

**PYCNOGENOL®**

Research Bibliography



<b>I. Applications</b>	<b>2</b>
1 Cardiovascular Health	2
2 Cognitive Function	6
3 Diabetes and metabolic Syndrome	9
4 Eye Health	11
5 Healthy Aging	12
6 Immunology	13
7 Joint health	16
8 Men's health	17
9 Oral Health	18
10 Pain management	19
11 Respiratory Health	20
12 Skin Care – oral and topical	22
13 Sports	25
14 Travel Health	25
15 Venous Health	26
16 Women's Health	29
<b>II. Mechanisms of action</b>	<b>31</b>
17 Anti-inflammatory Action	31
18 Antioxidant Activity	33
19 Endothelial Function	38
20 Platelet function	40
21 Reinforcement of the extracellular matrix	42
<b>III. Analytics, Bioavailability &amp; Metabolism</b>	<b>43</b>
<b>IV. Review Articles</b>	<b>45</b>

# I. Applications

## 1 Cardiovascular Health

- 
- Ref. 580** Review: Pycnogenol® has significantly beneficial effects on systolic and diastolic blood pressure.  
 Pourmasoumi M, Hadi A, Mohammadi H, Rouhani MH  
 Effect of Pycnogenol® supplementation on blood pressure: A systematic review and meta-analysis of clinical trials.  
 Phytotherapy Research. 2019;1-10, 2019
- 
- Ref. 577** Clinical study: Pycnogenol® has significant protective effects on metabolic syndrome parameters and improves body composition by leading to weight loss in obese subjects.  
 Sedighyan M, Abdolahi M, Taheri E, Qorbani M, Omidian P, Hosseini S.  
 The French Maritime Pine Bark Extract Reduce Metabolic Syndrome Risk and Improve Body Composition in Obesity: A New Clinical Approach.  
 Acta Medica Iranica. 2018;56(3), 2018
- 
- Ref. 570** Clinical study: Pycnogenol®, together with vitamins C and E improved renal functions as well as cardiovascular risk markers in patients after kidney transplantation.  
 Szentesiova Z, Trebaticky B, Zilinska Z, Breza J, Oravec S, Orszaghova Z, Muchova, J.  
 Improvement in cardiovascular risk markers by the combined effect of natural polyphenols and vitamins in patients after kidney transplantation.  
 Bratislava Medical Journal. 2022;123(04):254-61, 2022
- 
- Ref. 553** Clinical study: Pycnogenol® shows beneficial effects for managing some of the signs and symptoms associated with post-Covid-19 and improves cardiovascular risk factors.  
 Belcaro G, Cornelli U, Cesarone MR, Scipione C, Scipione V, Hu S, Feragalli B, Corsi M, Cox D, Cotellese R, Hosoi M, Burki C  
 Preventive effects of Pycnogenol® on cardiovascular risk factors (including endothelial function) and microcirculation in subjects recovering from coronavirus disease 2019 (COVID-19).  
 Minerva Med. 113(2):300-8, 2022
- 
- Ref. 532** Clinical Study: Pycnogenol® and Centellicum® reduce the rate of progression of the neointima after stenting.  
 Belcaro G, Cesarone MR, Scipione C, et al  
 Pycnogenol®+Centellicum®, post-stent evaluation: prevention of neointima and plaque re-growth.  
 Minerva Cardioangiol. 2019;67(6):450-455. doi:10.23736/S0026-4725.19.05048-5, 2019
- 
- Ref. 531** Clinical study: The combination Pycnogenol® and Centellicum® has beneficial effects in reducing the progressive diffusion of central/coronary-cardiovascular calcifications.  
 Hu S, Belcaro G, Cesarone MR, Feragalli B, Cotellese R, Dugall M, Scipione C, Scipione V, Maione C.  
 Central cardiovascular calcifications: supplementation with Pycnogenol® and Centellicum®: variations over 12 months.  
 Minerva Cardioangiol. 2020 Feb;68(1):22-26. doi: 10.23736/S0026-4725.19.05052-7. Epub 2019 Oct 15. PMID: 31633315, 2020
- 
- Ref. 530** Clinical study: The combined supplementation with Pycnogenol® and Centellicum® ameliorates the progression of atherosclerosis and the occurrence of cardiovascular events in this 3-year study.  
 Belcaro G, Cesarone MR, Scipione C, Scipione V, Dugall M, Shu H, Peterzan P, Corsi M, Luzzi R, Hosoi M, Feragalli B, Cotellese R.  
 Delayed progression of atherosclerosis and cardiovascular events in asymptomatic patients with atherosclerotic plaques: 3-year prevention with the supplementation with Pycnogenol®+Centellicum®.  
 Minerva Cardioangiol. 2020 Feb;68(1):15-21. doi: 10.23736/S0026-4725.19.05051-5. Epub 2019 Oct 11. PMID: 31625707, 2020
- 
- Ref. 508** Clinical study: Pycnogenol® improves erectile function in healthy and even more in diabetes mellitus patients. In parallel, Pycnogenol® lowers total and LDL-cholesterol, as well as glycaemia in diabetes mellitus patients.  
 Trebaticky, B., Muchova J, Ziaran S, Bujdak P, Breza J, Durackova Z  
 Natural polyphenols improve erectile function and lipid profile in patients suffering from erectile dysfunction.  
 Bratisl Lek Listy, 120(12): p. 941-944, 2019
- 
- Ref. 506** Clinical study: Pycnogenol® improves microcirculation and reduces main symptoms of patients with Raynaud syndrome.  
 Hu, S., M. Hosoi, G. Belcaro, M. Dugall, B. Feragalli, R. Cotellese and R. Luzzi (2019)  
 Management of mild, primary Raynaud Syndrome: supplementation with Pycnogenol®.  
 Minerva Cardioangiol 67(5): 392-398, 2019
- 
- Ref. 453** Clinical study: Further to alleviating menopausal symptoms, Pycnogenol® significantly improves blood sugar and -lipids, and supports healthy blood pressure, CRP- and homocysteine values.  
 Luzzi R, Belcaro G, Hosoi M, Feragalli B, Cornelli U, Dugall M, Ledda A  
 Normalization of cardiovascular risk factors in peri-menopausal women with Pycnogenol®.  
 Minerva Ginecol 69: 29-34, 2017

- 
- Ref. 445** Clinical study: Pycnogenol® increases muscular strength and heart ejection fraction in senior citizen with muscle weakness.  
Belcaro G, Dugall M  
Preservation of muscular mass and strength in aged subjects with Pycnogenol® supplementation.  
Minerva Ortopedica Traumatologica 67(3): 124-130, 2016
- 
- Ref. 442** Preclinical study describing mechanisms of Pycnogenol® related to atherosclerosis improvement.  
Liu R, Fan B, Cong H, Ikuyama S, Guan H, Gu J  
Pycnogenol® reduces toll-like receptor 4 signaling pathway-mediated atherosclerosis formation in apolipoprotein E-deficient mice.  
J Cardiovasc Pharmacol 68: 292-303, 2016
- 
- Ref. 438** Clinical study: Pycnogenol® in association with Centellicum® stabilises carotid artery plaques.  
Luzzi R, Belcaro G, Ippolito E  
Carotid plaque stabilization induced by the supplement association Pycnogenol® and centella asiatica (Centellicum®).  
Minerva Cardioangiologica 64: 603-609, 2016
- 
- Ref. 434** Review: A summary of investigations related to biological activities and clinical actions of Pycnogenol® related to oedema, ulcers, thromboses, CVI and haemorrhoids.  
Rohdewald P  
Gerbstoffhaltiger Extrakt zur oralen und topischen Behandlung bei CVI und Hämorrhoidalleiden.  
Phlebologie 44: 334-338, 2015
- 
- Ref. 426** Pycnogenol® is shown in pre-clinical study to reduce atherosclerotic plaque and lipid deposition, decreasing the lipid-related protein expression of adipose differentiation-related protein and adipocyte lipid-binding protein in dose dependent fashion.  
Luo H, Wang J, Qiao C, Ma N, Liu D, Zhang W  
Pycnogenol® attenuates atherosclerosis by regulating lipid metabolism through the TLR4-NF-kappaB pathway.  
Experimental & Molecular Medicine 47, e191; doi:10.1038/emm.2015.74, 2015
- 
- Ref. 415** This review article comprises the current knowledge on Pycnogenol® for improvement of health of individuals with metabolic syndrome and diabetes.  
Gulati O  
Pycnogenol® in Metabolic Syndrome and Related Disorders.  
Phytother Res 29: 949-968, 2015
- 
- Ref. 408** Clinical study: Endothelial function is improved by Pycnogenol®. Results of this open registry study indicate an important preventive possibility for borderline hypertensive, hyperglycemic and hyperlipidemic subjects.  
Hu S, Belcaro G, Cornelli U, Luzzi R, Cesarone MR, Dugall M, Feragalli B, Errichi B, Ippolito E, Grossi MG, Hosoi M, Gizzi G, Trignani M  
Effects of Pycnogenol® on endothelial dysfunction in borderline hypertensive, hyperlipidemic, and hyperglycemic individuals: the borderline study.  
Int Angiol 34(1): 43-52, 2015
- 
- Ref. 393** Clinical study: Patients with Meniere's disease and tinnitus benefit from Pycnogenol® supplementation.  
Luzzi R, Belcaro G, Hu S, Dugall M, Hosoi M, Cacchio M, Ippolito E, Corsi M  
Improvement in symptoms and cochlear flow with Pycnogenol® in patients with Meniere's disease and tinnitus.  
Minerva Med 105: 245-254, 2014
- 
- Ref. 385** Pycnogenol® shows beneficial effects in metabolic and cardiovascular health.  
Aribal-Ayral P, Özelci-Kavas G, Elhan AH  
Pycnogenol® supplementation and its beneficial effects in healthy rats.  
Saudi Med J 35(2): 195-197, 2014
- 
- Ref. 382** Clinical study: Pycnogenol® and Centella Asiatica reduce progression of arterial lesions and plaque progression in this pilot study.  
Belcaro G, Dugall M, Hosoi M, Ippolito E, Cesarone MR, Luzzi R, Cornelli U, Ledda A  
Pycnogenol® and Centella Asiatica for asymptomatic atherosclerosis progression.  
Int Angiol 1(33): 20-26, 2014
- 
- Ref. 360** Clinical study: Pycnogenol® improves all signs and symptoms of metabolic syndrome to healthy values within three months.  
Belcaro G, Cornelli U, Luzzi R, Cesarone MR, Dugall M, Feragalli B, Errichi S, Ippolito E, Grossi MG, Hosoi M, Cornelli M, Gizzi G  
Pycnogenol® supplementation improves health risk factors in subjects with metabolic syndrome.  
Phytother Res 27: 1572-1578, 2013

- 
- 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 33(13): 1589-97, 2012
- 
- 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
- 
- 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, Duggall M, Hosoi M, Ippolito E, Bavera P, Grossi MG  
 Investigation of Pycnogenol® in combination with coenzyme Q10 in heart failure patients (NYHA II/III).  
 Panminerva Med 52 (suppl. 1 to No. 2): 21-25, 2010
- 
- 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
- 
- 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
- 
- 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, Schönlaue F, Di Renzo A, Grossi MG, Duggall 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
- 
- 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
- 
- 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. 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 antihypertensive 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
- 
- 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
- 
- 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

---

**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

---

**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

---

**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

---

**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®.  
Clin Appl Thromb Hemost 12: 440-444, 2006

---

**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

---

**Ref. 177** Review: Pycnogenol® and Coenzyme Q10 enhance cardiovascular health synergistically.  
Watson RR  
Nutraceutical Synergism: Pycnogenol® and Coenzyme Q10 Enhance Cardiovascular Health.  
Evid Based Integrative Med 2: 67-70, 2005

---

**Ref. 168** Review: 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. 140** Pycnogenol® increases red blood cell membrane fluidity and protects erythrocytes against oxidative stress.  
Sivonova M, Waczulikova I, Kilanczyk E, Hrnčiarova M, Bryszewska M, Klajnert B, Durackova Z  
The effect of Pycnogenol® on the erythrocyte membrane fluidity.  
Gen Physiol Biophys 23: 39-51, 2004

---

**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

---

**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

---

**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

---

**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, Schönlaue 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

- 
- 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
- 
- 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
- 
- Ref. 053** Clinical study: Pycnogenol® inhibits smoking-induced increase of thromboxane B2 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
- 
- Ref. 043** Clinical study: Pycnogenol® inhibits platelet aggregation and adhesion and improves blood microcirculation 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
- 
- 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
- 
- 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, Grottemeyer 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
- 
- Ref. 027** Pycnogenol® counteracts the constriction of blood vessels. The vasorelaxant 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
- 
- Ref. 017** Pycnogenol® inhibits the angiotensin II converting enzyme (ACE) and produces a moderate hypotensive effect in rats.  
Blazso G, Gaspar R, Gabor M, Rűve 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

## 2 Cognitive Function

- 
- Ref 584** Clinical study: Pycnogenol® improves cognitive function and face / body expressions in subjects with Parkinson's disease.  
Belcaro G, Cesarone MR, Hu S, Hosoi M, Ledda A, Feragalli B, et al.  
Pycnogenol® supplementation alleviates symptoms of Parkinson's disease with mild cognitive impairment.  
Journal of neurosurgical sciences. 2022;66(4):371-7, 2022
- 
- Ref. 582** Clinical study: Different to Methylphenidate, Pycnogenol® did not lead to loss of appetite or weight loss in children with ADHD.  
Weyns A-S, Verlaet AAJ, Van Herreweghe M, Breynaert A, Franssen E, De Meester I, et al.  
Clinical Investigation of French Maritime Pine Bark Extract on Attention-Deficit Hyperactivity Disorder as compared to Methylphenidate and Placebo: Part 2: Oxidative Stress and Immunological Modulation.  
Journal of Functional Foods. 2022;97:105247, 2022
- 
- Ref. 581** Clinical study: Pycnogenol® is an effective and adverse-free alternative for the common medicine methylphenidate in paediatric ADHD regarding hyperactivity and impulsivity.  
Weyns A-S, Verlaet AAJ, Breynaert A, Naessens T, Franssen E, Verhelst H, et al.  
Clinical Investigation of French Maritime Pine Bark Extract on Attention-Deficit Hyperactivity Disorder as compared to Methylphenidate and Placebo: Part 1: Efficacy in a Randomised Trial.  
Journal of Functional Foods. 2022;97:105246, 2022

- 
- Ref. 566** In a Parkinson's disease model, Pycnogenol® significantly improved motor function, catalepsy and depression by exerting anti-inflammatory, antioxidant, and neuroprotective effects.  
Jafari F, Goudarzvand M, Hajikhani R, Qorbani M, Solati J.  
Pycnogenol® ameliorates motor function and gene expressions of NF-κB and Nrf2 in a 6-hydroxydopamine-induced experimental model of Parkinson's disease in male NMRI mice.  
Naunyn-Schmiedeberg's Archives of Pharmacology, 2022
- 
- Ref. 557** Review on the beneficial effects of Pycnogenol® on cognitive function.  
Schönlau F  
Chapter 23 - The multifactorial contributions of Pycnogenol® for cognitive function improvement.  
Nutraceuticals in Brain Health and Beyond, D. Ghosh Ed., pp. 335-341: Academic Press: 2021, 2021
- 
- Ref. 546** Curcumin as well as Pycnogenol® may help alleviate symptoms of Gulf War Illness.  
Donovan EK, Kekes-Szabo S, Lin JC, Massey RL, Cobb JD, Hodgin KS, Ness TJ, Hangee-Bauer C, Younger JW.  
A Placebo-Controlled, Pseudo-Randomized, Crossover Trial of Botanical Agents for Gulf War Illness: Curcumin (*Curcuma longa*), *Boswellia* (*Boswellia serrata*), and French Maritime Pine Bark (*Pinus pinaster*).  
International Journal of Environmental Research and Public Health 18(5): 2468., 2021
- 
- Ref. 511** Clinical study: Pycnogenol® improves some signs and symptoms associated with the decrease of cognitive function in Parkinson's disease.  
Cesarone, M. R., G. Belcaro, M. Hosoi, A. Ledda, B. Feragalli, C. Maione, C. Scipione, V. Scipione, R. Cotellese and S. Hu  
Supplementary management with Pycnogenol® in Parkinson's disease to prevent cognitive impairment.  
J Neurosurg Sci 64(3): 258-262, 2020
- 
- Ref. 503** This review summarizes the bio-modulating effects of Pycnogenol® to improve neurocognitive function via vascular, anti-inflammatory, neuroprotective, and antioxidant processes and gives an outlook to (possible) future studies.  
Simpson T, Kure C, Stough C  
Assessing the efficacy and mechanisms of Pycnogenol® on cognitive aging from in vitro animal and human studies.  
Frontiers in Pharmacology, 2019
- 
- Ref. 494** The results of this pre-clinical trial suggest to evaluate a potential use of Pycnogenol® for early stages of mild cognitive impairment and Alzheimer's disease in a clinical setting.  
Paarman K, Prakash SR, Krohn M, Möhle L, Brackhan M, Brüning T, Eiriz I, Pahnke J  
French maritime pine bark treatment decelerates plaque development and improves spatial memory in Alzheimer's disease mice.  
Phytomed 57: 39-48. doi: 10.1016/j.phymed.2018.11.033. Epub 2018 Nov 29, 2019
- 
- Ref. 474** Clinical Study: Due to Pycnogenol®'s effect on oxidative stress levels, a large number of positive effects in subjects with initial cognitive impairment could be shown.  
Hosoi M, Belcaro G, Saggino A, Luzzi R, Dugall M, Feragalli B  
Pycnogenol® supplementation in minimal cognitive dysfunction.  
J Neurosurg Sci 62(3): 279-284, 2018
- 
- Ref. 472** Review: Pycnogenol® is considered to have therapeutic benefits in ADHD, as it increased antioxidant levels, reduced oxidative damage and improved neurochemical status.  
Verlaeat AAJ, Maasackers CM, Hermans N, Savelkoul HFJ  
Rationale for Dietary Antioxidant Treatment of ADHD.  
Nutrients 10, 405; doi: 10.3390/nu10040405, 2018
- 
- Ref. 431** Clinical Study: Pycnogenol® supplementation for 12 months improves cognition and quenches oxidative stress in normal subjects aged 55 to 70 years.  
Belcaro G, Dugall M, Ippolito E, Hu S, Saggino A, Feragalli B  
The COFU3 Study: Improvement in cognitive function, attention, mental performance with Pycnogenol® in healthy subjects (55-70) with high oxidative stress.  
J Neurosurg Sci 59: 437-446, 2015
- 
- Ref. 424** Pycnogenol® counteracts inflammatory situations of brain microglia cells in pre-clinical study.  
Fan B, Dun S-H, Gu J-Q, Guo Y, Ikuyama S  
Pycnogenol attenuates the release of proinflammatory cytokines and expression of perilipin 2 in lipopolysaccharides-stimulated microglia in part via inhibition of NF-κB and AP-1 activation.  
PLOS ONE 10(9): e0137837. doi:10.1371/journal, 2015
- 
- Ref. 419** Pycnogenol® research on cognitive function with double-blind, placebo-controlled protocol.  
Stough C, Pase MP  
Improving cognition in the elderly with nutritional supplements.  
Current Directions in Psychological Science 24: 177-183, 2015



- 
- Ref. 407** Pycnogenol® supplementation for 12 weeks appears to improve cognitive function and oxidative stress in healthy professionals.  
Belcaro G, Luzzi R, Dugall M, Ippolito E, Saggino A  
Pycnogenol® improves cognitive function, attention, mental performance and specific professional skills in healthy professionals aged 35-55.  
J Neurosurg Sci 58: 239-248, 2014
- 
- 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
- 
- 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.  
J Psychopharmacol 22: 553-562, 2008
- 
- Ref. 231** Clinical Study: Pycnogenol® lowers stress-hormones in children with ADHD.  
Dvorakova M, Jezova D, Blazicek P, Trebaticka J, Skodacek I, Suba J, Waczulikova I, Rohdewald P, Durackova Z  
Urinary catecholamines in children with attention deficit hyperactivity disorder (ADHD): modulation by a polyphenolic extract from pine bark (Pycnogenol®).  
Nutr Neurosci 10: 151-157, 2007
- 
- Ref. 205** Clinical Study: Pycnogenol® improves antioxidant status in children with attention deficit hyperactivity disorder (ADHD).  
Dvorakova M, Sivonova M, Trebaticka J, Skodacek I, Waczulikova I, Muchova J, Durackova Z  
The effect of polyphenolic extract from pine bark, Pycnogenol®, on the level of glutathione in children suffering from attention deficit hyperactivity disorder (ADHD).  
Redox Rep 11: 163-172, 2006
- 
- 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
- 
- 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
- 
- Ref. 083** Neuronal apoptosis (early cell death) is induced by the amyloid- $\beta$ -peptide in the brain of Alzheimer patients. In vitro experiments demonstrated an inhibition of cell death of neurons by Pycnogenol®.  
Peng QL, Buz'Zard AR, Lau BHS  
Pycnogenol® protects neurones from amyloid  $\beta$  peptide-induced apoptosis.  
Brain Res Mol Brain Res 104: 55-65, 2002
- 
- Ref. 069** Pycnogenol® produces significant reduction in vascular damage caused by  $\beta$ -amyloid protein.  $\beta$ -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  $\beta$ -amyloid-induced injury.  
Biol Pharm Bull 23: 735-737, 2000
- 
- Ref.052** Pycnogenol® improves learning impairment and loss of memory, common signs 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
- 
- Ref. 048** Pycnogenol® is recommended for treatment of attention deficit disorder.  
Hanley JL  
Attention Deficit Disorder.  
Impact Communications Inc., Green Bay, WI, USA, 17-19, 1999
- 
- Ref. 047** Case report: Positive experience with Pycnogenol® in treating ADHD is mentioned in this letter to the Editor.  
Heimann SW  
Pycnogenol® for ADHD?  
J Am Acad Child Adolesc Psychiatry 38: 357-358, 1999

### 3 Diabetes and metabolic Syndrome

- 
- Ref. 534** Clinical study: Salivary flow and mucosal breaks and ulcerations improved after Pycnogenol® supplementation in diabetic and non-diabetic patients with dry mouth syndrome (Xerostomia).  
Belcaro G, Cesarone MR, Cornelli U, Scipione, C., Scipione, V., Dugall, M., Hu, S., Feragalli, B., Hosoi, M., Maione, C., Cotellese, R., Cesinaro Di Rocco, P.  
Xerostomia: prevention with Pycnogenol® supplementation: a pilot study.  
Minerva Stomatol. 2019;68(6):303-307, 2019
- 
- Ref. 508** Clinical study: Pycnogenol® improves erectile function in healthy and even more in diabetes mellitus patients. In parallel, Pycnogenol® lowers total and LDL-cholesterol, as well as glycaemia in diabetes mellitus patients.  
Trebaticky, B., Muchova J, Ziaran S, Bujdak P, Breza J, Durackova Z  
Natural polyphenols improve erectile function and lipid profile in patients suffering from erectile dysfunction.  
Bratisl Lek Listy, 120(12): p. 941-944, 2019
- 
- Ref. 448** A review suggesting Pycnogenol® as adjunct treatment to conventional therapy for hepatitis-associated diabetes.  
Ezzikouri S, Jadid FZ, Hamdi S, Wakrim L, Tsukiyama-Kohara K, Benjelloun S  
Supplementing Conventional Treatment with Pycnogenol® May Improve Hepatitis C Virus-Associated Type 2 Diabetes: A Mini Review.  
J Clin Translational Hepatol 4: 228-233, 2016
- 
- Ref. 435** Supplementation with Pycnogenol® as add-on to metformin medication suggests similar effects in diabetic animal model.  
Jankyova S, Rubintova D, Janosikova L, Panek P, Foltanova T, Kralova E  
The Effects of Pycnogenol® as Add-on Drug to Metformin Therapy in Diabetic Rats.  
Phytother Res 30: 1354-1361, 2016
- 
- Ref. 415** This review article comprises the current knowledge on Pycnogenol® for improvement of health of individuals with metabolic syndrome and diabetes.  
Gulati O  
Pycnogenol® in Metabolic Syndrome and Related Disorders.  
Phytother Res 29: 949-968, 2015
- 
- Ref. 408** Clinical Study: Endothelial function is improved by Pycnogenol®. Results of this open registry study indicate an important preventive possibility for borderline hypertensive, hyperglycemic and hyperlipidemic subjects.  
Hu S, Belcaro G, Cornelli U, Luzzi R, Cesarone MR, Dugall M, Feragalli B, Errichi B, Ippolito E, Grossi MG, Hosoi M, Gizzi G, Trignani M  
Effects of Pycnogenol® on endothelial dysfunction in borderline hypertensive, hyperlipidemic, and hyperglycemic individuals: the borderline study.  
Int Angiol 34(1): 43-52, 2015
- 
- Ref. 401** Clinical Study: Intake of Pycnogenol® decreases glucose levels and increases the antioxidative capacity of plasma.  
Muchova J, Orszaghova Z, Zitnanova I, Trebaticky B, Breza J, Durackova Z  
The effect of natural polyphenols on the oxidative stress markers in patients with diabetic nephropathy.  
Free Rad Biol Med 72: 42, 2014
- 
- Ref. 397** Pycnogenol® improves the function of the heart in rats with experimental diabetes mellitus.  
Kralova E, Jankyova S, Mucaji P, Gresakova E, Stankovicova T  
Pycnogenol and its fractions influence the function of isolated heart in rats with experimental diabetes mellitus.  
J Pathology Research & Practice, 211: 156-161, 2015
- 
- Ref. 385** Pycnogenol® shows beneficial effects in metabolic and cardiovascular health.  
Aribal-Ayral P, Özelci-Kavas G, Elhan AH  
Pycnogenol® supplementation and its beneficial effects in healthy rats.  
Saudi Med J 35(2): 195-197, 2014
- 
- Ref. 384** Pycnogenol® may be cost effective in reducing the risk for diabetes-related complications.  
Bentley G, Schönlau F, Zibadi S, Watson R  
Cost of Pycnogenol® Supplementation and Traditional Diabetes Treatments per Unit of Improved Health Outcome.  
Chapter 27 in R.R. Watson et al., (eds.), Nutrients, Dietary Supplements, and Nutraceuticals: Cost Analysis Versus Clinical Benefits, Nutrition and Health, Springer Science+Business Media LLC 2011
- 
- Ref. 381** The combination of Pycnogenol® and the β-blocker Carvedilol improve the myocardial function in diabetic mellitus animals. Pycnogenol® improves values of hemodynamic parameters – contraction and coronary flow.  
Králová E, Jankyová S, Pekářík A, Cubon J, Stankovicová T  
Carvedilol and Pycnogenol® improve the function of diabetic heart in rats.  
Acta Fax Pharm Univ Comen LX, 2013 (1)
- 
- Ref. 360** Clinical Study: Pycnogenol® improves all signs and symptoms of metabolic syndrome to healthy values within three months.  
Belcaro G, Cornelli U, Luzzi R, Cesarone MR, Dugall M, Feragalli B, Errichi S, Ippolito E, Grossi MG, Hosoi M, Cornelli M, Gizzi G  
Pycnogenol® supplementation improves health risk factors in subjects with metabolic syndrome.  
Phytother Res 27: 1572-1578, 2013  
Diabetic Syndrome

- 
- 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
- 
- 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
- 
- Ref. 300** Pycnogenol® is shown in an in vitro model to facilitate better glucose uptake by fat cells which suggests antidiabetic 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
- 
- 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
- 
- 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
- 
- 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
- 
- 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
- 
- 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 antihypertensive 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
- 
- 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
- 
- 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
- 
- Ref. 199** Clinical Study: Pycnogenol® reduces diabetic microangiopathy.  
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  
Improvement of diabetic microangiopathy with Pycnogenol®: A prospective, controlled study.  
Angiology 57: 431-436, 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. 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
- 
- 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
- 
- Ref. 153** Pycnogenol® either alone or in combination with other antioxidants reduces parameters of oxidative stress in diabetic rats.  
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
- 
- Ref. 142** Clinical Study: Pycnogenol® supplementation to diabetic patients lowers glucose levels.  
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
- 
- 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
- 
- 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
- 
- 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
- 
- 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
- 
- 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
- 
- 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

## 4 Eye Health

- 
- Ref. 528** Clinical study: Pycnogenol® prevents recurrent retinal vein thrombosis better than Aspirin, ticlopidine and sulodexide with no side effects.  
Belcaro G, Dugall M, Bradford HD, Cesarone MR, Feragalli B, Gizzi C, Cotellese R, Hu S, Rodriguez P, Hosoi M.  
Recurrent retinal vein thrombosis: prevention with Aspirin, Pycnogenol®, ticlopidine, or sulodexide.  
Minerva Cardioangiol. 2019 Apr;67(2):109-114, 2019

- 
- Ref. 417** Clinical Study: Pycnogenol® is shown to help prevent retinal vein thrombosis.  
Rodriguez P, Belcaro G, Dugall M, Hu S, Luzzi R, Ledda A, Ippolito E, Corsi M, Ricci A, Feragalli B, Cornelli U, Gizzi C, Hosoi M  
Recurrence of retinal vein thrombosis with Pycnogenol® or Aspirin® supplementation: a registry study.  
Panminerva Med 57: 121-125, 2015
- 
- 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
- 
- 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.  
J Clin Biochem Nutr 38: 204-210, 2006
- 
- 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
- 
- 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
- 
- Ref. 092** The review contains results of 5 clinical studies with Pycnogenol® showing the efficacy of Pycnogenol® supplementation for patients with diabetic retinopathy.  
Schönlau F, Rohdewald P  
Pycnogenol® for diabetic retinopathy: A review.  
Int Ophthalmol 24: 161-171, 2002
- 
- 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
- 
- 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 Q10.  
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
- 
- 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

## 5 Healthy Aging

- 
- Ref. 503** This review summarizes the bio-modulating effects of Pycnogenol® to improve neurocognitive function via vascular, anti-inflammatory, neuroprotective, and antioxidant processes.  
Simpson T, Kure C, Stough C  
Assessing the efficacy and mechanisms of Pycnogenol® on cognitive aging from in vitro animal and human studies.  
Frontiers in Pharmacology, 2019
- 
- Ref. 490** Review on the diverse beneficial effects of Pycnogenol® on relevant symptoms of aging.  
Rohdewald P  
Pleiotropic Effects of French Maritime Pine Bark Extract to Promote Healthy Aging.  
Rejuvenation Res. 2019 Jun;22(3):210-217, 2019

- 
- Ref. 488** Clinical Study: Pycnogenol® may improve the general fitness status in elderlies and decrease the burden of fatigue experienced during normal activities such as shopping, walking, house-keeping.  
Hosoi M, Cotellese R, Belcaro G, et al.  
Pycnogenol®: Prevention of muscular mass and strength loss in the elderlies.  
J Sports Med Physical Fitness, ahead of print, 2018; Pharma standard (PS) supplements. Papers from the London sessions January 2018. Eds. Belcaro G, Dugall M, Ledda A., ISBN; 978-88-7711-940
- 
- Ref. 453** Clinical Study: Further to alleviating menopausal symptoms, Pycnogenol® significantly improves blood sugar and -lipids, and supports healthy blood pressure, CRP- and homocysteine values.  
Luzzi R, Belcaro G, Hosoi M, Feragalli B, Cornelli U, Dugall M, Ledda A  
Normalization of cardiovascular risk factors in peri-menopausal women with Pycnogenol®.  
Minerva Ginecol 69: 29-34, 2017
- 
- Ref. 431** Clinical Study: Pycnogenol® supplementation for 12 months improves cognition and quenches oxidative stress in normal subjects aged 55 to 70 years.  
Belcaro G, Dugall M, Ippolito E, Hu S, Saggino A, Feragalli B  
The COFU3 Study: Improvement in cognitive function, attention, mental performance with Pycnogenol® in healthy subjects (55-70) with high oxidative stress.  
J Neurosurg Sci 59: 437-446, 2015
- 
- 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
- 
- 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
- 
- 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
- 
- Ref. 098** Pycnogenol® delays the aging process as shown by an increased life-span of fruit flies.  
Shuguang L, Xinwen Z, Sihong X, Gulati OP  
Role of Pycnogenol® in aging by increasing the Drosophila's life-span.  
Eur Bull Drug Res 11: 39-45, 2003

## 6 Immunology

- 
- Ref. 572** Pycnogenol® may exert antiviral effects against Foot-and-mouth disease virus (FMDV) and classical swine fever virus (CSFV) by suppressing the activities of their internal ribosomal entry site (IRES) elements.  
Ide Y, Kitab B, Ito N, Okamoto R, Tamura Y, Matsui T, Sakoda Y, Tsukiyama-Kohara, K.  
Characterization of host factors associated with the internal ribosomal entry sites of foot-and-mouth disease and classical swine fever viruses.  
Scientific Reports. 2022;12(1), 2022
- 
- Ref. 537** Clinical study: Pycnogenol® can be safely used for mild symptoms in subjects with systemic lupus with vasculitis in remission, ameliorating some signs and symptoms of lupus vasculitis.  
Cesarone MR, Belcaro G, Corsi M, Scipione C, Scipione V, Hu S, Hosoi M, Ledda A, Feragalli B, Cotellese R.  
Supplementary management with Pycnogenol® in patients with lupus vasculitis in remission phases: a pilot, concept registry study.  
Minerva Cardioangiol. 2020;68(2):146-152, 2020
- 
- Ref. 505** Mini Review, suggesting that toothpaste containing Pycnogenol® improves oral health and prevents the development of periodontal diseases  
Sato, T., K. Watanabe, H. Sasaki, H. Hiramine, S. Goda and N. Hamada.  
Antimicrobial activity and inhibitory effect of alveolar bone loss of toothpaste containing a natural plant extract.  
Kanagawa Shigaku 53(1/2): 40-44, 2018

- 
- Ref. 498** Gastrointestinal metabolism of Pycnogenol® reveals its immunomodulatory and anti-inflammatory properties.  
Verlaet A, van der Bolt N, Meijer B, Breynaert A, Naessens T, Konstanti P, Smidt H, Hermans N, Savelkoul HFJ, Teodorowicz M  
Toll-Like Receptor-Dependent Immunomodulatory Activity of Pycnogenol®.  
Nutrients 11: 214; doi:10.3390/nu11020214, 2019
- 
- Ref. 448** A review suggesting Pycnogenol® as adjunct treatment to conventional therapy for hepatitis-associated diabetes.  
Ezzikouri S, Jadid FZ, Hamdi S, Wakrim L, Tsukiyama-Kohara K, Benjelloun S  
Supplementing Conventional Treatment with Pycnogenol® May Improve Hepatitis C Virus-Associated Type 2 Diabetes: A Mini Review.  
J Clin Translational Hepatol 4: 228-233, 2016
- 
- Ref. 409** Supplementation with Pycnogenol® may be useful as a therapeutic and preventative agent for bone diseases such as periodontitis.  
Sugimoto H, Watanabe K, Toyama T, Takahashi S-s, Sugiyama S, Lee M-C-I, Hamada N  
Inhibitory Effect of French Pine Bark Extract, Pycnogenol®, on Alveolar Bone Resorption and on the Osteoclast Differentiation.  
Phytother Res 29(2): 251-259, 2015
- 
- Ref. 398** The efficacy of current standard anti-viral agents may be improved by Pycnogenol®.  
Ezzikouri S, Nishimura T, Kohara M, Benjelloun S, Kino Y, Inoue K, Matsumori A, Tsukijama-Kohara  
Inhibitory effects of Pycnogenol® on hepatitis C virus replication.  
Antiviral Res 113: 93-102, 2015
- 
- Ref. 396** Clinical Study: Pycnogenol® decreases symptoms of common cold and shorten its course also preventing some complications.  
Belcaro G, Shu H, Luzzi R, Dugall M, Ippolito E, Cesarone MR, Corsi M, Feragalli B  
Improvement of common cold with Pycnogenol®: a Winter registry study.  
Panminvera Med 56: 301-308, 2014
- 
- Ref. 395** Supplementation with Pycnogenol® ameliorates premature death by restoring immune dysfunction.  
Lee J, Nam D-E, Kim O-K, Lee M-Y  
Pycnogenol® attenuates the symptoms of immune dysfunction through restoring a cellular antioxidant status in low micronutrient-induced immune deficient mice.  
Nutr Res Pract 8(5): 533-538, 2014
- 
- Ref. 375** Clinical Study: Pycnogenol® given to children with Crohn's Disease at remission stage decreases oxidative stress levels.  
Kolacek M, Muchova J, Dvorakova M, Paduchova Z, Zitnanova I, Cierna I, Orszaghova Z, Szekyova D, Jajcaiova-Zednickova N, Kovacs L, Durackova Z  
Effects of natural polyphenols (Pycnogenol®) on oxidative stress markers in children suffering from Crohn's disease –a pilot study.  
Free Rad Res 47(8): 624-634, 2013
- 
- Ref. 369** Clinical Study: Pycnogenol® supplementation speeds-up recovery from a common cold, and even more efficiently in combination with vitamin C and zinc.  
Belcaro G, Luzzi R, Umberto C, Hu S, Dugall M, Ippolito E, Cesarone MR, Corsi M, Pellegrini L, Ledda A, Appendino G  
The common cold Winter Study: Effects of Pycnogenol® on Signs, Symptoms, Complications & Costs.  
Otorinolaringol 63: 151-161, 2013
- 
- Ref. 361** Pycnogenol® shows protective effects for prevention of Parkinson's Disease in a model system.  
Khan M, Kempuraj D, Thangavel R, Zaheer A  
Protection of MPTP-induced neuroinflammation and neurodegeneration by Pycnogenol®.  
Neurochem Int 62: 379-388, 2013
- 
- Ref. 356** Clinical Study: Pycnogenol® applied orally, dissolved in glycerol, significantly helps control mucositis in children undergoing chemotherapy.  
Khurana H, Pandey RK, Saksena AK, Kumar A  
An evaluation of vitamin E and Pycnogenol® in children suffering from oral mucositis during cancer chemotherapy.  
Oral Diseases 19: 456-464, 2012
- 
- 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
- 
- 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

---

**Ref. 236** Pycnogenol® increases phagocytosis of macrophages suggesting better defense 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

---

**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

---

**Ref. 228** Pycnogenol® inhibits viral replication in myocarditis.  
Matsumori A  
Treatment Options in Myocarditis.  
Herz 32: 452-456, 2007

---

**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

---

**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

---

**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

---

**Ref. 173** Pycnogenol® selectively kills cancerous ovarian germ cells.  
Buzzard AR, Lau BHS  
Selective toxicity of Pycnogenol® for malignant ovarian germ cells in vitro.  
Int J Cancer Prev 1: 207-212, 2004

---

**Ref. 150** Pycnogenol® shows broad anti-microbial activity in vitro.  
Torras MAC, Faura CA, Schönlaui F, Rohdewald P  
Antimicrobial activity of Pycnogenol®.  
Phytother Res 19: 647-648, 2005

---

**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

---

**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

---

**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, Schönlaui F, Rohdewald P, Szegli G  
Pycnogenol® Efficacy in the Treatment of Systemic Lupus Erythematosus Patients.  
Phytother Res 15: 698-704, 2001

---

**Ref. 059** Pycnogenol® selectively kills cancerous human mammary cells (MCF-7), without affecting the normal mammary cells (MCF-10).  
Huyhn HT, Teel RW  
Selective induction of apoptosis in human mammary cancer cells (MCF-7) by Pycnogenol®.  
Anticancer Res 20: 2417-2420, 2000

---

**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



- 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
- 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

## 7 Joint health

- Ref. 487** Clinical Study: Pycnogenol® patch is safe and effective to control pain and improve symptoms in idiopathic, benign, transient neck pain.  
Belcaro G, Dugall M, Feragalli B, et al.  
Prevention of symptoms associated to neck pain with a Pycnogenol® patch.  
J Sports Med Physical Fitness, Pharma standard (PS) supplements. Papers from the London sessions January 2018. Eds. Belcaro G, Dugall M, Ledda A., ISBN; 978-88-7711-940, 2018
- Ref. 477** Clinical Study: Patients with knee osteoarthritis control their symptoms and mild to moderate pain and inflammation with a Pycnogenol® patch.  
Feragalli B, Dugall M, Luzzi R, Ledda A, Hosoi M, Belcaro G, Cesarone MR  
Pycnogenol®: supplementary management of symptomatic osteoarthritis with a patch. An observational registry.  
Minerva Endocrinologica, Pharma standard (PS) supplements. Papers from the London sessions January 2018. Eds. Belcaro G, Dugall M, Ledda A., ISBN; 978-88-7711-940, 2018
- Ref. 464** Clinical Study: Pycnogenol®'s effects were systematically researched in patient's chondrocytes, synovial fluid and serum. The overall results suggest a chondroprotective potential of the maritime pine bark extract and provide a rational basis for understanding the reported clinical effects on symptom scores in OA patients.  
Jessberger S, Högger P, Genest F, Salter DM, Seefried L  
Cellular pharmacodynamic effects of Pycnogenol® in patients with severe osteoarthritis: a randomized controlled pilot study.  
BMC Complementary and Alternative Medicine 17: 537 DOI 10.1186/s12906-017-2044-1, 2017
- Ref. 461** Review: Pycnogenol® with its anti-inflammatory and chondroprotective effects acts like a sustained-release formulation by its combination of fast absorbed phenolic compounds and slowly metabolized procyanidins.  
Rohdewald PJ  
Review on sustained relief of osteoarthritis symptoms with a proprietary extract from pine bark extract, Pycnogenol®.  
J Med Food 21(1): 1-4, 2018
- Ref. 451** Clinical Study: Pycnogenol® applied topically as patch soothes muscular pain.  
Luzzi R, Belcaro G, Feragalli B, Dugall M  
Moderate, diffuse, somatic muscular pain: effects of supplementation with a Pycnogenol® patch.  
Minerva Ortopedica e Traumatologica 67(4): 170-176, 2016
- Ref. 440** Clinical Study: Supplementation with Pycnogenol® is demonstrated to lead to accumulation of constituents and metabolites in knee synovial fluid in osteoarthritis patients, representing the basis for symptom improvement.  
Mülele M, Seefried L, Genest F, Högger P  
Distribution of constituents and metabolites of maritime pine bark extract (Pycnogenol®) into serum, blood cells and synovial fluid of patients with severe osteoarthritis: a randomized controlled trial.  
Nutrients 9, 443, 2017
- 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
- 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

---

**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

---

**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

---

**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

---

**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

---

**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

---

**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

---

**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

## 8 Men's health

---

**Ref. 536** Clinical study: Pycnogenol® and Centellicum® have beneficial effects on penile fibrosis by reducing the keloidal aspects of penile plaques.  
Ledda A, Cornelli U, Belcaro G, et al.  
Keloidal penile fibrosis: improvements with Centellicum® (Centella asiatica) and Pycnogenol® supplementation: a pilot registry.  
Panminerva Med. 2020;62(1):13-18. doi:10.23736/S0031-0808.18.03572-3, 2020

---

**Ref. 508** Clinical study: Pycnogenol® improves erectile function in healthy and even more in diabetes mellitus patients. In parallel, Pycnogenol® lowers total and LDL-cholesterol, as well as glycaemia in diabetes mellitus patients.  
Trebaticky, B., Muchova J, Ziaran S, Bujdak P, Breza J, Durackova Z  
Natural polyphenols improve erectile function and lipid profile in patients suffering from erectile dysfunction.  
Bratisl Lek Listy, 120(12): p. 941-944, 2019

---

**Ref. 499** Clinical study: Pycnogenol® reduces Escitalopram (anti-depressant)-induced sexual dysfunction and elevated heart rate in both genders based on its ability to improve endothelial function.  
Smetanka A, Stara V, Farsky, I, Tonhajzerova I, Ondrejka I  
Pycnogenol® supplementation as an adjunct treatment for antidepressant-induced sexual dysfunction.  
Physiol Int 106(1): 59-69, 2019

- 
- Ref. 488** Clinical Study: Pycnogenol® may improve the general fitness status in elderly and decrease the burden of fatigue experienced during normal activities such as shopping, walking, house-keeping.  
Hosoi M, Cotellese R, Belcaro G, et al.  
Pycnogenol®: Prevention of muscular mass and strength loss in the elderly.  
J Sports Med Physical Fitness, ahead of print, 2018; Pharma standard (PS) supplements. Papers from the London sessions January 2018. Eds. Belcaro G, Dugall M, Ledda A., ISBN; 978-88-7711-940
- 
- Ref. 478** Clinical Study: All symptoms of benign prostatic hypertrophy were significantly improved by Pycnogenol®. Pycnogenol® may be an important option for self-management of benign prostatic hypertrophy in otherwise healthy men.  
Ledda A, Belcaro G, Feragalli B, Cornelli U, Dugall M, Corsi M, Cesarone MR  
Benign prostatic hypertrophy: Pycnogenol® supplementation improves prostate symptoms and residual bladder volume.  
Minerva Medica 109(4): 280-284, 2018
- 
- 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
- 
- 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
- 
- 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 O  
Improvement of sperm quality by Pycnogenol®.  
Eur Bull Drug Res 7: 33-36, 1999

## 9 Oral Health

- 
- Ref. 534** Clinical study: Salivary flow and mucosal breaks and ulcerations improved after Pycnogenol® supplementation in diabetic and non-diabetic patients with dry mouth syndrome (Xerostomia).  
Belcaro G, Cesarone MR, Cornelli U, Scipione, C., Scipione, V., Dugall, M., Hu, S., Feragalli, B., Hosoi, M., Maione, C., Cotellese, R., Cesinaro Di Rocco, P.  
Xerostomia: prevention with Pycnogenol® supplementation: a pilot study.  
Minerva Stomatol. 2019;68(6):303-307, 2019
- 
- Ref. 505** Mini Review, suggesting that toothpaste containing Pycnogenol® improves oral health and prevents the development of periodontal diseases.  
Sato, T., K. Watanabe, H. Sasaki, H. Hiramine, S. Goda and N. Hamada  
Antimicrobial activity and inhibitory effect of alveolar bone loss of toothpaste containing a natural plant extract.  
Kanagawa Shigaku 53(1/2): 40-44., 2018
- 
- Ref. 468** Clinical Study: Pycnogenol® chewing gum is effective in reducing oral malodor by decreasing the accumulation of tongue coating and the number of hydrogen sulfide-producing bacteria in saliva.  
Watanabe K, Hiramine H, Toyama T, Hamada N  
Effects of French Pine Bark Extract Chewing Gum on Oral Malodor and Salivary Bacteria.  
J Nutr Sci Vitaminol 64: 185-191, 2018
- 
- Ref. 409** Supplementation with Pycnogenol® may be useful as a therapeutic and preventative agent for bone diseases such as periodontitis.  
Sugimoto H, Watanabe K, Toyama T, Takahashi S-s, Sugiyama S, Lee M-C-I, Hamada N  
Inhibitory Effect of French Pine Bark Extract, Pycnogenol®, on Alveolar Bone Resorption and on the Osteoclast Differentiation.  
Phytother Res 29(2): 251-259, 2015
- 
- Ref. 356** Clinical Study: Pycnogenol® applied orally, dissolved in glycerol, significantly helps control mucositis in children undergoing chemotherapy.  
Khurana H, Pandey RK, Saksena AK, Kumar A  
An evaluation of vitamin E and Pycnogenol® in children suffering from oral mucositis during cancer chemotherapy.  
Oral Dis 19(5): 456-464, 2012

- 
- 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
- 
- 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
- 
- 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

## 10 Pain management

- 
- Ref. 576** Clinical study: Pycnogenol® relieves symptoms including leg pain associated with restless leg syndrome.  
Belcaro G, Rohdewald P, Cesarone MR, Scipione C, Scipione V, Cornelli U, Luzzi R, Cotellese R, Dugall M, Hosoi M, Corsi M, Feragalli B.  
Restless legs syndrome: prevention with Pycnogenol® and improvement of the venoarteriolar response.  
Panminerva Med. 2022;64(2):253-8, 2022
- 
- Ref. 564** Clinical study: Pycnogenol® improves mobility and pain in subjects with idiopathic back pain.  
Cox D, Belcaro G, Cesarone MR, Cotellese R, Dugall M, Feragalli B, Hosoi M, Corsi M, Luzzi R.  
Primary benign back pain: supplementation with Pycnogenol®  
Panminerva Med. 2021 Dec;63(4):472-477, 2021
- 
- Ref. 544** Clinical study: Pycnogenol® helps to control and reduce the intensity of pain in fibromyalgia patients.  
Belcaro G, Hu S, Cesarone MR, Dugall M, Scipione C, Scipione V, Hosoi M, Ledda A, Cornelli U, Feragalli B, Cotellese R  
Idiopathic myalgic pain (fibromyalgia): supportive management and prevention with Pycnogenol®  
Panminerva medica 63(1): 46-50, 2021
- 
- Ref. 510** Clinical study: Pycnogenol® reduces pain and the number and severity of symptoms in patients with migraine or moderate headache.  
Cesarone, M. R., M. Dugall, S. Hu, G. Belcaro, M. Hosoi, V. Scipione, C. Scipione and R. Cotellese  
Episodic primary migraine headache: supplementary prophylaxis with Pycnogenol® prevents attacks and controls oxidative stress.  
Panminerva Med 62(2): 102-108, 2020
- 
- Ref. 506** Clinical study: Pycnogenol® improves microcirculation and reduces main symptoms including pain of patients with Raynaud syndrome.  
Hu, S., M. Hosoi, G. Belcaro, M. Dugall, B. Feragalli, R. Cotellese and R. Luzzi (2019) "  
Management of mild, primary Raynaud Syndrome: supplementation with Pycnogenol®  
Minerva Cardioangiol 67(5): 392-398, 2019
- 
- Ref. 475** Clinical Study: The comparison with three different strategies (Buscopan, Antispasmina Col Forte and Pycnogenol®) revealed a higher efficacy of Pycnogenol® in reducing the chronic discomfort associated to irritable bowel disease.  
Belcaro G, Gizzi G, Pellegrini L, Feragalli B, Cotellese R, Cacchio M, Corsi M  
Pycnogenol® supplementation improves the control of irritable bowel syndrome symptoms.  
Panminerva Med 60(2): 65-69, 2018
- 
- Ref. 400** Clinical Study: In combination with low-dose oral contraceptives Pycnogenol® effectively decreases pain and number of bleeding days.  
Maia H, Haddad C, Casoy J  
The effect of Pycnogenol® on patients with dysmenorrhea using low-dose oral contraceptives.  
Int J Women's Health 6: 1019-1022, 2014
- 
- 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, Schönlau 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

- 
- 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
- 
- Ref. 219** Clinical Study: Pycnogenol® reduces pain from endometriosis, shows fewer 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
- 
- 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
- 
- 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
- 
- 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
- 
- 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

## 11 Respiratory Health

- 
- Ref. 555** Clinical study: Pycnogenol® and Centellicum® reduce the fibrotic component in idiopathic interstitial pneumonia and improve post-COVID-19 lung disease symptoms.  
Belcaro Gianni, Cornelli U, Cesarone MR, Hu Shu, Feragalli Beatrice, Corsi Marcello, Bombardelli Ezio, Cotellese Roberto, Hosoi Morio  
Supplementary management with Pycnogenol®-Centellicum® may slow down the progression of pulmonary fibrosis and improve Post-Covid-19 lung healing.  
Biomed J Sci & Tech Res 28(1): 21275-21280, 2020
- 
- Ref. 554** Clinical study: The combination of Pycnogenol® and Centellicum® improves the symptoms and slows down the development of lung fibrosis in idiopathic interstitial pneumonia and has beneficial effects in post-COVID-19 lung disease.  
Cesarone MR, Hu S, Belcaro G, Cornelli U, Feragalli B, Corsi M, Bombardelli E, Cotellese R, Hosoi M, Rosenkvist L.  
Pycnogenol®-Centellicum® supplementation improves lung fibrosis and Post-Covid-19 lung healing.  
Minerva Med. 2021 Jun 28, 2021
- 
- Ref. 452** Pycnogenol® is shown in preclinical research to help manage allergic rhinitis.  
Günel C, Demirci B, Eryilmaz A, Yılmaz M, Meteoglu I, Ömürlü IK, Basal Y  
Inhibitory Effect of Pycnogenol® on Airway Inflammation in Ovalbumin-Induced Allergic Rhinitis.  
Balkan Me J 33: 620-626, 2016
- 
- Ref. 447** This pre-clinical study indicates that Pycnogenol® inhibits the reduction of inflammatory response in CSE stimulated NCI-H292 cells and a COPD mouse model via the Erk-sp1 pathway. Pycnogenol® is suggested to have potential for improving chronic obstructive pulmonary disorder symptoms.  
Shin N-R, Ryu H-W, Ko J-W, Park J-W, Kwon O-K, Oh S-R, Kim J-C, Shin I-S, Ahn K-S  
A standardized bark extract of Pinus pinaster Aiton (Pycnogenol®) attenuated chronic obstructive pulmonary disease via Erk-sp 1 signaling pathway.  
J Ethnopharmacol 194: 412-420, 2016

- 
- Ref. 444** Review comprising Pycnogenol® virtues for allergic rhinitis (hayfever).  
 Ross SM  
 Allergic Rhinitis. A proprietary extract of Pinus pinaster Aiton (Pycnogenol®) is found to improve the symptoms associated with allergic rhinitis.  
 Hollist Nurs Pract 30: 301-304, 2016
- 
- Ref. 441** Clinical Study: Research finds Pycnogenol® effective for allergies.  
 Belcaro G, Feragalli B, Hosoi M, Dugall M, Cornelli U  
 Pycnogenol® reduces the wheal and flare response to histamine in normal subjects.  
 Minerva Biotechnologica 28(2): 114-119, 2016
- 
- Ref. 396** Clinical Study: Pycnogenol® decreases symptoms of common cold and shorten its course also preventing some complications.  
 Belcaro G, Shu H, Luzzi R, Dugall M, Ippolito E, Cesarone MR, Corsi M, Feragalli B  
 Improvement of common cold with Pycnogenol®: a Winter registry study.  
 Panminvera Med 56: 301-308, 2014
- 
- Ref. 380** Pycnogenol® inhibits asthma in rats.  
 Shin I-S, Shin N-R, Jeon C-M, Hong J-M, Kwon O-K, Kim J-C, O S-R, Hahn K-W, A K-S  
 Inhibitory effects of Pycnogenol® (French maritime pine bark extract) on airway inflammation in ovalbumin-induced allergic asthma.  
 Food Chem Toxicol 62: 681-686, 2013
- 
- Ref. 369** Clinical Study: Pycnogenol® supplementation speeds-up recovery from a common cold, and even more efficiently in combination with vitamin C and zinc.  
 Belcaro G, Luzzi R, Umberto C, Hu S, Dugall M, Ippolito E, Cesarone MR, Corsi M, Pellegrini L, Ledda A, Appendino G  
 The common cold Winter Study: Effects of Pycnogenol® on Signs, Symptoms, Complications & Costs.  
 Otorinolaringol 63: 151-161, 2013
- 
- 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
- 
- 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
- 
- 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
- 
- 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
- 
- Ref. 089** Pycnogenol® blocks release of histamine from mast cells in vitro to the same extent as the anti-asthmatic drug DNCG.  
 Sharma SC, Sharma S, Gulati OP  
 Pycnogenol® inhibits the release of histamine from mast cells.  
 Phytother Res 17: 66-69, 2003
- 
- 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

## 12 Skin Care – oral and topical

- 
- Ref. 571** Clinical study: Topically applied Pycnogenol® is effective for preventing inflammatory acne.  
Kim K-Y.  
The effect Pycnogenol has on the acne skin of Koreans in their 10s and 20s.  
Journal of Digital Convergence. 2022;20(3):487–95, 2022
- 
- Ref. 551** Pycnogenol® inhibits skin hyperpigmentation in vitro by downregulating tyrosinase and reducing pigmentation-related mediators thus reducing melanin production.  
Ayres EL, Silva JDS, Eberlin S, Facchini G, Vasconcellos C, Costa A.  
In-vitro effect of pine bark extract on melanin synthesis, tyrosinase activity, production of endothelin-1 and PPAR in cultured melanocytes exposed to Ultraviolet, Infrared, and Visible light radiation.  
J Cosmet Dermatol. 2021
- 
- Ref. 550** Clinical study: Pycnogenol® benefits the skin of urban outdoor workers under considerable environmental stress regarding skin moisture, elasticity and lightening.  
Zhao H., Wu J., Wang N., Grether-Beck S., Krutmann J., Wei L.  
Oral Pycnogenol® Intake Benefits the Skin in Urban Chinese Outdoor Workers: A Randomized, Placebo-Controlled, Double-Blind, and Crossover Intervention Study  
Skin Pharmacol Physiol: p. 1-11, 2021
- 
- Ref. 545** A bio adhesive film containing Pycnogenol® for topical application promotes the healing of damaged skin areas via stimulation of keratinocyte growth.  
Pagano C, Puglia D, Luzi F, Michele AD, Scuota S, Primavilla S, et al.  
Development and Characterization of Xanthan Gum and Alginate Based Bioadhesive Film for Pycnogenol Topical Use in Wound Treatment.  
Pharmaceutics 13(3): 324, 2021
- 
- Ref. 542** Pycnogenol® prevents hemosiderin deposits in human skin culture submitted to inflammatory stress as a model of skin hyperpigmentation after sclerotherapy for the treatment of varicose veins or due to chronic venous insufficiency.  
Mello Netto BAS, Corassa JM, Facchini G, da Silva MS, Pinheiro ALTA, Eberlin S  
Pre-clinical evaluation of the prophylactic effects of Pinus pinaster extract (Pycnogenol®) on skin hemosiderin deposits.  
Surg Cosmet Dermatol. Rio de Janeiro v.11 n.2 abr-jun. 2019 p. 121-5., 2019
- 
- Ref. 439** Pycnogenol® shows pigmentation reduction in human skin.  
Ayres EL, Costa A, Eberlin S, Clerici SP  
Ex vivo study for evaluating the whitening activity of Pycnogenol® after exposure to ultraviolet and infrared radiations, and visible lights.  
Surg Cosmet Dermatol 7: 303-307, 2015
- 
- Ref. 430** Clinical Study: This article reviews earlier clinical Pycnogenol® research of the group, identifying improved skin elasticity and hydration, highlighting new findings on oral Pycnogenol® supporting fairer skin complexion, as well as improved skin barrier function.  
Grether-Beck S, Marini A, Jaenicke T, Krutmann J  
French Maritime Pine Bark Extract (Pycnogenol®) Effects on Human Skin: Clinical and Molecular Evidence.  
Skin Pharmacol Physiol 29: 13-17, 2016
- 
- Ref. 429** Clinical Study: The study describes significant reduction of skin pigmentation with Pycnogenol® supplementation, taken in addition to the use of sunscreens, in 31 women with melasma.  
Pinto CAS, Zuchi Delfes MF, Montanheiro dos Reis L, Garbers LE, Vieira da Rosa Passos PC, Skusa de Torre D  
The use of Pycnogenol® in the treatment of melasma.  
Surg Cosmet Dermatol 7: 218-222, 2015
- 
- Ref. 414** Clinical Study: Research demonstrates that Pycnogenol® in combination with pomegranate extract brightens skin and helps decrease blotches in European and Asian women.  
De Schuyteneer A, Hamon I, Rohdewald P  
A formulation of extracts from pine bark and pomegranate improves complexion after oral intake.  
Esperienze Dermatologiche 17: 7-11, 2015
- 
- Ref. 389** Clinical Study: The oral administration of Pycnogenol® combined with daily sunscreen application should be added as an adjuvant to other treatments of melasma.  
Campos V  
Oral administration of Pycnogenol® associated with sunscreen improve clinical symptoms of melasma.  
J Am Acad Dermatol AB19 (P8471), 2014
- 
- Ref. 388** Clinical Study: Most common clinical aspects of psoriasis could be improved by Pycnogenol® supplementation.  
Belcaro G, Luzzi R, Hu S, Cesarone MR, Dugall M, Ippolito E, Corsi M, Caporale S  
Improvement in signs and symptoms in psoriasis patients with Pycnogenol® supplementation.  
Panminerva Med 56: 41-48, 2014

- 
- Ref. 348** Clinical Study: Pycnogenol® increases women’s skin elasticity and hydration which coincides with significantly new collagen and hyaluronic acid 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.  
Skin Pharmacol Physiol 25: 86-92, 2012
- 
- 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
- 
- 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
- 
- 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
- 
- 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 chemo preventive 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
- 
- 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
- 
- Ref. 172** Clinical Study: Ulcers of the lower legs heal faster with orally and topically applied 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. 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
- 
- 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
- 
- 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
- 
- 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
- 
- Ref. 111** Pycnogenol® applied topically after sunburn inhibits photo carcinogenesis.  
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



- 
- 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
- 
- Ref. 094** Review summarizing the beneficial effects of Pycnogenol® for skin care.  
Schönlau F  
The cosmeceutical Pycnogenol®.  
J Appl Cosmetol 20: 241-246, 2002
- 
- 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
- 
- Ref. 074** Clinical Study: Pycnogenol® dose-dependently inhibits UV-induced erythema in humans, demonstrating a potent anti-photoaging 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
- 
- Ref. 073** Pycnogenol® favorably 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
- 
- 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
- 
- 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
- 
- Ref. 026** Pycnogenol® protects  $\alpha$ -tocopherol from oxidation and extends its lifetime 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
- 
- 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  
Skin Care
- 
- 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 Flavon Derivate bei spontan hypertensischen Ratten.  
Phlebologie 22: 178-182, 1993
- 
- 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

## 13 Sports

- Ref. 488** Clinical Study: Pycnogenol® may improve the general fitness status in elderly and decrease the burden of fatigue experienced during normal activities such as shopping, walking, house-keeping.  
Hosoi M, Cotellese R, Belcaro G, et al.  
Pycnogenol®: Prevention of muscular mass and strength loss in the elderly.  
J Sports Med Physical Fitness, ahead of print, 2018; Pharma standard (PS) supplements. Papers from the London sessions January 2018. Eds. Belcaro G, Dugall M, Ledda A., ISBN; 978-88-7711-940
- Ref 483** Clinical Study: Pycnogenol® provides post-workout protection against oxidative stress.  
Aldret R, Bellar D  
A Double-Blind, Cross-Over Study to Examine the Effects of Maritime Pine Extract on Exercise Performance and Postexercise Inflammation, Oxidative Stress, Muscle Soreness, and Damage.  
Journal of dietary supplements: 1-12, 2018
- Ref. 368** Clinical Study: Pycnogenol® reduces oxidative stress and improves physical performance in athletes.  
Vinciguerra G, Belcaro G, Bonanni E, Cesarone MR, Ledda A, Hosoi M, Dugall M, Cacchio M, Cornelli U  
Evaluation of the effects of supplementation with Pycnogenol® on fitness in normal subjects with the Army Physical Fitness Test and in performances of athletes in the 100-minute triathlon.  
J sports Med Phys Fitness 53(6): 644-654, 2013
- 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
- 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  
Cramps and muscular pain: prevention with Pycnogenol® in normal subjects, venous patients, athletes, claudicants and in diabetic microangiopathy.  
Angiology 57: 331-339, 2006
- Ref. 044** Clinical Study: Pycnogenol® increases exercise endurance in recreational athletes by 21% on a treadmill.  
Pavlovic P  
Improved endurance by use of antioxidants.  
Eur Bull Drug Res 7: 26-29, 1999

## 14 Travel Health

- Ref. 469** Clinical Study: Pycnogenol® reduces edema and may control some thrombotic events.  
Belcaro G, Cornelli U, Dugall M, Hosoi M, Cotellese R, Feragalli B  
Long-haul flights, edema, and thrombotic events: prevention with stockings and Pycnogenol® supplementation (LONFLIT Registry Study).  
Minerva Cardioangiol 66: 152-159, 2018
- 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
- 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, Scocciati 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
- 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

- 
- Ref. 116** Clinical Study: Pycnogenol® in combination with Nattokinase prevents deep vein thrombosis in long-haul flights.  
 Cesarone MR, Belcaro G, Nicolaidas 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
- 
- 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

## 15 Venous Health

- 
- Ref. 542** Pycnogenol® prevents hemosiderin deposits in human skin culture submitted to inflammatory stress as a model of skin hyperpigmentation after sclerotherapy for the treatment of varicose veins or due to chronic venous insufficiency.  
 Mello Netto BAS, Corassa JM, Facchini G, da Silva MS, Pinheiro ALTA, Eberlin S  
 Pre-clinical evaluation of the prophylactic effects of Pinus pinaster extract (Pycnogenol®) on skin hemosiderin deposits.  
 Surg Cosmet Dermatol. Rio de Janeiro v.11 n.2 abr-jun. 2019 p. 121-5., 2019
- 
- Ref. 504** Clinical study: Pycnogenol® (both as a single treatment and in association with compression) is significantly effective in the management, treatment and control of chronic venous insufficiency.  
 Cesarone, M. R., G. Belcaro, G. B. Agus, E. Ippolito, M. Dugall, M. Hosoi, M. Corsi, R. Cotellese, B. Feragalli, C. Scipione, V. Scipione and C. Maione  
 Chronic venous insufficiency and venous microangiopathy: management with compression and Pycnogenol®.  
 Minerva Cardioangiol 67(4): 280-287, 2019
- 
- Ref. 476** Pycnogenol® is more effective in preventing of the post-thrombotic syndrome and a new venous thrombosis than Aspirin, sulodexide and ticlopidine.  
 Belcaro G, Dugall M, Hu S, Feragalli B, Cotellese R, Ledda A, Corsi M, Ricci A, Ippolito E, Errichi BM, Cornelli U, Cesarone MR, Hosoi M  
 Prevention of recurrent venous thrombosis and post-thrombotic syndrome.  
 Minerva Cardioangiol 66(3): 238-245, 2018
- 
- Ref. 469** Clinical Study: Pycnogenol® reduces edema and may control some thrombotic events.  
 Belcaro G, Cornelli U, Dugall M, Hosoi M, Cotellese R, Feragalli B  
 Long-haul flights, edema, and thrombotic events: prevention with stockings and Pycnogenol® supplementation (LONFLIT Registry Study).  
 Minerva Cardioangiol 66: 152-159, 2018
- 
- Ref. 463** Review: Pycnogenol® relieves venous edema. The combined topical and oral use of Pycnogenol® accelerates the healing of venous and diabetic ulcers and hemorrhoids.  
 Rohdewald P  
 Pycnogenol® bei Erkrankungen des venösen Systems – eine systematische Übersicht.  
 Schweiz Z Ganzheitsmed 29: 372-375, 2017
- 
- Ref. 459** Clinical Study: In comparison with stockings and several venoactive and anti-edema products Pycnogenol® appears to be the most potent and effective product.  
 Belcaro G, Dugall M, Luzzi R, Corsi M, Ledda A, Ricci A, Pellegrini L, Cesarone MR, Hosoi M, Errichi BM, Cornelli U, Cotellese R, Agus G, Feragalli B  
 Management of varicose veins and chronic venous insufficiency in a comparative registry with nine venoactive products in comparison with stockings.  
 Int J Angiol 26: 170-178, 2017
- 
- Ref. 434** Review: A summary of investigations related to biological activities and clinical actions of Pycnogenol® related to oedema, ulcers, thromboses, CVI and hemorrhoids.  
 Rohdewald P  
 Gerbstoffhaltiger Extrakt zur oralen und topischen Behandlung bei CVI und Hämorrhoidalleiden.  
 Phlebologie 44: 334-338, 2015
- 
- Ref. 420** Clinical Study: Pycnogenol® is suggested to be superior compared to other veno-tonic products.  
 Belcaro G  
 A clinical comparison of Pycnogenol®, Antistax, and Stocking in Chronic Venous Insufficiency.  
 Int J Angiol 24: 268-274, 2015

- 
- Ref. 392** **Clinical Study: The use of Pycnogenol® improves signs and symptoms of postpartum varicose veins and venous function. Veins regain shape faster.**  
 Belcaro G, Dugall M, Luzzi R, Ippolito E, Cesarone MR  
 Postpartum Varicose Veins: Supplementation with Pycnogenol® or Elastic Compression - A 12-Month Follow-Up.  
 Int J Angiol DOI 10.1055/s-0033-1363784, 2014
- 
- Ref. 386** **Clinical Study: Pycnogenol® seems to decrease passive dilatation and stretching and gives vein walls a greater tonic recovery and elasticity that allows the vein to recover its original shape after dynamic stresses.**  
 Belcaro G, Dugall M, Luzzi R, Hosoi M, Corsi M  
 Improvement of Venous Tone with Pycnogenol® in Chronic Venous Insufficiency: An Ex Vivo Study on Venous Segments.  
 Int J Angiol 23:47-52, 2014
- 
- Ref. 383** **Clinical Study: In the months after pregnancy, Pycnogenol® appears to positively affect hemorrhoid signs and symptoms.**  
 Belcaro G, Gizzi G, Pellegrini M, Dugall M, Luzzi R, Corsi M, Ippolito E, Ricci A, Cesarone MR, Ledda A, Bottari A, Errichi BM  
 Pycnogenol® in postpartum symptomatic hemorrhoids.  
 Minerva Ginecologica 66(1): 77-84, 2014
- 
- Ref. 370** **A concise, yet comprehensive, up to date review on preclinical and clinical research on Pycnogenol® related to venous insufficiency and thrombosis management.**  
 Gulati OP  
 Pycnogenol® in Chronic Venous Insufficiency and Related Venous Disorders.  
 Phytother Res. 2014 Mar;28(3):348-62, 2014
- 
- 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
- 
- 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
- 
- 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
- 
- 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. 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
- 
- 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, Ippolito 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, Scocciati 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, 2005
- 
- 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
- 
- 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
- 
- 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
- 
- 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
- 
- 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
- 
- 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
- 
- 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
- 
- 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 Flavon Derivate bei spontan hypertensischen Ratten.  
 Phlebologie 22: 178-182, 1993

## 16 Women's Health

- Ref. 563** Clinical study: The prophylaxis with Pycnogenol® decreases the occurrence and symptoms of urinary tract infections.  
Cotellese R, Hu S, Cesarone MR, Belcaro G, Dugall M, Feragalli B, Hosoi M, Ippolito E, Corsi M, Luzzi R.  
Pycnogenol® supplementation prevents inflammation and symptoms in recurrent, non-severe urinary infections.  
Panminerva Med. 2021 Sep;63(3):343-348., 2021
- Ref. 556** Clinical study: Pycnogenol® decreases the occurrence of urinary tract infections and interstitial cystitis with a higher efficacy than cranberry.  
A. Ledda, S. Hu, M. R. Cesarone, G. Belcaro, M. Dugall, B. Feragalli, R. Cotellese, M. Hosoi, E. Ippolito, 1 M. Corsi, and R. Luzzi  
Pycnogenol® Supplementation Prevents Recurrent Urinary Tract Infections/Inflammation and Interstitial Cystitis.  
Evidence-Based Complementary and Alternative Medicine, vol. 2021, p. 9976299, 2021
- Ref. 499** Pycnogenol® reduces Escitalopram (anti-depressant)-induced sexual dysfunction and elevated heart rate in both genders based on its ability to improve endothelial.  
Smetanka A, Stara V, Farsky, I, Tonhajzerova I, Ondrejka I  
Pycnogenol® supplementation as an adjunct treatment for antidepressant-induced sexual dysfunction.  
Physiol Int 106(1): 59-69, 2019
- Ref. 462** Review: Pycnogenol® improves women's health in a non-hormonal way.  
Rohdewald PJ  
Pycnogenol®, a Plant Extract for Women's Health.  
Int J Women's Health Care (IJWHC) 2(1): 1-5, 2017
- Ref. 453** Clinical Study: Further to alleviating menopausal symptoms, Pycnogenol® significantly improves blood sugar and -lipids, and supports healthy blood pressure, CRP- and homocysteine values.  
Luzzi R, Belcaro G, Hosoi M, Feragalli B, Cornelli U, Dugall M, Ledda A  
Normalization of cardiovascular risk factors in peri-menopausal women with Pycnogenol®.  
Minerva Ginecol 69: 29-34, 2017
- Ref. 449** A review on the efficacy of Pycnogenol® to alleviate climacteric symptoms by improving endothelial function and antioxidative status.  
Rohdewald P  
Relief from Menopausal Symptoms by Non-hormonal Treatment with Pycnogenol® (French Maritime Pine Bark Extract).  
J Genit Syst & Disor 5: 4, 2016
- Ref. 430** Clinical Study: This article reviews earlier clinical Pycnogenol® research of the group, identifying improved skin elasticity and hydration, highlighting new findings on oral Pycnogenol® supporting fairer skin complexion, as well as improved skin barrier function.  
Grether-Beck S, Marini A, Jaenicke T, Krutmann J  
French Maritime Pine Bark Extract (Pycnogenol®) Effects on Human Skin: Clinical and Molecular Evidence.  
Skin Pharmacol Physiol 29: 13-17, 2016
- Ref. 429** Clinical Study: The study describes significant reduction of skin pigmentation with Pycnogenol® supplementation, taken in addition to the use of sunscreens, in 31 women with melasma.  
Pinto CAS, Zuchi Delfes MF, Montanheiro dos Reis L, Garbers LE, Vieira da Rosa Passos PC, Skusa de Torre D  
The use of Pycnogenol® in the treatment of melasma.  
Surg Cosmet Dermatol 7: 218-222, 2015
- Ref. 423** Pycnogenol® inhibits bone demineralisation in preclinical menopause research.  
Huang G, Wu J, Wang S, Wei Y, Chen F, Chen J, Shi J, Xia J  
Pycnogenol® treatment inhibits bone mineral density loss and trabecular deterioration in ovariectomized rats.  
Int J Clin Exp Med 8(79): 10893-10901, 2015
- Ref. 400** Clinical Study: In combination with low-dose oral contraceptives Pycnogenol® effectively decreases pain and number of bleeding days.  
Maia H, Haddad C, Casoy J  
The effect of Pycnogenol® on patients with dysmenorrhea using low-dose oral contraceptives.  
Int J Women's Health 6: 1019-1022, 2014
- Ref. 392** Clinical Study: The use of Pycnogenol® improves signs and symptoms of postpartum varicose veins and venous function. Veins regain shape faster.  
Belcaro G, Dugall M, Luzzi R, Ippolito E, Cesarone MR  
Postpartum Varicose Veins: Supplementation with Pycnogenol® or Elastic Compression - A 12-Month Follow-Up.  
Int J Angiol DOI 10.1055/s-0033-1363784, 2014
- Ref. 389** Clinical Study: The oral administration of Pycnogenol® combined with daily sunscreen application should be added as an adjuvant to other treatments of melasma.  
Campos V  
Oral administration of Pycnogenol® associated with sunscreen improve clinical symptoms of melasma.  
J Am Acad Dermatol AB19 (P8471), 2014

- 
- Ref. 387** **Clinical Study: The combination of oral contraceptives with Pycnogenol® shows a positive synergetic effect on the eutopic endometrium of endometriosis patients.**  
 Maia H, Haddad C, Pinheiro N, Casoy J  
 The Effect of Oral Contraceptives Combined with Pycnogenol (Pinus Pinaster) On Aromatase and VEGF Expression in the Eutopic Endometrium of Endometriosis Patients.  
 Gynecol Obstet 4:2, 2014
- 
- Ref. 383** **Clinical Study: In the months after pregnancy, Pycnogenol® appears to positively affect hemorrhoid signs and symptoms.**  
 Belcaro G, Gizzi G, Pellegrini M, Dugall M, Luzzi R, Corsi M, Ippolito E, Ricci A, Cesarone MR, Ledda A, Bottari A, Errichi BM  
 Pycnogenol® in postpartum symptomatic hemorrhoids.  
 Minerva Ginecologica 66(1): 77-84, 2014
- 
- Ref. 378** **Clinical Study: Pycnogenol® taken with oral contraceptives alleviates endometriosis related pain.**  
 Maia H, Haddad C, Casoy J  
 Combining oral contraceptives with a natural nuclear factor-kappa B inhibitor for the treatment of endometriosis-related pain.  
 Int J Womens Health 6: 35-39, 2014
- 
- Ref. 376** **Clinical Study: Pycnogenol® significantly improved peri-menopausal symptoms at relatively low daily dosage of 60 mg and was demonstrated to not interfere with sexual hormone levels.**  
 Kohama T, Negami M  
 Effect of low-dose French maritime pine bark extract on climacteric syndrome in 170 perimenopausal women.  
 J Reprod Med 58(1-2): 39-46, 2013
- 
- Ref. 348** **Clinical Study: Pycnogenol® increases women's skin elasticity and hydration which coincides with significantly new collagen and hyaluronic acid 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.  
 Skin Pharmacol Physiol 25: 86-92, 2012
- 
- 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
- 
- 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
- 
- Ref. 219** **Clinical Study: Pycnogenol® reduces pain from endometriosis, shows fewer 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
- 
- 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
- 
- 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
- 
- 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
- 
- 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

## II. Mechanisms of action

### 17 Anti-inflammatory Action

- 
- Ref. 563** Clinical study: The prophylaxis with Pycnogenol® decreases the occurrence and symptoms of urinary tract infections. Cotellesse R, Hu S, Cesarone MR, Belcaro G, Dugall M, Feragalli B, Hosoi M, Ippolito E, Corsi M, Luzzi R. Pycnogenol® supplementation prevents inflammation and symptoms in recurrent, non-severe urinary infections. *Panminerva Med.* 2021 Sep;63(3):343-348., 2021
- 
- Ref. 556** Clinical study: Pycnogenol® decreases the occurrence of urinary tract infections and interstitial cystitis with a higher efficacy than cranberry. A. Ledda, S. Hu, M. R. Cesarone, G. Belcaro, M. Dugall, B. Feragalli, R. Cotellesse, M. Hosoi, E. Ippolito, M. Corsi, and R. Luzzi Pycnogenol® Supplementation Prevents Recurrent Urinary Tract Infections/Inflammation and Interstitial Cystitis. *Evidence-Based Complementary and Alternative Medicine*, vol. 2021, p. 9976299, 2021
- 
- Ref. 553** Clinical study: Pycnogenol® shows beneficial effects for managing some of the signs and symptoms associated with post-Covid-19 and improves cardiovascular risk factors. Belcaro G, Cornelli U, Cesarone MR, Scipione C, Scipione V, Hu S, Feragalli B, Corsi M, Cox D, Cotellesse R, Hosoi M, Burki C Preventive effects of Pycnogenol® on cardiovascular risk factors (including endothelial function) and microcirculation in subjects recovering from coronavirus disease 2019 (COVID-19). *Minerva Med.* 113(2):300-8, 2022
- 
- Ref. 498** Gastrointestinal metabolism of Pycnogenol® reveals its immunomodulatory and anti-inflammatory properties. Verlaet A, van der Bolt N, Meijer B, et al Toll-Like Receptor-Dependent Immunomodulatory Activity of Pycnogenol®. *Nutrients* 11: 214; doi:10.3390/nu11020214, 2019
- 
- Ref. 487** Clinical Study: Pycnogenol® patch is safe and effective to control pain and improve symptoms in idiopathic, benign, transient neck pain. Belcaro G, Dugall M, Feragalli B, et al. Prevention of symptoms associated to neck pain with a Pycnogenol® patch. *J Sports Med Physical Fitness, Pharma standard (PS) supplements. Papers from the London sessions January 2018.* Eds. Belcaro G, Dugall M, Ledda A., ISBN: 978-88-7711-940, 2018
- 
- Ref. 485** Clinical Study: Pycnogenol® supplementation in patients with Sjögren Syndrome in a remission phase may be effective to control inflammation and reduce symptoms. Luzzi R, Belcaro G, Hu S, et al. Efficacy of Pycnogenol® supplementation in remission phases of Sjögren syndrome. *Min Cardioangiol* 66(5): 543-546, 2018
- 
- Ref. 484** Clinical Study: Managing Behçet's Syndrome with Pycnogenol® supplementation is useful. Hu S, Belcaro G, Ledda A, et al. Behçet's Syndrome: Effects of Pycnogenol® addition during regression phases. *Minerva Cardioangiologica* 66(4): 386-390, 2018
- 
- Ref. 451** Clinical Study: Pycnogenol® applied topically as patch soothes muscular pain. Luzzi R, Belcaro G, Feragalli B, Dugall M Moderate, diffuse, somatic muscular pain: effects of supplementation with a Pycnogenol® patch. *Minerva Ortopedica e Traumatologica* 67(4): 170-176, 2016
- 
- Ref. 447** This pre-clinical study indicates that Pycnogenol® inhibits the reduction of inflammatory response in CSE stimulated NCI-H292 cells and a COPD mouse model via the Erk-sp1 pathway. Pycnogenol® is suggested to have potential for improving chronic obstructive pulmonary disorder symptoms. Shin N-R, Ryu H-W, Ko J-W, Park J-W, Kwon O-K, Oh S-R, Kim J-C, Shin I-S, Ahn K-S A standardized bark extract of *Pinus pinaster* Aiton (Pycnogenol®) attenuated chronic obstructive pulmonary disease via Erk-sp 1 signaling pathway. *J Ethnopharmacol* 194: 412-420, 2016
- 
- Ref. 427** Clinical Study: Blood- and synovial-fluid samples were analyzed for Pycnogenol® constituents and metabolites to elucidate tissue distribution in humans. The study determines which compounds of the French maritime pine bark extract are absorbed and how they are distributed in the body. Högger P PL4: Pharmacokinetics and cellular effects of a French maritime pine bark extract in humans. *Nutrition and Medicine* 3(S1): 20, 2015



- 
- Ref. 424** Pycnogenol® counteracts inflammatory situations of brain microglia cells in pre-clinical study.  
Fan B, Dun S-H, Gu J-Q, Guo Y, Ikuyama S  
Pycnogenol attenuates the release of proinflammatory cytokines and expression of perilipin 2 in lipopolysaccharides-stimulated microglia in part via inhibition of NF-κB and AP-1 activation.  
PLOS ONE 10(9): e0137837.doi:10.1371/journal, 2015
- 
- Ref. 418** Pycnogenol® helps avoid post-operative development of peritoneal fibrous adhesions.  
Sahbaz A, Aynioglu O, Isik H, Gun BD, Cengil O, Erol O  
Pycnogenol prevents peritoneal adhesions.  
Arch Gynecol Obstet. 292: 1279-1284, 2015
- 
- Ref. 408** Clinical Study: Endothelial function is improved by Pycnogenol®. Results of this open registry study indicate an important preventive possibility for borderline hypertensive, hyperglycemic and hyperlipidemic subjects.  
Hu S, Belcaro G, Cornelli U, Luzzi R, Cesarone MR, Dugall M, Feragalli B, Errichi B, Ippolito E, Grossi MG, Hosoi M, Gizzi G, Trignani M  
Effects of Pycnogenol® on endothelial dysfunction in borderline hypertensive, hyperlipidemic, and hyperglycemic individuals: the borderline study.  
Int Angiol 34(1): 43-52, 2015
- 
- Ref. 396** Clinical Study: Pycnogenol® decreases symptoms of common cold and shorten its course also preventing some complications.  
Belcaro G, Shu H, Luzzi R, Dugall M, Ippolito E, Cesarone MR, Corsi M, Feragalli B  
Improvement of common cold with Pycnogenol®: a Winter registry study.  
Panminvera Med 56: 301-308, 2014
- 
- Ref. 387** Clinical Study: The combination of oral contraceptives with Pycnogenol® shows a positive synergetic effect on the eutopic endometrium of endometriosis patients.  
Maia H, Haddad C, Pinheiro N, Casoy J  
The Effect of Oral Contraceptives Combined With Pycnogenol (Pinus Pinaster) On Aromatase and VEGF Expression in the Eutopic Endometrium of Endometriosis Patients.  
Gynecol Obstet 4:2, 2014
- 
- 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
- 
- 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
- 
- 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, Schönlau 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
- 
- 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
- 
- 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
- 
- 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-κappaB activation and MMP-9 secretion by plasma of human volunteers after ingestion of maritime pine bark extract (Pycnogenol®).  
J Inflamm 3: 1-6, 2006

- 
- Ref. 183** Pycnogenol® protects intestinal mucosa against radiotherapy induced damage: histo-morphological 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
- 
- 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
- 
- 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
- 
- 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
- 
- 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
- 
- 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
- 
- 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  
Anti-inflammatory activities of procyanidin containing extracts from Pinus pinaster Ait. after oral and cutaneous application.  
Pharmazie 52: 380-382, 1997
- 
- 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

## 18 Antioxidant Activity

- 
- Ref. 560** Clinical study: Pycnogenol® dose-dependently decreases oxidative stress in subjects with high oxidative stress, even at low doses.  
Belcaro G, Cesarone MR, Dugall M, Hu S, Peterzan P, Feragalli B, Hosoi M, Cotellese R.  
Effects of different doses of Pycnogenol® on plasma oxidative stress: a pilot, supplement study.  
Edizioni Minerva Medica, 180(6):289-94, 2021
- 
- Ref. 559** Pycnogenol® shows strong dose-dependent antioxidant properties, changing only slightly at different pH levels.  
Cizmarova, B.; Birkova, A.; Hubkova, B.; Bolerazska, B.  
Pycnogenol - extract from French maritime pine bark (Pinus pinaster), as an effective antioxidant against superoxide radical.  
Functional Food Science 1, 14-22, doi:10.31989/ffs.v1i8.816, 2021
- 
- Ref. 486** Clinical Study: Pycnogenol® may represent a useful tool to reduce levothyroxine-related side effects in patients treated with hormone replacement therapy for hypothyroidism.  
Belcaro G, Cornelli U, Dugall M, et al.  
Pycnogenol® prevents oxidative stress and side effects in patients with hypothyroidism during levothyroxine treatment.  
Min Endocrinol, 2018, Pharma standard (PS) supplements. Papers from the London sessions January 2018. Eds. Belcaro G, Dugall M, Ledda A., ISBN; 978-88-7711-940

- 
- Ref. 431** Clinical Study: Pycnogenol® supplementation for 12 months improves cognition and quenches oxidative stress in normal subjects aged 55 to 70 years.  
Belcaro G, Dugall M, Ippolito E, Hu S, Saggino A, Feragalli B  
The COFU3 Study: Improvement in cognitive function, attention, mental performance with Pycnogenol® in healthy subjects (55-70) with high oxidative stress.  
J Neurosurg Sci 59: 437-446, 2015
- 
- Ref. 430** Clinical Study: This article reviews earlier clinical Pycnogenol® research of the group, identifying improved skin elasticity and hydration, highlighting new findings on oral Pycnogenol® supporting fairer skin complexion, as well as improved skin barrier function.  
Grether-Beck S, Marini A, Jaenicke T, Krutmann J  
French Maritime Pine Bark Extract (Pycnogenol®) Effects on Human Skin: Clinical and Molecular Evidence.  
Skin Pharmacol Physiol 29: 13-17, 2016
- 
- Ref. 406** Pycnogenol® has a protective effect against acute hepatotoxicity.  
Ko J-W, Lee I-C, Park S-H, Moon C, Kang S-S, Kim S-H, Kim J-C  
Protective effects of pine bark extract against cisplatin-induced hepatotoxicity and oxidative stress in rats.  
Lab Anim Res 30(4): 174-180, 2014
- 
- Ref. 405** A single dose of 300mg Pycnogenol® induces apoptosis in human fibrosarcoma cells.  
Harati K, Slodnik P, Chromik AM, et al  
Pro-apoptotic effects of Pycnogenol on HT1080 human fibrosarcoma cells.  
Int J Oncol DOI 10.3892/ijo.2015.2854, 2014
- 
- Ref. 404** Pycnogenol® may be a fascinating therapeutic drug candidate for the treatment of mucoepidermoid carcinoma.  
Yang I-H, Shin J-A, Cho S-D  
Pycnogenol® induces nuclear translocation of apoptosis-inducing factor and caspase-independent apoptosis in MC-3 human mucoepidermoid carcinoma cell line.  
J Cancer Prevention 19: 265-272, 2014
- 
- Ref. 401** Clinical Study: Intake of Pycnogenol® decreases glucose levels and increases the antioxidative capacity of plasma.  
Muchova J, Orszaghova Z, Zitnanova I, Trebaticky B, Breza J, Durackova Z  
The effect of natural polyphenols on the oxidative stress markers in patients with diabetic nephropathy.  
Free Rad Biol Med 72: 42, 2014
- 
- Ref. 397** Pycnogenol® improves the function of the heart in rats with experimental diabetes mellitus.  
Kralova E, Jankyova S, Mucaji P, Gresakova E, Stankovicova T  
Pycnogenol and its fractions influence the function of isolated heart in rats with experimental diabetes mellitus.  
J Pathology Research & Practice, 211: 156-161; 2015
- 
- Ref. 396** Clinical Study: Pycnogenol® decreases symptoms of common cold and shorten its course also preventing some complications.  
Belcaro G, Shu H, Luzzi R, Dugall M, Ippolito E, Cesarone MR, Corsi M, Feragalli B  
Improvement of common cold with Pycnogenol®: a Winter registry study.  
Panminvera Med 56: 301-308, 2014
- 
- Ref. 395** Supplementation with Pycnogenol® ameliorates premature death by restoring immune dysfunction.  
Lee J, Nam D-E, Kim O-K, Lee M-Y  
Pycnogenol® attenuates the symptoms of immune dysfunction through restoring a cellular antioxidant status in low micronutrient-induced immune deficient mice.  
Nutr Res Pract 8(5): 533-538, 2014
- 
- Ref. 391** Treatment with Pycnogenol® might have a role in the prevention of sepsis-induced oxidative damage by decreasing DNA damage and increasing antioxidant status and DNA repair capacity in rats.  
Taner G, Aydin S, Bacanh M, Sarigöl Z, Sahin T, Başaran AA and Başaran N  
Modulating Effects of Pycnogenol® on Oxidative Stress and DNA Damage Induced by Sepsis in Rats.  
Phytother Res 28(11): 1692-700, 2014
- 
- Ref. 390** Pycnogenol®'s antioxidative activity leads to positive effects in depression-like behavior.  
Mei L, Mochizuki M, Hasegawa N  
Pycnogenol® Ameliorates Depression-Like Behavior in Repeated Corticosterone-Induced Depression Mice Model.  
BioMed Res Int Article – <http://dx.doi.org/10.1155/2014/942927>, 2014
- 
- Ref. 388** Clinical Study: Most common clinical aspects of psoriasis could be improved by Pycnogenol® supplementation.  
Belcaro G, Luzzi R, Hu S, Cesarone MR, Dugall M, Ippolito E, Corsi M, Caporale S  
Improvement in signs and symptoms in psoriasis patients with Pycnogenol® supplementation.  
Panminerva Med 56: 41-48, 2014

- 
- Ref. 385** Pycnogenol® shows beneficial effects in metabolic and cardiovascular health.  
Aribal-Ayral P, Özenci-Kavas G, Elhan AH  
Pycnogenol® supplementation and its beneficial effects in healthy rats.  
Saudi Med J 35(2): 195-197, 2014
- 
- Ref. 367** Clinical Study: Pycnogenol® given at 50 mg daily dosage to 155 volunteers significantly neutralises free radicals and quenches oxidative stress.  
Belcaro G, Hu S, Cesarone MR, Dugall M  
A controlled study shows daily intake of 50mg Pycnogenol® significantly lowers plasma reactive oxygen metabolites in 155 healthy smokers.  
Minerva Med 104(4): 439-446, 2013
- 
- 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 33(13): 1589-97, 2012
- 
- 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
- 
- 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
- 
- Ref. 241** Clinical Study: Pycnogenol® significantly decreases F2-isoprostane plasma levels in 101 senior citizens indicating that polyunsaturated 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
- 
- 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
- 
- 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
- 
- 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
- 
- Ref. 205** Clinical Study: Pycnogenol® improves antioxidant status in children with Attention Deficit Hyperactivity Disorder (ADHD).  
Dvorakova M, Sivonova M, Trebaticka J, Skodacek I, Waczulikova I, Muchova J, Durackova Z  
The effect of polyphenolic extract from pine bark, Pycnogenol® on the level of glutathione in children suffering from attention deficit hyperactivity disorder (ADHD).  
Redox Rep 11: 163-172, 2006
- 
- Ref. 204** Clinical Study: Pycnogenol® significantly protects DNA against oxidation in children with ADHD in a double-blind, placebo-controlled study.  
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

- 
- Ref. 203** Pycnogenol® prevents accumulation of oxidative damaged proteins and may reduce the risk of Alzheimer's, Parkinson's and Huntington's diseases.  
Voss P, Horakova L, Jakstadt M, Kiekebusch D, Grune T  
Ferritin oxidation and proteasomal degradation: Protection by antioxidants.  
Free Radic Res 40: 673-683, 2006
- 
- 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
- 
- Ref. 183** Pycnogenol® protects intestinal mucosa against radiotherapy induced damage: Histo-morphological 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
- 
- Ref. 140** Pycnogenol® protects the membrane of human red blood cells from oxidative damage.  
Sivonová M, Waczulíková I, Kilanczyk E, Hrnčiarová M, Bryszewska M, Klajnert B, Duracková Z  
The effect of Pycnogenol® on the erythrocyte membrane fluidity.  
Gen Physiol Biophys 23: 39-51, 2004
- 
- 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
- 
- Ref. 099** Pycnogenol® in combination with other antioxidants administered as dietary supplement increases the lifespan of mice. The findings suggest also beneficial effects against neurogenerative diseases.  
Veurink G, Liu D, Taddei K, Perry G, Smith MA, Robertson TA, Hone E, Groth DM, Atwood CS, Martins RN  
Reduction of inclusion body pathology in ApoE-deficient mice fed a combination of antioxidants.  
J Free Radic Biol Med 34: 1070-1077, 2003
- 
- Ref. 098** Pycnogenol® delays the aging process as shown by an increased life-span of fruit flies.  
Shuguang L, Xinwen Z, Sihong X, Gulati OP  
Role of Pycnogenol® in aging by increasing the Drosophila's life-span.  
Eur Bull Drug Res 11: 39-45, 2003
- 
- Ref. 093** Clinical Study: Pycnogenol® significantly elevates plasma FRAP values of men with dyslipidemia in a double-blind, placebo-controlled study.  
Durackova Z, Trebaticky 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
- 
- Ref. 090** Clinical Study: Pycnogenol® increases blood plasma oxygen radical absorbance capacity (ORAC) after oral consumption 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
- 
- Ref. 086** Pycnogenol® in combination with whey increases antioxidative capacity of plasma.  
Janisch K, Hippeli S, Dornisch K, Kern S, Elstner EF  
Determination of the antioxidative potential of human plasma after supplementation with Pycnogenol® and whey.  
Food Res Intern 35: 257-266, 2002
- 
- Ref. 083** Neuronal apoptosis (early cell death) is induced by the amyloid- $\beta$ -peptide in the brain of Alzheimer patients. In vitro experiments demonstrated an inhibition of cell death of neurons by Pycnogenol®.  
Peng QL, Buz'Zard AR, Lau BHS  
Pycnogenol® protects neurons from amyloid  $\beta$  peptide-induced apoptosis.  
Brain Res Mol Brain Res 104: 55-65, 2002
- 
- Ref. 072** Pycnogenol® selectively enhances activity of intracellular antioxidative enzymes.  
Bayeta E, Lau BHS  
Pycnogenol® inhibits generation of inflammatory mediators in macrophages.  
Nutr Res 20: 249-259, 2000

- 
- Ref. 070** Pycnogenol® by virtue of its high content of procyanidins has higher antioxidant potency than other plant derived antioxidants containing relatively higher content of regular flavon(ol)s. This fact is explained on structural and functional basis.  
Bors W, Michel C, Stettmaier K  
Electron paramagnetic resonance studies of radical species of proanthocyanidins and gallate esters.  
Arch Biochem Biophys 374: 347-355, 2000
- 
- Ref. 069** Pycnogenol® produces significant reduction in vascular damage caused by  $\beta$ -amyloid protein.  $\beta$ -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  $\beta$ -amyloid-induced injury.  
Biol Pharm Bull 23: 735-737, 2000
- 
- Ref. 063** Pycnogenol® shows free radical scavenging activity against reactive oxygen species. It inhibits the generation of pro-inflammatory mediators confirming the anti-inflammatory and immuno-modulatory profile of Pycnogenol®.  
Cho K-J, Yun C-H, Yoon D-Y, Cho Y-S, Rimbach G, Packer L, Chung A-S  
Effect of bioflavonoids extracted from the bark of Pinus maritime on proinflammatory cytokine interleukin-1 production in lipopolysaccharide-stimulated raw 264.7.  
Toxicol Appl Pharmacol 168: 64-71, 2000
- 
- Ref. 062** Pycnogenol® blocks oxidative modification of cellular proteins more effectively than other antioxidants.  
Kim J, Chehade J, Pinnas JL, Mooradian AD  
Effect of select antioxidants on malondialdehyde modification of proteins.  
Nutrition 16: 1079-1081, 2000
- 
- 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
- 
- Ref. 051** In a comparative study Pycnogenol® shows more potent antioxidant activity than vitamin C and E,  $\alpha$ -lipoic acid, Co-Q10 and grape seed. In combination Pycnogenol® enhances the effects of other antioxidants like Coenzyme Q10.  
Chida M, Suzuki K, Nakanishi-Ueda T, Ueda T, Yasuhara H, Koide R, Armstrong D  
In vitro testing of antioxidants and biochemical endpoints in bovine retinal tissue.  
Ophthalmic Res 31: 407-415, 1999
- 
- Ref. 033** Pycnogenol® is an efficient antioxidant due to the relative stability of its corresponding radical and its regeneration by vitamin C and vitamin E homologue Trolox.  
Guo Q, Zhao B, Packer L  
Electron spin resonance study of free radicals formed from a procyanidin-rich pine (Pinus maritime) bark extract, Pycnogenol®.  
J Free Radic Biol Med 27: 1308-1312, 1999
- 
- Ref. 030** Pycnogenol® protects vitamin C from oxidation and recycles oxidized vitamin C more effectively 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
- 
- 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.  
Cell Mol Life Sci 54: 1168-1172, 1998
- 
- 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
- 
- 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
- 
- 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
-

- 
- Ref. 021** Pycnogenol® is shown to be the strongest hydroxyl- and superoxide radical scavenger among other extracts tested. In addition, Pycnogenol® is shown to be resistant to heat.  
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
- 
- Ref. 020** Pycnogenol® stimulates synthesis of antioxidative enzymes in cell lining arteries thereby doubling their amount.  
Wei ZH, Peng QL, Lau BHS  
Pycnogenol® enhances endothelial cell antioxidant defenses.  
Redox Rep 3: 219-224, 1997
- 
- Ref. 014** Pycnogenol® protects endothelial cells lining from free radical damage. Damage to endothelial cells is considered a primary cause for atherosclerosis.  
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
- 
- 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
- 
- 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
- 
- 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 N.P., ed. Flavonoids in Biology & Medicine III: Current issues in Flavonoid Research: National University of Singapore Press: 227-235, 1990

## 19 Endothelial Function

- 
- Ref. 553** Clinical study: Pycnogenol® shows beneficial effects for managing some of the signs and symptoms associated with post-Covid-19 and improves cardiovascular risk factors.  
Belcaro G, Cornelli U, Cesarone MR, Scipione C, Scipione V, Hu S, Feragalli B, Corsi M, Cox D, Cotellese R, Hosoi M, Burki C  
Preventive effects of Pycnogenol® on cardiovascular risk factors (including endothelial function) and microcirculation in subjects recovering from coronavirus disease 2019 (COVID-19).  
Minerva Med. 113(2):300-8, 2022
- 
- Ref. 499** Pycnogenol® reduces Escitalopram (anti-depressant)-induced sexual dysfunction and elevated heart rate in both genders based on its ability to improve endothelial function.  
Smetanka A, Stara V, Farsky I, Tonhajzerova I, Ondrejka I  
Pycnogenol® supplementation as an adjunct treatment for antidepressant-induced sexual dysfunction.  
Physiol Int 106(1): 59-69, 2019
- 
- Ref. 449** A review on the efficacy of Pycnogenol® to alleviate climacteric symptoms by improving endothelial function and antioxidative status.  
Rohdewald P  
Relief from Menopausal Symptoms by Non-hormonal Treatment with Pycnogenol® (French Maritime Pine Bark Extract).  
J Genit Syst & Disor 5:4, 2016
- 
- Ref. 408** Clinical Study: Endothelial function is improved by Pycnogenol®. Results of this open registry study indicate an important preventive possibility for borderline hypertensive, hyperglycemic and hyperlipidemic subjects.  
Hu S, Belcaro G, Cornelli U, Luzzi R, Cesarone MR, Dugall M, Feragalli B, Errichi B, Ippolito E, Grossi MG, Hosoi M, Gizzi G, Trignani M  
Effects of Pycnogenol® on endothelial dysfunction in borderline hypertensive, hyperlipidemic, and hyperglycemic individuals: the borderline study.  
Int Angiol 34(1): 43-52, 2015

- 
- Ref. 372** The metabolites developing in humans after consumption of Pycnogenol® are actively internalised by red blood cells, leukocytes, endothelial cells and neurons via the GLUT1 transporter. The tissue-specific accumulation represents the common denominator for Pycnogenol® principal modes of action, as related to inflammation control, endothelial function, and cognition benefits.  
Kurlbaum M, Mülek M, Högger P  
Facilitated Uptake of a Bioactive Metabolite of Maritime Pine Bark Extract (Pycnogenol®) into Human Erythrocytes.  
PLOS ONE 8(4): 1-10, 2013
- 
- Ref. 371** Pycnogenol® as a natural blend performs better in endothelial dysfunction than fractions of the extract.  
Jankyova S, Hlavackova L, Kralova E, Slazneva J, Drobna V, Zuzik P, Drafi F, Mucaji P, Racanska E  
The Evaluation of Efficacy of Pycnogenol® Fractions on Endothelial Dysfunction.  
Acta Fac Pharm Univ Comen LX(1): 7-14, 2013
- 
- Ref. 353** Pycnogenol® metabolites developing after consumption by humans accumulate in immune cells (leukocytes) for modulation of inflammatory processes.  
Uhlenhut K, Högger P  
Facilitated cellular uptake and suppression of inducible nitric oxide synthase by a metabolite of maritime pine bark extract (Pycnogenol®).  
Free Radic Biol Med, 53: 305-313, 2012
- 
- 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 33(13): 1589-97, 2012
- 
- 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 antihypertensive 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
- 
- 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
- 
- 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
- 
- 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
- 
- Ref. 069** Pycnogenol® produces significant reduction in vascular damage caused by  $\beta$ -amyloid protein.  $\beta$ -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  $\beta$ -amyloid-induced injury.  
Biol Pharm Bull 23: 735-737, 2000
- 
- 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
- 
- Ref. 027** Pycnogenol® counteracts the constriction of blood vessels. The vasorelaxant 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



- 
- Ref. 026** Pycnogenol® protects α-tocopherol in endothelial cells.  
Virgili F, Kim D, Packer L  
Procyanidins extracted from pine bark protect α-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
- 
- Ref. 020** Pycnogenol® stimulates synthesis of antioxidative enzymes in cell lining arteries thereby doubling their amount.  
Wei ZH, Peng QL, Lau BHS  
Pycnogenol® enhances endothelial cell antioxidant defenses.  
Redox Rep 3: 219-224, 1997
- 
- Ref. 014** Pycnogenol® protects endothelial cells lining from free radical damage. Damage to endothelial cells is considered a primary cause for atherosclerosis.  
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

## 20 Platelet function

- 
- Ref. 553** Clinical study: Pycnogenol® shows beneficial effects for managing some of the signs and symptoms associated with post-Covid-19 and improves cardiovascular risk factors.  
Belcaro G, Cornelli U, Cesarone MR, Scipione C, Scipione V, Hu S, Feragalli B, Corsi M, Cox D, Cotellesse R, Hosoi M, Burki C  
Preventive effects of Pycnogenol® on cardiovascular risk factors (including endothelial function) and microcirculation in subjects recovering from coronavirus disease 2019 (COVID-19).  
Minerva Med. 113(2):300-8, 2022
- 
- Ref. 528** Clinical study: Pycnogenol® prevents recurrent retinal vein thrombosis better than Aspirin, ticlopidine and sulodexide with no side effects.  
Belcaro G, Dugall M, Bradford HD, Cesarone MR, Feragalli B, Gizzi C, Cotellesse R, Hu S, Rodriguez P, Hosoi M.  
Recurrent retinal vein thrombosis: prevention with Aspirin, Pycnogenol®, ticlopidine, or sulodexide.  
Minerva Cardioangiol. 2019 Apr;67(2):109-114, 2019
- 
- Ref. 507** Clinical study: Pycnogenol® lowers the risk of thromboembolic episodes in children with Crohn's disease by reducing blood levels of thromboxane a facilitator of platelet aggregation.  
Kolacek, M., Paduchova, Z., Dvorakova, M., Zitnanova, I., Cierna, I., Durackova, Z., Muchova, J.  
Effect of natural polyphenols on thromboxane levels in children with Crohn's disease.  
Bratisl Lek Listy, 120(12): p. 924-928, 2019
- 
- Ref. 499** Pycnogenol® reduces Escitalopram (anti-depressant)-induced sexual dysfunction and elevated heart rate in both genders based on its ability to improve endothelial function.  
Smetanka A, Stara V, Farsky, I, Tonhajzerova I, Ondrejka I  
Pycnogenol® supplementation as an adjunct treatment for antidepressant-induced sexual dysfunction.  
Physiol Int 106(1): 59-69, 2019
- 
- Ref. 476** Pycnogenol® is more effective in preventing of the post-thrombotic syndrome and a new venous thrombosis than Aspirin, sulodexide and ticlopidine.  
Belcaro G, Dugall M, Hu S, Feragalli B, Cotellesse R, Ledda A, Corsi M, Ricci A, Ippolito E, Errichi BM, Cornelli U, Cesarone MR, Hosoi M  
Prevention of recurrent venous thrombosis and post-thrombotic syndrome.  
Minerva Cardioangiol 66(3): 238-245, 2018
- 
- Ref. 469** Clinical Study: Pycnogenol® reduces edema and may control some thrombotic events.  
Belcaro G, Cornelli U, Dugall M, Hosoi M, Cotellesse R, Feragalli B  
Long-haul flights, edema, and thrombotic events: prevention with stockings and Pycnogenol® supplementation (LONFLIT Registry Study).  
Minerva Cardioangiol 66: 152-159, 2018
- 
- Ref. 434** Review: A summary of investigations related to biological activities and clinical actions of Pycnogenol® related to oedema, ulcers, thromboses, CVI and haemorrhoids.  
Rohdewald P  
Gerbstoffhaltiger Extrakt zur oralen und topischen Behandlung bei CVI und Hämorrhoidalleiden.  
Phlebologie 44: 334-338, 2015
- 
- Ref. 417** Clinical Study: Pycnogenol® is shown to help prevent retinal vein thrombosis.  
Rodriguez P, Belcaro G, Dugall M, Hu S, Luzzi R, Ledda A, Ippolito E, Corsi M, Ricci A, Feragalli B, Cornelli U, Gizzi C, Hosoi M  
Recurrence of retinal vein thrombosis with Pycnogenol® or Aspirin® supplementation: a registry study.  
Panminerva Med 57: 121-125, 2015

- 
- Ref. 370** A concise, yet comprehensive, up to date review on preclinical and clinical research on Pycnogenol® related to venous insufficiency and thrombosis management.  
Gulati OP  
Pycnogenol® in Chronic Venous Insufficiency and Related Venous Disorders.  
Phytother Res. 2014 Mar;28(3):348-62, 2014
- 
- 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
- 
- 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
- 
- 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
- 
- 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
- 
- Ref. 053** Clinical study: Pycnogenol® inhibits smoking-induced increase of thromboxane B2 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
- 
- Ref. 043** Clinical study: Pycnogenol® inhibits platelet aggregation and adhesion and improves blood microcirculation 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
- 
- 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
- 
- Ref. 039** Review: 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
- 
- 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, Grottemeyer 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

## 21 Reinforcement of the extracellular matrix

- 
- Ref. 551** Pycnogenol® inhibits skin hyperpigmentation in vitro by downregulating tyrosinase and reducing pigmentation-related mediators thus reducing melanin production.  
 Ayres EL, Silva JDS, Eberlin S, Facchini G, Vasconcellos C, Costa A.  
 In-vitro effect of pine bark extract on melanin synthesis, tyrosinase activity, production of endothelin-1 and PPAR in cultured melanocytes exposed to Ultraviolet, Infrared, and Visible light radiation.  
 J Cosmet Dermatol. 2021
- 
- Ref. 464** Clinical Study: Pycnogenol®'s effects were systematically researched in patient's chondrocytes, synovial fluid and serum. The overall results suggest a chondroprotective potential of the maritime pine bark extract and provide a rational basis for understanding the reported clinical effects on symptom scores in OA patients.  
 Jessberger S, Högger P, Genest F, Salter DM, Seefried L  
 Cellular pharmacodynamic effects of Pycnogenol® in patients with severe osteoarthritis: a randomized controlled pilot study.  
 BMC Complementary and Alternative Medicine 17: 537 DOI 10.1186/s12906-017-2044-1, 2017
- 
- Ref. 430** Clinical Study: This article reviews earlier clinical Pycnogenol® research of the group, identifying improved skin elasticity and hydration, highlighting new findings on oral Pycnogenol® supporting fairer skin complexion, as well as improved skin barrier function.  
 Grether-Beck S, Marini A, Jaenicke T, Krutmann J  
 French Maritime Pine Bark Extract (Pycnogenol®) Effects on Human Skin: Clinical and Molecular Evidence.  
 Skin Pharmacol Physiol 29: 13-17, 2016
- 
- Ref. 348** Clinical Study: Pycnogenol® increases women's skin elasticity and hydration which coincides with significantly new collagen and hyaluronic acid 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.  
 Skin Pharmacol Physiol 25: 86-92, 2012
- 
- 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
- 
- 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
- 
- 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

## III. Analytics, Bioavailability & Metabolism

- Ref. 540** Review: Comprehensive summary of the most important studies on Pycnogenol®, reviews Pycnogenol®'s properties and benefits.  
Oliff H  
Scientific and clinical Monograph for Pycnogenol®.  
American Botanical Council - ABC. 2019:1-46, 2019
- 
- Ref. 473** Pycnogenol® can effectively reduce body weight and body fat deposition.  
Cong H, Zhong W, Wang Y, Ikuyama S, Fan F, Gu J  
Pycnogenol® induces browning of white adipose tissue through the PKA signaling pathway in apolipoprotein e-deficient mice.  
Journal of Diabetes Research Volume 2018, Article ID 9713259  
<https://doi.org/10.1155/2018/9713259>, 2018
- 
- Ref. 465** Pycnogenol® protects the liver. It markedly suppressed genes related to hepatic lipogenesis, fatty acid uptake and lipid storage. Pycnogenol® may provide a new prophylactic approach of non-alcoholic fatty liver disease.  
Wang D, Cong H, Cao Y, Ikuyama S, Fan B, Gu J  
Pycnogenol® protects against diet-induced hepatic steatosis in Apolipoprotein-E deficient mice.  
Am J Physiol Endocrinol Metabol, doi: 10/1152/ajpendo.000009.2017, 2018
- 
- Ref. 440** Clinical Study: Supplementation with Pycnogenol® is demonstrated to lead to accumulation of constituents and metabolites in knee synovial fluid in osteoarthritis patients, representing the basis for symptom improvement.  
Mülele M, Seefried L, Genest F, Högger P  
Distribution of constituents and metabolites of maritime pine bark extract (Pycnogenol®) into serum, blood cells and synovial fluid of patients with severe osteoarthritis: a randomized controlled trial.  
Nutrients 9, 443; doi: 10.3390/nu9050443, 2017
- 
- Ref. 416** Elucidation of metabolic fate of Pycnogenol® metabolites in humans.  
Mülele M, Fekete A, Wiest J, Holzgrabe U, Mueller MJ, Högger P  
Profiling a gut microbiota-generated catechin metabolite's fate in human blood cells using a metabolomic approach.  
J Pharm Biomed Anal 114: 71-81, 2015
- 
- Ref. 403** Report of comparison of various sample preparation methods used for detection and quantification of plant derived compounds in human blood cells after ingesting Pycnogenol®.  
Mülele M, Högger P  
Highly sensitive analysis of polyphenols and their metabolites in human blood cells using dispersive SPE extraction and LC-MS/MS.  
Anal Bioanal Chem DOI 10.1007/s00216-014-8451-y, 2015
- 
- Ref. 379** Pycnogenol® acts as a promising natural compound for the prevention of fatty liver disease or atherosclerosis.  
Ikuyama S, Fan B, Gu J-Q, Mukae K, Watanabe H  
Molecular mechanism of intracellular lipid accumulation: Suppressive effect of Pycnogenol® in liver cells.  
FFHD 3(9): 252-264, 2013
- 
- Ref. 372** The metabolites developing in humans after consumption of Pycnogenol® are actively internalised by red blood cells, leukocytes, endothelial cells and neurons via the GLUT1 transporter. The tissue-specific accumulation represents the common denominator for Pycnogenol® principal modes of action, as related to inflammation control, endothelial function, and cognition benefits.  
Kurlbaum M, Mülele M, Högger P  
Facilitated Uptake of a Bioactive Metabolite of Maritime Pine Bark Extract (Pycnogenol®) into Human Erythrocytes.  
PLOS ONE 8(4): 1-10, 2013
- 
- Ref. 371** Pycnogenol® as a natural blend performs better in endothelial dysfunction than fractions of the extract.  
Jankyova S, Hlavackova L, Kralova E, Slazneva J, Drobna V, Zuzik P, Drafi F, Mujaji P, Racanska E  
The Evaluation of Efficacy of Pycnogenol® Fractions on Endothelial Dysfunction.  
Acta Fac Pharm Univ Comen LX(1): 7-14, 2013
- 
- Ref. 353** Pycnogenol® metabolites developing after consumption by humans accumulate in immune cells (leukocytes) for modulation of inflammatory processes.  
Uhlenhut K, Högger P  
Facilitated cellular uptake and suppression of inducible nitric oxide synthase by a metabolite of maritime pine bark extract (Pycnogenol®).  
Free Radic Biol Med, 53: 305-313, 2012
- 
- 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).  
J Pharm Biomed Anal 54: 127-132, 2011

- 
- 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
- 
- Ref. 197** Clinical Study: This study presents the appearance of Pycnogenol® constituents and metabolites in blood after oral administration in humans.  
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: 4, 2006
- 
- 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
- 
- Ref. 170** USP Monograph: Maritime Pine – USP  
30.964-965; The United States Pharmacopeia, United States Pharmacopeial Convention, Inc. official from May 1, 2007
- 
- 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
- 
- 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
- 
- 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
- 
- 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  
Bioavailability and metabolism of Pycnogenol®.  
Eur Bull Drug Res 7: 5-7, 1999

## IV. Review Articles

- 
- Ref. 580** Review: Pycnogenol® has a significantly beneficial effect on systolic and diastolic blood pressure.  
 Pourmasoumi M, Hadi A, Mohammadi H, Rouhani MH  
 Effect of Pycnogenol® supplementation on blood pressure: A systematic review and meta-analysis of clinical trials.  
 Phytotherapy Research. 2019:1-10, 2019
- 
- Ref. 573** This review explores the various beneficial properties of Pycnogenol® regarding mechanistic and physiological effects  
 Nattagh-Eshstivani E, Gheflati A, Barghchi H, Rahbarinejad P, Hachem K, Shalaby MN, Abdelbasset WK, Ranjbar G, Olegovich Bokov D, Rahimi P, Gholizadeh Navashenaq J, Pahlavani N.  
 The role of Pycnogenol® in the control of inflammation and oxidative stress in chronic diseases: Molecular aspects.  
 Phytother Res. 2022 May 18. doi: 10.1002/ptr.7454., 2022
- 
- Ref. 557** Review on the beneficial effects of Pycnogenol® on cognitive function.  
 Schönlau F  
 Chapter 23 - The multifactorial contributions of Pycnogenol® for cognitive function improvement.  
 Nutraceuticals in Brain Health and Beyond, D. Ghosh Ed., pp. 335-341: Academic Press: 2021, 2021
- 
- Ref. 543** Review on the possible beneficial effects of Pycnogenol® on health impairments after a SARS-CoV2 infection  
 Weichmann F and Rohdewald P.  
 Projected supportive effects of Pycnogenol® in patients suffering from multi-dimensional health impairments after a SARS-CoV2 infection.  
 Int J Antimicrob Agents 56(6): 106191, 2020
- 
- Ref. 540** Review: Comprehensive summary of the most important studies on Pycnogenol®, reviews Pycnogenol®'s properties and benefits.  
 Oliff H  
 Scientific and clinical Monograph for Pycnogenol.  
 American Botanical Council - ABC. 2019:1-46, 2019
- 
- Ref. 503** This review summarizes the bio-modulating effects of Pycnogenol® to improve neurocognitive function via vascular, anti-inflammatory, neuroprotective, and antioxidant processes.  
 Simpson T, Kure C, Stough C  
 Assessing the efficacy and mechanisms of Pycnogenol® on cognitive aging from in vitro animal and human studies.  
 Frontiers in Pharmacology, 2019
- 
- Ref. 490** Review on the diverse beneficial effects of Pycnogenol® on relevant symptoms of aging.  
 Rohdewald P  
 Pleiotropic Effects of French Maritime Pine Bark Extract to Promote Healthy Aging  
 Rejuvenation Res. 2019 Jun;22(3):210-217, 2019.
- 
- Ref. 472** Review: Pycnogenol® is considered to have therapeutic benefits in ADHD, as it increased antioxidant levels, reduced oxidative damage and improved neurochemical status.  
 Verlaeat AAJ, Maasackers CM, Hermans N, Savelkoul HFJ  
 Rationale for Dietary Antioxidant Treatment of ADHD.  
 Nutrients 10, 405; doi: 10.3390/nu10040405, 2018
- 
- Ref. 463** Review: Pycnogenol® relieves venous edema. The combined topical and oral use of Pycnogenol® accelerates the healing of venous and diabetic ulcers and hemorrhoids  
 Rohdewald P  
 Pycnogenol® bei Erkrankungen des venösen Systems – eine systematische Übersicht.  
 Schweiz Z Ganzheitsmed 29: 372-375, 2017
- 
- Ref. 462** Review: Pycnogenol® improves women's health in a non-hormonal way.  
 Rohdewald PJ  
 Pycnogenol®, a Plant Extract for Women's Health.  
 Int J Women's Health Care (IJWHC) 2(1): 1-5, 2017
- 
- Ref. 461** Review: Pycnogenol® with its anti-inflammatory and chondroprotective effects acts like a sustained-release formulation by its combination of fast absorbed phenolic compounds and slowly metabolized procyanidins.  
 Rohdewald PJ  
 Review on sustained relief of osteoarthritis symptoms with a proprietary extract from pine bark extract, Pycnogenol®.  
 J Med Food 21(1): 1-4, 2018
- 
- Ref. 449** A review on the efficacy of Pycnogenol® to alleviate climacteric symptoms by improving endothelial function and antioxidative status.  
 Rohdewald P  
 Relief from Menopausal Symptoms by Non-hormonal Treatment with Pycnogenol® (French Maritime Pine Bark Extract).  
 J Genit Syst & Disor 5:4, 2016

- 
- Ref. 448** A review suggesting Pycnogenol® as adjunct treatment to conventional therapy for hepatitis-associated diabetes.  
Ezzikouri S, Jadid FZ, Hamdi S, Wakrim L, Tsukiyama-Kohara K, Benjelloun S  
Supplementing Conventional Treatment with Pycnogenol® May Improve Hepatitis C Virus-Associated Type 2 Diabetes: A Mini Review.  
J Clin Translational Hepatol 4: 228-233, 2016
- 
- Ref. 444** Review comprising Pycnogenol® virtues for allergic rhinitis (hayfever).  
Ross SM  
Allergic Rhinitis. A proprietary extract of Pinus pinaster Aiton (Pycnogenol®) is found to improve the symptoms associated with allergic rhinitis.  
Holist Nurs Pract 30: 301-304, 2016
- 
- Ref. 430** This article reviews earlier clinical Pycnogenol® research of the group, identifying improved skin elasticity and hydration, highlighting new findings on oral Pycnogenol® supporting fairer skin complexion, as well as improved skin barrier function.  
Grether-Beck S, Marini A, Jaenicke T, Krutmann J  
French Maritime Pine Bark Extract (Pycnogenol®) Effects on Human Skin: Clinical and Molecular Evidence.  
Skin Pharmacol Physiol 29: 13-17, 2016
- 
- Ref. 422** Review: Summary of clinical studies with Pycnogenol® published between 2010 and 2015.  
Rohdewald P  
Update on the clinical pharmacology of Pycnogenol®.  
Medical Research Archives July 2015 Issue 3: 1-11, 2015
- 
- Ref. 415** This review article comprises the current knowledge on Pycnogenol® for improvement of health of individuals with metabolic syndrome and diabetes.  
Gulati O  
Pycnogenol® in Metabolic Syndrome and Related Disorders.  
Phytother Res 29: 949-968, 2015
- 
- 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
- 
- 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
- 
- Ref. 269** Review: 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
- 
- 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
- 
- 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
- 
- 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
- 
- 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** Review: 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. 180** Review: 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
- 
- Ref. 169** Review: 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
- 
- Ref. 168** Review: 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** Review: 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. 114** Review of the cardiovascular health benefits of Pycnogenol®.  
 Watson RR  
 Pycnogenol® and cardiovascular health.  
 Evid Based Integr Med 1: 27-32, 2003
- 
- Ref. 094** Summary of beneficial effects of Pycnogenol® for skin care.  
 Schönlau F  
 The cosmeceutical Pycnogenol®.  
 J Appl Cosmetol 20: 241-246, 2002
- 
- 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
- 
- Ref. 085** Review article on the pharmacological 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
- 
- 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
- 
- Ref. 039** Review: 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



- 
- 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
- 
- Ref. 034** Review: 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
- 
- Ref. 031** Review: The history of ancient pine bark uses to the present-day development of Pycnogenol®.  
Drehnen 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



*Horphag Research  
Administrative Office  
71 Av. Louis Casà  
CH-1216 Cointrin/Geneva  
Switzerland  
Phone +41 (0)22 710 26 26  
info@pycnogenol.com  
www.pycnogenol.com*

*Pycnogenol® is a registered trademark of Horphag Research.  
Use of this product is protected by one or more of U.S. Patents and  
other international patents.*

*The information provided in this document is for professional use only. Statements and information provided herein have not been evaluated by the Food and Drug Administration or other health authorities. This product is not intended to diagnose, treat, cure or prevent any disease. Horphag Research supplies Pycnogenol® as a raw material to manufacturers of finished products. Therefore, Horphag Research makes no claims regarding the use of finished products and each manufacturer is responsible for ensuring that any claims it chooses to make in connection with the use of its finished products fully comply with the regulatory and legal requirements of the locations in which it markets its products.*