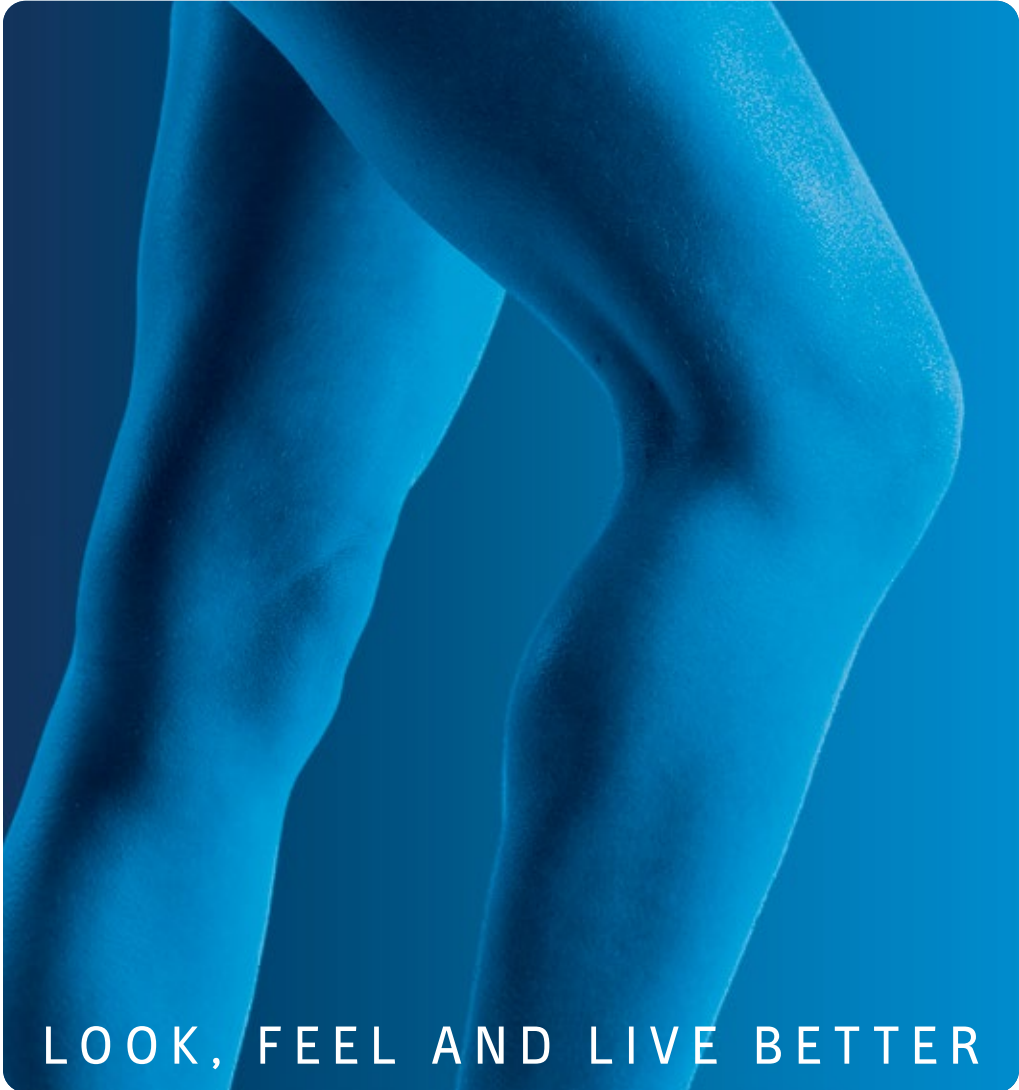


**PYCNOGENOL®**

Healthy Veins





## Pycnogenol® for Healthy Veins

The veins in our body return oxygen and nutrient depleted blood back to the heart. Unlike arterial blood, which is actively transported by ejection from the heart, venous blood is passively transported by compression of veins a long series of valves which allow movement only in one direction, leading to the heart. Blood in veins of the lower legs have the longest distance to travel and experiences the greatest gravity counterforce. When vein valves do not totally withstand gravity force, blood will pool in veins of the lower limbs. Veins may not withstand the pressure and fluid passes through vessel walls into tissue, which an affected individual experiences as swollen legs and feet. The swelling congests the lymphatic drainage causing fluids to be trapped and the swelling thus persists, which may gradually lead to development of chronic venous insufficiency. The swelling may in turn counteract the tissue perfusion with arterial blood, starving the tissue of oxygen and nutrients. Further to swellings, typical symptoms occurring may be itching skin of the legs and feet, aching, cramping or tiredness of legs, skin discoloration and appearance of new varicose veins.

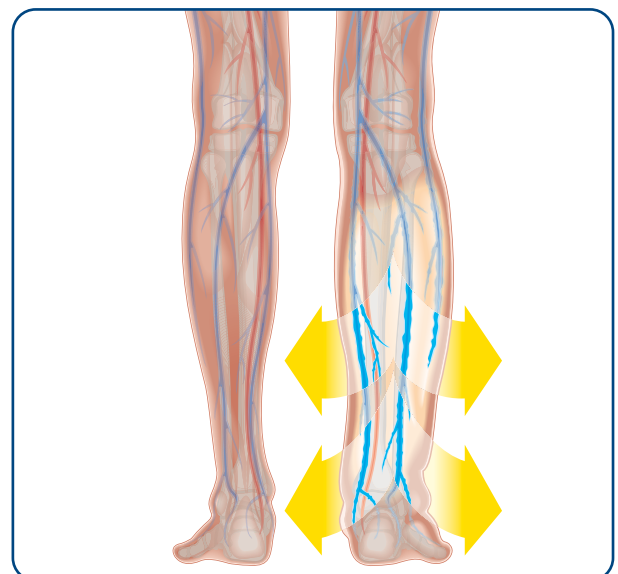
Left untreated the situation may further deteriorate with tiny capillaries in the skin bursting, leading to brownish discoloration and badly healing wounds (ulcers). A serious risk is the possibility of suffering a thrombosis which may clog a vessel or even travel to other parts of the body.

In general, extended periods of standing or sitting will increase the risk for developing chronic venous insufficiency (CVI). Statistics suggest that women are more commonly affected, even more so during pregnancy. Being overweight or suffering a deep vein thrombosis may lead to developing CVI. The circumstance that faulty venous valves cannot be healed or surgically repaired is responsible for the fact that CVI needs to be dealt with as early as possible to arrest progression of the disease.

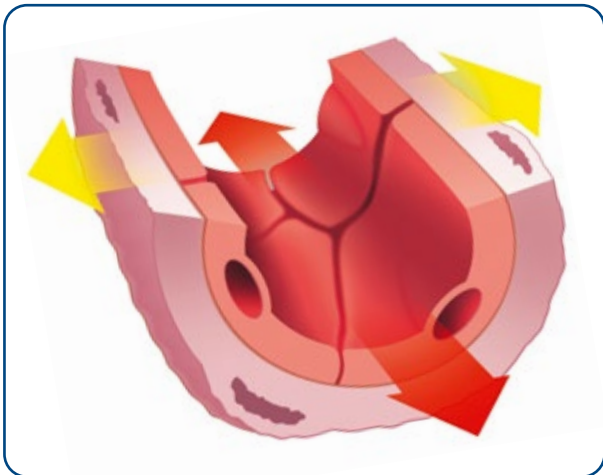
### Pycnogenol® strengthens veins and reduces fluid leakage

Pycnogenol® contributes in two from one another independent ways to prevent and diminish fluid accumulation in tissue.

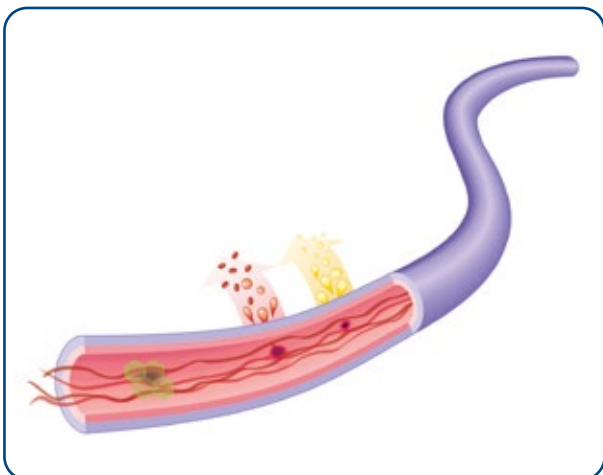
Pycnogenol® strengthens capillary walls and makes them more resistant against pressure with consequently lowered release of fluids into tissues. Further to the strengthening of blood vessel walls Pycnogenol® also improves endothelial function with enhanced nitric oxide synthesis, which in turn releases blood vessel constriction. Thus, blood flows easier as opposed to passing excessive fluid quantities into tissues. It is important to note that blood fluids are re-



quired to pass through blood vessel walls to nourish organs with nutrients and supply oxygen. However, when pressure builds up, blood vessels may leak excessive amounts of fluid into tissue, where it may be trapped, especially when lymphatic drainage is insufficient which is then referred to as an edema.



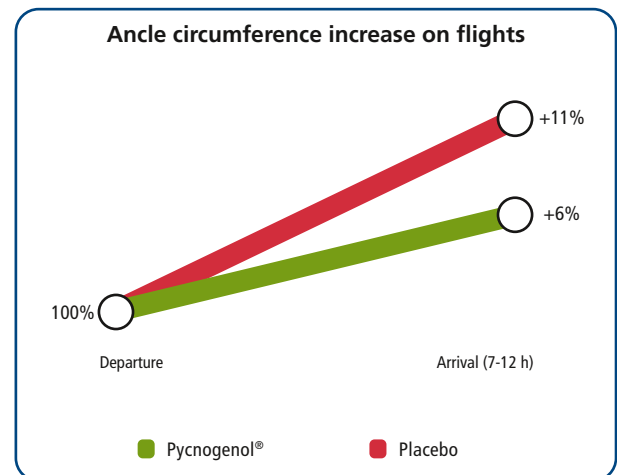
Pycnogenol® increases endothelial function in both healthy volunteers as well as in cardiovascular patients [Nishioka et al., 2007; Enseleit et al., 2012]. By restoring the endothelial function impaired in chronic venous insufficiency, Pycnogenol® improves blood flow. The resulting lowered pressure normalizes the outflow of fluid through capillary walls into tissues. Further studies have pointed to effects of Pycnogenol® for strengthening of blood vessel walls, rendering them



more resistant to pressure. Pycnogenol® strengthens blood vessel's basement membrane by strengthening collagen and inhibiting matrix metalloproteinases from destructing connective tissue.

### Pycnogenol® helps healthy people to prevent swellings

The benefits of Pycnogenol® for lowering swellings of the lower limbs can also be witnessed by healthy individuals. This was demonstrated with 169 healthy people who travelled on international flights lasting between seven and twelve hours [Cesarone et al., 2005].



A normal experience will be that the lower legs and feet present somewhat swollen at arrival which is typically noticed when shoes are put on again. In the study with flight passengers the ankle circumference was measured prior to departure and again right after arrival. In this study a group of passengers given placebo tablets developed an average increase of ankle circumference by 11% after arrival. Another group of passengers given Pycnogenol® prior to departure presented with an average increase of ankles swelling by only about half as much.

**Pycnogenol® is more effective for improving leg swellings than compression stockings**

A standard treatment option for relieving leg swellings are compression stockings. These are specially designed for providing graded compression intensity, applying the highest pressure to the ankles and the least to the thighs in an attempt to counterbalance the gravity impact.

In a study using strain gauge plethysmography with patients presenting with edema resulting from chronic venous insufficiency, Pycnogenol® was shown to be more effective, decreasing edema by 35%, whereas compression stockings lowered swellings by only 13% in a comparable control group [Cesarone et al., 2010].

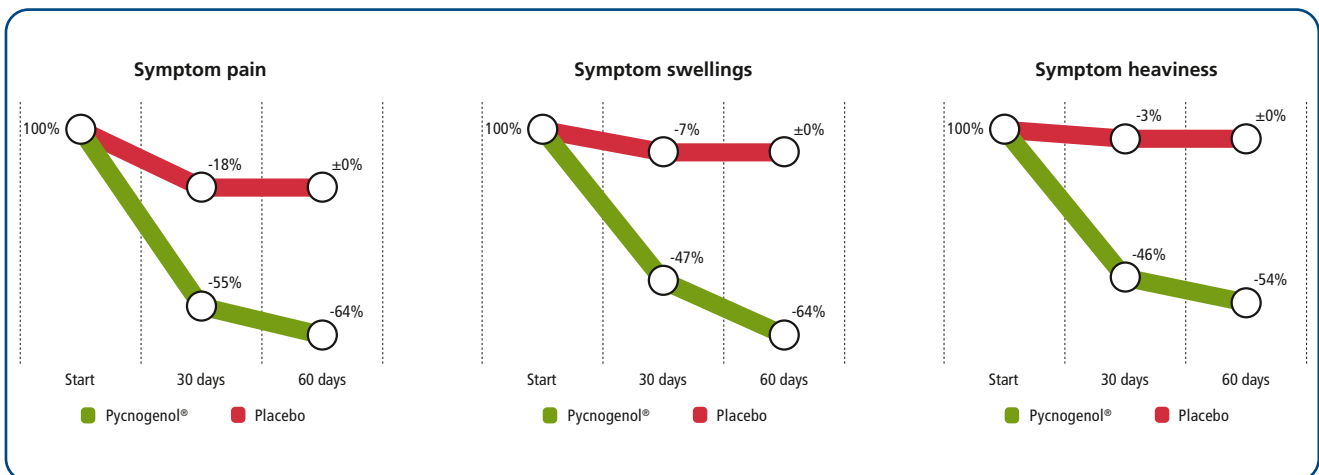
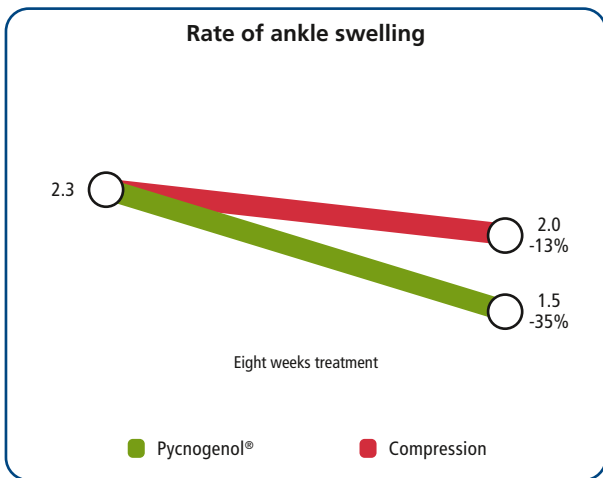
Interestingly, a third group wearing compression stockings and taking Pycnogenol® oral treatment in addition showed significant further reduction of ankle swellings by total 41%.

**Pycnogenol® rapidly improves venous insufficiency symptoms in double-blind, placebo-controlled studies**

To date Pycnogenol® has been investigated in 25 clinical studies with more than 1000 patients to identify health benefits related to venous health [Gulati, 2013].

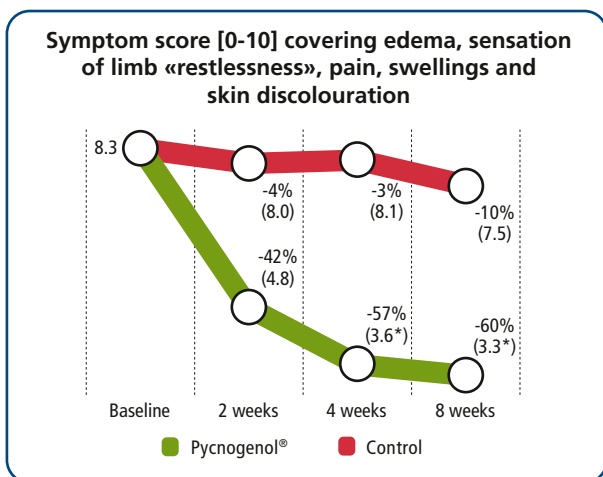
In one typical double-blind, placebo-controlled study Pycnogenol® significantly improved three of the most common symptoms related to the swellings, the perception of leg heaviness and the resulting leg pain already after 30 days treatment [Arcangeli, 2000]. Treatment with Pycnogenol® for further 30 days provided further symptom relief. Placebo contributed only marginally to improvement of symptoms. The results on individual clinical symptoms, pain, swellings and the perception of leg heaviness for both groups are illustrated below.

Another double-blind, placebo-controlled, study has likewise identified symptom relief after supplementation with Pycnogenol® and further investigated venous pressure before and after treatment. Whereas



placebo treatment resulted in marginal vein pressure reduction, patients treated with Pycnogenol® showed a significant vein pressure lowering by 5 mmHg corresponding to a 10% reduction [Petrassi et al., 2000].

Pycnogenol® was further shown to be helpful for significant improvement of symptoms in individuals presenting with more severe venous insufficiency [Cesarone et al., 2006]. Such cases are characterized by ambulatory venous pressure larger than 50 mmHg. In a controlled study Pycnogenol® proved to be helpful for all investigated symptoms, such as the sensation of leg «restlessness», furthermore pain, edema and skin discoloration.

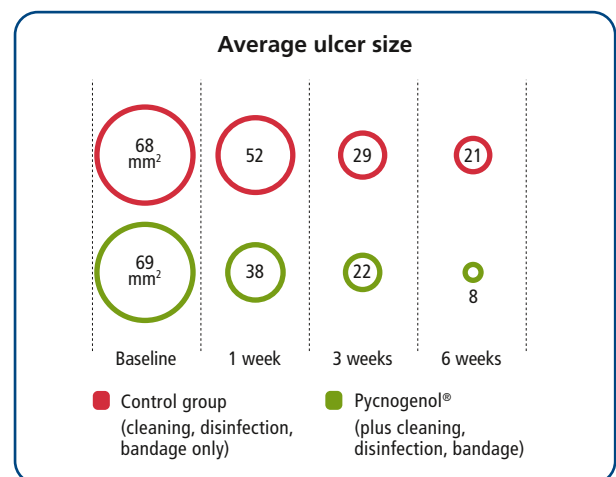


With Pycnogenol® symptoms are improved fast, with a noticeable 42% reduction already after two weeks treatment. After eight weeks of treatment a significant improvement of even severe cases of venous insufficiency is achievable with Pycnogenol®.

### Pycnogenol® accelerates healing of venous ulcers, a typical complication of chronic venous insufficiency

In patients who suffer from chronic venous insufficiency over longer periods of time certain complications may occur. The pronounced swellings impair blood supply to the lower legs and feet, which

depletes the skin from oxygen and nutrients. The skin, typically beginning at the ankles, but also affecting the feet, may turn red and later a discoloration to tan red or brownish. Eventually badly healing wounds (venous ulcers) may occur. Studies show that Pycnogenol® significantly contributes to the healing of venous ulcers.



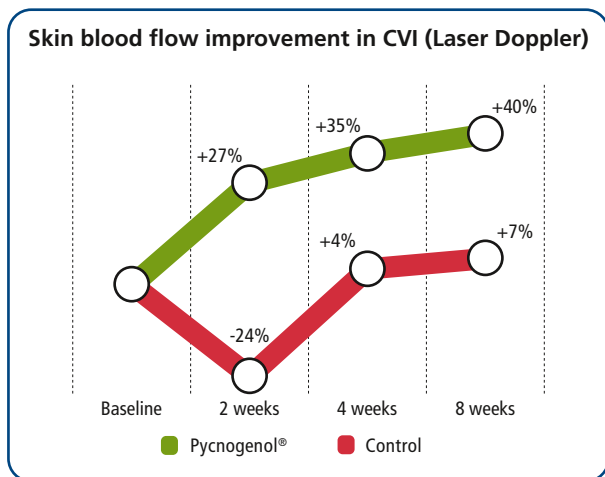
Compared to a control group of patients who received the best possible attention with regular wound cleaning, disinfection and bandage applied, additional oral supplementation with Pycnogenol® significantly sped-up the healing process. After six weeks of treatment with Pycnogenol®, the venous ulcers were almost closed [Belcaro et al., 2005].

This study identified a significant increase of skin oxygen partial pressure adjacent to venous ulcers. In parallel, using specific sensors, a decrease of carbon dioxide partial pressure was identified in vicinity to venous ulcers. The restoration of blood supply with oxygen and nutrients is understood to be the reason for the healing of venous ulcers with Pycnogenol®.

**Pycnogenol® restores dermal blood perfusion of lower legs and feet**

With Laser Doppler instruments it is possible to measure blood flow in vessels of the dermis. In patients with severe venous insufficiency, presenting with skin discoloration of ankles and feet, Pycnogenol® was demonstrated to significantly improve blood flow [Cesarone et al., 2006].

The improved skin perfusion is in agreement to the aforementioned improved healing of venous ulcers, which also found greater oxygen presence in the dermis.

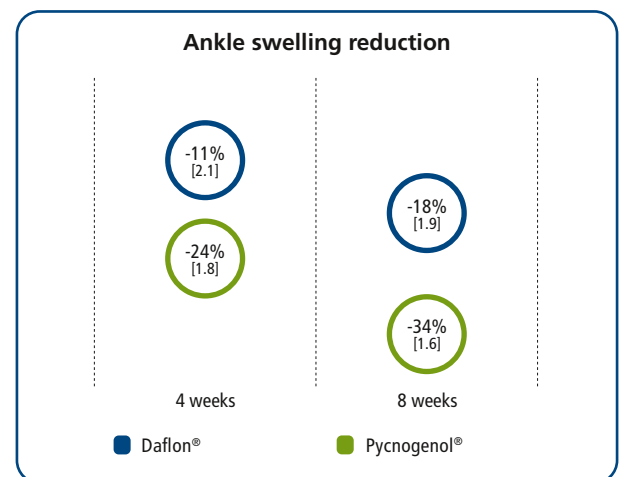


The cause for improved dermal blood flow is understood to partially result from lowered pressure in the lower legs, coinciding with edema relief. The major contribution is believed to stem from enhanced endothelial function. Pycnogenol® was demonstrated in various studies, including human pharmacological experiments, to render endothelial cells more effective in generating nitric oxide which stimulates arterial and arteriole dilatation and in consequence leads to greater tissue perfusion [Nishioka et al., 2007].

**Pycnogenol® is more efficacious than alternative phlebotonic remedies**

Great many products are marketed for improving signs and symptoms of venous insufficiency. Most of such remedies are plant derived, either plant extracts or chemically modified plant materials like troxerutin. Pycnogenol® was extensively researched in controlled comparative studies versus other established regimen for improving venous insufficiency.

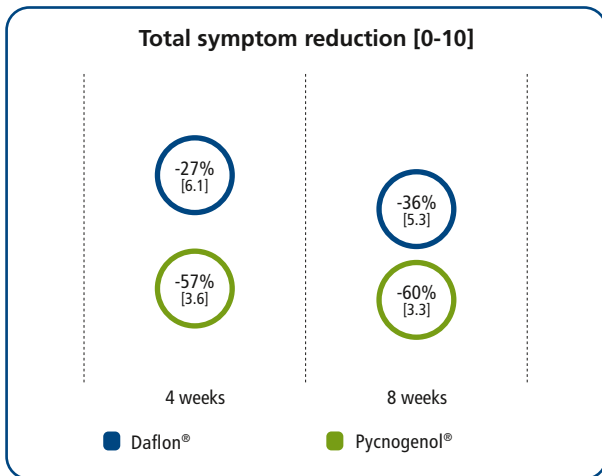
In one such study, Pycnogenol® has been compared versus Daflon® brand, bearing diosmin and hesperidin flavonoids as active ingredients, in 86 venous insufficiency patients [Cesarone et al., 2006]. Patients received a daily regimen of 1 g Daflon® or 150 mg Pycnogenol® over a period of eight weeks. The ankle swelling, as judged by strain gauge plethysmography, was found to be significantly lowered by 24% with Pycnogenol® already after four weeks treatment, which was not the case with Daflon®. After eight weeks treatment Pycnogenol® was found to be significantly more effective reducing edema than Daflon®.



This study further investigated the patient’s symptoms of pain, «restless legs», skin alterations and subjective feelings of swelling by visual analogue scale. As shown by composite value of all these symptoms, the study suggests a favorable outcome



for Pycnogenol®. The outcome confirms earlier studies with regard to early onset of symptoms improvement with Pycnogenol®, which requires no longer than four weeks. Daflon®, at much higher dosage requires longer intake to yield symptom improvement.

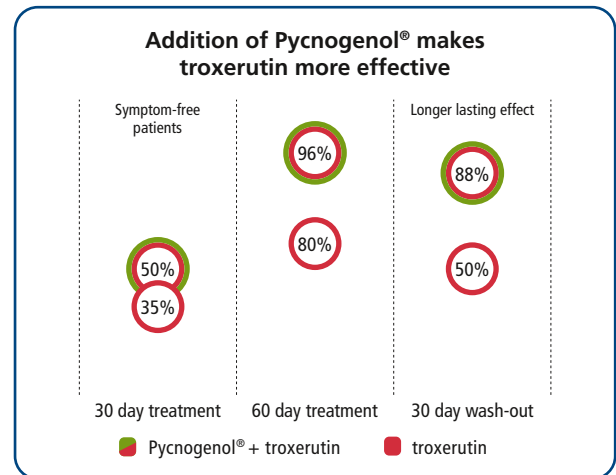


Various further comparative investigations were made, such as for partial dermal pressures of O<sub>2</sub> and CO<sub>2</sub>, which were found to be significantly improved in the Pycnogenol® group. With Pycnogenol® pO<sub>2</sub> increased by 16% and pCO<sub>2</sub> decreased by 15%. With Daflon® pO<sub>2</sub> increased by 3% and pCO<sub>2</sub> decreased 0.9%.

Another study was carried out for comparison of the efficacy of Pycnogenol® versus horse chestnut seed extract brand Venostasin®.

Pycnogenol® was shown to be significantly more effective for lowering leg swellings already after two weeks treatment, with further improvement after four weeks. In contrast, Venostasin® was found to provide only marginal, non-significant edema relief even after four weeks treatment [Koch et al., 2002]. Further developments have made use of adding Pycnogenol® to other existing venotropic ingredients. The flavonoid troxerutin (Venoruton®), a derivative of rutin was fortified by addition of 4% Pycnogenol®. In a comparative trial venous insufficiency patients

were given a combination of 940 mg troxerutin plus 40 mg Pycnogenol®, the control group received only the troxerutin [Riccioni et al., 2004].



The addition of comparatively low amounts of Pycnogenol® was found to make troxerutin significantly more efficacious. Moreover, following cessation of treatment for one month, symptoms remained improved with the Pycnogenol® troxerutin combination, whereas symptoms returned rapidly in patients who received troxerutin alone.

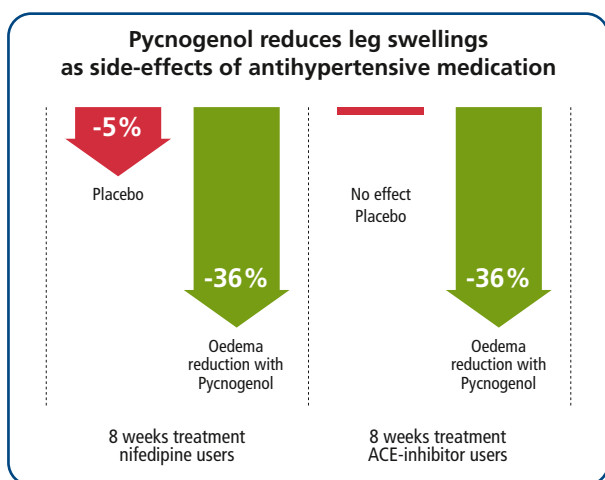
Pycnogenol® is demonstrated in controlled clinical studies to be more efficacious than other phlebotonics [Gulati, 2013]

Pycnogenol® relieves swellings significantly more potently than Venostasin® brand horse chestnut seed extract	Koch, 2002
Pycnogenol® is more effective than Daflon® brand citrus flavonoid hesperidin and its semisynthetic derivative diosmin	Cesarone et al., 2006
Pycnogenol® addition to the semisynthetic rutoside troxerutin renders the latter more effective than troxerutin alone	Riccione et al., 2004



**Pycnogenol® reduces edema developing as side-effect of anti-hypertensive medication**

Edema may develop in hypertension, either due to the disorder itself, more commonly though due to anti-hypertensive treatment. Chronic medication with ACE-inhibitors (angiotensin converting enzyme) or nifedipine (calcium channel blocker) typically presents with edema as side effect.

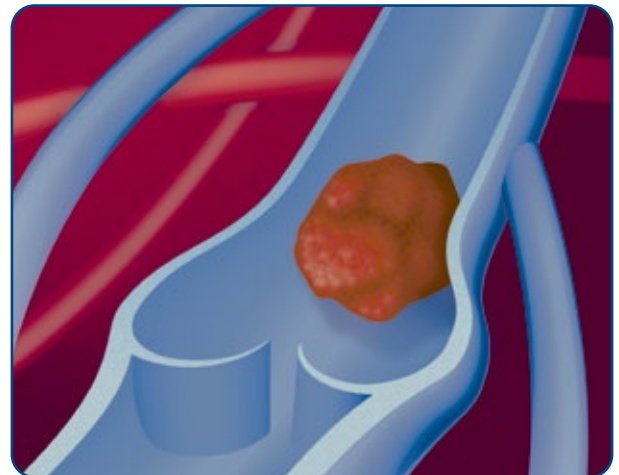


Pycnogenol® effectively lowers edema which developed in hypertensive patients due to their medications with either nifedipine or ACE-inhibitors (ramipril or trandolapril). The control group given placebo did not present with lowered edema while taking anti-hypertensive drugs [Belcaro et al., 2006].

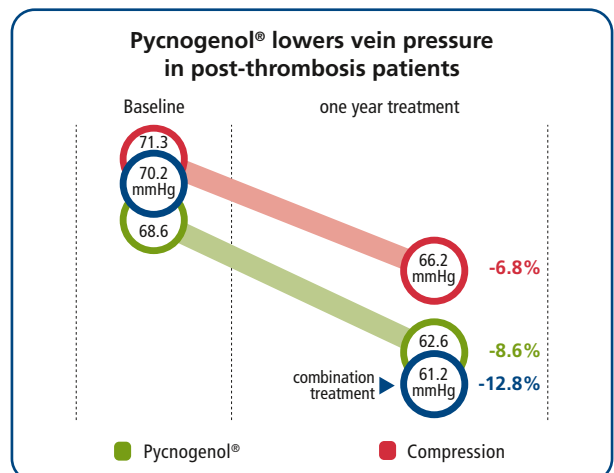
**Venous insufficiency and thrombotic complications**

Individuals with chronic venous problems live at elevated risk for suffering a thrombotic event, commonly also referred to as phlebitis. Pycnogenol® does contribute to prevention of platelet aggregation owed to the restoration of the endothelial synthesis of nitric oxide [Pütter et al., 1999]. Preventative effects of Pycnogenol® for defying thrombosis have been shown in flight passengers. Whereas a control group developed limited, transient thrombosis, another group taking Pycnogenol® before and

during the flight, were spared from developing any thrombosis [Belcaro et al., 2004].



A thrombosis in the leg, especially of the deep vein, may also be the cause for developing venous insufficiency. The pooling of blood and swelling due to blood clot may destroy vein valves and approximately every second affected individual may subsequently develop signs and symptoms of venous insufficiency. The best possible protection for individuals who suffered a deep vein thrombosis is the continuous wearing of compression stockings. In a comparative study, individuals who suffered a single episode of deep vein thrombosis without further complications, were treated for one year with compression stockings,



## Healthy Veins

or supplemented with Pycnogenol®, a third group received both treatments [Errichi et al., 2011]. Pycnogenol® was found to lower pressure in veins in comparatively fashion as compression stockings. In any case compression should be standard treatment, while the study suggests that additional supplementation with Pycnogenol® will be beneficial.

Pycnogenol® was found to provide greater relief from edema and related symptoms (pain, restless limbs, subjective swelling, skin alterations) during the one year trial than compression stockings. The results of a third patient group receiving combined treatment again point to the superiority of symptoms relief by wearing compression stockings and supplementing with Pycnogenol®.

In conclusion, Pycnogenol® is helpful for both, prevention of venous health problems, as well as for relieving symptoms of swollen legs. Pycnogenol® helps to address the root of venous insufficiency by relieving pressure in veins. More problematic consequences, such as skin discoloration and wounds of the ankles and feet can be effectively dealt with by supplementation with Pycnogenol®.

Pycnogenol® is demonstrated in 25 studies with in total more than 1000 people to support venous health [Gulati, 2013]

Pycnogenol® supports veins also in healthy individuals such as flight passengers to decrease swellings of feet and ankles

Cesarone et al., 2005

Pycnogenol® is efficacious for improving mild and severe forms of venous insufficiency, with a lasting effect

Arcangeli, 2000

Pycnogenol® presents with higher efficacy than other phlebotonic remedies for relieving venous insufficiency symptoms

Koch, 2002  
Cesarone et al., 2006

Pycnogenol® is suitable as preventative measure for protection from developing venous insufficiency symptoms

Errichi et al., 2011

Pycnogenol® has a well-documented safety track record [Oliff, 2009]

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