P  
 Anti-inflammatory activities of procyanidin containing extracts from *Pinus pinaster* Ait. after oral and cutaneous application.  
 Pharmazie 52: 380-382, 1997

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**Ref. 009** Pycnogenol® increases pathologically low capillary wall resistance. Pycnogenol® is shown to be the most potent among other bioflavonoids tested. Pycnogenol® provides strength to capillary walls and makes them less permeable and thus contributes to anti-oedema, anti-inflammatory effects.  
 Gabor M, Engi E, Sonkodi S  
 Die Kapillarwandresistenz und ihre Beeinflussung durch wasserlösliche Flavonderivate bei spontan hypertensischen Ratten.  
 Phlebologie 22: 178-182, 1993

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**Ref. 008** Pycnogenol® dose-dependently protects the skin from ultraviolet-radiation-induced oxidative stress injury (lipid peroxidation and cytotoxicity).  
 Guochang Z  
 Ultraviolet radiation-induced oxidative stress in cultured human skin fibroblasts and antioxidant protection.  
 Bio Res Rep Univ Jyväskylä 33: 1-86, 1993

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## 13. Oral Health Care

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- Ref. 150** Pycnogenol® inhibits growth of gram-positive and negative bacteria and *candida albicans* at concentrations of 0.025%.  
Torras MAC, Faura CA, Schönlau F, Rohdewald P  
Short Communication: Antimicrobial activity of Pycnogenol®.  
Phytother Res 19: 647-648, 2005
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- Ref. 133** Local application of Pycnogenol® dose-dependently speeds-up the wound healing process and reduces scar formation.  
Blazso G, Gabor M, Schönlau F, Rohdewald P  
Pycnogenol® accelerates wound healing and reduces scar formation.  
Phytother Res 18: 579-581, 2004
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- Ref. 084** CLINICAL STUDY: Pycnogenol® administered in chewing gum reduced bleeding of the gum and reduced plaque formation on the teeth in a controlled clinical trial.  
Kimbrough C, Chun M, de la Roca G, Lau BHS  
Pycnogenol® chewing gum minimizes gingival bleeding and plaque formation.  
Phytomed 9: 410-413, 2002
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- Ref. 030** Pycnogenol® prolongs the lifetime of vitamin C more than other flavonoids.  
Cossins E, Lee R, Packer L  
ESR studies of vitamin C regeneration, order of reactivity of natural source phytochemical preparations.  
Biochem Mol Biol Int 45: 583-597, 1998
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## 14. Benefits for Travelers

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- Ref. 244**      **CLINICAL STUDY: Pycnogenol® significantly lowers the severity of a wide range of typical jet-lag symptoms of flight passengers travelling intercontinental routes.**  
Belcaro G, Cesarone MR, Steigerwalt RJ, Di Renzo A, Grossi MG, Ricci A, Stuard S, Ledda A, Dugall M, Cornelli U, Cacchio M  
Jet-lag: Prevention with Pycnogenol®. Preliminary report: evaluation in healthy individuals and in hypertensive patients.  
Minerva Cardioangiol 56(5 Suppl): 3-9, 2008
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- Ref. 151**      **CLINICAL STUDY: Pycnogenol® effectively counteracts swelling of the lower-legs and ankles of passengers during long flights in a double-blind, placebo-controlled study.**  
Cesarone MR, Belcaro G, Rohdewald P, Pellegrini L, Ippolito E, Scoccianti M, Ricci A, Dugall M, Cacchio M, Ruffini I, Fano F, Acerbi G, Vinciguerra MG, Bavera P, Di Renzo A, Errichi BM, Mucci F  
Prevention of edema in long flights with Pycnogenol®.  
Clin Appl Thromb Hemost 11: 289-294, 2004
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- Ref. 135**      **Zinopin® (a combination of Pycnogenol® and Standardized Ginger Root Extract) – Rationale of its use as Food Supplement in Traveller’s thrombosis and motion sickness.**  
Scurr JH, Gulati OP  
Review article: Zinopin®- the Rationale for its use as Food Supplement in Traveller’s thrombosis and motion sickness.  
Phytother Res 18: 687-695, 2004
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- Ref. 134**      **CLINICAL STUDY: Pycnogenol® prevents thrombosis in passengers on long haul flights in a double-blind, placebo-controlled trial with 200 participants.**  
Belcaro G, Cesarone MR, Rohdewald P, Ricci A, Ippolito E, Dugall M, Griffin M, Ruffini I, Acerbi G, Vinciguerra MG, Bavera P, Di Renzo A, Errichi BM, Cerritelli F  
Prevention of Venous Thrombosis and Thrombophlebitis in Long-Haul Flights with Pycnogenol®.  
Clin Appl Thromb Hemost 10: 373-377, 2004
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- Ref. 116**      **CLINICAL STUDY: Pycnogenol® in combination with nattokinase prevents deep vein thrombosis in long-haul flights.**  
Cesarone MR, Belcaro G, Nicolaidis AN, Ricci A, Geroulakos G, Ippolito E, Brandolini R, Vinciguerra G, Dugall M, Griffin M, Ruffini I, Acerbi G, Corsi M, Riordan N, Stuard S, Bavera P, Di Renzo A, Kenyon J, Errichi BM  
Prevention of venous thrombosis in long-haul flights with Flite Tabs: The Lonflit- Flite randomized controlled trial.  
Angiology 54: 531-539, 2003
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**Ref. 036**

**CLINICAL STUDY:** Pycnogenol® inhibits platelet aggregation in a dose-dependent manner in humans. The effect lasts for more than 6 days and unlike aspirin, it does not produce an increase in bleeding time.

Pütter M, Grotemeyer KHM, Würthwein G, Araghi-Niknam M, Watson RR, Hosseini S, Rohdewald P

Inhibition of smoking-induced platelet aggregation by Aspirin and Pycnogenol®.

Thromb Res 95: 155-161, 1999

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## 15. Immunology, Anti-Microbial & Anti-Viral Activity

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- Ref. 247** Pycnogenol® decreases HIV viral replication and T-cell interaction in cell culture experiments.  
Feng WY, Tanaka R, Inagaki Y, Saitoh Y, Chang MO, Amet T, Yamamoto N, Yamaoka S, Yoshinaka Y  
Pycnogenol®, a procyanidin-rich extract from French maritime pine, inhibits intracellular replication of HIV-1 as well as its binding to host cells.  
Jpn J Infect Dis 61: 279-285, 2008
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- Ref. 245** **CLINICAL STUDY: Pycnogenol® helps to lower a wide range of typical side-effects patients suffer from during cancer chemo- and radiotherapy.**  
Belcaro G, Cesarone MR, Genovesi D, Ledda A, Vinciguerra G, Ricci A, Pellegrini L, Gizzi G, Ippolito E, Dugall M, Cacchio M, Di Renzo A, Stuard S  
Pycnogenol® may alleviate adverse effects in oncologic treatment.  
Panminerva Med 50: 227-234, 2008
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- Ref. 236** Pycnogenol® increases phagocytosis of macrophages suggesting better defence against pathogenic infections.  
Wu TF, Hsu CY, Huang HS, Chou SP, Wu H  
Proteomic analysis of Pycnogenol® effects in RAW 264.7 macrophage reveals induction of cathepsin D expression and enhancement of phagocytosis.  
J Agric Food Chem 55: 9784-9791, 2007
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- Ref. 229** Pycnogenol® inhibits viral replication in heart muscle (myocarditis).  
Matsumori A, Higuchi H, Shimada M  
French maritime pine bark extract inhibits viral replication and prevents development of viral myocarditis.  
J Card Fail 13: 785-791, 2007
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- Ref. 228** Pycnogenol® inhibits viral replication in myocarditis.  
Matsumori A  
Treatment Options in Myocarditis.  
Herz 32: 452-456, 2007
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- Ref. 225** Pycnogenol® inhibits growth of *Helicobacter pylori* and their adherence to mucosal cells of the stomach.  
Rohdewald P, Beil W  
*In vitro* inhibition of *Helicobacter pylori* growth and adherence to gastric mucosal cells by Pycnogenol®.  
Phytother Res 22: 685-688, 2007
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- Ref. 221**      **Pycnogenol® inhibits the harmful effects of two mutagenic chemicals.**  
Krizkova L, Chovanova Z, Durackova Z, Krajcovic J  
Antimutagenic *in vitro* Activity of Plant Polyphenols: Pycnogenol® and Ginkgo biloba Extract (EGb 761).  
Phytother Res 22: 384-388, 2007
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- Ref. 208**      **Pycnogenol® reduces cancerogenesis in human ovarian cells.**  
Buzzard AR, Lau BHS  
Pycnogenol® reduces Talc-induced Neoplastic Transformation in Human Ovarian Cell Cultures.  
Phytother Res 21: 579-586, 2007
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- Ref. 150**      **Pycnogenol® shows broad anti-microbial activity *in vitro*.**  
Torras MAC, Faura CA, Schönlau F, Rohdewald P  
Antimicrobial activity of Pycnogenol®.  
Phytother Res 19: 647-648, 2005
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- Ref. 173**      **Pycnogenol® selectively kills cancerous ovarian germ cells.**  
Buzzard AR, Lau BHS  
Research article: Selective toxicity of Pycnogenol® for malignant ovarian germ cells *in vitro*.  
Int J Cancer Prev 1: 207-212, 2004
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- Ref. 111**      **Pycnogenol® applied after sunburn inhibits UV-induced suppression of immune system.**  
Sime S, Reeve VE  
Protection from inflammation, immunosuppression and carcinogenesis induced by UV radiation in mice by topical Pycnogenol®.  
Photochem Photobiol 79: 193-198, 2004
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- Ref. 102**      **Pycnogenol® consumption by mice infected with protozoan parasite provides several protective benefits.**  
Kim HC, Healey JM  
Effects of Pine bark extract administered to immunosuppressed adult mice infected with *Cryptosporidium parvum*.  
Am J Chin Med 29: 469-475, 2001
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- Ref. 095**      **Pycnogenol® activates *in vitro* macrophages to kill more effectively invading bacteria.**  
Shah V, Bayeta E, Lau BHS  
Pycnogenol® augments macrophage phagocytosis and cytokine secretion.  
Pak J Nutr 1: 196-201, 2002
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- Ref. 082** CLINICAL STUDY: Pycnogenol® shows beneficial effects in patients with lupus erythematosus.  
Stefanescu M, Matache C, Onu A, Tanaseanu S, Dragomir C, Constantinescu I, Schönlau F, Rohdewald P, Szegli G  
Pycnogenol® Efficacy in the Treatment of Systemic Lupus Erythematosus Patients.  
Phytother Res 15: 698-704, 2001
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- Ref. 059** Pycnogenol® selectively kills cancerous human mammary cells (MCF-7), without affecting the normal mammary cells (MCF-10).  
Huynh HT, Teel RW  
Selective induction of apoptosis in human mammary cancer cells (MCF-7) by Pycnogenol®.  
Anticancer Res 20: 2417-2420, 2000
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- Ref. 055** Pycnogenol® increases TNF- $\alpha$  secretion in the macrophage system in a concentration and time dependent manner indicating that it acts as modulator of the immune response in macrophages.  
Park YC, Rimbach G, Saliou C, Valacchi G, Packer L  
Activity of monomeric, dimeric, and trimeric flavonoids on NO production, TNF-alpha secretion, and NF-kappaB-dependent gene expression in RAW 264.7 macrophages.  
FEBS Lett 465: 93-97, 2000
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- Ref. 029** Pycnogenol® slows down the aging related process of decline in the activities of immune- and blood cells generating systems and restores their functions to normal.  
Liu FJ, Zhang YX, Lau BHS  
Pycnogenol® enhances immune and haemopoietic functions in senescence-accelerated mice.  
Cell Mol Life Sci 54: 1168-1172, 1998
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- Ref. 016** Pycnogenol® enhances the activity of the immune system in mice infected with a leukemia-causing retrovirus. Pycnogenol® increases the natural killer cell cytotoxicity.  
Cheshier JE, Ardestani-Kaboudanian S, Liang B, Araghi Niknam M, Chung S, Lane L, Castro A, Watson RR  
Immunomodulation by Pycnogenol® in retro-virus infected or ethanol-fed mice.  
Life Sci 58: 87-96, 1996
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## 16. Antioxidant-& Anti-Ageing Activity

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- Ref. 349**      **CLINICAL STUDY: Pycnogenol® significantly lowers oxidative stress in heart attack patients as judged from lowered blood F2-isoprostane level.**  
 Enseleit F, Sudano I, Périat D, Winnik S, Wolfrum M, Flammer AJ, Fröhlich GM, Kaiser P, Hirt A, Haile SR, Krasniqi N, Matter CM, Uhlenhut K, Högger P, Neidhart M, Lüscher TF, Ruschitzka F, Noll G  
 Effects of Pycnogenol® on endothelial function in patients with stable coronary artery disease: a double-blind, randomized, placebo-controlled, cross-over study.  
 Eur Heart J. 2012 Jan 11. [Epub ahead of print]
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- Ref. 336**      **CLINICAL STUDY: Pycnogenol® significantly reduces oxidative stress in menopausal women.**  
 Errichi S, Bottari A, Belcaro G, Cesarone MR, Hosoi M, Cornelli U, Dugall M, Ledda A, Feragalli B  
 Supplementation with Pycnogenol® improves signs and symptoms of menopausal transition.  
 Panminerva Med 53: 65-70, 2011
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- Ref. 241**      **CLINICAL STUDY: Pycnogenol® significantly decreases F2-isoprostane plasma levels in 101 senior citizens indicating that poly-unsaturated fatty acids, such as those from neuronal membranes, are saved from oxidative destruction.**  
 Ryan J, Croft K, Wesnes K, Stough C  
 An examination of the effects of the antioxidant Pycnogenol® on cognitive performance, serum lipid profile, endocrinological and oxidative stress biomarkers in an elderly population.  
 J Psychopharmacol 22: 553-562, 2008
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- Ref. 226**      **Pycnogenol® demonstrates liver protective effects, shown in animal models with acute chemical intoxication.**  
 Yang Y-S, Ahn T-H, Lee J-C, Moon C-J, Kim S-H, Jun W, Park S-C, Kim H-C, Kim J-C  
 Protective effects of Pycnogenol® on carbon tetrachloride-induced hepato-toxicity in Sprague Dawley rats.  
 Food Chem Toxicol 46: 380-387, 2008
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- Ref. 218**      **Pycnogenol® lowers oxidative stress in the liver of rats challenged with a chemical toxin.**  
 Ahn T-H, Yang Y-S, Lee J-C, Moon C-J, Kim S-H, Jun W, Park S-C, Kim J-C  
 Ameliorative Effects of Pycnogenol® on Carbon Tetrachloride-Induced Hepatic Oxidative Damage in Rats.  
 Phytother Res 21: 1015-1019, 2007
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- Ref. 187**      **CLINICAL STUDY: Pycnogenol® significantly increases total antioxidant status (TAS) in a double-blind, placebo-controlled study with 155 menopausal women.**  
Yang HM, Liao MF, Zhu SY, Liao MN, Rohdewald P  
A randomised, double-blind, placebo-controlled trial on the effect of Pycnogenol® on the climacteric syndrome in peri-menopausal women.  
Acta Obstet Gynecol Scand 86: 978-985, 2007
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- Ref. 227**      **Pycnogenol® and Lutein display synergistic antioxidant effects for prevention of lipid peroxidation.**  
Nakanishi-Ueda T, Kamegawa M, Ishigaki S, Tsukahara M, Yano S, Wada K, Yasuhara H  
Inhibitory Effect of Lutein and Pycnogenol® on Lipid Peroxidation in Porcine Retinal Homogenate.  
J Clin Biochem Nutr 38: 204-210, 2006
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- Ref. 215**      **Pycnogenol® protects liposomes from lipid peroxidation and shows synergistic protective effects with vitamin C and vitamin E.**  
Sivonova M, Zitnanova I, Horakova L, Strosova M, Muchova J, Balgavy P, Dobrota D, Durackova Z  
The Combined Effect of Pycnogenol® with Ascorbic Acid and Trolox on the Oxidation of Lipids and Proteins.  
Gen Physiol Biophys 25: 379-396, 2006
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Bors W, Michel C, Stettmaier K  
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- Ref. 051** In a comparative study Pycnogenol® shows more potent antioxidant activity than vitamin C and E,  $\alpha$ -lipoic acid, Co-Q<sub>10</sub> and grape seed. In combination Pycnogenol® enhances the effects of other antioxidants like Coenzyme Q<sub>10</sub>.  
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- Ref. 030** Pycnogenol® protects vitamin C from oxidation and recycles oxidized vitamin C more effectively than other flavonoids.  
Cossins E, Lee R, Packer L  
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- Ref. 029** Pycnogenol® slows down the aging related process of decline in activities of immune- and blood cells generating systems and restores their functions to normal.  
Liu FJ, Zhang YX, Lau BHS  
Pycnogenol® enhances immune and haemopoietic functions in senescence-accelerated mice.  
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- Ref. 026** Pycnogenol® protects  $\alpha$ -tocopherol in endothelial cells.  
Virgili F, Kim D, Packer L  
Procyanidins extracted from pine bark protect  $\alpha$ -tocopherol in ECV 304 endothelial cells challenged by activated RAW 264.7 macrophages: role of nitric oxide and peroxynitrite.  
FEBS Lett 431: 315-318, 1998
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- Ref. 025** Pycnogenol® inhibits the effect of oxidative stress and minimises hydroxyl radical-induced DNA damage *in vitro*.  
Nelson AB, Lau BHS, Ide N, Rong Y  
Pycnogenol® inhibits macrophage oxidative burst, lipoprotein oxidation and hydroxyl radical-induced DNA damage.  
Drug Dev Ind Pharm 24: 139-144, 1998
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**Ref. 022** Pycnogenol® in addition to its free radical scavenging property, modulates the production of nitric oxide radicals in activated inflammatory cells.  
Virgili F, Kobuchi H, Packer L  
Procyanidins extracted from *Pinus maritima* (Pycnogenol®): scavengers of free radical species and modulators of nitrogen monoxide metabolism in activated murine raw 264.7 macrophages. *J Free Radic Biol Med* 24: 1120-1129, 1998

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Noda Y, Anzai K, Mori A, Kohno M, Shinmei M, Packer L  
Hydroxyl and superoxide anion radical scavenging activities of natural source antioxidants using the computerized JES-FR30 ESR spectrometer system. *Biochem Mol Biol Int* 42: 35-44, 1997

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Wei ZH, Peng QL, Lau BHS  
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Rong Y, Li L, Shah V, Lau BHS  
Pycnogenol® protects vascular endothelial cells from t-butyl hydroperoxide induced oxidant injury. *Biotechnol Ther* 5: 117-126, 1995

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**Ref. 010** Pycnogenol® scavenges superoxide radicals *in vitro* and inhibits oedema *in vivo*. The anti-inflammatory and free radical scavenging activities are closely correlated.  
Blazso G, Gabor M, Sibbel R, Rohdewald P  
Anti-inflammatory and superoxide radical scavenging activities of a procyanidins containing extract from the bark of *Pinus pinaster* sol. and its fractions. *Pharm Parmacol Lett* 3: 217-220, 1994

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**Ref. 007** Pycnogenol® is proven an excellent radical scavenger of enzymatically produced hydroxyl and singlet oxygen free radicals, two of the most dangerous free radical species.  
Elstner EF, Kleber E  
Radical scavenger properties of leucocyanidine.  
In: Das NP, ed. *Flavonoids in Biology & Medicine III: Current issues in Flavonoid Research*: National University of Singapore Press: 227-235, 1990

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## 17. Analytics, Bio-Availability & Metabolism

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**Ref. 301** Pycnogenol® constituents are transported in the blood stream bound to albumin, whereas the metabolites are not associated to blood proteins.  
Kurlbaum M, Högger P  
Plasma protein binding of polyphenols from maritime pine bark extract (USP).  
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Grimm T, Skrabala R, Chovanova Z, Muchova J, Sumegova K, Liptakova A, Durackova Z, Högger P  
Single and multiple dose pharmacokinetics of maritime pine bark extract (Pycnogenol®) after oral administration to healthy volunteers.  
BMC Clin Pharmacol 6: 1472-6904, 2006

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**Ref. 239** Pycnogenol® antagonises the neurotoxicity of alcohol, suggesting mitigation of hang-over symptoms.  
Siler-Marsiglio KI, Paiva M, Madorsky I, Serrano Y, Neeley A, Heaton MB  
Protective mechanisms of Pycnogenol® in ethanol-insulted cerebellar granule cells.  
J Neurobiol 61: 267-276, 2004

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**Ref. 171** **USP Monograph.**  
**Maritime Pine Extract – USP 34.1196-1197**  
The United States Pharmacopeia, United States Pharmacopeial Convention, Inc. official from May 1, 2011

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**Ref. 170** **USP Monograph.**  
**Maritime Pine – USP-30.964-965**  
The United States Pharmacopeia, United States Pharmacopeial Convention, Inc. official from May 1, 2007

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**Ref. 137** **Evidence of percutaneous absorption of Pycnogenol® in human skin.**  
Sarikaki V, Rallis M, Tanojo H, Panteri I, Dotsikas Y, Loukas YL, Papaioannou G, Demetzos C, Weber S, Moini H, Maibach HI, Packer L  
*In vitro* Percutaneous Absorption of Pine Bark Extract (Pycnogenol®) in Human Skin.  
J Toxicol Cutaneous Ocul Toxicol 23: 149-158, 2004

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- Ref. 060** CLINICAL STUDY: Bio-kinetics (absorption, metabolism and excretion) of Pycnogenol® in healthy human subjects has been demonstrated by studying the excretion pattern of ferulic acid (one of the components of Pycnogenol®).  
Virgili F, Pagana G, Bourne L, Rimbach G, Natella F, Rice-Evance C, Packer L  
Ferulic acid excretion as a marker of consumption of a French maritime pine (*Pinus maritima*) bark extract.  
J Free Radic Biol Med 28: 1249-1256, 2000
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- Ref. 058** CLINICAL STUDY: Pycnogenol®, its components and metabolites are bio-available in humans for more than 24 hours to exert their beneficial effects.  
Grosse-Düweler K, Rohdewald P  
Urinary metabolites of French maritime pine bark extract in humans.  
Pharmazie 55: 364-368, 2000
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- Ref. 040** Pycnogenol® is shown to be bioavailable based on its therapeutic effects *in vivo*: The prevention of platelet aggregation and the capillary sealing effect. Valerolactones as sulphates or glucuronides appear in the urine and they represent the active metabolites of Pycnogenol®.  
Rohdewald P  
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Eur Bull Drug Res 7: 5-7, 1999
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### Horphag Research

Avenue Louis-Casaï 71

CH-1216 Geneva, Switzerland

Phone: +41 (0) 22 710 26 26

Fax: +41 (0) 22 710 26 00

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