

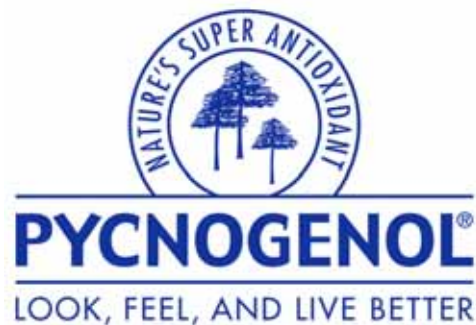
# Pycnogenol®

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## Diabetes Care

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Horphag Research  
Avenue Louis-Casari 71  
CH-1216 Geneva, Switzerland  
Phone: +41(0)22 710 26 26  
Fax: +41(0)22 710 26 00

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### Pycnogenol® for diabetes care

Pycnogenol® is a standardized extract prepared from bark of the French maritime pine (*Pinus pinaster*), which is world-wide exclusively distributed by Horphag Research Ltd., UK. Pycnogenol® constituents are bioflavonoids (for detailed description please see under section "What is Pycnogenol®"). A number of pharmacological functions award Pycnogenol® a prominent role for helping diabetic people to cope with their various health problems.

Pycnogenol® significantly and dose-dependently lowers both fasting- and after meal blood glucose in type II diabetics, who don't take other anti-diabetic medication. Pycnogenol® appears to facilitate cellular uptake of glucose, as it does not affect insulin levels. HbA1c, a lab test reflecting average blood glucose levels prevailing during the recent 2-3 months, was also found to be significantly lowered in type II diabetic patients taking Pycnogenol®.

The blood glucose-lowering effect of Pycnogenol® was confirmed by a double-blinded, placebo-controlled investigation of type II diabetics, who continued taking their prescribed anti-diabetic medication. Pycnogenol® was shown to significantly lower blood glucose as compared to the placebo group even though both groups were taking anti-diabetic medication. Moreover, Pycnogenol® helped restore healthy vascular functions, indicating better relaxation of blood vessels and improved blood flow.

In five clinical studies with in total more than 1200 patients, Pycnogenol® was demonstrated to be highly efficient for prevention and treatment of diabetic retinopathy. This disease involves bleeding capillaries in the eye causing irreversible vision loss. Retinopathy represents a serious threat for people, affecting 60% of type II diabetics and 90% of type I diabetics, 20 years after onset of diabetes. Pycnogenol® seals leaky capillaries in the eye, effectively stopping progression of this disease to save the remaining eye sight.

People with diabetes are living at increased risk of suffering from cardiovascular diseases, such as thrombotic events, heart infarction, stroke and poor micro-circulation.

Pycnogenol® enhances production of a body-own messenger molecule which controls at the same time the activity of blood platelets and the diameter of blood vessels. Clinical studies have demonstrated that Pycnogenol® prevents platelet aggregation and helps prevent thrombosis in high risk individuals. This function has awarded Pycnogenol® a patent (US patent 5,720,956). Pycnogenol® increases micro-circulation and improves blood perfusion in toes and fingertips.

50% of type II diabetics have hypertension and two clinical studies have shown that Pycnogenol® is able to normalize elevated blood pressure. 80% of type II diabetics are over-weight with high blood cholesterol profile. Three clinical studies have shown that Pycnogenol® supplementation lowers LDL cholesterol and increases HDL.

Pycnogenol® is the ideal daily supplement for people with diabetes. Pycnogenol® helps to tackle the primary problem: lowering of blood glucose. Moreover, Pycnogenol® safeguards the vascular system, maintaining the integrity of tiny capillaries as well as keeping the cardio-vascular system healthy. Pycnogenol® can safely be taken continuously, is free of side-effects and has GRAS status (“generally recognized as safe”) in the US.

## Pycnogenol® lowers blood glucose in type II diabetes patients

In an open, controlled, dose-finding study, Pycnogenol® was administered to 30 patients with II diabetes who were not treated with other anti-diabetic medication. Patients were treated with 50 mg, 100 mg, 200 mg and 300 mg Pycnogenol® per day, over a period of three weeks for each dose. As shown in figure 1, both fasting blood glucose and after-meal glucose were dose-dependently lowered. A dosage higher than 200 mg Pycnogenol® a day had no further glucose lowering effect. A dosage of 50 mg Pycnogenol significantly lowered blood glucose.

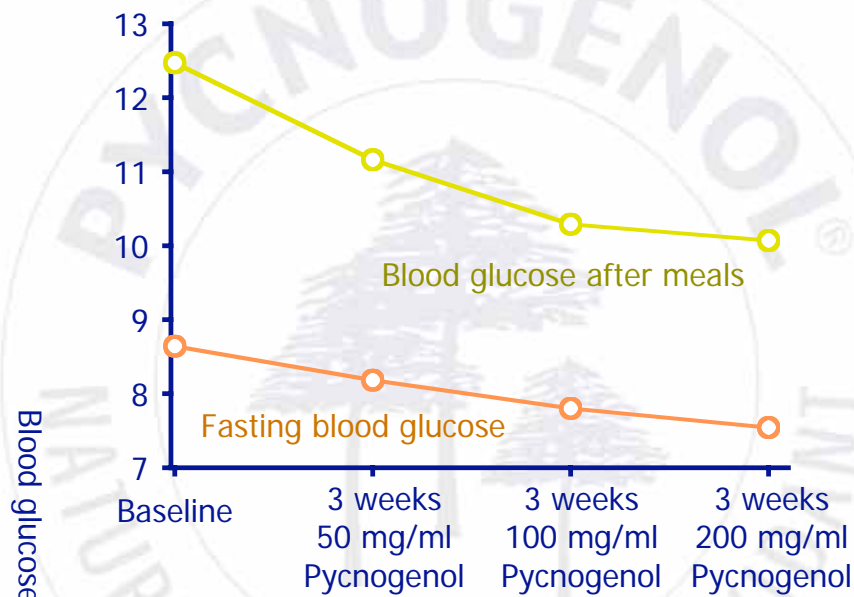


Figure 1: Mean blood glucose of 30 type II diabetes patients in response to supplementation with Pycnogenol®. Patients had to adhere to diet and sport program, but were not treated with anti-diabetic medication [Liu et al., Diabetes Care, 2004].

The lab test on HbA1c, a blood parameter reflecting an average blood glucose level in the past 2-3 months, was found to decrease continuously during the trial.

Insulin levels were investigated at all time points and found to be unaffected by all Pycnogenol® doses.

In a double-blind placebo controlled trial, Pycnogenol® was confirmed to lower blood glucose also in type II diabetes patients taking anti-diabetic medication (biguanide and/or sulfonylurea). In 77 patients participating in the trial, Pycnogenol® significantly lowered blood glucose as compared to placebo (figure 2). The study demonstrated a considerable placebo effect most likely resulting from better patient compliance to prescribed anti-diabetic medication.

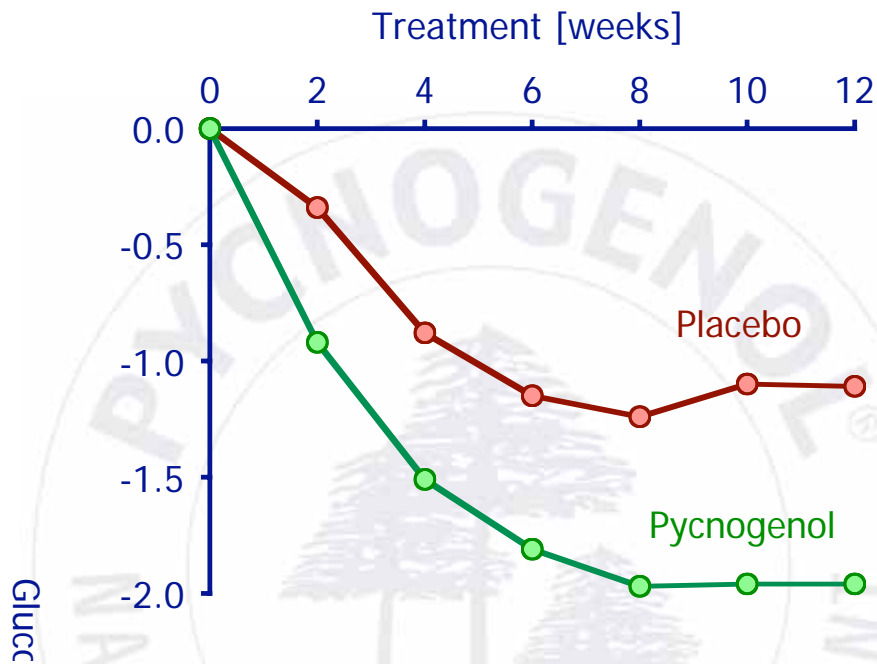


Figure 2: Mean fasting blood glucose lowering of 77 type II diabetes patients continuing their prescribed anti-diabetic medication and taking either Pycnogenol® or placebo in addition. Pycnogenol® supplementation statistical significantly lowered fasting blood glucose as compared to placebo [Liu et al., Life Sciences, 2004].

Though the exact mechanism of blood glucose lowering is not yet known, Pycnogenol® appears to overcome the blocked glucose uptake of cells in type II diabetes. This assumption is supported by a pharmacological study with streptozotocin-induced diabetic rats. While Pycnogenol® administration significantly lowered blood glucose in diabetic rats, in healthy control rats the blood sugar was not lowered in response to Pycnogenol® treatment [Maritim et al., 2003]. In two placebo-controlled clinical studies, high dosages of Pycnogenol® did not lower blood glucose in non-diabetic individuals [Arcangeli, 2000; Petrassi et al., 2000].



### Pycnogenol® for diabetic retinopathy

Retinopathy is an eye disease causing irreversible vision loss which occurs in about one out of two patients within 20 years after diagnosis of type II diabetes. In type I diabetes the likelihood of having retinopathy is even higher. The disease results from tiny capillaries in the eye turning leaky, allowing blood to flow into the retina. As a result light-sensing cells are destroyed and a gradual loss of vision occurs with time. The disease is symptom less, does not involve pain, and often is only diagnosed when considerable retinal damage has already taken place.



Figure 3: Compared to the background of a healthy eye (left), the capillaries of diabetics get brittle causing spot-like bleedings into the retina (center). The disease diabetic retinopathy causes gradual loss of vision which is irreversible as decayed cells of the retina are not replaced by new ones. Pycnogenol® effectively seals leaky capillaries and stops bleedings into the retina. Left untreated, retinopathy may progress to the more severe “proliferative stage”. New blood vessels develop to compensate for leaky vessels. This stage involves severe bleedings which usually can only be controlled by laser treatment to prevent blindness.

Pycnogenol® seals leaky capillaries and strengthens capillary walls. This was demonstrated in pharmacological studies as well as in clinical trials involving various pathologies.

Five clinical studies with in total more than 1200 diabetic patients have shown that Pycnogenol® effectively to stops further progression of retinopathy and save the remaining eye sight of diabetics. Pycnogenol® stabilizes and seals leaky capillaries of the retina, stopping further outflow of blood. In some cases even a slight improvement of visual acuity was found.

A double blind, placebo controlled study was conducted to demonstrate reduction of bleedings into the retina [Spadea & Balestrazzi, 2001]. Patients diagnosed with retinopathy were treated either with Pycnogenol® or placebo over a treatment period of 2 months.

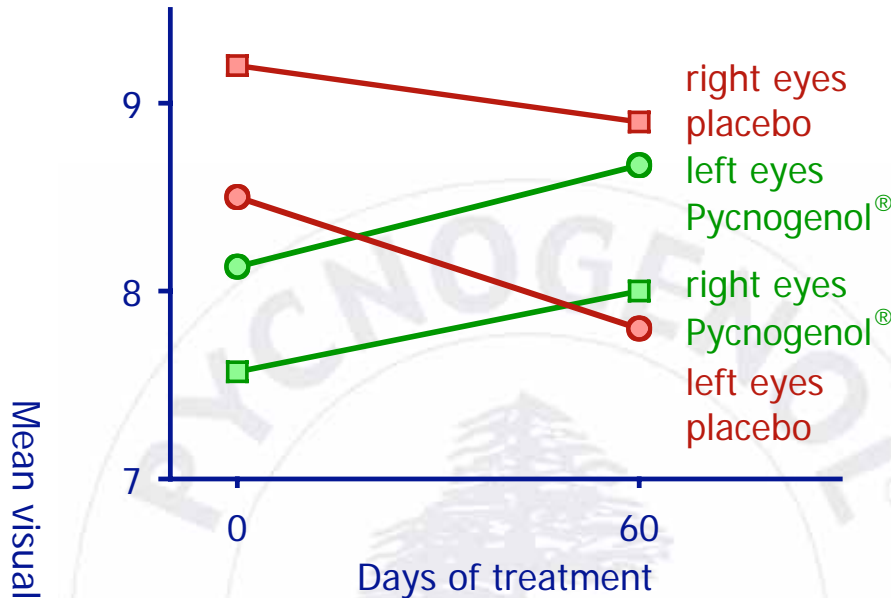


Figure 4: Retinopathy patients were treated for 2 months with either placebo or Pycnogenol®. Visual acuity deteriorated in patients receiving placebo, while treatment with Pycnogenol® stopped progression of retinopathy. The visual acuity did no longer deteriorate, but improved statistical significantly [Spadea & Balestrazzi, 2001].

This study demonstrated that without medication (placebo group) retinopathy of patients progresses and visual acuity deteriorates (figure 4). Treatment with Pycnogenol® statistical significantly improved visual acuity after 2 months treatment.

The development of the eye background was measured applying several techniques, ophthalmoscopy, fluorangiography and electroretinography, to obtain objective figures. Ophthalmoscopy showed a significant improvement of the ocular fundus, while placebo treatment was ineffective. For angiography a fluorescent dye is administered intravenously, which allows subsequent quantification of bleeding in the eye by UV-induced fluorescence techniques (figure 5).

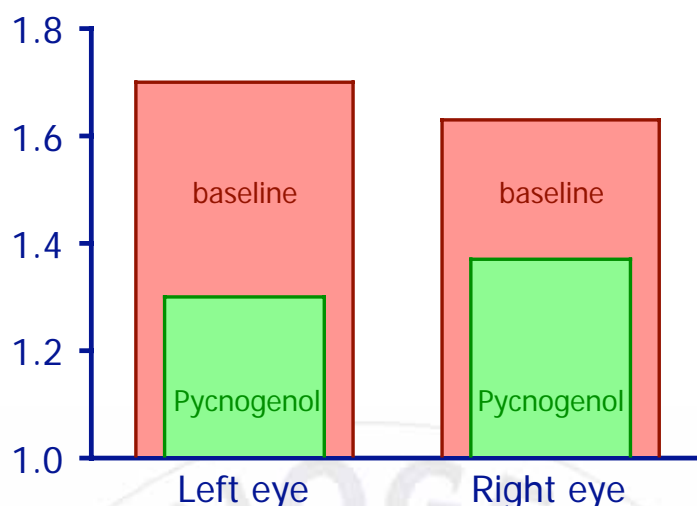


Figure 5: Pycnogenol® treatment significantly reduces bleeding from retinal capillaries. No effect was found in the placebo group (not shown) [Spadea & Balestrazzi, 2001].

Likewise, electroretinography gave significantly better values in the Pycnogenol® group indicating a better retinal integrity and function in these patients. The retinopathy was found to progressively reduce visual acuity in the placebo-treated patients, whereas a significant improvement was evident in the Pycnogenol® treated patients.

A multi-center field study was carried in Germany with a total number of 1169 patients with diabetic retinopathy. They were treated with daily dosages of 20 - 160 mg Pycnogenol®, according to severity of the condition, for 6 months [Schönlau & Rohdewald, 2002]. The objective of this trial was to demonstrate that Pycnogenol® stops progression of patient's vision loss. The mean age of the patients was 65.2 years and in average they were treated since eleven years for diabetes mellitus Type I and II. All had retinal degenerations and 49% of them were previously treated for diabetic retinopathy.

In response to treatment with Pycnogenol® over a period of 6 months the deterioration of visual acuity of patients was not only successfully stopped, but visual acuity improved to some extent (figure 6).

This trend towards improved vision is observable already after 3 months treatment and further improves after another 3 months treatment with Pycnogenol®.

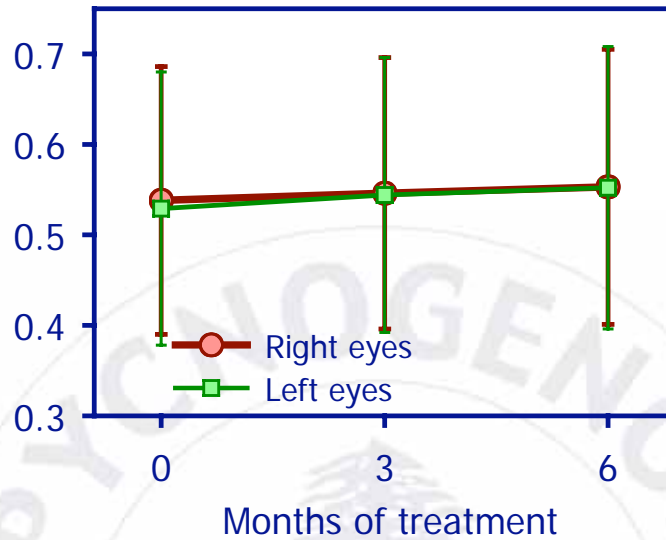


Figure 6: Visual acuity of patients does no longer deteriorate when treated with Pycnogenol®. On the contrary, even a slight improvement of visual acuity was found in the 1169 patients taking part in the German multi-center field study [Schönlau & Rohdewald, 2002].

The medication with Pycnogenol® was generally well tolerated, only 1.45 % of the 1169 patients experienced minor side effects, predominantly gastro-intestinal problems. In the study report it was concluded that Pycnogenol® has a considerable therapeutic benefit for patients suffering from diabetic retinopathy.

## **Pycnogenol® for the diabetic syndrome**

The chronically increased blood sugar level in diabetes has consequences for the organism. The blood sugar alters proteins as components of blood vessel walls as well as of blood cells. The alteration of blood vessel walls is responsible for typical problems in diabetes, such as vision loss and blindness, kidney problems, high blood pressure, insufficient micro-circulation, and thrombosis.

People with diabetes live at an increased risk of suffering from a thrombotic event, resulting from elevated activity of blood platelets. Diabetes is recognized as risk factor for stroke and myocardial infarction. Not only the incidence is increased in diabetes, the mortality is higher too and the majority of type II diabetic patients die from a thrombotic event. About one out of two persons with type II diabetes suffers from high blood pressure, which further increases the risk of acute cardiovascular events. The majority of people with type II diabetes is over-weight, with elevated blood lipid levels causing atherosclerosis. Consequently, prevention of platelet aggregation, reduction of blood pressure and control of blood lipids will help to decrease the thrombosis risk.

## **Pycnogenol® for vascular dysfunction in diabetes**

In a double-blind placebo-controlled study with type II diabetes patients, Pycnogenol® was tested for beneficial effects on endothelial function. These patients were continuing their prescribed anti-diabetic medication (biguanide and/or sulfonylurea) and received either Pycnogenol® or placebo in addition over a period of 3 months. Blood samples were taken in intervals one month to test for vaso-constrictor mediator endothelin-1 and vaso-dilatory mediator prostacyclin. In diabetes these hormone-like mediators are typically too high for endothelin-1 and too low for prostacyclin, respectively. As a result arteries are constricted, causing impaired blood flow, hypertension and increased risk of thrombosis.

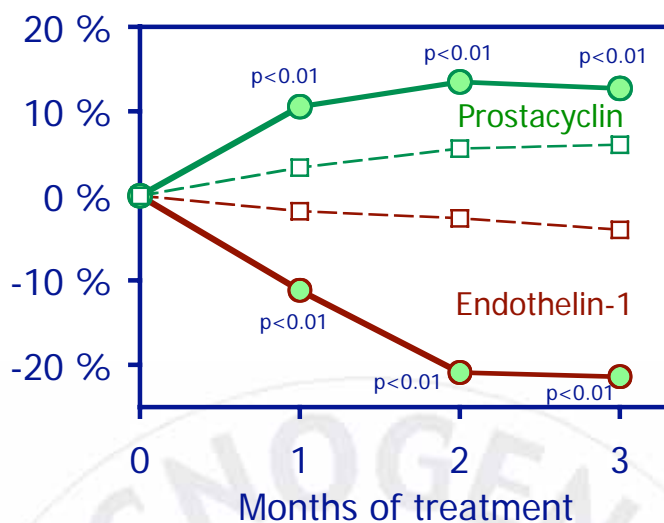


Figure 7: Type II diabetes patients were supplemented with Pycnogenol® (straight lines) or placebo (dotted lines) over a period of 3 months. Blood prostacyclin levels (green lines) were significantly increased in response to Pycnogenol® treatment, while endothelin-1 was significantly lowered. Placebo had only marginal and non-significant effects on the tested mediators. These results show an improved vascular function of diabetes patients by Pycnogenol® [Liu et al., Life Sciences 2004].

Pycnogenol® improved vascular function as evidenced by lowered vaso-constrictor endothelin-1 and increased vasodilator prostacyclin. These mediators are produced by the endothelial cells lining the inner wall of blood vessel. Another vasodilator produced by endothelial cells is nitric oxide. Nitric oxide production was also increased in response to Pycnogenol® supplementation. Pycnogenol® was shown in pharmacological studies to act on the enzyme endothelial nitric oxide synthase to more efficiently generate nitric oxide [Fitzpatrick et al., 1998]. Nitric oxide in endothelial cells regulates production endothelin-1 and prostacyclin and this may explain Pycnogenol's beneficial action on these mediators. In conclusion, Pycnogenol® relaxes constricted blood vessels of diabetes patients, which should support better blood circulation and normalize blood pressure.

Thus, Pycnogenol® does not only lower blood glucose. Pycnogenol® further normalizes vascular function, a benefit which is not provided by common antidiabetic medications.

## Pycnogenol<sup>®</sup> normalizes high blood pressure

Approximately 50% of type II diabetes patients suffer from hypertension. Pycnogenol<sup>®</sup> can help to control high blood pressure.

Because Pycnogenol<sup>®</sup> relaxes arteries, the increased vessel diameter allows easier blood flow with resulting lower blood pressure. Pycnogenol<sup>®</sup> was demonstrated to lower high blood pressure in two clinical trials with hypertensive patients.

Pycnogenol<sup>®</sup> was tested in a double blind, placebo controlled, cross-over study [Hosseini et al., 2001]. The patients chosen for this pilot study had mild hypertension, with systolic blood pressure of 140-159 mmHg, and/or diastolic blood pressure of 90-99 mgHg. People with a blood pressure within this range are diagnosed as stage I hypertensive and are not routinely treated with anti-hypertensive medication.

Supplementation with Pycnogenol<sup>®</sup> over a period of 8 weeks statistical significantly reduced systolic blood pressure (figure 7). Separate analysis of the four patients with the highest systolic blood pressure (average 150 mmHg) revealed that Pycnogenol<sup>®</sup> was particularly effective by decreasing their average value to 135 mmHg.

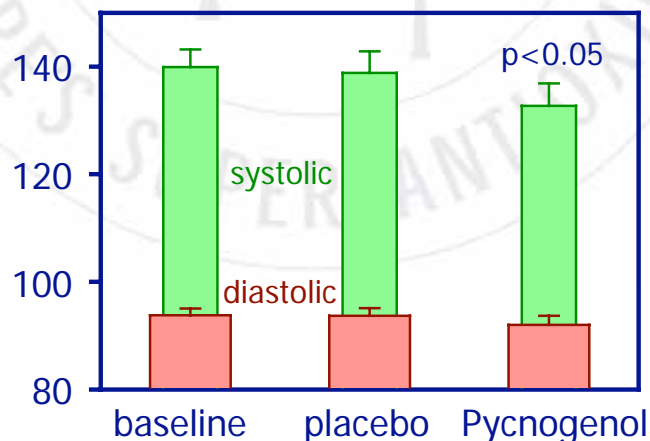


Figure 7: Patients with mild hypertension taking Pycnogenol<sup>®</sup> for 8 weeks had a significantly reduced systolic pressure as compared to the control group receiving placebo [Hosseini et al., 1998].

In another placebo-controlled study Pycnogenol<sup>®</sup> was given to hypertensive patients who were medicated with prescribed medication nifedipine (calcium channel blocker) [Liu et al., 2004]. Patients received either Pycnogenol<sup>®</sup> or placebo in addition to nifedipine. Every two weeks the nifedipine dosage was adjusted so that blood pressure did not exceed 140 mmHg. The results showed that patients supplemented with Pycnogenol<sup>®</sup> could in average lower their nifedipine medication by half. In contrast, placebo-treated patients could not lower their nifedipine dosage.

Blood samples from patients showed that Pycnogenol<sup>®</sup> increased blood vessel dilating nitric oxide and prostacyclin, while the vessel constricting endothelin-1 was reduced.

### **Pycnogenol<sup>®</sup> enhances micro-circulation**

Micro-circulatory disorders represent a major chronic complication in diabetes. Pycnogenol's effect on dilating constricted blood vessels supports better micro-circulation.

A double blind, placebo controlled study was carried out with 51 elderly patients (45 to 75 years). 44 patients previously had angina pectoris, 33 cases with hypertension, 7 with diabetes and 22 with hyperlipidemia. Blood perfusion and vessel diameter was estimated by capillaroscopy in patients' finger tips. The study demonstrated an improvement of micro-circulation by 53.8 % as a result of 4 weeks supplementation with Pycnogenol<sup>®</sup> [Wang et al., 1999].

### **Pycnogenol<sup>®</sup> helps prevent thrombosis**

Clinical studies with Pycnogenol<sup>®</sup> have been carried with subjects with elevated platelet activity, such as smokers and elderly, which live at high risk of thrombotic events in a similar way as diabetics [Pütter et al., 1999; Araghi-Niknam et al, 1999]. Pycnogenol<sup>®</sup> was found to dose-dependently reduce platelet activity ("stickiness"), thus reducing the ability of platelets to aggregate within an intact blood vessel (figure 8).

Pycnogenol<sup>®</sup> normalizes platelet activity by enhancing production of nitric oxide, which down-regulates increased “stickiness” of blood platelets. Thus, Pycnogenol<sup>®</sup> supports body-own mechanisms to normalize platelet activity. In contrast, aspirin irreversibly alters an enzyme chemically which is required by platelets to form a clot. As side-effect aspirin prolongs bleeding during an injury, which may cause serious complications, particularly when taken regularly.

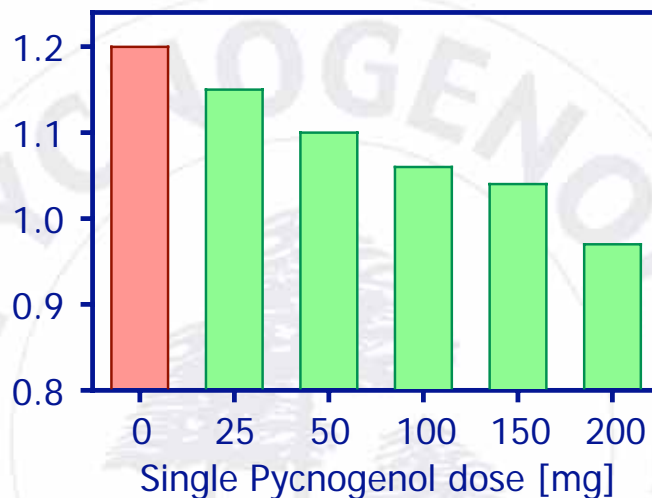


Figure 8: Dose response effect of a single administration of Pycnogenol<sup>®</sup> on platelet activity (“stickiness”). Blood was drawn from subjects before and 2 hours after Pycnogenol<sup>®</sup> consumption. Pycnogenol<sup>®</sup> does not prolong bleeding in case of injuries [Pütter et al., 1999].

A double-blind placebo controlled study with 200 individuals at high risk of developing thrombosis was carried out to test whether Pycnogenol<sup>®</sup> reduces the incidence of thrombosis. Participants were traveling on long-haul flights, a circumstance known to increase the likelihood of developing thrombosis in the legs due to the lack of movement. While 5 cases of thrombosis occurred in the placebo-treated group, none of the participants taking Pycnogenol<sup>®</sup> developed thrombosis [Belcaro et al., 2004].

## Pycnogenol<sup>®</sup> improves blood lipid profile

Approximately 80 % of type II diabetes patients are over-weight. The imbalanced metabolism is reflected by a high cholesterol load in the blood stream which implies a high risk of developing atherosclerosis.

Pycnogenol<sup>®</sup> was found in three from another independent clinical studies to lower LDL (“bad”) cholesterol and increase HDL (“good”) cholesterol. Already in young and healthy volunteers Pycnogenol significantly improved blood lipid profile with lower LDL- and higher HDL values [Devaraj et al., 2002].

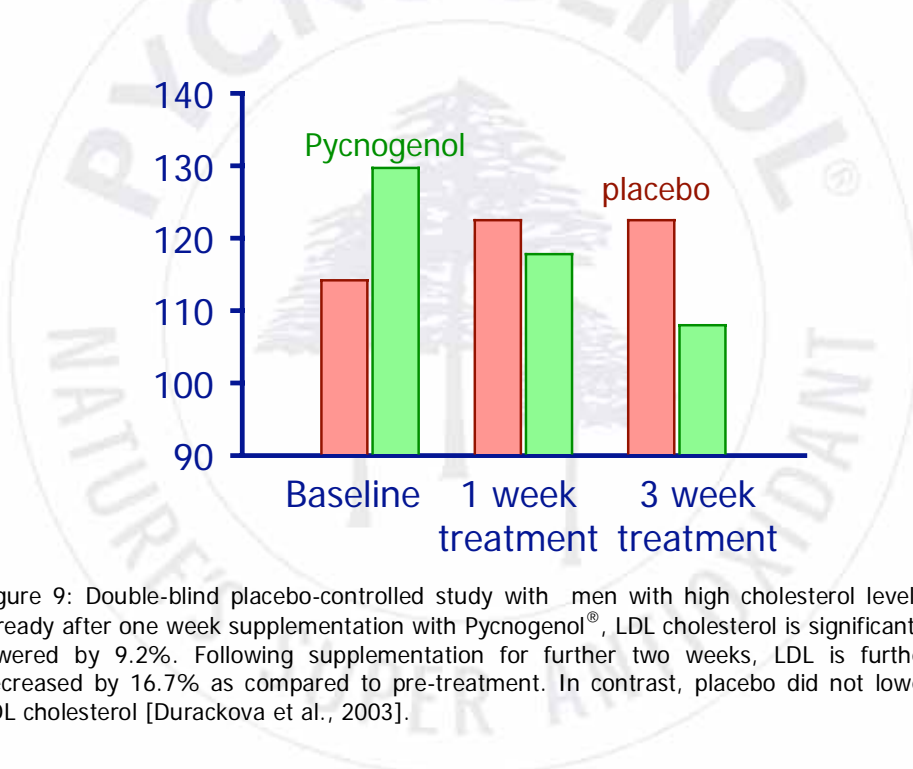


Figure 9: Double-blind placebo-controlled study with men with high cholesterol levels. Already after one week supplementation with Pycnogenol<sup>®</sup>, LDL cholesterol is significantly lowered by 9.2%. Following supplementation for further two weeks, LDL is further decreased by 16.7% as compared to pre-treatment. In contrast, placebo did not lower LDL cholesterol [Durackova et al., 2003].

In a double-blind placebo-controlled study with men having elevated cholesterol levels, Pycnogenol<sup>®</sup> was found to lower LDL cholesterol by 16.7% after 3 weeks treatment [Durackova et al., 2003].

### Pycnogenol® increases antioxidant capacity

The dysfunctional metabolism in type II diabetes is known to increase oxidative stress which has been suggested to largely contribute to the vascular and circulatory problems, but also neuro-degenerative processes occurring in diabetes.

Pycnogenol® was demonstrated in a clinical studies to significantly increase the blood oxygen radical absorbance capacity (ORAC) of human volunteers by 40% [Devaraj et al., 2002]. A second study has confirmed these findings [Durackova et al., 2003]. This study showed a significantly increased antioxidant activity of volunteer's blood already after one week supplementation with Pycnogenol®. Continuation of supplementation for another two weeks further increased antioxidant activity. This study suggests that particularly a continuous supplementation is effective for controlling the oxidative stress in diabetes.

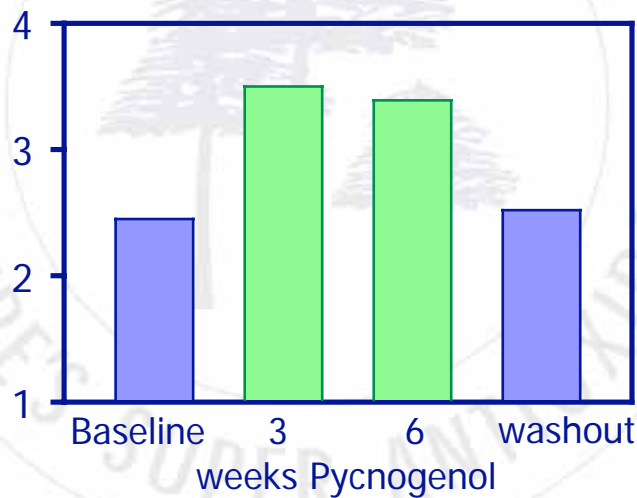


Figure 10: The antioxidant capacity (ORAC) of volunteers' blood is significantly increased by 40% after three weeks of supplementation with Pycnogenol®. Following a four weeks washout period, the blood's antioxidant capacity returns to baseline values [Devaraj et al., 2002].

### Rationale for using Pycnogenol® in Diabetes Care

- ✚ Pycnogenol® is shown in clinical trials to lower blood glucose in type II diabetes patients, both in absence and presence of anti-diabetic medication.
- ✚ Pycnogenol® seals leaky capillaries as they frequently occur in diabetes. In 5 clinical studies with 1200 patients Pycnogenol effectively sealed leaky capillaries in diabetic's eyes, saving their remaining eye sight.
- ✚ Pycnogenol® supports healthier vascular function in diabetes patients, thus helping to relax constricted blood vessels.
- ✚ Pycnogenol® reduces high blood pressure, a problem for approximately every second patient with type II diabetes.
- ✚ Pycnogenol® prevents platelet aggregation and helps to prevent thrombotic events, the serious risk of diabetics for having stroke and heart infarction.
- ✚ Pycnogenol® supports better micro-circulation.
- ✚ Pycnogenol® improves the blood lipid profile which is frequently too high in type II diabetes patients, with 80% being over-weight.
- ✚ Pycnogenol® is a powerful antioxidant and helps reduce the high oxidative stress prevalent in diabetes.
- ✚ Pycnogenol® has been extensively researched for its safety. It can safely be used for improvement of many chronic micro- and macro-vascular dysfunctions occurring in diabetes.

## What is Pycnogenol®?

Pycnogenol® is the water extract of the bark of French maritime pines (*Pinus pinaster* Ait.) growing in a mono-species forest – the unique source of Pycnogenol® – in the south-western coastal region of France. The pine trees from which Pycnogenol® is produced are grown entirely without pesticides and no toxic solvents are used during the production of Pycnogenol®. Consequently, there is no trace of pesticides or toxic solvents in Pycnogenol®. No genetically modified organisms (GMOs) are used to produce Pycnogenol®.

The standardized, validated and automated extraction procedure gives a yield of 70 ± 5% procyanidins. Additionally, Pycnogenol® contains monomeric bioflavonoids such as catechin, taxifolin and various fruit acids in naturally defined constant proportions. The specifications of Pycnogenol® conform to a typical European Pharmacopoeia monograph of a herbal extract, detailing its qualitative and quantitative composition and microbial limits [Rohdewald 2002].

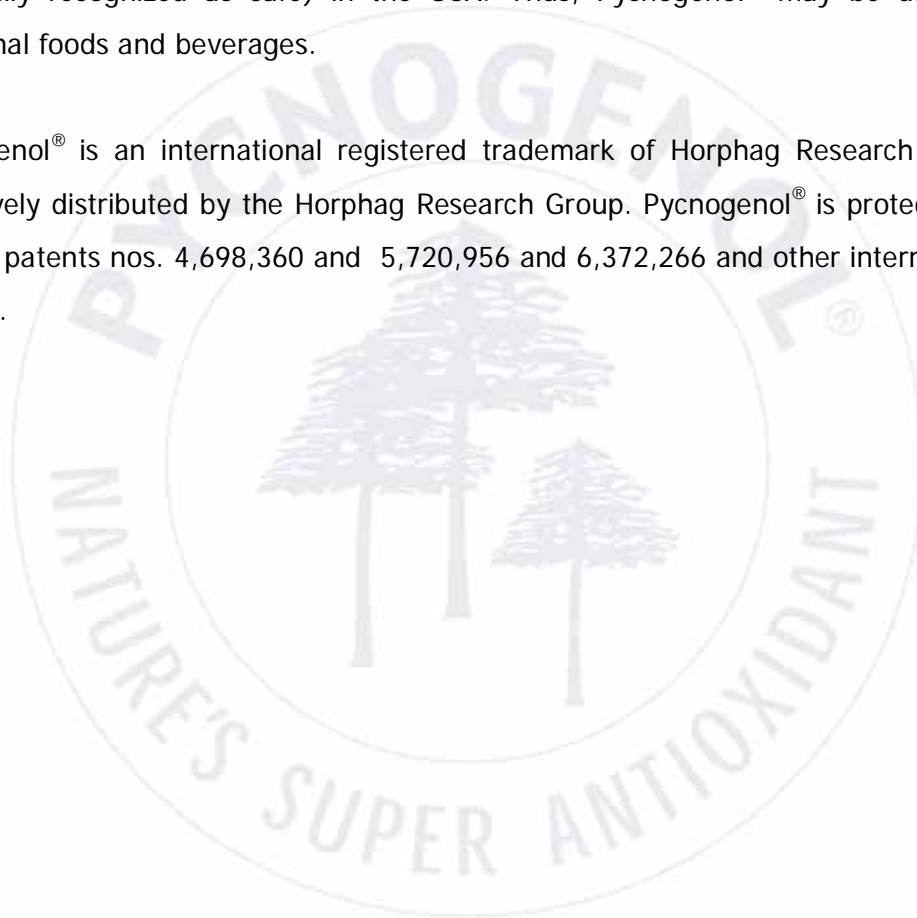
Pycnogenol® is a pink to reddish brown, freely flowing, very fine powder with a characteristic aromatic odor and astringent taste. It is soluble in water (>90%) at room temperature and is soluble in ethanol and acetone. It is moderately acidic with a pH between 2.5 and 4.4 in 1% aqueous solution. It is heat resistant and stable at room temperature for more than three years, if stored in well-closed containers away from direct exposure to light. These interesting physico-chemical properties make Pycnogenol® a versatile, easy to handle active ingredient, suitable for long-term use.

Pycnogenol® has passed stringent international safety requirements. Extensive research on its safety has demonstrated that Pycnogenol® has a very low acute toxicity and a very low chronic toxicity. Pycnogenol® is non-mutagenic and non-teratogenic.

Pycnogenol® has been tested on more than 2000 human subjects in clinical research studies, without showing any incidence of severe side effects. Pycnogenol® has been approved by the British Ministry of Agriculture, Fisheries and Food (MAFF) as an active food ingredient. Pycnogenol® is used as a food supplement in many countries of the world including the USA.

Due to the extensive safety documentation Pycnogenol® has been approved GRAS (generally recognized as safe) in the USA. Thus, Pycnogenol® may be used for functional foods and beverages.

Pycnogenol® is an international registered trademark of Horphag Research and is exclusively distributed by the Horphag Research Group. Pycnogenol® is protected by two US patents nos. 4,698,360 and 5,720,956 and 6,372,266 and other international patents.



Selected references

<b>Ref. 053</b>	Araghi-Niknam M, Hosseini S, Larson D, Rohdewald P, Watson RR (1999). Pine bark extract reduces platelet aggregation. Integrative Medicine. : 73-77
<b>Not it bibliography</b>	Belcaro G, Cesarone MR, Ricci A, Ippolito E, Brandolini R, Dugall M, Griffin M, Ruffini I, Acerbi G, Vinciguerra MG, Bavera P, Di Renzo A, Errichi BM. (2004) Prevention of venous thrombosis in long-haul flights with Pycnogenol®. Clin Appl Thromb Hemost, in print
<b>Ref. 090</b>	Devaraj S, Vega-López S, Kaul N, Schönlaue F, Rohdewald P, Jialal I. (2002) Supplementation with a pine bark extract rich in polyphenols increases plasma antioxidant capacity and alters the plasma lipoprotein profile. Lipids 37: 931-934
<b>Ref. 093</b>	Durackova Z, Trebaticky B, Novotny V, Zitnanova A, Breza J. (2003) Lipid metabolism and erectile function improvement by Pycnogenol®, extract from the bark of <i>Pinus pinaster</i> in patients suffering from erectile dysfunction – a pilot study. Nutr Res 23: 1189-1198
<b>Ref. 027</b>	Fitzpatrick DF, Bing B, Rohdewald P (1998). Endothelium dependent vascular effects of Pycnogenol. J Cardiovasc Pharmacol 32: 509-515
<b>Ref. 080</b>	Hosseini S, Lee J, Sepulveda RT, Fagan T, Rohdewald P, Watson RR (2001). 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. Nutrition Research 21: 1251-1260
<b>Ref. 109</b>	Liu X, Zhou HJ, Rohdewald P. (2004) French maritime pine bark extract Pycnogenol® dose-dependently lowers glucose in type II diabetes patients. Diabetes Care 27: 839
<b>Ref. 117</b>	Liu X, Wei J, Tan F, Zhou S, Wurthwein G, Rohdewald P. (2004) Pycnogenol®, French maritime pine bark extract, improves endothelial function of hypertensive patients. Life Sciences 74: 855-862
<b>Not it bibliography</b>	Liu X, Wei J, Tan F, Zhou S, Würthwein G, Rohdewald P. (2004) Antidiabetic Effect of Pycnogenol® French Maritime Pine Bark Extract in patients with diabetes type II. Life Sciences, in print

## SELECTED REFERENCES

<b>Ref. 105</b>	Maritim A, Dene BA, Sanders RA, Watkins JB. (2003) Effects of Pycnogenol® treatment on oxidative stress in streptozotocin induced diabetic rats. J Biochem Mol Tox 17: 193-199
<b>Ref. 036</b>	Pütter M, Grotemeyer KH, Würthwein G, Araghi-Niknam N, Watson RR, Rohdewald P (1999). Inhibition of smoking-induced platelet aggregation by aspirin and Pycnogenol. Thromb Res 95: 155-162
<b>Ref. 085</b>	Rohdewald P (2002). A review of the French maritime pine bark extract (Pycnogenol®), a herbal medication with a diverse clinical pharmacology. Int J Clin Pharm Ther 40: 158-168
<b>Ref. 092</b>	Schönlau F, Rohdewald R (2002). Pycnogenol® for diabetic retinopathy: A review. International Ophthalmology, 24: 161-171
<b>Ref. 075</b>	Spadea L, Balestrazzi E (2001). Treatment of vascular retinopathy with Pycnogenol®. Phytother Res 15: 219-23
<b>Ref. 114</b>	Watson RR. (2003) Pycnogenol® and cardiovascular health. Review. Evidence Based Integr Med 1: 27-32

**\*Referenced studies are available in the Pycnogenol® Bibliography or at Horphag Research.**