PHYTOTHERAPY RESEARCH
Phytother. Res. **22**, 518–523 (2008)
Published online in Wiley InterScience
(www.interscience.wiley.com) **DOI**: 10.1002/ptr.2376

Treatment of Osteoarthritis with Pycnogenol®. The SVOS (San Valentino Osteo-arthrosis Study). Evaluation of Signs, Symptoms, Physical Performance and Vascular Aspects

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The aim of this double-blind, placebo-controlled study was to evaluate the efficacy of 100 mg Pycnogenol® daily (oral capsules) in a 3 month study in patients with osteoarthritis (OA). OA symptoms were evaluated by WOMAC scores, mobility by recording their walking performance (treadmill). Treatment (77 patients) and placebo group (79) were comparable for age, sex distribution, WOMAC scores, walking distances and use of antiinflammatory drugs. The global WOMAC score decreased by 56% ($p < 0.05$) in the treatment group versus 9.6% in the placebo group. Walking distance in the treadmill test was prolonged from 68 m at the start to 198 m after 3 months treatment ($p < 0.05$), under placebo, from 65 m to 88 m (NS). The use of drugs decreased by 58% in the treatment group ($p < 0.05$) versus 1% under placebo. Gastrointestinal complications decreased by 63% in the treatment group, but only 3% under placebo. Overall, treatment costs were reduced significantly compared with placebo. Foot edema was present in 76% of the patients of the treatment group at inclusion and in 79% of the controls. After 3 months edema decreased in 79% of Pycnogenol patients ($p < 0.05$) vs 1% in controls. In conclusion, Pycnogenol offers an option for reduction of treatment costs and side effects by sparing antiinflammatory drugs.

Keywords: osteoarthrosis; WOMAC; joints; pain; antiinflammatory agents; noninvasive investigations; muscular performance; edema; Pycnogenol®.

INTRODUCTION

Osteoarthritis (OA) of the main joints is a diffuse social problem altering the quality of life of millions of older inhabitants in the most industrialized countries and, at a younger age, of inhabitants of developing countries (where severe bone and joint abnormalities may be associated with nutritional and developmental problems). The increase in the average weight with age, the diffusion of sedentary habits, the decrease in regular exercise patterns cause a progressive decrease in physical fitness has contributed to aggravate the problems due to OA.

A multitude of treatment and management options are available to manage the symptoms of OA, particularly pain, and the disabilities related to this disease.

The quantitative evaluation of the effects of OA on the quality of life of patients and a standardized quantification of the effects of treatments has been an important problem, considering the widespread clinical signs associated with several levels of handicap and alterations in the quality of life.

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The WOMAC (Western Ontario and McMaster Universities) index is now generally used to assess patients with OA of the hip or knee – two of the joints causing the most frequent and severe motion handicaps – using 24 main parameters (Baron *et al.*, 2007). The WOMAC can be used to monitor the course of the disease and how OA affects the life of patients or to determine the efficacy of antirheumatic/antiinflammatory treatments.

As a combination between OA and arterial or venous vascular problems and concomitant metabolic syndrome is relatively frequent, so the vascular aspects should be also considered in the management of these subjects. Impaired motion causes some level of edema of the affected limbs (i.e. in patients with chronic venous insufficiency or in subjects treated with antihypertensive drugs). Stasis and low mobility cause a chronic increase in local, distal venous pressure, therefore transforming a mild level of venous disease into a severe, chronic venous hypertension, often causing ulcerations. These, in turn, may contribute to the signs and symptoms of OA, altering mobility and social life and causing further handicaps.

Therefore, vascular complications should be evaluated together with aspects specifically concerning OA (i.e. pain, mobility) to judge the quality of life of OA patients.

Four main components – all contributing to the clinical picture – may be considered in the treatment management of OA:

Received 16 August 2007
Revised 28 March 2007
Accepted 4 September 2007

1. specific, OA-related, signs/symptoms (described by the WOMAC score);
2. inflammation causing a progression in the disease;
3. alteration (and improvement by treatment) of fatigue resistance and muscular performance;
4. reversing and blocking the vascular problems associated with altered mobility (i.e. often leading to edema and sometimes even to venous and stasis ulcerations).

These four aspects can all be considered as targets of a treatment evaluation.

Theoretically, treatment with a compound specifically active on all these four aspects could be highly effective. Therefore, a study involving Pycnogenol® – as the main treatment – was planned to evaluate changes in these main clinical aspects of OA.

Pycnogenol® is the trademark of Horphag Research Ltd, UK for a standardized extract from the bark of the French maritime pine. The extract is a concentrate of plant polyphenols, predominantly procyanidins. This compound has antiinflammatory actions *in vitro* and *in vivo* and scavenges free radicals (Rohdewald, 2005; Devaraj *et al.*, 2002; Durackova *et al.*, 2003). In the context of treatment of OA, inhibition of matrix metalloproteases (MMPs) is of great interest. After the intake of Pycnogenol®, release of MMP9 from macrophages is inhibited (Cisar *et al.*, 2006), thus blocking the destructive activity of MMP on cartilage.

Pycnogenol inhibits *in vitro* the activation of NFκB, a key element of inflammation (Grimm *et al.*, 2006). Furthermore, plasma from volunteers inhibited significantly the activation of NFκB in inflammatory cells *ex vivo*, blocking subsequent steps of the inflammatory reactions (Grimm *et al.*, 2006). Cyclooxygenases initiate the production of pain-producing prostaglandins. Plasma from human volunteers inhibited cyclooxygenases I and II following intake of Pycnogenol® (Schäfer *et al.*, 2006). The sum of these antiinflammatory effects suggests that this compound may have a positive effect in reducing the symptoms of mild to moderate osteoarthritis. Furthermore, Pycnogenol® demonstrated in several clinical trials its activity against edema formation and chronic venous insufficiency (Rohdewald, 2005; Cesarone *et al.*, 2005, 2006a, 2006b, 2006c; Belcaro *et al.*, 2006). In a range of clinical trials, the unwanted effects of Pycnogenol were minimal, mainly mild gastrointestinal symptoms or dizziness, and transient in most cases (Cesarone *et al.*, 1999). In the USA Pycnogenol obtained the GRAS status (Generally Recognized As Safe).

The aim of this study was to evaluate the efficacy of 100 mg Pycnogenol (oral capsules) in a 3-month, double-blind, placebo-controlled study in patients with OA and disability due to pain of the major joints altering their quality of life. The mobility of these patients was also evaluated by recording their walking performance on a treadmill.

PATIENTS AND METHODS

A total of 156 patients with osteoarthritis grade I or II, confirmed by x-ray analysis were included in this study. Patients were recruited the San Valentino vascular screening project. Patients were informed about aim of the study and treatment procedure according to the declaration of Helsinki and gave written informed consent. The study was approved by the ethical committee of the University of Pescara. Patients were informed that they could leave the study any time without difficulty.

Inclusion criteria. Primary osteoarthritis grade I or II in one or both knees was diagnosed by x-ray investigation. There was mild to moderate pain not adequately controlled with antiinflammatory drugs. Subjects had to be able to perform the treadmill test and to understand all questions from the questionnaire.

Exclusion criteria. Cardiovascular disease requiring drug treatment, particularly coronary heart diseases, diabetes, overweight, severe metabolic disorders, surgery or arthroscopy 3 months before inclusion or radio- or chemotherapy. Pregnancy, breast feeding, planned conception.

Randomization. Patients were allocated to treatment groups using randomization by blocks. Block allocation sequences were created at random by using randomly generated numbers from a computer program. The randomization list covered twice the number of subjects planned to be recruited. Each patient enrolled in the study received the respective lowest randomization number available.

Estimation of size of treatment groups. A recent study with a comparable population of osteoarthritis patients showed a significant response to Pycnogenol treatment using a group size of 37 patients (Farid *et al.*, 2007).

Taking into consideration a drop-out rate of 10–20% for a treatment period of 3 months, an alfa of 0.05 and a beta of 0.20 (power of 80%) a number of about 80 patients in each group was calculated to obtain a significant difference from the placebo.

Evaluation of symptoms of osteoarthritis. To describe and rate the symptoms of osteoarthritis the questionnaire developed by the Western Ontario and McMaster Universities (Baron *et al.*, 2007) was applied. The questionnaire gives scores for the diverse symptoms of osteoarthritis (WOMAC scores) (Baron *et al.*, 2007).

The status of osteoarthritis was evaluated by the investigator together with the patient at the start of study and after 3 months of treatment.

Evaluation of physical performance. Patients were trained how to do the treadmill test in two tutorial tests. At the start and after the end of treatment, the patient's performance was evaluated by the treadmill test with a speed of 3 km/h and an inclination of 10%. The total distance which could be covered without pain was noted.

Vascular aspects. The presence of any vascular (arterial, venous of lymphatic) problem was carefully evaluated to exclude the influence of vascular disease on the treadmill performance (i.e. claudication) and on pain. Color-duplex, Doppler (at rest and after the treadmill test) excluded the presence of peripheral vascular disease. After a treadmill test, in the presence of peripheral arterial disease, the Doppler signal at the distal tibial arteries may disappear for a variable period of time or become fainter with a decrease in tibial pressures

DOI: 10.1002/ptr

measured by Doppler. In the case of a normal arterial system the distal pressure is comparable to the pre-test value or higher (Belcaro *et al.*, 1996; Belcaro and Nicolaides, 2001). Also venous diseases and the possible presence of venous obstruction were evaluated before the inclusion and at the end of the study (Belcaro *et al.*, 1996).

Edema evaluation. Edema was scored by the investigator using the following scores: 0, not visible; 1, edema only visible after long standing or in the evening; 2, edema visible during the day but relieved overnight; 3, edema visible during the day but only partially relieved overnight; 4, edema present all the time.

Ankle/foot edema. Ankle/foot edema (foot edema levels 2 and 3 only) was also evaluated in a quantitative way by foot volumetry in a randomly selected subgroup of subjects within the two treatment groups. To normalize the values, the actual foot volume at inclusion was defined as 100% (by immersion in water, using a water displacement method) (Belcaro *et al.*, 1996; Belcaro and Nicolaides, 2001; Cesarone *et al.*, 1999). The intra-individual, relative percent variations with this test were within 8%, therefore any variation >10% can be defined as caused by external factors (treatment, management). The foot volume values were defined at the end of the study and compared. The variations in volume observed with this method can be considered as the measurement of the level of edema involving the distal part of the leg (Cesarone *et al.*, 1999). The plastic leggings included water up to the level of the knee (defined as the lower edge of the rotula, in these measurements). The leg was immersed in water and the water level was defined by eliminating water from a lower side tap down to the lower edge of the rotula. The relative volume was defined as 100%. A variation of this volume was measured as a percentage of the individual volume at the start.

Evaluation of associated treatments needed to manage arthrosis. A diary was kept to record the use of any other drug prescribed by the patient's GP, the use of which was free (with only a warning not to use an excess of treatment).

Evaluation of costs and side effects. The cost of treatments and other costs (including working disruption and hospital admission) occurring during the trial period were recorded in a specific costing file.

Medication. Pycnogenol and placebo tablets were prepared by Manhattan Drug Company Inc, New York, USA. Verum and placebo tablets had an identical appearance, size and shape. Containers of study drugs – verum and placebo – were delivered by the producer labeled as A and B and were identical in size, shape and appearance. Emergency envelopes were provided to identify A and B in the case of severe adverse events.

Treatment consisted of two tablets daily, taken after breakfast and after dinner, consisting either of placebo or 50 mg Pycnogenol.

Statistical evaluation. The results were evaluated using analysis of variance (ANOVA) and the non-parametric Mann-Whitney U test.

Table 1. Patient characteristics at inclusion

Patient data	Pycnogenol group	Placebo group
Age (years)	48.6 SD 8	47.8 SD 7.7
Male/female ratio	39/38	39/40
Mean global WOMAC score	79.2	76.9
Treadmill test mean distance achieved[a]	68 m (0–133 m)	65 m (12–98 m)

[a] Treadmill 8 km/h with an inclination of 10%.

RESULTS

The treatment group (77 patients) and placebo group (79 patients) did not differ in respect of age, male to female ratio, overall WOMAC score and performance on treadmill test at the start of the study (Table 1).

Six patients in the treatment group and five patients in the placebo group left the study for non-medical reasons such as moving to other places and work problems. Two patients had a localized trauma from accidents.

Symptoms of osteoarthritis

The results of the evaluation of treatment success after 3 months by WOMAC scores are given in detail in Table 2.

Scores for pain dropped significantly ($p < 0.05$) following Pycnogenol intake from 17.3 to 7.7, the placebo had no significant effect.

The scores for stiffness were reduced significantly from 6.6 to 3.1 ($p < 0.05$), scores for the placebo remained unchanged after 3 months.

Also the scores for physical function were more than halved, reducing from 55.3 at the start to 23.8 in the verum group ($p < 0.05$), the improvement under placebo was not significant.

The global WOMAC score (Table 2) decreased following Pycnogenol treatment significantly from 79.2 to 34.6, with the placebo insignificant from 76.9 to 69.5.

Negative alterations of social functions by OA decreased significantly in the treatment group ($p > 0.05$), but not in the placebo group (details in Table 3).

The well-being of patients (emotional function) was significantly ($p < 0.05$) enhanced under verum treatment, as reflected in scores for emotional function (Table 3), the placebo produced a marginal improvement.

In conclusion, all WOMAC scores improved significantly ($p < 0.05$) after 3 months treatment relative to the start and versus the placebo.

Muscular performance

The results of the exercise test on the treadmill demonstrate a convincing increase of performance of patients following the 3 month treatment with Pycnogenol (Table 4). Patients could walk just 68 m as mean distance covered at the start, but could go for a mean of 198 m after treatment, versus only 65 m to 88 m in the placebo group.

DOI: 10.1002/ptr

Table 2. Change of WOMAC scores after 3 months of treatment (mean and SD)

	Pycnogenol group		Placebo group	
Symptoms and functions	Inclusion	3 months	Inclusion	3 months
Pain:				
Walking	3.3 (1.1)	2.1 (1.0)	3.0 (1.0)	3.0 (1.1)
Stair climbing	3.2 (1.0)	1.2 (1.0)	3.3 (1.0)	3.1 (1.6)
Nocturnal	3.1 (2.0)	1.1 (1.0)	3.1 (1.2)	2.5 (2.0)
Rest	3.5 (2.5)	1.1 (1.0)	3.6 (3.0)	3.0 (1.0)
Weight bearing	4.2 (3.0)	2.2 (1.0)	4.1 (2.6)	3.6 (2.0)
Sum of pain scores	17.3	7.7	17.1	15.2
Stiffness:				
Morning stiffness	3.4 (1.6)	2.1 (1.0)	3.3 (2.0)	3.6 (2.0)
Stiffness during the day	3.2 (1.0)	1.1 (0.5)	3.4 (1.1)	3.1 (2.0)
Sum of stiffness scores	6.6	3.1	6.7	6.7
Physical function:				
Descending stairs	3.3 (1.1)	1.4 (1.1)	3.1 (1.0)	2.5 (2.0)
Ascending stairs	3.2 (2.0)	0.5 (0.2)	3.3 (1.0)	2.6 (2.0)
Rising from sitting	3.1 (1.0)	0.8 (0.5)	3.0 (2.0)	3.1 (1.0)
Standing	3.3 (1.0)	1.2 (0.5)	3.1 (2.0)	3.1 (1.0)
Bending to floor	3.4 (1.0)	2.1 (1.0)	3.2 (1.1)	3.3 (2.0)
Walking on flat	3.1 (2.0)	1.1 (0.5)	3.0 (1.5)	2.6 (1.0)
Getting in or out of car	4.0 (2.1)	1.2 (1.0)	3.8 (2.0)	3.0 (1.5)
Going shopping	3.2 (2.0)	1.8 (1.0)	3.3 (2.0)	3.2 (2.0)
Putting on socks	3.6 (2.0)	2.1 (1.0)	3.4 (2.2)	3.2 (2.1)
Rising from bed	3.5 (1.9)	2.2 (1.1)	3.2 (2.0)	3.0 (2.0)
Taking off socks	3.1 (1.0)	1.1 (0.3)	3.1 (1.0)	2.4 (1.0)
Lying in bed	2.8 (1.0)	0.6 (0.1)	2.9 (1.1)	2.3 (1.0)
Sitting (a)	2.3 (1.0)	1.2 (0.5)	2.4 (1.0)	2.5 (1.0)
Sitting (b)	2.2 (2.0)	1.3 (1.0)	2.1 (1.0)	2.0 (1.8)
Getting on or off toilet	3.8 (1.0)	2.1 (0.4)	3.5 (1.1)	3.0 (2.0)
Heavy house duties	3.8 (2.0)	2.0 (1.0)	3.2 (2.2)	2.8 (2.0)
Light domestic duties	3.6 (2.8)	1.1 (1.0)	3.5 (3.0)	3.0 (2.0)
Sum of physical function scores	55.3	23.8	53.1	47.6
Global WOMAC score	79.2	34.6	76.9	69.5

Interpretation:

- Minimum total score: 0 (no symptoms) maximum total score: 96
- Minimum pain subscore: 0 maximum pain subscore: 20
- Minimum stiffness score: 0 maximum stiffness subscore: 8
- Minimum physical function score: 0 maximum physical function subscore: 68

Table 3. Change of WOMAC scores for social functions and of emotional WOMAC scores during treatment

	Pycnogenol group		Placebo group	
	Inclusion	3 months	Inclusion	3 months
Negative alterations in:				
Leisure activities	3.4 (2.0)	2.2 (1.0)	3.4 (2.0)	3.2 (2.0)
Community events	3.3 (2.0)	2.0 (1.0)	2.8 (2.0)	3.0 (2.0)
Church attendance	3.4 (2.0)	1.1 (2.0)	3.2 (2.0)	3.1 (2.0)
With spouse	3.4 (2.2)	1.2 (1.0)	3.1 (2.0)	2.4 (2.0)
With family	3.2 (2.1)	1.3 (1.0)	2.9 (2.0)	3.0 (2.0)
With friends	3.2 (2.0)	1.0 (0.5)	3.0 (2.0)	2.6 (2.0)
With others	3.2 (2.0)	1.1 (1.0)	2.9 (2.0)	3.1 (2.1)
Symptoms:				
Anxiety	3.4 (2.0)	0.3 (0.1)	3.2 (2.1)	2.5 (2.0)
Irritablility	3.6 (1.9)	1.2 (1.0)	2.6 (2.0)	2.0 (1.2)
Frustration	3.3 (2.0)	1.3 (1.0)	2.9 (1.9)	3.0 (1.0)
Depression	2.2 (1.6)	1.0 (0.2)	3.0 (1.6)	2.1 (1.0)
Relaxation	2.3 (1.0)	1.1 (0.5)	2.0 (1.0)	2.2 (2.0)
Insomnia	2.5 (2.0)	0.4 (1.0)	2.1 (1.4)	2.1 (2.0)
Boredom	3.4 (2.0)	0.7 (1.0)	2.8 (2.1)	2.2 (2.0)
Loneliness	3.3 (2.0)	2.1 (1.0)	2.8 (2.1)	2.2 (2.0)
Stress	3.8 (2.0)	2.3 (1.0)	3.3 (1.8)	3.1 (2.0)
Well-being	3.6 (2.0)	1.1 (0.5)	3.5 (2.0)	3.0 (2.0)
Sum of emotional parameters	31.4	11.5	28.4	24.1

DOI: 10.1002/ptr

Table 4. Results of exercise test before and after 3 month treatment

	Pycnogenol	Placebo	Diff. Pycnogenol – Placebo significance level
Inclusion	68 m (0–133)	65 m (12–98)	n.s.
3 months	198 m (55–374)	88 m (25–102)	< 0.05

Treadmill with an inclusion of 10% and speed of 8 km/h.

Vascular problems

A high percentage of patients (76% in the Pycnogenol group and 79% in the placebo group) showed visible ankle and foot edema at inclusion. At the end of the treatment period, edema decreased under verum in 79% of the patients but only in 1% of patients under placebo.

Foot volume, evaluated by the water-displacement method, decreased in a subgroup of 40 patients with slight to moderate edema after Pycnogenol ($n = 20$) by 32% (19–69%), after placebo ($n = 20$) by 7% (0–22%). The difference with the placebo was significant ($p > 0.05$).

Reduction of concomitant medication

Patients were allowed to use concomitant medication during treatment. The use of NSAIDs dropped by 58% during treatment with Pycnogenol, whereas under placebo NSAID use was reduced by only 1%. The difference between both treatments was significant ($p > 0.05$) (Table 5). Treatment costs evaluated from patients files indicate a decrease in the need for drugs (other than NSAIDs) and treatment by 54% versus 11% in the placebo group (Table 5).

Decrease of management costs

The days spent in hospital and the number of hospital admissions decreased over the study period of 3 months by 60% in the treatment group versus 3% in the placebo group. The decrease of non-drug related treatment costs as lost working days, consultations, insurance costs was estimated as 55% versus 3.5% with placebo (Table 5).

Unwanted effects

Unwanted effects of treatment were reported by patients in diaries. Evaluation of data demonstrated a decrease of gastrointestinal complications of 63% in the Pycnogenol group versus 3% in the placebo group.

DISCUSSION

The evaluation of treatment success of Pycnogenol by using the WOMAC scores resulted in a very significant decrease of OA symptoms by about 50%. This judgement by patients was supported by the objective test of treadmill performance of OA patients, showing that patients could walk more than twice the distance after Pycnogenol treatment compared with placebo. Thus, this double-blind, placebo-controlled study confirmed the hypothesis that Pycnogenol, due to its diverse antiinflammatory actions, could be used as an alternative treatment of OA to relieve pain and increase mobility. The WOMAC questionnaire revealed not only an improvement of physical function of patients but showed a gain of quality of life, by enabling the patients to be engaged in social activities, staying in better mood.

Another important advantage of the treatment with Pycnogenol is the reduction of unwanted effects, mainly gastrointestinal troubles connected with the reduced use of NSAIDs.

The improved symptoms of OA and enhanced the well-being of patients leading to reduced treatment costs. The estimation of the sparing effect of Pycnogenol to treatment costs of OA point to the possibility of a better cost management by adding the pine bark extract to regular treatment. However, studies with a larger population and for a longer treatment period are needed to confirm the findings of this study on a broader basis.

While some effects of OA can be easily calculated as costs (as medical care/management) costs and disrupted or lost working days, other costs are not easy to detect. These hidden costs include quality of life, the need of a family member support (who may alter his/her working and life habits), the inability to enjoy leisure activities or a reduction in housekeeping activities. Therefore the

Table 5. Percentage reduction of health care costs under treatment with Pycnogenol and placebo

Costs	Pycnogenol	Placebo	Diff. Pycnogenol – Placebo, significance level
Drugs and treatments beside NSAIDs	54%	11%	$p < 0.05$
Average management	59%	2%	$p < 0.05$
Hospital admissions	55%	5%	$p < 0.05$
Days hospitalized	60%	11%	$p < 0.05$
Indirect costs	55%	5%	$p < 0.05$

DOI: 10.1002/ptr

global impact of OA is often underestimated because of the difficulties in quantifying many of its consequences. New safe and cost-effective methods of treatment – not associated with complications and side effects – which may be directly used by patients both as a base treatment or as a substitute treatment for a period of time are useful for expanding the therapeutic range.

In addition to the amelioration of OA symptoms, the study provided information about clinical effects which have been generally overlooked in previous studies on OA. The decrease of limb mobility is generally associated with variable degrees of edema, limb swelling and deterioration of microcirculation, which in turn leads to a more severe level of disability. During Pycnogenol treatment, edema of the lower legs and the foot volume were significantly reduced compared with placebo, in accordance with our previous publications showing the high efficacy of Pycnogenol in edema reduction (Cesarone *et al.*, 2005, 2006a, 2006b, 2006c; Belcaro *et al.*, 2006).

The medication used in this protocol was therefore not only characterized by its potential to improve the symptoms of OA, but also by its efficacy in improving peripheral vascular disease and controlling edema.

The reduction of signs and symptoms of OA and of vascular problems may be attributed to the diverse antiinflammatory mechanisms of Pycnogenol, as the unspecific inhibition of cyclooxygenases I and II (Schäfer *et al.*, 2006) and the inhibition of matrix metalloproteases (Grimm *et al.*, 2006).

Further clinical studies have to clarify whether the increase of muscular performance is due to inflammation control or to a direct action on muscular function.

CONCLUSIONS

This study provides a new window to the management of OA by showing significant actions of Pycnogenol on four main, clinical components of OA:

1. the signs/symptoms and disability;
2. inflammation causing a progression in the disease;
3. the altered fatigue resistance and muscular performance;
4. severe, vascular problems associated with altered mobility (i.e. sometimes leading to venous and stasis ulcerations).

The study demonstrated an important clinical action of Pycnogenol on OA and shows an interesting potential in the management of this diffuse disease.

The aspects concerning cardiovascular toxicity of antiinflammatory drugs used in OA (Stillman and Stillman, 2007; Rahme and Nedjar, 2007) have received great attention lately. As many OA patients have concominant cardiovascular diseases, the use of Pycnogenol may reduce the load of antiinflammatory agents and offers important alternative management solutions for cardiovascular patients.

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