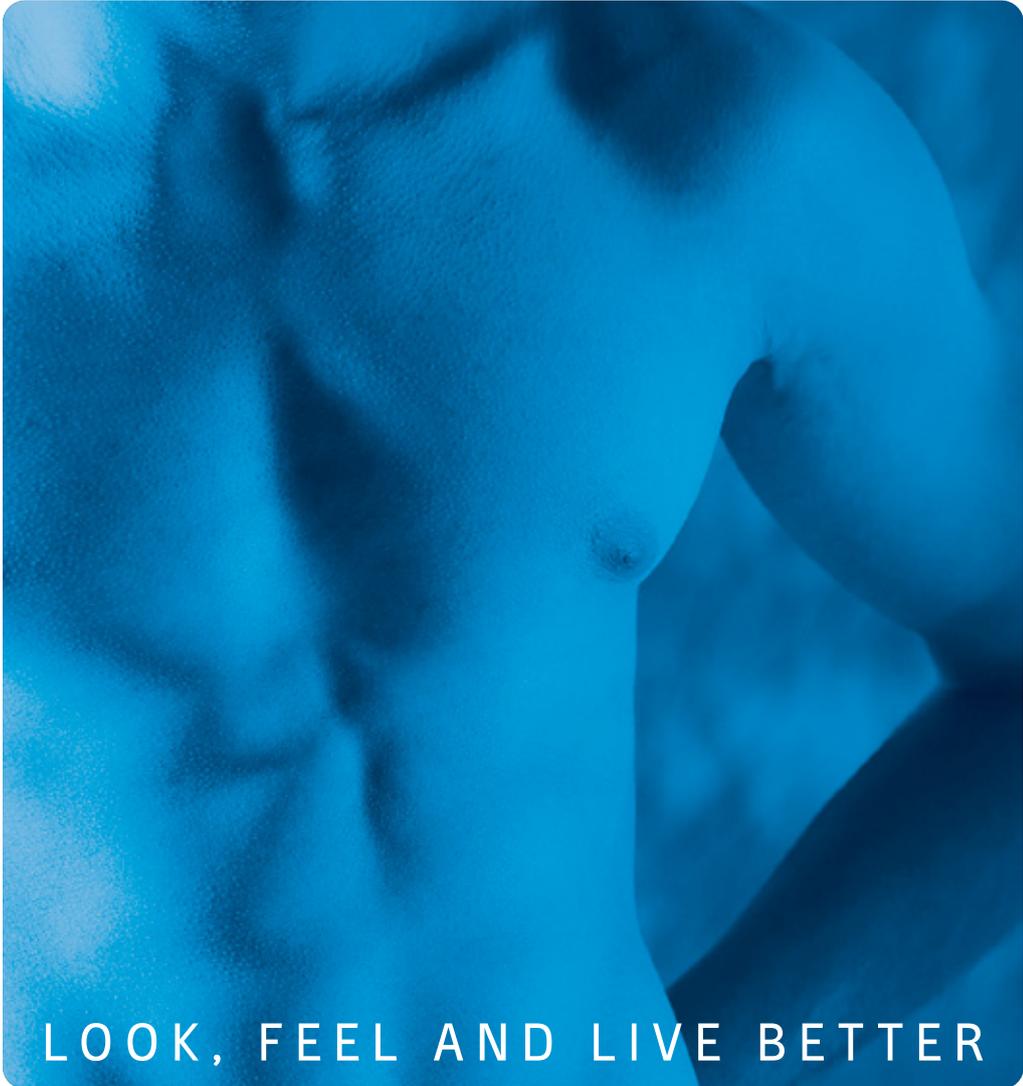
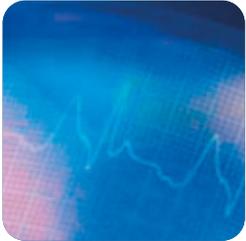


**PYCNOGENOL®**

Cardiovascular Health



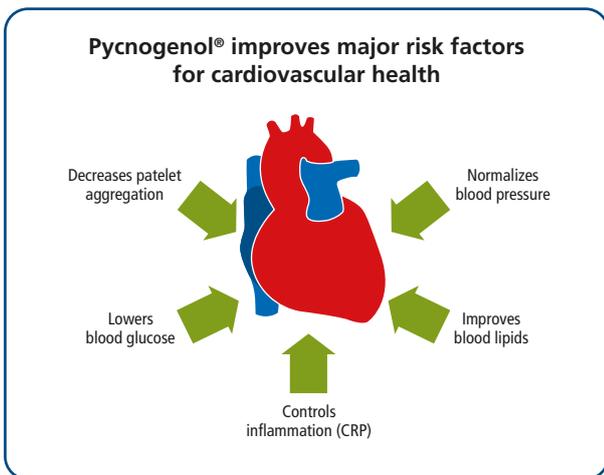
LOOK, FEEL AND LIVE BETTER



## Pycnogenol® for Cardiovascular Health

Keeping the cardiovascular system healthy is key for maintaining good vitality, physical strength, mental health and for general well being. Vascular function may be at risk because of only few factors beyond our control, such as gender and the normal ageing process. In contrast, there are numerous variable risk factors such as cigarette smoking, obesity, sedentary life-style and the stealth risk factors hypertension, hypercholesterolemia and hyperglycemia.

Pycnogenol® as part of a healthier life-style may significantly contribute to the improvement of stealth heart health risk factors, owing to the normalisation of blood pressure and platelet function, improvement of blood lipids as well as blood sugar values. An ever increasing number of clinical studies demonstrate the efficacy of Pycnogenol® for keeping cardiovascular health problems at bay. Pycnogenol® was investigated in healthy people, individuals with borderline high risk factors but also as an adjunct in people taking prescription medicine for cardiovascular health issues.

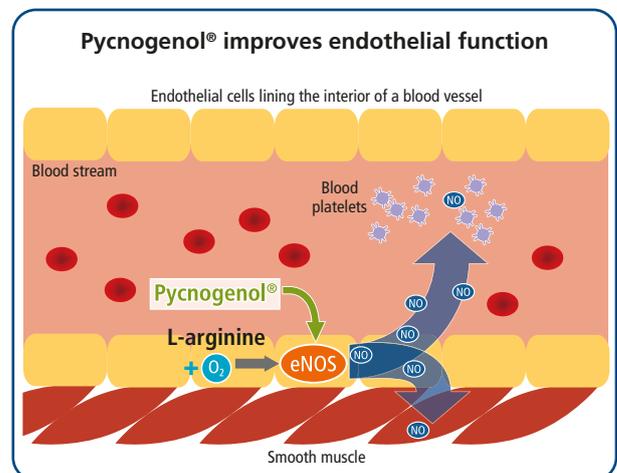


### Pycnogenol® improves endothelial function

The common denominator of most cardiovascular risk factors is the inability of a blood vessel to generate the most important vascular mediator: nitric oxide (NO). Nitric oxide is synthesized by (endothelial) cells which line the interior wall of blood vessels. NO molecules diffuse through the blood vessel wall to finally interact with a specific receptor in smooth muscle enveloping the vessel. This causes the muscle to relax and in turn the vessel lumen increases. This self-regulation mechanism allows for relieving insufficient tissue perfusion and pressure build-up in blood

vessels. Furthermore, nitric oxide also acts on blood platelets to decrease their tendency to form aggregates which translates to a protection from developing thrombosis.

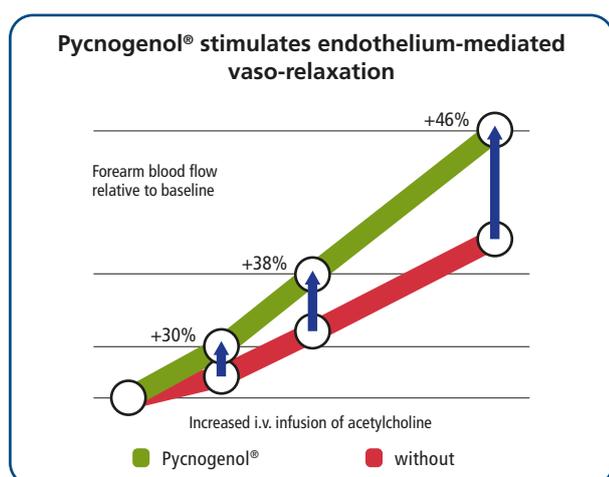
In various clinical situations such as hypertension, atherosclerosis and diabetes, but also with increasing age, the endothelial synthesis of nitric oxide declines. This results in chronic blood vessel constriction which impairs blood flow, elevates blood pressure and increases the risk for thrombosis.



Pycnogenol® activates the enzyme endothelial nitric oxide synthase (eNOS), present in endothelial cells, to more efficiently generate nitric oxide (NO) from the precursor amino acid L-arginine.

### Human pharmacological trials show that Pycnogenol® enhances endothelial function

The effect of Pycnogenol® on endothelium dependent vasodilatation and blood flow was investigated in a pharmacological investigation with 16 young healthy volunteers in a double blind, placebo controlled fashion [Nishioka et al., 2007]. Endothelium-dependent forearm artery dilatation and corresponding blood flow increase was initiated by infusion of increasing amounts of neurotransmitter acetylcholine, which stimulates activity of the eNOS enzyme to enhance generation of NO. After two weeks supplementation with Pycnogenol® the endothelium could generate significantly more NO to increase forearm blood flow by up to 46% higher than at baseline. This effect of Pycnogenol® was significant as compared to placebo which did not increase forearm blood flow. Further control experiments using an L-arginine antagonist proved that Pycnogenol® did indeed enhance vasodilatation by stimulation of endothelial NO synthesis.

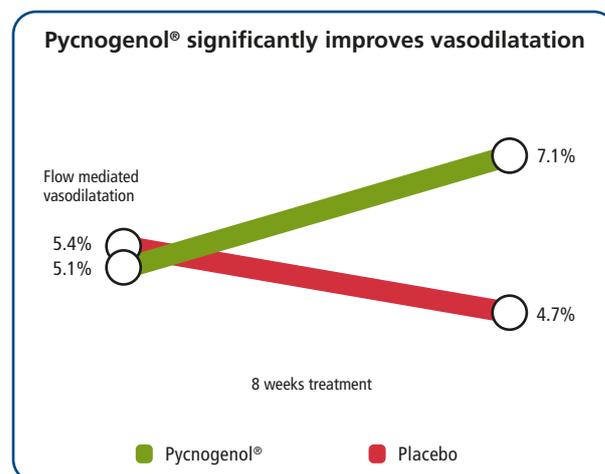


The result of this pharmacologic study is impressive because it demonstrates enhanced endothelial

function response in healthy individuals. Thus even healthy people will benefit from supplementing with Pycnogenol®, resulting in better blood flow and tissue perfusion.

### Pycnogenol® improves endothelial function in cardiovascular patients

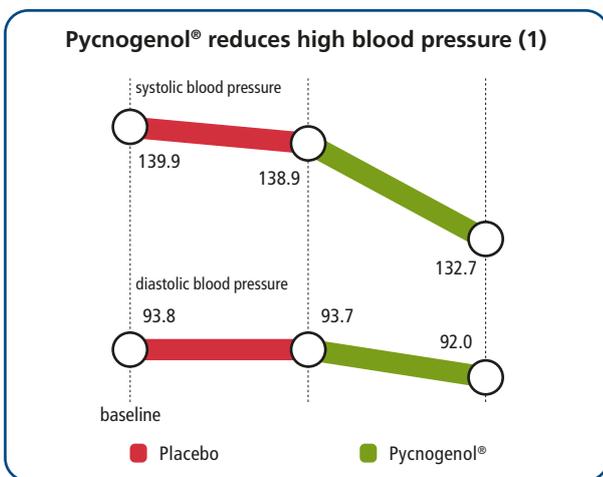
A double-blind, placebo-controlled, cross-over study with coronary artery disease patients showed that Pycnogenol® significantly improved endothelial function, whereas no effect was found with placebo [Enseleit et al., 2010]. These patients were under excellent control with medications for blood pressure, platelet function and blood lipids. Patients had blood pressure 120/75 mmHg which did not change during treatment. However, endothelial function improved as Pycnogenol® was shown to significantly improve flow-mediated vasodilatation by 33%, whereas this figure slightly decreased with placebo. Thus, taking Pycnogenol® as an adjunct to standard medication for cardiovascular disease, helps to restore body-own regulatory mechanisms to improve vascular function.



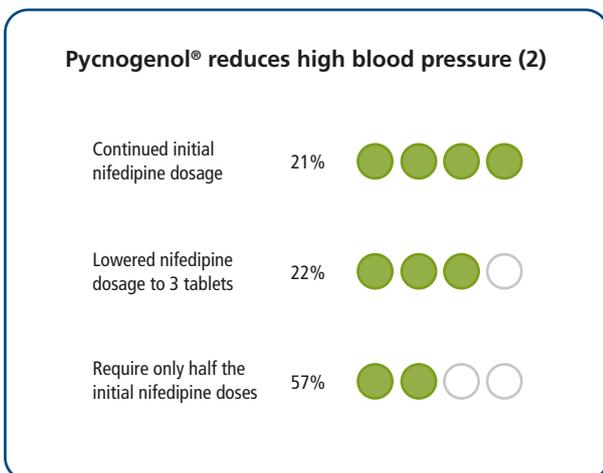
### Pycnogenol® normalises high blood pressure

In most cases an elevated blood pressure coincides with a compromised endothelial function. The improved endothelial function with Pycnogenol® allows for healthier vasodilatation which in turns aids to normalize elevated blood pressure.

Pycnogenol® was investigated in a double-blind, placebo-controlled, cross-over- study for patients presenting with borderline hypertension, who were not yet receiving hypotensive medication. Pycnogenol® supplementation over a period of 8 weeks significantly lowered blood systolic blood pressure as compared to placebo and diastolic pressure was found to be lowered as well [Hosseini et al, 2001].



Pycnogenol® has further been tested in hypertensive patients receiving treatment with calcium channel blocker nifedipine (20 mg per day). One group of patients received Pycnogenol® in addition to nifedipine, whereas the control group was administered placebo in addition to the nifedipine regimen. Every two weeks the individual nifedipine dosage was ad-



justed so that a blood pressure below 130 mmHg was achieved. Almost 60% of the patients who supplemented with Pycnogenol® were able to cut their individual nifedipine medication dosage by half to keep their blood pressure in a healthier range [Liu et al, 2004].

Moreover, the effect of Pycnogenol® was again shown to significantly improve impaired endothelial function in these individuals. Vaso-constrictory endothelin-1 was significantly lowered, whereas vasodilatory NO and prostacyclin were increased.

**Pycnogenol® improves kidney function and CRP-levels in hypertension**

In hypertensive individuals progressive kidney damage is frequent. Further to lowering elevated blood pressure, kidney-protective measures represent an important target in advanced hypertension management and treatment.

In patients with previously untreated hypertension and early signs of kidney damage, as judged by elevated urinary albumin levels, Pycnogenol® was taken as an adjunct to medication with ACE-inhibitor Ramipril over a period of six months [Cesarone et al., 2010]. After treatment for six months patients taking Ramipril alone had an average blood pressure of 123/88 mmHg, while those receiving Pycnogenol® in addition to Ramipril had an average blood pressure of 119/83 mmHg. The group taking Pycnogenol® plus Ramipril had 24 hours urinary albumin decrease from baseline 91 to 39 mg/day after six months. In the group taking only Ramipril the urinary albumin decreased from 87 to 64 mg/day. The major improvement of kidney function with Pycnogenol® was shown to coincide with better kidney cortical blood flow velocity which increased significantly compared to the group taking Ramipril only. The cardiovascular risk factor CRP decreased significantly with Pycnogenol® from initial 2.2 to 1.1 mg/dL after six months, while Ramipril non-significantly lowered the inflammatory marker from 2.1 to only 1.8 mg/dL.



### Pycnogenol® improves blood pressure and kidney function in diabetes as well as metabolic syndrome

One of the major characteristic of metabolic syndrome is hypertension. Pycnogenol® taken by patients affected by metabolic syndrome criteria, such as obesity, hypertension, elevated blood sugar and high cholesterol for six months showed significant improvement of most parameters [Stuard et al., 2010]. Compared to a control group medicated with ACE-inhibitor Lisinopril only, patients taking Pycnogenol® in addition to Lisinopril achieved a significantly healthier blood pressure, HbA1c level, body mass index and also better total blood cholesterol and HDL values. Kidney function was significantly improved as judged from lowered 24 hour urinary albumin as well as better kidney cortical blood flow velocity

In a double-blind, placebo controlled study with type II diabetic patients medicated with ACE inhibitor Lisinopril and hypoglycaemic medication, Pycnogenol® significantly lowered blood pressure and half of the patients were able to lower their individual hypotensive medication dosage [Zibadi et al.,

2008]. Improved endothelial function was identified by significantly lowered levels of vaso-constrictory endothelin-1 in serum of patients. Urinary albumin values were significantly lowered with Pycnogenol®, while only marginal effects were found for placebo. Pycnogenol® was shown to significantly improve blood sugar as compared to the placebo group. Elevated blood glucose represents another serious threat to cardiovascular health and Pycnogenol® was shown effective for normalising blood glucose in several clinical trials. This effect was found to result from inhibition of duodenal  $\alpha$ -glucosidase. For more information on Pycnogenol® for blood glucose lowering, diabetes and metabolic syndrome please consider the brochure “Pycnogenol® for Diabetes Care”.

In summary, Pycnogenol® is helpful on its own for normalising borderline hypertension and also beneficial when taken as an adjunct to standard hypotensive medication. In the latter cases Pycnogenol® further improves blood pressure and/or allows for modifying medication dosage and improves endothelial function.

### Overview of clinical studies with Pycnogenol showing blood pressure benefits

Study	Patient's Medication	Pycnogenol® benefits	Reference
Hosseini (USA)	None	Blood pressure decreased significantly from 140/94 to 133/92 mmHg	Nutr Res 2001
Yang (Taiwan)	None	Blood pressure decreased significantly from 116/72 to 112/70	Acta Obstetrica et Gynecol 2007
Liu (China)	Calcium channel blocker	Less medication required for keeping sBP $\leq$ 130 mmHg	Life Sci 2004
Zibadi (USA)	ACE-inhibitor	Less medication required and BP further lowered	Nutr Res 2008
Cesarone (Italy)	ACE-inhibitor	Addition of Pycnogenol to ACE-inhibitor further lowered BP	J Cardiovasc Pharmacol 2010
Stuard (Italy)	ACE-inhibitor	Addition of Pycnogenol to ACE-inhibitor further lowered BP	Panminerva Med 2010
Enseleit (Switzerland)	Various	Pycnogenol improved endothelial function and vasodilatation	Submitted



**Pycnogenol® is safe for individuals with low pressure**

In an investigation of people with low blood pressure and hypotension a daily intake of 100 mg Pycnogenol® over a period of 30 days did not significantly lower diastolic and systolic blood pressure. None of the patients experienced any unfavourable side effects during intake of Pycnogenol® [Pella et al., unpublished results].

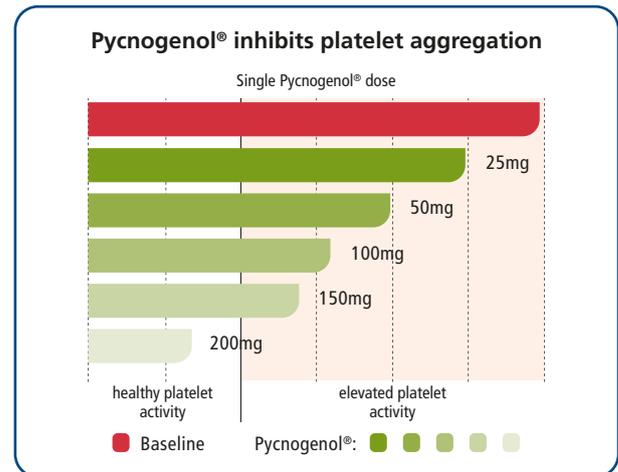
**Pycnogenol® normalizes blood platelet activity**

Whereas hypertension, atherosclerosis and diabetes contribute to progressive damage of blood vessel walls, the acute problems occurring during heart attack and stroke result from aggregation of blood platelets. An impaired endothelial function and decreased availability of nitric oxide leads to an increased platelet activity. Situations involving impaired endothelial function, hypercoagulability and altered haemodynamics such as stasis promote the development of platelet aggregates and thrombosis. The resulting thrombus may cause clogging of blood vessels (embolism) and subsequently interrupt the blood flow to certain areas of the body. This may be life-threatening when a blood clot obstructs arteries of the lung, disabling vital oxygen uptake (pulmonary embolism). When arteries supporting heart muscle (coronaries) are affected, oxygen supply is interrupted causing myocardial infarction.

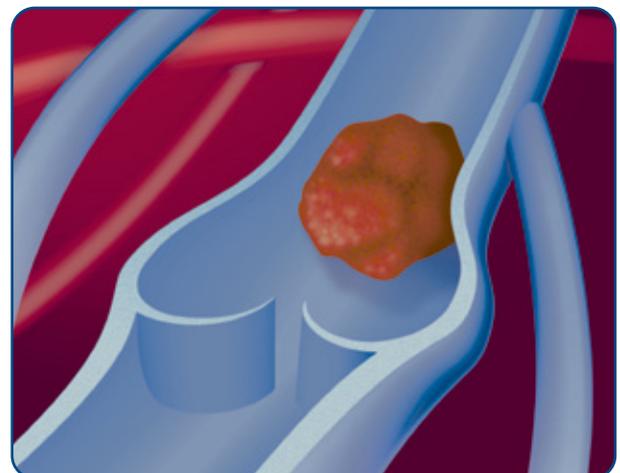
By virtue of increasing the production of endothelial nitric oxide, Pycnogenol® significantly lowers the activity of blood platelets. Nitric oxide represents the natural body-own messenger molecule for releasing elevated thrombocyte activity.

Pycnogenol® was shown to dose-dependently lower platelet activity in individuals typically presenting with increased platelet aggregation: cigarette smokers. Blood was drawn before and 2 hours after administration of a single Pycnogenol® dose. The results clearly showed a dose-dependent reduction of

platelet activity. Already the lowest dose of 25 mg Pycnogenol® noticeably lowered the blood platelet activity [Pütter et al., 1999]. Further research revealed that Pycnogenol® inhibits release of thromboxane from platelets of cigarette smokers to levels of healthy non-smokers [Araghi-Niknam et al., 1999].



Pycnogenol® was shown to be as effective for controlling platelet activity as aspirin in these experiments [Pütter et al., 1998]. Moreover, Pycnogenol® was found not to increase bleeding time, an effect which is well known in case of aspirin, which significantly prolongs bleeding. The use of Pycnogenol® for regulation of platelet function is patented (US 5,720,956).



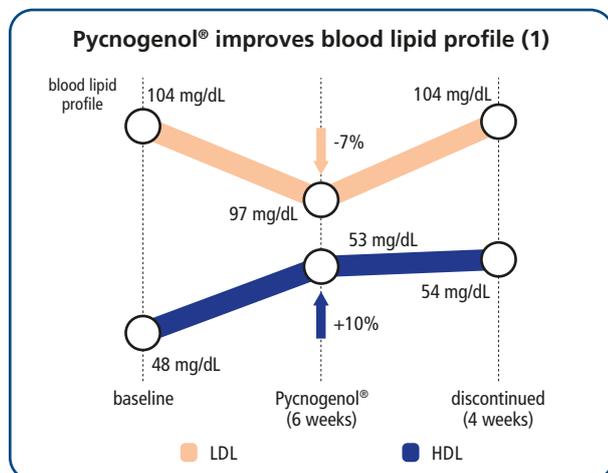
Pycnogenol® was tested in a group of 200 individuals at risk for developing thrombosis [Belcaro et al., 2004]. Subjects were remaining in sedentary position for prolonged time during long-haul travel exceeding 8 hours. These conditions are known to cause pooling of venous blood in the legs, involving blood stasis, which contributes to the development of thrombosis. The results showed 5 incidents of transitional thrombosis in total 97 subjects (5.15 %) in the placebo group. In contrast, none of the 101 high-risk subjects in the Pycnogenol®-treated group developed thrombosis during the long-haul flight.

	Placebo	Pycnogenol®
Number of passengers	97	101
Superficial vein thrombosis	1	0
Deep vein thrombosis	4	0
Thrombosis frequency	5.51%	0%

### Pycnogenol® improves blood lipid profile

To date Pycnogenol® was found in five controlled clinical trials to lower LDL cholesterol and increase HDL. A significantly improved blood lipid profile was initially discovered in young healthy subjects [Devaraj et al., 2002].

Supplementation with Pycnogenol® for 6 weeks significantly increased HDL and lowered LDL cholesterol.

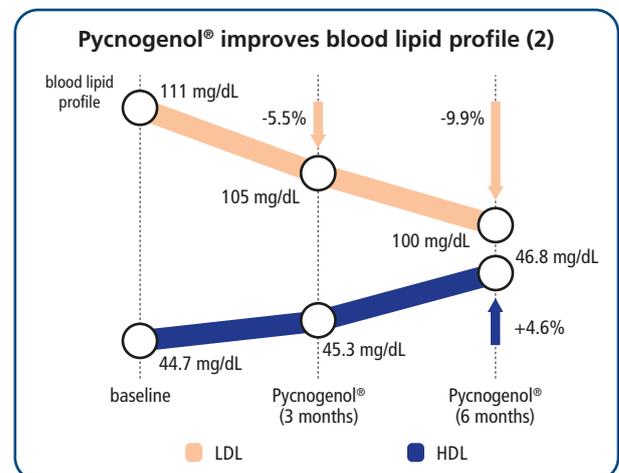


A follow-up measurement 4 weeks after discontinuation of Pycnogenol® showed that LDL returned to baseline values whereas HDL largely remained unchanged. Blood triglyceride levels were unaffected.

A substantial improvement of blood lipids was discovered in a study with patients treated with Pycnogenol® for venous insufficiency (Koch 2002). These patients presented with serious dyslipidemia, with total cholesterol at 264 mg/dL, LDL at 169 mg/dL and HDL at 46 mg/dL. After taking Pycnogenol® for only four weeks, blood lipids decreased to 212, 147 and 51 mg/dL for total, HDL and LDL cholesterol, respectively.

In men with mild hypercholesterolemia supplementation with Pycnogenol® over a period of three months statistical significantly lowered both total cholesterol and LDL by 9.4% and 16%, respectively. HDL increased by 5.5% during this time period [Durackova et al., 2003].

A large scale double-blind, placebo-controlled clinical trial with 200 peri-menopausal women showed a significant decrease of LDL by 9.9% as compared to baseline as well as ineffective placebo [Yang et al., 2007]. HDL cholesterol increased significantly by 4.6% during the six months treatment period. No effect on total triglycerides was found.

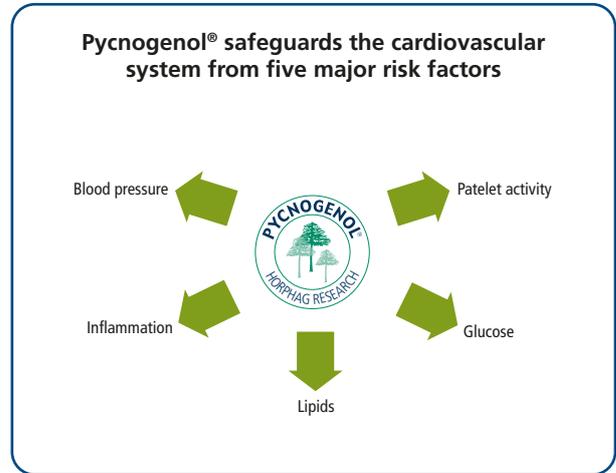


A study with type II diabetic patients found a significant reduction by 12% of LDL cholesterol from baseline 106.4 mg/dL to 93.7 mg/dL after three months treatment with Pycnogenol®. HDL values were not investigated in this trial [Zibadi et al., 2008].

Thus, Pycnogenol® significantly improves the atherosclerotic index and thus contributes to protection from atherogenesis.

**Conclusion**

Pycnogenol® offers a nutritional approach to safeguard the cardio-vascular system from five major risk factors simultaneously.



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