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# Fruit allergies: Beware of the seed allergens!

## *Allergies aux fruits : attention aux allergènes des graines !*

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**Abstract**

Anaphylactic reactions associated with the consumption of a number of fruits have been identified so far. Stone fruits belonging to the Rosaceae family have been particularly investigated in this respect, due to the occurrence of lipid transfer protein major allergens LTP, in both the pulp and the skin of the fruits. Other offending allergens like the PR-5 thaumatin-like proteins TLP, profilins and a variety of enzymes (β1,3 glucanase, chitinase) also occur in many fruits. However, stone fruits consist of another source of major allergens located in the fruit kernel, namely the cupin and 2S albumin allergens. Cupin allergens consist of three categories of seed storage proteins: germins (< 7S protein), vicilins (7S globulins) and legumins (11S globulins). All of these allergens exhibit the canonical protomeric structure made of a single (germin) or two cupin motifs (vicilin, legumin) associated to two α-helical arms. In both proteins, three identical protomeric structures become non-covalently associated by their α-helical arms to form a flattened triangle-shaped homotrimer. Germins (90 kDa) and vicilins (150 kDa) consist of a single homotrimer whereas legumins result from the non-covalent stacking of two homotrimers to form a huge hexameric structure of 300 kDa. Here, we present a catalogue of the cupin allergens distributed in the commonly consumed stone fruits. All of these cupin allergens behave as major allergens that are susceptible to trigger severe anaphylactic responses following their inadvertently consumption by previously sensitized consumers. In fact, it is noteworthy that kernels of a variety of stone fruits including apple, grape, physalis, tomato etc., are often consumed together with the pulp of the fruits. Faced with a fruit allergy, allergologists have to bear in mind the possible involvement of seed and kernel allergens in the fruit allergenic response. In this respect, both the measurement of cupin-specific IgE and the possible occurrence of allergic manifestations cross-linked to the consumption of other cupin-containing foods, should be useful to assess the severity of the fruit allergy, and to decide on the most appropriate management and treatment for this allergy.


*Keywords:* Fruit allergies; Cupin; Germin; Vicilin; Legumin; Lipid Transfer protein; Thaumatin-like protein; Seed; Kernel; Almond

**Résumé**

Les réactions anaphylactiques associées à la consommation de fruits sont connues depuis longtemps. Les fruits à noyau de la famille des Rosacées sont particulièrement concernés en raison de leurs allergènes majeurs qui appartiennent aux groupes des protéines PR, les protéines de transfert des lipides ou LTP (groupe des PR 14) et les protéines thaumatin-like ou TLP (groupe des PR 5). Le noyau de ces fruits renferme une autre source d'allergènes majeurs, les cupines et les albumines 2S. Les cupines correspondent à trois catégories de protéines de réserve, les germines (globulines < 7S), les vicillines (globulines 7S) et les légumines (globulines 11S). Toutes ces protéines résultent de l'association en homotrimères de protomères à un (germine) ou deux motifs cupine (vicilline et légumine). Dans les légumines, deux homotrimères s'associent en hexamères très volumineux. Nous présentons dans cet article les allergènes du groupe des cupines que l'on peut rencontrer dans les fruits à noyau. Ces allergènes, et ceux des fruits à pépins en particulier, peuvent être responsables de manifestations allergiques sévères. Devant une allergie sévère associée à la consommation de fruits à pépins ou à noyau, l'allergologue devra prendre en compte cette possibilité d'une intervention des cupines, notamment

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lorsque la recherche des allergènes typiques des fruits à noyau comme les LTP, les TLP ou les glucanases, s'avère négative. L'existence éventuelle de manifestations croisées avec des aliments riches en cupines, devra également être prise en compte.


*Mots clés :* Allergies aux fruits ; Cupines ; Germines ; Vicillines ; Légumines ; Protéines de transfert des lipides ; Protéines Thaumatin-like ; Graines ; Pépins ; Noyaux ; Amandes

## 1. Introduction

Adverse anaphylactic reactions to edible fruits have now become a relevant facet of food allergy, especially with the increasing introduction of a variety of exotic fruits in the diet. The widespread allergy to kiwifruit (*Actinidia chinensis*, *A. deliciosa*) offers a nice example for a fruit allergy developed over the last decades, in particular among young people [1]. Moreover, the encouragement on eating more vegetable and fruit for their supposed health benefits or even to adopt a vegetarian diet, are so many factors susceptible to account for the growing incidence of fruit allergies in European countries [2]. So far, in addition to profilins [3], most of the allergenic proteins identified in edible fruits belong to different pathogenesis-related (PR)-protein families, namely PR-2 β1,3-glucanases, PR-3 P, PR-4 and PR-8 chitinases, PR-5 thaumatin-like proteins TLP, PR-10 Bet v 1-like proteins and PR-14 lipid transfer proteins LTP [4]. Additionally, PR-12 defensins, initially classified as γ-thionins, are now considered as possible fruit allergens, especially in bell pepper [5,6]. All of these fruit allergens occur in the pulp and thus, readily differ from other important allergens located into the kernels and seeds. Seeds of higher plants and especially dicot, contain a set of specific proteins, the so-called seed storage proteins, which belong to two distinct classes of allergenic proteins: 2S albumins and cupins, which consist of vicilins (7S globulins), germins and germin-like proteins (7S globulins), and legumins (11S globulins) [7]. All of these seed allergens are closely related to other major allergens occurring in peanut and tree nuts, like Ara h 1 (vicilin/7S globulin), Ara h 2 and Ara h 6 (2S albumin) and Ara h 3 (legumin/11S globulin) [8]. Accordingly, the most abundant cupin proteins occurring in the seeds of edible fruit might behave as hidden allergens and trigger some hypersensitive responses wrongly attributed to the pulp allergens. Moreover, their close phylogenetical relationships with other cupin allergens from edible seeds could account for some crossed allergenicity with e.g. cupin-containing legume seeds. In the present paper, we have been focused on the occurrence of cupin allergens of a variety of edible fruits as a possible source of hidden allergens susceptible to trigger some unexpected allergenic responses in previously sensitized people.

## 2. Fruit allergens

Allergens from pome and stone fruits, e.g. allergens of the Rosaceae Prunoidae (apple, apricot, cherry, peach, pear, plum), Vitaceae (grapefruit) and Rutaceae (lemon, orange, tangerine), have been deeply investigated due to the occurrence of lipid transfer protein (LTP) in both the skin and the pulp of the fruits [9]. Non-specific LTP (nsLTP) consists of secreted proteins, which accumulate, in the cell walls during the fruit ripening process [10]. In peach, Pru p 3 essentially accumulates in the fuzzy covering the ripe fruit [11]. As a practical consequence, peeling off the fruits before their consumption helps to significantly reduce their LTP content. As defence proteins belonging to the PR-14 family of pathogenesis-related proteins, LTP participate in the building and thickening of the cuticle covering the plant organs, leaves and stems, for protecting the exposed organs from attack by phytopathogenic fungi like rusts, smuts and mildew [12]. LTP consist of tightly packed small proteins (9 kDa) built up from five α-helices connected by four disulfide bridges, which makes these fruit allergens particularly resistant to both the digestive proteolysis by pepsin and trypsin, and thermal denaturation (cooking) [13]. In addition, peach LTP is responsible for severe anaphylactic reactions, especially in Mediterranean countries [14,15]. In this respect, marked differences occur among European populations with respect to allergies caused by PR-10 Bet v 1-like proteins, LTP and profilins [16,17].

Besides LTP, other allergens occur in fruits but they have been lesser investigated compared to LTP allergens. Among these, we should mention several allergens that belong to different groups of pathogenesis-related (PR)-proteins including the PR-2 β1,3-glucanases, the PR-3 class I chitinases and PR-8 class III chitinases, the PR-5 thaumatin-likeproteins TLP and the PR-10 Bet v 1-like proteins like the apple Mal d 1 allergen [18]. Like LTP, TLP possess a tightly packed three-dimensional conformation maintained by eight disulfide briges, that confer to these fruit allergens a strong resistance to both the digestive proteolysis and thermal denaturation [19]. In addition to PR-proteins, profilins also consist of widespread distributed fruit allergens. Both profilins and PR-10 Bet v 1-like proteins readily differ from other PR-proteins by their lower resistance to proteolysis and thermal denaturation. They are primarily involved in food allergenic responses associated to pollinosis [20].

Both the synthesis and accumulation of PR-proteins in fruits highly depend on the response of the plant to a fungal attack. However, large discrepancies in the PR-protein content were observed among different cultivars of apple and peach [21–23], in relation with other abiotic stress conditions, e.g. the degree of maturity and the post-harvest storage conditions [24,25].

Smaller antimicrobial polypeptides with allergenic properties also exist in fruits, especially the so-called peamacleins or gibberellin-regulated proteins (GRP) or snakins [26,27] and defensins as well. Like LTP, Pru p 7 of peach, pommaclein of pomegranate (*Punica granatum*) and other peamacleins [28], consist of tightly structured α-helical proteins which display

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