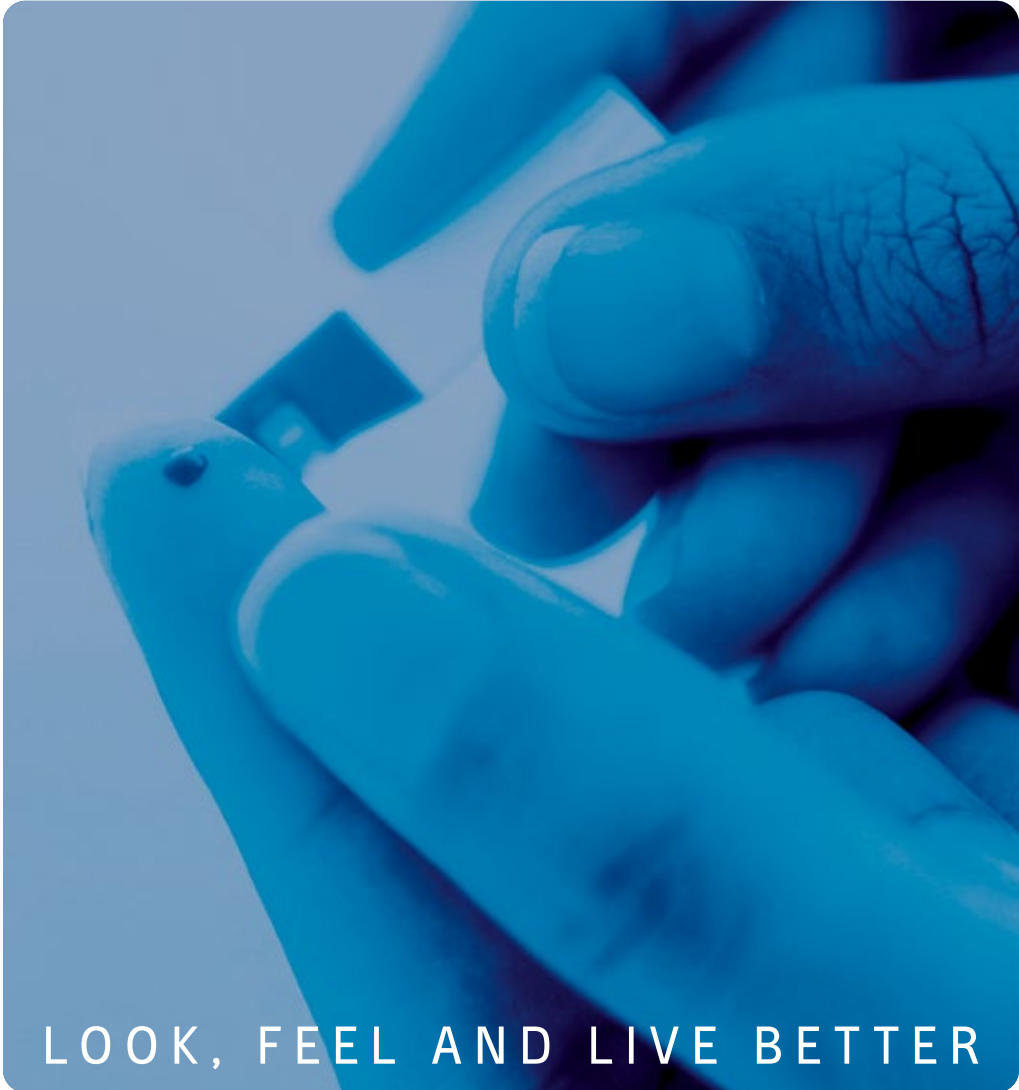


PYCNOGENOL®

Diabetes Care



Pycnogenol® for Diabetes Care

Pycnogenol® in Metabolic Syndrome and Diabetes Care

Habitual high consumption of carbohydrates, especially in absence of physical exercise, leads to gradual weight gain, progressively increasing fasting glucose blood and insulin resistance and, left unaddressed, to metabolic syndrome and eventually type II diabetes. With exception of weight gain, the fateful developments typically take place unnoticed.

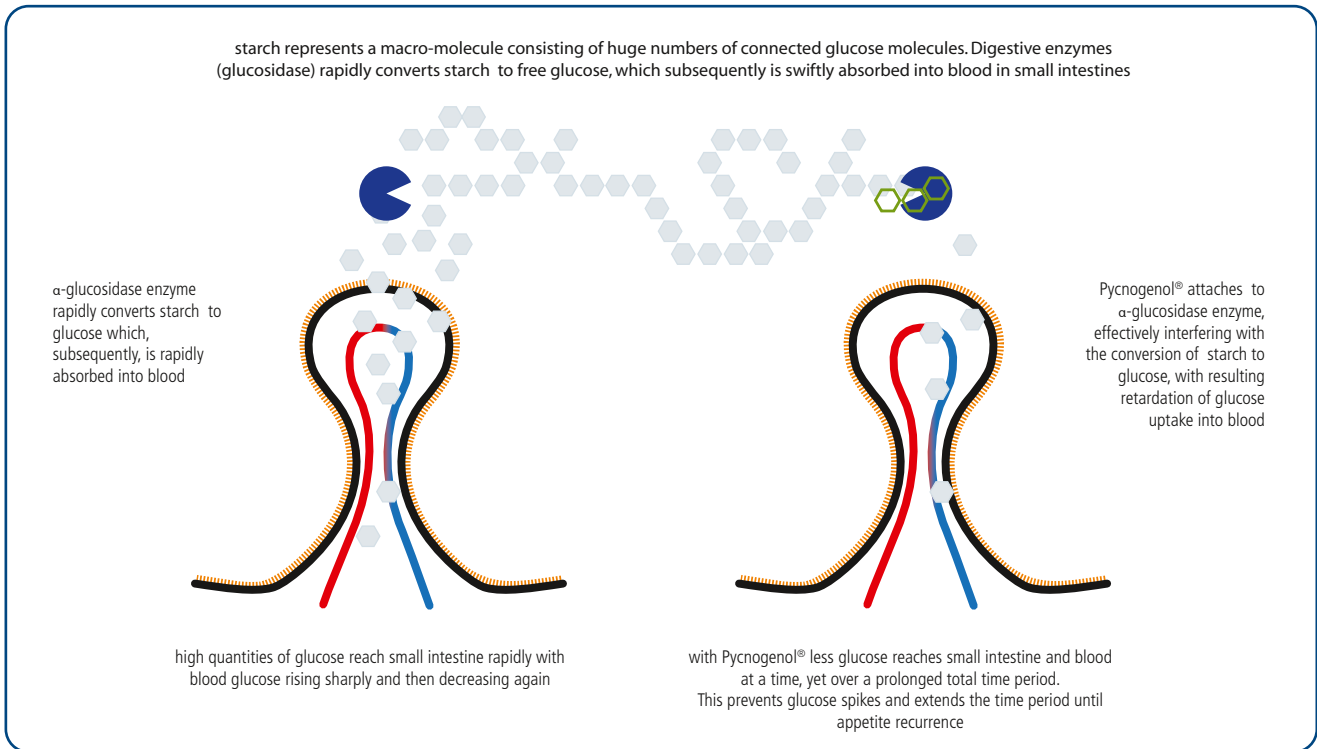
Both metabolic syndrome and type II diabetes, especially when inadequately addressed, will with time lead to development of health risks affecting the kidneys, eyes and cardiovascular functions. Metabolic syndrome and type II diabetes represent dietary conditions and suitable dietary interventions substantially improve health situations of affected individuals. Clinical research proves that dietary supplementation with Pycnogenol® substantially contributes to improve health of individuals burdened with diabetes and metabolic syndrome. Pycnogenol® addresses the major culprit: significantly decreasing blood sugar levels, especially the post-prandial peaks following carbohydrate-rich meals. Equally important, Pycnogenol® significantly improves cardiovascular health, with healthier blood pressure, improved blood micro-circulation, and quenched inflammatory processes [Gulati, 2015]

Pycnogenol® potently lowers blood sugar by retardation of dietary carbohydrate absorption

When dietary carbohydrates are absorbed into blood less rapidly, over extended time periods, the post-prandial glucose peaks rebound less markedly, with physiologic glucose level sustained longer, and appetite rebound occurring significantly later after the previous meal. As a result, unhealthy blood sugar spikes are avoided, which spares blood vessels from harm to the endothelium, such as loss of vascular flexibility and -dilatation which in turn may cause hypertension and hyper-coagulability.

The largest consumption of dietary carbohydrates originates from starch-bearing foods. Starch is a macromolecule consisting of millions of connected glucose moieties. Digestion of starch involves enzymes, such as α-glucosidase and α-amylase, which disassemble starch to glucose in small intestine for subsequent transfer into the blood stream. The time required in small intestines for liberation of glucose from starch is affected by other foods consumed with the meal. Especially vegetable flavonoids stall the release of glucose from starchy foods.



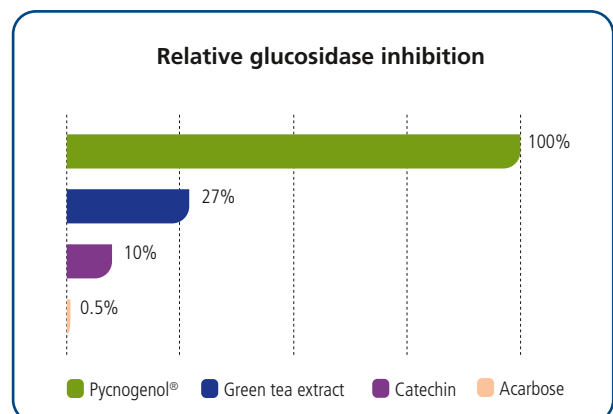


Pycnogenol® more potently inhibits α -glucosidase than pharmaceutical glucosidase inhibitor acarbose

Starchy dietary carbohydrates consumed require enzymatic cleavage to monomeric glucose, as only the latter may enter the blood stream. The cleavage is undertaken by particular enzymes in small intestines, predominantly α -glucosidase, which under ideal conditions occurs rapidly and typically may require only 15 minutes. Starch cleavage and glucose absorption take longer when the diet includes proteins and fats. Because flavonoids by nature display natural physical affinity to proteins, they attach also to enzymes, such as the α -glucosidase, which defers cleavage of starch to glucose. Pycnogenol® has a particularly high binding affinity to glucosidase with consequential potent retardation of carbohydrate absorption [Schäfer & Högger, 2007]. As an immediate result, blood sugar does not rise as rapidly and as high, instead sugar is absorbed

for protracted time period after meals, thereby preventing unhealthy glucose spikes.

Analytical comparison for α -glucosidase inhibition suggests that Pycnogenol® is 200-fold more potent as compared to acarbose, and much more efficient than green tea extract or catechin.



The high potency of Pycnogenol® for α -glucosidase inhibition, and in consequence blood glucose lowering, is demonstrated to result from presence of particularly large procyanidin species present in the product.

Whereas essentially all flavonoid species exhibit some inhibitory activity to α -glucosidase, the particularly large procyanidins limited to Pycnogenol®, exhibit glucosidase-inhibitory potency by an order of magnitude greater.

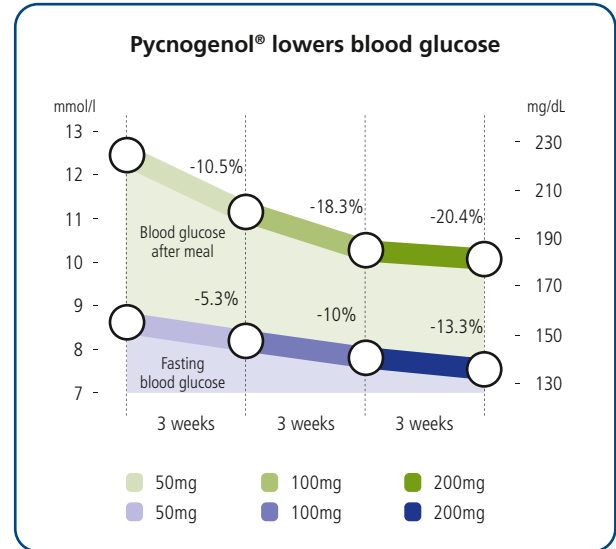
Pycnogenol® in blood sugar management

Pycnogenol® assists individuals with borderline elevated blood sugar, as well pre-diabetes and type II diabetes, not requiring medication, to achieve significantly healthier blood sugar levels. In a study with 30 type II diabetic individuals, not requiring medication, Pycnogenol® was demonstrated to dose-dependently and significantly lower fasting and post-prandial glucose levels [Liu & Zhou et al., 2004].

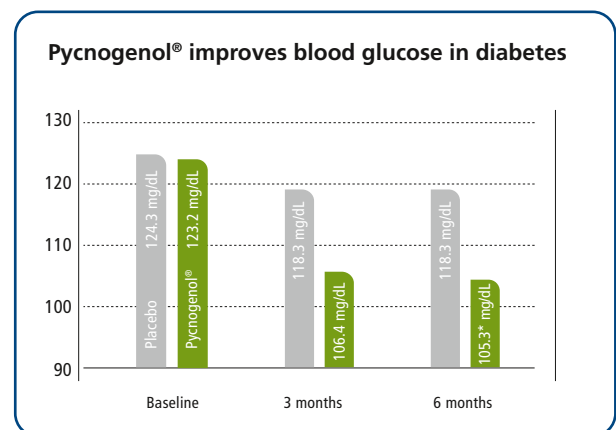
Study participants were treated in succession with 50, 100 and 200 mg Pycnogenol® daily, for a period of three weeks for each dosage. A noticeable reduction with 50 mg daily Pycnogenol® supplementation is apparent after three weeks. Dose escalation showed significantly greater fasting- and post-prandial glucose reduction for 100 mg Pycnogenol® and 200 mg Pycnogenol®, respectively. Average HbA_{1c} levels decreased continuously during the investigation from baseline 8.0 to 7.4. This study published in Diabetes Care, found that Pycnogenol® does not affect insulin levels. Pycnogenol® appears to facilitate blood sugar uptake by previously insulin-unresponsive body cells. Pycnogenol® therefore may offer a nutritional approach for people to prevent developing diabetes.

Pycnogenol® improves Metabolic Syndrome

Research suggests that Pycnogenol® helps arrest progression of metabolic syndrome to manifest type II di-



abetes [Belcaro et al., 2013]. One hundred and thirty seven participants with metabolic syndrome, presenting with all five risk factors (central obesity, high blood triglycerides, high LDL, low HDL and hypertension) were counselled for healthier life style including dietary advice, an educational programme and a moderate exercise programme. Seventy one subjects were additionally supplemented with Pycnogenol®. All subjects were surveyed for six months. This study identified significant fasting glucose improvements after three and six months of daily supplementation with Pycnogenol®.

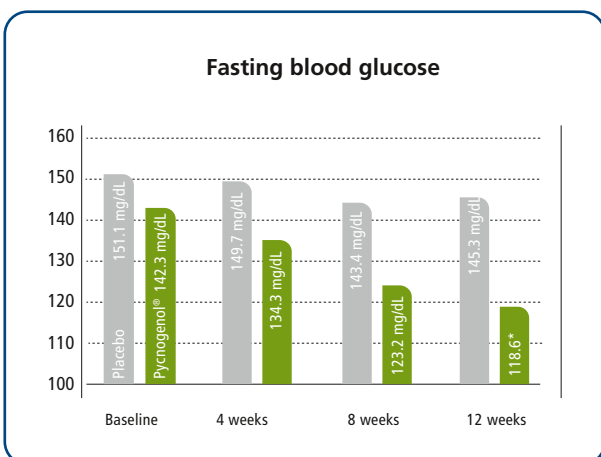


Furthermore, study participants presented with significantly healthier systolic- and diastolic blood pressure, as well as significant cholesterol- and triglyceride reduction, which were statistically significant after six months study completion.

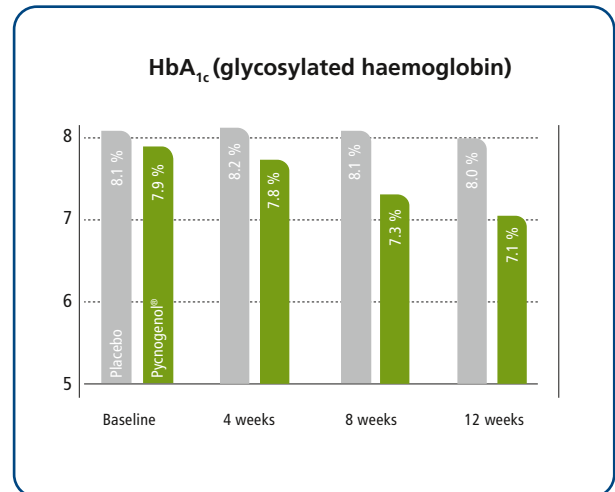
Pycnogenol® taken in addition to medications, significantly further reduces blood glucose and cardiovascular risk factors in two independent studies

Forty-eight individuals medicating with metformin and/or sulfonylurea, as well as thiazolidinediones, received in addition either Pycnogenol® or placebo [Zibadi et al., 2008]. Fasting glucose was significantly lower in subjects who received Pycnogenol® in addition to their standard medications, as compared to the control group which received placebo in addition to prescription medications.

Because prescription medications for diabetes exert pharmacologic activities which are distinct from Pycnogenol®’s natural effects related to slowed starch digestion, the additional supplementation with Pycnogenol® yields significantly better blood sugar control. Study participants treated supplementing with Pycnogenol® presented with significantly lowered fasting glucose as well as with lowered HbA_{1c}.



The mean HbA_{1c} levels of participants in the study of Zibadi (2008) decreased from one month to the next in subjects supplementing with Pycnogenol®, with no identifiable improvements in the placebo group.



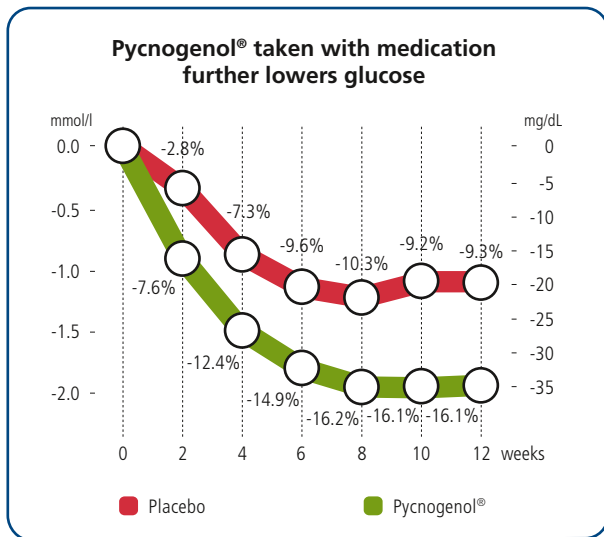
Further to significant lowering of blood sugar with Pycnogenol®, this study identified improvement of typical diabetic complications related to vascular-constriction, kidney function and LDL cholesterol. Pycnogenol® significantly lowered LDL cholesterol from mean 106.4 mg/dL to 93.7 mg/dL after twelve weeks, whereas no changes were identifiable for the placebo-treated group.

Research demonstrates that Pycnogenol® taken as an adjunct to diabetes medications significantly further improves blood glucose management

Another study corroborates the virtues of Pycnogenol®, when taken in addition to diabetes medication, for further improvement of hyperglycaemia [Liu & Wei al., 2004]. Seventy seven type II diabetic study participants continued their standard medication with metformin and/or sulfonylurea and received either 100 mg Pycnogenol® or placebo in addition. Despite applying conventional diabetes treatment, fasting glucose was



high at trial start with average 216 mg/dL. Blood sugar controlled in two weeks intervals showed glucose reduction in both groups, including placebo, which suggests better conventional treatment compliance. Yet, additional supplementation with Pycnogenol® statistical significantly further lowered fasting glucose than did prescription medication alone, thus underlining the proposition of Pycnogenol® as adjuvant treatment for optimal glycaemic control and prevention of diabetic complications.



Pycnogenol® ameliorates Diabetic Complications

Hyperglycaemia, especially when inadequately addressed for pro-longed periods of time, may lead to gradual development of vascular health complications.

Diabetes entails the risk for developing a cluster of cardio-vascular health issues, comprising altered insulin response, excess weight gain especially around the waist, rising LDL cholesterol, risk factors commonly referred to as metabolic syndrome. Obesity, hypertension, elevated cholesterol, a pro-thrombotic state and increasing insulin resistance are responsible for the high mortality related to diabetes.

Persisting and acute hyperglycaemia affects vascular function, which is critically involved in modulating vascular tone. Especially endothelial function is at risk, which regulates vascular tone, tissue blood perfusion and blood fluidity. Generation of vasodilatory nitric oxide (NO) is impaired in hyperglycaemia and insulin resistance, resulting in increased vascular constriction, blood pressure elevation and a pro-thrombotic state. The endothelial dysfunction in diabetes leads to increased vascular constriction with inability for vascular relaxation, representing the major culprit in the pathogenesis of diabetic complications. These complications have different consequences for large blood vessels in cardiovascular health issues and small capillary, micro-circulation related diabetic complications, resulting from impaired tissue perfusion.

Pycnogenol® improves Macrovascular Complications in Diabetes

Major cardiovascular risk factors are related to type II diabetes and metabolic syndrome: hypertension dyslipidaemia, oxidative stress, insulin resistance and a pro-thrombotic state. Pycnogenol® is demonstrated to contribute to all these cardiovascular health parameters. Pycnogenol® is described to dose-dependently decrease platelet aggregation in humans and correspondingly contributes to prevention of thromboses [Pütter et al., 1999; Belcaro et al. 2004]. In a clinical setting Pycnogenol® was demonstrated to significantly improve flow-mediated vasodilatation in coronary artery patients, in double-blind, placebo-controlled, cross-over study design [Enseleit et al., 2012].

Pycnogenol® alleviates Micro-circulatory Complications in Diabetes

Impaired blood micro-circulation in diabetes represents the cause for a range of diabetic complications. Because Pycnogenol® contributes to restoration of endothelial function, with greater availability of vessel-expanding nitric oxide, tissue perfusion with oxygen-



rich blood is improved. Correspondingly, Pycnogenol® is demonstrated in clinical trials to significantly alleviate diabetic complications.

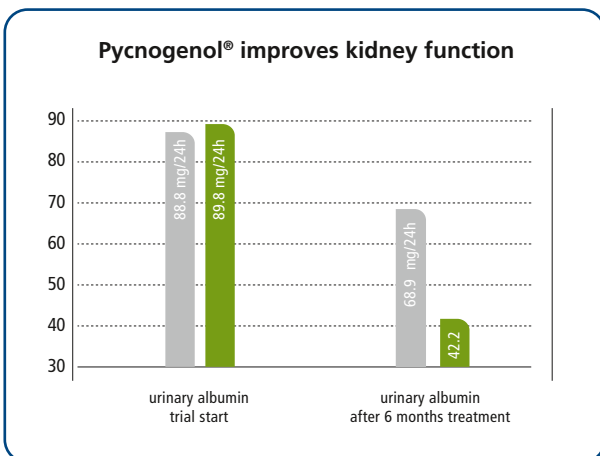
Diabetic Ulcers

Diabetic individuals commonly experience that even tiny bruises and wounds heal extremely slowly or even hardly at all. This is a result of capillaries being unable to perfuse harmed tissues with required oxygen- and nutrient-rich blood, because perfusion with arterial blood is insufficient. Pycnogenol® improves capillary relaxation and hence vessel diameter, increasing oxygen and nutrient supply and, in turn wounds heal well [Belcaro et al., 2006; Cesarone et al., 2006].

Diabetic Nephropathy

Three clinical studies have ascribed improved kidney function for Pycnogenol®, as judged from significantly lowered urinary albumins in diabetic and hypertensive individuals. [Zibadi et al., 2008; Stuard et al., 2010;].

insufficiently nourished in diabetic retinopathy, progressively affecting vision. At advanced stages leaking dysfunctional retinal capillaries spill blood into retina causing irreversible vision loss. Left untreated, retinopathy may progress to more severe forms characterised by compensatory growth of new capillaries, causing scarring and eventually blindness.



Pycnogenol® was demonstrated in three clinical studies, one of which represents a multi-centre field study with 1169 diabetic patients, to be helpful for treatment and prevention of diabetic retinopathy [Spadea et al., 2001; Schönlau et al., 2002; Steigerwalt et al., 2009]. For more information please refer to [PYCNOGENOL® FOR EYE HEALTH](#) brochure.

Diabetic Retinopathy

In diabetes the smallest capillaries bear the greatest burden, as they are the most fragile vessels, and once damaged, are difficult to heal because of the diminished blood flow and lack of nutrients. This is the case with retinal light sensing cones and rods, which are



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