

Asthma caused by *Ficus benjamina* latex: evidence of cross-reactivity with fig fruit and papain

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Background: *Ficus benjamina* or weeping fig is a plant used increasingly for indoor decoration that can cause allergic rhinitis and asthma.

Objective: We report a clinical and immunologic study in a patient with perennial asthma caused by *F. benjamina* latex in whom several episodes of angioedema of the oropharyngeal tract and tongue followed ingestion of figs and kiwi.

Methods: Hypersensitivity to latex from *F. benjamina* and from *Hevea brasiliensis*, fig fruit, kiwi, papain, and bromelain was investigated by means of skin prick test, specific IgE determination by CAP, histamine release test, and bronchial provocation test to *F. benjamina* latex. CAP-inhibition assays were carried out to study possible cross-reactivity among these antigens.

Results: Hypersensitivity to *F. benjamina* latex, fig, kiwi, and proteases was demonstrated by means of skin prick test, determination of specific IgE and histamine release test. Bronchial provocation test with *F. benjamina* latex resulted in a dual asthmatic reaction, confirming the etiologic role of this plant. A rise of eosinophil cationic protein in patient's serum was observed 21 hours after bronchial challenge, suggesting activation of eosinophils. Inhibition assays showed that *F. benjamina* latex as liquid-phase inhibited up to 95% the CAP to fig and up to 57% the CAP to papain. Neither sensitization nor cross-allergenicity with *H. brasiliensis* latex was found.

Conclusions: Hypersensitivity to *F. benjamina* latex may cause IgE-mediated respiratory allergy. The association with allergy to fig and papain is likely due to the existence of cross-reactive allergen structures.

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INTRODUCTION

Ficus benjamina or weeping fig (Fig 1) is a non-flowering green plant from the family Moraceae frequently used in the decoration of homes, office premises and public buildings. It grows into a very leafy small tree, with a mean height of 1.5 to 2 meters.

Hypersensitivity to this plant was first described by Axelsson et al as an occupational disease in 1985.¹ They reported two atopic plant keepers working for a company specialized in

the leasing of green plants in whom rhinoconjunctivitis and asthma developed on exposure to *F. benjamina*. Specific IgE against leaf and twig extracts from this plant was demonstrated by skin tests and RASTs. In a subsequent study² in four plant-leasing firms employing 60 plant keepers, it was found that 26.6% of the workers had positive skin-prick tests and RAST against *F. benjamina* latex. All sensitized subjects suffered from rhinitis or conjunctivitis and six had asthma.

The fig is the fruit of the fig tree (*Ficus carica*) which also belongs to the family Moraceae. A single case of anaphylactic reaction after eating a fresh fig has been recently described in a nonatopic patient. In this patient, serum specific IgE antibodies against

both fig and *F. benjamina* were found. A partial inhibition of CAP to *F. benjamina* with fig suggested the existence of cross-reactivity between both species of *Ficus*.³

We describe a clinical and immunologic study of an atopic patient suffering from perennial rhinoconjunctivitis and asthma. Sensitization to *F. benjamina* latex was demonstrated by in vivo and in vitro tests. The patient had also had several episodes of angioedema after ingestion of figs and kiwi (*Actinidia chinensis*). Cross-reactivity between *F. benjamina* latex, fig, papain, and the latex of the rubber tree *Hevea brasiliensis* was investigated.

CASE REPORT

A 36 year-old woman, who was a smoker of ten cigarettes/day, had suffered from allergic rhinoconjunctivitis due to *Olea europaea* (Mediterranean olive) pollen during more than 10 years as well as cough, dyspnea, and wheezing during the last pollen season (from May to June). She took antihistamines and disodium cromoglycate for symptom relief, and she received immunotherapy with *O. europaea* pollen during 2 years but it had been stopped due to large local reactions.

Since 1993 she had suffered from perennial episodes of shortness of breath, coughing, wheezing, and rhinoconjunctivitis. Antiasthma therapy with nedocromil, salmeterol, and theophylline daily as well as albuterol as needed had been prescribed. At a routine follow-up allergy evaluation in January, 1996, she reported that rhinoconjunctivitis as well as dyspnea and wheezing developed immediately when she was cleaning and taking care

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Figure 1. *Ficus benjamina*.

of her weeping fig. She also noticed itching and erythema of her hands when handling the leaves from this plant. She had kept two weeping figs at home for 12 years and she took care of them regularly. These plants were approximately 2 m high and were located near the sofa in the living-room.

In October, 1995, she experienced oral itching and angioedema of the oropharyngeal tract and tongue as well as dizziness shortly after eating a fresh fig. A few weeks after this episode she had similar symptoms within a few minutes after eating a kiwi, and thereafter after ingestion of a dried fig.

Clinical examination was normal. Blood tests, chest, and sinus radiographs and spirometry were within normal limits.

MATERIAL AND METHODS

Allergen Extracts

The sap (latex) from *F. benjamina* was collected by cutting the leaves and twigs and gently squeezing them by hand. The protein concentration of this sap estimated by Bio-Rad protein assay (Bio-Rad, Munich, Germany) was 1 mg/mL. The sap was diluted 1:10 vol/vol in normal saline and passed through a 0.22- μ m Millipore filter (Millipore Corp, Bedford, MA) for sterilization. Serial 2-fold dilutions of this extract in phosphate-buffered saline (PBS) were obtained for skin and bronchial provocation tests (from 1:20 to 1:10240 vol/vol). Papain (from *Carica papaya*) and bromelain (from *Ananas comosus*) were purchased from

Merck (Darmstadt, Germany) and prepared at a concentration of 10 mg/mL in PBS.

Fig extract was prepared by crushing one dried fig in 10 mL of PBS and then centrifuged at 1000 *g* for 30 minutes. The supernatant was then passed through a 0.45- μ m filter (Nucleopore Corp, Syrifil-MF, USA). The protein concentration of this extract was 0.98 mg/mL. Kiwi extract was prepared in a similar way.

Natural latex from *H. brasiliensis* (Syntex Latino SA, Barcelona, Spain) was diluted 1:10 vol/vol in sodium carbonate-bicarbonate buffer (0.1 mol/L, pH 9.6) and after centrifugation at 1000 *g* for ten minutes the supernatant was passed through a 0.45- μ m filter (Nucleopore Corp, Syrifil-MF, USA). The protein concentration of this extract was 1 mg/mL.

Skin Tests

Prick skin tests were performed. Testing with a battery of common inhalant allergens included *Dermatophagoides pteronyssinus*, *Alternaria tenuis*, *Cladosporium herbarum*, *Aspergillus fumigatus*, *Penicillium notatum*, mixed grass pollen, *Lolium perenne*, *Olea europaea*, *Fraxinus* spp, *Chenopodium album*, *Parietaria judaica*, *Artemisia vulgaris*, *Taraxacum* spp, dog and cat dander (ALK-Abelló, Madrid, Spain). *F. benjamina* latex (as is), *H. brasiliensis* latex (Alyostal, Stallergenes S.A., France), papain, and bromelain (10 mg/mL) were also used for testing. Skin tests were also performed using the prick by prick method⁴ with the leaf and twig of *F. benjamina*, with a dried fig and with a fresh kiwi. In addition, skin end-point titration with *F. benjamina* latex was done by testing decreasing concentrations of the extract from 1:20 vol/vol to 1/10240 vol/vol using the prick method.

Histamine phosphate at 10 mg/mL and normal saline were used as positive and negative controls, respectively. A wheal with a mean diameter 3 mm or greater with erythema, occurring 15 minutes after testing, was defined as a positive reaction, with the saline prick test negative.

Skin prick tests with *F. benjamina* latex, fig, kiwi, and plant proteases were also performed in ten atopic and ten nonatopic subjects.

Rub Testing

The patient's forearm was moistened with water and then rubbed for 30 seconds with a bunch of *F. benjamina* leaves. The skin response was examined 15 minutes later.

Total and Specific IgE Determination

Total serum IgE was measured by Pharmacia CAP System IgE FEIA (Pharmacia Diagnostics, Uppsala, Sweden) according to the manufacturer's instructions.

Specific IgE against *Ficus* spp., fig, kiwi, papain, bromelain, *H. brasiliensis* latex, *D. pteronyssinus*, *O. europaea*, *L. perenne*, *A. tenuis*, *C. herbarum*, *A. fumigatus*, and *P. notatum* were determined by Pharmacia CAP System RAST FEIA (Pharmacia Diagnostics AB, Uppsala, Sweden). Specific IgE antibodies against r(recombinant) Bet v 1 and rBet v 2 (profilin) were measured with a kit (CAP technique) generously supplied by Pharmacia.

CAP Inhibition Assays

CAP inhibition studies were carried out to investigate a possible cross-reactivity between *F. benjamina* latex and other allergens to which the patient had developed immediate hypersensitivity. We also determined whether *H. brasiliensis* latex inhibited CAP to *Ficus*. Twenty microliters of three progressive 10-fold dilutions of the inhibitor allergens in PBS and 20 μ L of PBS as negative control were preincubated with 50 μ L of patient's serum for 15 minutes and then the assay was continued following the standard CAP technique.

The inhibition of CAP to *Ficus* was determined using the following liquid-phase allergens: (1) dried fig extract, (2) *H. brasiliensis* latex (Syntex Latino S.A., Barcelona, Spain), and (3) *O. europaea* pollen 2.5% wt/vol (Bencard, Worthing, UK). Inhibition of CAP to fig, papain, and *O. europaea*

was investigated with *F. benjamina* latex as liquid-phase allergen.

Results were expressed as the percent inhibition of CAP obtained with the inhibitor allergen as compared with a control assay with PBS inhibitor.

Histamine Release Test

Histamine release tests were carried out using an automated fluorometric method according to Siraganian⁵ with the modifications previously described.⁶ Twenty-five microliters of four 5-fold dilutions (1:5, 1:25, 1:125, 1:625 vol/vol) of the extracts of *F. benjamina* latex, *H. brasiliensis* latex, fig, kiwi, papain, and bromelain (both at 0.1 mg/mL) were added. Before allergen challenge, blood samples were tested with four dilutions of equine antihuman IgE (Diagnostic Pasteur, France). These assays were also performed in five control subjects. The percentage of histamine release was calculated as follows:

$$\frac{(\text{allergen-induced histamine release} - \text{histamine release with diluent}) \times 100}{\text{total histamine content} - \text{histamine release with diluent}}$$

A result greater than 10% release was considered positive.⁵

Bronchial Provocation Tests

Methacholine inhalation test. This test was performed according to Cockcroft et al⁷ with some modifications. The aerosolized particles were generated by a continuous pressurized nebulizer model DeVilbiss 646 (DeVilbiss Co., Somerset, PA, USA) with an output of 0.28 mL/min. The result of this test was expressed as the provocative concentration of methacholine causing a 20% fall in forced expiratory volume in one second (PC₂₀) and it was determined by interpolation of the last two concentrations.

Specific bronchial challenge. The patient inhaled the aerosolized allergen using the nebulizer method mentioned above in progressive concentrations at tidal breathing for two minutes. A control challenge with PBS was carried out before antigen provocation. Increasing concentrations of *F. ben-*

jamina extract were given by inhalation starting with a concentration that induced a 2 to 3-mm wheal on skin prick testing (1:10240 vol/vol), as previously described.⁸ The dose was increased in twofold increments at intervals of ten minutes and FEV₁ and FVC were measured at five and ten minutes after inhalation of each concentration. Bronchial challenge test was discontinued when there was a fall in FEV₁ of 20% or greater from the lowest post-saline value or when the highest concentration had been given. At the end of the inhalation challenge test, spirometry was performed at 20, 30, 40, and 60 minutes after challenge, and thereafter hourly for nine hours, and again the following day. A fall in FEV₁ of 20% or more from the lowest post-saline within 60 minutes of challenge was considered a positive immediate reaction while a fall in FEV₁ greater than 20% between 2 to 24 hours after challenge was considered a positive late reaction if no change was observed during the control day.

Eosinophil Cationic Protein Measurement

Eosinophil cationic protein in the patient's serum was determined by Pharmacia CAP System ECP FEIA that was kindly supplied by Pharmacia (Uppsala, Sweden). Eosinophil cationic protein was measured immediately before bronchial challenge with *F. benjamina* extract and 21 hours after specific bronchial challenge. Eosinophil cationic protein is present in eosinophil granules and it is secreted upon stimulation. Determination of released eosinophil cationic protein may be used to monitor conditions involving eosinophil activation such as asthma.⁹

RESULTS

Skin Tests

Skin prick tests with common inhalants were positive to *O. europaea* (24 mm wheal with pseudopods), *Fraxinus* spp. (5 mm), grass mix (5 mm), and *L. perenne* (5 mm). Skin prick tests were also positive with all dilutions of *F. benjamina* latex from 1:20 vol/vol (15

mm wheal with pseudopods) to 1:10240 vol/vol (3 mm). Positive skin responses were also observed to twig and leaf from the *F. benjamina* plant, as well as to fig, kiwi, papain, and bromelain (Table 1). The skin prick test with *H. brasiliensis* latex was negative. Histamine-induced wheal was 5 mm while no reaction was observed to saline. No response was observed in the contact area with *F. benjamina* leaves after rub testing.

Skin prick tests with *F. benjamina* latex in ten control subjects were negative.

Total and Specific IgE Determination

Total IgE was 130 KU/L. CAP was positive to *Ficus spp.*, fig, papain, and pollen of *O. europaea* and *L. perenne* as shown in Table 1. CAP was negative (≤ 0.35 KU/L) against kiwi, bromelain, *H. brasiliensis* latex, rBet v 1, rBet v 2, *D. pteronyssinus*, and molds.

CAP Inhibition Assays

Ficus benjamina latex as liquid-phase allergen inhibited up to 95% the CAP to fig and up to 57% the CAP against papain. On the contrary, no inhibition of CAP to *O. europaea* pollen was observed (Fig 2). When *Ficus* was used as solid-phase, fig extract inhibited up to 33% the CAP to *Ficus*, while neither *H. brasiliensis* latex nor *O. europaea* pollen significantly inhibited IgE-binding.

Histamine Release Tests

This test was positive with extracts of *F. benjamina* latex, fig, kiwi, papain and bromelain and it was negative with *H. brasiliensis* latex. The maximum

percentages of histamine release obtained with papain and bromelain extracts (dilution 1:5) and with *F. benjamina* latex, fig and kiwi extracts (dilution 1:25) are shown in Table 1. Dilution 1:5 of *F. benjamina* latex, fig and kiwi extracts produced nonspecific histamine release in control subjects.

Bronchial Provocation Tests

Inhalation challenge with methacholine revealed bronchial hyperresponsiveness with a PC₂₀ of 1.5 mg/mL. Specific bronchial provocation test with *F. benjamina* latex (1:40 vol/vol) elicited an early asthmatic response, with a 43% fall in FEV₁ from baseline five minutes after challenge, followed by a late asthmatic reaction five hours later (Fig 3).

Eosinophil Cationic Protein

Eosinophil cationic protein before bronchial challenge was 10.9 μ g/L and 21 hours after specific inhalation challenge increased to 19.70 μ g/L.

DISCUSSION

We report a patient with perennial asthma in whom sensitization to *F. benjamina* latex was demonstrated by means of skin prick test, determination of specific IgE, histamine release test, and specific bronchial challenge test. In addition, hypersensitivity to fig and kiwi as well as to plant proteases (papain and bromelain) was confirmed by in vivo and in vitro tests.

Since *F. benjamina* is widely used for decoration of houses and offices, sensitization to this plant is not limited to occupationally exposed personnel.

In Sweden, Axelsson et al¹⁰ studied the prevalence of sensitization to *F. benjamina* in 395 consecutive patients non-occupationally exposed to these plants and in 107 employees from two offices decorated with an abundance of *F. benjamina* plants. Positive skin prick test and RAST were found in 13 patients (3.3%) and in three employees (2.8%). In this study, all patients sensitized to *F. benjamina* suffered from rhinitis, asthma, or both and were atopic.

Routine skin prick testing with *F. benjamina* extract in 156 patients evaluated for respiratory symptoms was positive in 7.5% of them.¹¹ Although hypersensitivity to allergens from *F. benjamina* has been reported both in atopic and in nonatopic individuals,^{12,13} it is more frequent in the former.^{10,14} Patients with rhinitis, conjunctivitis, or perennial asthma and not-occupationally exposed to these plants usually do not relate their symptoms with exposure to *F. benjamina*.^{2,12} Because of the ubiquity of this plant, routine skin testing with *F. benjamina* extract has been recommended in all patients investigated for respiratory allergy.^{12,14}

The allergens of *F. benjamina* are located in the plant sap, so-called latex, contained in the leaves and in the twigs. Sensitization to *F. benjamina* probably occurs through inhalation of airborne allergenic particles emanating from the leaves of the plants. It has been suggested that soluble allergens will accompany the water by osmosis and deposit on the surface of the leaves when the water evaporates.¹⁰ *Ficus*

Table 1. Results of Skin and in Vitro Tests

Allergens	Skin prick tests		IgE, KU/L	HR, %
	Concentration	Wheal, mm*		
<i>F. benjamina</i> latex	as is	15 ps	15.1	33
Fig	dried, as is	6	7.56	28
Kiwi	as is	4	<0.35	36
Papain	10 mg/mL	8 ps	3.78	30
Bromelain	10 mg/mL	4	<0.35	24
<i>O. europaea</i>	100 BU/mL	24	34.6	ND
<i>L. perenne</i>	100 BU/mL	5	1.74	ND
<i>H. brasiliensis</i> latex	10% wt/vol	0	<0.35	10

* Mean wheal diameter; ps: pseudopods; HR: histamine release (maximum percentage); ND: not done; and BU: biologic units.

benjamina allergen could be found in the dust collected from the leaf surface and in the dust samples from the floor of rooms where these plants are placed as demonstrated by RAST-inhibition studies¹⁴ and polyclonal antibody sandwich ELISA.¹⁵ Further, there is some evidence that allergen may persist in the floor dust several months after removal of the plant, which may explain persistence of symptoms.^{13,14}

Although skin tests can be performed with a leaf or twig from *F. benjamina* using the prick by prick method,⁴ as well as with latex and dust accumulated on the surface of the leaves, skin testing with latex extract is more reliable for the diagnosis of *F. benjamina* allergy.^{2,16} Axelsson et al² performed bronchial provocation tests with *F. benjamina* latex extract in six patients with asthma and all of them had immediate responses. In two patients a single asthmatic reaction was elicited at low allergen concentrations and dual asthmatic reactions followed increased concentrations.² In our patient, bronchial provocation test with *F. benjamina* latex resulted in a dual asthmatic response. Interestingly, eosinophil cationic protein in serum significantly increased after specific inhalation challenge, suggesting activation of eosinophils and release of their granule products. Serum eosinophil cationic protein has been found to be increased after inhalation challenge with allergen.¹⁷

A total of 11 allergenic components have been identified in *F. benjamina* latex by means of immunoblotting. Three of them were found to be major allergenic components and had molecular weight of approximately 25, 28, and 29 kDa.¹⁸

Axelsson et al¹⁹ studied the possible cross-reactivity of *F. benjamina* latex and seven other indoor plants of the genus *Ficus* with RAST and RAST-inhibition techniques in patients with allergy to *F. benjamina*. Important cross-allergenicity among extracts from different species of *Ficus* with small leaves was found. The cross-reactivity between *F. benjamina* and those *Ficus* species with larger leaves,

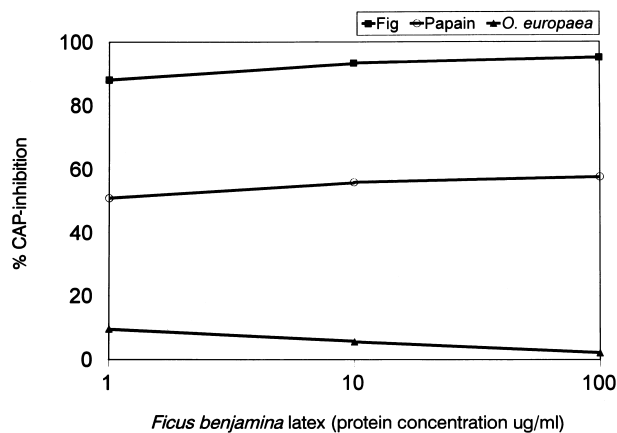


Figure 2. CAP-inhibition assays using fig, papain and *O. europaea* pollen as solid-phase allergens and *F. benjamina* latex as inhibitor allergen.

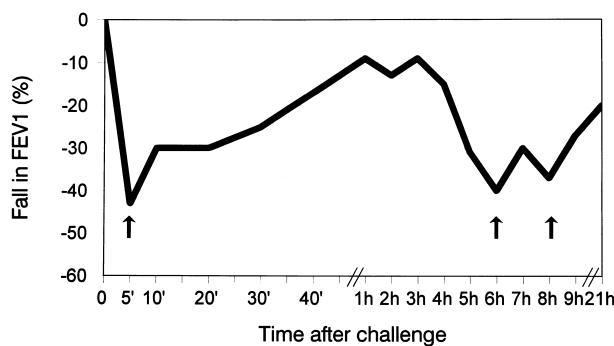


Figure 3. Dual asthmatic response after bronchial provocation test with *F. benjamina* latex extract (inhalation of 200 µg albuterol is indicated by arrows).

such as the india rubber tree *Ficus elastica*, was less pronounced.¹⁹

Whether there would be some degree of cross-reactivity between *F. benjamina* latex and *H. brasiliensis* latex, two botanically unrelated plants, also has been investigated. It has been reported that some patients with serum-specific IgE against *F. benjamina* latex also had positive RASTs to *H. brasiliensis* latex although the patients may not have had symptoms on exposure to *H. brasiliensis* latex.^{14,16,18,20} Specific IgE against *F. benjamina* allergens in patients allergic to *H. brasiliensis* latex also has been found.²¹

Delbourg et al²⁰ reported cross-reactivity between *F. benjamina* latex and *H. brasiliensis* latex in two patients, demonstrated by reciprocal inhibition of CAP RAST and immunodot by the two extracts. One of these patients,

however, showed no response to bronchial provocation test with *H. brasiliensis* latex. We found neither sensitization to *H. brasiliensis* latex nor cross-reactivity between *F. benjamina* and *H. brasiliensis* latex in our patient. The discrepancy might be due to sensitization by different epitopes in *H. brasiliensis* and *F. benjamina* latex. Our results, however, are in keeping with those of Dechamp et al³ who showed negative skin test and specific IgE to *H. brasiliensis* latex in the first patient with documented allergy to fig and *F. benjamina* latex.

Similar to the association between hypersensitivity to *H. brasiliensis* latex and to some fruits (banana, chestnut, and others)²²⁻²⁴ there seems to exist an association between allergy to *F. benjamina* latex and fruits such as fig and possibly kiwi, as observed in our pa-

tient. Inhibition assays showed significant cross-reactivity between *F. benjamina* latex and fig. There is only a previous case report of anaphylactic reaction after fig ingestion.³ In this patient specific IgE antibodies against both fig and *F. benjamina* were detected and CAP to *F. benjamina* was partially inhibited by fig extract. Although this patient did not have respiratory allergy due to *F. benjamina*, it was hypothesized that allergy to fig fruit was a consequence of initial sensitization to weeping fig.³

Our patient was also sensitized to the plant proteases papain and bromelain as demonstrated by in vivo and in vitro tests. *Ficus benjamina* latex inhibited IgE binding to papain by 57%, suggesting the existence of cross-reactive allergen structures. Sensitization to papain has not been investigated previously in patients allergic to *F. benjamina* or fig fruit. Positive CAP to papain has been reported in three patients allergic to *H. brasiliensis* latex and fruits (banana, kiwi, and avocado)²⁵ and cross-reacting IgE antibodies recognizing *H. brasiliensis* latex and papain have also been found by CAP-inhibition studies in patients sensitized to *H. brasiliensis* latex and fruits.²⁶ Hypersensitivity to bromelain in our patient is likely to be due to cross-reactivity between this enzyme and papain.^{27,28}

Gall et al²⁹ studied ten patients allergic to both kiwi and birch pollen and two of them had a positive RAST against papain and seven against bromelain. RAST-inhibition studies showed that both enzymes partially inhibited the RAST to kiwi. Baur et al³⁰ reported that up to 50% of 22 workers sensitized to papain had specific IgE against *H. brasiliensis* latex and in sera from most of these patients the binding of IgE antibodies to papain was strongly blocked by *H. brasiliensis* latex, suggesting that one or several major papain epitopes are also present in *H. brasiliensis* latex.

The fig lysozyme from dried fig latex (MW 29 kDa) has physical and enzymatic properties strikingly similar to those of papaya lysozyme (MW 25

kDa).³¹ Further, one of the allergenic proteins in *H. brasiliensis* latex has lysozyme activity (MW 27 kDa) and it is similar to that of fruits.³² In patients with allergy to *H. brasiliensis* latex, sensitization to papain is strongly associated with allergy to botanically unrelated fruits.³³ In our patient, however, sensitization to papain was associated with allergy to fig and kiwi but not with allergy to *H. brasiliensis* latex, suggesting sensitization by a different set of cross-reactive epitopes.

The existence of cross-reactive allergenic structures in plant-derived products, such as latex, fruits, and enzymes may explain extensive allergenic reactivity. The role that plant enzymes (such as papain, bromelain, and lysozyme) may play in cross-reactivity between fruits and latex from *F. benjamina* and from *H. brasiliensis* needs further research.

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