

Cross-reactivity between *Ficus benjamina* latex and fig fruit in patients with clinical fig allergy

M. Focke*, W. Hemmer*, S. Wöhrl*†, M. Götz*‡ and R. Jarisch*

*FAZ – Floridsdorf Allergy Centre, Vienna, Austria, †Division of Immunology, Allergy and Infectious Diseases (DIAID), Department of Dermatology, University of Vienna Medical School, Vienna, Austria, and ‡Department of Pediatrics, Wilhelminenspital, Vienna, Austria

Summary

Background Anaphylactic reactions to fig fruits (*Ficus carica*) have been reported from subjects sensitized to *Ficus benjamina* (FB) latex allergens. Figs may also be involved in the latex–fruit syndrome.

Objective To study the immunologic relationship between fig fruit, *Ficus benjamina*, natural rubber latex (*Hevea brasiliensis*), and other tropical fruits.

Methods RAST inhibition and Western blotting with FB and fruit extracts was performed in five patients with oral allergy syndrome (OAS) or anaphylaxis after the ingestion of figs and one patient with symptoms from exposure to FB trees. Co-sensitization to rubber latex and tropical fruits (kiwi, banana, avocado, papaya, pineapple, mulberry) was studied by skin testing.

Results RAST to FB was inhibited >95% by FB extracts and 16–65% (mean 49%) by extracts from fresh fig. RAST to fig fruit was inhibited >95% by FB and fresh fig, 63–97% (mean 86%) by dried fig, and 0–84% (mean 35.5%) by kiwi fruit. FB and fig extracts lost most of their allergenicity when denatured by heat (95 °C) or reduced by dithiothreitol. Western blotting after non-reducing gel electrophoresis revealed IgE binding to proteins of 22 and 28–34 kDa in FB latex; however, no corresponding allergens could be detected in fig extracts. Positive skin tests were obtained most often with kiwi fruit, papaya, and avocado. Sensitization to rubber latex could not be demonstrated in any of the patients. RAST to papain was positive in three of five patients.

Conclusions Allergic reactions to fresh or dried figs can present as a consequence of primary sensitization to airborne FB allergens independent of sensitization to rubber latex allergens. Kiwi fruit, papaya, and avocado as well as pineapple and banana may be other fruits associated with sensitization to *Ficus* allergens.

Keywords *Ficus benjamina*, *Ficus carica*, fig fruit, latex–fruit syndrome, ornamental plants

Submitted 6 August 2002; revised 10 December 2002; accepted 24 February 2003

Introduction

Ornamental *Ficus* trees, particularly the weeping fig *Ficus benjamina* (FB), have been recognized as a cause of indoor allergy in atopic and non-atopic individuals [1–5]. The plant's twig and leaf sap ('latex') may cause respiratory sensitization when latex proteins transported to the leaf surfaces become airborne after adhesion to dust particles [5, 6].

Figs are the fruits of the fig tree (*Ficus carica*, Moraceae), which is the only species within this large genus producing high-quality edible fruits. From a morphological point of view, fig fruits are complex structures developing from a composite inflorescence with the pulp material not deriving from the flowers' reproductive structures but from the hypertrophied latex-containing inflorescence axis. It is thus not surprising that figs can cause allergic reactions in subjects sensitized to FB latex allergens, although the number of such

reports is very low [7–9]. These data suggest that fig allergy is a consequence of primary inhalant sensitization to FB latex proteins and the perseverance of cross-reactive proteins in fig fruits, resembling the situation in pollen-associated food allergy.

Apart from the described association between fig fruit and FB latex, another line of evidence indicates an immunologic relationship of fig and FB latex allergens with allergens in natural rubber latex (*Hevea brasiliensis*, Euphorbiaceae). Figs have been described to be involved in the 'latex–fruit syndrome' [10–12], and *in vitro* cross-reactivity between FB latex and rubber latex has been shown by RAST inhibition and Western blot [13, 14]. In a recent study, Chen et al. [15] demonstrated that 25% of patients with clinical latex allergy have IgE antibodies that bind with two heat-resistant proteins of 45 and 26 kDa in FB latex. IgE binding to these allergens could be inhibited by purified Hev b 6.02 (hevein), and N-terminal sequencing of the 45 kDa protein revealed a 76–84% sequence identity with Hev b 6.02 and other plant endochitinases. However, the relevance of these hevein-like proteins in clinical *Ficus* allergy remains obscure since

Correspondence: Wolfgang Hemmer, PhD, FAZ – Floridsdorf Allergy Centre, Franz Jonas Platz 8/6, A-1210 Vienna, Austria.

E-mail: science@faz.at

Axelsson et al. [16] previously identified a thermolabile 28 kDa FB latex protein as the major allergen in patients with clinical FB allergy. It seems reasonable to assume that the proteins involved in fig fruit hypersensitivity are identical with those in respiratory FB allergy, but this has been hardly investigated hitherto.

The present study examines the relationship between fig fruit and FB allergens by means of Western blot and RAST inhibition in patients with a history of fig hypersensitivity. Special emphasis was laid on the effects of protein denaturation and protein reduction usually performed during gel electrophoresis on the IgE-binding capacity of *Ficus* allergens because previous studies had indicated a high susceptibility of *Ficus* allergens to thermal or chemical treatment. Furthermore, we studied cross-sensitization to rubber latex, pollens and other tropical fruits by skin testing.

Material and methods

Patients

Five patients reporting adverse reactions after the ingestion of figs were recruited from a patient collective undergoing routine allergy testing in our outpatient clinic (Table 1). A sixth patient, who never ever ate figs, was included because she reported respiratory symptoms from contact with ornamental FB trees. Ocular or nasal symptoms from contact with FB plants were also noticed by three others. The remaining patients had contact with FB but were not aware of adverse reactions. All patients had specific IgE ($= 0.35 \text{ kU/L}$) to *Ficus* ssp. latex allergens (k81) and to fig fruit (Rf328) as determined by the Pharmacia CAP system (Pharmacia, Sweden).

Skin prick testing

Patients were routinely prick tested with pollens, animal danders, moulds, and rubber latex at their first visit (all Soluprick, ALK, Denmark). At the second visit, the patients were retested with selected pollens (birch, grass, mugwort) and rubber latex, and additionally tested with fresh FB leaves and several fruits (fig, kiwi fruit, banana, avocado, mulberry, pineapple, papaya) by means of the prick-to-prick method. To exclude toxic effects by FB latex, prick-to-prick testing with FB was performed by puncturing freshly collected leaves with the lancet and subsequently pricking the patient's skin. Thus direct skin contact with the latex was avoided.

Reactions were judged as ++ if the weal diameter exceeded 3 mm, and as +++ if equivalent to or greater than the positive control (histamine dihydrochloride 10 mg/mL). Weals between 2 and 3 mm with surrounding erythema were classified as weakly positive (+).

Reference sera

Two rabbit sera and one human serum were used as reference sera to detect carbohydrate epitopes in fig and FB extracts: ' αHRP ': a polyclonal rabbit antiserum specifically binding with fucosylated N-glycans of horseradish peroxidase [17]; ' $\alpha\text{Bra n}$ ': a polyclonal rabbit antiserum binding with fucosylated N-glycans of high molecular weight glycoproteins

in oilseed rape (*Brassica napus*) pollen [18]; ' αCCD ': serum from an atopic subject known to react with fucosylated N-glycans (cross-reactive carbohydrate determinants: CCDs) of oilseed rape pollen and other pollens.

Ficus benjamina and fruit allergen extracts

One fresh fig (pulp and skin) was cut into little pieces, ground under liquid nitrogen, and extracted for 1 h in 10 mL of either phosphate-buffered saline (PBS) or physiological saline (0.9% NaCl). The extracts were centrifuged and the supernatants dialysed, lyophilized and stored at -20°C . To prevent protein degradation, a standard cocktail of enzyme inhibitors including antificin was added (2 mmol EDTA, 10 mmol disodium diethyldithiocarbamate, 1 mmol phenylmethane sulphonylfluoride, 1 mmol leupeptin, 1 mmol antificin). Extracts from dried figs and kiwi fruit were prepared with the same method. Allergen extracts from FB leaves were made from ground leaves using PBS (approximately 15 leaves in 10 mL), and sap (latex) extracts were prepared by dissolving freshly collected sap in physiological saline. Further steps were the same as for fig extracts. The determination of total protein content in the extracts was made following Bradford [19].

SDS-PAGE

SDS-PAGE was carried out using 12% homogeneous gels ($10.5 \times 8.0 \times 0.1 \text{ cm}$) with 5% stacking gels at 25 mA and constant voltage. The resuspended lyophilized proteins (15 μg protein/lane) were mixed 3 : 1 with sample buffer (tris buffer containing 0.1% SDS) [20] and, prior to SDS-PAGE, were (1) either denatured and reduced by boiling in the presence of mercaptoethanol (95°C , 5 min), or (2) reduced with 0.22 mol dithiothreitol (DTT) (37°C , 30 min) and subsequent incubation with 0.5 mol iodoacetamide for 10 min to alkylate reduced disulphide bonds, or 3) separated by electrophoresis without any denaturation and reduction steps.

Western blotting

Electrophoretically separated proteins were blotted to nitrocellulose according to Towbin et al. [21]. After transfer, sheets were cut into strips of 3 mm and blocked with bovine serum albumin (BSA)-containing buffer (50 mmol/L sodium phosphate, 0.5% (v/v) Tween 20, 0.5% (w/v) BSA, and 0.05% (w/v) sodium azide, giving a final pH of 7.5) for 30 min. Each strip was incubated overnight with 1 mL of serum (diluted either 1 : 10 or 1 : 4) at 4°C under continuous shaking, washed twice in buffer for 30 min and incubated overnight at room temperature with ^{125}I -labelled rabbit anti-human IgE (dilution 1 : 10, Kallestad, Germany).

RAST inhibition

Autologous and heterologous inhibition of RAST to FB and fig by FB latex and fig extracts was performed in five patients (patients 1, 2, 4, 5, and 6). Patients' sera were mixed with the respective inhibitor protein solution to give a final protein concentration of 100 $\mu\text{g/mL}$. To investigate the effect of protein denaturation and protein reduction on IgE binding, the inhibitor solutions were differently pretreated as follows:

Table 1. Anamnestic data and skin prick test and RAST results in six patients with respiratory allergy to *Ficus benjamina* and/or adverse reactions to figs (*Ficus carica*)

Pt	Sex/age (years)	Clinical reaction to figs (FF: fresh fig; DF: dried fig)	Other food hyper-sensitivities	Symptoms from FB exposure	Total IgE	RAST (KU/L)					Prick-to-prick test					Skin prick test				
						FB	Fig	Papain	Latex	FB leaf	Fresh fig	Dried fig	Kiwi	Ban- ana	Pine- apple	Avocado	Pap- aya	Mul- berry	Bi- rch	Gras- ses
1	F/60	FF: oro-pharyngeal itch and swelling DF: tolerated	Kiwi	Sneezing	20	2.4	1.8	<0.35	<0.35	++	++	+	-	+	-	-	-	-	+	-
2	F/47	FF: unknown DF: Severe pharyngeal constriction, pruritus, breathing difficulties	No	Ocular itch, asthma?	30	60.8	5.0	3.4	<0.35	+++	+++	+++	++	-	+	++	+++	-	-	-
3	M/44	FF: swelling of lids, pruritus, urticaria? DF: unknown	Banana? citrus fruits?, avocado?	No	230	5.3	1.7	n.d.	2.75	-	+	-	+	-	++	-	-	+++	-	-
4	F/33	FF: unknown DF: unknown	Kiwi, banana	Itching and swelling of eyes	240	22.3	4.2	2.8	<0.35	+++	+++	+	++	+	-	++	-	-	-	-
5	F/34	FF: unknown DF: urticaria, angioedema, nasal congestion	Pineapple?	No	50	90.4	3.6	<0.35	<0.35	++	++	++	-	-	-	-	+++	-	+++	-
6	F/45	FF: nausea, vomiting, angioedema DF: unknown	Peach?	Swelling of eyes, nasal congestion	480	22.3	13.7	24.9	<0.35	+++	+++	+++	++	+	-	+	-	-	-	-

- (1) native proteins dissolved in SDS-free sample buffer,
- (2) native proteins dissolved in SDS-containing sample buffer,
- (3) proteins heated to 95 °C for 5 min in the absence of SDS,
- (4) proteins heated to 95 °C for 5 min in the presence of SDS,
- (5) proteins reduced by DTT at 37 °C in the presence of SDS (followed by extensive dialysis to remove excessive DDT from the extract).

All experiments were carried out using the Pharmacia CAP system. In a second set of experiments, RAST to fig fruit was inhibited by crude extracts from fresh figs, dried figs, and kiwi fruit (final protein concentration 100 µg/mL each).

Periodate oxidation of glycoproteins

To investigate the potential involvement of glycoprotein oligosaccharides in IgE binding to fig proteins, single nitrocellulose strips with electroblotted proteins were oxidized with periodate (10 mM periodic acid in 0.1 M sodium acetate buffer, pH 5.5, 1 h, 20 °C), and subsequently the IgE-binding patterns were compared with those from untreated strips.

Results

Skin test and RAST results

Results from skin tests and RAST are summarized in Table 1 along with clinical data. Skin testing with fresh FB leaves and fig fruit was positive in five of the six patients. In patient 3, only fresh fig induced a weakly positive reaction. Sensitization to pollen allergens was present in four patients but was clinically relevant only in patient 3. Skin testing with *H. brasiliensis* latex was negative in all. A positive RAST to latex was obtained only in patient 3 (2.75 kU/L). RAST to papain (Rf328) was positive in three of five patients, and RAST to pineapple bromelain (Rk202) was negative in all patients (pts 1, 2, 4–6).

Skin testing with fruits revealed a variable pattern of reactivity. Kiwi fruit most often provoked positive reactions (4 times), followed by papaya and avocado (3 times each).

Western blots

Western blots with fig proteins previously reduced by mercaptoethanol or DTT were positive only in patient 3 (data shown for DTT treatment in Fig. 1). This patient bound with several bands between 30 and 70 kDa. An identical pattern was obtained with the carbohydrate-specific human reference serum (αCCD) and both carbohydrate-specific rabbit antisera (αHRP, αBra n) (Fig. 1). Periodate treatment completely abrogated IgE binding in patient 3, suggesting that the observed antibody binding was due to glycoprotein glycans (Fig. 1).

As no IgE binding to fig proteins except binding with putative protein glycans was obtained with reduced extracts, all subsequent experiments were carried out under non-reducing conditions.

Immunoblots with native FB leaf and latex extracts revealed IgE binding to allergens of 22 and 28–34 kDa in all patients except in patient 3. Additional blurred IgE binding

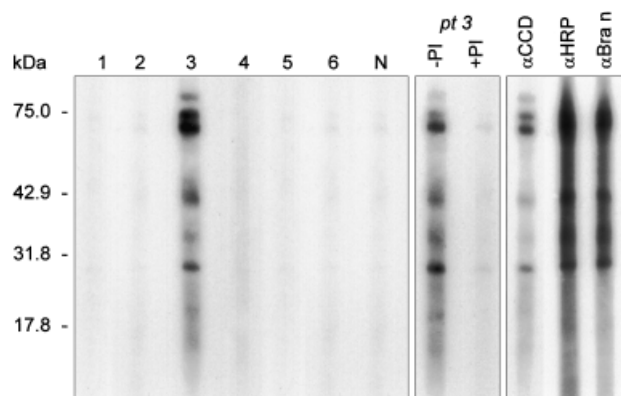


Fig. 1. IgE binding to fig extracts reduced by DTT at 37 °C and subsequently separated by SDS-PAGE. Blotted proteins were incubated with sera from six patients sensitized to fig and FB latex allergens (lanes 1–6). α CCD: atopic reference serum with IgE against cross-reactive carbohydrate epitopes; α HRP, polyclonal rabbit antiserum specific for carbohydrates in horseradish peroxidase; α Bra n, polyclonal rabbit antiserum against high-molecular-weight oilseed rape pollen glycoproteins. Patient 3 was retested on nitrocellulose strips pre-treated with 10 mM periodate (+PI: periodate-treated strip; –PI: untreated control strip). N: normal human control serum.

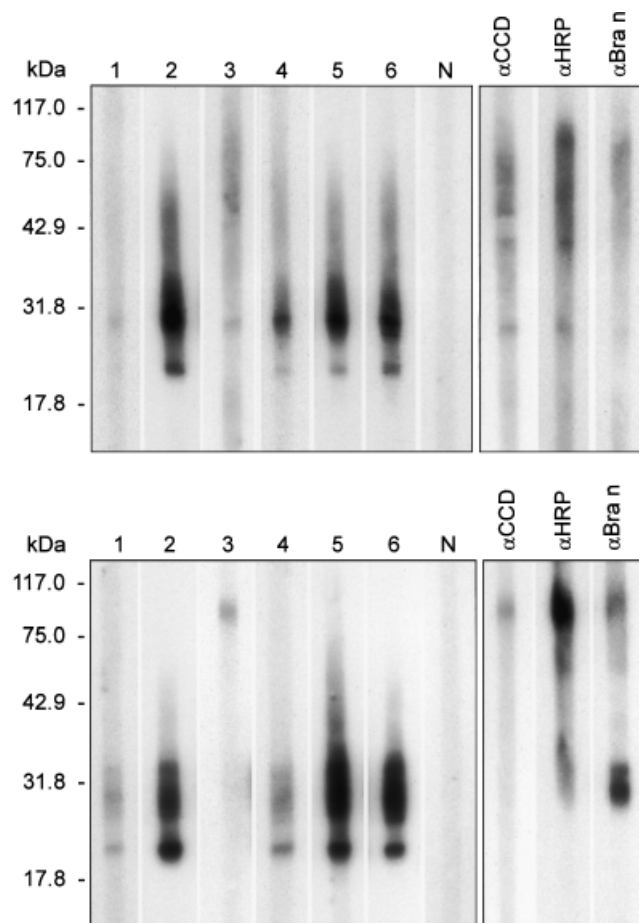


Fig. 2. IgE binding to non-reduced and non-denatured FB leaf and latex extracts separated by SDS-PAGE. Blotted proteins were incubated with the same patients' sera and control sera as in Fig. 1. Upper panel: FB whole leaf extract; lower panel: FB latex extract. For abbreviations see Fig. 1.

around 45 kDa occurred especially in leaf extracts (Fig. 2). The rabbit antisera bound in the FB latex extract with the 28–34 kDa cluster (mainly α Bra n) and with a 95 kDa band also

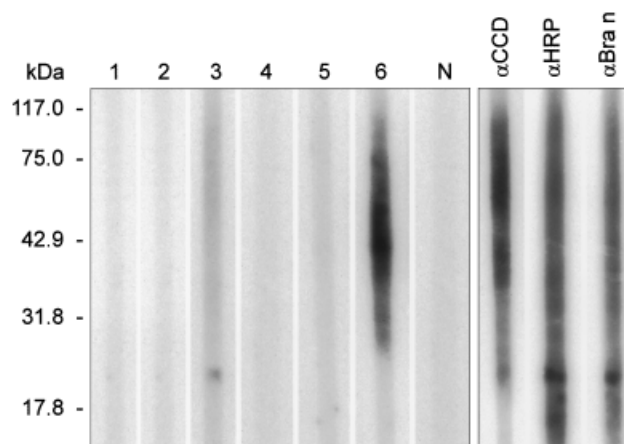


Fig. 3. IgE binding to non-reduced and non-denatured fig fruit extracts separated by SDS-PAGE. Blotted proteins were incubated with the same patients' sera and control sera as in Fig. 1. For abbreviations see Fig. 1.

recognized by patient 3 and α CCD. Antibody binding in the leaf extract was directed predominantly against HMW proteins.

Despite non-reducing conditions, only two patients were positive in the fig fruit blots. Patient 3 reacted moderately with a protein smear between 40 and 100 kDa and a 20 kDa band. Patient 6 reacted with allergens between 30 and 100 kDa, with two poorly delineated bands near 45 and 55 kDa (Fig. 3).

RAST inhibition

Results from RAST inhibition experiments are summarized in Figs. 4 and 5. FB latex extracts (100 µg/mL) were able to inhibit both the FB and the fig RAST by more than 95% in all patients (mean 96.5 ± 1.1). In contrast, the same amount of fig extract inhibited the FB RAST by only 16–65% (mean 48.9 ± 19.8) (Fig. 4). Inhibition with 500 µg/mL fig protein in patients 2 and 5 raised the inhibition from 16% to 29% and from 50% to 66%, respectively, but was still clearly less than the autologous inhibition.

Boiling of FB latex extracts in SDS-free buffer led to a 50% reduction of the IgE-binding capacity. If SDS was added during boiling, the allergenicity of the extracts was almost completely lost. Also, DTT treatment led to a nearly complete loss of the IgE-binding capacity. SDS alone had no obvious effect.

The inhibition of fig fruit RAST by fig and kiwi extracts is shown in Fig. 5. Extracts from dried figs inhibited IgE binding to the fig RAST as good as fresh figs in four of five patients (mean 86.4%, range 63–97%). With kiwi fruit, >50% inhibition was seen in two patients, one patient showed moderate inhibition, and in two patients, no inhibition was achieved (mean 35.5%, range 0–84%).

Discussion

The present study confirms previous observations of a close relationship between fig allergy and sensitization to ornamental *Ficus benjamina* plants [7–9]. Although fig allergy was not confirmed by a placebo-controlled food challenge in our

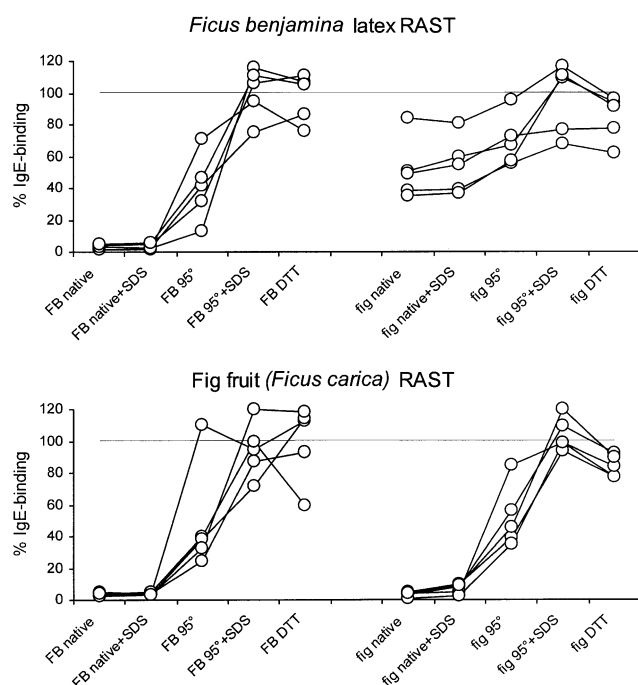


Fig. 4. Reciprocal RAST inhibition of *Ficus* latex RAST (Pharmacia CAP k81) (upper panel) and fig fruit (lower panel) by *Ficus benjamina* latex and fig fruit. Inhibitor proteins were used at a final concentration of 100 µg/mL and differently pre-treated as follows: native: native proteins without SDS; SDS: native proteins dissolved in SDS-containing sample buffer; 95°: proteins heated to 95 °C for 5 min in the absence of SDS; 95°+SDS: proteins heated to 95 °C for 5 min in the presence of SDS; DTT: proteins reduced by DTT at 37 °C in the presence of SDS. Individual values (open circles) represent percent IgE binding in comparison to the non-inhibited RAST.

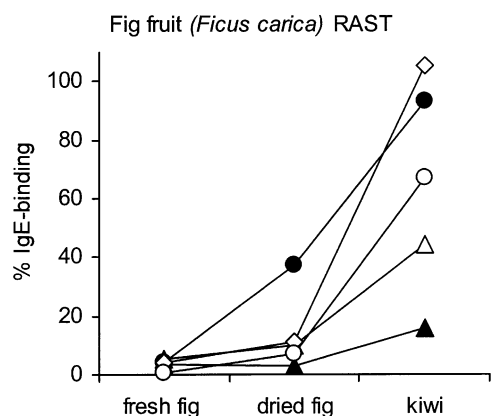


Fig. 5. Inhibition of RAST to fig fruit (Pharmacia CAP Rf328) by extracts from fresh fig, dried fig, and kiwi fruit, in patients 1, 2, 4, 5, and 6. All inhibitor proteins were used at a final concentration of 100 µg/mL.

patients, the test results together with anamnestic data make this diagnosis very likely, with the exception of patient 3, in whom evidence for IgE-mediated fig hypersensitivity is less convincing. All patients except patient 3 were also sensitized to FB allergens, although not all of them were aware of symptoms to be elicited by these plants. The results from reciprocal RAST inhibition support the view that the primary IgE response in these patients was directed against FB allergens, whereas fig allergy appears to be a consequence of cross-reacting homologous proteins in fig fruits.

Allergy to FB had been first described as an occupational disease [1, 2], but more recent papers indicate that sensitization may not be uncommon also in subjects moderately exposed to FB plants in their personal environment [4–6, 22, 23]. Considering that the prevalence of sensitization to FB may be 4–12% [4, 22, 24], fig allergy has been surprisingly rarely reported so far. One reason for this may be that, in non-Mediterranean countries, figs are rarely consumed and, if so, in only small quantities. Sensitization thus may be easily underdiagnosed. This is particularly true for fresh figs. In this study, three out of six patients never in their life ate fresh figs. As dried figs are consumed much more often than fresh figs in our area, it is important to know that figs seem to retain much of their allergenicity during the drying process, even if fresh fruits tended to provoke stronger skin test reactions than dried ones. Altogether, the severity of the reported clinical reactions provoked by dried figs in our collective was comparable to that reported from fresh figs. It cannot be excluded, however, that those patients reporting symptoms from dried figs would have reacted even more severely to fresh figs. In most cases, consumption of a single fig was sufficient to elicit the allergic reaction similar to previous reports [7, 9].

Consistent with earlier papers [1, 2], many of our patients were atopic showing sensitization to pollens. In this study, we could not find any obvious association between fig allergy and sensitization to a particular pollen species. However, it is possible that some of the observed skin test reactions to fruits are primarily due to cross-reactivity with pollen allergens. Mulberries (*Morus* spp.) were considered in this study because they are the fruits most closely related with figs, belonging to the same plant family Moraceae. However, fig allergy does not seem to be jointly tied up with sensitization to mulberry.

The relationship between FB, fig, and natural rubber latex appears to be complex. There is substantial evidence now that fruit class I chitinases displaying N-terminal hevein-like domains play a major role as cross-reactive allergens in the latex–fruit syndrome [25]. Class I chitinases have been studied in detail in avocado, chestnut, and banana but are known to occur in many other fruits [26]. Taking into account that adverse reactions to figs have been reported from latex-allergic patients [10–12] and that hevein-like sequences have been detected in FB latex [15], a role of class I chitinases in *Ficus*-associated fruit hypersensitivity appears plausible. However, our data together with previous papers [7–9] indicate that *Ficus* and fig allergy is a distinct entity not necessarily associated with latex allergy. None of our patients had a positive skin test to latex nor a history suggestive of latex allergy. The positive latex RAST encountered in patient 3 most likely is due to clinically unimportant IgE against CCDs [26, 27], an observation that emphasizes the importance of discriminating between IgE against peptide epitopes and IgE against CCDs in future studies investigating the cross-reactivities between FB and rubber latex allergens.

We assume that the patients investigated by us were primarily sensitized to FB allergens and that the observed cross-sensitization to fig and other tropical fruits is due to epitopes not shared by rubber latex, even if many of these fruits are typically involved in the latex–fruit syndrome. Ficin, a thiolprotease from fig fruit, may represent such a relevant

cross-reactive protein involved in fig allergy [28]. Diez-Gomez et al. [8] recently described IgE binding to the thiolproteases papain (from papaya) and bromelain (from pineapple) in a fig-allergic patient without concomitant rubber latex allergy. In this study, we obtained positive RAST results to papain in the majority of our patients. This finding further supports a role of thiolproteases in Ficus-associated fruit hypersensitivity, even if we did not observe IgE reactivity with bromelain.

The role of thiolproteases would not be surprising as there is long-standing evidence that these enzymes are potent allergens. Papain and bromelain have long been known to cause respiratory allergy in occupationally exposed workers [29], and actinidin, a 30 kDa thiolprotease from kiwi fruit, has been proposed as a major allergen in kiwi allergy [30]. The concomitant food hypersensitivities reported by our patients and the results from prick-to-prick testing would be fairly consistent with the proposed role of thiolproteases, but the data available so far are not sufficient to identify reliably the fruits specifically associated with FB. Interestingly, several authors observed *in vitro* cross-reactivity between papain and Hev b 1 [31–33] so that not only hevein-like domains but also thiolproteases may represent potentially cross-reactive allergens connecting FB, fruits, and rubber latex.

The allergens in FB latex have not been characterized very well, and those in fig have hardly been investigated so far [9]. Two thermolabile proteins of 25 and 28–29 kDa were previously described to bind IgE if reduced with DTT at 37 °C but not if reduced with mercaptoethanol at 95 °C [16]. Later, Mock et al. [9] reported that fig proteins already lose their allergenicity when dissolved in SDS-containing buffer, irrespective of any other treatment. We performed extensive RAST inhibition studies to identify the crucial steps that might lead to the loss of allergens' IgE-binding capacity. Our data confirm that Ficus allergens are sensitive to heat, although this effect seems to be much more deleterious if SDS is present. According to our results, DTT treatment also leads to a substantial loss of the IgE-binding capacity. The 22 and 28–34 kDa allergens subsequently identified by non-reducing SDS-PAGE in both FB latex and leaf extracts match the proteins previously described by Axelsson et al. [16]. However, we were unable to locate the corresponding allergens in fig extracts. Apart from IgE binding to carbohydrates in patient 3, which we do not consider to be relevant in fig allergy, only one patient bound with a protein smear around 50 kDa. The relationship of these proteins with the identified FB latex allergens remains uncertain.

In summary, we demonstrated primary sensitization to FB latex allergens and clinically relevant cross-reactivity with fig fruit (*Ficus carica*) independent of co-sensitization to rubber latex. Sensitization to FB allergens may also comprise specific cross-sensitization to kiwi fruit, banana, pineapple, avocado, and papaya.

References

- 1 Axelsson G, Skedinger M, Zetterström O. Allergy to weeping fig: a new occupational disease. *Allergy* 1985; 40:461–4.
- 2 Axelsson IGK, Johansson SGO, Zetterström O. Occupational allergy to weeping fig in plant keepers. *Allergy* 1987; 42:161–7.
- 3 Schmid P, Stöger P, Wüthrich B. Severe isolated allergy to *Ficus benjamina* after bedroom exposure. *Allergy* 1993; 48:466–7.
- 4 Bircher AJ, Wüthrich B, Langauer S, Schmid P. *Ficus benjamina*, ein perennielles Inhalationsallergen von zunehmender Bedeutung. *Schweiz Med Wochenschr* 1993; 123:1153–9.
- 5 Axelsson IGK. Allergy to *Ficus benjamina* (weeping fig) in non-atopic subjects. *Allergy* 1995; 50:284–5.
- 6 Bircher AJ, Langauer S, Levy F, Wahl R. The allergen of *Ficus benjamina* in house dust. *Clin Exp Allergy* 1995; 25:228–33.
- 7 Dechamp C, Bessot JC, Pauli G, Deviller P. First report of anaphylactic reaction after fig (*Ficus carica*) ingestion. *Allergy* 1995; 50:514–6.
- 8 Diez-Gomez ML, Quirce S, Aragonese E, Cuevas M. Asthma caused by *Ficus benjamina* latex: evidence for cross-reactivity with fig fruit and papain. *Ann Allergy Asthma Immunol* 1998; 80:24–30.
- 9 Mock B, Rudeschko O, Henzgen M, Schlenvoigt G, Jäger L. Feigenallergie. Kreuzreaktionen zu *Ficus benjamina* und Versuch der Allergencharakterisierung. *Allergologie* 1998; 21:588–92.
- 10 Blanco C, Carrillo T, Castillo R, Quiralte R, Cuevas M. Latex allergy: clinical features and cross-reactivity with fruits. *Ann Allergy* 1994; 73:309–14.
- 11 Lavaud F, Cossard C, Reiter V, Bernard J, Deltour G, Holmquist I. Latex allergy in patients with allergy to fruit. *Lancet* 1992; 339:492–3.
- 12 Brehler R, Theissen U, Mohr C, Luger T. 'Latex-fruit syndrome': frequency of cross-reacting IgE antibodies. *Allergy* 1997; 52:404–10.
- 13 Delbourg MF, Moneret-Vautrin DA, Guilloux L, Ville G. Hypersensitivity to latex and *Ficus benjamina* allergens. *Ann Allergy Asthma Immunol* 1995; 75:496–500.
- 14 Brehler R, Abrams E, Sedlmayr S. Cross-reactivity between *Ficus benjamina* (weeping fig) and natural rubber latex. *Allergy* 1998; 53:402–6.
- 15 Chen Z, Düser M, Flagge A et al. Identification and characterization of cross-reactive natural rubber latex and *Ficus benjamina* allergens. *Int Arch Allergy Immunol* 2000; 123:291–8.
- 16 Axelsson IGK, Johansson SGO, Larsson PH, Zetterström O. Characterization of allergenic components in sap extract from the weeping fig (*Ficus benjamina*). *Int Arch Allergy Appl Immunol* 1990; 91:130–5.
- 17 Wilson IBH, Harthill JE, Mullin NP, Ashford DA, Altmann F. Core α 1,3-fucose is a key part of the epitope recognized by antibodies reacting against N-linked oligosaccharides and is present in a wide variety of plant extracts. *Glycobiology* 1998; 8:651–61.
- 18 Hemmer W, Focke M, Kolarich D et al. Antibody binding to venom carbohydrates is a frequent cause for double positivity to honeybee and yellow jacket venom in patients with stinging-insect allergy. *J Allergy Clin Immunol* 2001; 108: 1045–52.
- 19 Bradford MM. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. *Anal Biochem* 1976; 72:248–4.
- 20 Laemmli UK. Cleavage of structural proteins during the assembly of the head of bacteriophage T4. *Nature* 1970; 227: 680–5.
- 21 Towbin H, Staehlin T, Gordon J. Electrophoretic transfer of proteins from polyacrylamide gels to nitrocellulose sheets: procedure and some applications. *Proc Natl Acad Sci USA* 1979; 76:4350–4.
- 22 Axelsson IGK, Johansson SGO, Zetterström O. A new indoor allergen from a common non-flowering plant. *Allergy* 1987; 42:604–11.
- 23 Schenkelberger V, Freitag M, Altmeyer P. *Ficus benjamina* – das heimliche Allergen im Haus. *Hautarzt* 1998; 49:2–5.
- 24 Kanerva L, Estlander T, Petman L, Mäkinen-Kiljunen S. Occupational allergic contact urticaria to yucca (*Yucca aloifolia*),

- weeping fig (*Ficus benjamina*), and spathe flower (*Spathiphyllum wallisii*). *Allergy* 2001; 56:1008–11.
- 25 Salcedo G, Diaz-Perales A, Sanchez-Monge R. The role of plant panallergens in sensitization to natural rubber latex. *Curr Opin Allergy Clin Immunol* 2001; 1:177–83.
- 26 Diaz-Perales A, Collada C, Blanco C et al. Cross-reactions in the latex–fruit syndrome: a relevant role of chitinases but not complex asparagine-linked glycans. *J Allergy Clin Immunol* 1999; 104: 681–7.
- 27 van Ree R, Aalberse RC. Specific IgE without clinical allergy. *J Allergy Clin Immunol* 1999; 103:1000–1.
- 28 Sasaki M, Kato T, Iida S. Antigenic determinant common to four kinds of thiol proteases of plant origin. *J Biochem (Tokyo)* 1973; 74:635–7.
- 29 Baur X. Studies in the specificity of human IgE-antibodies to the plant proteases papain and bromelain. *Clin Allergy* 1979; 9: 451–7.
- 30 Pastorello EA, Conti A, Pravettoni V et al. Identification of actinidin as the major allergen in kiwi fruit. *J Allergy Clin Immunol* 1998; 101:531–7.
- 31 Baur X, Chen Z, Düser P, Raulf-Heimsoth M. Cross-reacting antibodies recognizing latex allergens, including Hev b 1, as well as papain. *Allergy* 1995; 50:604–9.
- 32 Quarre JP, Lecomte J, Lauwers D, Gilbert P, Thiriaux J. Allergy to latex and papain. *J Allergy Clin Immunol* 1995; 95:922.
- 33 Vandenplas O, Vandezande LM, Halloy JL, Delwiche JP, Jamart J, Looze Y. Association between sensitization to natural rubber latex and papain. *J Allergy Clin Immunol* 1996; 97:1421–4.