

Letter to the Editor

Induced bronchospasm after handling of orange flavedo (zest)

To the Editor:

Orange (*Citrus sinensis*) fruit and juice are widely consumed in Europe. Oranges belong to the Rutaceae family, members of which are found in warm regions worldwide and also include limes, lemons, tangerines, and grapefruit. Despite their wide consumption, sensitization to Rutaceae is rare, but the diagnosis should not be overlooked.¹

Oranges are clinically relevant allergenic fruits. Reports describe allergic reactions from eating fresh orange skin and pulp or drinking juice or soda,^{1,2} with symptoms including oral allergy syndrome, urticaria, and atopic dermatitis. Systemic reactions are reported, and case reports describe the development of food-dependent, exercise-induced anaphylaxis after orange ingestion.³ Oropharyngeal symptoms (oral allergy syndrome), an association with hay fever, and sensitization to other plant foods are the most common manifestation of orange allergy.⁴

Three major allergens have been described to date in orange peel and pulp: Cit s 1 (germin-like protein, 23 kDa), Cit s 2 (profilin, 14 kDa), and Cit s 3 (nonspecific lipid transfer protein [LTP], 9 kDa).⁴⁻⁶ Although most reported cases of orange allergy are due to ingestion of fresh fruit or derived products (eg, juice and jam), contact allergy to citrus peel oil should be considered in patients with hand dermatitis who are occupationally exposed to citrus fruits.⁷ Occupational asthma in persons employed in removing the peel from oranges to produce the enzyme (pectinase and glucanase) solution used in soaking the fruits has been reported.⁸ However, no cases of allergic respiratory symptoms caused by orange peel allergens have been reported.

Fruits with thick peels, such as oranges, are classified as hesperidia, and contain an inner layer of peel called the mesocarp (the white *albedo* or pith) and an outer layer of peel called the exocarp (*flavedo* or *zest*), which together form the peel. Flavedo is mostly composed of cellulosic material but also contains other components, including essential oils, paraffin waxes, steroids and triterpenoids, fatty acids, pigments (carotenoids, chlorophylls, and flavonoids), bitter principles (limonene), and enzymes (α -D-glucosidase, α -D-mannosidase, α -L-arabinosidase, β -D-glucosidase, β -D-xylosidase, and β -D-galactosidase).

We report the case of a 22-year-old woman with a family history of atopy. The medical history revealed perennial rhinoconjunctivitis and persistent moderate bronchial asthma caused by sensitization to dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*). The patient received specific immunotherapy for 5 years with a mix of *Dermatophagoides* species, but rhinitis and symptoms of mild intermittent asthma persisted. Currently, she requires occasional symptomatic treatment and also presents with discrete seasonal exacerbations during the spring caused by allergy to *Parietaria* species pollen.

Some months ago, the patient presented with intense dyspnea, coughing, and wheezing triggered by the handling (peeling) of oranges or after entering a room where different varieties of freshly picked or bought-in oranges were being peeled, resulting in having to leave the room. The symptoms disappeared after inhalation of a dose of terbutaline. The patient reports tolerating orange pulp and juice well.

Skin tests for common aeroallergens in the Valencia region were positive for mites (*D pteronyssinus* and *D farinae*) and *Parietaria* species pollen. We performed specific skin prick tests for the flavedo, albedo, pulp, and juice of orange, lemon, and grapefruit. Skin prick test responses for orange albedo, pulp, and juice and lemon and grapefruit flavedo, albedo, and pulp were negative. However, the skin prick test response for orange flavedo was positive, resulting in a 3-mm wheal (histamine control of 5 mm). The same skin prick tests were carried out in 5 healthy control subjects, all with negative results.

We carried out challenge tests (peeling oranges, lemons, and grapefruit) with baseline and postchallenge spirometric controls. Test responses for lemon and grapefruit were negative. However, the challenge test result for oranges was positive: the patient had clinical symptoms (cough, dyspnea, and expiratory wheezing in both lungs) within 2 minutes. Spirometry showed a 23% reduction in FEV₁ from baseline, which was reversed after administration of bronchodilators.

We performed SDS-PAGE according to the method described by Laemmli⁹ and immunoblotting with extracts of orange flavedo, albedo, and pulp from 3 varieties (Navel Lane, Navel Late and Valencia Late). IgE immunoblotting of sera revealed 2 IgE-binding bands of approximately 9 to 10 kDa and 23 kDa in the flavedo of the 3 orange varieties, which are not present in pulp or albedo (Fig 1).

We believe this is the first report of selective sensitization to allergens of the outer layer of orange peel (flavedo), which manifests with acute bronchospasm triggered by peeling oranges. We identified 2 allergens (of 9-10 and 23 kDa, respectively) in orange flavedo that are not present in the albedo or pulp, which explains the tolerance to orange pulp. These allergens, by reason of their molecular weight, might correspond to orange Cit s 1 (germin-like protein, 23 kDa) and Cit s 3 (nonspecific LTP, 9 kDa). Although Crespo et al⁶ reported the presence of these allergens in pulp, none of the study subjects showed IgE binding to a 9- to 10-kDa band in orange pulp extract. Further studies could evaluate whether Cit s 3 is predominantly present in orange peel.

Positive responses induced by Cit s 1 in some subjects suggest potential clinical relevance in some patients with orange allergy. The presence of a single N-glycan, which is the target of IgE response to this protein, and the apparent lack of polypeptide epitopes, might explain its equivocal nature as a clinically relevant allergen. LTPs are located in the outer layers of the plants and are especially abundant in the peels of many fruits. Cit s 3 is present both in orange pulp and peel, but the latter is a stronger reactive. These data, together with the fact that oranges are eaten peeled, could explain both the low prevalence and mild symptoms in allergic responses after ingestion, but when peeled, they could act as a respiratory allergen and patients could be sensitized through respiratory exposure.

In conclusion, inhalation of airborne orange peel proteins with an LTP-equivalent IgE-binding pattern can cause respiratory allergy in sensitized patients. A detailed medical history is vital to the correct diagnosis of this condition, which might have an occupational origin.

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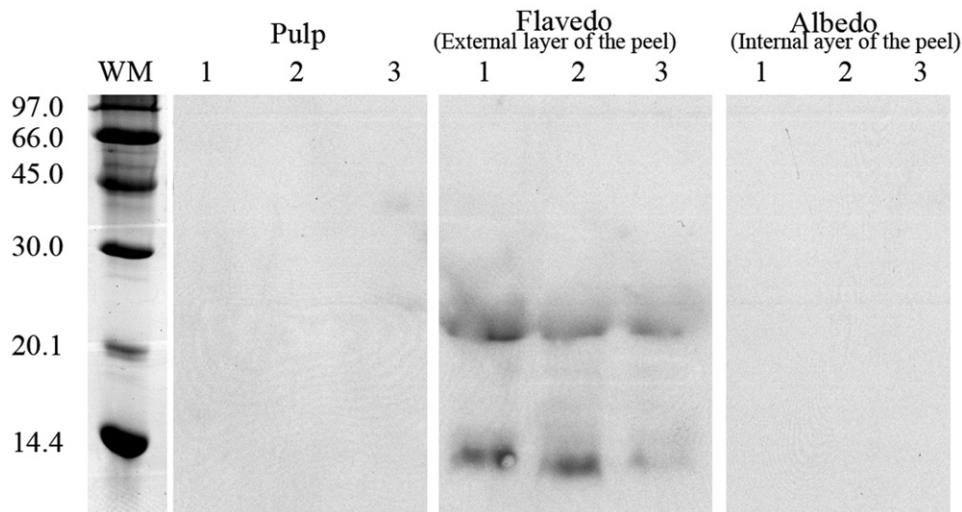


FIG 1. IgE immunoblotting. Lane 1, Navel Lane orange. Lane 2, Navel Late orange. Lane 3, Valencia Late orange. WM, Weight marker.

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