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# Effect of Pine Bark Extract (Pycnogenol®) on Symptoms of Knee Osteoarthritis

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**Objective.** The safe and efficacious use of Pycnogenol® (French maritime pine bark extract) in other inflammatory diseases prompted this study of its antiinflammatory effects in patients with osteoarthritis (OA).

The aim of the study was to evaluate whether Pycnogenol® reduces the symptoms of OA in a double-blind, placebo-controlled, randomly allocated trial with patients suffering from knee osteoarthritis stages I and II.

**Methods.** 100 patients were treated for 3 months either by 150 mg Pycnogenol® per day at meals or by placebo. Patients had to report any change of use of previously prescribed antiinflammatory medication during the study period. Patients filled the Western Ontario and Mc Masters University (WOMAC) questionnaire for osteoarthritis every 2 weeks and evaluated weekly pain symptoms using a visual analogue scale for pain intensity.

**Results.** Following treatment with Pycnogenol® patients reported an improvement of WOMAC index ( $p < 0.05$ ), and a significant alleviation of pain by visual analogue scale ( $p < 0.04$ ), the placebo had no effect. The use of analgesics diminished in the verum group but increased under the placebo. Treatment with Pycnogenol® was well tolerated.

**Conclusion.** Results show that Pycnogenol® in patients with mild to moderate OA improves symptoms and is able to spare NSAIDs. Copyright © 2008 John Wiley & Sons, Ltd.

**Keywords:** osteoarthritis; Pycnogenol®; pine bark extract; WOMAC.

## INTRODUCTION

Osteoarthritis (OA) is a chronic, progressive disease that particularly affects weight-bearing joints such as hips and knees. The risk increases with aging. The severity of OA varies from person to person, but the consonant clinical signs include pain, reduced range of motion, inflammation and deformity (Malemud *et al.*, 2003). The entire joint is affected by a complex combination of degradative and reparative processes, which alter the anatomy and function of articular cartilage, subchondral bone and other joint tissues. Symptoms of local inflammation and synovitis are present in many patients with OA and are also seen in animal models of OA (Goldring, 1999). Of the joints affected, knee OA in particular is a major cause of morbidity, often resulting in knee replacement (Dixon *et al.*, 2004; Melzer *et al.*, 2003). The costs associated with OA are high – in the USA alone in 1991, the annual cost of knee re-

placements was estimated to be more than one billion dollars (Quam *et al.*, 1991).

At the molecular level, OA is characterized by an imbalance between anabolic (i.e. extracellular matrix biosynthesis) and catabolic (i.e. extracellular matrix degradation) pathways in which articular cartilage is the principal site of tissue injury responses (Malemud *et al.*, 2003). Interleukin-1 (IL-1)-induced inflammatory response in arthritic joints include the enhanced expression and activity of matrix metalloproteinases (MMPs). Their matrix degrading activity contribute to the irreversible loss of cartilage and may also be associated with sustained chronic inflammation (Ahmed *et al.*, 2004).

Current treatment modalities for OA are mostly symptomatic and include a wide range of analgesics (e.g. nonsteroidal antiinflammatory drugs (NSAIDs) and specific cyclooxygenase-2 (COX-2) inhibitors. The major side effects of NSAIDs are their propensity to cause stomach ulcers, GI bleeding and perforations. Although a new class of NSAIDs – the specific inhibitors of COX-2 – was developed, these drugs have similar efficacy to the general NSAIDs, but fewer gastrointestinal troubles. However, some of these COX-2 inhibitors were recently withdrawn from the market or ordered by the United States Food and Drug Administration (FDA) to have a black box warning on the label because of concerns that their long-term use may increase the risk

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of stroke and heart attack (Ahmed *et al.*, 2005). The group of drugs known as SYSADOA (Symptomatic Slow Acting Drugs of Osteoarthritis), or chondroprotectives, act differently. The onset of effect is slow, but can remain for a longer period. They can be applied locally – intraarticularly (derivates of hyaluronic acid), or systemically (glucosamine sulfate, chondroitine sulfate). It is believed that SYSADOA bind to chondrocyte receptors and influence the cell metabolism, stimulating chondrocytes to synthesize matrix elements and inhibit MMPs.

Pycnogenol is a special standardized extract from the bark of the French maritime pine (*Pinus pinaster*) (Rohdewald, 2005). This extract represents a concentrate of polyphenols, composed of several phenolic acids, catechin, taxifolin and procyanidins with diverse biological and clinical effects (Rohdewald, 2005). In the context of the treatment of OA, the interaction of Pycnogenol with MMPs is of great interest. *In vitro*, Pycnogenol inhibits selectively MMPs (Grimm *et al.*, 2004). After intake of Pycnogenol, the plasma from volunteers inhibited the release of MMP-9 from activated macrophages (Grimm *et al.*, 2006) thus demonstrating the bioavailability of the inhibitor of MMP-9. These findings led to the assumption that Pycnogenol could be helpful in OA by blocking the deleterious actions of MMPs on cartilage.

The transcription factor NF $\kappa$ B is a key element in inflammation as its activation starts the synthesis of cytokines and adhesion factors. It could be shown *in vitro* that Pycnogenol inhibits the activation of NF $\kappa$ B (Peng *et al.*, 2000; Saliou *et al.*, 2001; Cho *et al.*, 2001). Recently, it could be proven that after intake of Pycnogenol plasma contains enough activity to inhibit significantly the activation of NF $\kappa$ B in inflammatory cells (Grimm *et al.*, 2004). This inhibition, down-regulating the subsequent steps of inflammation, explains the antiinflammatory activity of Pycnogenol which had been observed in many studies (Rohdewald, 2005). As cyclooxygenases are the enzymes driving the production of pain-producing prostaglandins, it is important for the treatment of OA that Pycnogenol inhibits unspecifically COX1 and COX2 (Schäfer *et al.*, 2006). Also this effect was found *ex vivo* in plasma of human volunteers after supplementation with Pycnogenol. The sum of these antiinflammatory effects encouraged us to initiate a controlled clinical trial to investigate the effect of Pycnogenol on OA.

## MATERIALS AND METHODS

**Study design and selection of patients.** This study was conducted as a 3-month prospective, double-blind, placebo-controlled, single centre study at 2nd Department of Orthopaedics of the Comenius University School of Medicine, University Hospital Ružinov, Bratislava, Slovakia.

One hundred outpatients with mild OA stages and corresponding clinical symptoms were enrolled into the study.

Inclusion criteria were mild primary OA (stage I or II, according to Kellgren-Lawrence in standard AP view radiographs) in at least one target knee, mild to moderate pain in the target knee for at least 3 months pre-

ceding the study, and/or morning knee stiffness and/or knee crepitus and age of more than 25 years. At baseline, female subjects of childbearing potential must have confirmed that they were not pregnant at the time of enrolment and that they did not plan to get pregnant for at least 1 year after the end of the trial. Postmenopausal female subjects must have been amenorrhoeic for at least 1 year, in this case the confirmation was not required.

Exclusion criteria were participation in another study, less than 30 days before the start of this study, moderate or severe stage OA (stage III and IV according to Kellgren-Lawrence), rheumatoid arthritis (RA) or other chronic inflammatory process in the target joint, any other secondary OA, arthroscopic surgery or other major surgery of the target knee, major trauma of the target joint, intra-articular injection of corticosteroids or SYSADOA drugs in the target joint in the past 3 months preceding study entry. Acute infection of the target joint in the last 6 months or if subject has started any form of physiotherapy in the 3 weeks preceding study entry. Excluded were subjects with a significant psychiatric disorder (including depression), or subjects receiving antipsychotic medication. Breastfeeding female subjects were also excluded.

Subjects were withdrawn in the case of serious adverse event (SAE), if the subjects revoked the consent or if the investigator considered that for safety reasons it was in the best interest of the subject to be withdrawn.

The study was approved by Local Ethical Committee of the University Hospital in Bratislava.

**Main outcome criteria.** The main outcome criteria were: (1) reduction of symptoms of OA using WOMAC scores; (2) reduction of pain using visual analogue scale (VAS). The secondary outcome criterion was a decrease of the use of analgesics.

**Treatment assignment.** The subjects were randomly allocated to Pycnogenol<sup>®</sup>, product of Horphag Research Ltd, UK, or the placebo group by the principal investigator responsible for the biochemical, but not for the clinical part.

**Sample size.** The sample size was estimated assuming the power of 90% (beta of 10%), the type-one error (alpha) of 5% and the number of controls per subject of 1. The recommended number of patients to study was calculated as 35 per group. To compensate *a priori* for dropouts, 50 patients were included in each arm.

**Medication.** Patients were allowed to continue with their medication with NSAIDs or analgesics prescribed before the start of the study. Patients were allowed to change medication on demand but were instructed to report at each visit whether dosage or frequency of intake was lowered or increased.

The patients received 150 mg Pycnogenol per day, taken as 50 mg t.i.d. with the meals, or identically looking coated placebo pills, produced by the same manufacturer (Manhattan Drug Co, N.Y., USA)

**Study design.** Patients were examined at enrolment to fulfil inclusion criteria. After signing informed consent, patients received medication for 4 weeks. The WOMAC questionnaire, translated into Slovakian language, and

the visual analogue scale (VAS) were given to the patients every 2 weeks. VAS was used to rate pain by the patient on a scale of 0, no pain, to 100, very severe pain at weekly intervals. Patients received new medication every month.

Patients were investigated at the start, at 3 months and 4 weeks after finishing treatment. Patients visited the center at the start and each 4 weeks.

The WOMAC questionnaire (Bellamy, 1995) (5-point Likert format in Slovak version) for pain, stiffness and daily activities was filled in by the patients every 2 weeks during the whole study (14 weeks).

The VAS (visual analogue scale) for pain was filled in by the patients each week during the whole study (14 weeks).

The patients were asked whether analgesics consumption had changed at each visit.

**Determination of biochemical parameters.** Blood samples for biochemical analyses were taken from fasting venous blood in the morning at the start, after 3 months of treatment and after the washout period into commercial tubes without anticoagulant for determination of biochemical parameters. Basic biochemical parameters (glucose, uric acid, lipid profile, total cholesterol, HDL-, LDL-cholesterol, TAG, hSCRp, gamma-glutamyl transferase, alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase) were analysed in the serum by standard biochemical procedures using the Hitachi 911 automatic analyser and kits, Roche, Switzerland.

**Unwanted effects.** Patients were asked every 2 weeks to report any unwanted or unusual effects.

**Statistical evaluation.** The copies of all data obtained from questionnaires and outputs from computerized analysers were checked twice before their evaluation and statistical analysis. The effect of Pycnogenol or placebo was evaluated with two-way randomized block analysis of variance. For multiple comparisons of treatment periods with the baseline value Dunnett's test was used. For the statistical evaluation of the differ-

ences between the Pycnogenol and placebo group, a non-parametric Mann-Whitney test was used. For statistical analysis statistical programmes StatsDirect 2.3.7 (StatsDirect Sales, Sale, Cheshire M33 3UY, UK) and Statistica 6.0 (StatSoft, Inc. 2000) were employed.

## RESULTS

### Patient's characteristics

The demographic data of patients, given in Table 1, did not differ significantly in age, male to female ratio and BMI. From 100 patients included in the study, 90 patients completed the 12 weeks treatment period, 81 completed after 14 weeks the washout period. Ten patients dropped out before the end of the treatment period, nine more did not finish the wash-out period. The group of 19 dropout patients consisted of 13 from the placebo group and six from the Pycnogenol group. Data of all patients were evaluated in the intention-to-treat analysis.

### WOMAC scores

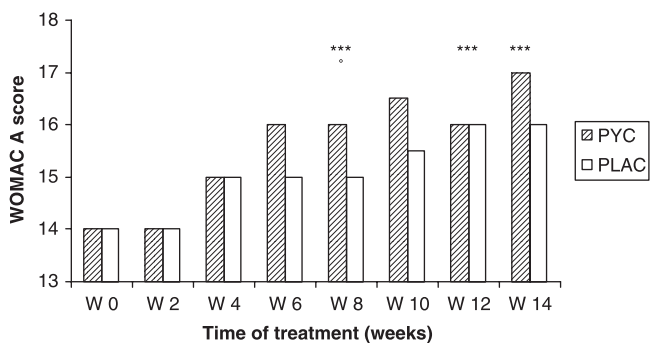
The WOMAC-A score, summarizing the scores for pain, improved significantly in Pycnogenol group ( $p = 0.0004$ ) with time (Fig. 1). The time dependence of pain reduction for placebo showed only a trend ( $p = 0.26$ ). The difference to baseline was statistically significant for the Pycnogenol group after weeks 8, 12 and 14 ( $p < 0.001$ ). The difference between the Pycnogenol and placebo groups was near to significance level at week 8 of the investigation ( $p = 0.08$ ).

Stiffness (WOMAC B score) improved in the Pycnogenol group versus baseline after 8, 12 and 14 weeks significantly ( $p = 0.01$ ) (Fig. 2). Statistically significant differences between the Pycnogenol and placebo groups were observed at weeks 8 and 12 ( $p < 0.05$ ).

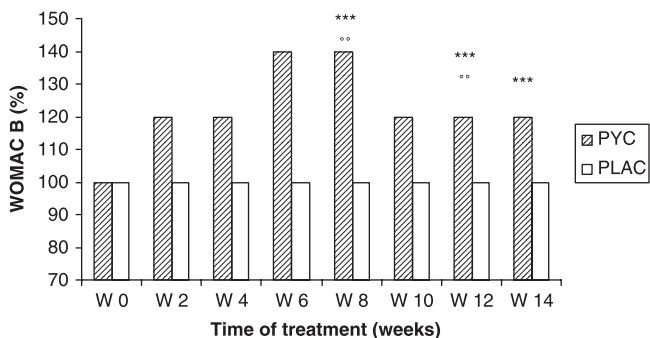
The WOMAC score, characterizing the ability to perform daily activities, improved significantly versus

**Table 1.** Basic characteristic of patients

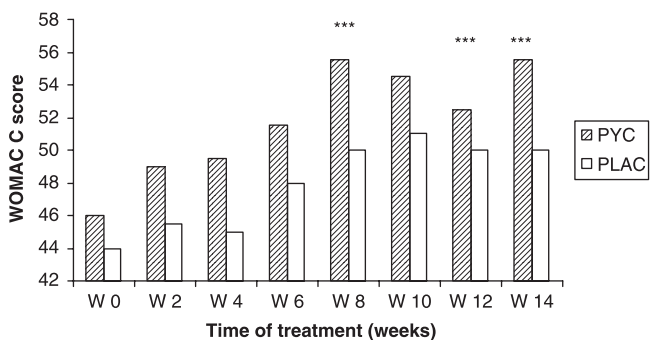
Parameter	Pycnogenol group	Placebo group
Included patients	50	50
Patients finishing treatment period	48	42
Patients finishing the whole study	44	37
Age (average)	54 (25–65)	54 (30–65)
M/F number (M/F ratio)	14/36 (0,39/1)	18/32 (0,56/1)
BMI (average)	27,29 (16,9–35,4)	27,17 (20,7–37,2)
Drop-outs	6	13
<i>Treatment period</i>		
Together	2	8
No compliance/No effect	0	4
Increased pain	0	3
Chest pain	1	0
Foetor from mouth	1	0
Gastric pain	0	1
<i>Wash-out period</i>		
Together	4	5
No compliance/No effect	4	4
Illness	0	1



**Figure 1.** Reduction of pain according to WOMAC A score for pain (median). \*\*\* Statistical significance of differences Pycnogenol versus start after 8, 12 and 14 weeks:  $p = 0.001$ . ° Statistical significance of difference Pycnogenol versus placebo after week 8:  $p < 0.08$ .



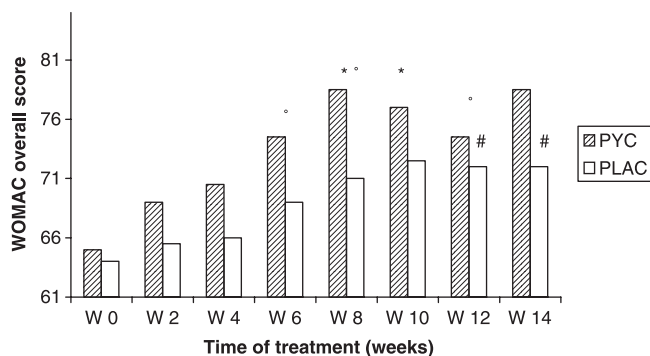
**Figure 2.** Reduction of stiffness according to WOMAC B score (median). \*\*\* Statistical significance of differences Pycnogenol versus start after 8, 12 and 14 weeks:  $p < 0.01$ . °° Statistical significance of difference Pycnogenol versus placebo after 8 and 12 weeks:  $p < 0.05$ .



**Figure 3.** Influence of treatment on daily activities according to WOMAC C scores (median). \*\*\* Statistical significance of differences Pycnogenol versus start after 8, 12 and 14 weeks:  $p = 0.01$ .

baseline at weeks 8, 12 and 14 ( $p < 0.01$ ), the increase was not significant under placebo (Fig. 3). However, the difference between the Pycnogenol and placebo groups was not significant.

The overall WOMAC score, summarizing pain, stiffness and daily activities in one score, improved significantly during the time of the treatment in the Pycnogenol group (Fig. 4). Statistical significant differences between Pycnogenol and placebo ( $p < 0.05$ ) were observed at weeks 6, 8 and 12 of investigation. The difference to baseline was significantly ( $p < 0.05$ ) different after week 8. Overall the WOMAC score of the placebo group



**Figure 4.** Reduction of symptoms of osteoarthritis. Medians of overall WOMAC scores. \* Statistical significance of differences Pycnogenol versus start after 8 weeks:  $p = 0.032$ , 10 weeks:  $p = 0.06$ . ° Statistical significance of differences Pycnogenol versus placebo after 6 weeks:  $p = 0.04$ , 8 weeks:  $p = 0.03$ , 12 weeks:  $p = 0.03$ . # Statistical significance of difference of placebo versus start after 12 weeks:  $p = 0.02$ , 14 weeks:  $p = 0.01$ .

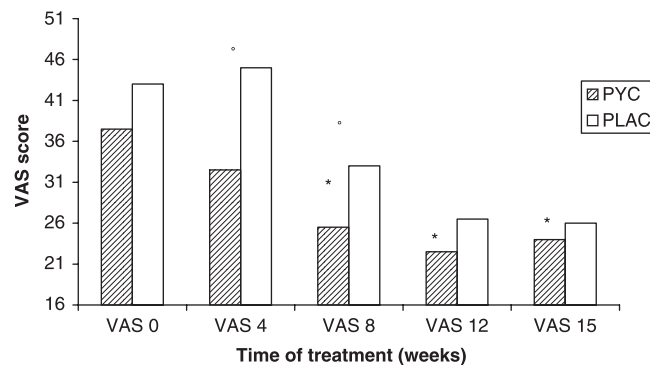
was significantly different from start ( $p < 0.05$ ) after weeks 12 and 14.

### Pain scores by VAS

At the start, the pain caused by OA scored by VAS was somewhat higher in the placebo group compared with the Pycnogenol group (Fig. 5), however, the difference between groups was not significant. Following treatment for 4 weeks, the verum group reported less pain relative to the placebo, pain diminished successively over the study period until month 3. The VAS scores increased slightly, but not significantly after the washout period, but remained significantly lower compared with the start of treatment. The same trend, but not significant, was reported for the placebo group.

The correlation of pain attenuation with the time of treatment was statistically significant ( $p < 0.04$ ) for the Pycnogenol group, whereas this correlation was poor for placebo ( $p < 0.17$ ).

A marginal statistical significance for comparisons of the effect of Pycnogenol versus placebo was seen at weeks 4 ( $p = 0.08$ ) and 8 ( $p = 0.07$ ) of treatment (Fig. 5).



**Figure 5.** Alleviation of pain scored by the visual analogue scale (VAS), medians. \* Statistical significance of differences Pycnogenol versus start after 8 weeks:  $p = 0.054$ , 12 weeks:  $p = 0.058$ , 14 weeks:  $p = 0.032$ . ° Statistical significance of differences Pycnogenol versus placebo after 4 weeks:  $p = 0.08$ , 8 weeks:  $p = 0.07$ .



**Table 2. Analgesics consumption in Pycnogenol/placebo group during the time of the treatment**

	Pycnogenol group	Placebo group
Same level	62%	82%
Increased dosage	0%	10%
Decreased dosage	38%	8%

### Consumption of analgesics

Patients in the Pycnogenol group could reduce the intake of analgesics or NSAIDs to a higher percentage than patients under placebo (Table 2). In contrast, 10% of patients had to increase the dose of analgesics in the placebo group but no higher dose was needed in the Pycnogenol group.

### Data of clinical chemistry

Basic biochemical parameters (glucose, uric acid, parameters of lipid profile – total cholesterol, HDL-cholesterol, LDL-cholesterol, TAG, hCRP, gamma-glutamyl transferase, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase) were investigated in serum obtained from fasting venous blood. All average values of biochemical parameters were in the physiological range before the trial in both groups. None of the analysed biochemical parameters raised or decreased beyond the range of physiological values after 3 months of Pycnogenol or placebo administration. No statistically significant change of any biochemical parameter was observed.

### Adverse effects

No serious adverse effects (SAEs) were reported. In the Pycnogenol group, one patient with previous myocardial infarction left the study because of chest pain, another patient because of bad breath. In the placebo group, three patients left the study because of worsening of pain, one left because of gastric pain, one patient felt ill. Four patients from the Pycnogenol group and eight patients from placebo group were excluded because of non-compliance.

### Additional observations

Elevated blood pressure decreased in six patients in the Pycnogenol group and in two patients in the placebo group. Ten patients reported an improvement of mental condition (be longer awake, better learning, better memory) in the Pycnogenol group vs three in the placebo group, four noted an improvement of skin quality and three an improvement of hair quality (stronger hair, less loosening of hair). In the placebo group, blood pressure decreased in two patients and three patients reported an improvement of mental condition. In the Pycnogenol group, an ophthalmologist registered a decrease of intraocular pressure in one patient.

## DISCUSSION

The results demonstrate an onset of action of Pycnogenol following the first month of treatment, reaching borderline level of significance. WOMAC scores as well as VAS signalize the maximum effect after the second month of treatment. Thereafter values declined until the end of washout period, but remained at higher scores compared with the start.

The results cannot be evaluated without taking into consideration the concomitant medication with analgesics and NSAIDs in both groups. Patients consumed different types of drugs, brands and dosages of analgesics and NSAIDs at inclusion prescribed by practitioners. Therefore, only a qualitative evaluation of use of medication could be done. As consumption of analgesics diminished in the Pycnogenol group, Pycnogenol's effect had to compensate first of all for the lower dose of analgesics. The results demonstrate that Pycnogenol lowered pain and WOMAC scores to a greater extent compared with the placebo group, despite the fact that the mean intake of analgesics was increased under placebo during the study period. It is reasonable to assume that patients in the placebo group compensated for the lack of effect of placebo by taking more analgesics, especially after a longer period of treatment. The higher dropout rate in the placebo group due to a lack of pain relief demonstrates that the placebo effect was not sufficient to satisfy the needs of the patients. These findings point to a reasonable antiinflammatory action of Pycnogenol in patients with OA.

The basis for the observed positive effects in OA delivers the cascade of inhibitory actions by Pycnogenol on inflammation, starting from inhibition of free radicals to inhibition of transcription factors and proteases, ending with inhibition of cytokines, adhesion factors and of COX1 and COX2 (Rohdewald, 2005). After oral administration of Pycnogenol two major metabolites are formed *in vivo* (Grimm *et al.*, 2004). Both metabolites exhibit antioxidant activities and strong inhibitory effects towards the activity of proteases.

The treatment with Pycnogenol was well tolerated. The two drop-outs during treatment period, caused by bad breath or chest pain were not attributed to Pycnogenol treatment.

Unexpectedly, patients in the verum group reported spontaneously a number of positive side effects. The findings of reduced high blood pressure in hypertensive patients are in agreement with the antihypertensive effects of Pycnogenol in hypertensive patients (Hosseini *et al.*, 2001; Liu *et al.*, 2004). The lowering of blood pressure is caused by the beneficial effects of Pycnogenol on endothelial health. Pycnogenol stimulates e-NOS activity which leads to enhanced NO production, causing vasodilatation. Simultaneously, vasodilatation is stimulated by enhanced prostacyclin levels in plasma and lower levels of endothelin-1 and thromboxan, which act as vasoconstrictory agents (Rohdewald, 2005). Interestingly, Pycnogenol had no effect on blood pressure in clinical trials with normotensive persons, but normalized moderate hypertension.

Reports on the improvement of mental condition, skin and hair quality correspond to results obtained with climacteric women. Pycnogenol improved significantly

mental condition and appearance of skin in Taiwanese women in a double-blind, placebo-controlled study (Liao *et al.*, 2007).

## CONCLUSION

Pycnogenol offers an interesting alternative to treatment of early knee OA with NSAIDs or analgesics because of its low rate of unwanted effects and its efficacy. As a concomitant supplement, Pycnogenol may spare the use of NSAIDs, thus reducing unwanted effects.

## Acknowledgements

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PC, RJ, PR and ZD planned the study and prepared the manuscript. PC and RJ performed the clinical part of the study. IW performed the statistical analysis. JV assisted with the manuscript and recruited patients. ML assisted at the clinical part of the study. KS and JM treated blood samples before analyses and organized blood procedure. All authors read and approved the final manuscript.

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