
Two-spotted spider mite (*Tetranychus urticae*): an important allergen in asthmatic non-farmers symptomatic in summer and fall months

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Background: The *Tetranychus urticae* (two-spotted spider mite, TSM) is a spider mite commonly found on fruit trees, herbaceous plants, and greenhouse flowers.

Objective: To evaluate the clinical significance of TSM-derived allergens in non-farmers with asthma living around pear orchards, and to assess the allergenic relationship with house dust mite.

Methods: Skin prick tests with TSM were performed in 50 asthmatic non-farmers living around pear orchards. The serum TSM-specific IgE was measured in the 16 asthmatics with a positive skin response to TSM. To diagnose TSM-induced asthma, specific bronchial challenges with TSM were performed in the 16 asthmatics. ELISA inhibition tests were performed to assess the allergenic cross-reactivity with house dust mites.

Results: Ten of the 16 asthmatics with positive skin responses to TSM showed a significant bronchoconstriction following inhalation of TSM. Eight of the ten TSM-induced asthmatics had high serum TSM-specific IgE and one showed a positive skin response only to TSM. Their asthmatic symptoms were aggravated seasonally, especially in summer and early fall. On ELISA inhibition tests, partial inhibitions with *D. pteronyssinus* antigens were noted in sera from five asthmatics with positive skin responses to both TSM and *D. pteronyssinus*, although no inhibition was noted in serum from an asthmatic with a positive skin response only to TSM.

Conclusion: *Tetranychus urticae* may be an important allergen in asthmatic non-farmers living around pear orchards and TSM extracts contain species-specific allergens as well as commonly shared allergens with house dust mite.

Ann Allergy Asthma Immunol 2000;84:543–548.

INTRODUCTION

Tetranychus urticae, also known as the two-spotted spider mite (TSM), is a common phytophagous mite which damages fruit trees, herbaceous plants, and greenhouse flowers. This mite is

known to be distributed worldwide, and is usually encountered in humid and warm areas.¹ Colonies of these mites are formed on the surface of leaves, and each colony can contain hundreds of individual mites. This mite belongs to the order Acari, to the suborder Prostigmata, to the family Tetranychidae, and to the genus *Tetranychus*. It represents its own species.² Previous reports about spider mite allergy, including TSM allergy, have only been done on occupational situations, although these mites may cause asthma, rhinoconjunctivitis, and urticaria in other exposed individuals.^{3–10}

Two-spotted spider mite is known to be the most important mite damaging pear leaves in Korea. Many adults living in the rural areas of the Korean mainland have worked in pear orchards. We can also assume that many inhabitants living around pear orchards have been exposed to this mite, and that this mite may be an offending allergen in the exposed non-farmers as well as in pear-cultivating farmers. House dust mites are known as a major cause of respiratory allergy in subtropical areas including Korea.¹¹ The house dust mites also belong to the order of Acari, but to the suborder of Astigmata. Previous reports have not demonstrated any clear allergenic relationship between TSM and house dust mites.^{3–8}

The aim of this study was to evaluate the clinical significance of TSM-derived allergens in asthmatic non-farmers living around pear orchards, the clinical characteristics of TSM-induced asthma, and the possible allergenic relationship of TSM to house dust mites.

SUBJECTS AND METHODS

Subjects

A total of 50 asthmatics visiting the allergy clinic of Dankook University Hospitals were enrolled in this study. Asthma was diagnosed if patients with asthmatic symptoms showed reversible airway obstruction, defined as improvement of FEV₁ more than 15% of predictive value after inhalation of short-acting β_2 -agonists. Sixteen (31.3%) of the 50 asthmatics showed a positive skin response to TSM extracts on skin prick tests. All

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Received for publication October 5, 1999.
Accepted for publication in revised form December 22, 1999.

16 asthmatics underwent methacholine bronchial provocation tests to assess nonspecific bronchial hyperresponsiveness, and allergen-specific bronchial provocation tests with TSM extracts to diagnose TSM-induced asthma. Peripheral bloods were drawn from all the asthmatics to measure serum TSM-specific IgE and total serum IgE levels. To determine the allergenic cross-reactivity with house dust mite, ELISA inhibition tests were performed using sera from five asthmatics with positive skin responses to TSM and house dust mites, and from an asthmatic with a positive skin response only to TSM. All of the 16 subjects gave their informed consents, which were regulated by Dankook University College of Medicine. The study protocol was approved by the Ethics Committee of Dankook University Hospital.

Methacholine Bronchial Challenge

FEV₁ was measured with a spirometer (Master Lab, Germany), and the largest value of triplicate FEV₁ was adopted. Methacholine bronchial challenge was carried out, using the methods of Chai et al with some modifications.¹² Concentrations of 0.0625, 0.125, 0.625, 1.25, 2.5, 6.25, 12.5, 25, and 50 mg/mL of methacholine were prepared by dilution with buffered saline. A Rosenthal-French dosimeter (Laboratory for Applied Immunology, Baltimore, USA) was used to deliver the aerosol generated by a nebulizer (Devilbiss, USA). If the concentration

of methacholine causing a 20% fall in FEV₁ (PC₂₀-methacholine) was less than 16 mg/mL, a subject was considered to be hyperresponsive to methacholine.

Preparation of TSM extract

Two-spotted spider mites were provided from the Apple Research Center in Korea. They were extracted with phosphate-buffered saline with a 1:5 wt/vol ratio at 4°C for 1 hour, followed by centrifugation at 3,000 *g*. The supernatant was dialyzed (the cut-off molecular weight was 6,000 D) against 4 L of distilled water at 4°C for 48 hours. The protein content was measured using the Lowry method. The protein content of the supernatant was 2.795 mg/mL. For skin prick tests, the extract was mixed with an equal amount of sterile glycerin. The extract was lyophilized and stored at -70°C for ELISA and ELISA inhibition tests.

Skin Prick Test

Skin prick tests were performed using 55 commonly available inhalant allergens (Allergopharma Co, Germany) and TSM. A positive control of histamine (1 mg/mL, Allergopharma Co, Germany), along with a negative control of diluent (Allergopharma Co, Germany), was included in all tests. None of the subjects had received antihistamines orally during the 5 days preceding the study. Fifteen minutes after the prick test, the mean diameter of the wheal formed by the allergen was measured. A positive skin re-

sponse was defined as a mean wheal size larger than 3 mm.

ELISA for Serum-Specific IgE to TSM Extract

The presence of serum-specific IgE to TSM was determined by ELISA. Microtiter plates (Dynatech, USA) were coated with 50 μ L/well of TSM extracts (10 μ g/well) according to the preliminary result (Fig 1), and stored overnight at 4°C. Each well was washed three times with 0.05% Tween phosphate buffered saline (PBS-T). The remaining binding sites were blocked by incubation with 350 μ L of 3% BSA-PBS-T for 1 hour at room temperature. The wells were then incubated for 2 hours at room temperature with 50 μ L of the patient's serum. Control serum (undiluted) was prepared from 30 asthmatic patients showing negative responses to skin prick test for common inhalant allergens as well as with TSM. After being washed three times with PBS-T, 50 μ L of the 1:1,000 vol/vol biotin-labeled goat anti-human IgE antibody (Vector Co, USA) were added to the wells and incubated for 2 hours at room temperature. The wells were then washed three times with PBS-T and incubated with 1:1,000 vol/vol streptavidin-peroxidase (Sigma Co, USA) for 30 minutes. One hundred microliters ABTS (2,2'-azinobis-3-ethyl-benzthiazoline sulfuric acid in a citrate phosphate buffer) was added to the wells, incubated for 10 minutes at room temperature, and washed with PBS-T. The reaction was stopped by the addition of 100 μ L 2 M sodium azide and the absorbance was read at 410 nm by an automated microplate reader. All assays were performed in duplicate. The cut-off value (120) of the positive IgE binding was determined from the mean plus 2-fold standard deviation of the absorbance value (OD, $\times$ 1000) from 30 control subjects.

ELISA Inhibition Test

Competitive ELISA inhibition tests were performed to determine the specificity of the IgE binding to the TSM and the allergenic cross-reactivity to

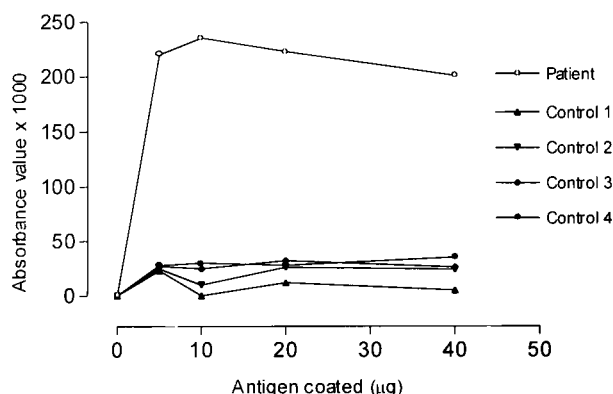


Figure 1. Specific IgE bindings to *Tetranychus urticae* in sera from one asthma patient and four controls.

house dust mites. The sera of the patients who had high specific IgE binding were pooled. Fifteen microliters from these pooled sera was preincubated with four concentrations (0.1 to 100 μ g/mL protein concentration) of TSM, *Dermatophagoides pteronyssinus* (Pharmacia, Uppsala, Sweden), and Hop Japanese (*Humulus japonicus*) pollen (Allergopharma, Germany) for 1 hour at room temperature. Each sample was then incubated with the TSM-coated microtiter plate for 2 hours. The same steps were followed as in the ELISA. After studying the control samples in which equal volumes of phosphate-buffered saline (pH 7.5) were preincubated instead of inhibitors, we found that the inhibition of the specific IgE binding was expressed as [100 – (absorbance of samples preincubated with allergens/absorbance of samples pre-incubated with PBS) $\times$ 100 (%)].

TSM-Specific Bronchial Challenge

After measurement of baseline lung function, FEV₁ was measured after

five inspiratory capacity breaths of buffered saline for a reference value. As in methacholine bronchial challenges, a Rosenthal-French dosimeter (Laboratory for Applied Immunology, Baltimore, USA) was used to deliver the aerosol generated by a nebulizer (Devlbiss, USA). For the tests, the TSM extract (protein content was 2.795 mg/mL) was diluted with buffered saline. After five inspiratory capacity breaths with the extract of 1:100 dilution, FEV₁ was measured every 10 minutes. If FEV₁ did not decreased more than 15% compared with the reference FEV₁ during the first hour after the inhalation, an extract of 1:10 dilution was inhaled. FEV₁ was then measured again every 10 minutes for 1 hour after the inhalation, and then every 30 minutes for the next 9 hours. The test was defined as positive if FEV₁ decreased more than 15% compared with a reference FEV₁.

Statistical Analysis

Results were expressed as the mean $\pm$ standard deviation (SD) unless other-

wise indicated. The Mann-Whitney U test was used to evaluate the statistical significance between the two groups. A *P* value of less than .05 level was considered to be significant.

RESULTS

Table 1 shows the clinical characteristics of the 16 asthmatic subjects with positive skin responses to TSM extracts. The mean duration of asthmatic symptoms in the 10 TSM-induced asthmatics was 90.2 $\pm$ 88.2 months. Their asthmatic symptoms were aggravated between May and October, especially in summer and early fall. Seven positive responders had rhinitis symptoms, one had conjunctivitis symptoms, and one had urticaria. None of them had worked in pear orchards, although all of them had lived around pear orchard areas from childhood. All except one patient showed bronchial hyperresponsiveness to methacholine. There were no significant differences in age, duration of asthmatic symptoms, % predictive value of FEV₁ at

Table 1. Clinical Characteristics of the Patients

Patient	Sex	Age (yr)	Diagnosis	Symptom duration (m)	Occupation	Smoking (pack year)	Aggravated season	FEV ₁ /FVC (%)/(%)	PC ₂₀ (mg/mL)
Positive responders†									
1	M	18	BA	24	Student	0	May–Oct	96.0/104.1	1.34
2	M	32	BA + AR	2	Salaried man	10	Aug–Oct	88.2/97.6	1.88
3	M	17	BA + AR	24	Student	1.5	May–June, Sep–Oct	92.9/101.0	4.49
4	F	17	BA + AR + U	36	Student	0	May–July, Sep–Oct	97.0/94.9	0.14
5	M	25	BA + AR	120	Student	0	June–Sep, Nov–Feb	103.0/92.6	50
6	M	33	BA	240	Driver	10	June–Sep	98.7/113.0	2.5
7	M	58	BA	36	Mushroom cultivator	10	July–Aug	84.0/105.0	0.5
8	F	50	BA + AR + AC	240	House wife	0	June–Aug	110.0/105.0	4.65
9	M	20	BA + AR	120	Soldier	2	Aug–Oct	92.0/105.0	8.41
10	M	55	BA + AR	60	breeder of fowl	10	July–Oct	77.6/93.0	1.5
Negative responders‡									
1	M	64	BA	120	Teacher	40	July–Oct	95.3/107.0	2.17
2	M	38	BA + AR	36	Merchant	20	June–Aug, Nov–Feb	120.0/120.0	25
3	F	63	BA + AR	3	House wife	0	May–Nov	103.0/105.0	17.43
4	M	44	BA + AR	2	Merchant	0	July–Oct	69.1/70.7	4.27
5	M	61	BA	72	Soldier	0	May–July, Sep–Oct	92.6/105	5.23
6	M	17	BA + AR	24	Student	0	Perennial	104/109.6	9.47

BA: bronchial asthma; AR: allergic rhinitis; m: month; PC₂₀: PC₂₀-methacholine; U: urticaria; and AC: allergic conjunctivitis.

† Asthmatics with positive bronchial response to TSM extracts.

‡ Asthmatics with negative bronchial response to TSM extracts.

Table 2. Allergy Test Profiles of the Patients

Patient	Skin Responses to Common Allergen	Skin Responses* (A/H, mm)	Total IgE (IU/mL)	ABPT† Response	ABPT Threshold for Allergen (vol/vol)
Positive responders*					
1	<i>D. farinae</i> , grass	5/4	650.8	Early	1:100
2	<i>D. pteronyssinus</i> , <i>D. farinae</i> , cat tree, grass, weed	5/5	1,000	Early	1:100
3	<i>D. pteronyssinus</i> , <i>D. farinae</i> , cat	5/3	210.9	Early	1:100
4‡	None	4/4	208.6	Dual	1:100
5	Grass	3/5	846.7	Late	1:100
6	<i>D. pteronyssinus</i> , <i>D. farinae</i> , weed	4/5	530.4	Dual	1:100
7	<i>D. pteronyssinus</i> , <i>D. farinae</i> , dog	5/3	1,000	Late	1:100
8	<i>D. pteronyssinus</i> , tree, grass	5/4	1,000	Early	1:100
9	<i>D. pteronyssinus</i> , <i>D. farinae</i> , weed	8/4	152.9	Early	1:100
10	Rabbit	5/3	798	Early	1:10
Negative responders**					
1	Weed	4/3	556.4		
2	<i>D. pteronyssinus</i> , <i>D. farinae</i> , weed	3/4	1,000		
3	None	3/4	69.6		
4	None	3/4	304.1		
5	None	3/5	74.7		
6	<i>D. pteronyssinus</i> , <i>D. farinae</i>	3/3	510		

* Skin response to *Tetranychus urticae*. A/H; wheal size formed by allergen/histamine.

† ABPT: specific bronchial provocation test to TSM extracts.

‡ Patient who showed sensitization only to *Tetranychus urticae*.

* Asthmatics with positive bronchial response to TSM extracts.

** Asthmatics with negative bronchial response to TSM extracts.

initial visit, or PC₂₀-methacholine between TSM-induced asthmatics and the asthmatics with negative bronchial response to TSM extract ($P > .05$, respectively).

Table 2 shows allergy test profiles of the study subjects. All patients showed positive skin-prick response to TSM extract. Ten of the 16 asthmatics showed a positive bronchial response after inhalation of TSM extracts. Six showed an early reaction, two a late, and two a dual reaction. Nine of the ten positive responders showed concurrent positive skin responses to other inhalant allergens, among which *D. pteronyssinus* was the most common sensitizing allergen. Three of the positive responders showed a negative skin response to house dust mites, and one of the three showed a positive skin response only to TSM. The patient with a positive skin response only to TSM showed strong dual bronchial responses to TSM extracts, which was persisted for several days.

On skin prick tests, the mean wheal size in reaction to TSM was larger in the positive responders than in the neg-

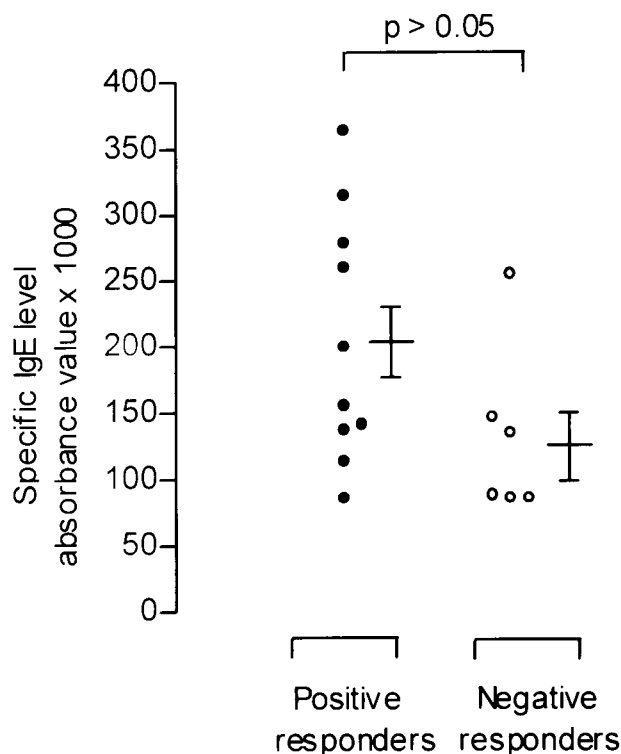


Figure 2. Comparison of specific IgE bindings to *Tetranychus urticae* in positive and negative responders on specific bronchial provocation tests. Horizontal bars indicate mean $\pm$ SEM.

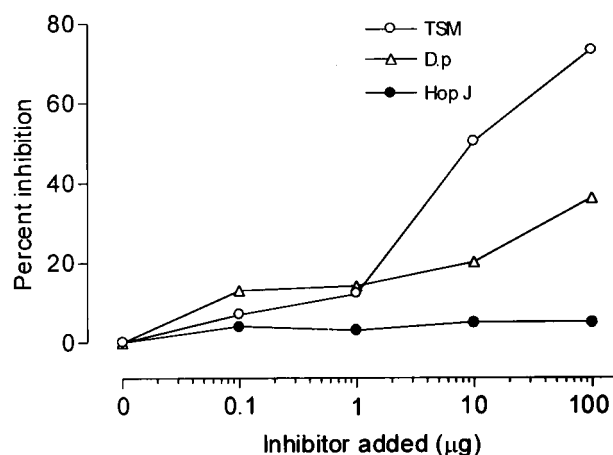


Figure 3. Percent inhibitions of specific IgE bindings to *Tetranychus urticae* with serial additions of *Tetranychus urticae*, *Dermatophagoides pteronyssinus*, and Hop Japanese pollen extracts using sera from five patients who showed positive skin responses to both *Tetranychus urticae* and *D. pteronyssinus*. Abbreviations: TSM, *Tetranychus urticae*; D.p, *Dermatophagoides pteronyssinus*; and Hop J: Hop Japanese (*Humulus Japonicus*) pollen.

ative responders (4.90 ± 1.29 mm versus 3.17 ± 0.41 , $P < .05$). The absorbance (OD, $\times 1000$) of TSM-specific IgE showed a higher tendency in the positive responders than in the negative responders, although this tendency was not statistically significant (204.40 ± 93.83 versus 132.17 ± 66.70 , $P > .05$) (Fig 2). Eight of the ten positive responders showed high serum specific IgE, but only three of the six negative responders showed

high serum specific IgE. The geometric values of total serum IgE levels were not different between the two groups (639.8 ± 345.8 IU/mL versus 419.1 ± 351.7 IU/mL, $P > .05$).

The dose-response patterns of the inhibitory effects with the addition of TSM and HDM antigens are illustrated in Figure 3 and Figure 4. Partial inhibitions were noted with the additions of DP antigens in sera from five TSM-induced asthmatics who showed posi-

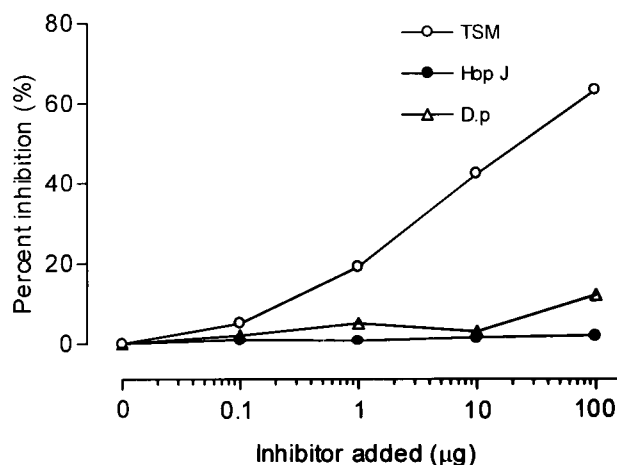


Figure 4. Percent inhibitions of specific IgE bindings to *Tetranychus urticae* with serial additions of *Tetranychus urticae*, *Dermatophagoides pteronyssinus*, and Hop Japanese pollen extracts using serum from a patient who showed a positive skin response only to *Tetranychus urticae*. Abbreviations: TSM, *Tetranychus urticae*; D.p: *Dermatophagoides pteronyssinus*; and Hop J: Hop Japanese (*Humulus Japonicus*) pollen.

tive skin responses to both TSM and *D. pteronyssinus* (Fig 3). Minimal inhibition was noted with the additions of *D. pteronyssinus* antigens in serum from a TSM-induced asthmatic with a negative skin response to *D. pteronyssinus* (Fig 4).

DISCUSSION

In this study, ten out of 16 asthmatics who were non-farmers, but showed a positive skin response to TSM, were confirmed as having TSM-induced asthma by a specific bronchial provocation tests. Their asthmatic symptoms were aggravated seasonally, especially in summer and early fall.

House dust mites are the most important causative allergens of respiratory allergic diseases around the world including Korea.¹¹ Recent investigations have revealed that non-pyroglyphid mites, such as storage mites and spider mites, are also important allergens in the development of allergic diseases.^{3-10,13} There have been several reports concerning TSM-associated allergic diseases.³⁻⁸ Nowadays, TSM is known to be the most common infesting mite in the fruit-growing orchards, especially in pear and apple orchards of Korea.¹⁴ Results of preliminary skin prick test obtained from 105 allergic patients who visited our allergy clinic showed that the sensitization rates to TSM was 34.3%. This figure was similar to the sensitization rates to *D. farinae* (32.4%) and *D. pteronyssinus* (28.6%). This high sensitization rate to TSM can be explained by the fact that many people have been exposed to this mite because the densities of TSM in outdoor environments have been increasing dramatically. Two spotted spider mite was a negligible mite in fruit cultivation before World War II but now this mite has become one of the most important fruit-cultivation pests since pesticides were introduced approximately 40 years ago in order to eliminate other fruit pests.¹⁴

To the best of our knowledge, this study is the first report concerning TSM-induced asthma confirmed by specific bronchial challenge tests in non-farmers. Asthmatic symptoms of

the TSM-induced asthmatics were aggravated between May and October, especially in summer and early fall. This period was well-correlated with the time when the densities of TSMs were high on pear leaves.¹⁵ These findings suggest that TSM may be one of the important allergens among asthmatics exposed to TSM whose asthma is aggravated in summer and early fall. We can assume that TSM may be one of the most important outdoor allergens in rural areas, especially around pear orchards, and that the TSM allergen must be included in a skin test battery to determine as possible causative allergens in allergic patients exposed to TSM.

There is an agreement that the closer the taxonomic relationship between mites is, the greater the level of cross-allergenicity.^{16–18} Burches et al⁶ reported that specific IgE to spider mites could not be detected in the absence of the specific IgE to *D. pteronyssinus* and all TSM-sensitive workers in their study were RAST positive to *D. pteronyssinus*. Kim et al,¹⁹ however, revealed that allergens derived from the citrus red mite (*Panonychus citri*), which is closely related to TSM, contained species-specific allergens in addition to commonly shared allergens with house dust mites in their study of citrus-cultivating farmers. In our study, ELISA inhibition tests showed minimal inhibition with additions of *D. pteronyssinus* and Hop Japanese antigens in an asthmatic with skin response only to TSM. On the other hand, in those with positive skin responses to both TSM and *D. pteronyssinus*, partial inhibitions were noted with additions of *D. pteronyssinus* antigens in a dose-dependent manner with the exception of Hop Japanese. These results suggest that TSM-derived extracts contain species-specific allergens in addition to commonly shared allergens with house dust mites.

In conclusion, TSM (*Tetranychus urticae*) may be an important causative allergen in asthmatics living around pear orchards with summer-season aggravation of their asthmatic symptoms. In addition, *Tetranychus urticae*-derived extracts contain species-specific

allergens as well as commonly shared allergens with house dust mites.

ACKNOWLEDGMENTS

We would like to thank Sun-Won Lee, PhD, from the Apple Research Institute, Korea, who provided the two-spotted spider mites.

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