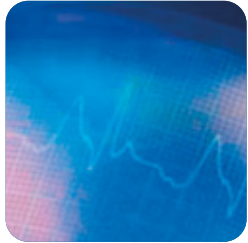


**PYCNOGENOL®**

Diabetes Care



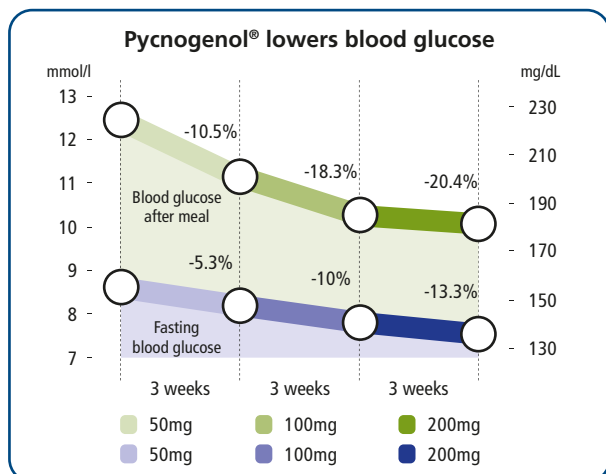
## Pycnogenol® for Diabetes Care

The incidence of type II diabetes is increasing dramatically in most countries of the world. Unlike type I diabetes, type II is predominantly considered as nutritional disorder. Chronic over-eating grossly contrasted by lack of physical activity leads to insulin resistance and hyperglycemia. The disease develops from early stages of impaired glucose tolerance (Pre-diabetes; Syndrome-X) and typically coincides with increasing body weight and obesity.

A chronically high blood glucose level needs attention comprising routine blood sugar monitoring, medication and diet. Left untreated hyperglycemia takes its toll on the health of arteries and veins which supply blood to organs as well as the small capillaries which nourish tissues. Pathological harm to large vessels accounts for a three-fold increased risk for acute cardiovascular disease in diabetes. The damage caused to capillaries (microangiopathy) affects blood micro-circulation and is responsible for numerous diabetic complications such as vision loss, kidney problems, foot ulcers and many others.

### Pycnogenol® lowers blood glucose

Pycnogenol® offers help for people with pre-diabetes and type II diabetes, as it was shown to dose-dependently lower blood sugar levels in 30 type II diabetes patients not requiring medication. These patients followed a diet and exercise program during the trial [Liu et al., 2004].



Pycnogenol® was given in a daily dosage of 50 mg per day for the first 3 weeks. The following 3 weeks dosage was increased to 100 mg and then

200 mg for another 3 weeks. A daily dosage of 50 mg Pycnogenol® lowered both fasting and post-prandial blood glucose significantly, as compared to baseline. Higher dosages of 100 and 200 mg Pycnogenol® were more effective.

HbA<sub>1c</sub> levels decreased continuously during the trial from baseline 8.02 to 7.37 at trial end. This study, published in Diabetes Care, found that Pycnogenol® did not affect insulin levels. Pycnogenol® appears to facilitate blood sugar uptake by previously insulin-unresponsive body cells. Thus, Pycnogenol® may offer a nutritional approach for people to prevent development of diabetes.

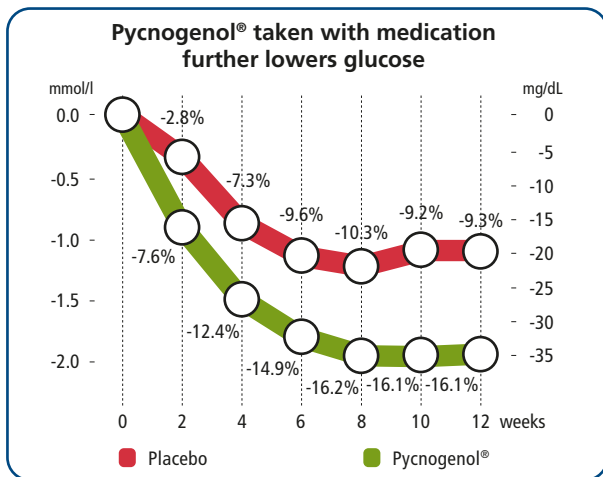
Pycnogenol® was also tested in type II diabetes patients who were continuing their conventional anti-diabetic medication with biguanide (metformin) and/or sulfonylurea to control hyperglycemia. Seventy seven patients received either Pycnogenol® (100 mg a day) or placebo in addition to their conventional medication. Fasting blood glucose was measured in intervals of two weeks over the trial period of twelve weeks.



# PYCNOGENOL®

## Diabetes

Despite anti-hyperglycemic medication fasting blood glucose was high at trial start with 12.0 mmol/l (216.2 mg/dL) and 12.14 mmol/l (218.7 mg/dL) in the placebo- and Pycnogenol® group, respectively. Pycnogenol® gradually lowered fasting blood glucose levels with treatment duration. The highest effect was found after 8 weeks supplementation with Pycnogenol®. The study showed a considerable placebo effect which is understood to result from patient's better compliance to their conventional medication. Despite the placebo effect the glucose-lowering effect of Pycnogenol® was statistically significant as compared to placebo over the entire treatment period [Liu et al., Life Sciences, 2004].

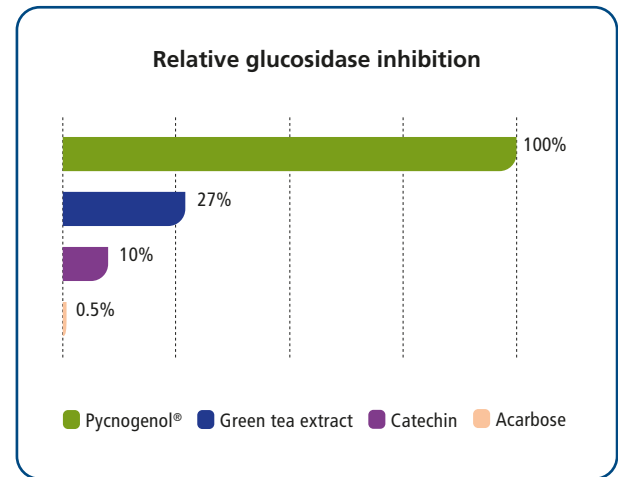


### Pycnogenol® inhibits carbohydrate absorption

Pycnogenol® significantly delays uptake of complex sugars such as starch because it was demonstrated to potently inhibit the digestive enzyme  $\alpha$ -glucosidase in the duodenum [Schäfer et al., 2006]. This enzyme is required for decomposing complex sugars for liberation of single glucose entities. Even sucrose, the standard table sugar, requires cleavage by  $\alpha$ -glucosidase to glucose and fructose prior to absorption.

Compared to other  $\alpha$ -glucosidase inhibitors, with Pycnogenol® activity set to 100%, green tea extract, pure catechin and the oral antidiabetic medication

acarbose (Precose, Glucobay) are dramatically less potent. Green tea extract was shown to likewise inhibit  $\alpha$ -glucosidase, yet Pycnogenol® in direct comparison proved to be four times more potent [Schäfer et al., 2006].



Inhibition of  $\alpha$ -glucosidase was shown to correlate with the size of procyanidin molecules present in Pycnogenol®. These molecules were recently shown in pharmacokinetic studies to last very long in the digestive tract before being absorbed into the blood stream, typically only 4-6 hours post consumption [Grimm et al., 2006]. Thus, these large procyanidin molecules remain available for inhibition of  $\alpha$ -glucosidase for a long period of time in the intestines. Pycnogenol® taken in the morning retains sufficient potency for delaying sugar absorption during lunch time.

### Macrovascular Complications and Diabetic Syndrome

In type II diabetes major cardio-vascular risk factors prevail which are involved in the development of diabetes and referred to as "metabolic syndrome". Obesity, hypertension, hyper-cholesterolaemia, a prothrombotic state and insulin resistance are responsible for the high mortality from cardiovascular disease in diabetes.



Further to lowering blood glucose, Pycnogenol® was shown to significantly lower systolic blood pressure, improve blood lipid profile and normalize platelet activity in several double-blind, placebo-controlled, clinical trials [Watson, 2003].

The investigation of vascular mediators in blood of above mentioned diabetic patients receiving Pycnogenol® in addition to standard anti-diabetic medication points to a general circulatory improvement. Pycnogenol®-supplemented patients showed lower amounts of vascular mediator endothelin-1, which triggers blood vessel constriction, and at the same time elevated amounts of the vaso-dilator prostacyclin [Liu et al., 2004].

Pycnogenol® thus offers a multi-factorial approach for improving the diabetic syndrome and lower cardio-vascular risk factors in diabetes. For further information please refer to PYCNOGENOL® FOR CARDIO-VASCULAR HEALTH.

**Microvascular Complications (Microangiopathy)**

Small blood capillaries are responsible for supplying tissue with nutrients and oxygen, as well as for waste removal. In diabetes the chronic exposure to elevated glucose levels causes basal membranes of capillary walls to swell and this affects the blood flow. Furthermore, capillary walls are gradually getting brittle allowing liquid and at later stages also blood to seep into the tissue. Diabetic microangiopathy affects essentially everybody with long-standing diabetes and is responsible for many complications in diabetes. Microvascular complications are often present at diagnosis of diabetes.

A double-blind, placebo-controlled clinical trial with 60 patients (diabetes in average since 7.5 years, on diet, oral anti-diabetic and insulin treatment) has demonstrated that Pycnogenol® is effective for improving microangiopathy [Cesarone et al., 2006]. Following four weeks treatment with Pycnogenol® capil-

lary leakage was significantly lowered, and capillary blood perfusion characteristics were significantly improved. No improvements took place in the placebo group. Physiologic parameters such as blood glucose, HbA<sub>1c</sub>, total cholesterol, HDL and blood pressure were improved only in the Pycnogenol® group.

**Diabetic Ulcers**

Impaired blood flow and edema as a result of diabetic microangiopathy may cause ischaemic and necrotic tissue. The first visible signs are skin discoloration and severe edema and the insufficient blood supply will gradually lead to development of ulcers. These wounds are very difficult to heal because the tissue continuous to be insufficiently supplied with blood.

As Pycnogenol® is helpful for restoring capillary health in diabetic microangiopathy, Pycnogenol® was found to be effective for healing diabetic ulcers [Belcaro et al., 2006]. Thirty diabetic patients with ulcers received standard treatment involving daily wound cleaning, disinfection and bandaging. Six patients received oral treatment with Pycnogenol®, another eight had Pycnogenol® powder applied directly onto the wound, and further eight patients received both local and oral treatment with Pycnogenol®. The remaining eight patients represented the control group and received only standard treatment.

Following six weeks treatment only 61% of patients in the control group had ulcers completely healed. In the Pycnogenol® groups, patients healed 84% ulcers (oral only), 85% (topical only), and 89% (oral and topical), respectively. Laser Doppler evaluation of blood flow characteristics pointed to significant improvement of microangiopathy. Sensors applied around onto intact skin surrounding ulcers revealed a significantly increased oxygen presence in the skin, whereas carbon dioxide was significantly decreased. The findings suggest that Pycnogenol® improves capillary function and restores blood flow to tissues which allows diabetic ulcers to heal.



### Cramps and Muscular Pain in diabetic microangiopathy

Some individuals with diabetic microangiopathy suffer from frequent episodes of muscle pain and cramps in their legs even after walking only short distances. The impaired blood supply causes rapid muscle fatigue and cramping pain.

In a pilot trial with 22 patients with frequent leg cramps and pain with diagnosed diabetic microangiopathy treatment with Pycnogenol® dramatically improved symptoms which were significant as compared to placebo treatment [Vinciguerra et al., 2006]. The average number of leg cramping episodes in a week decreased from 8.9 to 3 after treatment with Pycnogenol® for 4 weeks, whereas numbers in the placebo group decreased from average 9 to 7.8. The assessment of leg muscle pain by a visual analogue scale revealed a significant decrease by 79.2% in the Pycnogenol® group, whereas pain reduction in the placebo group was only 15.4%.

### Diabetic Retinopathy

In diabetic retinopathy the microangiopathy causes capillaries to insufficiently nourish the light sensing cones and rods of the retina. Furthermore, capillaries spill blood into the retina which causes irreversible damage and gradual vision loss. Left untreated retinopathy will progress to a more severe form known as proliferative retinopathy characterized by growth of new capillaries to compensate for the lack of oxygen.

Pycnogenol® was demonstrated in more than 1200 diabetic patients to be helpful for treatment and prevention of diabetic retinopathy. A double-blind, placebo-controlled study with retinopathy patients showed that Pycnogenol® taken for two months can significantly lower the bleeding from retinal capillaries and restore visual acuity to some extent [Spadea et al., 2001]. A multi-center field study with 1169 diabetic patients showed that Pycnogenol® taken over a period of six months can stop the progression of retinopathy and save the remaining eye sight [Schönlau et al., 2002]. For more information please refer to PYCNOGENOL® FOR EYE HEALTH.



Pycnogenol® provides significant health protection in diabetes as demonstrated in controlled clinical trials:

- Glucose lowering (also in addition to anti-diabetic treatment)
- Cardiovascular health risk reduction
- Improvement of microvascular health problems: Diabetic microangiopathy, foot ulcer healing, muscle cramps
- Prevention and improvement of diabetic retinopathy

## References

*Belcaro G et al.* Diabetic ulcers: Microcirculatory improvement and faster healing with Pycnogenol®. *Clinical and Applied Thrombosis/Hemostasis* 12: 318-323, 2006.

*Cesarone MR et al.* Improvement of diabetic microangiopathy with Pycnogenol®: A prospective, controlled study. *Angiology* 57: 431-436, 2006.

*Grimm T, Skrabala R, Chovanova Z, Muchova J, Sumegova K, Liptakova A, Durackova Z, Hogger P.* Single and multiple dose pharmacokinetics of maritime pine bark extract (Pycnogenol®) after oral administration to healthy volunteers. *BMC Clin Pharmacol* 6: 1-12, 2006.

*Liu X et al.* French maritime pine bark extract Pycnogenol® dose-dependently lowers glucose in type II diabetes patients. *Diabetes Care* 27: 839, 2004.

*Liu X et al.* Antidiabetic Effect of Pycnogenol® French Maritime Pine Bark Extract in patients with diabetes type II. *Life Sciences*, 75: 2505-2513, 2004.

*Schäfer A. and Högger P.* Oligomeric procyanidins of French maritime pine bark extract (Pycnogenol®) effectively inhibit alpha-glucosidase. *Diabetes Research and Clinical Practice* (2006) in press.

*Schönlau F et al.* Pycnogenol® for diabetic retinopathy. A review. *Int Ophthal* 24: 161-171, 2002.

*Spadea L et al.* Treatment of vascular retinopathies with Pycnogenol®. *Phytother Res* 15: 219-223, 2001.

*Vinciguerra G et al.* Cramps and muscular pain: prevention with Pycnogenol® in normal subjects, venous patients, athletes, claudicants and in diabetic microangiopathy. *Angiology* 57: 331-339, 2006.

*Watson RR.* Pycnogenol® and cardiovascular health. Review. *Evidence Based Integr Med* 1: 27-32, 2003.

*Horphag Research  
Administrative Office  
P.O. Box 80  
71 Av. Louis Casarì  
CH-1216 Cointrin/Geneva  
Switzerland  
Phone +41(0)22 710 26 26  
Fax +41(0)22 710 26 00  
info@pyncogenol.com  
www.pyncogenol.com*

*Pyncogenol® is a registered trademark of Horphag Research.*

*Use of this product is protected by one or more U.S. patents and other international patents.*

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