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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 (β 1,3 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.

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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 légumineuses (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 légumineuses, 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.

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Mots clés : Allergies aux fruits ; Cupines ; Germines ; Vicillines ; Légumineuses ; 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 β 1,3-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 β 1,3-glucanases, the PR-3 class I chitinases and PR-8 class III chitinases, the PR-5 thaumatin-like proteins 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 bridges, 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

some antioxidant properties [29,30]. Recently, a GRP/snakin was identified as a major allergen of the pollen food-associated syndrome (PFAS) between cypress pollen and citrus or peach fruits [31]. Defensins consist of a small polypeptide chain made of β -strands structured by three disulfide bridges, which adopts a very resistant knottin conformation [32].

Apart from allergens located into the pulp, other allergens exist in the kernels and seeds of edible fruits. Seed allergens consist of the so-called seed storage proteins, which have been classified in two categories according to their solubility in water (albumins) and salt-buffered solutions (globulins). Seed albumins consist of 2S albumins, whereas seed globulins or cupins consist of three distinct groups of germans (7S globulins), vicilins (7S globulins) and legumins (11S globulins) [33,34]. The scientific name of cupin is derived from the latin *cupa*, which means a cup, due to the shape of a cup adopted by two bundles of β -sheets forming the monomeric structure of plant globulins. Vicilins (7S globulin) result from the non-covalent association of three identical monomers to build a flattened triangle shaped homotrimer [33,35], whereas the more bulky legumins (11S globulin) result from the non-covalent stacking of two flattened triangle shaped homotrimer to form a hexamer [33]. Both 2S albumins, vicilins and legumins consist of the major allergens occurring in peanut and tree nuts [33]. Germans possess a homotrimeric conformation very similar to that of vicilins but each monomer contains a single cupin motif, instead of two. Germans and germin-like proteins play a key role in the embryogenesis and also in the response of higher plants to different biotic and abiotic stresses [36,37]. They have been identified as relevant allergens [38].

3. Cupins as hidden allergens from edible fruits

Enclosed inside the kernels and seeds, seed allergens of some fruits are not directly available for triggering a hypersensitive response in previously sensitized consumers. In this respect, allergic manifestations to stone fruits like peach, apricot and cherry, do not relate to the seed allergens except if, incidentally, a seed fragment becomes swallowed together with the pulp of the fruit, for example, because of the rupture of the stone in some ripe fruits. In other fruits, however, seeds and kernels are currently consumed with the pulp and seed allergens thus become directly available for an allergic response. This is the case for many fruits including cucumber, tomato, banana, kiwifruit, strawberry, fig and pomegranate. In grapefruit, except for seedless varieties, and citrus like lemon, orange and tangerine, kernels may be accidentally consumed with the pulp and trigger an allergenic response.

Accordingly, cupin allergens acting as hidden allergens were identified in citrus fruits [39], which cross-react with peanut [39] and cashew nut [40], and cosensitize with cashew nut, as well [41].

Cupin allergens were also identified as hidden allergens in kiwifruit (*Actinidia deliciosa*) [42] and subsequently characterized and cloned as the legumin Act d 12 and Act d 13 allergens [43]. Moreover, allergenic structures common to kiwifruit and rye grain, hazelnut, sesame and poppy seeds had been previously

Table 1

List of edible fruits containing cupin allergens (legumin, vicilin and germin and germin-like protein).

Fruit	Legumin(11S)	Vicilin(7S)	Germin(7S)
Kiwifruit (<i>Actinidia chinensis</i>)	X		
Apple (<i>Malus domestica</i>)	X	X	X
Peach (<i>Prunus persica</i>)	X		X
Pear (<i>Pyrus x bretschneideri</i>)	X		
Bell pepper (<i>Capsicum annuum</i>)	X		X
Physalis (<i>Physalis alkekengi</i>)		X	
Tomato (<i>Solanum lycopersicum</i>)	X	X	X
Eggplant (<i>Solanum melongena</i>)		X	
Grape (<i>Vitis vinifera</i>)	X	X	X
Mulberry (<i>Morus alba</i>)	X		X
Orange (<i>Citrus sinensis</i>)	X	X	X
Lemon (<i>Citrus x limon</i>)			X
Clementine (<i>Citrus clementina</i>)		X	
Tangerine (<i>Citrus mandarina</i>)		X	
Banana (<i>Musa acuminata</i>)	X	X	X
Cocoa (<i>Theobroma cacao</i>)	X	X	X
Strawberry (<i>Fragaria vesca</i>)	X		
Fig (<i>Ficus pumila</i>)	X	X	
Pomegranate (<i>Punica granatum</i>)		X	
Papaya (<i>Carica papaya</i>)	X	X	
Gac (<i>Momordica cochinchinensis</i>)	X		
Chestnut (<i>Castanea sativa</i>) ^a	X		
Cucumber (<i>Cucumis sativus</i>)	X	X	
Pumpkin (<i>Cucurbita maima</i>)		X	

^a Chestnut is a fruit with an edible seed once roasted or as a meal.

reported [44]. More recently, a high frequency of sensitization of kiwifruit seed storage proteins was observed in peanut allergic people experiencing an associated kiwifruit allergy, thus suggesting that crossed-reactions/allergies can occur between kiwifruit and peanut [45,46].

A severe anaphylactic reaction was observed in a 9-year-old girl upon consumption of a single Japanese lantern cherry (*Physalis alkekengi*) fruit [Gallen et al., unpublished observation]. She further experienced an anaphylactic response upon consumption of a freshly harvested broadbean (*Vicia faba*). Protein extracts prepared from the tiny seeds present in the *Physalis* fruit (50 kDa and 35 kDa fractions) and broad bean seeds (50–60 kDa fractions), were shown to strongly react with the IgE-containing serum from the patient. All of these IgE-reactive protein fractions were identified as convicilin and legumin (broad bean) and cupin subunits closely related to tomato vicilin (*Physalis* fruit) by mass spectrometry. No IgE-binding protein fractions were identified in the pulp from *Physalis* fruit. These results suggest that cupin allergens exist as hidden allergen in the *Physalis* fruit seeds, not in the pulp, and can possibly trigger crossed-anaphylactic reactions with legume seeds.

4. Cupin allergens identified in edible fruits

Table 1 is provided as a summary of some of the cupin allergens that have been identified and characterized in edible fruits, including exotic fruits. Obviously, the most investigated vicilin and legumin allergens are most represented, compared to germans and germin-like proteins. Figs. 1–4 show all the

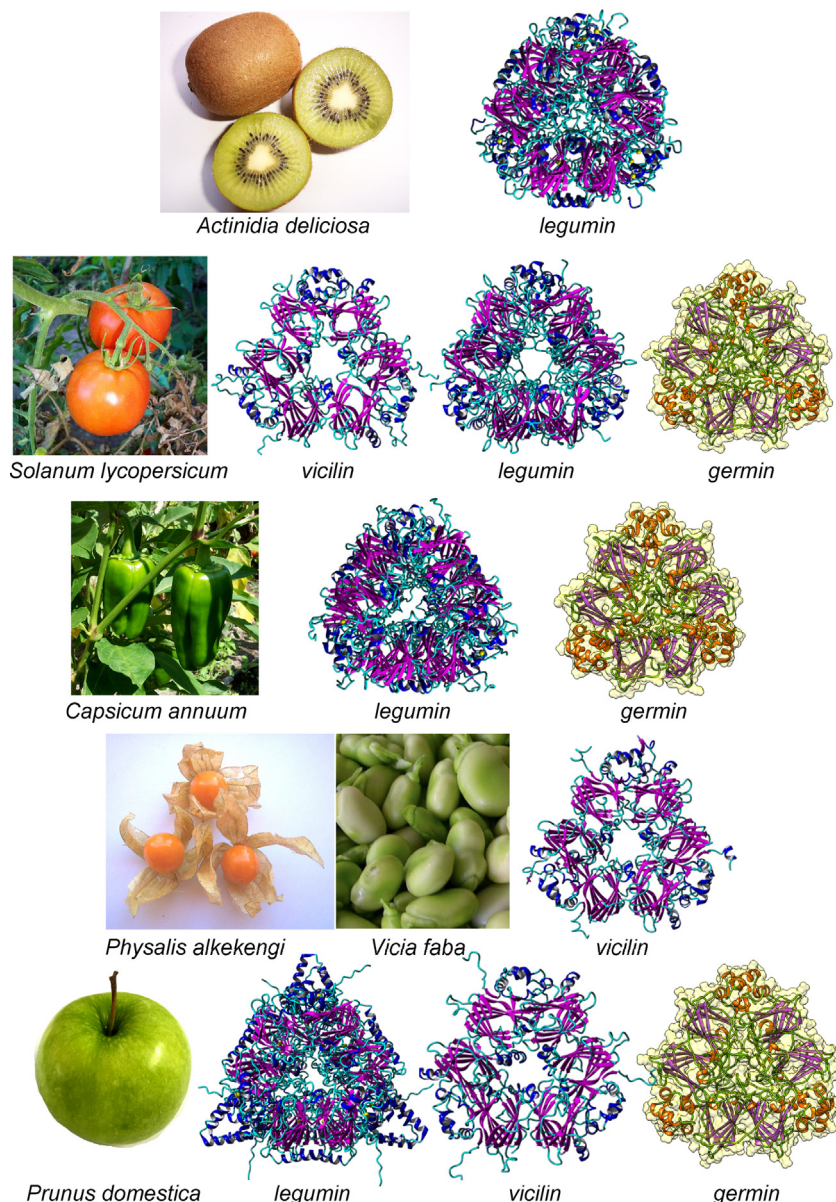


Fig. 1. Cupin allergens (germins and germin-like proteins, vicilins, legumins) identified and characterized in kiwifruit (*Actinidia chinensis*), tomato (*Lycopersicum esculentum*), bell pepper (*Capsicum annuum*), physalis (*Physalis alkekengi*) and apple (*Malus domestica*).

incriminated fruits together with the three-dimensional models built up by homology modeling for their germin (7S globulin), vicilin (7S globulin) and legumin (11S globulin) seed components.

All of these cupin allergens exhibit conserved amino acid sequences as shown from the multiple alignment of germin and germin-like proteins of different edible fruits (Fig. 5). As conserved seed storage proteins commonly found in all the higher plants, vicilin and legumin allergens exhibit a similar degree of sequence identities and homologies (results not shown).

In addition, depending to their phylogenetical relationships, cupin allergens are closely structurally-related to the major allergens of peanut (*Arachis hypogaea*), tree nuts like cashew nut (*Anacardium occidentale*), pistachio (*Pistacia vera*), wall nut (*Juglans regia*), but also to legume seeds like lentil (*Lens culinaris*), pea (*Pisum sativum*), fava bean (*Vicia faba*), chickpea

(*Cicer aritinum*) and kidney bean (*Phaseolus vulgaris*). They also resemble the major cupin allergens of buckwheat (*Fagopyrum esculentum*) and sesame (*Sesamum indicum*). As previously pointed out, all of these legumin allergens exhibit a similar molecular organization, made of the non covalent superposition of two identical homotrimers, each of them resulting from the terminal end-interchange association of three monomers displaying two cupin motifs (see Figs. 1–4).

Due to these sequence and structural similarities, cupin allergens are susceptible to trigger crossed reactions/allergies between fruits and seeds, as previously reported between kiwifruit and peanut [39], and between *Physalis* fruit (*Physalis alkekengi*) and broadbean (*Vicia faba*) [unpublished]. In this respect, the phylogenetic tree built for seed legumins show close relationships between the stone fruits and strongly allergenic seeds like wallnut (Jug r 4), cashew nut (Ana o 2) and Pecan

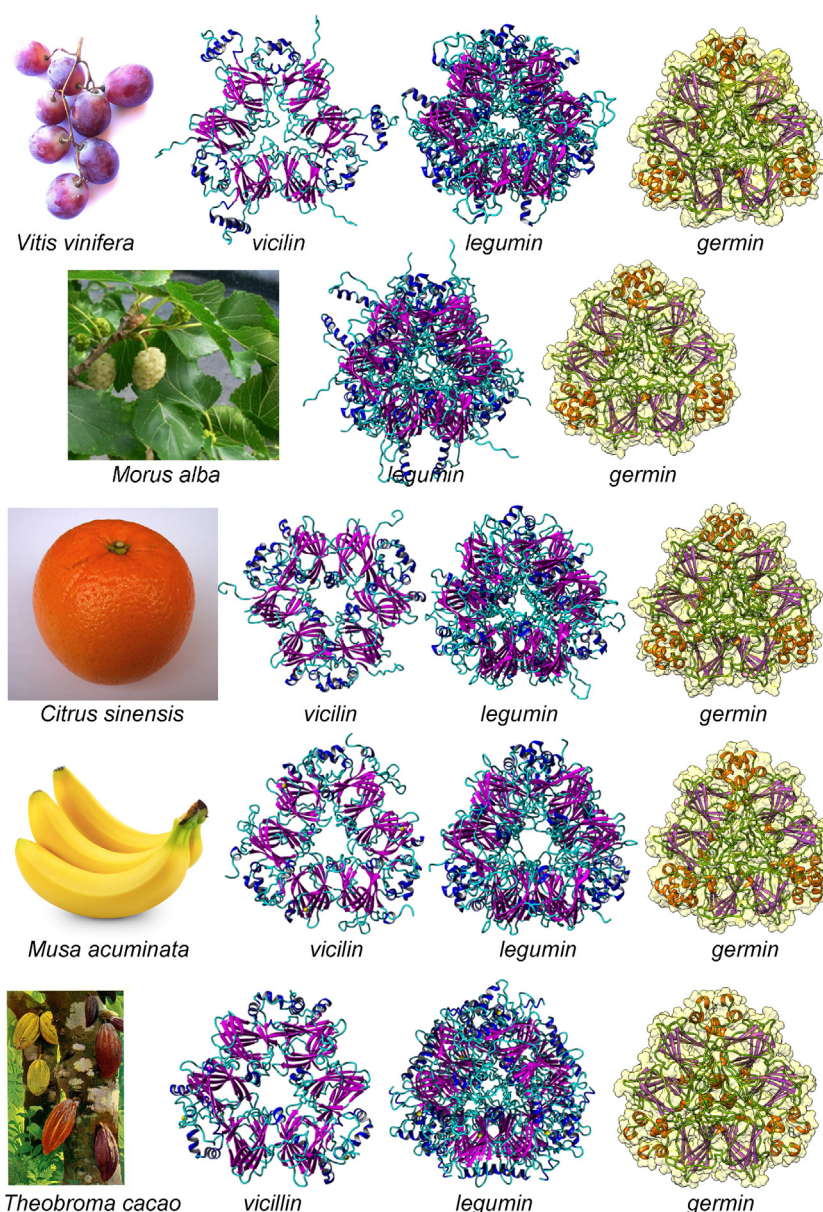


Fig. 2. Cupin allergens (germins and germin-like proteins, vicilins, legumins) identified and characterized in grapefruit (*Vitis vinifera*), mulberry (*Morus alba*), orange (*Citrus sinensis*), banana (*Musa acuminata*) and cacao (*Theobroma cacao*).

nut (Car i 4) (Fig. 6). They are close enough from the peanut legumin Ara h 3 and other legumins e.g. legumins of pea, lentil and kidney bean, and Cic a 6 of chickpea, to cross-react and possibly trigger some crossed-allergies (Fig. 6). Similarly, the close relationship occurring in the legumin tree between the citrus legumin and Ana o 2 from cashew nut, fully agrees with the already reported crossed-allergenicity and cosensitization observed between citrus (*Citrus aurantium*) and cashew nut (*Anacardium occidentale*) [40,41].

5. Conclusion

Obviously, seed cupin allergens of the germin, vicilin and legumin groups consist of major providers of crossed-

reactions/allergies to sensitized people [47]. As components of edible fruits, they can be either currently or incidentally swallowed with the pulp of the fruits and trigger some unexpected allergenic reactions in susceptible individuals. In this respect, kiwifruit and citrus fruits represent good examples of currently (kiwifruit) or incidentally (citrus) swallowed IgE cross-reacting cupin allergens together with the pulp of the fruits [43]. Of course, crossed reactivity essentially occurs with peanut, legume seeds and other tree nuts, which represent the most important and largely consumed sources of cupin allergens in our European diet, especially in Mediterranean countries [48]. However, many other edible fruits contain seed cupin allergens that are susceptible to become incidentally swallowed upon consumption (Table 1). Moreover, the publicly via the social networks

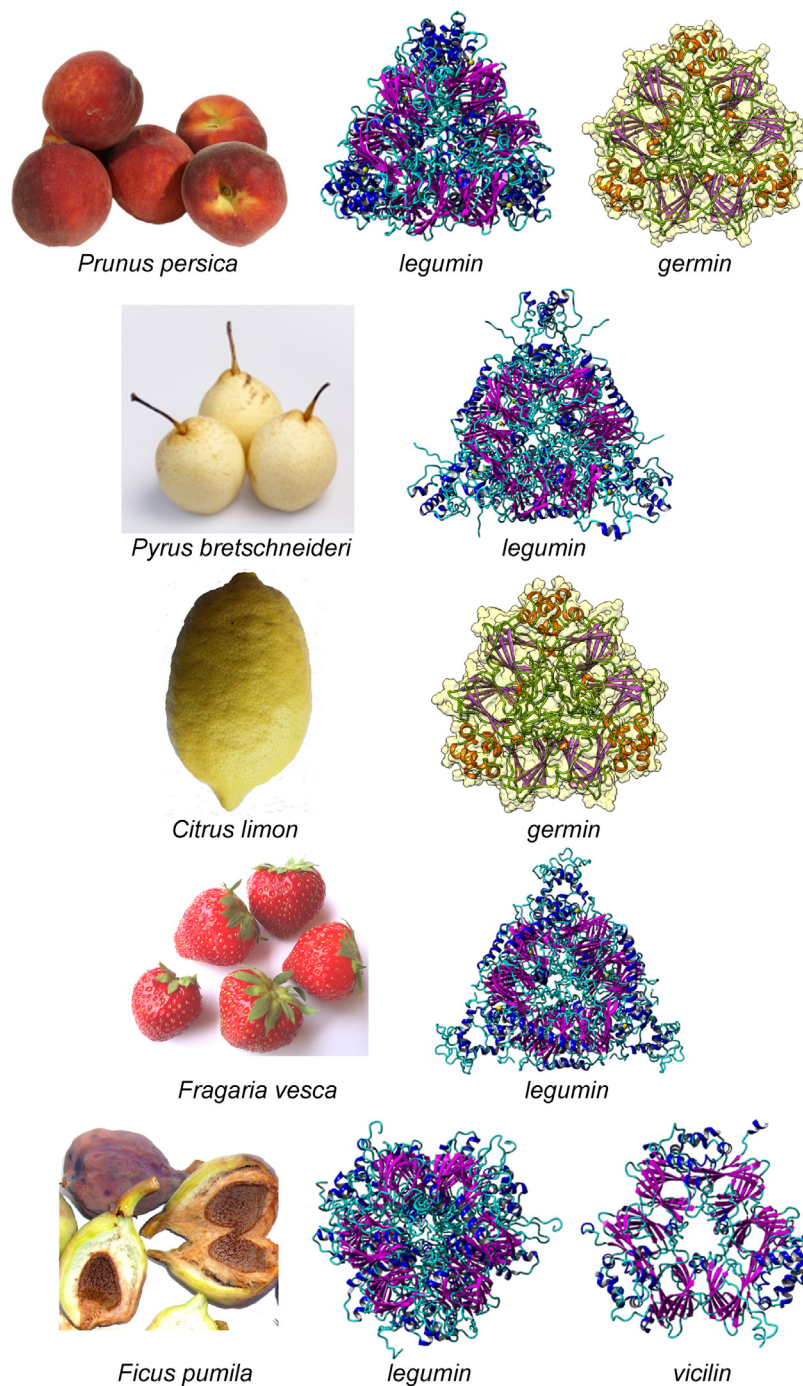


Fig. 3. Cupin allergens (germins and germin-like proteins, vicilins, legumins) identified and characterized in peach (*Prunus persica*), pear (*Pyrus bretschneideri*), lemon (*Citrus limon*), strawberry (*Fragaria vesca*) and creeping fig (*Ficus pumila*).

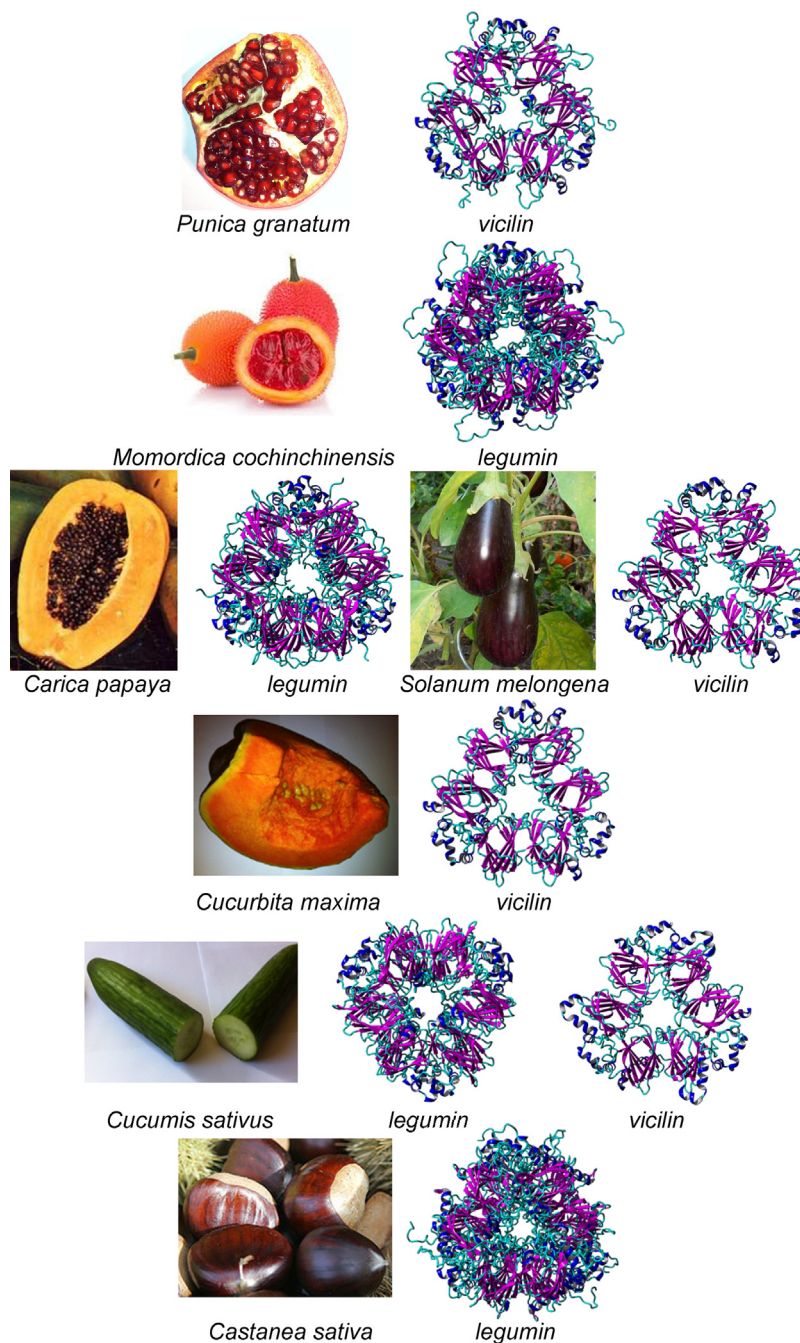


Fig. 4. Cupin allergens (germins and germin-like proteins, vicilins, legumins) identified and characterized in pomegranate (*Punica granatum*), gac (*Momordica cochinchinensis*), papaya (*Carica papaya*), eggplant (*Solanum melongena*), pumpkin (*Cucurbita maxima*), cucumber (*Cucumis sativus*) and chestnut (*Castanea sativa*).

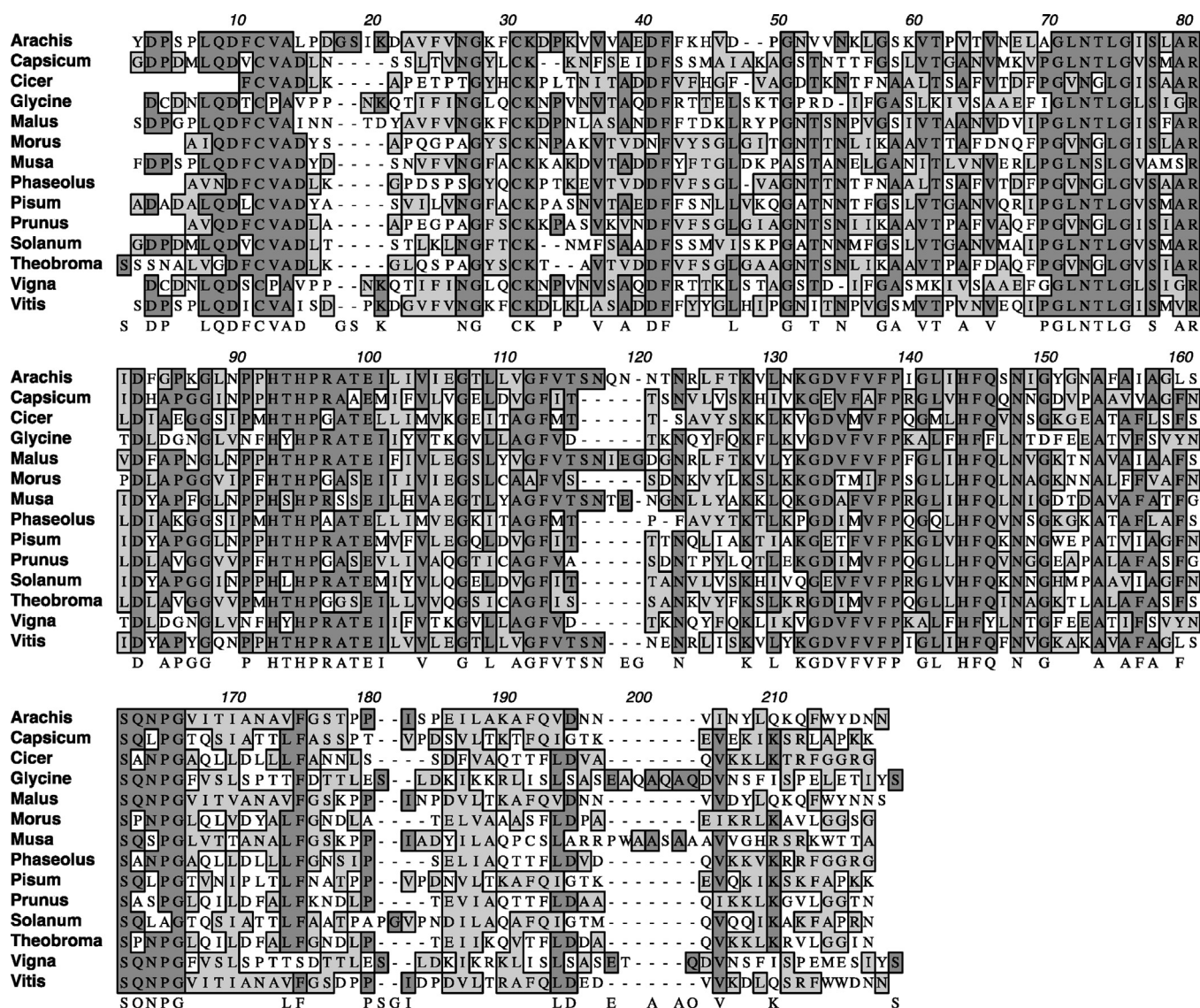


Fig. 5. Multiple amino acid sequence alignment of germin and germin-like proteins found in edible fruits and seeds from different plant species: peanut (*Arachis hypogaea*), bell pepper (*Capsicum annuum*), chickpea (*Cicer arietinum*), soybean (*Glycine max*), apple (*Malus domestica*), mulberry (*Morus alba*), banana (*Musa acuminata*), kidney bean (*Phaseolus vulgaris*), pea (*Pisum sativum*), peach (*Prunus persica*), tomato (*Lycopersicon esculentum*), cacao (*Theobroma cacao*), azuki bean (*Vigna angularis*) and grapefruit (*Vitis vinifera*). Identical and homologous amino acid residues are deep grey boxed and light grey boxed, respectively.

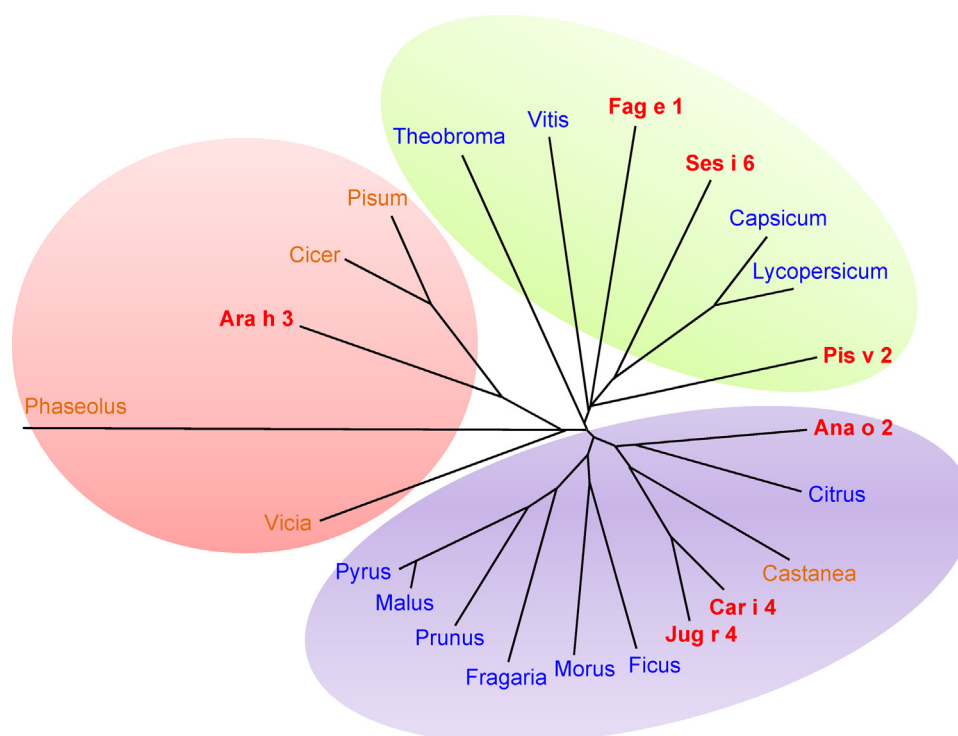


Fig. 6. Phylogenetic tree built up for leguminous of stone fruits (*Citrus*, *Malus*, *Prunus*, *Pyrus*), peanut (*Ara h 3*), tree nuts (*Jug r 4*, *Ana o 2*, *Car i 4*), legumes (*Cicer*, *Pisum*, *Phaseolus*, *Vicia*) and other fruits (*Capsicum*, *Castanea*, *Ficus*, *Fragaria*, *Lycopersicum*, *Morus*, *Theobroma*, *Vitis*). Allergen *Fag e 1* of *Fagopyrum*, and *Ses i 6* of *Sesamum*, were also included.

surrounding the so-called healthy beneficial consumption of avocado or apricot kernels in powder form, is likely to increase the risk of unexpected allergenic reactions to cupin allergens.

Due to the often severe allergenic reactions caused by cupin allergens e.g. peanut and many tree nut allergens, it would be advisable to recommend to allergologists faced to a genuine fruit allergy, to take into account the possible involvement of seed cupin allergens as being the causative offending allergens. Besides the clinical examination and questioning of patients, this point could be successfully achieved through the prescription of biological tests aimed at identifying the IgE-binding activity of the patient sera towards the most probably incriminated cross-reacting cupin allergens. In addition, cross-reactions/allergies of fruits with other cupin-containing foods may be an additional warning sign for the possible implication of cupins as the offending allergens.

Disclosure of interest

The authors declare that they have no competing interest.

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