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Figure 1 Wilson et al(Pycnogenol for rhinitis).xps	



Review

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A randomized, double-blind, placebo-controlled exploratory study to evaluate the potential of Pycnogenol[®] for improving allergic rhinitis symptoms

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Short title: Pycnogenol improves allergic rhinitis

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ABSTRACT

We explored the potential of Pycnogenol® for relieving allergic rhinitis (birch pollen) symptoms in a double-blind, placebo-controlled trial. In 2008 19 subjects started treatment three weeks prior to the onset of birch pollen season in Ontario Canada. While there was an improvement of eye and nasal symptoms with Pycnogenol, there was no significance versus placebo. It was postulated that Pycnogenol may require a lag-time between start of therapy and the onset of action. Therefore 39 subjects were treated five to eight weeks prior the 2009 birch allergy season. The evaluation of subjects in 2009 showed much lower scores for eye (-35%) and nasal (-20.5%) symptoms with Pycnogenol compared to placebo. In succession of the allergy season birch specific IgE increased by 31.9% in the placebo group compared to only 19.4% in the Pycnogenol group. Detailed analysis suggested that symptom-relief was better the longer subjects were on Pycnogenol prior to allergen exposure. The best results were found with subjects who took Pycnogenol 7-8 weeks ahead of the allergy season. With the limited number of 39 patients statistical predications were unattainable. In conclusion, Pycnogenol improved allergic rhinitis symptoms when supplementation was started at least five weeks before onset of the allergy season.

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4 Key words: Allergic rhinitis, Pycnogenol, nasal symptoms, pollen season,
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11 12 13 14 15 16 17 INTRODUCTION 18

19
20 Allergic rhinitis is not life-threatening and considered by many to be a trivial
21 health problem with mild symptoms and easy to deal with. However, people
22 suffering from "hay-fever" experience many challenges associated with their
23 condition and report a dramatic impairment of their quality of life. In view of
24 the population affected, ranging between 20 to 40%, the economic burden is
25 considerable (Laekeman *et al.*, 2010; Cueppens, 2000). In a recent survey 85%
26 of patients felt that their daily activities related to their professional, personal
27 and social life, their outdoor activities and their ability to function properly at
28 work or at school and their sleep were impaired moderately or severely
29 (Valovirta *et al.*, 2008). Allergic rhinitis represents a major burden to school age
30 children as the disease compromises learning and placing those affected
31 children at a disadvantage. In a survey of adolescents with seasonal allergic
32 rhinitis, more than 70% reported difficulties with doing school work,
33 concentrating and in accomplishing school activities (Vuurman *et al.*, 2003). A
34 population based survey suggested that 36% of allergic rhinitis patients were
35 less effective at their jobs (Blanc *et al.*, 2001). As allergic rhinitis is one of the
36 most frequent diseases encountered in clinical practice, the cost implications to
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4 society is enormous. Since second generation antihistamines largely replaced H₁
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6 antihistamines, side effects of sedation such as urinary retention and
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8 arrhythmias are less pronounced. However, none of the continuous or on-
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10 demand medications available for seasonal allergic rhinitis are free of side-
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12 effects. Substantial numbers of patients with allergic rhinitis are not satisfied
13
14 with conventional medical treatment and repeatedly report side effects. As a
15
16 result, a large number of affected patients are seeking complementary and
17
18 alternative treatments (Kim *et al.*, 2009, Passalacqua *et al.*, 2006).
19
20 Pycnogenol[®], a standardised bark extract of the French maritime pine (*Pinus*
21
22 *pinaster* Ait.) has anecdotally been ascribed benefits for people with “hay-fever”
23
24 and two controlled clinical trials have shown significantly improved respiratory
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26 distress and lowered leukotriene levels in asthma patients (Rohdewald, 2002;
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28 Hosseini *et al.*, 2001; Lau *et al.*, 2004).
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The objective of the present study was to evaluate the optimum conditions in
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50 which Pycnogenol may be effective for improving symptoms of allergic rhinitis
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52 in adults allergic to birch pollen.
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MATERIALS & METHODS

Participants

This study was designed as a single-centre, randomized, double-blind, placebo-
controlled pilot study with 60 subjects. Volunteers were recruited from the clinic

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4 database or by advertisement. Medical/medication history was reviewed
5 including all known allergies, concomitant therapies, including allergy
6 medications and inclusion/exclusion criteria were reviewed. Also at screening,
7 anthropologic measurements, routine blood tests, a skin prick test for birch
8 allergy confirmation and a urine pregnancy test (if applicable) were conducted.
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10 A skin prick test was performed including the following pollen allergens: alder,
11 birch, oak, maple, elm, poplar and grasses. Only subjects with a positive
12 response to birch pollen were eligible for the study. The inclusion criteria
13 required an age of 18 to 65 years, male or female in good health as determined
14 by laboratory examination, medical history and physical exam.
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30 Subjects were excluded for the following reasons: pregnancy, breastfeeding or
31 if planning to get pregnant during the course of the trial, a history of alcohol or
32 drug abuse within the past year. Unstable medical conditions, asthma, sinusitis,
33 otitis media or conditions other than allergies known to cause rhinitis, subjects
34 that had a cold or flu at time of randomisation, subjects with conditions
35 including diabetes, any autoimmune disease, abnormal liver function or
36 anaemia, cognitive impairment, or taking any prescription or "over the counter"
37 products for allergies, or using immunosuppressant medications, or using any
38 natural health products other than multivitamin and mineral supplements
39 containing vitamins and minerals as the sole medicinal ingredients.
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56 This study was conducted in accordance with Good Clinical Practice Guidelines
57 and the ethical principles of the Declaration of Helsinki (2000). The study
58 protocol and materials were approved by the Institutional Review Board
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4 Services (Aurora, Ontario, Canada) and all subjects gave informed consent prior
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6
7 to participation. The study was approved by Health Canada authorities.
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10 *Investigational treatment*

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13 Patients were assigned to Pycnogenol[®] or placebo group according to a
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16 computer generated randomisation schedule. Neither the patient, nor
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19 investigator, nor research staff, were informed which test order the subject was
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22 assigned to. Blinding of data was maintained throughout statistical data
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25 analysis. Tablets were film coated and indistinguishable by appearance and
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28 weight.
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32 Subjects were supplied with containers of tablets together with a treatment
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35 diary. The diary together with returned original container with remaining tablets
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38 at each visit was utilised for determination of compliance. Subjects were
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41 instructed to take one study tablet in the morning and another in the evening,
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44 with a meal, daily starting the day after randomisation. Pycnogenol (50 mg)
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47 and placebo tablets were manufactured by Manhattan Drug Company, 255
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50 Long Avenue, Hillside NJ, USA.
51

52 *Observations and Procedures*

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55 Eligible subjects returned to the clinic approximately three to four weeks before
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58 the predicted start in mid April of the birch pollen season in 2008 and five to six
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61 weeks before the start of the season in 2009. However, in 2009 the pollen
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64 season was delayed due to an unseasonably cold winter and many subjects
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4 were using the product 7-8 weeks prior to the birch allergen onset. Recruited
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7 subjects were again screened at baseline (Day 0), during which they were also
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10 randomly assigned to groups. At this time and again 28 days later (48 in 2009),
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12 and 56 days later (70 in 2009) and at 84 days (2008) and 98 days (2009) from
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14 baseline a container with the test product and a treatment/symptom diary were
15
16 dispensed. Symptoms, adverse events, as well as concomitant therapies were
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18 reviewed, weight, blood pressure and heart rate were checked. This was
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20 repeated at completion of the trial 84 days post randomisation (98 days in
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22 2009). Blood was collected for the measurement of total IgE and allergen
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24 specific IgE determination at each of these visits.
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31 Subjects were instructed to rate nasal and eye symptoms by means of a self-
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33 administered questionnaire every day and record values in a treatment diary.
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35 All nasal and eye symptoms were scored with values ranging from 0 (symptom
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37 absent), 1 (mild, symptoms notice but well tolerated), 2 (moderate, symptom
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39 impairs normal activity) to 3 (severe, symptom completely prevents normal
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41 activity). This score was used for each of the following eye symptoms: "burning
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43 or itchy eyes", "watering or tearing eyes", "redness". The score was applied to
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45 judge nasal symptoms "sneezing", "stuffy nose", runny nose" and "itchy nose".
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51 At screening and after completion of the trial fasting blood samples were
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53 collected in EDTA vacutainer tubes for standard blood chemistry.
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57 The local pollen forecast was checked daily and grains/m³ were recorded for
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59 the duration of the study (www.theweathernetwork.com).
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Statistical Methods

Statistical evaluation was carried out using SAS version 9.1 software. As primary endpoints the onset of nasal symptoms was estimated using the Kaplan-Meier technique and the two groups were compared using a log-rank statistic. As secondary endpoints changes of nasal-, and eye symptoms scores between groups were compared using analysis of the variance and unpaired t-tests. Comparisons of frequencies were made using Chi-square test. Birch allergen IgE comparisons between groups were made with unpaired t-tests and analysis of covariance, adjusting for the baseline value. Difference of compliance between group was compared using an unpaired t-test. Probability values less than 0.05 were considered to be statistically significant between groups. Parameters are presented as mean values and standard deviation.

RESULTS

Subjects in both groups were comparable for age and gender (table 1). While all patients were allergic to birch pollen, the allergies to other pollen species varied between groups. In 2008 birch pollen season was predicted to begin in mid April and 19 subjects were recruited and began treatment three to four weeks before the start of the birch pollen season. There was no significant difference of patient's scores between groups for total eye symptom (0.50 ± 0.58 vs 0.23 ± 0.29) and total nasal symptom (0.62 ± 0.48 vs 0.54 ± 0.40) scores, Pycnogenol versus placebo, respectively. During the pollen season the

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4 birch allergen IgE titre increase was more pronounced in the placebo group
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6 (7.8 ± 15.0 KU/L) than in the Pycnogenol group (5.0 ± 13.1 KU/L), however,
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8 these results were not statistically significant.
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12 In 2009 we recruited 41 subjects into the study and they were instructed to
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14 take the product earlier prior to the onset of the allergy season than 3-4 weeks,
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16 hoping that with a longer lag-time for Pycnogenol results would improve. The
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18 subjects began taking the product took Pycnogenol at least 5 weeks prior to the
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20 birch allergy season onset. Eight subjects started 6-7 weeks, and another 18
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22 subjects even 7-8 weeks before start of the birch pollen season. The total
23
24 average nasal symptom score for the allergy season was lower in the
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26 Pycnogenol group (n= 19) (0.31 ± 0.30) than in the placebo group (n=20)
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28 (0.39 ± 0.33). The corresponding average total eye symptom score was lower
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30 with Pycnogenol (0.13 ± 0.18) versus 0.20 ± 0.21 with placebo, however did
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32 not reach statistical significance. Interestingly, the symptoms scores of groups
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34 in 2009 were significantly lower than in 2008 (p=0.028) in spite of a much
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36 higher birch pollen count in the 2009 season compared to 2008.
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46 Figure 1 illustrates the development of total nasal symptoms in both groups of
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48 subjects taking the product at least seven weeks before onset of birch pollen.
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50 As the birch pollen season began in mid April birch pollen nasal symptoms were
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52 found to increase. The nasal symptoms recorded each week remained
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54 remarkably lower for the Pycnogenol group than in the placebo-treated group
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56 throughout the birch pollen season. As shown in table 1, more subjects taking
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58 Pycnogenol than in the placebo group were also allergic to grass pollen.
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4 Patients were permitted to use rescue medication and the proportion of
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6 subjects making use of this option at least once during the study was slightly
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8 lower in the Pycnogenol group (11/30; 36.7%) compared to the placebo group
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10 (15/30; 50%). Interestingly, sub-analysis showed that the group starting
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12 Pycnogenol >7 weeks prior to the birch pollen appearance required very little
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14 rescue medication (1/8; 12.5%) compared to the placebo group (5/10; 50%).
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18 The limited number of subjects in this sub-analysis did not allow for statistical
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20 evaluation. Comparison of birch specific IgE titre between trial start and the end
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22 of the allergy season showed an increase of 31.9% in the placebo group and
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24 only 19.4% in the Pycnogenol group.
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30 Fifteen subjects in the Pycnogenol group and 17 in the placebo group
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32 experienced adverse events. The majority of these events were considered
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34 unlikely a result of treatment (headaches, dizziness, common cold, dry mouth).
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36 Three of the adverse events were assessed as having a possible relationship to
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38 treatment. One subject (placebo) with severe vertigo was withdrawn. Another
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40 subject on placebo had severe hives which required concomitant therapy. One
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42 subject in the Pycnogenol group presented with elevated liver enzymes (ALT
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44 and AST), which did not require discontinuation. The subject had a medical
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46 history of hepatitis C in 1998. Further to this no changes in clinical chemistry
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48 and haematology were observed. There were no significant differences in the
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50 number of subjects reporting adverse events.
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DISCUSSION

The results of the present study indicate that subjects treated with Pycnogenol had better nasal and ocular symptoms when treatment was started for periods longer than 5 weeks before the onset of birch allergy season. Furthermore, subjects on Pycnogenol required less rescue medication compared to subjects receiving placebo.

It is likely that the immune-modulating effect of Pycnogenol may require sufficient time to manifest in noticeable symptom reduction. Pycnogenol has previously been investigated in two clinical trials with asthma patients (Hosseini *et al.*, 2001; Lau *et al.*, 2004). The double-blind, placebo-controlled study of 6-18 year old patients with mild- to moderate asthma showed that Pycnogenol gradually decreased symptoms and leukotriene levels over the treatment period of three months (Lau *et al.*, 2004). Both asthma studies utilised a higher Pycnogenol dosage of 1 mg per lb (2.2 mg/kg) body weight. Though the pathophysiology of allergic rhinitis and asthma are distinct, the dosage of 100 mg Pycnogenol we applied in our current studies may have been on the lower end of the effective levels for immune-modulation.

Pycnogenol has been extensively investigated in human pharmacologic studies for elucidation of its anti-inflammatory potential and mechanisms involved (Rohdewald, 2002). Following consumption of 200 mg Pycnogenol by healthy volunteers for five days peripheral blood monocytes were investigated *ex vivo* in presence of volunteer's plasma (Grimm *et al.*, 2006). Upon stimulation with

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4 LPS, nuclear factor-kappa B (NF- κ B) was found to be significantly inhibited after
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6 consumption of Pycnogenol. As a result monocytes secreted significantly less
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8 matrix metalloproteinase MMP-9, which is governed by NF- κ B. Another
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10 pharmacologic study had healthy volunteers take 150 mg Pycnogenol for five
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12 days (Canali *et al.*, 2009). Neutrophils were isolated from donor's blood and
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14 challenged ex vivo to elucidate expression of cyclo-oxygenase (COX) type 1 and
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16 -type2, 5-lipoxygenase (5-LOX), 5-lipoxygenase activating protein (FLAP) as
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18 well as prostaglandin and leukotrienes synthesis. Pycnogenol significantly
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20 inhibited COX-2, 5-LOX and FRAP expression. Synthesis of leukotrienes was
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22 found to be significantly inhibited, which is in confirmation with the two clinical
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24 studies with Pycnogenol in asthma patients. Both clinical studies with
25
26 Pycnogenol found significantly lowered serum leukotrienes and urinary
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28 leukotrienes, respectively (Hosseini *et al.*, 2001; Lau *et al.*, 2004).

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30 Pycnogenol was shown to have anti-inflammatory activity in very diverse
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32 pathologies such as arthritis, sunburn and dysmenorrhoea (Belcaro *et al.*, 2008;
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34 Saliou *et al.*, 2001; Suzuki *et al.*, 2008). Anecdotal and personal
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36 communications have suggested a relief from allergic rhinitis symptoms with
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38 Pycnogenol, but no clinical trials exist on this subject to date. Limited
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40 information is available from an animal model involving rats, subcutaneously
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42 sensitized with DNP-IgE and challenged 24 hours later with HSA-DNP (Choi *et*
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44 *al.*, 200). Pycnogenol, administered orally one hour prior to challenge, dose-
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46 dependently inhibited passive cutaneous anaphylaxis as judged by local
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48 extravasation of i.v. injected Evans blue. With 10 mg Pycnogenol per kg body
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4 weight a 40% decrease of extravasation was found, whereas the same dosage
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6 of the established anti-histamine "azelastine" resulted in 73% inhibition.
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10 Using Pycnogenol as an alternative natural therapy for controlling hay-fever
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12 would be appealing for many people affected. The typical side effects with
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14 sedation, urinary retention and arrhythmias of first generation H₁-
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16 antihistamines are less bothersome in second generation anti-histamines (Phan
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18 *et al.*, 2009). Though some of the latter, however, present with serious drug-
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20 interactions.
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26 We attempted in our study to identify the circumstances under which
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28 Pycnogenol may help to relieve hay-fever symptoms. We chose subjects with
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30 birch allergies as these would be the easiest to recruit. However, the
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32 identification of subjects exclusively allergic to birch pollen was challenging.
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34 Several subjects appeared to show an allergic response also to grass pollen
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36 despite the fact that the prick test suggested the opposite. Interestingly,
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38 subjects taking Pycnogenol had lower nasal and ocular symptom scores during
39
40 the grass pollen season than the control group. From previous studies with
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42 Pycnogenol such as for asthma we concluded that the anti-inflammatory effect
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44 developed slowly and would take at least one month. With the limited number
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46 of subjects we were able to recruit in 2008 we realised that Pycnogenol did
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48 contribute to significant symptom reduction. Therefore, we concluded that
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50 starting to take Pycnogenol more timely prior to allergy season 2009 would be
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52 more effective. A lag-time between starting a pharmacotherapy and the onset
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54 of action is a well described phenomenon in the therapy of allergic rhinitis
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5 (Laekeman *et al.*, 2010). To address this issue it was required that patients
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7 enrolled for the study would need to take Pycnogenol or placebo at least five
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9 weeks before onset of birch pollen, preferably even much longer than five
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11 weeks. Our findings suggest that taking Pycnogenol in a timely manner does
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13 dramatically contribute to better symptom relief. Unfortunately, the small cohort
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15 of eight best responding subjects, those who took Pycnogenol seven to eight
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17 weeks prior to birch pollen exposure was too small to provide statistical
18
19 relevance. As a further variable, a higher Pycnogenol dosage, such as applied in
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21 previous asthma studies should be expected to contribute to more pronounced
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23 rhinitis symptoms relief. Based on the positive results of this study it is likely
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25 that a higher sample size would provide significance between the Pycnogenol
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27 and placebo group.
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35 In conclusion, the present study demonstrated that Pycnogenol decreases nasal
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37 and ocular symptoms in allergic rhinitis patients. It is possible to suggest that
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39 Pycnogenol may represent a new and promising therapeutic modality for
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41 subjects with allergic rhinitis.
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4 Table 1: Demographics of patients recruited in 2008 and 2009. The percentage
5 of subjects allergic to pollen as judged by prick tests at the time of enrolment is
6 given.
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	Study group 2008	Study group 2009
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	Pycnogenol	placebo	Pycnogenol	placebo
Number	10	9	20	21
Age	42.0 ± 9.2	43.5 ± 12.8	46.2 ± 12.7	43.5 ± 13.9
Gender f + m	6 + 4	7 + 2	13 + 7	13 + 8
Birch allergy	100%	100%	100%	100%
Alder allergy	50%	67%	84%	75%
Elm allergy	50%	33%	53%	45%
Poplar allergy	25%	17%	37%	30%
Maple allergy	50%	33%	47%	35%
Oak allergy	62.5%	50%	68%	75%
Grass allergy	75%	75%	79%	60%

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8 Figure 1: Presented are the mean weekly nasal symptoms scores of subjects
9 treated in 2009 with Pycnogenol® (green bars) or placebo (red bars). The
10 occurrence of pollen species from poplar, maple, oak, grass during the allergy
11 season are shown as indicated, with birch pollen density highlighted. The pollen
12 count of elm and alder are not shown as they were absent from the end of April
13 onwards. From mid April to end of May birch pollen is present and this coincides
14 with an increase of nasal symptoms, which are higher in the placebo group
15 (red) compared to lower symptoms scores with Pycnogenol (green). Beginning
16 from mid May many subjects also respond to increasing presence of grass
17 pollen.
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