

Mini Review

Fruit cross-reactive allergens: A theme of uprising interest for consumers' health

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Abstract. Regular consumption of fruits has a positive influence on human health by disease prevention. However parallel to dietetic benefits, IgE-mediated fruit allergies have been shown to be an increasing health risk for children and adults in the Northern hemisphere. The spectrum of food allergies ranges from chronic symptoms to more acute problems and even anaphylaxis. Fruit proteins with high primary sequence similarity display also homologous tertiary structures, resulting in similar epitopes to IgEs and consequently in cross-reactivity. In this review we present the major allergens of stone and pome fruits and discuss the presence of homologous proteins in small fruits. Interestingly these proteins, which might pose an allergenic potential for pre-sensitised individuals are expressed also in strawberry, raspberry and blueberry, otherwise rich in beneficial biofactors.

Keywords: Fruit allergy, small fruits, cross reactivity, pathogenesis related proteins (PRPs), cross-reactive carbohydrate determinants (CCDs)

1. Introduction

The importance of regular consumption of fruits and vegetables in the prevention of cancer and cardiovascular diseases has been widely acknowledged [4,17,24,49]. The World Health Organisation recommends the daily intake of some 400 g of fresh fruits and vegetables per person [21]. However, consumption of particular fruits and vegetables may elicit adverse effects in allergic individuals [36]. Epidemiological data estimate the prevalence of food allergy to be 1.4 to 2.4% [22,51], with children, adolescents and young adults being particularly affected [22,33,43]. Recent studies indicate higher numbers of food allergic patients in the European population, particularly when also secondary food allergies resulting from cross-reactivity with common inhalant allergens, such as pollen, house dust mite or rubber latex, were taken into account. According to investigations in Germany, Sweden and UK, 12–16% of adult people report food allergy and exhibit at least one positive reaction in skin prick test to food allergens [43]. While clinical symptoms elicited by secondary food allergens are often mild, although not always, this type of food allergy is much more common among adults than “true” primary food

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Table 1

Designated cross-reactivity for main apple allergens with proteins from other fruits. Allergenic proteins were identified in fruits of *Rosaceae* with high sequence and conformational homology. These similarities have been repeatedly confirmed to be responsible for cross-reactivity in the patients response

Family	Apple allergen	Other fruit allergens
PRP-10	Mal d 1	peach (Pru p 1), apricot (Pru ar 1), cherry (Pru av 1), pear (Pyr c 1)
PRP-5	Mal d 2	cherry (Pru av 2), kiwi (Act c 2), grape (Vit v TLP)
PRP-14	Mal d 3	peach (Pru p 3), apricot (Pru ar 3) plum (Pru d 3), cherry (Pru av 3), grape (Vit v 1)
—	Mal d 4	cherry (Pru av 4), pear (Pyr c 4), apple (Mal d 4), peanut (Ara h 5), hazelnut (Cor a 2)

allergies. It is obvious from these studies that concomitant respiratory and food allergy is particularly found in individuals primarily sensitised to birch pollen [43]. The observation, that patients allergic to birch pollen develop more frequently hypersensitivity to fresh fruits and vegetables than patients allergic to pollen of mugwort, grasses, ragweed or plane, can be explained by the presence of common epitopes in birch pollen and fruits allergens, as suggested by RAST inhibition studies (Table 1 [5,10,12]). The cross-reactivity between proteins from birch (*Betulaceae*) and apple (*Rosaceae*) indicates that structural homology of the allergens can occur in distantly related taxa.

Most plant allergens belong to only four protein families, indicating that conserved structures and biological activities may play a central role in determining or promoting allergenic properties [23]. The conservation of both surface residues and main chain conformations in the Bet v 1 family plays an important role in conservation of IgE-binding epitopes, which explains cross-reactive allergy syndromes [34]. In contrast to a common opinion, sensitisation to rosaceous fruit allergens can occur without related pollinosis and may have severe consequences [16].

Fruit allergens can be classified depending on their stability to digestion and modification in the gastrointestinal tract and denaturation e.g. during thermal processing of food. Bet v 1-related allergens like Mal d 1 or Pru a 1 are unstable. Therefore, allergic reactions to raw apples and cherries in birch pollen-allergic subjects remain localised to the oral mucosa, while cooked apples or cherries do not elicit allergic reactions at all in the majority of patients. The allergenicity of profilin-related allergens and of allergenic cross-reactive carbohydrate determinants (CCDs) in celery and hazelnut might be derived from their relative stability against digestion or cooking.

So far four major allergens have been reported in apple and included in the official allergen list of the WHO allergen nomenclature subcommittee (see Table 1) (<http://www.allergen.org>). They include Mal d 1 (PRP-10), homologous to Bet v 1 with a molecular mass of 17.5 kD, Mal d 2 (PRP-5), a thaumatin-like protein (TLP), with a molecular mass of 23 kD, Mal d 3 (PRP-14) a lipid transfer protein (LTP) with a molecular mass of 9 kD and Mal d 4 (profilin), homologous to Bet v 2 with a molecular mass of 14 kD.

Mal d 1 is the major allergen in pollen-associated fruit allergies, belonging to the pathogenesis-induced proteins PRP-10. Hybridisation studies uncovered Bet v 1-homologue genes in apples, pea, parsley, bean and potato [11] with sequence homologies between 50–70%. Recovering the three-dimensional structure of Bet v 1 [14,19,45] and Pru a 1, the major cherry allergen, confirmed significant structural homologies (see Fig. 1) [35]. Unlike other PRP-10, whose expression is strongly induced under stress conditions or pathogen attack, the fruit allergens appear to be constitutively expressed. Particularly interesting is the double band of strawberry and blackberry extract reacting with a pAb raised against Mal d 1 (see Fig. 2A and 2C).

Mal d 2 belongs to the thaumatin-like proteins (TLPs), reported as a novel family of fruit allergens. TLPs are generally resistant to pH- or heat induced denaturation due to the presence of 8 disulfide bridges [6]. Up to now several TLPs from fruits have been reported with ability to bind IgE antibodies of allergic patients e.g. apple, kiwi, grape and cherry with about 50% sequence identity [31]. TLPs with



Fig. 1. The 3D structure models are based on the crystal structure of Bet v 1. The models of fruit allergens using cDNA sequences of: Mal d 1: AF020542.1; Pru av 1: AY540508 were generated using Swiss model server (<http://swissmodel.expasy.org/SWISS-MODEL.html>) and visualized in the Protein Explorer program (<http://molvis.sdsc.edu/protexpl/frntdoor.htm>). Ovals indicate a conserved glycine-rich loop crucial for Bet v 1 epitope-binding [32].

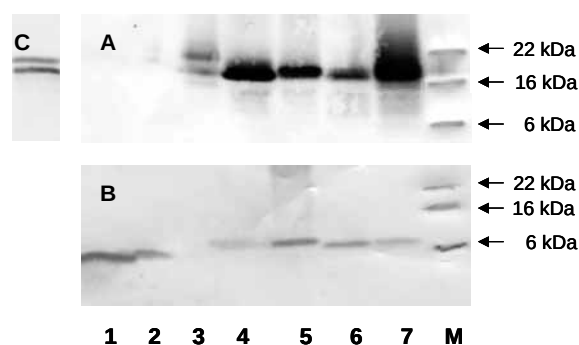


Fig. 2. Mal d 1 (A) and Mal d 3 (B) homologous proteins detected in different fruits of *Rosaceae* and *Ericaceae* using polyclonal antibodies raised in rabbit against purified Pru p 3 of peach (kindly provided by R. van Ree) and apple Mal d 1. The lanes contained: 1) blueberry 2) raspberry 3) strawberry 4) cherry 5) peach 6) apricot 7) apple M) molecular weight marker. In almost all fruit extracts at least one of the two main allergen homologues was found. Strawberry (lane 3A) and blackberry (C) showed a comparable double band reacting with the polyclonal anti-Mal d 1 antiserum. The absence of Mal d 1 homologous protein bands in raspberry and blueberry or Mal d 3 in strawberry might be due to the low sensitivity of alkaline phosphatase western blotting or reduced cross-reactivity.

pollen-origin have been also described in pollen of Cupressaceae and reported as an important allergen source in Spain, United States and Northern Mexico [26].

Mal d 3, a non-specific lipid-transfer protein (LTP), has been identified as the major allergen in *Rosaceae* fruit as peach and apple, particularly in the birch-free Mediterranean area [41]. This protein and its homologous in other fruits and vegetables have been claimed as elicitors of the true food allergy [3]. LTPs can resist denaturation by heat processing and degradation by digestion long enough to induce both sensitisation and systemic symptoms through the gut mucosa [47]. Currently, an increasing number of LTP-homologous proteins with more than 80% similarity, have been identified in several plant foods, particularly in stone fruits, e.g. Pru p 3 (peach), Pru a 3 (apricot), Pru av 3 (cherry) (see Fig. 2B). However, blueberry and raspberry also contain an LTP homologous protein. Besides, LTPs could be identified in grape [39], chestnut [8], hazelnut [38], maize [37], barley [20], asparagus [9], carrot [2] and

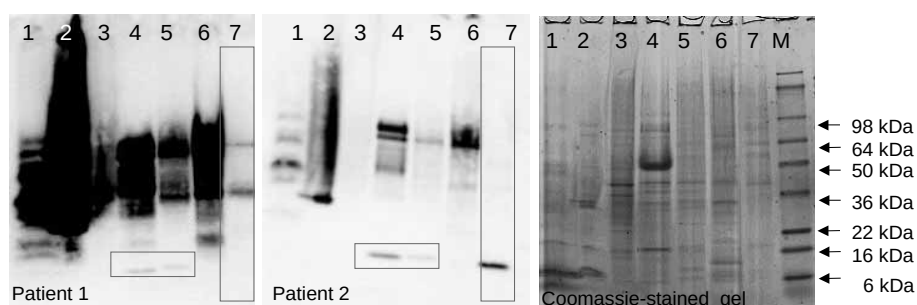


Fig. 3. Cross reactivity to different fruits was characterized by IgE Western blot for 1) blueberry 2) raspberry 3) strawberry 4) cherry 5) peach 6) apricot 7) apple M) molecular weight marker using patient sera. Two patients with birch-apple-syndrome and a well-studied allergy history demonstrated a very different sensitisation pattern to fruit extracts. While patient 2 shows a clear reaction against apple Mal d 1 and homologous proteins (17.5 kDa) in peach and cherry, patient 1 is reactive to proteins with a molecular weight of >36 kDa in apple but not with Mal d 1. However patient 1 serum recognizes the Mal d 1 homologous proteins in cherry and peach. Very strong reactivity could be detected for high molecular weight proteins in blueberry, raspberry, cherry, apricot, and peach, which reflects indeed their clinical case history.

lettuce [42].

Mal d 4 belongs to the profilins, a group of plant allergens representing minor allergens in pollen allergy and playing a role in pollen-associated food allergy [48]. Profilins, present in all eukaryotes, regulate the polymerization of cytoskeletal actin and mediate signal transduction in the cell [44]. Bet v 2 (birch pollen profilin) sensitizes approximately 20% of the pollen-allergic patients. Human IgE recognizing pollen profilins are highly cross-reactive to profilins in cherry (Pru av 4), pear (Pyr c 4), apple (Mal d 4), celery (Api g 4), soybean (Gly m 3), peanut (Ara h 5), hazelnut (Cor a 2), tomato (Lyc e 1) and bell pepper (Cap a 1) [50].

Fruits like blueberry, raspberry and strawberry may be nutritionally underestimated, but scientific research shows that they may have huge impact on human health due to their high content of antioxidants and unknown biofactors, which play a role in ageing, cancer and infection prevention. Reports on allergenicity of small fruits such as strawberry, raspberry, blackberry and blueberry are still rare. Whether this is related to a general low allergenicity, the small amounts consumed or the restricted time frame of consumption still remains to be answered. As a matter of fact, low exposure to certain allergens might be the reason for the limited complaints recorded so far. However, with the ongoing encouragement for the consumption of small fruits, this situation might change. About 30% of patients reported hypersensitivity or adverse effects after consumption of strawberries, although many of these reactions might be related to food intolerance rather than food allergy [13]. Small fruits are not only consumed fresh but are also eaten as common ingredients in different food products as main or additional component e.g. jam, ice cream, cornflakes. Strawberries are under investigation and strong evidence for the existing Bet v 6, Bet v 1 and Mal d 3 homologous proteins have been confirmed by existence of IgE-binding assays and skin prick test [26]. Allergic reactions were also reported in contact to raspberry proteins (see Fig. 3). Inhalation of frozen raspberry powder was reported to cause occupational asthma [7], however no raspberry allergens have been identified so far.

People vary in their reactivity to food and show a different pattern of reactivity depending on their individual characteristics. Persons following specific diets tend to show a different pattern of allergic response. Clinical reactivity depends on a variety of factors including frequency of exposure to foodstuffs [25]. The interpretation of the phenomena depends strongly on the availability of patient independent detection tools and the sensitivity of the method. In many cases it is still unclear how results between *in vitro* assays, skin prick tests and oral challenge are correlated and what is the clinical

importance of *in vitro* results. Will the patient, whose serum recognises a certain protein epitope develop an allergy in the near future? We actually do not know it, but we are developing tests to answer this in the near future.

From apple data we know that we have a high variability in Mal d 1-content among different cultivar, years and production systems. Analogous studies on small fruit allergens content are still under study. In Southern blot analyses DNA fragments homologues to Mal d 1 and Mal d 3 could be detected in genomic DNA from apple [29], strawberry, raspberry, blueberry and cranberry, and the respective genes are being cloned (unpublished data). The putative allergenicity of the recombinant gene products remains to be defined.

Recent studies have demonstrated that not only epitopes on peptides, but also on carbohydrates, so called cross-reactive carbohydrate determinants (CCD), can act as cross-reacting elements [40]. It has been shown that α 1–3 linked fucose and β 1–2 linked xylose present in a common cross-reactive antigenic determinants [15,40]. Due to their small size, when compared to peptide epitopes, carbohydrate residues appear to stabilize the binding to IgE [27,30]. IgE antibodies specific for certain N-glycans of plant glycoproteins, which are highly cross-reactive with almost all foods of plant origin, may occur in as much as 10–20% of pollen-allergic individuals [18]. The clinical relevance of CCDs is very controversial [46]. Allergic reactions to celery and kaki fruit in some individuals have been reported to be caused by specific IgE reactivity with CCDs without additional recognition of any other proteins [1,28].

Since many identified allergens belong to plant pathogen-related proteins, their presence is expected in almost all type of plant-derived food. The question about the clinical relevance of *in vitro* assays still remains to be answered, and a challenging field of investigations. The minimization of fruit-pollen-syndrome demands a change of life style, or even profession, adhering to an elimination diet or avoidance, long-term symptomatic treatment and immunotherapy [7]. Therefore apart from an effective therapy, research on mechanisms of allergies and methods for avoiding exposure to allergens is prerequisite for improved life quality of affected individuals.

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