



Prevalence of sensitization to weed pollens of *Humulus scandens*, *Artemisia vulgaris*, and *Ambrosia artemisiifolia* in northern China

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Abstract: Objective: Weed pollens are common sources of allergens worldwide. The prevalence of weed pollen sensitization is not yet fully known in China. The purpose of this study was to investigate the prevalence of sensitization to weed allergens from *Artemisia*, *Ambrosia*, and *Humulus* in northern China. Methods: A total of 1 144 subjects (aged from 5 to 68 years) visiting our clinic from June to October 2011 underwent intradermal testing using a panel of 25 allergen sources. Subjects with positive skin responses to any pollen were further tested for their serum concentrations of IgE antibodies against *Artemisia vulgaris*, *Ambrosia artemisiifolia*, and *Humulus scandens*, and against the purified allergens, Art v 1 and Amb a 1. Results: Of 1 144 subjects, 170 had positive intradermal reactions to pollen and 144 donated serum for IgE testing. The prevalence of positive intradermal responses to pollens of *Artemisia sieversiana*, *Artemisia annua*, *A. artemisiifolia*, and *H. scandens* was 11.0%, 10.2%, 3.7%, and 6.6%, respectively. Among the intradermal positive subjects, the prevalence of specific IgE antigens to *A. vulgaris* was 58.3%, to *A. artemisiifolia* 14.7%, and to *H. scandens* 41.0%. The prevalence of specific IgE antigens to the allergen Art v 1 was 46.9%, and to Amb a 1 was 11.2%. The correlation between the presence of IgE antibodies specific to *A. vulgaris* and to the Art v 1 antigen was very high. Subjects with *A. artemisiifolia* specific IgE also had *A. vulgaris* specific IgE, but with relatively high levels of *A. vulgaris* IgE antibodies. There were no correlations between the presence of IgE antibodies to *H. scandens* and *A. vulgaris* or to *H. scandens* and *A. artemisiifolia*. Conclusions: The intradermal prevalence of weed pollen sensitization among allergic subjects in northern China is about 13.5%. Correlations of specific IgE antibodies suggest that pollen allergens from *Artemisia* and *Humulus* are independent sources for primary sensitization.

Key words: *Humulus scandens*, *Artemisia vulgaris*, *Ambrosia artemisiifolia*, Intradermal test, Specific IgE, Sensitization
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1 Introduction

Pollens from weeds are common sources of allergens worldwide. The most well described wind-pollinated genera are *Artemisia* (mugwort) and *Ambrosia* (ragweed) belonging to the family Asteraceae. Japanese hop (*Humulus scandens*) belonging to the family Cannabaceae, is also a wind-pollinated weed.

It has recently spread across large parts of northern China. A recent cross-sectional survey of 6304 Chinese allergic subjects showed that *Artemisia vulgaris* and *Ambrosia artemisiifolia* sensitizations are associated with the severity of intermittent rhinitis (Li et al., 2011).

Mugwort comprises several closely related species, of which *A. vulgaris* is most widespread across Europe, North America, and parts of Asia, and is one of the main causes of pollen allergy late in summer and in autumn. In Central Europe, mugwort pollination

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starts at the end of July and lasts until the end of August (Oberhuber *et al.*, 2008), whereas in the Mediterranean area the flowering period shifts to September and the beginning of October (Spiekma *et al.*, 1980). The prevalence of sensitization caused by mugwort pollen is 17% in Italy (Verini *et al.*, 2001). Mugwort is an important cause of sensitization and allergy in Germany and Switzerland (Schmid-Grendelmeier, 1998; Schäfer *et al.*, 1999; Krämer *et al.*, 2001). A multicenter study showed that about 24% of subjects with asthma and/or rhinitis had positive skin prick tests (SPTs) to *A. vulgaris* in northern China (Li *et al.*, 2009). Allergen microarray analyses of sera from 100 Chinese allergic subjects showed that the highest specific IgE-reactivity towards the pollen allergens investigated was against allergens of Art v (Zheng *et al.*, 2011). An *A. vulgaris* specific IgE prevalence of 88% was found among 50 sera derived from weed-allergic rhinitis patients from Beijing (China) as well as a strong correlation between *A. vulgaris* specific IgE and Art v 1 specific IgE (Han *et al.*, 2011).

Ragweed is the common name for several closely related species of which *A. artemisiifolia* is most widespread. Ragweed is an invasive species in North America, Europe, Australia, and Asia (European Aeroallergen Network <https://ean.polleninfo.eu/Ean> and European Pollen Information <http://www.polleninfo.org>). The flowering period lasts from August to October in Central Europe (Brandes and Nitzsche, 2006). In America, 45% of asthma patients were sensitized to ragweed (Kang *et al.*, 1993). In northern China, about 13% of patients with asthma and/or rhinitis had a positive SPT reaction to *A. artemisiifolia* (Li *et al.*, 2009). The prevalence of ragweed specific IgE among SPT weed pollen positive Chinese subjects has been reported to be 38% (Han *et al.*, 2011).

Japanese hop is widespread in China and Korea with a flowering period lasting from August to October (Yin *et al.*, 1996; Park J.W. *et al.*, 1999; Park H.S. *et al.*, 2001). Aerobiological studies in Beijing (China) and Korea showed that *H. scandens* pollen counts are larger than those of both mugwort and ragweed and account for about 18% of total pollen during the pollination period (Park J.W. *et al.*, 1999). The flowering periods of mugwort, ragweed, and Japanese hop almost overlap, making it difficult to

distinguish which pollen species is responsible for sensitization and allergic reactions. Specific diagnosis and identification of primary sensitizing weed species is also hampered because many allergy clinics in China do not have access to species specific IgE testing (Han *et al.*, 2011). Thus, the true prevalence of weed pollen sensitization is probably not yet fully known. The purpose of this study was to investigate the prevalence of sensitization to mugwort, ragweed, and Japanese hop as measured by intradermal testing of 1144 allergic subjects visiting an allergy department in the city of Tangshan in Hebei Province in northern China, and by specific IgE testing of 144 subjects having positive intradermal reactivity against weed pollen allergens.

2 Materials and methods

Subjects with a clinical history of allergic rhinitis/asthma and/or allergic dermatitis, who visited the Department of Allergy, Tangshan Gongren Hospital, China, from mid-June to mid-October 2011, were included in this study. A total of 1144 subjects, from 5 to 68 years old, underwent intradermal testing using a panel of 25 allergen sources (1:5 to 1:50 (w/v) extract dependent on allergens and with 100 times dilution for intradermal tests; Beijing Macro-Union Pharmaceutical Co. Ltd., China), including *Artemisia sieversiana*, *Artemisia annua*, *A. artemisiifolia*, and *H. scandens* (1000 times dilution) (Table 1). Histamine (0.01 mg/ml) and saline were used as positive and negative controls, respectively. None of the subjects included in the study took medications, such as antihistamines or steroids for at least two weeks before the intradermal tests. The means of the longest diameter and the length of a perpendicular line through the middle of the wheal after 15 min were measured. Positive reaction was defined as a wheal size of >5 mm. All the subjects ($N=170$) having positive skin responses to any pollen (Table 1) were asked to donate blood for specific IgE tests. All subjects provided informed consent. A total of 144 serum samples were collected and stored in a freezer before specific IgE measurements were made.

Specific IgE concentrations against *A. vulgaris*, Art v 1, *A. artemisiifolia*, Amb a 1, and *H. scandens* were measured using the ADVIA Centaur® (Siemens

Table 1 Overall prevalence of positive skin responses in intradermal tests

Allergen source	Positive patient ^a	Wheal size (mm) ^b
House dust	361 (31.6%)	7.2 (6.0; 3.0–15.5)
<i>Dermatophagoides pteronyssinus</i>	466 (40.7%)	8.8 (8.0; 3.0–19.0)
<i>Dermatophagoides farinae</i>	453 (39.6%)	8.4 (8.0; 3.0–20.0)
Cotton	143 (12.5%)	6.1 (6.0; 5.0–10.0)
Silk	103 (9.0%)	3.6 (6.0; 5.0–12.0)
Buckwheat shell	139 (12.2%)	6.5 (6.0; 5.0–10.0)
<i>Ricinus communis</i>	101 (8.8%)	6.5 (6.0; 5.0–10.0)
Cat	164 (14.3%)	6.5 (6.0; 5.0–12.0)
Dog	163 (14.2%)	6.3 (6.0; 5.0–10.0)
Cockroach	301 (26.3%)	6.1 (6.0; 5.0–12.5)
Mold mix I	227 (19.8%)	7.5 (7.0; 5.0–12.0)
Mold mix II	186 (16.3%)	7.0 (6.0; 4.0–15.0)
Animal hair mix	100 (8.7%)	6.5 (6.0; 5.0–15.0)
Feather mix	132 (11.5%)	6.5 (6.0; 5.0–12.0)
Tobacco	165 (14.4%)	5.9 (6.0; 5.0–10.0)
Spring pollen mix I*	55 (4.8%)	8.3 (8.0; 4.5–16.0)
Spring pollen mix II*	54 (4.7%)	9.9 (10.0; 5.0–22.0)
Spring pollen mix III*	59 (5.2%)	9.9 (10.0; 4.5–21.0)
Summer/autumn pollen mix I*	116 (10.1%)	11.0 (10.0; 3.5–21.0)
Summer/autumn pollen mix II*	58 (5.1%)	9.5 (9.75; 5.0–17.0)
<i>Platanus acerifolia</i> *	24 (2.1%)	9.9 (10.0; 6.0–16.0)
<i>Artemisia sieversiana</i> *	126 (11.0%)	12.5 (12.0; 3.0–25.0)
<i>Artemisia annua</i> *	117 (10.2%)	12.5 (12.0; 5.0–22.0)
<i>Ambrosia artemisiifolia</i> *	42 (3.7%)	9.7 (8.0; 5.0–19.0)
<i>Humulus scandens</i> *	75 (6.6%)	13.0 (12.5; 5.0–24.5)

Mold mix I: *Penicillium chrysogenum*, *Aspergillus niger*, *Trichoderma koningii*, *Mucor racemosus*, *Rhizopus stolonifer*; Mold mix II: *Stemphylium* spp., *Curvularia lunata*, *Cladosporium macrocarpum*, *Helminthosporium sorokinianum*, *Saccharomyces cerevisiae*; Animal hair mix: wool, camel hair, cony hair, pig hair, horse; Feather mix: chicken feather, duck feather, goose feather; Spring pollen mix I: *Cryptomeria fortunei* (*Crypomeria japonica*, sugi), *Cunninghamia lanceolata* (China fir), *Populus deltoids* (cottonwood), *Ulmus pumila* (Siberian elm), *Salix caprea* (willow); Spring pollen mix II: *Betula verrucosa* (birch), *Platanus acerifolia* (maple), *Quercus alba* (white oak), *Juglans californica* (walnut), *Brassica campestris* (rape); Spring pollen mix III: *Morus alba* (white mulberry), *Ginkgo biloba* (ginkgo), *Spinacia oleracea* (spinach), *Typha angustifolia* (bulrush); Summer/autumn pollen mix I: *Helianthus annuus* (sunflower), *Xanthium sibiricum* (cockle bur), *Chenopodium album* (goosefoot), *Cannabis sativa* (hemp fumble); Summer/autumn pollen mix II: *Zea mays* (corn), *Sorghum vulgare* (sorghum), *Scirpus planiculmis* (sedge), *Ricinus communis* (castor-oil-plant). * Pollen allergen sources used in intradermal tests; ^a Number (percentage), total number is 1144; ^b Mean (median; range)

Medical Solutions, Diagnostics, NY, USA), which is a reverse sandwich immunoassay using direct chemoluminescent technology (Petersen *et al.*, 2004). Allergen extracts, calibrators, controls, and universal reagent packs were produced by ALK-Abelló (Hørsholm, Denmark). Single allergens Art v 1 and Amb a 1 were purified by ALK-Abelló as described by Jimeno *et al.* (2004). The assay procedure was automatically performed and the results are expressed as kU/L for *H. scandens*, *A. vulgaris*, and *A. artemisiifolia*, while for Art v 1 and Amb a 1 the results are reported in arbitrary units (AU/L) only. A result of ≥ 0.35 kU/L (or AU/L) was defined as positive: <0.35 , class 0; 0.35–0.70, class 1; 0.70–3.50, class 2; 3.50–17.50, class 3; 17.50–50.00, class 4; 50.00–100.00, class 5; >100.00 , class 6.

The linear regressions were plotted and *P* values were calculated at 95% confidence intervals using Graph Pad Prism Version 5.04.

3 Results

3.1 Intradermal reactivity against 25 allergen sources

Tangshan is the largest city in Hebei, a province with 68.5 million inhabitants located in the northern part of China. In the period mid-June to mid-October 2011, 1144 subjects (aged 5–68 years; M/F, 612/532) with allergic symptoms were given intradermal tests. Of the 1144 patients, 355 (31.0%) showed negative reactions to all allergens. Multiple sensitizations were

common in the intradermal tests and 63.8% of subjects had positive reactions to more than three allergen sources. Positive reactions to the house dust mite were by far the largest group of positive reactions (40%). Of the 1144 subjects tested, 170 (14.9%) had at least one positive reaction to pollens and 154 subjects (13.5%) were positive to weed pollens. The proportions of patients having skin positive responses to *A. sieversiana*, *A. annua*, *A. artemisiifolia*, and *H. scandens* were 11.0%, 10.2%, 3.7%, and 6.6%, respectively (Table 1). A significant correlation ($P<0.001$, $N=174$, $R^2=0.69$) of skin positive reaction (mm vs. mm, diameter) between *A. sieversiana* and *A. annua* was observed. No correlations were found by comparing intradermal test results among the other weed pollens.

3.2 Weed pollen allergen specific IgE

A total of 144 serum samples were collected from subjects with positive intradermal test results for pollens and analyzed for specific IgE against *A. vulgaris*, Art v 1, *A. artemisiifolia*, Amb a 1, and *H. scandens*. The results are shown in Fig. 1.

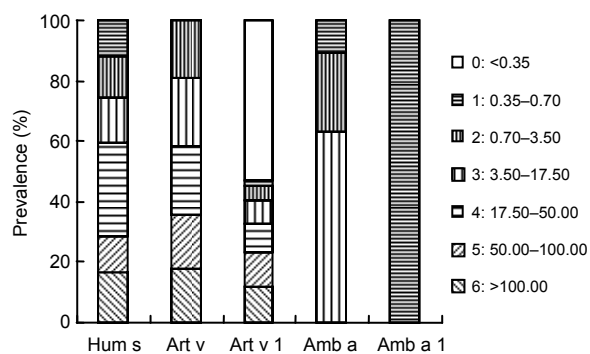


Fig. 1 Prevalence of specific IgE reactivity (positive percentage in different classes) to weed pollen and individual major allergens ($N=144$)

Hum s: *Humulus scandens*

The prevalence of IgE antibodies specific to *A. vulgaris* was 58.3%, to Art v 1 46.9%, to *A. artemisiifolia* 14.7%, to Amb a 1 11.2%, and to *H. scandens* 41.0%.

Table 2 shows that 64 of the 84 *A. vulgaris* specific IgE positive subjects (76.2%) were also found to be specific IgE positive to Art v 1. Only 3 of the 20 *A. vulgaris* negative subjects (15%) were IgE positive to Art v 1 (with low IgE levels). Among the 21 *A. artemisiifolia* IgE positive subjects, only 8 (38.1%) were IgE positive to Amb a 1. There were 16 subjects with specific IgE-reactivity towards Amb a 1 but only 8 of these subjects were specific IgE positive to *A. artemisiifolia*. The correlation for the presence of specific IgE between *A. vulgaris* and Art v 1 was very high ($P<0.001$, $R^2=0.96$, $N=110$). However, the correlation for the presence of specific IgE between *A. artemisiifolia* and Amb a 1 was low ($R^2=0.05$, Fig. 2). *A. artemisiifolia* specific IgE reactivity was strongly associated with *A. vulgaris* sensitivity. Almost all *A. artemisiifolia* sensitive subjects were sensitized to *A. vulgaris*, with a much higher IgE level. No subjects were found to be specific IgE mono-sensitized to *A. artemisiifolia*.

Of the 59 subjects with *H. scandens* specific IgE, 29 (49.2%) and 12 (20.3%) were found to be IgE positive to *A. vulgaris* and *A. artemisiifolia*, respectively. However, there were no correlations between *H. scandens* and *A. vulgaris* or between *H. scandens* and *A. artemisiifolia* for the presence of specific IgE.

A total of 144 serum samples were collected in this study. The highest number of sera with specific IgE against *A. vulgaris* was collected during August and September. For *H. scandens*, the highest number of sera was collected during August to October and, for *A. artemisiifolia* it was in September. However, the correlation (positive vs. negative) between intradermal tests and specific IgE tests was low in this study (data not shown).

Table 2 Combined specific IgE sensitizations

Specific IgE	Sensitization (%)				
	<i>Humulus</i>	<i>Artemisia</i>	<i>Ambrosia</i>	Art v 1	Amb a 1
All ($N=144$)	41.0	58.3	14.7	46.9	11.2
<i>Humulus</i> IgE positive ($N=59$)	100.0	49.2	20.3	33.9	11.9
<i>Artemisia</i> IgE positive ($N=84$)	34.5	100.0	22.6	76.2	19.1
<i>Ambrosia</i> IgE positive ($N=21$)	57.1	90.5	100.0	81.0	38.1
Art v 1 IgE positive ($N=67$)	29.9	99.5	25.4	100.0	23.9
Amb a 1 IgE positive ($N=16$)	43.8	100.0	50.0	100.0	100.0

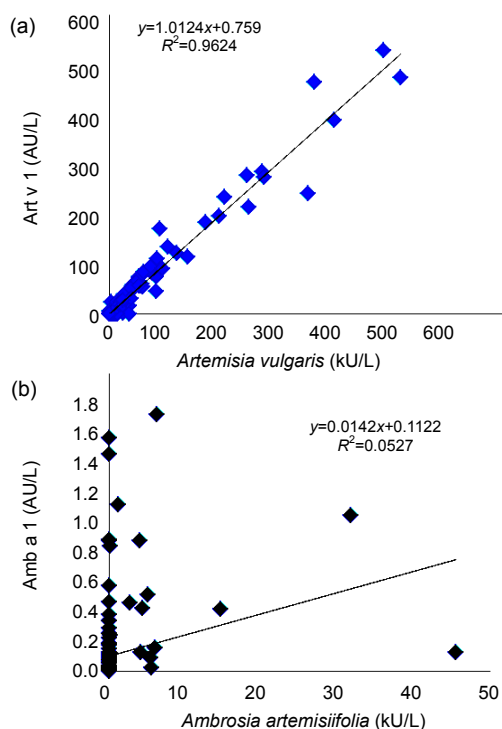


Fig. 2 Specific IgE correlations between *Artemisia vulgaris* and Art v 1 (a) and between *Ambrosia artemisiifolia* and Amb a 1 (b)

4 Discussion

In this study, the sensitization of 1 144 subjects visiting an allergy clinic in northern China during the period June to October was tested by intradermal testing using a panel of 25 allergen sources. In agreement with other studies (Li *et al.*, 2009; Yang *et al.*, 2011), the highest prevalence of sensitization (40%) was found for house dust mites. The number of sera collected having specific IgE against weed pollens was highest during the period August to October, reflecting the period of peak levels of exposure to weed pollens in northern China. Of the 1 144 subjects visiting the clinic, 154 showed positive intradermal reactivity to weed pollens, suggesting a prevalence of weed pollen allergy of 13.5% among this selected group of subjects. The highest allergy prevalence among weed pollens was for the *Artemisia* species (10%–11%). A relatively high prevalence of 6.6% was also shown for Japanese hop, whereas the prevalence of ragweed allergy was below 4%. The percentages of positive reactions to mugwort and ragweed in intradermal tests in the present study were

lower compared to those from SPT results obtained in a previous study (Li *et al.*, 2009). The difference may be due to the methods used to measure skin sensitivity and/or differences in the allergenic extracts being used. Furthermore, in the present study all the subjects with allergic symptoms in the pollen season underwent intradermal tests whereas Li *et al.* (2009) investigated only selected subjects diagnosed with rhinitis and/or asthma throughout the year.

The present study shows a close correlation in intradermal skin sensitization between *A. sieversiana* and *A. annua*, suggesting a strong IgE-mediated cross-reactivity among the *Artemisia* species, in agreement with the findings of Katial *et al.* (1997). For *Artemisia* specific IgE testing, we chose to use *A. vulgaris* since it is best characterized of the *Artemisia* species.

Specific IgE testing showed that many weed pollen sensitized subjects are sensitized against two or more different weeds. A strong correlation between the presence of *A. vulgaris* and *A. artemisiifolia* specific IgE together with the finding that all subjects with ragweed IgE also had specific IgE against mugwort, suggests a high degree of IgE-mediated cross-reactivity between ragweed and mugwort. This is also in agreement with previous findings (Han *et al.*, 2011). For Japanese hop, even if multiple sensitizations were evident, the lack of significant correlations between the presence of specific IgE of *H. scandens* and *A. vulgaris* and *A. artemisiifolia*, suggests a low degree of cross-reactivity towards other weed pollen allergens. This is further supported by the fact that the major allergen of Japanese hop appears to be a protein of 10 kDa that is unique to Japanese hop, and that its binding to *H. scandens* specific IgE cannot be inhibited by extracts from mugwort or ragweed (Park J.W. *et al.*, 1999). Given its specific sensitization and the relatively high specific IgE prevalence of 41%, it is likely that pollen from Japanese hop is an important source for primary sensitization in northern parts of China.

Specific IgE tests in the present study suggest that mugwort and Japanese hop are important primary sensitizing allergen sources whereas the apparent ragweed sensitization is largely a result of IgE-mediated cross-reactivity primarily towards mugwort. This observation is supported by previous findings among allergic subjects from Beijing, China (Han *et*

al., 2011). The reason why ragweed seems to be of minor importance as a primary sensitizing source in China compared to other parts of the world is probably related to the levels of pollen exposure in different geographical regions. Short ragweed is abundant in Europe and USA, but has also spread in northern China (Qiao and Ye, 2005). However, it grows best under warm and moist conditions, while low temperatures and inadequate water supply delay its development (Brandes and Nitzsche, 2006). The relatively dry climate and cold winters in northern China may hamper its development.

Movérare *et al.* (2011) showed that the prevalence of *A. vulgaris* specific IgE was significantly higher in serum samples from North Europe than in those from North America, but *A. artemisiifolia* specific IgE was more common in North American than in European samples. Asero *et al.* (2006) showed that in Italy only 7% of *A. vulgaris* sensitive patients were not sensitized to *A. artemisiifolia*, whereas 62% of *A. artemisiifolia* sensitive patients were not sensitized to *A. vulgaris*. In this study, the prevalence of specific IgE against tree and grass pollens has not been investigated, in part due to the complexity of tree and grass pollen mixtures used for intradermal testing, and to the relatively low skin-prick and specific IgE prevalence reported elsewhere (Li *et al.*, 2009; Zheng *et al.*, 2011).

As the flowering periods of Japanese hop, mugwort, and ragweed are partly overlap in northern China, accurate weed pollen specific diagnosis is very difficult during routine clinical practice. The poor correlation between intradermal tests and specific IgE measurements in this work indicates that diagnosis of specific pollen allergies cannot be achieved solely by intradermal testing. For example, there were 21 subjects who showed positive reactions to *H. scandens* in intradermal tests, but no specific IgE to *H. scandens*. On the other hand, 10 subjects with negative skin reactions to *Humulus* had high *Humulus* specific IgE concentrations. The use of major allergens as diagnostic tools may be of help to facilitate proper diagnosis. Art v 1 is a major allergen with a prevalence of specific IgE in 79%–95% of *Artemisia* allergic patients (Himly *et al.*, 2003; Oberhuber *et al.*, 2008). The present study showed that 76% of patients positive to *Artemisia* were also positive to Art v 1; only 15% of *Artemisia* negative patients were Art v 1

positive. There was a very strong correlation between the levels of specific IgE to Art v 1 and to *A. vulgaris*, in agreement with Han *et al.* (2011), indicating that generally Art v 1 can be regarded as a good indicator of true ragweed sensitization. A previous study also showed that Amb a 1 was a major allergen in ragweed and more than 95% of ragweed allergic patients have been reported to have IgE antibodies to Amb a 1 (Gadermaier *et al.*, 2008). However, in this study the IgE positive reaction against ragweed was likely due to cross-reactivity with mugwort. Similar specific molecular indicators for Japanese hop sensitization still need to be identified.

In conclusion, based on intradermal testing and specific IgE measurements, pollens of *A. vulgaris* and *H. scandens* are independent and important allergen sources giving rise to a relatively high prevalence of allergic sensitizations in northern parts of China.

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