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Birch Pollen Honey for Birch Pollen Allergy – A Randomized Controlled Pilot Study

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Key Words
Birch pollen · Complementary medicine · Honey · Rhinitis

Abstract
Background: Only a few randomized controlled trials have been carried out to evaluate various complementary treatments for allergic disorders. This study assessed the effects of the preseasonal use of birch pollen honey (BPH; birch pollen added to honey) or regular honey (RH) on symptoms and medication during birch pollen season. ***Methods:*** Forty-four patients (59% female, mean age 33 years) with physician-diagnosed birch pollen allergy consumed either BPH or RH daily in incremental amounts from November 2008 to March 2009. Seventeen patients (53% female, mean age 36 years) on their usual allergy medication served as the control group. From April to May, patients recorded daily rhinoconjunctival and other symptoms and their use of medication. Fifty patients completed the study. ***Results:*** During birch pollen season in 2009, BPH patients reported a 60% lower total symptom score ($p < 0.01$), twice as many asymptomatic days ($p < 0.01$), and 70% fewer days with severe symptoms ($p < 0.001$), and they used 50% less antihistamines ($p < 0.001$) compared to the control group. The differences between the BPH and RH groups were not significant. However, the BPH patients used less antihistamines than did the RH patients ($p < 0.05$). ***Conclusions:*** Patients who preseasonally used BPH had significantly better control of their symptoms than did those on conventional medication only, and they had marginally better control compared to those on RH. The results should be regarded as preliminary, but they indicate that BPH could serve as a complementary therapy for birch pollen allergy.

Introduction

Complementary and alternative medicine (CAM), including therapeutic and diagnostic approaches different from conventional medicine such as homeopathy and antioxidant therapy, is widely used for allergic disorders [1, 2]. In the treatment of seasonal (intermittent) rhinitis some dietary supplements such as butterbur (a plant, i.e. *Petasites hybridus*) and vitamin C have been associated with some beneficial effects, but most products lack supporting clinical evidence [3–5]. A few other therapies, including spirulina (blue-green algae), acupuncture, and phototherapy, also hold some promise [6, 7] but have not been integrated into the general treatment of allergic rhinitis. Given the high prevalence of allergic diseases and the associated costs of CAM treatments, Resnick et al. [5] concluded that the efficacy of CAM modalities should be challenged with randomized placebo-controlled trials in

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order to establish appropriate guidelines for the use of CAM.

Wild honey, which has a variety of positive nutritional and health effects, is taken as an alternative medicine for the treatment of gastrointestinal diseases, coronary artery disease, and infected wounds [8–10]. Honey and other bee products have antibacterial activity [11]. Even antibiotic-resistant strains such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) have been shown to be as sensitive to honey as the antibiotic-sensitive strains of the same species [12]. Phenolic acids and flavonoids have been claimed to be the main cause of the protective effect [13]. Microbes form an integral part of honey, but most of them are in an inactive form due to the hygroscopicity, hyperosmolarity, acidity, peroxide content, and antibiotic activities of honey [11]. The primary sources of the microbial community present in honey seem to be pollen and the microflora of the honeybee's digestive tract [14].

According to animal studies, daily oral administration of bee-collected pollen causes an antiallergic action by reducing the cutaneous mast cell activation elicited by IgE and specific antigens [15, 16]. On the other hand, honey consists of both proteins derived from secretions of the pharyngeal and salivary glands of honeybee heads and pollen which can cause allergic reactions to honey [17]. Among patients with allergic rhinoconjunctivitis, Rajan et al. [18] compared the effects of unpasteurized honey, pasteurized honey, and corn syrup with synthetic honey flavoring ingested daily during pollen season. The members of neither honey group experienced relief from their symptoms in excess of that seen in the placebo group. There is little clinical evidence that honey has some value in the control of allergic symptoms, yet this is a common belief in folk medicine.

We assessed the effects of the preseasonal use of honey in patients with allergic symptoms during birch pollen season. In Finland, birch pollinosis afflicts 10–15% of people and is often accompanied by cross-reactions to various food substances [19].

Material and Methods

Honey Products

Two types of honey were used: locally collected, unpasteurized, and unfiltered organic honey, i.e. regular honey (RH), and the same honey enriched with bee-collected pollen, i.e. birch pollen honey (BPH). Both products were produced and provided by Kyösti Pitkänen in Kerimäki, SE Finland. Based on microscopical counting, BPH contained 8,400 birch pollen grains and 50 alder pollen grains per gram of honey, on average. RH did not contain birch or alder pollen. The total pollen amounts were considerably higher: 250,000 grains in BPH and 400 grains per gram in RH, mostly due to dominant willows *(Salix)* being the main sources of nectar and pollen for honeybees in the early season.

Patient Recruitment

Members of the local Allergy and Asthma Society were targeted by a newspaper advertisement, resulting in 110 responses. The responders were interviewed in detail by telephone to confirm their physician-diagnosed birch pollen allergy. Sixty-one volunteers were recruited. In 72% of the subjects, the diagnosis was based on a positive skin prick test to birch pollen in addition to typical symptom history. No further testing was performed during the recruitment period. Asthma was not regarded as an exclusion criterion. Informed consent was obtained from all of the subjects in conjunction with the personal delivery of honey. Those in the control group returned their consent by mail.

Study Design

A single-blind randomized trial was performed. A double-blind study design was not applicable due to constraints in the manufacturing and pollen analysis of BPH. Subjects were assigned to 3 groups: BPH, RH, and control. By the end of October 2008, all subjects in the first 2 groups had received 900 g of honey in similar containers without labels. The 2 types of honey (BPH and RH) were indistinguishable in appearance or taste. Each subject was instructed to consume honey on a daily basis, starting with a small droplet (<1 g) in November and increasing the intake at intervals of 3 weeks to a daily maximum of 1 teaspoon (approximately 8 g) till the end of March. The honey had to be taken 'as is' so that it could dissolve slowly in the mouth. Incorporating honey in tea or other substances was not permitted. The participants used diaries to record both the dosage and possible allergy symptoms each day. Treatment compliance was checked from the diaries. Subjects in the control group were advised not to take any honey products during the course of the study.

After the honey regimen all subjects were given a new symptom diary for April and May, accompanied by 2 questionnaires. The first questionnaire was about using honey during the preseason, its useful effects, and its adverse events. The patients filled in a second questionnaire in June after birch pollen season and rated their symptoms and the need for medication.

The main outcomes were the symptoms and the use of medication (antihistamine tablets, nasal sprays, or eye drops) recorded daily in the diary. The study subjects graded 3 groups of symptoms: (1) conjunctival symptoms (itchy, swollen, watery, or sore eyes), (2) nasal symptoms (sneezing, runny, itchy, or blocked nose), and (3) other symptoms, such as itchy skin, from 0 (no symptoms) to 3 (severe symptoms). Daily pollen concentrations were measured by the South Karelia Allergy and Environment Institute in Lappeenranta, SE Finland. Most of the study subjects (85%) lived within a radius of less than 50 km from the pollen-monitoring site.

Data Analysis

The 3 study groups were compared with respect to symptom-free days (no need for medication), days with mild-to-moderate

Table 1. Baseline characteristics of the 61 study patients

	BPH	RH	Control
Subjects, n	25	19	17
Sex ratio (male/female)	12/13	6/13	8/9
Dropouts, n	5	3	3
Age, years [1]	33.0 (17.4)	32.9 (14.8)	35.6 (15.0)
Asthma (physician-diagnosed), %	8	11	0
Birch pollen allergy			
Duration, years[1]	22.7 (10.9)	18.6 (9.0)	18.4 (11.0)
Discomfort (0–10)[1]	6.6 (2.0)	7.3 (2.2)	6.8 (1.7)
Other allergies (physician-diagnosed), %			
Oral allergy syndrome	65	81	43
Grass pollen	25	44	43
Cat or dog	35	56	36
Use of allergy medication, %			
Year round	5	18	7
Regularly during pollen season	75	69	86
As needed during pollen season	20	13	7

[1] Means with standard deviations.

symptoms, and days with severe symptoms using a 1-way analysis of variance. Multiple comparison procedures were used to isolate pairwise the mean differences in those cases where statistically significant results were obtained. A day with severe symptoms was defined as a day in which the sum of eye, nasal, and other symptoms exceeded the value 3. Comparisons were also performed separately for conjunctival symptoms, nasal symptoms, other symptoms, and total symptom scores, i.e. the sum of all symptoms over the 2-month period. The frequencies of days with medication were likewise compared.

Results

Pollen Season

The study season for birch pollination was the long-term average in terms of the total pollen count. The sums of the daily concentrations were 27,460 in 2009 compared to 29,700 which was the mean for 2002–2008. The number of days with high concentrations was 23 compared to 18 (the daily average exceeding 100 pollen grains per cubic meter), and the total number of days with birch pollen in the air was 51 compared to 57. Birch pollen season started on April 25 and high concentrations were measured up to May 26. Pollination of the closely related alder was rather late (from April 2 to May 14, peaking on April 26), and the total concentration remained 30% lower than the average (2,950 in 2009 compared to 4,270 for 2002–2008).

Study Subjects

The 61 subjects (35 females and 26 males) ranged from 8 to 79 years of age (mean 34.2) (table 1). Four patients also reported asthma. The subjects had a long history of birch pollen allergy (mean 20 years) and they rated the severity of their symptoms, on average, at 6.8 on a scale from 0 to 10. All patients had suffered from nasal symptoms, 96% from conjunctival symptoms, and 58% from other symptoms. Ninety-two percent of the patients reported daily symptoms during pollen season, and all patients had used antihistamine medication, usually on a regular basis during the season. Nasal sprays were used by 22 study subjects (topical corticosteroids in 77%): 7/8 in the BPH group, 4/5 in the RH group, and 6/9 in the control group.

Fifty subjects completed the study and 11 dropped out. Two patients did not like the sweetness of the honey, 1 had pronounced itching in the mouth (BPH group), 1 experienced a worsening of atopic eczema (RH group), and 7 had undefined personal reasons.

Effect of Honey on Birch Pollen Allergy

During the 5 preseasonal months (November to March), BPH was consumed on 117 days and RH on 127 days, on average. The total consumption of honey was a rather constant 700 g per participant in both honey groups. In the BPH group this corresponded to approximately 1.2 g of pollen (0.04 g of birch) ingested prior to pollen season. A strong correlation between the reported

Table 2. Number of days in relation to allergic symptoms and use of medication during the birch pollen season from April to May 2009 (61 days)

	BPH	RH	Control	p
Symptom-free days	32.1 ± 14.2^{a}	26.6 ± 16.5^{a}	14.1 ± 12.6^{b}	0.004
Mild-to-moderate symptoms	20.5 ± 11.3	17.2 ± 11.2	18.4 ± 15.0	0.721
Severe symptoms	8.4 ± 10.8^{a}	$17.2 \pm 15.8^{a,b}$	28.6 ± 20.9^{b}	0.003
Conjunctival symptoms	17.3 ± 16.2^{a}	19.5 ± 17.6^{a}	35.5 ± 21.6^{b}	0.016
Nasal symptoms	23.0 ± 12.9^{a}	29.8 ± 20.5^{a}	44.2 ± 12.3^{b}	0.001
Other symptoms	6.5 ± 11.2^{a}	$15.2 \pm 15.3^{a,b}$	22.7 ± 20.8^{b}	0.016
Antihistamine tablets	19.3 ± 15.7^{a}	32.3 ± 18.4^{b}	43.3 ± 20.0^{b}	0.001
Nasal sprays	8.0 ± 13.5	13.4 ± 23.4	19.5 ± 22.0	0.247
Eye drops	6.9 ± 13.4	10.9 ± 19.7	6.0 ± 11.0	0.623

Values are presented as means ± SD. Different superscript letters indicate significant differences between the 3 groups in a pairwise post hoc Duncan test.

amount of honey consumed and the number of consumption days (Spearman's rank correlation, $\rho = 0.581$; $p < 0.001$) indicated good treatment compliance.

Subjects who took BPH had a significantly lower total symptom score during pollen season in comparison to the control group (fig. 1). The difference remained significant when analyzed separately for both April and May. Differences between the 2 honey groups were not statistically significant.

Subjects with either honey treatment had more asymptomatic days than did those in the control group (table 2). The difference was more significant for the BPH group ($p < 0.01$) than for the RH group ($p < 0.05$). Days with mild-to-moderate symptoms were manifested rather equally in all 3 groups, but severe symptoms were reported significantly less in the BPH group compared to the control group ($p < 0.001$), especially during the late pollen season (fig. 2). Conjunctival and nasal symptoms were less frequent in both honey groups compared to the control subjects, but differences between the BPH and RH regimens remained nonsignificant.

During pollen season, patients using BPH needed significantly less antihistamine medication than did the control subjects ($p < 0.001$). The difference was also significant between the BPH and RH groups ($p < 0.05$) but not between the RH and control groups.

In addition to the effects on birch pollen allergy, favorable comments were made by 45% of the BPH group and 38% of the RH group. Specifically, fewer common colds and stomach upsets and better general health were reported by 35% of the patients in the BPH group and by 38% in the RH group compared to 7% in the control group.

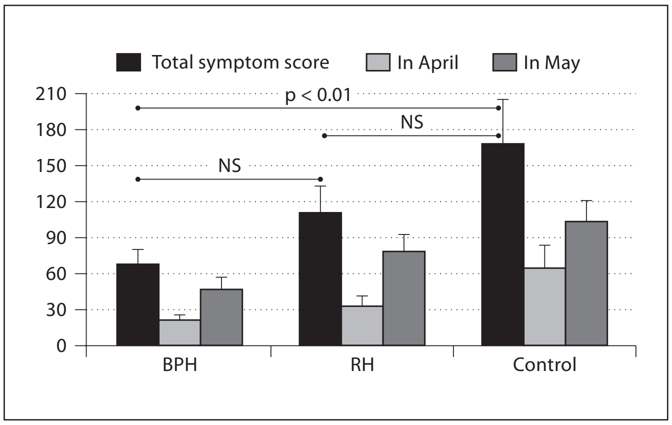

Fig. 1. Total scores of conjunctival, nasal, and other symptoms over the 2-month period. The sums of daily values (0–3) in April and May are presented as subject-specific averages with standard errors in the 3 study groups. The difference between the BPH group and the control group was significant in April ($p < 0.05$) and in May ($p < 0.05$). NS = Not significant.

'Too sweet' or 'did not like the taste' were the commonest reasons for any negative comments, these coming from 35% of the BPH group and 44% of the RH group. Adverse events, mostly mild itching in the mouth or skin or a runny nose, were coincidentally recorded at the beginning of the regimen or following the dosing increase. No severe systemic adverse events were reported.

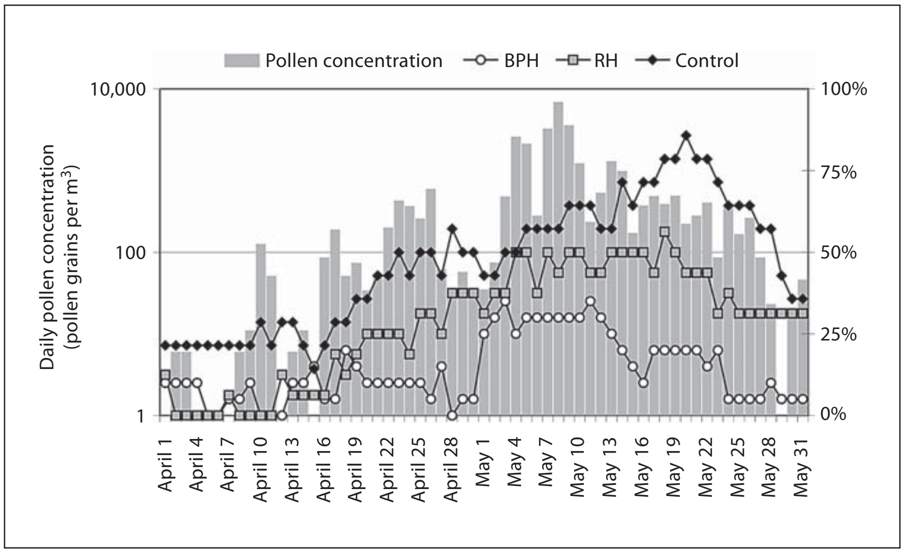

Fig. 2. Proportion of subjects with severe symptoms (symptom score >3) in the 3 study groups over the course of the pollen season from April to May 2009. The bars indicate daily concentrations of alder and birch pollen combined.

Discussion

As birches are the major deciduous trees in northern Europe producing allergenic pollen [20], full avoidance is not possible during pollen season. More than half a million people are allergic to birch pollen in Finland. In the present study, the total symptom scores and severe symptoms correlated well with the daily pollen concentrations in ambient air, as expected [21].

This was a preliminary study of the combined effects of plain organic honey and bee-collected pollen, both of interest in the treatment of allergic disorders. The patients used the study preparation preseasonally, which may not be optimal. BPH is also difficult to standardize, and the result is only valid for the particular honey used. Clinical criteria were used to evaluate the outcome. Immunological tests could have provided additional information.

Traditionally, pollen allergic patients have been instructed to be wary of honey, or to avoid it altogether, as honey often contains traces of compositae pollen in particular [22]. The clinical outcome was contrary to our expectations. The preseasonal use of BPH benefited most subjects. In comparison to the control group, BPH doubled the number of asymptomatic days, reduced the number of severe-symptom days by 70%, lowered the total symptom scores by 60 %, and halved the need for antihistamine medication. The differences between the 2 honey regimens (BPH and RH) were mostly nonsignificant, yet all the outcomes favored BPH. For example, in the BPH group mild symptoms dominated, whereas in the RH group symptomatic days were evenly distributed among mild, moderate, and severe symptoms. Alleviation of the more severe symptoms probably explained the significant decrease in the need for antihistamines following the use of BPH.

After pollen season, 65% of the BPH group and 38% of the RH group were in favor of the honey regimen in general. Two thirds of the subjects (65%) who took BPH reported less of a need for medication than during an average season before treatment. This was true for 44% of those taking RH and for 36% of the control subjects.

BPH contained about 600 times more pollen than did RH. A daily maximum dose of 1 teaspoon contained some 2 million pollen grains, the majority of which were willows (92%), together with approximately 67,000 birch pollen grains (3.4%). This corresponds to temporal concentrations in the ambient air during the peak flowering period in May. Despite the considerable number of pollen grains, immunospot analysis of the allergenicity of BPH resulted only in weak binding to the IgE in a laboratory serum pool of birch-pollen-allergic patients (other than the study subjects) [Mäkinen-Kiljunen, pers. comm. 23]. It is possible that enzymatic and microbial components in honey have an effect on pollen proteins, reducing their allergenic properties, but this hypothesis needs to be tested. RH showed no binding.

The benefit of BPH might be explained by a specific immunotolerance developed during oral use of birch pollen in the complex honey vehicle [14]. BPH may have an effect on specific and innate immunity at the same time [24]. This suggestion certainly warrants further studies but may provide new insight for the development of effective immunotherapy.

Regular organic honey, manufactured and stored below +28°C, also seemed to have some positive effects as indicated by significant differences between the patients on RH and the controls. This may be a placebo effect, but a true benefit cannot be excluded. It should be emphasized that the organic honey used in the study was a prime product based on carefully selected bee communities and hives. It did include a range of pollens, albeit not birch pollen.

Specific immunotherapy administrated via the sublingual (SLIT) or subcutaneous route is currently the only therapy modifying or downregulating the allergic immune response [25]. Gradually increasing amounts of allergen are taken as drops, by oral spray, or as sublingual tablets. Clinical use of SLIT is on the increase as evidence has accumulated showing its efficacy and safety [26–29]. SLIT may even prevent new sensitizations and reduce the risk of developing asthma, and its clinical efficacy lasts several years [27, 30].

Boukraa and Sulaiman [12] state that when using any hive product for medical purposes the challenging problems are dosage and safety. Participants in the present study took BPH daily in incremental amounts, kept the honey in the mouth for several minutes, rubbed it against the palate with the tongue, and then swallowed. This practice may have reduced adverse effects. If the allergenic preparation is swallowed immediately with water, it may cause gastrointestinal side effects [27]. Altogether, honey treatment was well tolerated with few expected local adverse effects. Patients adhered to the regimen and 89% of them wanted to participate in a follow-up study.

A new national allergy program for 2008–2018 has taken off in Finland endorsing tolerance rather than allergen avoidance [31, 32]. More emphasis is placed on specific immunotherapy and the development of practical and safe immunotherapies. Substantial evidence shows that the balance between allergy and tolerance is dependent on regulatory T cells. Especially in early life, an environment rich in microbes reduces the subsequent risk of allergic diseases [32, 33]. As reviewed by von Hertzen et al. [32], continuous stimulation of the immune system by environmental saprophytes via the skin, respiratory tract, and gut appears to be necessary for the activation of the regulatory network, including regulatory T cells and dendritic cells. Exposure to microbial antigens, as well as allergens in foodstuffs and the environment, is decisive. Tolerance induced by allergen-specific regulatory T cells appears to be the normal immunological response to allergens in nonatopic healthy individuals. Healthy subjects have an intact functional regulatory T cell response which is impaired in allergic subjects. Restoration of this response and tolerance induction has been demonstrated during specific immunotherapy and is crucial for a good therapeutic outcome. Honey with pollen together with microbial elements might strengthen both unspecific and specific tolerance and serve as an easy, cheap, and safe therapeutic option against various pollen allergies.

Lots of questions remain. What would be an effective and safe amount and formulation of pollen in honey? What is the best way to administer honey to patients? Which are the allergy-modifying elements in honey: microbes, enzymes, sugars, or proteins, and what are their interactions? What are the mechanisms of the effects on acquired or innate immunity? There now seems to be some foundation for seeking the answers to such questions.

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