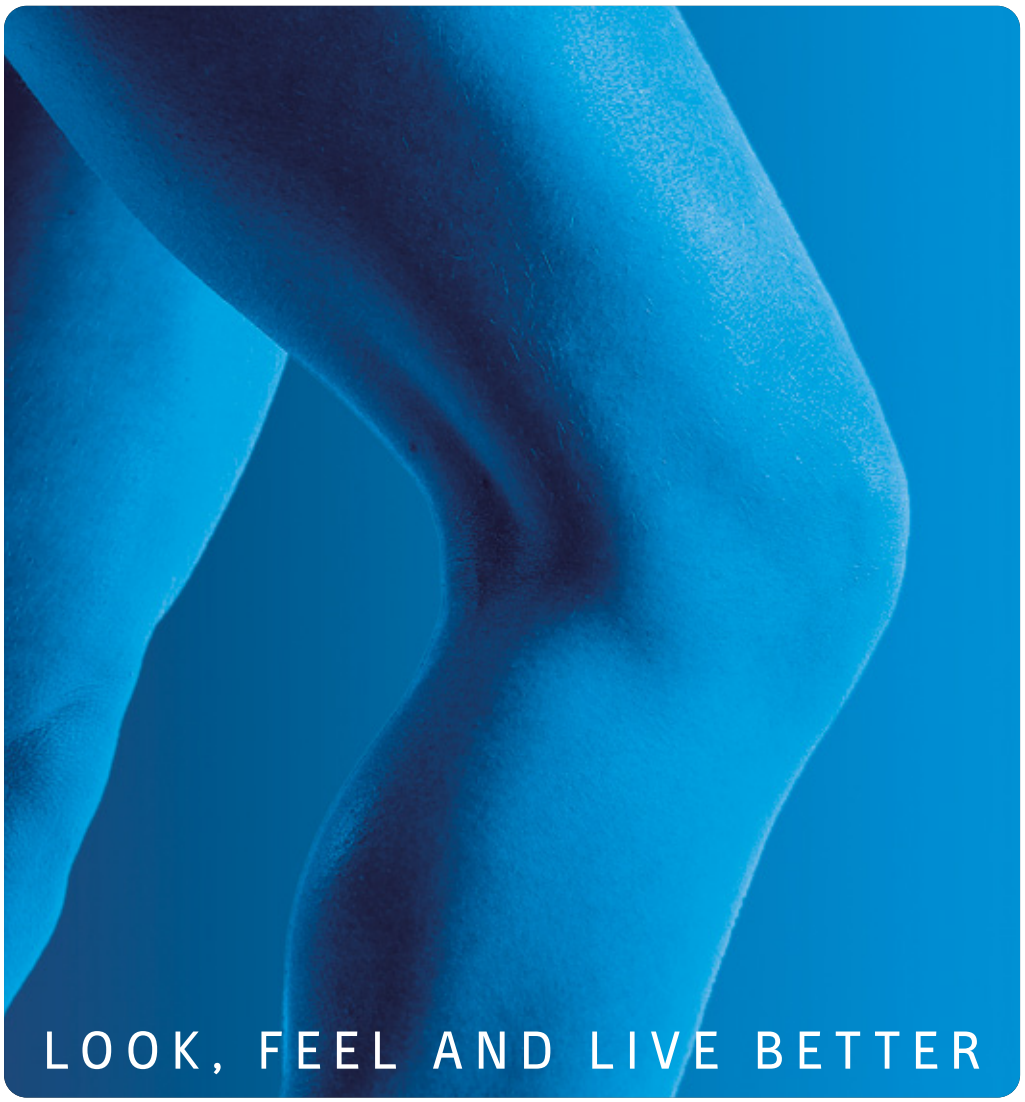
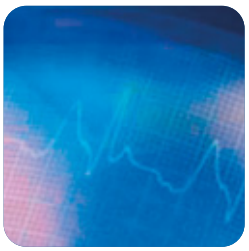
PYCNOGENOL®

Joint Health



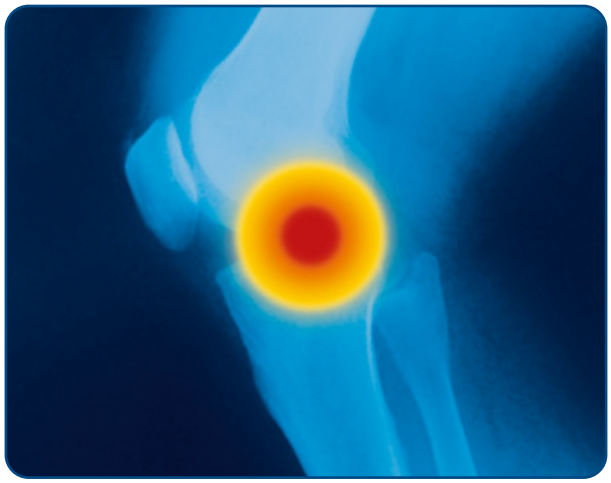


HORPHAG

Pycnogenol® for Joint Health

Our joints are subject to wear and tear and with increasing age the lining of joints, the cushioning cartilage, gradually degenerates. When cartilage has reached significant abrasion articular tissue will be affected and tissue trauma initiates a local inflammation. The consequence is a reduced flexibility of joints and predominantly pain. Inflammatory cells accelerate degeneration of joints by secreting reactive oxygen species ("oxidative burst"), pro-inflammatory cytokines and degenerative enzymes matrix metalloproteinases (MMPs). This process is paralleled by increasing pain which, left untreated, may reach excruciating levels.

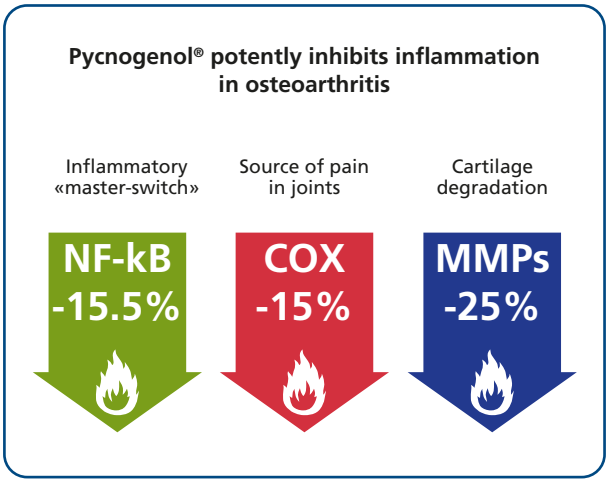
A majority of people over the age of 65 years show signs of osteoarthritis. Essentially all joints may be affected, but the most commonly affected are hips, knees, fingers and the spine. There are specific risk factors for developing osteoarthritis, such as obesity as it increases mechanical destruction of joints. According to statistics women are more frequently affected than men. It is now understood that mechanical rupture triggers inflammatory mechanisms which, in concert with repetitive injury to joints, causes a progressive degradation of cartilage.



Osteoarthritis is the leading medical condition for which people use alternative therapies. The primary goal is the relief from joint pain and stiffness and with time the restoration of mobility.

Pycnogenol® potently inhibits inflammation in arthritis

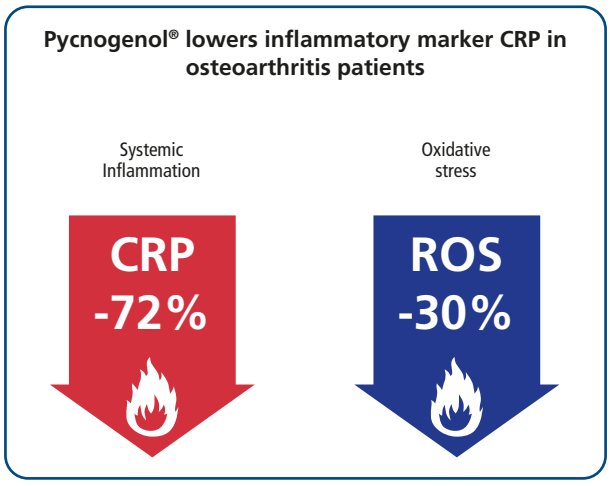
The pharmacological activities of Pycnogenol® in humans allow to address several pathologic processes of osteoarthritis simultaneously. Consumption of Pycnogenol® was shown to inhibit the activation of the pro-inflammatory "master switch" NF-kB by 15.8% [Grimm et al., 2006]. The activated NF-kB protein commands the mobilization of essentially all proinflammatory molecules which play a destructive role in arthritis. As a consequence of NF-kB inhibition immune cells of Pycnogenol® consumers generate less MMP enzymes which are responsible for degenerating cartilage collagen in osteoarthritis [Grimm et al., 2006]. Pycnogenol® consumption was found to naturally inhibit COX-enzymes in humans, which are predominantly responsible for joint pain [Schäfer et al., 2006].



Experiments with leukocytes from blood of human Pycnogenol® consumers revealed further anti-inflammatory mechanisms. Pycnogenol® significantly inhibited the synthesis of COX-2 enzyme as well as 5-LOX and FLAP enzymes [Canali et al., 2008]. Particularly the gene expression of COX-2 is controlled by NF-kB and after Pycnogenol® consumption for 5 days the COX-2 production was decreased by 78%. The gene expression of 5-LOX is inhibited by 75.5% in leukocytes after 5 days of Pycnogenol® consumption. The mediators arising from the cyclooxygenase (COX) and lipoxygenase (LOX) cascade modulate or mediate many aspects of inflammation.

Pycnogenol® lowers inflammatory marker CRP in osteoarthritis patients

Pycnogenol® was demonstrated in a study with 55 osteoarthritis patients to significantly lower the inflammatory marker C-reative protein (CRP) by 72%. Moreover, this study found a significant reduction of reactive oxygen species in arthritis patients by 30% [Belcaro et al., 2008]. This finding proves that the anti-inflammatory activity of Pycnogenol® is effective in arthrtis patients.



Pycnogenol® promotes new synthesis of hyaluronic acid within the body

Hyaluronic acid is a major constituent of the synovial fluid (http://en.wikipedia.org/wiki/Synovial_fluid) and was found to increase its viscosity playing the role in joint lubrification.

Hyaluronic acid is also an important component of articular cartilage, the shock absorber of the joint. It contributes to the cartilage resistance to compression. A clinical study run in 20 healthy volunteers demonstrated that Pycnogenol® intake for 4 weeks increased gene expression of hyaluronic acid synthase an enzyme critically involved in the synthesis of hyaluronic acid by 44%. In addition, the study revealed a noticeable increase in gene expression involved in collagen de novo synthesis [Marini et al. 2012]. This explains how Pycnogenol® contributes to restoring health in the damaged joint.

Three clinical trials with Pycnogenol® for osteoarthritis

To date the improvement of osteoarthritis symptoms was validated in three double-blind, placebo-controlled studies. All three studies utilized the well established WOMAC score for evaluation of joint pain, joint stiffness and function for primary osteoarthritis (grade I or II) of the knee.

First pilot trial with Pycnogenol® for osteoarthritis

Pycnogenol® was shown in a first clinical pilot trial to improve pain and symptoms in osteoarthritis at the University of Arizona Tucson [Farid et al., 2007]. In this trial 37 patients received Pycnogenol® or placebo in addition to their standard NSAID of selective COX-2 inhibitor medication over a period of three months. With Pycnogenol® the pain gradually decreased from one month to another reaching a significant change to placebo after two months. After three months a significant reduction of 43%, 35%, and 52% in self-reported pain, stiffness and physical function, respectively, were reported in the Pycnogenol® group whereas the placebo group showed no significant changes. Subjects required significantly less NSAID or selective COX-2 inhibitors when taking Pycnogenol® and the number of days during which they required

analgesics decreased as well. In contrast, the placebo group required increased pain medication during the 3 months trial.

Second clinical trial with Pycnogenol® in 100 osteoarthritis patients

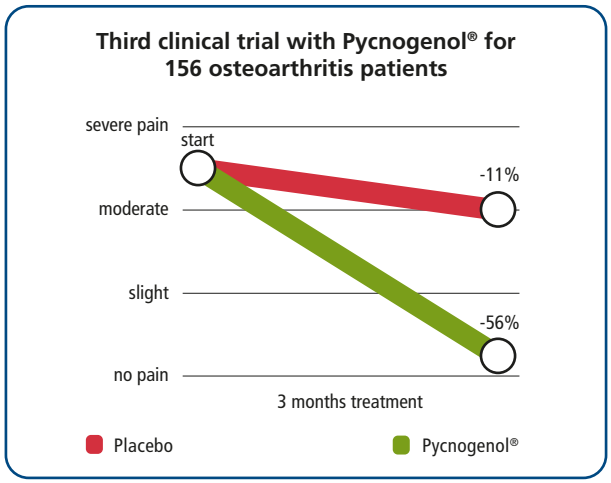
A larger study was carried out in Europe with 100 patients [Cisar et al., 2008]. The results of this study are in accordance with the previous study. Again the pain is gradually decreasing during the course of three months treatment with Pycnogenol®. An improvement is found after the first month and a further improvement is seen after 2 months, were values are significantly different to the placebo group. This study had a follow-up investigation period two weeks after discontinuation of treatment. Interestingly, no sudden relapse of pain sensation and symptoms occurred. This study again showed that patients required significantly less analgesic medication while supplementing with Pycnogenol®, whereas this was not the case with the placebo-treated control group.

Third clinical trial with Pycnogenol® for 156 osteoarthritis patients

A third clinical trial in Italy investigated Pycnogenol® for treatment of osteoarthritis in 156 patients. After three months treatment with Pycnogenol® the pain score decreased from average 17.3 (maximum possible score of 20 representing severe pain) to 7.7. In the placebo-treated control group the pain value decreased insignificantly from mean 17.1 to 15.2. The stiffness score decreased from 6.6 (on a scale 0 to 8) to 3.1 and joint physical function decreased from average 55.3 (on a scale 0 to 68) to 23.8. The control had no change of joint stiffness and only a marginal improvement of physical function. The patient's concomitant medication with NSAIDs dropped by 58% during treatment with Pycnogenol®, whereas it decreased in the control group only by 1%. This study found a significant decrease of gastrointestinal complications in the Pycnogenol® group, attributed to the lowered NSAID intake.

In this study the negative impact of the disease for involvement in social functions including emotional aspects was investigated. This questionnaire comprises the ability to interact with family and friends, participate in community events and church attendance. Furthermore, the emotional impact including frustration, irritability, loneliness and similar aspects was investigated. The global score of these parameters decreased from baseline average value 31.4 to 11.5 after three months treatment with Pycnogenol®.

This study evaluated the mobility of patients under controlled condition on a treadmill. The distance patients could walk increased from a baseline average 68 m to 198 m after three months treatment with Pycnogenol®, whereas the control group only improved from 65 m to 88 m.



Overview of three clinical trials demonstrating efficacy of Pycnogenol® for arthritis

		Arthritis symptom relief after 3 months Pycnogenol® relative to baseline (* after 2 months)		
Study	Number of patients	Pain	Joint stiffness	Physical function
Farid et al.	37	- 43 %	- 35 %	+ 52 %
Cisar et al.	100	- 40 %	- 40 %*	+ 22 %*
Belcaro et al.	156	- 55 %	- 53 %	+ 56 %

Clinical research suggests Pycnogenol® provides significant benefits for individuals suffering from arthritis:

- Natural, yet very effective lowering of joint pain
- Less pain medication required for joint pain
- Improvement of joint stiffness
- Restoration of joint physical function
- Improvement of mobility

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