

# Pycnogenol®

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## For Economy Class Syndrome V.16.01.03



**PYCNOGENOL®**

LOOK, FEEL, AND LIVE BETTER

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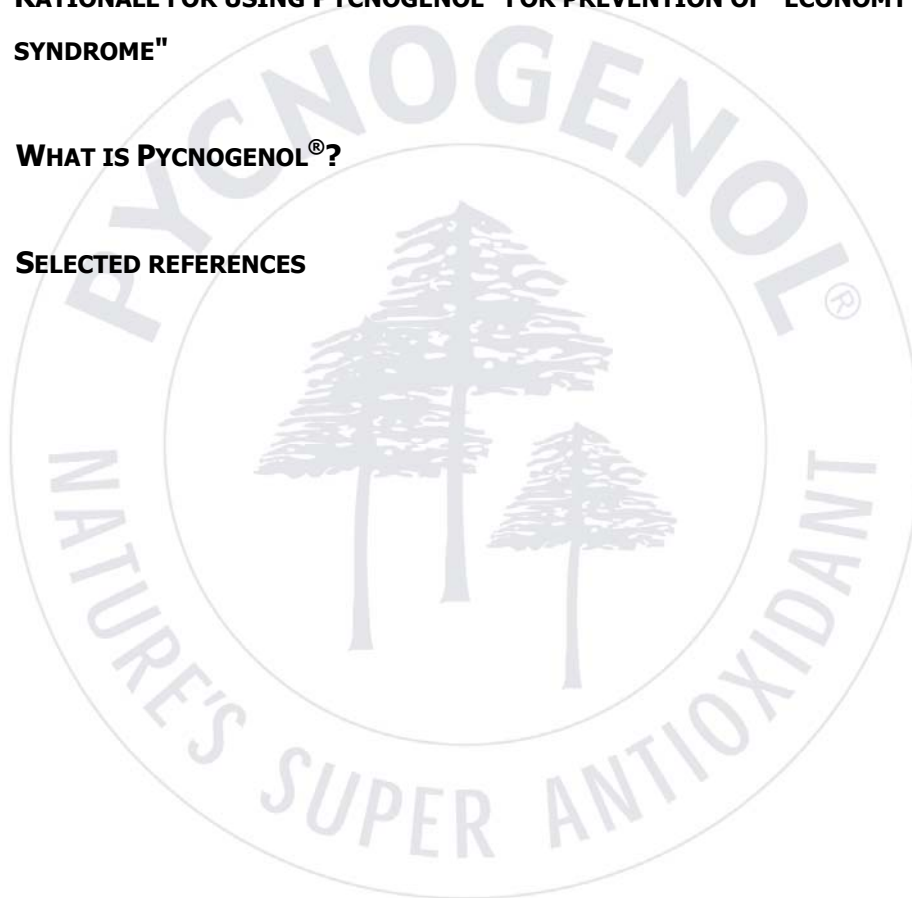
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### **Pycnogenol® for "economy class syndrome"**

The danger of the so-called "economy class syndrome" has gained much media covering in the recent years. This incident of a deep vein thrombosis ascribes formation of a blood clot in veins of the lower limbs, where blood flow is reduced by a prolonged sitting position [Ferrari et al., 1999]. When the blood clot travels to an artery of the lung it may get stuck and block blood flow. This "pulmonary embolism" often has a fatal outcome. In the meantime it is understood that this phenomenon is not limited to the economy class, but may occur after prolonged sitting in an environment with low pressure / humidity.

The search for alternative options requires the understanding of the underlying mechanisms causing increased aggregation of blood platelets. Remaining in a sitting position reduces venous blood flow velocity by 2/3 [Wright & Osborn, 1952]. The increasing venous blood pressure in the lower limbs causes small capillaries to leak plasma into the surrounding tissue [Eklof et al., 1996]. This causes swellings, a phenomenon well known to passengers when they put on their shoes at destination. Wearing elastic stockings would be helpful but is not applicable as general precaution measurement.

Dehydration due to low cabin humidity, insufficient fluid intake and the diuretic effect of alcohol consumption leads to thickening of the blood [Ferrari et al., 1999]. The reduced blood velocity in legs and feet allows blood platelets to interact more closely. When blood platelets are in an activated state they may coagulate and form a clot. A recent study published in THE LANCET has identified the decreased air pressure prevalent in aeroplane cabins to activate coagulation of the blood [Bendz et al., 2000]. This also gives a consistent explanation why deep vein thrombosis occurs particularly during air travel. Furthermore, this study implies that the deep vein thrombosis is not restricted to the economy class.

Therefore, counteracting swelling of the lower limbs and decreasing platelet activity represent the ideal measure for airlines to control the "economy class syndrome" and to generally improve the well-being of their passengers.

A food supplement has demonstrated in clinical studies to provide both of these actions: Pycnogenol®, the standardised extract of the bark of the French maritime pine (*Pinus pinaster*) world-wide exclusively distributed by Horphag Research Ltd., UK. Pycnogenol® constituents are bioflavonoids (for detailed description please see below).

The French maritime pine bark extract, Pycnogenol®. Pycnogenol® reduces the activity of platelets to aggregate (US patent No 5,720,956). This has recently been demonstrated for smokers, another group of people living at risk of thrombosis [Pütter et al., 1999; Watson, 1999]. When taking 200 mg Pycnogenol®, smokers' platelets no longer displayed an increased activity, banning the danger of a clot formation. Another clinical study has shown that Pycnogenol® inhibits the production of thromboxane [Araghi-Niknam et al., 1999], a substance produced by activated platelets. Thromboxane activates other previously quiescent platelets. This vicious circle leads to a local accumulation of activated platelets which may ultimately coagulate and form a clot.

Pycnogenol® has the advantage of not sharing the side effect of Aspirin, commonly used for this purpose. Aspirin increases the bleeding time, frequently causing gastric bleedings and therefore is not well tolerated by everyone. Moreover, Pycnogenol® powerfully counteracts the grossly visible effect of a long-term flight: The swelling of the lower limbs and feet. Several clinical studies have demonstrated that Pycnogenol® increases capillary resistance and seals leaky capillaries, and thus prevents the accumulation of liquid in the tissue [Petrassi et al., 2000; Arcangeli, 2000].

In addition to preventing thrombus formation, taking a single dose of 200 mg Pycnogenol® two hours prior to take-off will bring an immediately noticeable benefit to every flight passenger: The reduction of swellings! The most intriguing point of using Pycnogenol® to enjoy a pleasant flight in good health is the fact that Pycnogenol® is a totally natural, safe and healthy substance.

**Clinical studies on Pycnogenol®**

**Pycnogenol® reduces platelet aggregation**

Clinical studies with Pycnogenol® 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 during long haul flights [Pütter et al., 1999; Watson, 1999; Araghi-Niknam et al., 1999]. Two hours after supplementation with Pycnogenol®, blood was drawn from volunteers and the platelet activity ("stickiness") was measured in a laboratory. Pycnogenol® was found to dose-dependently reduce platelet activity, with statistical significance after using a single dose of at least 100 mg Pycnogenol® (figure 1). The method of controlling human platelet reactivity by Pycnogenol® is patented (US patent 5,720,956)

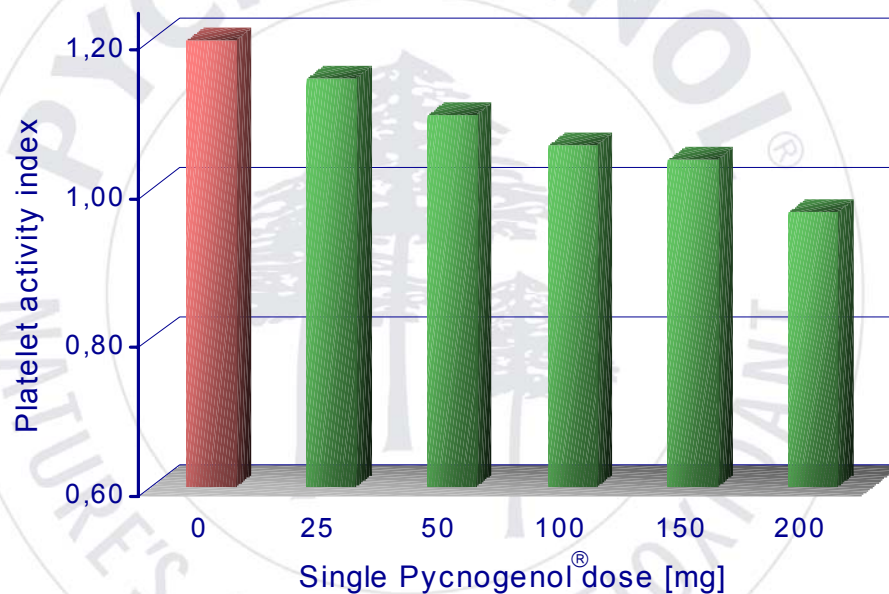


Figure 1: Response of platelet activity of 19 smokers on oral administration of a single dose of Pycnogenol®. Blood was drawn from subjects before and 2 hours after Pycnogenol® consumption. Reduction of platelet activity was found to be statistical significant after consumption of at least 100 mg Pycnogenol® [Pütter et al., 1999].

The authors of the study propose that stimulation of nitric oxide production by Pycnogenol® inhibits aggregation of platelets. Thus, Pycnogenol® supports body-own mechanisms to maintain healthy platelet functions.

A single dose of 100 mg Pycnogenol® was found to be as effective for reduction of platelet activity as acetyl-salicylic acid, a substance widely used for suppression of platelet aggregation. However, acetyl-salicylic acid irreversibly inhibits the enzyme COX involved in platelet aggregation. As a result acetyl-salicylic acid dramatically increases the bleeding time, causing severe adverse effects, primarily gastrointestinal problems. Fortunately, Pycnogenol® does not significantly increase bleeding time (figure 2), allowing a long-term use for prevention of thrombotic events.

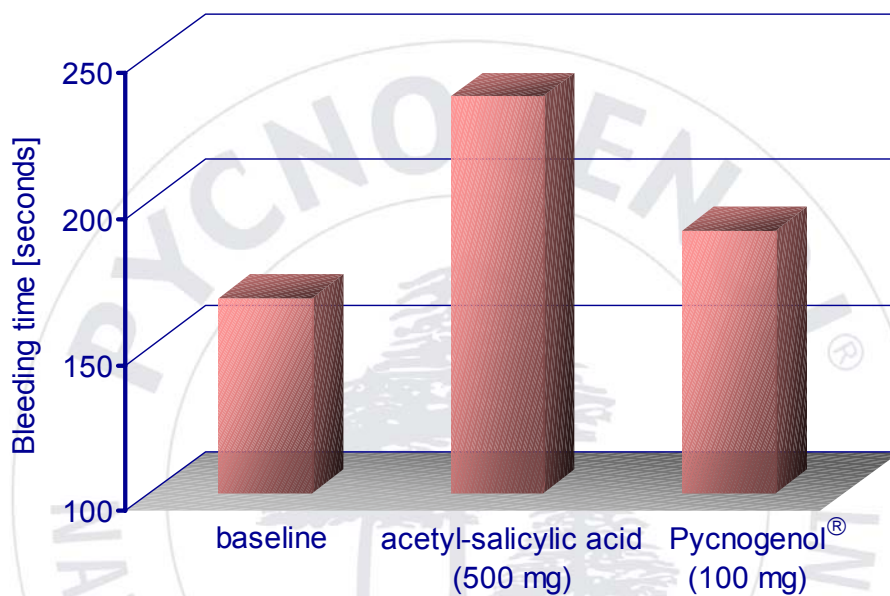


Figure 2: Bleeding time was measured with a stop watch after initiation by small incision of the ear lobe with a lancet. Mean values of 19 subjects are presented without supplementation, and acetyl-salicylic acid and Pycnogenol®, respectively [Pütter et al, 1999].

### **Pycnogenol® helps against swollen legs and feet**

Sitting for prolonged periods of time causes lower legs and feet to swell. Lack of movement inhibits back-flow of blood through veins, causing accumulation of blood in lower extremities. Furthermore, gravity force lets liquid seep out of fragile capillaries into the tissue.

Pycnogenol® can help to prevent the swellings as it decreases the permeability of blood vessel walls. In fact, the ability of Pycnogenol® to stabilise fragile capillaries is the rationale for using Pycnogenol® to overcome venous insufficiency. This has been demonstrated in more than 15 clinical studies with in total more than 500 people [Gulati, 1999].

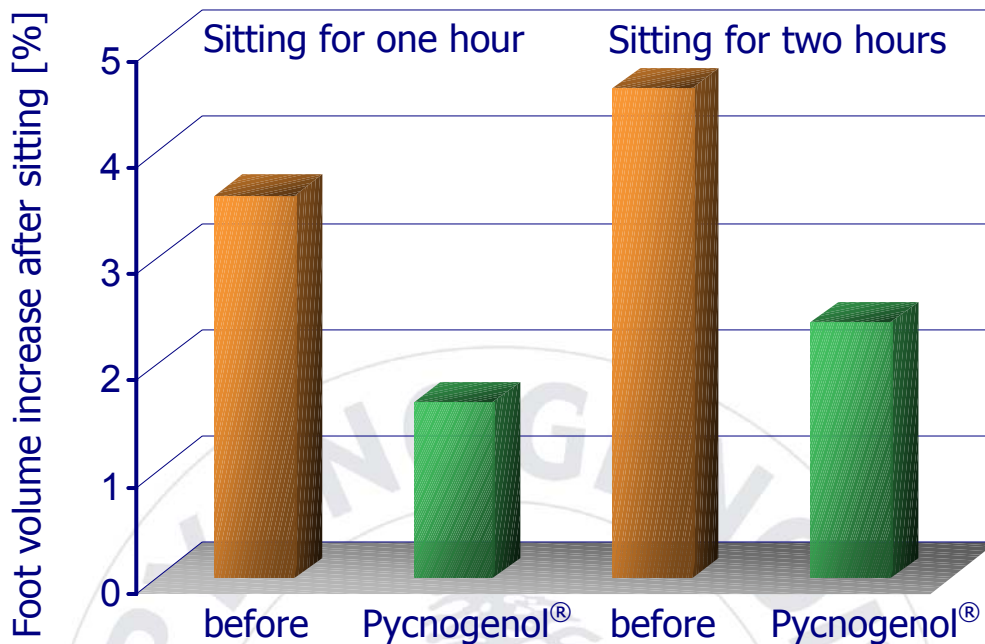


Figure 3: The increase of foot volume of individuals with venous insufficiency was measured by water displacement after changing from a lying to a sitting position. Subjects had to remain in bed for 2 hours and then sat for 1 hour (left two bars), at another occasion for two hours (right two bars), respectively. The foot volume increase is expressed relative (in percent) to the corresponding volume in lying position. After supplementation with 360 mg Pycnogenol® per day (6 days) (green bars) the foot volume increase was statistical significantly lower than without supplementation (orange).

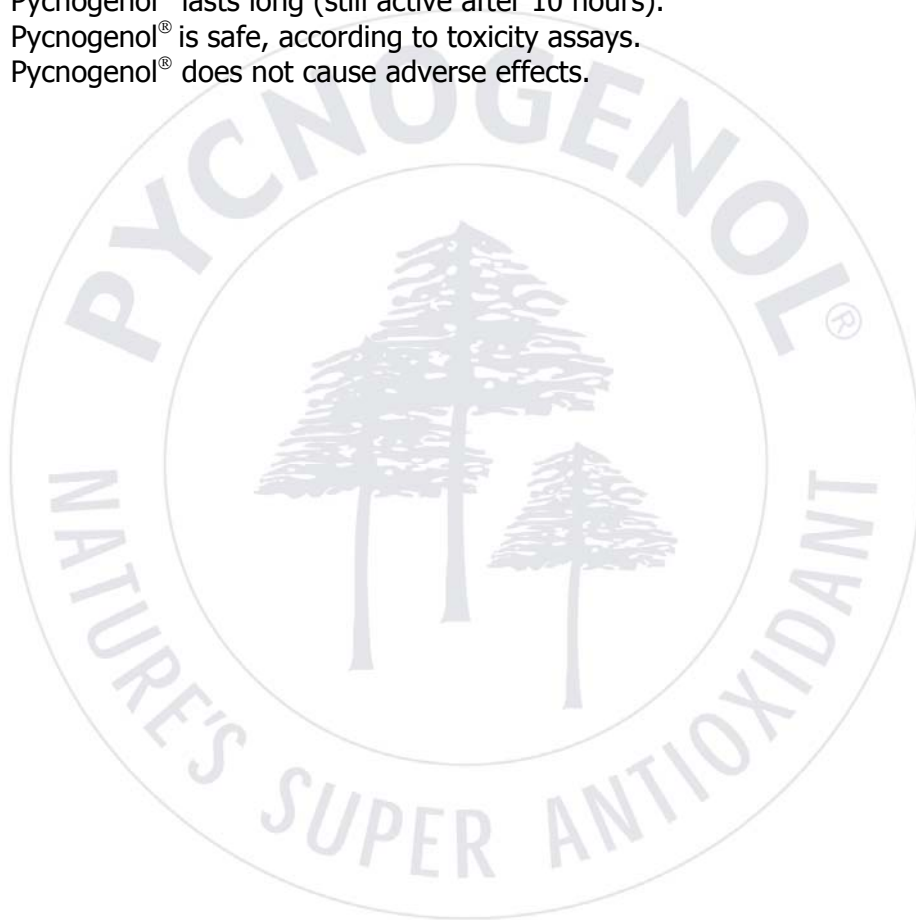
In one of the clinical studies a statistical significant reduction of swelling was found in 30 subjects supplemented with Pycnogenol®. This study also showed that blood capillaries were less permeable to fluid outflow and were more resistant to pressure after treatment with Pycnogenol® [Petrassi et al., 2000].

Another clinical study was carried out in which the increase of volume of feet was measured when a sedentary position was taken, after having remained in bed for 2 hours. As expected the foot volume increased considerably after sitting for one or two hours. However, when subjects had been supplemented with Pycnogenol® (360 mg per day for 6 days), the foot volume increase during sitting was statistical significantly lower than before (figure 3).

These studies point to the possibility of preventing feet from getting swollen during long haul flight can by taking Pycnogenol® prior to take-off. It might be considered to take Pycnogenol® already a couple of days in advance to the journey for best effects.

**Rationale for using Pycnogenol® for "economy class syndrome"**

Pycnogenol® reduces the activity of platelets in the blood.  
Pycnogenol® prevents thrombotic events and helps prevent pulmonary embolism.  
Pycnogenol® reduces swellings of the lower legs and feet.  
Pycnogenol® supports a better circulation  
Pycnogenol® acts quickly (2 hours prior to take-off).  
Pycnogenol® lasts long (still active after 10 hours).  
Pycnogenol® is safe, according to toxicity assays.  
Pycnogenol® does not cause adverse effects.



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

Pycnogenol® has passed stringent international safety requirements. Extensive research on its safety has demonstrated that Pycnogenol® has a very low acute toxicity. It has a very low chronic toxicity with an NOAEL of 150 mg / kg body weight. Pycnogenol® is non-mutagenic and non-teratogenic.

Pycnogenol® has been tested in more than 2000 human subjects/patients, 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 active food ingredient. Pycnogenol® is used as a food supplement in many countries of the world including the USA.

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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 2(2/3): 73-77
<b>Ref. 066</b>	Arcangeli P (2000) Pycnogenol® in chronic venous insufficiency. Fitoterapia 71: 236-244
<b>Not in bibliography</b>	Bendz B, Rostrup M, Sevre K, Andersen TO, Sandset PM (2000) Association between acute hypobaric hypoxia and activation of coagulation in human beings. The Lancet 356: 1657-1658
<b>Not in bibliography</b>	Eklof B, Kistner RL, Masuda EM, Sonntag BV, Wong HP (1996) Venous thromboembolism in association with prolonged air travel. Dermatol Surg 22: 637-641
<b>Not in bibliography</b>	Ferrari E, Chevallier T, Chapelier A, Baudouy M (1999). Travel as a risk factor for venous thromboembolic disease. Chest 115: 440-444
<b>Ref. 041</b>	Gulati OP (1999) Pycnogenol® in venous disorders: A review. Eur Bull Drug Res 7(2): 8-13
<b>Ref. 067</b>	Petrassi C, Mastromarino A, Spartera C (2000). Pycnogenol® in chronic venous insufficiency. Phytomedicine 7(5): 383-388
<b>Ref. 036</b>	Pütter M, Grotemeyer KHM, Würthwein G, Atagi-Niknam M, Watson RR, Hosseini S, Rohdewald P (1999) Inhibition of smoking-induced platelet aggregation by Aspirin and Pycnogenol®. Thromb Res 95: 155-161
<b>Ref. 039</b>	Watson RR (1999) Reduction of cardiovascular disease risk factors by french maritime pine bark extract. Cardiovasc Rev Rep 20: 326-329
<b>Not in bibliography</b>	Wright HP, Osborn SB (1952) Effect of posture on venous velocity measured with <sup>24</sup> NaCl. Br Heart J 14: 325-330.

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