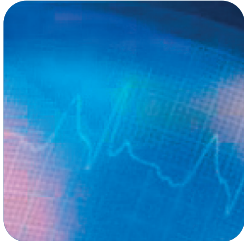


PYCNOGENOL®

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LOOK, FEEL AND LIVE BETTER



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1. Review Articles

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- Ref. 211** **Beneficial effects of Pycnogenol® in wrinkles - A review.**
 Rona, C., Vailati, F., Berardesca, E. (2004)
 The cosmetic treatment of wrinkles.
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 Rohdewald, P. (2006)
 Clinical Pharmacology of Pycnogenol®.
Pharma Bio World, Nov. 2006: 79-81.
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- Ref. 160** **Review article – Update of Pycnogenol® until 2005.**
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The American Botanical Council guide to Herbs, 369-373.
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Maritime Pine- USP-28. 2023-2024.
The United States Pharmacopeia, United States Pharmacopeial Convention, Inc. official from January 1, 2004.
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- Ref. 171** **USP Monograph.**
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 Matsumori, A. (2007)
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 A review of the French maritime pine bark extract (Pycnogenol®), a herbal medication with a diverse clinical pharmacology.
Int J Clin Pharmacol Ther, **40(4)**: 158-168.

Ref. 114 Review of the positive effects of Pycnogenol® for cardiovascular health, based on the published clinical studies in the cardiovascular area.
 Watson, R.R. (2003)
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 The cosmeceutical Pycnogenol®.
J Appl Cosmetol, **20**: 241-246.

Ref. 092 Review article: Summary of 5 clinical studies describing the effects of Pycnogenol® supplementation in patients with diabetic retinopathy.
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 Pycnogenol® for diabetic retinopathy: A review.
Int Ophthalmol, **24**: 161-171.

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 Antioxidant activity and biologic properties of a procyanidin-rich extract from pine (*Pinus maritima*) bark, Pycnogenol®.
J Free Radic Biol Med, **27(5/6)**: 704-724.

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Cardiovasc Rev Rep, **XX(VI)**: 326-329.



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 Pycnogenol®, pharmakologische und klinische Wirkungen eines Extraktes aus der Rinde von *Pinus pinaster*.
Schweiz. Zschr. GanzheitsMedizin, **12**: 188-193; 237-241.

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Ref. 031 **Review article: discusses the history of ancient pine bark uses to the present day development of Pycnogenol®.**
 Drehsen, G. (1999)
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 Procyanidins from *Pinus maritima* bark: Antioxidant activity, effects on the immune system and Modulation of Nitrogen Monoxide Metabolism.
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Progr Med, **24**: 1503-1510.



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 Matsumori, A., Higuchi, H. and Shimada, M. (2007)
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J Card Fail, **20**, in print.
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Phytother Res, **21**: 181-182.
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- Ref. 200** **Pycnogenol® reduces oedema side effects in hypertensive subjects taking anti-hypertensive therapy.**
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- Ref. 177** **Pycnogenol® and Coenzyme Q10 enhance cardiovascular health synergistically.**
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 Watson, R.R. (2003)
 Pycnogenol® and cardiovascular health.
Evid Based Integrative Med, **1(1)**: 27-32.
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- Ref. 080** 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, R. T., Rohdewald, P., Watson, R. R. (2001)
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Nutr Res, **21**: 1251-1260.
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- Ref. 117** Pycnogenol® improves endothelial function of hypertensive patients and helps to lower the dose of the antihypertensive drug (Nifedipine) when administered simultaneously.
 Liu, X., Wei, J., Tan, F., Zhou, S., Würthwein, G. and Rohdewald, P. (2004)
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Life Sci, **74**: 855-862.
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- Ref. 017** Pycnogenol® inhibits the angiotensin II converting enzyme (ACE) and produces a moderate hypotensive effect in rats.
 Blazso, G., Gaspar R., Gabor, M., Rüge H-J and Rohdewald, P. (1996)
 ACE inhibition and hypotensive effect of procyanidinis containing extract from the bark of *Pinus pinaster* Sol.
Pharm Pharmacol Lett, **6(1)**: 8-11.
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- Ref. 036** Pycnogenol® inhibits smoking induced platelet aggregation in dose-dependent manner in humans. The effect lasts for more than 6 days and unlike aspirin, it does not produce increase in bleeding time.
 Pütter, M., Grotemeyer, K.H.M., Würthwein, G., Araghi-Niknam, M., Watson R.R., Hosseini, S. and Rohdewald, P. (1999)
 Inhibition of smoking-induced platelet aggregation by Aspirin and Pycnogenol®.
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 Araghi-Niknam, M., Hosseini, S., Larson D., Rohdewald, P. and Watson R.R. (1999)
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Ref. 027 Pycnogenol® counteracts the constriction of blood vessels due to stress. The vaso-relaxant activity of Pycnogenol® is mediated through nitric oxide.
 Fitzpatrick, D.F., Bing, B. and Rohdewald, P. (1998)
 Endothelium-dependent vascular effects of Pycnogenol®.
J Cardiovasc Pharmacol, 32: 509-515.

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 Rohdewald, P. (1999)
 Reducing the risk for stroke and heart infarction with Pycnogenol®.
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 Supplementation with a pine bark extract rich in polyphenols increases plasma antioxidant capacity and alters plasma lipoprotein profile.
Lipids, 37(10): 931-934.

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 Sivonova, M., Waczulikova, I., Kilanczyk, E., Hrnčiarova, M., Bryszewska, M., Klajnert, B. and Durackova, Z. (2004)
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Gen Physiol Biophys, 23: 39-51.



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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.
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- Ref. 230** Pycnogenol® increases endothelium-dependent vasodilation by 42%, by enhancing 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. and Higashi, Y. (2007)
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Hypertens Res, **30**: 775-780.
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Ref. 206 **Pycnogenol® provides relief in venous microangiopathy.**
 Cesarone, M.R., 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. (2006)
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 Control of Edema in Hypertensive Subjects Treated With Calcium Antagonist (Nifedipine) or Angiotensin-Converting Enzyme Inhibitors With Pycnogenol®.
Clin Appl Thromb Hemost, **12(4)**: 440-444.

Ref. 182 **Pycnogenol® demonstrates superior activity versus Daflon® in treatment of chronic venous insufficiency in a comparative clinical study.**
 Cesarone, M.R., Belcaro, G., Rohdewald, P., Pellegrini, L., Ledda, A., Vinciguerra, G., Ricci, A., Gizzi, G., Ippoliti, E., Fano, F., Dugall, M., Acerbi, G., Cacchio, M., Di Renzo, A., Hosoi, M., Stuard, S., Corsi, M. (2006)
 Comparison of Pycnogenol® and Daflon® in Treating Chronic Venous Insufficiency: A Prospective, Controlled Study.
Clin Appl Thromb Hemost, **12(2)**: 205-212.

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 Venous Ulcers: Microcirculatory Improvement and Faster Healing with Local Use of Pycnogenol®.
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- Ref. 134** **Pycnogenol® prevents thrombosis and thrombophlebitis in long-haul flights.**
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Clin Appl Thromb Hemost, **10(4)**: 373-377.
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- Ref. 116** **Pycnogenol® in combination with nattokinase prevents deep vein thrombosis in long-haul flights.**
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Angiology, **54(5)**: 531-539.
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 Prevention of edema in long flights with Pycnogenol®.
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- Ref. 041** **Review article: describes efficacy and safety profile of Pycnogenol® in treating venous disorders in humans. Mechanisms of reducing oedema are also discussed.**
 Gulati, O. P. (1999)
 Pycnogenol® in venous disorders: A review.
Eur Bull Drug Res, **7(2)**: 8-13.
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Gabor, M., Engi, E. and Sonkodi, S. (1993)

Die Kapillarwandresistenz und ihre Beeinflussung durch wasserlösliche Flavonderivate bei spontan hypertensiven Ratten.

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Schmidtke, I. and Schoop, W. (1995)

Le pycnogéol: Thérapeutique médicamenteuse de l'œdème statique.

Journal Suisse de médecine globale, 3/95:114-115.

Ref. 012 Pycnogenol® produces a vaso-protective effect at the level of capillaries as shown in clinical studies. Pycnogenol® decreases oedema and haemorrhagic tendencies in conditions characterised by increased capillary permeability.

Becker, S.R. (1995)

Le pycnogéol: une substance douée de propriétés angioprotectrices dans le traitement de l'insuffisance veineuse chronique.

Journal Suisse de médecine globale, 1/95: 11-14 and 2/95: 69-73.

Ref. 067 Pycnogenol® tested in a placebo-controlled, double-blind phase as well as in open phase clinical trial, has been shown to produce significant relief and disappearance of symptoms of chronic venous insufficiency. Safety is confirmed by lack of side effects or changes in blood biochemistry and haematological parameters.

Petrassi, C., Mastromarino, A. and Spartera, C. (2000)

Pycnogenol® in chronic venous insufficiency.

Phytomedicine, 7(5): 383-388.

Ref. 066 Pycnogenol® tested in a placebo-controlled, double-blind clinical trial, has been shown to produce significant relief and disappearance of symptoms of chronic venous insufficiency.

Arcangeli, P. (2000)

Pycnogenol® in chronic venous insufficiency.

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- Ref. 079** Pycnogenol® demonstrated higher efficacy at a lower dosage compared to horse chestnut seed extract in a clinical trial.
Koch, R. (2002)
Comparative study of Venostasin® and Pycnogenol® in chronic venous insufficiency.
Phytother Res, **16**: 1-5.
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- Ref. 112** Addition of Pycnogenol® to troxerutin enhances significantly efficacy of treatment
Ref. 112a and prolongs symptom relief.
Riccioni, C., Sarcinella, R., Izzo, A., Palermo, G., and Liguori, L. (2004)
Efficacia della troxerutina associata al Pycnogenol® nel trattamento farmacologico dell'insufficienza venosa.
Minerva Cardioangiol, **52**: 43-48.
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Clin Appl Thromb Hemost, **10(4)**: 373-377.
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- Ref. 135** Zinopin® (a combination of Pycnogenol® and Standardized Ginger Root Extract) - Rationale of its use as Food Supplement in Traveller's thrombosis and motion sickness.
 Scurr, J.H. and Gulati, O.P. (2004)
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Phytother Res, **18**: 687-695.
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- Ref. 036** 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, K.H.M., Würthwein, G., Araghi-Niknam, M., Watson R.R., Hosseini, S. and Rohdewald, P. (1999)
 Inhibition of smoking-induced platelet aggregation by Aspirin and Pycnogenol®.
Thromb Res, **95**: 155-161.
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- Ref. 027** Pycnogenol® counteracts the constriction of blood vessels due to stress. The vaso-relaxant activity of Pycnogenol® is mediated through nitric oxide.
 Fitzpatrick, D.F., Bing, B. and Rohdewald, P. (1998)
 Endothelium-dependent vascular effects of Pycnogenol®.
J Cardiovasc Pharmacol, **32**: 509-515.
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- Ref. 041** Review article: describes efficacy and safety profile of Pycnogenol® in treating venous disorders in humans. Mechanisms of reducing oedema are also discussed.
Gulati, O. P. (1999)
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Eur Bull Drug Res, **7(2)**: 8-13.
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- Ref. 067** Pycnogenol® tested in a placebo-controlled, double-blind phase as well as in open phase clinical trial, has been shown to produce significant relief and disappearance of symptoms of chronic venous insufficiency. Safety is confirmed by the lack of side effects or changes in blood biochemistry and haematological parameters.
Petrassi, C., Mastromarino, A. and Spartera, C. (2000)
Pycnogenol® in chronic venous insufficiency.
Phytomedicine, **7(5)**: 383-388.
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5. Cholesterol Lowering

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- Ref. 090** Pycnogenol® supplementation reduced blood levels of the “bad” cholesterol LDL in human volunteers.
 Devaraj, S., Vega-López, S., Kaul, N., Schönlau, F., Rohdewald, P. and Jialal, I. (2002)
 Supplementation with a pine bark extract rich in polyphenols increases plasma antioxidant capacity and alters plasma lipoprotein profile.
Lipids, **37(10)**: 931-934.
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- Ref. 079** Pycnogenol® lowered LDL significantly in patients with chronic venous insufficiency while horse chestnut seed extract had no effect.
 Koch, R. (2002)
 Comparative study of Venostasin® and Pycnogenol® in chronic venous insufficiency.
Phytother Res, **16**: 1-5.
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- Ref. 093** Pycnogenol® supplementation lowered total cholesterol and LDL and increased HDL, resulting in a better atherosclerotic index.
 Durackova, Z., Trebaticka, B., Novotny, V., Zitnanova, I. and Breza, J. (2003)
 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.
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- Ref. 187** Pycnogenol® significantly lowered LDL and increased HDL in 155 menopausal women during a treatment period of 6 months.
 Yang, H.-M., Liao, M.-F., Zhu, S.Y., Liao, M.-N. and Rohdewald, P. (2007)
 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.
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6. Eye Health

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. and Rohdewald, P. (2002)
 Pycnogenol® for diabetic retinopathy: A review.
Int Ophthalmol, **24**: 161-171.

Ref. 075 Pycnogenol® shows beneficial effects in retinopathy.
 Spadea, L. and Balestrazzi, E. (2001)
 Treatment of vascular retinopathies with Pycnogenol®.
Phytother Res, **15**: 219-223.

Ref. 051 Pycnogenol® protects retina of the eye against damage caused by oxidative stress. The effect is more pronounced when compared to other antioxidant bioflavonoids. Pycnogenol® enhances the effects of other antioxidants like Coenzyme Q₁₀ when combined together.
 Chida, M., Suzuki, K., Nakanishi-Ueda, T., Ueda, T., Yasuhara, H., Koide, R. and Armstrong, D. (1999)
 In vitro testing of antioxidants and biochemical end-points in bovine retinal tissue.
Ophthalmic Res, **31**: 407-415.

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

Ref. 184 Pycnogenol® increases anti-oxidative enzyme concentrations in the retina of rats, suggesting a lower risk for retinopathy and cataract formation.
 Kamuren, Z.T., McPeck, C.G., Sanders, R.A., Watkins III, J.B. (2006)
 Effects of Low-Carbohydrate Diet and Pycnogenol® Treatment on Retinal Antioxidant Enzymes in Normal and Diabetic Rats.
J Ocul Pharmacol Ther, **22(1)**: 10-18.

Ref. 156 Pycnogenol® either alone or in combination with other antioxidants stimulates antioxidant enzyme activities in the retina of diabetic rats.
 Dene, B.A., Maritime, A.C., Sanders, R.A. and Watkins III J.B. (2005)
 Effects of Antioxidant Treatment on Normal and Diabetic rat retinal enzyme activities.
J Ocul Pharmacol Ther, **21(1)**: 28-35.



7. Diabetic Syndrome

Ref. 209 Pycnogenol® inhibits dietary carbohydrate absorption by inhibition of alpha-glucosidase.
 Schäfer, A. and Högger, P. (2007)
 Oligomeric procyanidins of French maritime pine bark extract (Pycnogenol®) effectively inhibit alpha-glucosidase.
Diabetes Res Clin Pract, **77**: 41-46.

Ref. 199 Pycnogenol® reduces diabetic microangiopathy.
 Cesarone, M.R., 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. (2006)
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Angiology, **57(4)**: 431-436.

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. and Rohdewald, P. (2002)
 Pycnogenol® for diabetic retinopathy: A review.
Int Ophthalmol, **24**: 161-171.

Ref. 109 In a dose-finding study Pycnogenol® lowers glucose levels of type II diabetic patients and improves endothelial function.
 Liu, X., Zhou, H.-J. and Rohdewald, P. (2004)
 French maritime pine bark extract Pycnogenol® dose-dependently lowers glucose in type II diabetic patients.
Diabetes Care, **27(3)**: 839.

Ref. 195 Pycnogenol® accelerates healing of diabetic ulcers.
 Belcaro, G., Cesarone, M.R., Errichi, B.M., 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. and Hosoi, M. (2006)
 Diabetic Ulcers: Microcirculatory Improvement and Faster Healing with Pycnogenol®
Clin Appl Thromb Hemost, **12(3)**: 318-323.



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- Ref. 142** Pycnogenol® supplementation to diabetic patients lowers glucose levels.
Liu, X., Wei, J., Tan, F., Zhou, S., Würthwein, G. and Rohdewald, P. (2004)
Antidiabetic effect of Pycnogenol® French maritime pine bark extract in patients with diabetes type II.
Life Sci, **75**: 2505-2513.
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- Ref. 105** Pycnogenol® lowers blood glucose and increases intracellular antioxidant defense mechanism in diabetic rats.
Maritim, A., Dene, B.A., Sanders, R.A. and Watkins, J.B. (2003)
Effect of Pycnogenol treatment on oxidative stress in streptozotocin-induced diabetic rats.
J Biochem Mol Toxicol, **17(3)**: 193-199.
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- Ref. 153** Pycnogenol® either alone or in combination with other antioxidants reduces parameters of oxidative stress in diabetic rats.
Berryman, A.M., Maritim, A.C., Sanders, R.A. and Watkins III, J.B. (2004)
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(6)**: 345-52.
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- Ref. 156** Pycnogenol® either alone or in combination with other antioxidants stimulates antioxidant enzyme activities in the retina of diabetic rats.
Dene, B.A., Maritim, A.C., Sanders, R.A. and Watkins III, J.B. (2005)
Effects of Antioxidant Treatment on Normal and Diabetic rat retinal enzyme activities.
J Ocul Pharmacol Ther, **21(1)**: 28-35.
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- Ref. 184** Pycnogenol® increases anti-oxidative enzyme concentrations in the retina of rats, suggesting a lower risk for retinopathy and cataract formation.
Kamuren, Z.T., McPeck, C.G., Sanders, R.A. and Watkins III, J.B. (2006)
Effects of Low-Carbohydrate Diet and Pycnogenol® Treatment on Retinal Antioxidant Enzymes in Normal and Diabetic Rats.
J Ocul Pharmacol Ther, **22(1)**: 10-18.
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- Ref. 110** Pycnogenol® inhibits in vitro the undesirable modification of proteins in presence of glucose, which occurs in proteins of diabetic patients.
Zhang, T.M., Han, C.H., Han, Y.W., Gong, H., Zhang, E.Y. and Zhang, Y. (2003)
Inhibitory effect of Pycnogenol® on generation of advanced glycation end products in vitro.
Chinese Pharmacological Bulletin, **19(4)**: 437-440.
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Ref. 080 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, R.T., Rohdewald, P. and Watson, R.R. (2001)

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Nutr Res, 21: 1251-1260.

Ref. 090 Pycnogenol® supplementation reduced blood levels of the “bad” cholesterol LDL in human volunteers.

Devaraj, S., Vega-López, S., Kaul, N., Schönlau, F., Rohdewald, P. and Jialal, I. (2002)

Supplementation with a pine bark extract rich in polyphenols increases plasma antioxidant capacity and alters plasma lipoprotein profile.

Lipids, 37(10): 931-934.

Ref. 043 Pycnogenol® helps fighting against heart disease by inhibiting adhesion and aggregation of platelets and improving microcirculatory blood flow in humans.

Wang, S., Tan, D. , Zhao, Y., Gao, G., Gao, X. and Hu, L. (1999)

The effect of Pycnogenol® on the microcirculation, platelet function and ischemic myocardium in patients with coronary artery diseases.

Eur Bull Drug Res, 7(2): 19-25.

Ref. 114 Review of the positive effects of Pycnogenol® for cardiovascular health, based on the published clinical studies in the cardiovascular area.

Watson, R.R. (2003)

Pycnogenol® and cardiovascular health.

Evid Based Integrative Med, 1(1): 27-32.

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. (1999)

Reducing the risk for stroke and heart infarction with Pycnogenol®.

Eur Bull Drug Res, 7(2): 14-18.

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- Ref. 098** Pycnogenol® delays the aging process as shown by an increased life-span of fruit flies.
Shuguang, L., Xinwen, Z., Sihong, X. and Gulati, O.P. (2003)
Role of Pycnogenol® in aging by increasing the Drosophila's life-span.
Eur Bull Drug Res, **11(3)**: 39-45.
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- Ref. 099** Pycnogenol® in combination with other antioxidants administered as a dietary supplement increases life-span of mice. The findings support its beneficial effects against neurogenerative diseases.
Veurink, G., Liu, D., Taddei, K., Perry, G., Smith, M.A., Robertson, T.A., Hone, E., Groth, D.M., Atwood, C.S. and Martins R.N. (2003)
Reduction of inclusion body pathology in ApoE-deficient mice fed a combination of antioxidants.
J Free Radic Biol Med, **34(8)**: 1070-1077.
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- Ref. 052** Pycnogenol® improves learning impairment and loss of memory, common symptoms of the ageing process.
Liu, F., Zhang, Y., and Lau, B.H.S. (1999)
Pycnogenol® improves learning impairment and memory deficit in senescence-accelerated mice.
J Anti Aging Med, **2(4)**: 349-355.
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- Ref. 029** Pycnogenol® slows down the aging related process of decline in activities of immune- and blood cells generating systems and restores their functions to normal.
Liu, F.J., Zhang, Y.X. and Lau B.H.S. (1998)
Pycnogenol® enhances immune and haemopoietic functions in senescence-accelerated mice.
Cell Mol Life Sci, **54**: 1168-1172.
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- Ref. 069** Pycnogenol® produces significant reduction in vascular damage caused by β -amyloid protein. β -amyloidosis is one of the neuropathological hallmarks of Alzheimer's disease (AD). This explains the role of Pycnogenol® in reducing the risk of AD.
Liu, F., Lau, B.H.S., Peng, Q. and Shah, V. (2000)
Pycnogenol® protects vascular endothelial cells from β -amyloid-induced injury.
Biol Pharm Bull, **23(6)**: 735-737.
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- Ref. 083** Neuronal apoptosis (early cell death) is induced by the amyloid- β -peptide in the brain of Alzheimer patients. In vitro experiments demonstrated an inhibition of cell death of neurons by Pycnogenol®.
- Peng, Q.L., Buz'Zard, A.R. and Lau, B.H.S. (2002)
Pycnogenol® protects neurones from amyloid β peptide-induced apoptosis.
Brain Res Mol Brain Res, **104**: 55-65.
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- Ref. 208** **Pycnogenol® in vitro study provides evidence of chemoprevention.**
 Buz'Zard, A.R. and Lau, B.H.S. (2007)
 Pycnogenol® reduces Talc-induced Neoplastic Transformation in Human Ovarian Cell Cultures.
Phytother Res, **21(6)**: 579-586.
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- Ref. 202** **Pycnogenol® reduces symptoms of knee osteoarthritis.**
 Cisar, P., Jany, R., Vojtassak, J., Rohdewald, P. and Durackova, Z. (2006)
 Effect of Pine Bark Extract (Pycnogenol®) On Symptoms Of Knee Osteoarthritis.
Proceedings of 1st European Congress on antiaging Medicine and 16th Congress on Menopause andropause antiaging as abstract in "Prevention and antiaging for Professionals – Journal of Preventive, Regenerative and Aesthetic Medicine (special issue October-2006)" **2**: 58.
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- Ref. 185** **Pycnogenol® inhibits key triggers of inflammation.**
 Grimm, T., Chovanova, Z., Muchova, J., Sumegova, K., Liptakova, A., Durackova, Z. and Högger, P. (2006)
 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)**: 1-6.
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- Ref. 176** **Pycnogenol® inhibits the most important pro-inflammatory enzymes, showing a strikingly rapid bioavailability.**
 Schäfer, A., Chovanová, Z., Muchová, J., Sumegová, K., Liptáková, A., Duracková, Z. and Högger P. (2005)
 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.
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- Ref. 107** **The tissue destroying enzymes (matrix metalloproteinases) collagenase, elastase and gelatinase are inhibited in vitro. Release of these enzymes from inflammatory cells is also inhibited by Pycnogenol® and its metabolites.**
 Grimm, T., Schäfer, A. and Högger, P. (2004)
 Antioxidant activity and inhibition of matrix metalloproteinases by metabolites of maritime pine bark extract (Pycnogenol®).
J Free Radic Biol Med, **36(6)**: 811-822.
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- Ref. 180** Pycnogenol®'s beneficial effects in a series of painful conditions as stiff shoulder, endometriosis, herniated disc.
Kohama, T. (2004)
Nutritional supplements in clinical practice.
Progr Med, **24**: 1503-1510.
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- Ref. 010** Pycnogenol® scavenges superoxide radicals *in vitro* and inhibits oedema *in vivo*. The anti-inflammatory and free radical scavenging activities are closely correlated.
Blazso, G., Gabor, M., Sibbel, R. and Rohdewald, P. (1994)
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.
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- Ref. 183** Pycnogenol® protects intestinal mucosa against radiotherapy induced damage: histomorphological evidence in rats.
Ramos, F.M., Schönlau, F., Novaes, P.D., Manzi, F.R., Bóscolo, F.N. Almeida, S.M. (2006)
Pycnogenol® protects against ionizing radiation as shown in the intestinal mucosa of rats exposed to X-rays.
Phytother Res, **20(8)**: 676-679.
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- Ref. 111** Pycnogenol® applied topically after sunburn inhibits photocarcinogenesis.
Sime, S. and Reeve, V.E. (2004)
Protection from inflammation, immunosuppression and carcinogenesis induced by UV radiation in mice by topical Pycnogenol®.
Photochem Photobiol, **79(2)**: 193-198.
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- Ref. 013** Applied topically, Pycnogenol® significantly reduces UVB radiation induced-erythema, the procyanidins are the protecting factors.
Blazso, G., Rohdewald, P., Sibbel, R. and Gabor, M. (1995)
Anti-inflammatory activities of procyanidin-containing extracts from *Pinus pinaster* sol.
Proceedings of the International Bioflavonoid Symposium, Vienna, Austria, ed. Antus, S., Gabor, M. and Vetschera, K. July 16-19, 1995, pages 231-238.
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- Ref. 019** Pycnogenol® produces an anti-oedema effect in two different models. Topical application of Pycnogenol® gel protects the skin against UV radiation.
Blazso, G., Gabor, M. and Rohdewald, P. (1997)
Antiinflammatory activities of procyanidin containing extracts from *Pinus pinaster* Ait. after oral and cutaneous application.
Pharmazie, **52(5)**: 380-382.
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Ref. 193 Oral administration of Pycnogenol® is able to delay and to reduce skin cancer following UV radiation.

Kyriazi, M., Yova, D., Rallis, M and Lima A. (2006)

Cancer chemopreventive effects of Pinus maritima bark extract on ultraviolet radiation and ultraviolet radiation -7,12 dimethylbenz(a) anthracene induced skin carcinogenesis of hairless mice.

Cancer Lett, 237: 234-241.

Ref. 074 Pycnogenol® inhibits UV-induced erythema in humans. This effect was concentration dependent indicating the beneficial effects of Pycnogenol® in skin disorders induced by UV radiation.

Saliou, C., Rimbach, G., Moini, H., McLaughlin, L., Hosseini, S., Lee, J., Watson R.R. and Packer, L. (2001)

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(2): 154-160.

10. Skin Care

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- Ref. 211** **Beneficial effects of Pycnogenol® in wrinkles- A review article.**
 Rona, C., Vailati, F. and Berardesca, E. (2004)
 The cosmetic treatment of wrinkles.
J Cosmet Dermatol, **3(1)**: 26-34.
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- Ref. 172** **Ulcers of the lower legs heal faster after oral plus topical application of Pycnogenol®.**
 Belcaro, G., Cesarone, M.R., Errichi, B.M., Ledda, A., Di Renzo, A., Stuard, S., Dugall, M., Pellegrini, L., Rohdewald, P., Ippolito, E., Ricci, A., Cacchio, M., Ruffini, I., Fano, F. and Hosoi M. (2005)
 Venous Ulcers: Microcirculatory Improvement and Faster Healing with Local Use of Pycnogenol®.
Angiology, **56(6)**: 699-705.
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- Ref. 195** **Pycnogenol® accelerates healing of diabetic ulcers.**
 Belcaro, G., Cesarone, M.R., Errichi, B.M., 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. and Hosoi, M. (2006)
 Diabetic Ulcers: Microcirculatory Improvement and Faster Healing with Pycnogenol®.
Clin Appl Thromb Hemost, **12(3)**: 318-323.
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- Ref. 133** **Pycnogenol® dose-dependently speeds-up the wound healing process and reduces scar formation.**
 Blazso, G. Gabor, M., Schönlau, F. and Rohdewald, P. (2004)
 Short communication: Pycnogenol® accelerates wound healing and reduces scar formation.
Phytother Res, **18**: 579-581.
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- Ref. 081** **Pycnogenol® shows beneficial effects in melasma.**
 Ni, Z., Mu, Y. and Gulati, O. (2002)
 Treatment of melasma with Pycnogenol®.
Phytother Res, **16**: 567-571.
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- Ref. 094** **Review summarizing the positive effects for skin care.**
 Schönlau, F. (2002)
 The cosmeceutical Pycnogenol®.
J Appl Cosmetol, **20**: 241-246.
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Ref. 132 **Supplementation with Evelle® improves skin smoothness and elasticity.**
 Segger, D. and Schönlau, F. (2004)
 Supplementation with Evelle® improves smoothness and elasticity in a double blind, placebo-controlled study with 62 women.
J Dermatolog Treat, **15**: 222-226.

Ref. 074 **Pycnogenol® inhibits UV-induced erythema in humans. This effect was concentration dependent indicating the beneficial effects of Pycnogenol® in skin disorders induced by UV radiation.**
 Saliou, C., Rimbach, G., Moini, H., McLaughlin, L., Hosseini, S., Lee, J., Watson R.R. and Packer, L. (2001)
 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(2)**: 154-160.

Ref. 111 **Pycnogenol® applied topically after sunburn inhibits photocarcinogenesis.**
 Sime, S. and Reeve, V.E. (2004)
 Protection from inflammation, immunosuppression and carcinogenesis induced by UV radiation in mice by topical Pycnogenol®.
Photochem Photobiol, **79(2)**: 193-198.

Ref. 193 **Oral administration of Pycnogenol® is able to delay and to reduce skin cancer following UV radiation.**
 Kyriazi, M., Yova, D., Rallis, M and Lima A. (2006)
 Cancer chemopreventive effects of Pinus maritima bark extract on ultraviolet radiation and ultraviolet radiation -7,12 dimethylbenz(a) anthracene induced skin carcinogenesis of hairless mice.
Cancer Lett, **237**: 234-241.

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. and Rohdewald, P. (1997)
 Anti-inflammatory activities of procyanidin containing extracts from *Pinus pinaster* Ait. after oral and cutaneous application.
Pharmazie, **52(5)**: 380-382.

Ref. 013 **Applied topically, Pycnogenol® significantly reduces UVB radiation induced-erythema, the procyanidins are the protecting factors.**
 Blazso, G., Rohdewald, P., Sibbel, R. and Gabor, M. (1995)
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Proceedings of the International Bioflavonoid Symposium, Vienna, Austria, ed. Antus, S., Gabor, M. and Vetschera, K. July 16-19, 1995, pages 231-238.



Ref. 008 Pycnogenol® protects the skin from ultraviolet-radiation-induced oxidative stress injury (lipid peroxidation and cytotoxicity). The protective effects were related to dose, with the highest concentration providing the greatest benefits.
Guochang, Z. (1993)
Ultraviolet radiation-induced oxidative stress in cultured human skin fibroblasts and antioxidant protection.
Bio Res Rep Univ Jyväskylä, **33**:1-86.

Ref. 073 Pycnogenol® affects favourably the gene expression profile in human keratinocytes in vitro, thus having a great potential in treatment of psoriasis and dermatoses.
Rihn, B., Saliou, C., Bottin, MC., Keith, G. and Packer, L. (2001)
From ancient remedies to modern therapeutics: Pine bark uses in skin disorders revisited.
Phytother Res, **15**: 76-78.

Ref. 137 Evidence of percutaneous absorption of Pycnogenol® in human skin.
Sarikaki, V., Rallis, M., Tanojo, H., Panteri, I., Dotsikas, Y., Loukas, Y.L. Papaioannou, G. Demetzos, C., Weber, S., Moini, H., Maibach, H.I. and Packer, L. (2004)
In vitro Percutaneous Absorption of Pine Bark Extract (Pycnogenol®) in Human Skin.
J Toxicol Cutaneous Ocul Toxicol, **23(3)**: 149-158.

Ref. 107 The tissue destroying enzymes (matrix metalloproteinases) collagenase, elastase and gelatinase are inhibited in vitro. Release of these enzymes from inflammatory cells is also inhibited by Pycnogenol® and its metabolites.
Grimm, T., Schäfer, A. and Högger, P. (2004)
Antioxidant activity and inhibition of matrix metalloproteinases by metabolites of maritime pine bark extract (Pycnogenol®).
J Free Radic Biol Med, **36(6)**: 811-822.

Ref. 185 Pycnogenol® inhibits key triggers of inflammation.
Grimm, T., Chovanova, Z., Muchova, J., Sumegova, K., Liptakova, A., Durackova, Z., Högger, P. (2006)
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)**: 1-6.

Ref. 057 Pycnogenol® inhibits Interferon-γ (IFN-γ)-induced ICAM-1 expression in human skin cells (keratinocytes). This effect is dose and time dependent indicating the therapeutic potential of Pycnogenol® in inflammatory skin disorders.
Bito, T., Roy, S., Sen, C.K. and Packer, L. (2000)
Pine bark extract Pycnogenol® down regulates IFN-γ- induced adhesion of T cells to human keratinocytes by inhibiting inducible ICAM-1 expression.
J Free Radic Biol Med, **28(2)**: 219-227.



Ref. 150

Pycnogenol® shows antimicrobial activity in vitro.

Torras, M.A.C., Faura, C.A., Schönlau, F. and Rohdewald, P. (2005)
Anti-microbial activity of Pycnogenol®.
Phytother Res, **19**: 647-648.

Ref. 030

Pycnogenol® prolongs the lifetime of vitamin C more than other flavonoids.

Cossins, E., Lee, R. and Packer, L. (1998)
ESR studies of vitamin C regeneration, order of reactivity of natural source phytochemical preparations.
Biochem Mol Biol Int, **45(3)**: 583-597.

Ref. 026

Pycnogenol® protects α -tocopherol in endothelial cells.

Virgili F., Kim, D. and Packer, L. (1998)
Procyanidins extracted from pine bark protect α -tocopherol in ECV 304 endothelial cells challenged by activated RAW 264.7 macrophages: role of nitric oxide peroxynitrite.
FEBS Lett, **431**: 315-318.

Ref. 009

Pycnogenol® increases the 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. and Sonkodi, S. (1993)
Die Kapillarwandresistenz und ihre Beeinflussung durch wasserlösliche Flavonderivate bei spontan hypertensischen Ratten.
Phlebologie, **22**: 178-182.

11. Oral Health Care

Ref. 084 A Pycnogenol® - containing chewing gum tested in a clinical trial reduced bleeding of the gum and plaque formation on the teeth.
 Kimbrough, C., Chun, M., de la Roca, G. and Lau, B.H.S. (2002)
 Pycnogenol® chewing gum minimizes gingival bleeding and plaque formation.
Phytomedicine, **9**: 410-413.

Ref. 009 Pycnogenol® increases the 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. and Sonkodi, S. (1993)
 Die Kapillarwandresistenz und ihre Beeinflussung durch wasserlösliche Flavonderivate bei spontan hypertensischen Ratten.
Phlebologie, **22**: 178-182.

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

Ref. 150 Pycnogenol® shows antimicrobial activity *in vitro*.
 Torras, M.A.C., Faura, C.A., Schönlau, F. and Rohdewald, P. (2005)
 Short Communication: Antimicrobial activity of Pycnogenol®.
Phytother Res, **19**: 647-648.

Ref. 030 Pycnogenol® prolongs the lifetime of vitamin C more than other flavonoids.
 Cossins, E., Lee, R. and Packer, L. (1998)
 ESR studies of vitamin C regeneration, order of reactivity of natural source phytochemical preparations.
Biochem Mol Biol Int, **45(3)**: 583-597.



12. Immunology

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- Ref. 082** Pycnogenol® shows beneficial effects in case of lupus erythematosus.
Stefanescu, M., Matache, C., Onu, A., Tanaseanu, S., Dragomir, C., Constantinescu, I., Schönlau, F., Rohdewald, P. and Szegli G. (2001)
Pycnogenol® Efficacy in the Treatment of Systemic Lupus Eythematosus Patients.
Phytother Res, **15**: 698-704.
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- Ref. 029** Pycnogenol® slows down the aging related process of decline in the activities of immune- and blood cells generating systems and restores their functions to normal.
Liu, F.J., Zhang, Y.X. and Lau B.H.S. (1998)
Pycnogenol® enhances immune and haemopoietic functions in senescence-accelerated mice.
Cell Mol Life Sci, **54**: 1168-1172.
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- Ref. 016** Pycnogenol® enhances the activity of the immune system in mice infected with a leukemia-causing retrovirus. Pycnogenol® increases the natural killer cell cytotoxicity.
Cheshier, J.E., Ardestani-Kaboudanian, S., Liang B., Araghi Niknam, M., Chung, S., Lane, L., Castro, A. and Watson, R.R. (1996)
Immunomodulation by Pycnogenol® in retro-virus infected or ethanol-fed mice.
Life Sci, **58(5)**: 87-96.
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- Ref. 055** Pycnogenol® increases TNF- α 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, Y.C., Rimbach, G., Saliou, C., Valacchi, G. and Packer, L. (2000)
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.
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- Ref. 095** Pycnogenol® activates in vitro macrophages to kill more effectively invading bacteria.
Shah, V., Bayeta, E. and Lau, B.H.S. (2002)
Pycnogenol® augments macrophage phagocytosis and cytokine secretion.
Pakistan Journal of Nutrition, **1(5)**: 196-201.
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- Ref. 111** Pycnogenol® applied after sunburn inhibits UV-induced suppression of immune system.
Sime, S. and Reeve, V.E. (2004)
Protection from inflammation, immunosuppression and carcinogenesis induced by UV radiation in mice by topical Pycnogenol®.
Photochem Photobiol, **79(2)**: 193-198.
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Ref. 228 Pycnogenol® inhibits viral replication in myocarditis.

Matsumori, A. (2007)
 Treatment Options in Myocarditis.
Herz, **32(6)**: 452-456.

Ref. 173 Pycnogenol® selectively kills cancerous ovarian germ cells.

Buz'Zard, A.R. and Lau, B.H.S. (2004)
 Research article: Selective toxicity of Pycnogenol® for malignant ovarian germ cells *in vitro*.
International Journal of Cancer Prevention, **1(3)**: 105-112.

Ref. 059 Pycnogenol® selectively kills cancerous human mammary cells (MCF-7), without affecting the normal mammary cells (MCF-10).

Huynh, H.T. and Teel R.W. (2000)
 Selective induction of apoptosis in human mammary cancer cells (MCF-7) by Pycnogenol®.
Anticancer Res, **20**: 2417-2420.

Ref. 208 Pycnogenol® reduces cancerogenesis in human ovarian cells.

Buz'Zard, A.R. and Lau, B.H.S. (2007)
 Pycnogenol® reduces Talc-induced Neoplastic Transformation in Human Ovarian Cell Cultures.
Phytother Res, **21(6)**: 579 – 586.

Ref. 221 Pycnogenol® inhibits the harmful effects of two mutagenic chemicals.

Krizkova, L., Chovanova, Z., Durackova, Z. and Krajcovic, J. (2007)
 Antimutagenic In Vitro Activity of Plant Polyphenols: Pycnogenol® and *Ginkgo biloba* Extract (EGb 761).
Phytother Res, **21**: in print.

13. Allergies and Asthma

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- Ref. 077** Pycnogenol® reduces asthma symptoms and improves lung function of asthmatic patients in a placebo-controlled, cross-over study.
 Hosseini, S., Pishnamazi, S., Sadrzadeh, M.H., Farid, F., Farid, R. and Watson, R.R. (2001)
 Pycnogenol® in the management of asthma.
J Med Food, **4(4)**: 201-209.
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- Ref. 149** Pycnogenol® improves pulmonary functions and reduces symptoms of asthma in children.
 Lau, B.H.S., Riesen, S.K., Truong, K.P., Lau, E.W., Rohdewald, P. and Barreta, R.A. (2004)
 Pycnogenol® as an adjunct in the management of childhood Asthma.
J Asthma, **41(8)**: 825-832.
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- Ref. 089** Pycnogenol® blocks release of histamine from mast cells in vitro to the same extent as the antiasthmatic drug DNCG.
 Sharma, S.C., Sharma, S. and Gulati, O.P. (2003)
 Pycnogenol® inhibits the release of histamine from mast cells.
Phytother Res, **17**: 66-69.
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14. Sport & Endurance

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- Ref. 230** Pycnogenol® increases vasodilation by 42% in young health men to warrant, 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. and Higashi, Y. (2007)
Pycnogenol®, French Maritime Pine Bark Extract, augments endothelium-dependent vasodilation in humans.
Hypertens Res, **30**: 775-780.
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- Ref. 044** Pycnogenol® increases human endurance during exercise by 21% providing antioxidant reserves.
Pavlovic, P. (1999)
Improved endurance by use of antioxidants.
Eur Bull Drug Res, **7(2)**: 26-29.
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- Ref. 189** Pycnogenol® reduces muscular pain and cramps in athletes and in patients with chronic venous insufficiency, diabetes or poor circulation in the legs.
Vinciguerra, G., Belcaro G., Cesarone, M.R., Rohdewald P., Stuard, S., Ricci, A., Di Renzo A., Hosoi, M., Dugall, M., Ledda, A., Cacchio M., Acerbi, G., Fano, F. (2006)
Cramps and Muscular Pain: Prevention with Pycnogenol® in Normal Subjects, Venous Patients, Athletes, Claudicants and in Diabetic Microangiopathy.
Angiology, **57(3)**: 331-339.
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- Ref. 096** Pycnogenol® stimulates Human Growth Hormone (HGH) secretion in vitro thousand times more effectively than other natural compounds. Treatment with HGH increases muscle mass and decreases fat mass.
Buz'Zard, A.R., Peng, Q. and Lau, B.H.S.(2002)
Kyolic and Pycnogenol® increase human growth hormone secretion in genetically-engineered keratinocytes.
Growth Horm IGF Res, **12**: 34-40.
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15. Menstrual Disorders, Pregnancy Associated Pain and Endometriosis

Ref. 219 Pycnogenol® reduces pain from endometriosis and shows less side effects compared to hormonal treatment.
 Kohama, T., Herai, K and Ioue, M (2007)
 Effect of French Maritime Pine Bark Extract on endometriosis as compared with Leuprorelin acetate.
J Reprod Med, **52(8)**: 703-708.

Ref. 174 Pycnogenol® reduces low-back pain in late period of pregnancy.
 Kohama T. and Inoue M. (2006)
 Pycnogenol® Alleviates Pain Associated with Pregnancy.
Phytother Res, **20**: 232-234.

Ref. 145 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. and Inoue, M. (2004)
 Analgesic efficacy of French maritime pine bark extract in dysmenorrhea. – An open clinical trial.
J Reprod Med, **49(10)**: 828-832.

Ref. 045 Pycnogenol® helps in gynaecological disorders such as endometriosis and dysmenorrhea. It reduces menstrual cramps, abdominal pain and tenderness.
 Kohama, T. and Suzuki, N. (1999)
 The treatment of gynaecological disorders with Pycnogenol®.
Eur Bull Drug Res, **7(2)**: 30-32.

Ref. 180 Pycnogenol®'s beneficial effects in a series of painful conditions as stiff shoulder, endometriosis, herniated disc.
 Kohama, T. (2004)
 Nutritional supplements in clinical practice.
Progr Med, **24**: 1503-1510.

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- Ref. 118** Caffeic and protocatechic acids (components of Pycnogenol®) produce anti-spasmodic activity contributing to beneficial effects of Pycnogenol® in Premenstrual syndrome (PMS).
Ortiz de Urbina, J.J., Martin, M.L., Sevilla, M.A., Montero, M.J., Carron, R. and San Roman, L.(1990)
Antispasmodic activity on rat smooth muscle of polyphenol compounds caffeic and protocatechic acids.
Phytother Res, **4(2)**: 71-76.
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- Ref. 220** 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., Ohno, S., Moniwa, N., Kanayama, N., Koike, K., Arai, T., Sugiura, K. and Inoue M. (2007)
Effect of Pycnogenol®, French Maritime Pine Bark Extract, on Dysmenorrhea: a multicenter, randomized, double-blind, placebo-controlled study.
J Reprod Med, in print
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- Ref. 187** Pycnogenol® improves a broad range of climacteric symptoms in menopausal women.
Yang, H.-M., Liao, M.-F., Zhu, S.Y., Liao, M.-N. and Rohdewald, P. (2007)
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.
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16. Fertility

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- Ref. 046** Pycnogenol® improves the morphology of spermatozoa. The percentage of non-deformed sperms in sub-fertile men was increased by 99% after supplementation with Pycnogenol® for three months.
 Roseff, S and Gulati, R. (1999)
 Improvement of sperm quality by Pycnogenol®.
Eur Bull Drug Res, **7(2)**: 33-36.
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- Ref. 091** After treatment with Pycnogenol® increase in functionally normal sperm may allow infertile couples to forgo in vitro fertilization.
 Roseff, S. J. (2002).
 Improvement in sperm quality and function with French maritime pine tree bark extract.
J Reprod Med, **47(10)**: 821-824.
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- Ref. 143** Pycnogenol® and Ginkgo biloba supplementation showed beneficial effects in erectile dysfunction.
 Muchova, J., Chovanova, Z., Hauserova, M., Liptakova, A., Vuznakova, M., Trebaticky, B., Breza, J. and Durackova, Z. (2004)
 The effect of natural polyphenols (Extract from Pinus pinaster (Pycnogenol®) and Ginkgo biloba (EGB 761) on the oxidative stress and erectile function in patients suffering from erectile dysfunction.
 Proceedings. (Abstract No L 61)
4th International Conference Vitamins 2004 Targeted Nutritional Therapy, 13-15.9.2004, Aula Univerzity Pardubice.
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17. Attention Deficit Hyperactivity Disorder (ADHD)

Ref. 205 Pycnogenol® improves antioxidant status in children with Attention Deficit Hyperactivity Disorder (ADHD).
 Dvorakova, M., Sivonova, M., Trebaticka, J., Skodacek, I., Waczulikova, I., Muchova, J. and Durackova, Z. (2006)
 Research Article: The effect of polyphenolic extract from pine bark, Pycnogenol®, on the level of glutathione in children suffering from attention deficit hyperactivity disorder (ADHD).
Redox Rep, **11(4)**: 163-172.

Ref. 204 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. and Durackova, Z. (2006)
 Effect of polyphenolic extract, Pycnogenol®, on the level of 8-oxoguanine in children suffering from attention deficit/hyperactivity disorder.
Free Radic Res, **40(9)**: 1003-1010.

Ref. 190 Pycnogenol® provides relief of 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. and Durackova, Z. (2006)
 Treatment of ADHD with French maritime pine bark extract, Pycnogenol®.
Eur Child Adolesc Psychiatry, **15(6)**: 329-335.

Ref. 047 Positive experience with Pycnogenol® in treating ADHD is mentioned in this letter to the Editor.
 Heimann, S.W. (1999)
 Pycnogenol for ADHD?
J Am Acad Child Adolesc Psychiatry, **38(4)**: 357-358.

Ref. 048 Pycnogenol® is recommended for treatment of Attention Deficit Disorder.
 Hanley, J.L. (1999)
 Attention Deficit Disorder.
Impact Communications Inc., Green Bay, WI, USA, 17-19.



Ref. 231

Pycnogenol® lowers stress-hormones in children with ADHD.

Dvorakova, M., Jezova, D., Blazicek, P., Trebaticka, J., Skodacek, I., Suba, J., Waczulikova, I., Rohdewald, P. and Durackova, Z. (2007)

Urinary catecholamines in children with attention deficit hyperactivity disorder (ADHD): modulation by a polyphenolic extract from pine bark (Pycnogenol®).

Nutr Neurosci, in print.

18. Antioxidant and Free Radical Scavenger

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- Ref. 205** Pycnogenol® improves antioxidant status in children with Attention Deficit Hyperactivity Disorder (ADHD).
Dvorakova, M., Sivonova, M., Trebaticka, J., Skodacek, I., Waczulikova, I., Muchova, J. and Durackova, Z. (2006)
Research Article: The effect of polyphenolic extract from pine bark, Pycnogenol® on the level of glutathione in children suffering from attention deficit hyperactivity disorder (ADHD).
Redox Rep, **11(4)**: 163-172.
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- Ref. 204** 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. and Durackova, Z. (2006)
Effect of polyphenolic extract, Pycnogenol®, on the level of 8-oxoguanine in children suffering from attention deficit/hyperactivity disorder.
Free Radic Res, **40(9)**: 1003-1010.
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- 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. (2006)
Ferritin oxidation and proteasomal degradation: Protection by antioxidants.
Free Radic Res, **40(7)**: 673-683.
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- Ref. 090** Pycnogenol® increases antioxidant capacity and lowers cholesterol in obese volunteers in a double-blind, placebo-controlled study.
Devaraj, S., Vega-López, S., Kaul, N., Schönlau, F., Rohdewald, P. and Jialal, I. (2002)
Supplementation with a pine bark extract rich in polyphenols increases plasma antioxidant capacity and alters plasma lipoprotein profile.
Lipids, **37(10)**: 931-934.
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- Ref. 183** Pycnogenol® protects intestinal mucosa against radiotherapy induced damage: histomorphological evidence in rats.
Ramos, F.M. Schönlau, F., Novaes, P.D., Manzi, F.R., Bóscolo, F.N. and Almeida, S.M. (2006)
Pycnogenol® protects against ionizing radiation as shown in the intestinal mucosa of rats exposed to X-rays.
Phytother Res, **20(8)**: 676-679.
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- Ref. 021** Pycnogenol® is shown to be the strongest hydroxyl and superoxide radical scavenger among other extracts tested. In addition, Pycnogenol® is resistant to heat and ascorbate oxidase.
Noda, Y., Anzai, K., Mori, A., Kohno, M., Shinmei, M. and Packer, L. (1997)
Hydroxyl and superoxide anion radical scavenging activities of natural source antioxidants using the computerized JES-FR30 ESR spectrometer system.
Biochem Mol Biol Int, **42(1)**: 35-44.
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- Ref. 030** Pycnogenol® prolongs the lifetime of vitamin C more than other flavonoids.
Cossins, E., Lee, R. and Packer, L. (1998)
ESR studies of vitamin C regeneration, order of reactivity of natural source phytochemical preparations.
Biochem Mol Biol Int, **45(3)**: 583-597.
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- Ref. 026** Pycnogenol® protects α -tocopherol in endothelial cells.
Virgili F., Kim, D. and Packer, L. (1998)
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.
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- 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. and Packer, L. (1999)
Electron spin resonance study of free radicals formed from a procyanidin-rich pine (*Pinus maritime*) bark extract, Pycnogenol®.
J Free Radic Biol Med, **27(11-12)**: 1308-1312.
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- Ref. 025** Pycnogenol® inhibits the effect of oxidative stress and minimises hydroxyl radical-induced DNA damage in vitro.
Nelson, A.B., Lau, B.H.S., Ide, N. and Rong, Y. (1998)
Pycnogenol inhibits macrophage oxidative burst, lipoprotein oxidation and hydroxyl radical-induced DNA damage.
Drug Dev Ind Pharm, **24(2)**: 139-144.
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- Ref. 020** Pycnogenol® stimulates synthesis of antioxidative enzymes inside cells of the arteries thereby doubling the amount of antioxidative enzymes.
Wei, Z. H., Peng, Q. L. and Lau, B.H. S. (1997)
Pycnogenol® enhances endothelial cell antioxidant defenses.
Redox Rep, **3(4)**: 219-224.
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- Ref. 072** Pycnogenol® selectively enhances activity of intracellular antioxidative enzymes.
 Bayeta, E. and Lau, B.H.S. (2000)
 Pycnogenol® inhibits generation of inflammatory mediators in macrophages.
Nutr Res, **20**: 249-259.
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- Ref. 105** Pycnogenol® lowers blood glucose and increases intracellular antioxidant defense mechanism in diabetic rats.
 Maritim, A., Dene, B.A., Sanders, R.A. and Watkins, J.B. (2003)
 Effect of Pycnogenol® treatment on oxidative stress in streptozotocin-induced diabetic rats.
J Biochem Mol Toxicol, **17(3)**: 193-199.
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- Ref. 051** Pycnogenol® protects retina of the eye against damage caused by oxidative stress. The effect is more pronounced when compared to other antioxidant bioflavonoids. Pycnogenol® enhances the effects of other antioxidants like Coenzyme Q10 when combined together.
 Chida, M., Suzuki, K., Nakanishi-Ueda, T., Ueda, T., Yasuhara, H., Koide, R. and Armstrong, D. (1999)
 In vitro testing of antioxidants and biochemical end-points in bovine retinal tissue.
Ophthalmic Res, **31**: 407-415.
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- Ref. 010** Pycnogenol® scavenges superoxide radicals *in vitro* and inhibits oedema *in vivo*. The anti-inflammatory and free radical scavenging activities are closely correlated.
 Blazso, G., Gabor, M., Sibbel, R. and Rohdewald, P. (1994)
 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.
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- Ref. 014** Pycnogenol® protects the endothelial cells which line the blood vessels from free radicals damage. Damage to endothelial cells is considered a prime cause for atherosclerosis.
 Rong Y., Li, L., Shah, V. and Lau, B.H.S. (1995)
 Pycnogenol® protects vascular endothelial cells from t-butyl hydroperoxide induced oxidant injury.
Biotechnol Ther, **5(3&4)**: 117-126.
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- Ref. 070** Pycnogenol® by virtue of its high content of procyanidins is more potent antioxidant than other herbal-sourced antioxidants containing relatively higher content of regular flavon(ol)s. This fact is explained on structural and functional basis.
 Bors, W., Michel C and Stettmaier, K (2000)
 Electron paramagnetic resonance studies of radical species of proanthocyanidins and gallate esters.
Arch Biochem Biophys, **374(2)**: 347-355.
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- Ref. 022** Pycnogenol® in addition to its free radical scavenging property, modulates the production of nitric oxide radicals in activated inflammatory cells.
Virgili, F., Kobuchi, H. and Packer, L. (1998)
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(7/8)**: 1120-1129.
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- Ref. 062** Pycnogenol® blocks oxidative modification of cellular proteins more effectively than other antioxidants.
Kim, J., Chehade, J., Pinnas, J.L., and Mooradian, A.D. (2000)
Effect of select antioxidants on malondialdehyde modification of proteins.
Nutrition, **16**: 1079-1081.
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- 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 and Chung A-S. (2000)
Effect of bioflavonoids extracted from the bark of *Pinus maritima* on proinflammatory cytokine interleukin-1 production in lipopolysaccharide-stimulated raw 264.7.
Toxicol Appl Pharmacol, **168**: 64-71.
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- Ref. 007** Pycnogenol® is proven an excellent radical scavenger of enzymatically produced hydroxyl and singlet oxygen free radicals, two of the most dangerous free radicals.
Elstner, E.F. and Kleber, E. (1990)
Radical scavenger properties of leucocyanidine.
In: Das NP, ed. *Flavonoids in Biology & Medicine III: Current issues in Flavonoid Research*: National University of Singapore Press (1990): 227-235.
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- Ref. 086** Pycnogenol® in combination with whey increases antioxidative capacity of plasma.
Janisch, K., Hippeli, S., Dornisch, K., Kern, S. and Elstner, E.F. (2002)
Determination of the antioxidative potential of human plasma after supplementation with Pycnogenol® and whey.
Food Res Intern, **35**: 257-266.
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- Ref. 218** Pycnogenol® lowers oxidative stress in the liver of rats challenged with a chemical toxin.
Ahn, T.-H., Yang, Y.-S., Lee, J.-C., Moon, C.-J., Kim, S.-H., Jun, W., Park, S.-C. and Kim J.-C. (2007)
Ameliorative Effects of Pycnogenol® on Carbon Tetrachloride-Induced Hepatic Oxidative Damage in Rats.
Phytother Res, in print.
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- Ref. 227** Pycnogenol® and Lutein display synergistic antioxidant effects for prevention of lipid peroxidation.
Nakanishi-Ueda, T., Kamegawa, M., Ishigaki, S., Tsukahara, M., Yano, S., Wada, K. and Yasuhara, H. (2006)
Inhibitory Effect of Lutein and Pycnogenol® on Lipid Peroxidation in Porcine Retinal Homogenate.
J Clin Biochem Nutr, **38**: 204-210.
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- Ref. 215** Pycnogenol® protects liposomes from lipid peroxidation and shows synergistic protective effects with vitamin C and vitamin E.
Sivonova, M., Zitnanova, I., Horakova, L., Strosova, M., Muchova, J., Balgavy, P., Dobrota, D. and Durackova, Z. (2006)
The Combined Effect of Pycnogenol® with Ascorbic Acid and Trolox on the Oxidation of Lipids and Proteins.
Gen Physiol Biophys, **25**: 379-396.
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19. Bio-Availability and Metabolism

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- Ref. 040** Pycnogenol® is shown to be bioavailable based on its therapeutic effects in vivo: the prevention of platelet aggregation and the capillary sealing effect. Valerolactones as sulphates or glucuronides appear in the urine and they represent the active metabolites of Pycnogenol®.
Rohdewald, P. (1999)
Bioavailability and metabolism of Pycnogenol®.
Eur Bull Drug Res, **7(2)**: 5-7.
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- Ref. 058** Pycnogenol®, its components and metabolites are bio-available in human for more than 24 hours to produce their beneficial effects.
Grosse-Düweler, K. and Rohdewald, P. (2000)
Urinary metabolites of French maritime pine bark extract in humans.
Pharmazie, **55**: 364-368.
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- Ref. 060** 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 and Packer, L. (2000)
Ferulic acid excretion as a marker of consumption of a French maritime pine (*Pinus maritima*) bark extract.
J Free Radic Biol Med, **28(8)**: 1249-1256.
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- Ref. 137** Evidence of percutaneous absorption of Pycnogenol® in human skin.
Sarikaki, V., Rallis, M., Tanojo, H., Panteri, I., Dotsikas, Y., Loukas, Y.L. Papaioannou, G. Demetzos, C., Weber, S., Moini, H., Maibach, H.I. and Packer, L. (2004)
In vitro Percutaneous Absorption of Pine Bark Extract (Pycnogenol®) in Human Skin.
J Toxicol Cutaneous Ocul Toxicol, **23(3)**: 149-158.
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- Ref. 197** Pycnogenol® is bioavailable after oral administration.
Grimm, T., Skrabala, R., Chovanova, Z., Muchova, J., Sumegova, K., Liptakova, A., Durackova, Z. and Högger, P. (2006)
Single and multiple dose pharmacokinetics of maritime pine bark extract (Pycnogenol®) after oral administration to healthy volunteers.
BMC Clin Pharmacol, **6(4)**: doi:10.1186/1472-6904-6-4.
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20. Anti-microbial and anti-viral activity

Ref. 150

Pycnogenol® shows antimicrobial activity in vitro.

Torras, M.A.C., Faura, C.A., Schönlau, F. and Rohdewald, P. (2005)
Short Communication: Antimicrobial activity of Pycnogenol®.
Phytother Res, **19**: 647-648.

Ref. 229

Pycnogenol® inhibits viral replication in the heart muscle of mice.

Matsumori, A., Higuchi, H. and Shimada, M. (2007)
French maritime pine bark extract inhibits viral replication and prevents development of viral myocarditis.
J Card Fail, **20**, in print.

Ref. 225

Pycnogenol® inhibits growth of Helicobacter pylori and their adherence to mucosal cells of the stomach.

Rohdewald, P. and Beil, W. (2007)
In vitro inhibition of Helicobacter pylori growth and adherence to gastric mucosal cells by Pycnogenol®.
Phytother Res, in print.

21. Joint Health

Ref. 223 Pycnogenol® improves pain and mobility and lowers required pain medication in osteoarthritis.

Belcaro, G., Cesarone, M.R., Errichi, S., Zulli, C., Errichi, B.M., 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. and Rohdewald, P. (2007)
Treatment of osteoarthritis with Pycnogenol®. The SVOS (San Valentino Osteo-Arthrosis Study). Evaluation of Signs, Symptoms, Physical Performance and Vascular Aspects.
Phytother Res, in print.

Ref. 188 Pycnogenol® reduces pain and stiffness of knee osteoarthritis.

Farid, R., Mifteizi, Z., Mirheidari, M., Yasdi, S., Torghabeh, H., Esmaelli, H., Zibadi, S., Rohdewald, P. and Watson, RR. (2007)
Pycnogenol® supplementation reduces pain and stiffness and improves physical function in adults with knee osteoarthritis.
Nutr Res, in print.

Ref. 176 Pycnogenol® consumption non-selectively, inhibits cox enzyme, which are involved in pain sensation during inflammation.

Schäfer, A., Chovanova, Z., Muchova, J., Sumegova, K., Liptakova, A., Durackova, Z. and Högger, P. (2006)
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.

Ref. 185 Pycnogenol® inhibits key trigger of inflammation.

Grimm, T., Chovanová, Z., Muchová, J., Sumegová, K., Liptáková, A., Duracková, Z. and Högger, P. (2006)
Inhibition of NF- κ B activation and MMP-9 secretion by plasma of human volunteers after ingestion of maritime pine bark extract (Pycnogenol®).
J Inflamm, **3(1)**: 1-6.

Ref. 107 The tissue destroying enzymes (matrix metalloproteinases) collagenase, elastase and gelatinase are inhibited ex-vivo. Release of these enzymes from inflammatory cells is also inhibited by Pycnogenol® and its metabolites.

Grimm, T., Schäfer, A. and Högger, P. (2004)
Antioxidant activity and inhibition of matrix-metalloproteinases by metabolites of maritime pine bark extract (Pycnogenol®).
J Free Radic Biol Med, **36(6)**: 811-822.

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