Clinical manifestations of Fruit Allergy

Subjects: Allergy

Contributor: Thanachit Krikeerati, Pongsawat Rodsaward, Jutamard Nawiboonwong, Kanokkarn Pinyopornpanish, Songwut Phusawang, Mongkhon Sompornrattanaphan

Fruit allergies manifest with a diverse array of clinical presentations, ranging from localized contact allergies and oral allergy syndrome to the potential for severe systemic reactions including anaphylaxis. The scope of population-level prevalence studies remains limited, largely derived from single-center or hospital-based investigations.

Keywords: anaphylaxis ; fruit allergy ; food allergy ; food safety

1. Introduction

In recent decades, both children and adults globally have experienced a rise in food allergy prevalence rates. Factors such as heightened exposure to food allergens, early diagnostic recognition, and evolving environmental elements disrupting immune tolerance have played significant roles. Interestingly, the prevalence exhibits variation based on regional dietary practices. Notably, industrialized or westernized communities are more impacted than their agricultural or non-westernized counterparts, with the younger population being more susceptible than adults. Food allergy manifestations span a spectrum from mild to severe reactions and potentially life-threatening conditions such as anaphylaxis. While most food allergies stem from the production of and subsequent response to allergen-specific immunoglobulin E (IgE) against allergenic proteins, categorized as type I hypersensitivity reactions, a minority are non-IgE mediated.

In the field of food allergies, plant-based allergens emerge as the predominant culprits, often appearing during childhood but potentially manifesting in adulthood as well [1]. While plant-based foods, especially fruits and vegetables, are promoted for their health benefits and their role in preventing cardiovascular and metabolic diseases, some individuals with predispositions may face allergic reactions when consuming these foods. Allergens are present in the peel, pulp, and seeds of fruits. They can be found in an array of products including juices, pastries, sweets, preserves, and even as components in various recipes. Even without heat processing or pasteurization, merely cutting a fruit like an apple could cause the oxidative breakdown of its allergenic substances [1][2].

Allergic responses to fruits can present in two predominant clinical patterns: one that originates directly from the fruit and is not associated with pollen sensitivities, and another that is intricately linked to pollen allergies. The latter phenotype is attributed to the cross-reactivity between inhalant allergens and those found in foods. This phenomenon is underpinned by the generation of cross-reactive specific IgE (sIgE) antibodies, which identify and bind to structurally analogous allergenic epitopes, irrespective of the degree of taxonomic relation between their respective sources [3]. An illustrative example of such a cross-reactivity syndrome is pollen food allergy syndrome (PFAS). Within this category of secondary food allergies, the spectrum of allergic symptoms can range from localized reactions confined to the oropharynx (oral allergy syndrome, OAS) to severe systemic reactions such as anaphylaxis [4]. Accurate diagnosis requires a comprehensive medical history assessment, complemented by objective confirmation of sensitization through either skin tests or specific IgE testing. Understanding molecular sensitization patterns and host-specific factors holds promise for predicting the clinical severity of plant-based food allergies [5].

2. Pollen Food Allergy Syndrome (PFAS)

Pollen food allergy syndrome (PFAS) is a common condition where initial sensitization through pollen exposure leads to respiratory symptoms. Subsequent consumption of cross-reactive fruits triggers allergic reactions. Various associations have been documented in relation to PFAS. In the context of PFAS, the involved pan-allergens include various proteins such as profilin, PR-10 (pathogenesis-related protein 10), TLP (Thaumatin-like proteins), nsLTP (non-specific lipid transfer protein), GRP (gibberellin-regulated protein), seed storage proteins, cysteine protease, and β-1,3-glucanase [6].

In temperate regions characterized by notable temperature fluctuations, four distinct seasons—spring, summer, autumn, and winter—bring about varying patterns in plant pollination. Typically, trees release pollen in spring, grasses in summer, and weeds in autumn. For example, in Europe, birch trees typically begin to pollinate from March to May, while grasses usually pollinate from March to August. Ragweed, on the other hand, begins to pollinate from July to September [6][7]. The timing of pollination varies depending on the specific zone within Europe. However, certain plant species may exhibit unique pollination behaviors that diverge from these general patterns [8]. Cypress and Japanese cedar can pollinate in winter and extend to spring [6].

2.1. Tree Pollen

Many plant families are the sources of allergens: Betulaceae (Birch family), Oleaceae (Olive family), Platanaceae (Plane-tree family), and Cupressaceae (Cypress family). The main allergen that causes allergic reactions is the pathogenesis-related protein family 10 (PR-10) protein. PR-10 protein is a 'pan-allergen' found only in plant species, and is not present in animal sources. It can cause cross-reactivity with unrelated biological sources. PR-10 protein has a labile structure, similar to profilin, which is why most clinical symptoms are also mild. The most common type of pollen–fruit allergy is birch-related food allergy. The major birch allergen is Bet v1, which belongs to the PR-10 protein family. It has been found that up to 70% of Bet v1 (PR-10 protein) in the birch family is identical to other plant families. The study showed 70% of birch-sensitized patients had allergic symptoms to fruits, especially Rosaceae fruits (apple, pear, cherry, peach, plum, apricot, etc.), nuts, and vegetables, especially those from the Apiaceae family (like celery and carrots). The most common tree pollen-fruit cross-reactivity, accounting for over 75% of cases, is the Birch-apple syndrome. Most patients suffer from oral allergy symptoms. The symptom is triggered when the patient is exposed to the pollen allergen "PR-10 protein" (Bet v1 in Birch, and Mal d1 in apple). A recent study showed that sensitized birch individuals could be sensitized to apples by up to 94%, On the other hand, a sensitized apple individual could be sensitized to birch by up to 100%. Besides apple, the fruits that could be correlated with the birch pollen are peach (86%), and kiwi (28%) [3][9][10][11]. Recent reports indicate a rising prevalence of cypress sensitization in Europe and Japan, particularly among atopic individuals. These sensitization cases have been linked to various fruits, with the primary allergen remaining the PR-10 protein, resulting in OAS. However, more severe allergic symptoms have been reported in cases of peach allergy, known as Cypress-peach syndrome, often associated with the allergenic protein known as GRP [12].

2.2. Grass Pollen

In contrast to tree and weed pollen, there are relatively limited data available on grass pollen sensitization and its association with pollen–fruit syndrome. However, historical data suggest that individuals with grass sensitization have experienced allergic reactions to a wide range of foods, including melon, watermelon, orange, tomato, potato, peanut, and Swiss chard [13]. Sensitization to grasses like Bermuda, Timothy, and Orchard grass has been linked to melon allergy, with profilin playing a role [14][15][16]. Furthermore, sensitization to orchard grass has shown associations not only with melon allergies but also with peach allergies [16].

2.3. Weed Pollen

Most weed-causing PFAS are in the Asteraceae family, primarily including mugwort (*Artemisia vulgaris*) and ragweed (*Ambrosia artemisiifolia*). Individuals who exhibit allergies to mugwort may experience allergic symptoms upon consuming foods like carrots, celery, onion, garlic, mango, and various spices including anise, caraway, coriander, fennel, black pepper, paprika, and cumin. This interaction is mediated by a profilin called celery–mugwort–spice syndrome. Additionally, other associations have been observed, such as Asteraeae–lychee association, mugwort–peach association (nsLTP), and mugwort–chamomile association. On the other hand, ragweed cross-reacts with banana and melon via profilin and nsLTP, forming what is known as the 'ragweed–melon–banana' association [3][17].

3. Lipid Transfer Protein (LTP) Syndrome

Lipid transfer proteins (LTPs) are pan-allergens present in various foods and plants, including fruits, vegetables, nuts, and cereals. Sensitization to LTP can lead to symptoms in affected individuals. Some patients require co-factors such as NSAIDs, alcohol consumption, or exercise to trigger these symptoms. The most common presentation is anaphylaxis, which is more prevalent in adults and Mediterranean countries. LTPs are found in plants like mugwort, plane tree, olive, ragweed, and cypress, which are the primary sources of sensitization. Among fruits, those from the Rosaceae family are the most frequent culprits, with peach being a notable example. Clinical symptoms range from mild to severe anaphylaxis, but LTP syndrome is associated with a high incidence of anaphylaxis, affecting up to 75.6% of individuals [18][19].

4. Gibberellin-Regulated Protein (GRP) Syndrome

GRPs are a class of heat-stable hormones synthesized by plants in response to various stages of plant growth and development [20]. They are expressed in both the pulp and peel of fruits, with a particularly notable presence in fruits such as peach, citrus, apricot, cherry, and pomegranate [6]. In trees, GRPs are primarily found within the Cupressaceae family, which includes cypress trees [6]. Sensitization to PFAS via GRPs has been reported in southern France and Japan, and attributed to cypress and Japanese cedar, respectively [21][22]. However, patients can develop sensitization to GRPs directly through fruit exposure, independently of any cross-sensitization to tree pollens. Remarkably, 59% of patients with no prior sensitization to cypress GRP displayed sensitization to fruit GRP [23]. GRP allergies are most commonly observed in adolescents and adults, and clinical manifestations can encompass a spectrum of symptoms, including OAS, urticaria, angioedema, anaphylaxis, and FDEIA [24]. Notably, anaphylactic reactions are frequently associated with peach and apricot GRP allergies [24]. In cases of peach allergy, patients allergic to the GRP component often exhibit distinct symptoms such as facial swelling, especially in the eyelids, laryngeal tightness, and a higher prevalence of urticaria compared to patients allergic to the PR-10 component of peach [24].

5. Latex-Fruit Syndrome (LFS)

Latex is a sap derived from *Hevea brasiliensis*, containing a complex mixture of proteins, including soluble and particle-bound proteins. Some of these proteins share a structural similarity with proteins found in fruits, resulting in the presence of common antigenic determinants. This relationship has led to the recognition of a clinical syndrome known as ‘Latex-fruit syndrome’, where individuals experience allergic reactions to both latex and various fruits [25][26]. Clinical symptoms can be life-threatening, and the plant foods typically involved in the syndrome include avocado, banana, kiwifruit, and chestnut. Symptoms can vary in severity, including itching, hives, swelling, abdominal pain, vomiting, and, in more severe cases, anaphylaxis [26][27].

Among NRL (natural rubber latex) allergens, class 1 chitinases (Hev b 6) play a significant role in the LFS. Class 1 chitinases have a defensive function, and Hev b 6 exhibits high sequence homology with chitinases found in fruits like bananas, avocados, and chestnuts [28]. Other significant NRL allergens include β-1,3-glucanase (Hev b 2), found in various fruits such as avocado, banana, chestnut, fig, kiwi, and olive pollen, as well as the acidic protein (Hev b 5), which has the potential for cross-reactivity with kiwi acid protein. In a retrospective study involving 137 patients with a history of natural rubber allergy and positive latex tests, symptoms were reported upon exposure to a range of fruits, including banana, avocado, kiwi, tomato, watermelon, peach, chestnut, cherry, apple, apricot, and strawberry [29].

Brehler et al. (1997) conducted a study demonstrating that the levels of latex-specific IgE were inhibited when serum samples from individuals with latex allergies were preincubated with extracts from specific fruits. Fruits such as avocado, banana, fig, tomato, kiwi, melon, and passion fruit were found to be particularly effective in inhibiting latex-specific IgE levels [30]. Nevertheless, there are still groups of patients who exhibit sensitization to specific fruits independently of NRL sensitization. This suggests that there are responsible allergens for fruit allergies in specific regions or cases [31].

6. Thaumatin-Like Proteins (TLP) Syndrome

Thaumatin, found in the fruits of the West African rainforest shrub *Thaumatococcus daniellii*, shares sequence homology with PR-5 proteins and imparts a sweet taste. These proteins belong to the family known as thaumatin-like proteins (TLPs). TLPs are known for their resistance to proteases and resistance to changes in pH or heat. They respond to pathogen infection, osmotic stress (osmotins), and antifungal proteins [32] Both TLPs and PR-5 are expressed in ripening fruits [6]. TLPs serve as allergenic molecules in many fruit allergies including apple, banana, cherry, kiwi, and peach [6], and might also be a causative allergen in patients with orange-dependent exercise-induced anaphylaxis [33]. In mouse models, there are reports of percutaneous sensitization to TLP. Given that cherries are widely utilized in cosmetics, including lip care products, this raises the potential for percutaneous sensitization in humans [34]. TLPs are prevalent in numerous fruits and can act as pan-allergens, provoking allergic reactions to a variety of fruits. Nonetheless, data on cross-reactivity patterns and clinical severity are limited.

References

1. Li, S.K.; Liu, Z.; Huang, C.K.; Wu, T.C.; Huang, C.F. Prevalence, clinical presentation, and associated atopic diseases of pediatric fruit and vegetable allergy: A population-based study. Pediatr. Neonatol. 2022, 63, 520–526.

2. Unhapipatpong, C.; Julanon, N.; Krikeerati, T.; Vichara-Anont, I.; Sompornrattanaphan, M. Adult IgE-mediated food allergy is on the rise: A review of phenotypes, pathophysiologic mechanisms, diagnosis, and advances in management. Asian Pac. J. Allergy Immunol. 2022, 40, 308–320.
3. Popescu, F.D. Cross-reactivity between aeroallergens and food allergens. World J. Methodol. 2015, 5, 31–50.
4. Webber, C.M.; England, R.W. Oral allergy syndrome: A clinical, diagnostic, and therapeutic challenge. Ann. Allergy Asthma Immunol. 2010, 104, 101–108.
5. Fernandez-Rivas, M. Fruit and vegetable allergy. Chem. Immunol. Allergy 2015, 101, 162–170.
6. Dramburg, S.; Hilger, C.; Santos, A.F.; de Las Vecillas, L.; Aalberse, R.C.; Acevedo, N.; Aglas, L.; Altmann, F.; Arruda, K.L.; Asero, R.; et al. EAACI Molecular Allergology User's Guide 2.0. Pediatr. Allergy Immunol. 2023, 34 (Suppl. S28), e13854.
7. Kolek, F.; Plaza, M.D.P.; Leier-Wirtz, V.; Friedmann, A.; Traidl-Hoffmann, C.; Damialis, A. Earlier Flowering of Betula pendula Roth in Augsburg, Germany, Due to Higher Temperature, NO2 and Urbanity, and Relationship with Betula spp. Pollen Season. Int. J. Environ. Res. Public. Health 2021, 18, 10325.
8. Lo, F.; Bitz, C.M.; Battisti, D.S.; Hess, J.J. Pollen calendars and maps of allergenic pollen in North America. Aerobiologia 2019, 35, 613–633.
9. Blankestijn, M.A.; Knulst, A.C.; Knol, E.F.; Le, T.M.; Rockmann, H.; Otten, H.G.; Klemans, R.J.B. Sensitization to PR-10 proteins is indicative of distinctive sensitization patterns in adults with a suspected food allergy. Clin. Transl. Allergy 2017, 7, 42.
10. Scala, E.; Alessandri, C.; Palazzo, P.; Pomponi, D.; Liso, M.; Bernardi, M.L.; Ferrara, R.; Zennaro, D.; Santoro, M.; Rasi, C.; et al. IgE recognition patterns of profilin, PR-10, and tropomyosin panallergens tested in 3,113 allergic patients by allergen microarray-based technology. PLoS ONE 2011, 6, e24912.
11. Kim, J.H.; Kim, S.H.; Park, H.W.; Cho, S.H.; Chang, Y.S. Oral Allergy Syndrome in Birch Pollen-Sensitized Patients from a Korean University Hospital. J. Korean Med. Sci. 2018, 33, e218.
12. Ehrenberg, A.E.; Klingebiel, C.; Ostling, J.; Larsson, H.; Mattsson, L.; Vitte, J.; Lidholm, J. Characterization of a 7 kDa pollen allergen belonging to the gibberellin-regulated protein family from three Cupressaceae species. Clin. Exp. Allergy 2020, 50, 964–972.
13. Vieths, S. Allergenic cross-reactivity, food allergy and pollen. Environ. Toxicol. Pharmacol. 1997, 4, 61–70.
14. Sankian, M.; Varasteh, A.; Pazouki, N.; Mahmoudi, M. Sequence homology: A poor predictive value for profilins cross-reactivity. Clin. Mol. Allergy 2005, 3, 13.
15. Tordesillas, L.; Pacios, L.F.; Palacin, A.; Cuesta-Herranz, J.; Madero, M.; Diaz-Perales, A. Characterization of IgE epitopes of Cuc m 2, the major melon allergen, and their role in cross-reactivity with pollen profilins. Clin. Exp. Allergy 2010, 40, 174–181.
16. Maeda, N.; Inomata, N.; Morita, A.; Kirino, M.; Ikezawa, Z. Correlation of oral allergy syndrome due to plant-derived foods with pollen sensitization in Japan. Ann. Allergy Asthma Immunol. 2010, 104, 205–210.
17. Egger, M.; Mutschlechner, S.; Wopfner, N.; Gadermaier, G.; Briza, P.; Ferreira, F. Pollen-food syndromes associated with weed pollinosis: An update from the molecular point of view. Allergy 2006, 61, 461–476.
18. Albert, E.; Walsemann, T.; Behrends, J.; Jappe, U. Lipid transfer protein syndrome in a Northern European patient: An unusual case report. Front. Med. 2023, 10, 1049477.
19. Mota, I.; Gaspar, A.; Benito-Garcia, F.; Correia, M.; Arede, C.; Piedade, S.; Sampaio, G.; Pires, G.; Santa-Marta, C.; Borrego, L.M.; et al. Anaphylaxis caused by lipid transfer proteins: An unpredictable clinical syndrome. Allergol. Immunopathol. 2018, 46, 565–570.
20. Hedden, P.; Sponsel, V. A Century of Gibberellin Research. J. Plant Growth Regul. 2015, 34, 740–760.
21. Senechal, H.; Santrucek, J.; Melcova, M.; Svoboda, P.; Zidkova, J.; Charpin, D.; Guilloux, L.; Shahali, Y.; Selva, M.A.; Couderc, R.; et al. A new allergen family involved in pollen food-associated syndrome: Snakin/gibberellin-regulated proteins. J. Allergy Clin. Immunol. 2018, 141, 411–414.e4.
22. Iizuka, T.; Takei, M.; Saito, Y.; Rumi, F.; Zheng, J.; Lu, X.; Chafey, P.; Broussard, C.; Guilloux-Assalet, L.; Charpin, D.; et al. Gibberellin-regulated protein sensitization in Japanese cedar (Cryptomeria japonica) pollen allergic Japanese cohorts. Allergy 2021, 76, 2297–2302.
23. Alessandri, C.; Ferrara, R.; Bernardi, M.L.; Zennaro, D.; Tuppo, L.; Giangrieco, I.; Ricciardi, T.; Tamburrini, M.; Ciardiello, M.A.; Mari, A. Molecular approach to a patient's tailored diagnosis of the oral allergy syndrome. Clin. Transl. Allergy 2020, 10, 22.
24. Inomata, N. Gibberellin-regulated protein allergy: Clinical features and cross-reactivity. Allergol. Int. 2020, 69, 11–18.

25. Blanco, C. Latex-fruit syndrome. Curr. Allergy Asthma Rep. 2003, 3, 47–53.
26. Wagner, S.; Breiteneder, H. The latex-fruit syndrome. Biochem. Soc. Trans. 2002, 30, 935–940.
27. Sompornrattanaphan, M.; Kreetapirom, P.; Srinoulprasert, Y.; Kanistanon, D.; Klinniyom, A.; Wongsa, C.; Thongngarm, T. Severe anaphylaxis after pelvic examination: A case report of dual latex and chlorhexidine allergies. Allergy Asthma Clin. Immunol. 2019, 15, 19.
28. Radauer, C.; Adhami, F.; Furtler, I.; Wagner, S.; Allwardt, D.; Scala, E.; Ebner, C.; Hafner, C.; Hemmer, W.; Mari, A.; et al. Latex-allergic patients sensitized to the major allergen hevein and hevein-like domains of class I chitinases show no increased frequency of latex-associated plant food allergy. Mol. Immunol. 2011, 48, 600–609.
29. Kim, K.T.; Hussain, H. Prevalence of food allergy in 137 latex-allergic patients. Allergy Asthma Proc. 1999, 20, 95–97.
30. Brehler, R.; Theissen, U.; Mohr, C.; Luger, T. “Latex-fruit syndrome”: Frequency of cross-reacting IgE antibodies. Allergy 1997, 52, 404–410.
31. Julanon, N.; Thiravetyan, B.; Unhapipatpong, C.; Xanthavanij, N.; Krikeerati, T.; Thongngarm, T.; Wongsa, C.; Songnuan, W.; Naiyanetr, P.; Sompornrattanaphan, M. Not Just a Banana: The Extent of Fruit Cross-Reactivity and Reaction Severity in Adults with Banana Allergy. Foods 2023, 12, 2456.
32. Breiteneder, H. Thaumatin-like proteins—A new family of pollen and fruit allergens. Allergy 2004, 59, 479–481.
33. Townsend, K.; Watts, T.J. Food-dependent exercise-induced anaphylaxis to orange, with possible underlying thaumatin-like protein allergy. Ann. Allergy Asthma Immunol. 2023, 130, 669–671.
34. Izumi, E.; Hidaka, S.; Hiroi, A.; Kinugasa, S.; Yano, E.; Zaima, N.; Moriyama, T. Thaumatin-Like Protein (Pru av 2) Is a Cherry Allergen That Triggers Percutaneous Sensitization in Mice. Foods 2021, 10, 134.
