

Bibliography

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1. Economy Class Syndrome

Pycnogenol®: -

Review article: describes cardiovascular pharmacologic profile of Pycnogenol®, mainly highlighting its inhibitory effects on the smoking induced platelet aggregation in humans.

Watson, R.R. (1999)

Cardiovascular Rev Rep **20**: 326-329

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.

Putter, M., Grotemeyer, K.H.M., Wurthwein, G., Araghi-Nicknam, M., Watson, R.R., Hosseini, S. and Rohdewald, P. (1999)

Thrombosis Research, **95**: 155-161.

Pycnogenol® inhibits smoking induced increased levels of thromboxane B2, the noxious agent involved in the increased platelet reactivity/aggregation in smokers. These results explain the mechanism of anti-platelet aggregation activity of Pycnogenol®, observed in smokers.

Araghi-Nicknam, M., Hosseini, S., Larson, D., Rohdewald, P. and Watson R.R. (1999)

Integrative Medicine, **2 (2/3)**: 73-77

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 Rodhewald, P (1998)

Journal Cardiovascular Pharmacology, **32**: 509

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, changes in blood biochemistry and haematological parameters

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

Phytomedicine, **7 (5)**: 383-388

Review article summarizing published data on Pycnogenol® until 2001

Rodhewald, P. (2002)

International Journal of Clinical Pharmacology and Therapeutics, **40 (4)**: 158-168

1. Antioxidants and Free Radical Scavengers

Ginger: -

Amrita Bindu - A salt spice herbal health food supplement for the prevention of nitrosamine induced depletion of antioxidants

Shanmugasundaram, K.R., et al. (1994)

J. Ethnopharmacol. **42 (4)**: 83-93

Scavenging of superoxide anions by spice principle

Krishnakantha, T.P. & Lokesh, B.R. (1993)

Indian J. Biochem. Biophys. **30 (2)**: 133-134

Scavenging effects of ginger on superoxide anions and hydroxyl radical.

Cao, Z.F., et al (1993)

Chung Kuo Chung Yao Tsa Chih. **18 (12)**: 750-751, 764

Antioxidative effect of Chinese Drugs

Zhou, Y. & Xu, R. (1992)

Chung Kuo Chung Yao Tsa Chih. **17 (6)**: 368-369, 373

Studies on spice principles as antioxidants in the inhibition of lipid peroxidation of rat liver microsomes

Reddy, A.C. & Lokesh, B.R. (1992)

Mol. Cell. Biochem. **111 (1-2)**: 117-124

Antioxidant effects of some ginger constituents.

Kikuzaki, H, and Nakatani, N. (1993).

Journal of Food Science. **58 (6): 1407-1410**

Structure of antioxidative compounds in ginger.

Kikuzaki, H., Kawasaki, Y. and Nakatani, N. (1994)

ACS Sympisium series. **547: 237 –243**

The antioxidant activity of gingerol.

Lee, I.K. and Ahn, S.Y. (1985)

Korean Journal of Food Science and Tech. 17 (2): 55-59

Pycnogenol®:-

Pycnogenol® show free radical scavenging activity against reactive oxygen species. It inhibits the generation of pro-inflammatory mediators confirming the immuno-modulatory profile of Pycnogenol®

Cho, K-J., Yun C-H., Cho, Y-Srimbach, G., Packer, L ands Chung A-S. (200)

Toxicology and Applied Pharmacology , **168: 64-71**

Pycnogenol® produces cell protection by reducing the malonaldehyde (MDA) modified protein, a known biochemical marker of free radical related cell injury.

Kim, J., Chehade, J., Pinnas,J.L., and Mooradian, A.D. (2000)

Nutrition, **16: 1079-1081**

Pycnogenol® produces selective action on cell enzyme system relating to their binding capacity, explaining its specificity of action against oxidative stress

Moini,H., Guo,Q., and Packer ,L. (2000)

J.Agric. Food Chem., **48: 5630-5639**

Pycnogenol® by virtue of its relatively higher content of procyanidins is a more potent antioxidant than other herbal-sourced antioxidants containing relatively higher content of regular flavan(ol)s. This fact is explained on structural and functional basis.

Bors, W., Michel C and Stettmaier, K (2000)

Archives of Biochemistry and Biophysics, **374 (2)**: 347-355

Pycnogenol® and one of its components caffeic acid, modulate cellular response to oxidative stress, contributing to the mechanisms involved in their biological effects.

Nardini, M., Scaccini, C., Packer, L. and Virgili, F (2000)

Biochimica et Biophysica Acta, **1474**:219-225

Pycnogenol® in addition to its antioxidant activity, affects the regulation of nitric oxide metabolism and cell adhesion, contributing to its beneficial effects in inflammatory and degenerative conditions.

Packer, L. *et al.*, (2000)

Experimental Biology 99 (FASEB) Washington D.C., April, 1999; (Abstract)

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. and Packer, L. (1999)

Oxygen Club of California (OCC) World Congress, March 1999; (abstract)

Pycnogenol® significantly enhances the level of antioxidant defence against reactive nitrogen species *in vitro* cell (macrophage) model system.

Rimbach, G., Virgili, F., Park, Y.C. and Packer, L. (1999)

Redox Report, **4 (4)**: 171-177

The beneficial effects of electron donating and protein binding properties of Pycnogenol® with respect to SAR of different enzyme system have been demonstrated and discussed

Packer, L., Bito, T., Cossins, E., Kobuchi, H., Moini, H., Noda, Y., Rimbach, G., Roy, S., Vaya, J. and Virgili, F. (1999)

Oxygen Club of California (OCC) World Congress, March 1999; (presentation)

Pycnogenol® protects α -tocopherol in endothelial cells.

Virgili, F., Kim, D. And Packer, L. (1998)

FEBS letters, **431**: 315-318

Pycnogenol® inhibits the effect of oxidative stress and minimizes hydroxyl radical-induced DNA damage *in vitro*.

Nelson, A.B., Lau, B.H.S., Ide, N. and Rong, Y. (1998)

Drug Development and Industrial Pharmacy, **24 (2)**: 139-144

Pycnogenol® modulates the production of nitric oxide radicals in activated inflammatory cells. Pycnogenol® produces beneficial effects in pathologies relating to oxidative stress

Virgili, F., Kobuchi, H. and Packer, L (1998)

In flavanoids in Health and Disease, ed. Catherine A. Rice-evans and Lester Packer, Marcel Dekker Inc. NY, 1998. Chapter 18. Pages 421-436

Pycnogenol® prolongs the lifetime of Vitamin C more than other flavanoids.

Cossins, E., Lee, R. and Packer, L. (1998)

Biochem. & Mol. Biol. Int., **45 (3)**: 583-597

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., Mori, A., Kohno, M., Shinmei, M. And Packer, L. (1997)

Biochem. & Mol. Biol. Int., **42 (1)**: 35-44.

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)

Biotechnology Therapeutics, **5(3 & 4):117-126**

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)

Pharm. Parmacol. Lett., **3: 217-220**

Pycnogenol® is proved to be 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)

In: Das NP, ed. *Flavanoids in Biology & Medicine III: Current issues in Flavanoid Research*: National University of Singapore Press (1990): 221-235

2. Cardiovascular System

Ginger: -

Effects of aqueous extracts of onion, garlic and ginger on the platelet aggregation and metabolism of arachidonic acid in the blood vascular system: In Vitro study.

Srivastava, K.C. (1984)

Prostaglandins Leukotrienes Med. **13(2): 227-235**

Pharmacological studies on ginger. IV. Effect of (6)-shogol on the arachidonic cascade.

Suekawa, M., et al (1986)

Nippon Yakurigaku Zasshi. **88 (4): 263-269**

Isolation and effects of some ginger components on platelet aggregation and eicosanoid biosynthesis

Srivastava KC. (1986)

Prostaglandins Leukotrienes in Medicine **25**: 187-198

Ginger: inhibition of thromboxane synthetase and stimulation of prostacyclin: relevance for medicine and psychiatry.

Backon, J. (1986)

Med. Hypotheses **20**: 271-8

Effect of onion and ginger consumption on platelet thromboxane production in humans.

Srivastava, K.C. (1989)

Prostaglandins Leukotrienes Essent Fatty Acids. **35 (3)**: 183-185

Effects of ginger on platelet aggregation in man

Verma, S.K., et al. (1993)

Indian J. Med. Res. **98**: 240-242

Antiplatelet effect of gingerol isolated from *Zingibar Officinale*.

Guh, J.H., et al. (1995)

J. Pharm. Pharmacol. **47 (4)**: 329-332

Effect of ginger (*Zingiber officinale* Rosc.) and fenugreek (*Trigonella foenumgraecum*) on blood lipids, blood sugar and platelet aggregation in patients with coronary heart disease.

Bordia, A., Verma, S.K. & Srivastava, K.C. (1997)

Prostaglandins Leukotrienes Essent Fatty Acids. **56 (5)**: 379-384

Pycnogenol® :-

Pycnogenol® reduces blood pressure, as shown in a randomized, double blind, placebo-controlled study in mildly hypertensive patients. Furthermore, Pycnogenol® significantly decreases the level of vasoconstrictor factor (thromboxane) in the blood of these patients

Hosseinie, S., Lee, J., Sepulveda, R.T., Rohdewald, P., Watson R.R. (2001)

Nutrition Research, **21**: 1251-1260

Pycnogenol® inhibits smoking induced platelet aggregation in dose dependent manner in human. The effect last for more than 6 days and unlike aspirin, it does not produce increase in bleeding time.

Putter, M., Grotemeyer, K.H.M., Wirthwein, G., Araghi-Nicknam, M., Watson, R.R., Hosseini, S. and Rohdewald, P (1999)

Thrombosis Research, **95**: 155-161

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Araghi-Nicknam, M., Hosseini, S., Larson, D., Rohdewald, P. and Watson R.R. (1999)

Integrative Medicine, **2 (2/3)**. 73-77

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

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

European Bulletin of Drug Research **7 (2)**:19-25

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)

Journal Cardiovascular Pharmacology, **32**: 509-515

Pycnogenol® helps to maintain a healthy circulation through vasodilation, anti-platelet aggregation, free radical scavenging and capillary sealing effects. The role of endothelial nitric oxide (NO) is also discussed.

Rohdewald, P. (1999)

European Bulletin of Drug Research, 7(2): 14-18

3. Venous Disorders

Pycnogenol®:-

Pycnogenol® increases the pathologically low capillary wall resistance. Pycnogenol® is shown to be the most potent among other bioflavanoids 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)

Phlebologie, 22: 178-182

The efficacy of Pycnogenol® has been confirmed on the basis of objective and subjective signs and symptoms of static oedema in a double blind study in 40 patients suffering from chronic venous insufficiency. Pycnogenol® is a safe veno-protector.

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

Journal Suisse de Medecine Globale, 3/95:114-115

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

Becker, S.R. (1995)

Journal Suisse de Medecine Globale, 1/95: 11-14 et 2/95: 69-73

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, changes in blood biochemistry and haematological parameters

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

Phytomedicine, **7(5)**: 383-388

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)

Fitotherapia, **71**: 236-244

Pycnogenol® demonstrated higher efficacy in a lower dosage compared to horse chestnut seed extract in a clinical trial

Koch, R. (2002)

Phytotherapy research, **16**: S1-S5

Pycnogenol® produces an anti-oedema effect. Topical application of Pycnogenol® gel protects the skin against UV radiation

Blazso, G., Gabor, M. and Rohdewald

Pharmazie, **52 (5)**: 380-382

4. Motion sickness

Ginger: -

Motion sickness, ginger and psychophysics

Mowrey, D.B. and Clayson, D.E. (1982)

The Lancet **I**: 655-657

Ginger root against seasickness – a controlled trial on the open sea

Grontved, A., et al. (1988)

Acta Otolaryngol. **105 (1/2):** 45-49

The anti-motion sickness mechanism of ginger. A comparative study with placebo and dimenhydrinate.

Holtmann, S., et al. (1989)

Acta Otolaryngol. **108 (3-4):** 168-174

Vertigo-reducing effect of ginger root – a controlled clinical study.

Grontved, A. and Hentzer, e. (1986)

ORL J. Otorhinolaryngol. Relat. Spec. **48 (5):** 282-286

Pharmacologic studies of anti-motion sickness actions of ginger

Qian, D.S. and Liu, Z.S (1992)

Chung Kuo Chiung His I Chieh Ho Tsa Chih. **12 (2):** 95-98, 70

Comparison of seven commonly used agents for prophylaxis of seasickness

Schmid, R et al., (1994)

Journal of Travel Medicine 1: 203-206

A double-blind comparative trial of powdered ginger root, hyosine hydrobromide, and cinnarizine in the prophylaxis of motion sickness by cross coupled simulation

Stott, JR., Hubble, MP. And Spencer M.B. (1984)

Advisory Group for Aerospace Research Development conference proceedings **39: 1-6**

5. Bioavailability & Metabolism

Ginger:-

The metabolism of zingerone, a pungent principle of ginger

Monge, P., Kobayshi, M. and Nakatani, N. (1991)

Xenobiotica **6 (7)**: 411-423

Enzymatic reduction of shogol: a novel biotransformation pathway for the α,β -unsaturated ketone system.

Surh, Y.J. and Lee, S.S. (1992)

Biochem. Int. **27 (1)**: 179-187

Enzymic reduction of [6]-gingerol, a major pungent principle of ginger, in the cell free preparation of rat liver.

Surh, Y.J. and Lee S.S. (1994)

Life Sci. **54 (19)**: 321-326

Scientific evidence on the role of Ayurvedic herbals on bioavailability of drugs.

Atal, C.K., Zutshi U. And Rao, P.G. (1981)

J Ethnopharmacol. Sep; **4 (2)**: 229-32

Pycnogenol[®]

Pycnogenol[®] is shown to be bioavailable based on its therapeutic effects *in vivo*:- the prevention of platelet aggregation and the capillary sealing effect. Valerolactines as sulphates or glucuronides appear in the urine and they represent the active metabolites of Pycnogenol[®].

Rohdewald, P. (1999)

European Bulletin of Drug Research, **7 (2)**: 5-7

Pycnogenol[®], its components and metabolites are bio-available in human for more than 24 hours to produce their beneficial effects.

Grosse-Duweler, K. And Rohdewald, P. (2000)

Pharmazie, **55**: 364-368

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)

Free Radical Biology and Medicine, **28 (8)**: 1249-1256