

A Randomized, Double-Blind, Placebo-Controlled Exploratory Study to evaluate the potential of Pycnogenol® for Improving Allergic Rhinitis Symptoms

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The potential of Pycnogenol® for relieving allergic rhinitis (birch pollen) symptoms was explored in a double-blind, placebo-controlled trial. In 2008 19 subjects started treatment 3 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 the start of therapy and the onset of action. Therefore 39 subjects were treated 5–8 weeks prior to 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 with placebo. In succession of the allergy season birch specific IgE increased by 31.9% in the placebo group compared with only 19.4% in the Pycnogenol group. Detailed analysis suggested that symptom-relief was better the longer subjects were on Pycnogenol prior to the 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 5 weeks before the onset of the allergy season. Copyright © 2010 John Wiley & Sons, Ltd.

Keywords: allergic rhinitis; Pycnogenol; nasal symptoms; pollen season; asthma.

INTRODUCTION

Allergic rhinitis is not life-threatening and considered by many to be a trivial health problem with mild symptoms and is easy to deal with. However, people suffering from 'hay-fever' experience many challenges associated with their condition and report a dramatic impairment of their quality of life. In view of the population affected, ranging between 20% to 40%, the economic burden is considerable (Laekeman *et al.*, 2010; Cueppens, 2000). In a recent survey 85% of patients felt that their daily activities related to their professional, personal and social life, their outdoor activities and their ability to function properly at work or at school and their sleep were impaired moderately or severely (Valovirta *et al.*, 2008). Allergic rhinitis represents a major burden to school age children as the disease compromises learning and placing those affected children at a disadvantage. In a survey of adolescents with seasonal allergic rhinitis, more than 70% reported difficulties with doing school work, concentrating and in accomplishing school activities (Vuurman *et al.*, 2003). A population based survey suggested that 36% of allergic rhinitis patients were less effective at their jobs (Blanc *et al.*, 2001). As allergic rhinitis is one of the most frequent diseases encountered in clinical practice, the cost implications to society is

enormous. Since second generation antihistamines largely replaced H₁ antihistamines, side effects of sedation such as urinary retention and arrhythmias are less pronounced. However, none of the continuous or on-demand medications available for seasonal allergic rhinitis are free of side-effects. Substantial numbers of patients with allergic rhinitis are not satisfied with conventional medical treatment and repeatedly report side effects. As a result, a large number of affected patients are seeking complementary and alternative treatments (Kim *et al.*, 2009; Passalacqua *et al.*, 2006). Pycnogenol®, a standardized bark extract of the French maritime pine (*Pinus pinaster* Ait.) has anecdotally been ascribed benefits for people with 'hay-fever' and two controlled clinical trials have shown significantly improved respiratory distress and lowered leukotriene levels in asthma patients (Rohdewald, 2002; Hosseini *et al.*, 2001; Lau *et al.*, 2004).

The objective of the present study was to evaluate the optimum conditions in which Pycnogenol may be effective for improving the symptoms of allergic rhinitis in adults allergic to birch pollen.

MATERIALS AND 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 database or by advertisement. Medical/medi-

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cation history was reviewed including all known allergies, concomitant therapies, including allergy medications and inclusion/exclusion criteria were reviewed. Also at screening, anthropologic measurements, routine blood tests, a skin prick test for birch allergy confirmation and a urine pregnancy test (if applicable) were conducted. A skin prick test was performed including the following pollen allergens: alder, birch, oak, maple, elm, poplar and grasses. Only subjects with a positive response to birch pollen were eligible for the study. The inclusion criteria required an age of 18–65 years, male or female in good health as determined by laboratory examination, medical history and physical examination.

Subjects were excluded for the following reasons: pregnancy, breastfeeding or if planning to get pregnant during the course of the trial, a history of alcohol or drug abuse within the past year. Unstable medical conditions, asthma, sinusitis, otitis media or conditions other than allergies known to cause rhinitis, subjects that had a cold or flu at time of randomization, subjects with conditions including diabetes, any autoimmune disease, abnormal liver function or anaemia, cognitive impairment, or using any natural health products other than multivitamin and mineral supplements containing vitamins and minerals as the sole medicinal ingredients.

This study was conducted in accordance with Good Clinical Practice Guidelines and the ethical principles of the Declaration of Helsinki (2000). The study protocol and materials were approved by the Institutional Review Board Services (Aurora, Ontario, Canada) and all subjects gave informed consent prior to participation. The study was approved by Health Canada authorities.

Investigational treatment. Patients were assigned to Pycnogenol® or placebo group according to a computer generated randomization schedule. Neither the patient, nor investigator, nor research staff, were informed which test order the subject was assigned to. Blinding of data was maintained throughout statistical data analysis. Placebo and verum tablets were film coated and indistinguishable by appearance, weight, size, colour, shape and taste.

Subjects were supplied with containers of tablets together with a treatment diary. The diary together with returned original container with remaining tablets at each visit was utilized for determination of compliance. Subjects were instructed to take one study tablet in the morning and another in the evening, with a meal, daily starting the day after randomization. Pycnogenol (50 mg) and placebo tablets were manufactured by Manhattan Drug Company, 255 Long Avenue, Hillside NJ, USA.

Observations and procedures. Eligible subjects returned to the clinic approximately 3–4 weeks before the predicted start in mid April of the birch pollen season in 2008 and 5–6 weeks before the start of the season in 2009. However, in 2009 the pollen season was delayed due to an unseasonably cold winter and many subjects were using the product 7–8 weeks prior to the birch allergen onset. Recruited subjects were again screened at baseline (day 0), during which they were also randomly assigned to groups. At this time and again 28 days later (48 in 2009), and 56 days later (70 in 2009) and at 84 days (2008) and 98 days (2009) from baseline

a container with the test product and a treatment/symptom diary were dispensed. Symptoms, adverse events, as well as concomitant therapies were reviewed, weight, blood pressure and heart rate were checked. This was repeated at completion of the trial 84 days post randomisation (98 days in 2009). Blood was collected for the measurement of total IgE and allergen specific IgE determination at each of these visits.

Subjects were instructed to rate nasal and eye symptoms by means of a self-administered questionnaire every day and record values in a treatment diary. All nasal and eye symptoms were scored with values ranging from 0 (symptom absent), 1 (mild, symptom notice but well tolerated), 2 (moderate, symptom impairs normal activity) to 3 (severe, symptom completely prevents normal activity). This score was used for each of the following eye symptoms: 'burning or itchy eyes', 'watering or tearing eyes', 'redness'. The score was applied to judge nasal symptoms 'sneezing', 'stuffy nose', 'runny nose' and 'itchy nose'.

Patients were allowed to use non-prescription (over-the-counter) antihistamines as required and each usage and the dosage were recorded in their diary.

At screening and after completion of the trial fasting blood samples were collected in EDTA vacutainer tubes for standard blood chemistry.

The local pollen forecast was checked daily and grains/m³ were recorded for the duration of the study (www.theweathernetwork.com).

Statistical methods. Statistical evaluation was carried out using SAS version 9.1 software. As primary 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. As secondary endpoints 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 <0.05 were considered to be statistically significant between the 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 the birch pollen season was predicted to begin in mid April and 19 subjects were recruited and began treatment 3–4 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 birch allergen IgE titre increase was more pronounced in the placebo group (7.8 ± 15.0 KU/L) than in the Pycnogenol group (5.0 ± 13.1 KU/L), however, these results were not statistically significant.

In 2009 41 subjects were recruited into the study and they were instructed to take the product earlier prior to

Table 1. Demographics of patients recruited in 2008 and 2009. The percentage of subjects allergic to pollen as judged by prick tests at the time of enrolment is given

	Study group 2008		Study group 2009	
	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%

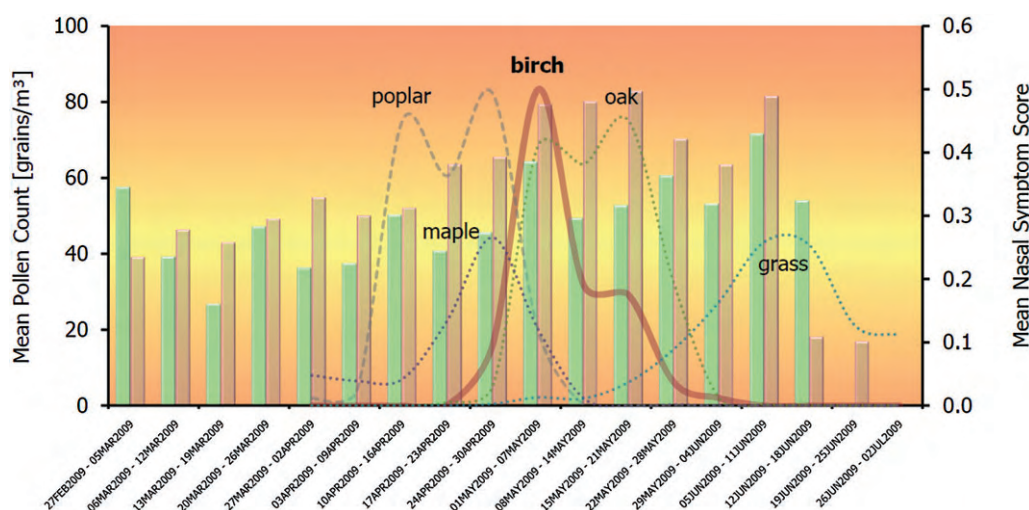


Figure 1. Presented are the mean weekly nasal symptoms scores of subjects treated in 2009 with Pycnogenol® (green bars) or placebo (red bars). The occurrence of pollen species from poplar, maple, oak, grass during the allergy season are shown as indicated, with birch pollen density highlighted. The pollen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

the onset of the allergy season than 3–4 weeks, hoping that with a longer lag-time for Pycnogenol the results would improve. The subjects began taking the product, took Pycnogenol at least 5 weeks prior to the birch allergy season onset. Eight subjects started 6–7 weeks, and another 18 subjects even 7–8 weeks before the start of the birch pollen season. The total average nasal symptom score for the allergy season was lower in the Pycnogenol group ($n = 19$) (0.31 ± 0.30) than in the placebo group ($n = 20$) (0.39 ± 0.33). The corresponding average total eye symptom score was lower with Pycnogenol (0.13 ± 0.18) versus 0.20 ± 0.21 with placebo, however, did not reach statistical significance. Interestingly, the symptoms scores of groups in 2009 were significantly lower than in 2008 ($p = 0.028$) in spite of a much higher birch pollen count in the 2009 season compared with 2008.

Figure 1 illustrates the development of total nasal symptoms in both groups of subjects taking the product at least 7 weeks before the onset of birch pollen. As the birch pollen season began in mid April birch pollen nasal symptoms were found to increase. The nasal symp-

toms recorded each week remained markedly lower for the Pycnogenol group than in the placebo-treated group throughout the birch pollen season. As shown in Table 1, more subjects taking Pycnogenol than in the placebo group were also allergic to grass pollen.

Patients were permitted to use non-prescription (over-the-counter) antihistamines as rescue medication and the proportion of subjects making use of this option at least once during the study was slightly lower in the Pycnogenol group (11/30; 36.7%) compared with the placebo group (15/30; 50%). Interestingly, sub-analysis showed that the group starting Pycnogenol > 7 weeks prior to the birch pollen appearance required very little rescue medication (1/8; 12.5%) compared with the placebo group (5/10; 50%). The limited number of subjects in this sub-analysis did not allow for statistical evaluation. Comparison of birch specific IgE titre between trial start and the end of the allergy season showed an increase of 31.9% in the placebo group and only 19.4% in the Pycnogenol group.

Fifteen subjects in the Pycnogenol group and 17 in the placebo group experienced adverse events. The

majority of these events were considered unlikely a result of treatment (headaches, dizziness, common cold, dry mouth). Three of the adverse events were assessed as having a possible relationship to treatment. One subject (placebo) with severe vertigo was withdrawn. Another subject on placebo had severe hives which required concomitant therapy. One subject in the Pycnogenol group presented with elevated liver enzymes (ALT and AST), which did not require discontinuation. The subject had a medical history of hepatitis C in 1998. Further to this no changes in clinical chemistry or haematology were observed. There were no significant differences in the number of subjects reporting adverse events.

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 the birch allergy season. Furthermore, subjects on Pycnogenol required less rescue medication compared with 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 3 months (Lau *et al.*, 2004). Both asthma studies utilized a higher Pycnogenol dosage of 1 mg per lb (2.2 mg/kg) body weight. Though the patho-physiologies of allergic rhinitis and asthma are distinct, the dosage of 100 mg Pycnogenol 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 pharmacological studies for elucidation of its antiinflammatory potential and mechanisms involved (Rohdewald, 2002). Following consumption of 200 mg Pycnogenol by healthy volunteers for 5 days peripheral blood monocytes were investigated *ex vivo* in the presence of volunteer's plasma (Grimm *et al.*, 2006). Upon stimulation with LPS, nuclear factor-kappa B (NF- κ B) was found to be significantly inhibited after consumption of Pycnogenol. As a result monocytes secreted significantly less matrix metalloproteinase MMP-9, which is governed by NF- κ B. Another pharmacological study had healthy volunteers take 150 mg Pycnogenol for 5 days (Canali *et al.*, 2009). Neutrophils were isolated from donor's blood and challenged *ex vivo* to elucidate expression of cyclo-oxygenase (COX) type 1 and type 2, 5-lipoxygenase (5-LOX), 5-lipoxygenase activating protein (FLAP) as well as prostaglandin and leukotrienes synthesis. Pycnogenol significantly inhibited COX-2, 5-LOX and FRAP expression. Synthesis of leukotrienes was found to be significantly inhibited, which is in confirmation with the two clinical studies with Pycnogenol in asthma patients. Both clinical studies with Pycnogenol found significantly lowered serum leukot-

rienes and urinary leukotrienes, respectively (Hosseini *et al.*, 2001; Lau *et al.*, 2004).

Pycnogenol was shown to have antiinflammatory activity in very diverse pathologies such as arthritis, sunburn and dysmenorrhoea (Belcaro *et al.*, 2008; Saliou *et al.*, 2001; Suzuki *et al.*, 2008). Anecdotal and personal communications have suggested a relief from allergic rhinitis symptoms with Pycnogenol, but no clinical trials exist on this subject to date. Limited information is available from an animal model involving rats, subcutaneously sensitized with DNP-IgE and challenged 24 h later with HSA-DNP (Choi *et al.*, 200). Pycnogenol, administered orally 1 h prior to challenge, dose-dependently inhibited passive cutaneous anaphylaxis as judged by local extravasation of i.v. injected Evans blue. With 10 mg Pycnogenol per kg body weight a 40% decrease of extravasation was found, whereas the same dosage of the established antihistamine, azelastine, resulted in 73% inhibition.

Using Pycnogenol as an alternative natural therapy for controlling hay-fever would be appealing for many people affected. The typical side effects with sedation, urinary retention and arrhythmias of first generation H₁-antihistamines are less bothersome in second generation antihistamines (Phan *et al.*, 2009). Though some of the latter, however, present with serious drug interactions.

This study attempted to identify the circumstances under which Pycnogenol may help to relieve hay-fever symptoms. Subjects with birch allergies were chosen as these would be the easiest to recruit. However, the identification of subjects exclusively allergic to birch pollen was challenging. Several subjects appeared to show an allergic response also to grass pollen despite the fact that the prick test suggested the opposite. Interestingly, subjects taking Pycnogenol had lower nasal and ocular symptom scores during the grass pollen season than the control group. From previous studies with Pycnogenol such as for asthma it was concluded that the antiinflammatory effect developed slowly and would take at least 1 month. With the limited number of subjects we were able to recruit in 2008 we realised that Pycnogenol did contribute to significant symptom reduction. Therefore, we concluded that starting to take Pycnogenol more timely prior to allergy season 2009 would be more effective. A lag-time between starting a pharmacotherapy and the onset of action is a well described phenomenon in the therapy of allergic rhinitis (Laekeman *et al.*, 2010). To address this issue it was required that patients enrolled for the study would need to take Pycnogenol or placebo at least 5 weeks before the onset of birch pollen, preferably even much longer than 5 weeks. Our findings suggest that taking Pycnogenol in a timely manner does substantially contribute to better symptom relief. Unfortunately, the small cohort of eight best responding subjects, those who took Pycnogenol 7–8 weeks prior to birch pollen exposure was too small to provide statistical relevance. As a further variable, a higher Pycnogenol dosage, such as applied in previous asthma studies should be expected to contribute to more pronounced rhinitis symptoms relief. Based on the positive results of this study it is likely that a higher sample size would provide significance between the Pycnogenol and the placebo group.

In conclusion, the present study demonstrated that Pycnogenol decreases nasal and ocular symptoms in

allergic rhinitis patients. It is possible to suggest that Pycnogenol may represent a new and promising therapeutic modality for subjects with allergic rhinitis.

Conflict of Interest

The authors have declared that there is no conflict of interest.

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