

Review

Pollen–Food Allergy Syndrome: Allergens, Clinical Insights, Diagnostic and Therapeutic Challenges

Laura Haidar ^{1,2}, Camelia Felicia Bănărescu ^{1,3,*}, Cristina Uța ^{1,3}, Sandra Iulia Moldovan ^{1,3}, Elena-Larisa Zimbru ^{1,2,4}, Răzvan-Ionuț Zimbru ^{1,2,4}, Elena Ciurariu ^{1,2}, Marius Georgescu ^{1,2} and Carmen Panaitescu ^{1,3,4}

- ¹ Center of Immuno-Physiology and Biotechnologies, Department of Functional Sciences, “Victor Babeș” University of Medicine and Pharmacy, 2 Eftimie Murgu Square, 300041 Timisoara, Romania; haidar.laura@umft.ro (L.H.); cristina.uta@umft.ro (C.U.); sandrauliamoldovan@yahoo.com (S.I.M.); elena.zimbru@umft.ro (E.-L.Z.); razvan.zimbru@umft.ro (R.-I.Z.); ciurariu.elena@umft.ro (E.C.); georgescu.marius@umft.ro (M.G.); cbunu@umft.ro (C.P.)
- ² Physiology Discipline, Department of Functional Sciences, Faculty of Medicine, “Victor Babeș” University of Medicine and Pharmacy Timisoara, 2 Eftimie Murgu Square, 300041 Timisoara, Romania
- ³ Emergency Clinical Hospital “Pius Brinzeu”, 156 Liviu Rebreanu Bd., 300723 Timisoara, Romania
- ⁴ Research Center for Gene and Cellular Therapies in the Treatment of Cancer—OncoGen, Timis County Emergency Clinical Hospital “Pius Brinzeu”, 156 Liviu Rebreanu Bd., 300723 Timisoara, Romania
- * Correspondence: felicia.banarescu@umft.ro; Tel.: +40-724006830

Featured Application: This work provides a detailed exploration of pollen–food allergy syndrome (PFAS), offering practical insights for clinicians managing patients with this condition. By addressing the diagnostic challenges and discussing emerging therapeutic approaches, including allergen immunotherapy and biologics, the findings have potential applications in improving diagnostic accuracy and optimizing personalized treatment strategies. The work could also guide future research on innovative management techniques and promote awareness among healthcare providers dealing with allergic diseases.



Academic Editors: José Antonio Canas, Rubén Fernán-dez-Santamaría and Blanca Cárdbaba

Received: 24 November 2024

Revised: 18 December 2024

Accepted: 23 December 2024

Published: 25 December 2024

Citation: Haidar, L.; Bănărescu, C.F.; Uța, C.; Moldovan, S.I.; Zimbru, E.-L.; Zimbru, R.-I.; Ciurariu, E.; Georgescu, M.; Panaitescu, C. Pollen–Food Allergy Syndrome: Allergens, Clinical Insights, Diagnostic and Therapeutic Challenges. *Appl. Sci.* **2025**, *15*, 66. <https://doi.org/10.3390/app15010066>

Copyright: © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Abstract: Pollen–food allergy syndrome (PFAS), also known as oral allergy syndrome, is a common condition affecting individuals sensitized to pollens such as birch, ragweed, and grass. This syndrome arises from immunological cross-reactivity between pollen allergens and structurally similar proteins found in various fruits, vegetables, and nuts. Although typically presenting with mild oral and pharyngeal symptoms, PFAS can occasionally result in severe allergic reactions, underscoring its clinical significance. This review explores the pathophysiology of PFAS, highlighting the molecular mechanisms underlying cross-reactivity and examining the main protein families involved, including those contributing to variations in symptom severity. Current diagnostic approaches, including skin prick testing, specific immunoglobulin E measurements, and component-resolved diagnostics, are discussed. Emerging diagnostic tools and biomarkers with potential to enhance accuracy are also examined. Therapeutic strategies for PFAS primarily focus on symptom management and avoidance of trigger foods. However, novel approaches such as allergen immunotherapy and biologics targeting key immune pathways are gaining traction as potential interventions for more severe or refractory cases. By addressing the diagnostic and therapeutic challenges of PFAS, this paper aims to provide clinicians and researchers with a comprehensive understanding of this condition, fostering improved patient care and the development of innovative treatment strategies.

Keywords: pollen–food allergy syndrome; oral allergy syndrome; cross-reactivity; allergen immunotherapy; food allergens; diagnostic strategies; component-resolved diagnostics; biologics in allergy; food-pollen syndrome; allergy management

1. Introduction

Allergic diseases have become a significant public health concern globally, affecting both developed and developing countries, with prevalence rates ranging from 10% to 30% in adults and exceeding 40% in children [1]. Among all allergic conditions, allergic rhinitis (AR) stands out as the most common, affecting a substantial portion of the global population and exemplifying the growing burden of allergies worldwide. Together with asthma and atopic eczema, AR forms the cornerstone of what has been aptly termed the “allergy epidemic”, a term that captures the rising prevalence of allergic conditions worldwide.

Respiratory allergies such as allergic rhinitis and asthma are triggered by various allergens such as tree and grass pollens from anemophilous plants, house dust mites, animal dander, and molds [2]. Respiratory allergies, especially to pollens and molds, often follow seasonal patterns, with symptoms typically coinciding with specific times of the year when certain allergens are most prevalent [3]. In the Northern hemisphere, for instance, tree pollen allergies are common in spring [4], grass pollen allergies peak in late spring and summer [5], and weed pollen, such as ragweed, becomes more prominent in late summer and fall [6]. These patterns are closely tied to the life cycles of plants and the release of airborne pollen, which varies regionally and climatically. Seasonal changes in temperature, humidity, and weather patterns, such as wind, can further influence the dispersion and concentration of allergens in the environment, contributing to the periodic nature of symptoms [7]. As a result, individuals with respiratory allergies often experience predictable flare-ups, which can serve as valuable indicators for preventive measures and treatment planning [8–10]. However, factors such as pollution and climate change have begun to blur these traditional seasonal boundaries. Rising temperatures, altered rainfall patterns, and increased levels of airborne pollutants are extending pollen seasons and intensifying allergen concentrations, leading to more unpredictable and prolonged allergy symptoms [11–13]. These changes challenge the conventional understanding of seasonal allergies, requiring adjustments in management strategies to address this evolving environmental landscape.

Initially affecting wealthier populations [14], respiratory allergies have expanded to middle- and lower-income groups [15], reflecting broader environmental and lifestyle changes. Urbanization, reduced microbial exposure, and dietary shifts are among the factors contributing to this trend [16], particularly in middle-income countries experiencing rapid socioeconomic transitions. Therefore, AR prevalence demonstrates a wide range of variability across different continents, reflecting the influence of environmental, genetic, and lifestyle factors on its distribution. In Africa, the prevalence is relatively low, between 3.6% and 22.8%, possibly due to differences in exposure to allergens, climate, or underreporting in some regions [17]. In contrast, the Americas show the broadest range, from 3.5% to 54.5%, which could be attributed to diverse climates, urbanization levels, and healthcare access across North and South America [18,19]. Asia and Europe also exhibit considerable variation, with prevalence rates ranging from 1.0% to 47.9% in Asia and 1.0% to 43.9% in Europe [20–22]. These variations may be linked to differences in pollen exposure, pollution levels, and awareness or diagnosis of AR. Interestingly, Oceania presents consistently higher prevalence rates, ranging from 19.2% to 47.5%, likely due to high allergen loads in the environment, such as grass pollens, combined with genetic predis-

positions in the population [23,24]. Overall, these variations underscore the multifactorial nature of AR, shaped by both environmental exposures and socioeconomic conditions. This highlights the need for region-specific public health strategies to address the burden of AR effectively [25,26].

In recent decades, food allergies have emerged as an alarming “second wave” of the allergy epidemic, particularly in westernized societies [27,28]. The increasing prevalence of food allergies is particularly concerning due to their potential for life-threatening reactions, especially in children and adolescents [29,30]. This trend places a growing burden on healthcare systems, many of which are ill-prepared to address the challenges posed by the allergy epidemic.

The association between respiratory allergies and food allergies, exemplified by conditions like pollen–food allergy syndrome (PFAS), highlights the complex interplay between different allergic conditions. Cross-reactivity between pollen allergens and plant-derived foods is a key mechanism driving PFAS, as this phenomenon occurs due to structural similarities between proteins found in pollens and those present in certain fruits, vegetables, nuts, and seeds [31]. These shared protein epitopes, known as panallergens, are mistakenly recognized by the immune system as identical, triggering an allergic response in sensitized individuals [32]. Key panallergen families involved in PFAS include pathogenesis-related protein class 10 (PR-10) proteins, profilins, lipid transfer proteins (LTPs), and gibberellin-regulated proteins (GRPs), each contributing to distinct patterns of cross-reactivity [31].

Clinically, PFAS presents a spectrum of symptoms, ranging from mild oral irritation, such as itching or tingling in the mouth and throat, to more severe reactions. These may include angioedema, gastrointestinal discomfort, or in rare cases, systemic anaphylaxis, which can be life-threatening [33]. The allergens involved in PFAS are typically labile, losing their allergenicity with heat or enzymatic digestion, which explains the mild symptoms in most cases. However, when symptoms are severe, they may reflect primary sensitization to stable, genuine food allergens that retain their immunogenic properties even after processing, blurring the distinction between PFAS and classical IgE-mediated food allergies [34].

Environmental and individual factors can further modulate the clinical presentation of PFAS. Cofactors such as physical exercise, alcohol consumption, or the use of nonsteroidal anti-inflammatory drugs (NSAIDs) can exacerbate symptoms, potentially tipping mild reactions into severe systemic responses [35]. Understanding these cross-reactive mechanisms is critical for accurate diagnosis and effective management of PFAS, highlighting the need for personalized therapeutic approaches and patient education to mitigate risks.

This clinical entity was first described in 1942 as the connection between pollinosis and reactions to labile allergens in fresh vegetables and termed oral allergy syndrome (OAS) [36]. This initial understanding emphasized the localized oral and pharyngeal symptoms caused by cross-reactivity between pollen allergens and homologous proteins in raw fruits, vegetables, and nuts. In 1987, the term pollen–food allergy syndrome was proposed to provide a more comprehensive descriptor of this condition, recognizing its broader clinical implications and relationship with pollen-associated food allergies [37]. OAS is still a term sometimes used interchangeably with PFAS, but is now typically reserved for allergic reactions confined to the oropharynx after the ingestion of certain foods [38]. However, OAS can occur as the initial symptom of both class I and class II food allergies [31]. Therefore, the confusion between OAS and PFAS poses a clinical risk. Patients with primary food allergies (sensitized to class I allergens) may exhibit mild oral symptoms to small allergen doses but are at risk of progressing to systemic reactions or anaphylaxis. Misdiagnosing these patients as having PFAS may result in inadequate

management, including failure to prescribe life-saving epinephrine auto-injectors, thereby increasing the risk of severe outcomes [34].

This nuanced understanding of PFAS has important implications for diagnosis and management, emphasizing the need for precise allergen characterization and tailored therapeutic approaches to address the diverse clinical spectrum of the syndrome. Advances in molecular allergology and component-resolved diagnostics have further enhanced the ability to distinguish between cross-reactive and primary food allergens, providing better tools for predicting symptom severity and guiding patient care, and offering promising avenues for managing these conditions [31]. However, equitable access to such interventions remains a significant challenge, particularly in low- and middle-income countries [39]. Addressing the allergy epidemic requires a comprehensive strategy that includes public health education, preventive measures, early diagnosis, and personalized treatment plans to mitigate its impact on individuals and society.

2. Food Allergens

Food allergens are classified into class I and class II allergens based on their stability, source, and immunological properties [40]. Class I allergens are typically heat- and digestion-stable proteins found in foods such as nuts, shellfish, and eggs. These allergens are capable of sensitizing individuals through the gastrointestinal tract and are often associated with systemic and severe allergic reactions, including anaphylaxis. Their resilience to thermal processing and enzymatic digestion allows them to retain their allergenic properties even after cooking, making them a significant concern for individuals with food allergies [41].

In contrast, class II allergens are heat- and digestion-labile proteins that are often homologous to pollen allergens. These allergens, such as PR-10 proteins, profilins, and lipid transfer proteins (LTPs), are the ones commonly implicated in PFAS. They are primarily responsible for localized allergic reactions, which typically manifest as itching or swelling in the mouth and throat after consuming raw plant-based foods. The labile nature of class II allergens means that they generally lose their allergenicity when foods are cooked or processed, reducing the risk of severe systemic reactions in most cases [42]. Class II allergens are proteins that typically do not cause primary sensitization through the gastrointestinal tract but instead trigger allergic reactions due to cross-reactivity with aeroallergens (such as pollen) that have already sensitized the immune system. This means that an individual first develops an allergic response to an aeroallergen, such as birch pollen, which contains proteins structurally similar to those found in certain foods [33,43].

The distinction between class I and class II allergens is clinically significant, as it informs both the diagnosis and management of food allergies. Class I allergens often necessitate strict avoidance and emergency preparedness for anaphylaxis, while class II allergens may allow for dietary flexibility with processed or cooked forms of the triggering foods [33]. Advances in component-resolved diagnostics have further enhanced the ability to classify allergens accurately, enabling personalized approaches to allergy care that consider the unique properties of these allergenic proteins. Understanding the differences between these allergen classes is crucial for developing targeted therapies and improving the quality of life for individuals with food allergies.

3. PFAS Epidemiology

While precise global prevalence rates for PFAS are difficult to determine due to geographical variability, it is estimated to affect 5–8% of the general population and up to 50–70% of individuals with pollen sensitization [33,44,45]. It is also challenging to determine specific prevalences of PFAS to different allergens due to the typically small

size of studies, significant variability in methodology, and notable differences even among populations with similar allergen exposures, which can be influenced by genetic, dietary, and environmental factors [46].

PFAS is more frequently observed in regions where certain pollens, such as birch, ragweed, or grass pollens, are highly prevalent. The specific foods that trigger PFAS are closely tied to regional pollen sensitizations and local dietary habits, reflecting a dynamic interplay between environmental exposure and cultural food preferences. For example, birch pollen-related PFAS is more common in Northern and Central Europe [31,47]. Birch pollen contains the major allergen Bet v 1, a PR-10 protein known for its strong cross-reactivity with homologous proteins in many plant-based foods, such as apples, pears, cherries, carrots, and celery [48]. This strong cross-reactivity explains why PFAS associated with birch pollen is one of the most frequently observed forms of the syndrome in these regions. In contrast, ragweed pollen-related PFAS is more dominant in North America, Central and Eastern Europe, and Japan [49]. Ragweed, particularly common ragweed (*Ambrosia artemisiifolia*), produces large quantities of highly allergenic pollen, making it a significant contributor to allergic rhinitis and PFAS in these areas [6]. The allergens Amb a 8 (profilin) and Amb a 6 (LTP) cross-react with proteins in foods such as melons, bananas, and cucumbers, leading to the development of PFAS symptoms in sensitized individuals [42,50]. The prevalence of ragweed-related PFAS in North America is partly due to the widespread distribution of ragweed and its ability to thrive in urban and suburban environments, further exacerbated by climate change and increased pollen production. In Central and Eastern Europe, ragweed has become an invasive species [51,52], significantly increasing its impact on public health, including the prevalence of PFAS. Similarly, in Japan, ragweed-related cases are rising, likely due to environmental factors and increased awareness of cross-reactivity [53]. In Mediterranean countries, LTPs play a significant role in PFAS, with peaches (which contain the Pru p 3 LTP) being a major trigger, alongside other fruits like apricots, plums, and nectarines, which are staples of the local diet [54,55]. Cultural factors also influence PFAS triggers. For example, soy and soy-based products, such as tofu and soy milk, are significant triggers in East Asian countries and Japan, where soy is a dietary staple [56]. The allergen Gly m 4, a PR-10 protein in soy, cross-reacts with birch and other pollens, making soy a frequent cause of PFAS in these regions. In Mexico, pineapples are a notable PFAS trigger, likely related to the local dietary prominence of this fruit and its cross-reactivity with pollens such as oak and ash [57]. These regional differences highlight how the type of pollen prevalent in a given area directly influences the pattern of PFAS, demonstrating the interplay between environmental exposure and dietary habits in shaping the epidemiology of the syndrome [49,57]. Geographical differences are also influenced by cultural dietary habits, as the types of foods associated with PFAS vary depending on local cuisine and the availability of fresh produce [58,59]. In regions where raw fruits and vegetables are frequently consumed, the risk of triggering PFAS symptoms may be higher. These findings underscore the importance of understanding local allergen profiles and dietary practices when diagnosing and managing PFAS in diverse populations.

PFAS tends to be more prevalent in adults and adolescents than in young children [60], as the development of PFAS often follows prolonged sensitization to pollen allergens over time [61]. The rise in urbanization, pollution, and climate change has also been linked to an increase in pollen-related allergies, potentially contributing to a growing prevalence of PFAS in recent years. PFAS has been shown to disproportionately affect urban populations, likely due to increased exposure to airborne allergens and reduced microbial diversity associated with urban living [28]. Moreover, PFAS is recognized as part of the “allergy epidemic”, which has seen a global rise in allergic diseases over the

past century, particularly in industrialized and middle-income countries undergoing rapid socioeconomic transitions.

The burden of PFAS extends beyond its prevalence, as it significantly impacts the quality of life for affected individuals. Although most cases involve mild symptoms localized to the oral cavity, severe systemic reactions, including anaphylaxis, are reported in a small but significant subset of patients [62,63], underscoring the importance of early diagnosis and management. Despite its widespread occurrence, PFAS (as well as genuine food allergies) remains underdiagnosed and underreported, especially in regions with limited access to advanced diagnostic tools [64]. These epidemiological patterns highlight the need for increased awareness, improved diagnostic capabilities, and tailored public health strategies to address the growing impact of PFAS worldwide.

4. PFAS Pathogenesis

Briefly, the pathogenesis of PFAS, like that of other IgE-mediated allergic reactions, involves a complex interplay of immune mechanisms. It begins with sensitization, where allergen exposure, typically through inhalation or ingestion, leads antigen-presenting cells, such as dendritic cells, to process the allergen and present it to naive T-helper (Th) cells [65]. In allergic individuals, these Th cells differentiate into Th2 cells, which release cytokines like IL-4, IL-5, and IL-13. These cytokines promote the production of allergen-specific IgE antibodies by B cells. The IgE antibodies bind to receptors on mast cells and basophils, priming them for subsequent exposures. Upon re-exposure to the allergen, cross-linking of IgE on the surface of these cells triggers their degranulation, releasing histamine and other inflammatory mediators (Figure 1) [66]. Th2 cytokines might further amplify the allergic cascade by recruiting eosinophils, which exacerbate tissue inflammation and sustain hypersensitivity reactions [67]. This cascade of immune events demonstrates the centrality of Th2-driven responses in PFAS. However, the interaction between other immune cells and pathways adds further complexity. For example, basophils and mast cells play complementary roles, with basophils serving as a primary source of IL-4 during the sensitization phase [68]. Additionally, eosinophils, recruited through chemotactic signals such as eotaxin, release cytotoxic granules that damage epithelial barriers and exacerbate inflammation [67]. The chronic involvement of these cells may lead to tissue remodeling, potentially compounding the allergic response over time [69].

In the case of PFAS, this mechanism occurs in individuals previously sensitized to pollen who subsequently consume raw plant-based foods containing allergens that cross-react with the sensitizing pollen allergens [31]. For cross-reactivity to occur, a significant degree of similarity—typically more than 70%—is required between the primary protein sequences of the pollen allergens and those in the triggering food [70]. This degree of molecular homology is critical because IgE antibodies, which were initially generated in response to the pollen allergen, recognize and bind to similar epitopes on food proteins. These epitopes trigger the immune response, resulting in the characteristic symptoms of PFAS, which may range from mild oral itching to severe systemic reactions like anaphylaxis [44]. In addition to protein sequence similarity, the three-dimensional conformation of these proteins plays a pivotal role in cross-reactivity. Proteins with conserved structural motifs that resemble those of pollen allergens are more likely to bind IgE and activate immune cells. Advances in molecular modeling have revealed that even minor variations in protein folding or side-chain orientation can influence allergenicity, underscoring the complexity of immune recognition in PFAS [71].

Moreover, the stability of the allergenic proteins influences whether the cross-reactive epitopes remain intact during food processing or digestion, directly impacting the severity and type of allergic reaction [72]. Proteins that resist degradation by digestive enzymes

such as trypsin and pepsin are more likely to remain intact during gastrointestinal transit. These stable proteins can retain their allergenic potential, increasing the likelihood of interaction with immune cells in the gut-associated lymphoid tissue (GALT). For example, LTPs, known for their robust stability, are frequently implicated in severe PFAS cases [73].

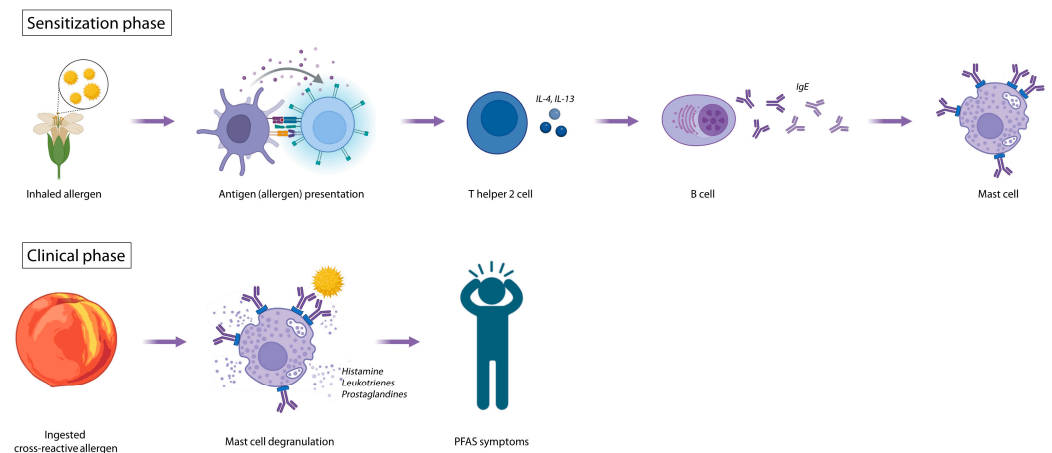


Figure 1. The figure illustrates the PFAS mechanism, highlighting its two main phases: the sensitization phase and the clinical phase. During the sensitization phase, inhaled allergens, such as pollen, are presented by antigen-presenting cells to T helper 2 cells. These cells release cytokines like IL-4 and IL-13, which stimulate B cells to produce allergen-specific IgE antibodies. The IgE antibodies bind to the surface of mast cells, effectively priming them for future allergen exposure. During the clinical phase, ingestion of a cross-reactive allergen (e.g., fruits or vegetables) leads to the binding of the allergen to IgE on the surface of mast cells. This triggers mast cell degranulation, releasing inflammatory mediators such as histamine, leukotrienes, and prostaglandins. These mediators cause the characteristic symptoms of PFAS, including itching, swelling, or discomfort in the oral cavity, and also systemic symptoms. The cross-reactivity between pollen allergens and structurally similar food allergens is central to the development of PFAS symptoms.

Environmental factors and food processing methods can further modulate the allergenicity of these proteins. Heat treatment, for instance, can denature some proteins, reducing their allergenic potential, while others, like profilins, are highly heat-labile and lose their IgE-binding capacity when cooked [74]. Conversely, certain processing techniques, such as fermentation, can enhance the immunogenic properties of allergens, highlighting the importance of dietary habits in PFAS pathophysiology [72].

The gut microbiota also plays a role in modulating the immune response to food allergens. Individuals with disrupted microbial diversity or dysbiosis may exhibit heightened allergic reactions due to altered immune regulation. Short-chain fatty acids (SCFAs) produced by commensal bacteria have been shown to influence the activity of regulatory T cells (Tregs), which are essential for maintaining immune tolerance [75]. A reduction in SCFA levels could impair Treg function, exacerbating the allergic response in PFAS [76].

Lastly, individual genetic predispositions, including polymorphisms in genes encoding cytokines or immune receptors, may influence susceptibility to PFAS. Certain genetic variants may promote a stronger Th2-skewed immune response or impair mechanisms of tolerance, making affected individuals more prone to cross-reactivity [77]. Understanding these genetic and environmental interactions is crucial for developing targeted interventions and improving the management of PFAS.

The intensity of the allergic reaction depends on multiple factors beyond just the molecular similarity between the inhalant and food allergens. One critical factor is the concentration of the allergen in the food, as higher levels of allergenic proteins are more likely to elicit a stronger immune response. Another important determinant is the amount

of food consumed, as consuming larger quantities of a triggering food increases the overall allergen load, thereby amplifying the risk and severity of the reaction [78]. Additionally, the individual's sensitivity threshold plays a pivotal role. This threshold varies significantly between individuals and is influenced by factors such as the degree of prior sensitization, the individual's immune response, and the presence of comorbid conditions such as asthma or mast cell disorders [66]. For example, highly sensitized individuals may experience symptoms with even trace amounts of allergens, whereas others may tolerate small exposures without significant reactions [78].

Environmental and physiological cofactors, such as alcohol, exercise, or medications, can further amplify the immune response, making the reaction more severe [79]. These cofactors influence the body's immune or physiological state in ways that enhance allergen absorption, increase immune cell activation, or lower the threshold for triggering a reaction. Alcohol, for example, is known to affect the permeability of the gastrointestinal lining, allowing allergens to cross into the bloodstream more readily [80]. It also impacts the immune system by modulating the activity of mast cells and basophils, leading to an exaggerated release of histamine and other inflammatory mediators. This heightened response can turn a mild, localized reaction into a more systemic one [60]. Similarly, exercise can amplify the severity of allergic reactions by increasing gastrointestinal permeability and altering blood flow dynamics, particularly to the digestive system. Physical activity accelerates the movement of allergens into the bloodstream and can lower the activation threshold for mast cells, increasing the likelihood of a systemic allergic response [35]. This phenomenon is often observed in exercise-induced anaphylaxis, where exercise acts as a trigger for severe allergic reactions, especially when combined with allergen exposure [81]. Certain medications, such as NSAIDs and proton pump inhibitors (PPIs), can also exacerbate allergic reactions. NSAIDs, by inhibiting prostaglandin synthesis, can enhance mast cell degranulation and reduce the body's ability to counteract inflammatory responses [82]. PPIs, on the other hand, alter the acidic environment of the stomach, impairing protein digestion and allowing more intact allergens to reach the immune system in the gut, thereby increasing the risk of an allergic response [79]. Other cofactors, such as stress, hormonal changes, and underlying infections, can similarly influence the severity of allergic reactions by modulating immune function or increasing the bioavailability of allergens. The interplay of these cofactors with allergen exposure is a critical aspect of managing PFAS and other allergic conditions, emphasizing the need for comprehensive patient education and individualized management strategies to minimize risks.

There are other food allergy syndromes that share similar mechanisms, specifically sensitization through the airways followed by allergic reactions upon food ingestion. These syndromes underscore the importance of understanding cross-reactivity between inhalant allergens and food proteins.

Pork-cat syndrome is an IgE-mediated allergic condition where individuals sensitized to cat dander, specifically the protein Fel d 2 (a serum albumin), develop allergic reactions upon consuming pork. The cross-reactivity occurs because of the high degree of homology between Fel d 2 and porcine serum albumin (Sus s 1) [83]. Serum albumins are major carrier proteins in the bloodstream and they are conserved across mammalian species to a high degree, which contributes to cross-reactivity [84]. Notably, this condition is more commonly observed in individuals with chronic exposure to cats, such as pet owners or individuals living in households with multiple cats, where repeated inhalation of Fel d 2 drives immune sensitization. Symptoms may include OAS as well as systemic reactions [85,86].

Fungus-food allergy syndrome (FFAS) is a condition characterized by sensitization to airborne fungal spores, which subsequently leads to allergic reactions to foods containing structurally similar fungal proteins. Environmental molds such as *Alternaria alternata*, *As-*

pergillus fumigatus, and *Cladosporium* are well-documented allergens found in both outdoor and indoor environments, particularly in damp or poorly ventilated spaces [87]. Repeated inhalation of these fungal spores can prime the immune system, inducing the production of specific IgE antibodies against fungal allergens. Over time, sensitized individuals may experience allergic symptoms upon ingesting certain foods that contain fungal components or are contaminated with mold [88]. The cross-reactivity between fungal spores and food allergens is primarily attributed to shared allergenic proteins, such as enolases and thioredoxins, which are conserved across fungi and certain foods. These foods include fermented products like cheese, beer, wine, and soy sauce, as well as foods susceptible to mold contamination such as nuts, dried fruits, and grains [88,89]. *Alternaria* and *Aspergillus* allergens are also known to exhibit cross-reactivity with proteins found in edible fungi (e.g., mushrooms) [90]. *Alternaria*–spinach syndrome has also been recently described, with Alt a 1 identified as the likely allergen involved in the reaction [91].

Bird–egg syndrome predominantly affects individuals who have been sensitized to bird allergens, often through inhalation of feather dust or exposure to bird droppings, followed by allergic reactions to egg yolk proteins. The hallmark allergenic component in this syndrome is chicken serum albumin or alpha-livetin (Gal d 5), a heat-labile protein that becomes denatured during cooking [92]. Consequently, allergic symptoms are more commonly triggered by raw or lightly cooked eggs, where the allergenic structure of Gal d 5 remains intact [93].

These examples emphasize the broader relevance of inhalant-to-food allergen cross-reactivity beyond PFAS. While the exact allergens and clinical presentations differ, the underlying mechanisms remain consistent, involving IgE-mediated responses to homologous proteins encountered in both environmental and dietary contexts.

5. PFAS Symptoms and Effect on Quality of Life

PFAS symptoms typically appear within minutes of consuming fresh fruits, vegetables, nuts, legumes, or seeds and range from mild, localized reactions to rare but potentially severe systemic manifestations [44]. The clinical presentation depends on various factors, including the specific allergen involved, individual sensitivity, and the presence of exacerbating cofactors, as previously mentioned.

The hallmark of PFAS is its localized manifestation in the oropharyngeal region (OAS). Most patients experience pruritus and paresthesia in the mouth, lips, tongue, and throat shortly after ingesting raw fruits, vegetables, nuts, seeds, or legumes. These symptoms are often accompanied by mild swelling (angioedema) of the oral mucosa, lips, or tongue [31]. In some cases, erythema or vesicle formation on the mucosa may occur, further contributing to discomfort [58]. Laryngospasm and dysphonia are less common but can occur when swelling affects the laryngeal structures [33]. Despite their discomfort, these localized symptoms are usually transient, resolving within a few minutes to half an hour without medical intervention.

While PFAS predominantly affects the oropharynx, it can occasionally extend to other systems. Gastrointestinal symptoms, including nausea, abdominal pain, vomiting, and diarrhea, have been reported in some cases [94]. These symptoms are more likely when larger quantities of the triggering food are consumed or when cofactors such as exercise or alcohol are present, which can amplify the allergic response [95]. Respiratory symptoms, though rare, may include nasal congestion, sneezing, or mild wheezing. These manifestations suggest a broader systemic immune activation rather than localized reactivity [96].

Although uncommon, systemic manifestations of PFAS can occur, with symptoms ranging from urticaria (hives) and widespread angioedema to potentially life-threatening anaphylaxis [97]. Systemic reactions are estimated to occur in approximately 2–10% of

PFAS cases, with severe outcomes such as hypotension and respiratory distress being extremely rare (1–2%) [54,57,62,63]. These more serious presentations are often linked to heat-stable allergens, such as those found in nuts, LTPs, and GRPs, or when cofactors like NSAIDs or physical activity lower the reaction threshold [54,94,96]. Anaphylaxis represents the most critical concern in PFAS and underscores the need for vigilance in susceptible individuals [63]. For patients who experience severe systemic reactions to specific foods, strict avoidance of those foods in any form is strongly advised [98,99].

The clinical spectrum of PFAS is influenced by the stability of the allergenic proteins involved. Allergens from the PR-10 and profilin families are heat- and digestion-labile, often leading to mild, localized reactions that resolve with cooking or processing of the food. In contrast, heat-stable proteins, such as those found in nuts, peanuts, and LTPs, are more likely to cause severe or systemic reactions, even after the food has been cooked [33]. The type of food consumed and the patient's underlying pollen sensitization profile also play a significant role [54,63,100]. For example, individuals sensitized to birch pollen are more likely to react to apples and carrots, while those with ragweed sensitization may react to melons or bananas.

Although PFAS symptoms are generally mild and self-limiting, they can significantly impact the quality of life for affected individuals. Fear of reactions may lead to the avoidance of specific foods, potentially resulting in nutritional deficiencies or a restricted diet [58]. Moreover, the unpredictability of symptoms, particularly in the presence of cofactors, can contribute to anxiety and a reduced sense of well-being [101]. Patients with PFAS often find it difficult to anticipate the severity of their reactions, as seemingly benign foods may trigger mild symptoms in one instance and more severe reactions in another. For instance, a person might tolerate a certain fruit on one occasion but experience systemic symptoms like gastrointestinal distress or respiratory issues when that same food is consumed after exercise or with alcohol [79]. This unpredictability can lead to constant vigilance and worry, particularly during social events or dining out, where control over food preparation and exposure to potential triggers may be limited. The fear of public symptoms, such as swelling, difficulty breathing, or hives, can discourage individuals from participating in social or professional activities, leading to isolation and a reduced quality of life [102–105]. For children, even though they are more often affected by primary food allergies and not PFAS, this can mean missing out on social activities like birthday parties or school events due to fear of exposure to allergens in shared meals or snacks [106]. The anxiety surrounding potential reactions—whether mild or severe—can make children feel isolated or different from their peers, affecting their self-esteem and emotional well-being [105]. Families, in turn, may experience heightened stress as they navigate the complexities of managing their child's condition, from planning safe meals to ensuring that schools and caregivers understand the potential risks [103,107,108]. Additionally, the potential for severe, life-threatening reactions such as anaphylaxis—though rare—further heightens the psychological burden, as patients may feel unprepared or anxious about the availability of emergency medical care [109–111]. For individuals managing PFAS, this unpredictability can also erode their confidence in food choices and nutritional balance, particularly when their reactions involve staple foods or culturally significant dishes [112]. The emotional toll of constant dietary vigilance and the fear of missing hidden allergens in foods can contribute to stress and, over time, impact mental health. This cycle of anxiety and hyper-awareness not only affects the individual but also their relationships and ability to enjoy everyday activities [106,113].

Healthcare providers should be aware of this psychological burden and address it as part of a holistic approach to managing PFAS. Providing patients with accurate information about their triggers, the role of cofactors, and effective strategies to reduce

risk can help empower them and alleviate anxiety [114]. Encouraging the use of tools like allergen testing, personalized dietary plans, and carrying emergency medications like antihistamines or epinephrine auto-injectors can also foster a sense of security and control [115]. By addressing both the physical and emotional aspects of PFAS, clinicians can help patients achieve a better quality of life despite the challenges of this condition.

6. Protein Families Involved in PFAS

As mentioned before, PFAS is a result of immunological cross-reactivity between air-borne pollen allergens and structurally similar proteins present in various plant-based foods. These shared allergens, referred to as panallergens, are proteins with highly conserved structures found across diverse plant species. Their stability and ubiquitous presence make them central to the pathophysiology of PFAS, as they form the molecular link between pollinosis (pollen allergy) and food allergy [33]. Understanding these panallergens provides critical insight into the mechanisms of PFAS and informs diagnostic and therapeutic approaches. In 2004, Breiteneder et al. proposed a systematic classification of allergens into families based on their structural and functional properties [116]. Among the many allergenic protein families, six have been identified as significant contributors to PFAS due to their ability to induce IgE cross-reactivity between pollens and foods. Of these, three families are particularly well-characterized: PR-10 proteins, profilins, and LTPs [44]. These proteins are involved in essential biological processes in plants, such as defense against pathogens and environmental stress, but in humans, they act as allergens that trigger hypersensitivity reactions. Three additional families—thaumatin-like proteins (TLPs), β -1,3-glucanases, and isoflavone reductases (IFRs)—have also been implicated in PFAS, though they are less well understood [44,117]. Emerging research highlights other promising candidates, such as gibberellin-regulated proteins (GRPs), which are beginning to be recognized as cross-reactive allergens [118]. Figure 2 illustrates the relative stability and potential for severe systemic allergic reactions of various allergenic protein families, ranging from highly heat- and digestion-sensitive proteins such as PR-10 and profilins, to highly stable proteins like LTPs. The gradient highlights the continuum of allergenic risk, with more stable proteins generally associated with a higher likelihood of systemic reactions, including anaphylaxis [119]. This visualization underscores the varying allergenic profiles of these protein families, which play a critical role in the diagnosis and management of IgE-mediated allergic conditions [44,98].

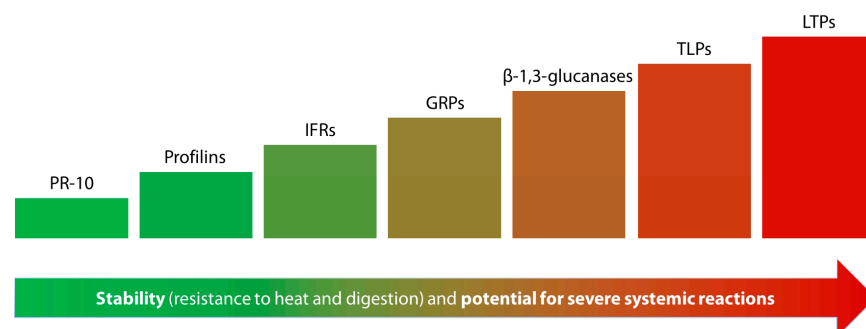


Figure 2. Stability and potential for severe systemic reactions of allergenic proteins [33,44,119,120]. The chart illustrates the relative stability (resistance to heat and digestion) and associated risk of severe systemic allergic reactions among different allergenic protein families. Proteins such as PR-10 and profilins are shown with lower stability and reduced potential for systemic reactions, while LTPs exhibit high stability and significant potential for systemic allergic responses. The arrow gradient represents the continuum from low to high stability and systemic reaction potential. GRPs: Gibberellin-Regulated Proteins; IFRs: Isoflavonoid reductases; LTPs: Lipid Transfer Proteins; PR-10: pathogenesis-related protein group 10; TLPs: Thaumatin-like proteins.

Table 1 and Figure 3 provide a list of major allergen sources, their specific allergenic proteins, and distribution worldwide. This table has been compiled using information from the Allergen Nomenclature Database (WHO/IUIS), which provides standardized data on allergen sources, protein families, and nomenclature, as well as from the Global Biodiversity Information Facility (GBIF), an authoritative resource on species distribution and biodiversity [121,122].

Table 1. Comprehensive overview of major allergen sources and their specific allergenic proteins [121,122].

Allergen Source	Plant Family	Pathogenesis-Related 10 (PR-10)	Profilin	Lipid Transfer Protein (LTP)	Gibberellin-Regulated Protein (GRP)	Thaumatococcal Protein (TLP)	β -1,3-Glucanase	Isoflavonoid Reductase
Birch pollen (<i>Betula pendula</i> Roth)	Betulaceae	Bet v 1	Bet v 2	-	-	-	-	Bet v 6
Hazel pollen (<i>Corylus avellana</i> L.)	Betulaceae	Cor a 1	Cor a 2	Cor a 8	-	-	-	Cor a 6
Grass pollen (<i>Phleum pratense</i> L.)	Poaceae	-	Phl p 12	-	-	-	-	-
Olive pollen (<i>Olea europaea</i> L.)	Oleaceae	-	Ole e 2	Ole e 7	-	Ole e 13	Ole e 9	Ole e 12
Japanese cedar pollen (<i>Cryptomeria japonica</i> (Thunb. ex L.f.) D.Don)	Cupressaceae	-	-	-	Cry j 7	Cry j 3	-	-
Mediterranean cypress pollen (<i>Cupressus sempervirens</i> L.)	Cupressaceae	-	-	-	Cup s 7	Cup s 3	-	-
Common ragweed pollen (<i>Ambrosia artemisiifolia</i> L.)	Asteraceae	-	Amb a 8	Amb a 6	-	-	-	-
Mugwort pollen (<i>Artemisia vulgaris</i> L.)	Asteraceae	Art v 2	Art v 4	Art v 3	-	-	-	-
Pellitory-of-the-wall (<i>Parietaria judaica</i> L.)	Urticaceae	-	Par j 3	Par j 1, Par j 2	-	-	-	-
Apple (<i>Malus domestica</i> (Suckow) Borkh.)	Rosaceae	Mal d 1	Mal d 4	Mal d 3	-	Mal d 2	-	-
Peach (<i>Prunus persica</i> (L.) Batsch)	Rosaceae	Pru p 1	Pru p 4	Pru p 3	Pru p 7	Pru p 2	-	-
Cherry (<i>Prunus avium</i> L.)	Rosaceae	Pru av 1	Pru av 4	Pru av 3	Pru av 7	Pru av 2	-	-
Plum (<i>Prunus domestica</i> L.)	Rosaceae	Pru d 1	Pru d 4	Pru d 3	-	Pru d 2	-	-
Almond (<i>Prunus dulcis</i> Batsch)	Rosaceae	-	-	Pru du 3	-	-	-	-
Pear (<i>Pyrus communis</i> L.)	Rosaceae	Pyr c 1	Pyr c 4	Pyr c 3	-	-	-	Pyr c 5
Strawberry (<i>Fragaria × ananass</i> Duchesne)	Rosaceae	Fra a 1	Fra a 4	Fra a 3	-	-	Fra a Glucanase	-
Orange (<i>Citrus × sinensis</i> (L.) Osbeck)	Rutaceae	-	Cit s 2	Cit s 3	Cit s 7	-	-	Cit s IFR
Grape (<i>Vitis vinifera</i> L.)	Vitaceae	-	Vit v 4	Vit v 1	-	Vit v TLP	Vit v Glucanase	-
Tomato (<i>Solanum lycopersicum</i> L.)	Solanaceae	Sola l 4	Sola l 1	Sola l 3, Sola l 6, Sola l 7	-	Sola l TLP	Sola l Glucanase	-
Bell pepper (<i>Capsicum annuum</i> L.)	Solanaceae	-	Cap a 2	-	Cap a 7	Cap a 1	Cap a Glucanase	-
Banana (<i>Musa acuminata</i> Colla)	Musaceae	-	Mus a 1	Mus a 3	-	Mus a 4	Mus a 5	-
Celery (<i>Apium graveolens</i> L.)	Apiaceae	Api g 1	Api g 4	Api g 2	-	-	-	-
Carrot (<i>Daucus carota</i> subsp. <i>Sativus</i> (Hoffm.) Schübl. and G. Martens)	Apiaceae	Dau c 1	Dau c 4	-	-	-	-	Dau c 5
Walnut (<i>Juglans regia</i> L.)	Juglandaceae	Jug r 5	Jug r 7	Jug r 3, Jug r 8	-	Jug r TLP	-	-
Kiwi (<i>Actinidia deliciosa</i> (A.Chev.) C.F.Liang and A.R.Ferguson)	Actinidiaceae	Act d 8, Act d 11	Act d 9	Act d 10	-	Act d 2	-	-
Sunflower (<i>Helianthus annuus</i> L.)	Asteraceae	-	Hel a 2	Hel a 3	-	-	-	-
Soybean (<i>Glycine max</i> (L.) Merr.)	Fabaceae	Gly m 4	Gly m 3	-	-	-	-	-
Peanut (<i>Arachis hypogaea</i> L.)	Fabaceae	Ara h 8	Ara h 5	Ara h 9, Ara h 16, Ara h 17	-	-	-	-
Barley (<i>Hordeum vulgare</i> L.)	Poaceae	-	Hor v 12	Hor v 14, Hor v 7k-LTP	-	-	-	-
Wheat (<i>Triticum aestivum</i> L.)	Poaceae	-	Tri a 12	Tri a 14	-	-	-	-
Rice (<i>Oryza sativa</i> L.)	Poaceae	-	Ory s 12	-	-	-	-	-
Corn (<i>Zea mays</i> L.)	Poaceae	-	Zea m 12	Zea m 14	-	Zea m TLP	-	-

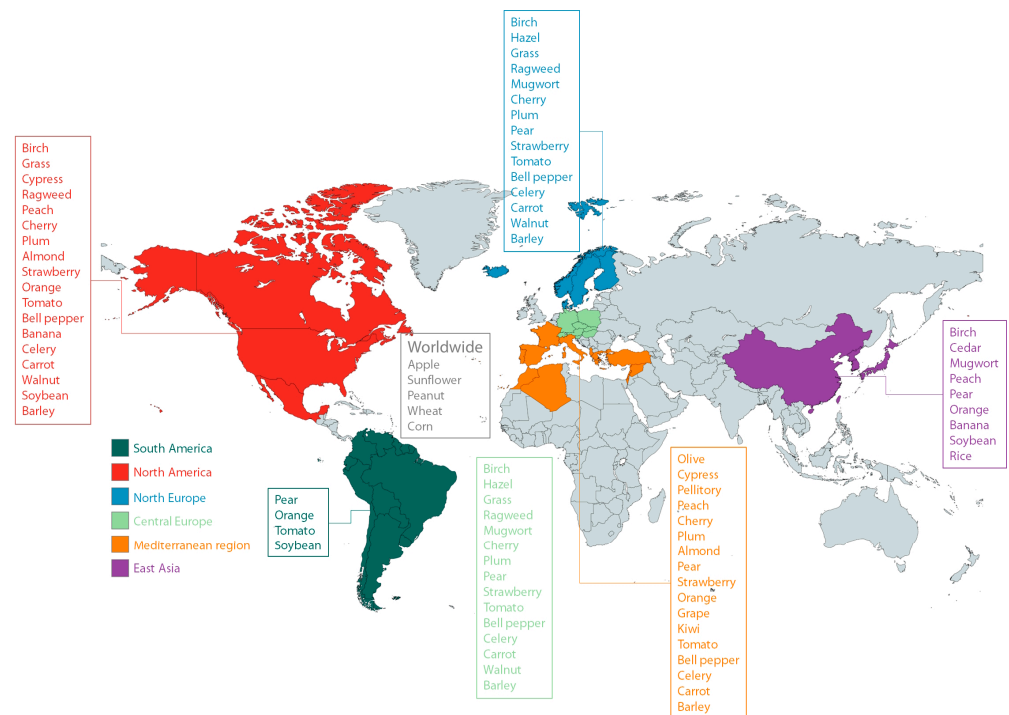


Figure 3. Global distribution of key plants associated with PFAS, highlighting the most relevant species and their geographical ranges [121,122]. Created with ChartMap.net.

6.1. Pathogenesis-Related Protein Group 10 (PR-10 Proteins)

The PR-10 protein family, with Bet v 1 (17.5 kDa) from birch pollen as its prototype, is one of the most extensively studied allergen families implicated in PFAS [48]. These proteins are part of the pathogenesis-related protein class 10 family, which plays a defensive role in plants, helping them respond to environmental stressors such as pathogens, pests, and physical damage [123–125]. In humans, however, these proteins act as allergens, triggering immune responses in individuals sensitized to pollen.

The prevalence of birch pollen allergy varies significantly across regions, particularly in Europe, where birch trees are widespread and a major source of seasonal pollen exposure [47]. Sensitization to birch pollen affects approximately 8% to 16% of the general population in Europe, with higher rates reported in countries with dense birch forests, such as Scandinavia and parts of Central Europe [126], but also China [127]. The prevalence of PR-10-mediated PFAS is particularly high in regions where birch pollen allergy is common, where it may affect more than 75% of birch-allergic patients [57,127], as this geographic correlation reflects the widespread sensitization to Bet v 1, which primes the immune system to recognize structurally similar proteins in fruits, vegetables, and nuts [43,57].

PR-10 proteins are characterized by their small molecular size (17–18 kDa) and structural features, including a hydrophobic cavity that binds small ligands [128,129]. This structural similarity across different plant species accounts for the high degree of cross-reactivity between PR-10 proteins in pollen and homologous proteins in plant-based foods. For instance, individuals allergic to birch pollen (Bet v 1) often experience symptoms after consuming raw apples (Mal d 1), apricots (Pru ar 1f), cherries (Pru av 1), peaches (Pru p 1), celery (Api g 1), soy (Gly m 4), peanuts (Ara h 8), hazelnuts (Cor a 1), chestnuts (Cas s 1), or tomatoes (Sola l 4), because of shared epitopes recognized by IgE antibodies [57,100].

One defining feature of PR-10 proteins is their heat- and digestion-labile nature. These proteins denature rapidly upon exposure to heat or enzymatic digestion in the gastrointestinal tract, which largely limits their allergenic effects to the oropharyngeal region [73]. As a result, PR-10-mediated PFAS typically manifests with mild oral symptoms, such as itching,

tingling, and swelling of the lips, tongue, throat, and palate. These localized reactions are often transient, resolving within minutes to half an hour after food ingestion [130]. Additionally, the lability of PR-10 proteins explains why cooked or processed forms of implicated foods are generally well-tolerated by most patients [129]. However, despite their mild nature, PR-10-mediated symptoms can significantly impact quality of life, especially in individuals with extensive cross-reactivities who must avoid a variety of fresh plant-based foods.

6.2. Profilins

Profilins are a family of small proteins, typically 12–15 kDa in size, with a highly conserved three-dimensional structure [131]. They interact with actin monomers (G-actin) and polyproline sequences, regulating the assembly of actin filaments [132]. This function is critical for maintaining the integrity of the cytoskeleton and facilitating processes such as cell elongation and vesicle trafficking. Therefore, in plants, profilins are essential for cell growth, division, and response to environmental stimuli [44]. The structural conservation of profilins across plant species forms the basis of their allergenic potential, enabling them to act as panallergens in sensitized individuals by triggering immune responses through their shared molecular similarities. Their ubiquity and high degree of conservation make them key contributors to PFAS [133].

The prevalence of profilin sensitization varies geographically, reflecting differences in pollen exposure and dietary habits. Profilin-related PFAS is particularly common in areas with high exposure to pollen from birch, grass, or ragweed, such as Northern and Central Europe or North America, where it can affect up to 30% of profilin-sensitized patients [55,134]. However, the prevalence of profilin-related PFAS is lower in Mediterranean regions, where other allergens, such as LTPs, dominate the clinical spectrum of food-pollen cross-reactivity [135].

Profilins from pollens such as Bet v 2 from birch, Phl p 12 from grass pollen, and Amb a 8 from ragweed pollen play a crucial role as primary sensitizers in individuals who develop PFAS [136]. Their cross-reactivity with profilins in plant-derived foods is responsible for allergic reactions to foods like peaches (Pru p 12), apples (Mal d 4), and cherries (Pru av 4). Other food profilins include Ara h 5 in peanuts, Cor a 2 in hazelnuts, Cuc m 2 in melons, Mus a 1 in bananas, Api g 4 in celery, and Sola l 2 in tomatoes [31,44].

Profilin-mediated allergic reactions are generally mild and confined to the oropharyngeal region, manifesting as itching, tingling, or mild swelling of the lips, tongue, and throat [137]. This localized response is attributed to the heat- and digestion-labile nature of profilins, which rapidly denature during cooking or enzymatic digestion in the gastrointestinal tract [119,138]. As a result, cooked or processed forms of profilin-containing foods are often well-tolerated by affected individuals. However, severe reactions, including anaphylaxis, have been reported after consuming large amounts of profilins, which may overwhelm gastric digestion capacity and lead to significant absorption [139]. Alvarado et al. noted severe reactions even after small quantities of food in patients previously exposed to high levels of grass pollen [140].

6.3. Lipid Transfer Proteins (LTPs)

LTPs are a family of small (9–10 kDa), highly stable proteins, part of the prolamin superfamily, and involved in plant defense and lipid transport. This stability arises from four conserved disulfide bridges that create a rigid tertiary structure, making LTPs resistant to heat, enzymatic digestion, and acidic conditions. Unlike other panallergens such as PR-10 proteins or profilins, this stability allows LTPs to retain their allergenic properties even after cooking or digestion, significantly increasing their potential to cause severe allergic reactions. LTPs bind and transport lipids between membranes, playing an essential role

in plant cell metabolism and protection against environmental stressors such as drought, pathogens, and UV radiation.

Pollens such as Ole e 7 from olive trees, Pla a 3 from plane trees, Art v 3 from mugwort, and Par j 1 from pellitory-of-the-wall are well-documented sources of LTP sensitization. Among fruits, peach (Pru p 3) stands out as the most significant allergen, often serving as the prototype for LTP-mediated allergic reactions [141]. Similarly, apple (Mal d 3) and cherry (Pru av 3) are common triggers, along with apricot (Pru ar 3) and plum (Pru d 3). In the category of vegetables, tomato (Sola l 3) and celery (Api g 2) are frequently implicated, particularly in regions where these foods are staples. Nuts are another major source of LTP allergens, with hazelnut (Cor a 8) and walnut (Jug r 3) often associated with systemic reactions due to their heat-stable properties [142]. Peanut (Ara h 9) also contributes significantly to LTP-related allergies (LTP syndrome), particularly in individuals who experience severe reactions [100,141,143]. There have also been cases of PFAS to pistachios due to cross-reactivity with LTPs from pellitory-of-the-wall, particularly in the Mediterranean region [144,145].

The prevalence of LTP sensitization and its clinical significance vary by geographic region. In Mediterranean countries, LTPs are the most significant cause of food allergies and PFAS, with a high prevalence (up to 30%) of sensitization to Pru p 3, the peach LTP that serves as the archetype of this allergen family [54,143,146,147]. In contrast, LTP-related allergies are less common in Northern and Central Europe, where PR-10 proteins (e.g., Bet v 1) and profilins dominate the allergenic landscape [100]. This regional variation reflects differences in dietary habits, pollen exposure, and environmental factors. In Mediterranean regions, the high consumption of LTP-rich foods such as peaches, nuts, and apricots [148,149], coupled with frequent exposure to olive and plane tree pollen [150,151], increases the likelihood of sensitization. In non-Mediterranean regions the primary LTP sensitizer may not be Pru p 3, but other pollens, such as mugwort [142] or cannabis [152].

LTP-mediated PFAS often presents with more severe symptoms compared to other allergenic families such as PR-10 proteins or profilins. Due to their heat and digestion stability, LTPs can trigger systemic reactions, including anaphylaxis, even after ingestion of cooked or processed foods [141]. LTPs are also unique among panallergens in their potential to elicit allergic reactions to wheat and other cereals, especially in the context of exercise. Unlike other allergen families, LTPs, such as Tri a 14 in wheat, are implicated not only in PFAS but also in wheat-dependent exercise-induced anaphylaxis (WDEIA) [153]. In these cases, ingestion of wheat followed by physical activity amplifies the immune response, leading to severe systemic reactions, including anaphylaxis. Furthermore, Tri a 14 plays a distinct role in baker's asthma, an occupational allergy caused by inhaling wheat flour allergens. Unlike many other LTP-related allergies, baker's asthma does not require prior sensitization to pollens containing LTPs, as sensitization occurs directly through inhalation of wheat flour particles [154]. This distinguishes Tri a 14 from other LTPs, emphasizing its role as a primary sensitizer and highlighting its clinical significance in both food and occupational allergies.

6.4. Gibberellin-Regulated Proteins (GRPs)

Gibberellin-Regulated Proteins (GRPs) are an emerging family of plant allergens that play a role in PFAS. These proteins are regulated by gibberellins, a class of plant hormones involved in growth and development [155]. While GRPs were initially studied for their role in plant physiology, their identification as allergens in both pollens and foods has highlighted their clinical significance in allergic diseases [118,156].

GRPs are small proteins (7–8 kDa) with a high degree of stability, owing to their conserved cysteine residues that form multiple disulfide bridges [118]. This structural

feature makes them resistant to heat and enzymatic digestion, enabling them to retain their allergenic potential even after cooking or processing. Their primary function in plants includes regulating cell wall modifications, responding to stress conditions, and facilitating growth processes mediated by gibberellins [155]. These properties are crucial for plant survival and adaptation to environmental changes but also contribute to their allergenicity in humans.

In the context of allergies, GRPs have been identified as significant sensitizers in certain pollens. The most notable example is BP14 (cypmaclein, Cup s 7), a GRP found in cypress pollen (*Cupressus sempervirens*), which is highly allergenic in regions where cypress trees are abundant, such as the Mediterranean basin [157]. Sensitization to Cup s 7 has been shown to cross-react with GRPs in foods, such as Pru p 7 in peaches and similar GRPs in oranges and other fruits [158]. This cross-reactivity forms the basis of the “cypress-peach syndrome”, where individuals sensitized to cypress pollen experience allergic reactions after consuming peaches [159–161].

The prevalence of GRP-related allergies is closely linked to environmental and dietary factors. In the Mediterranean region, where cypress trees are widespread and fruits such as peaches and oranges are dietary staples, GRP sensitization is relatively common [162]. In contrast, GRP-related allergies are less frequently reported in Northern and Central Europe, where exposure to cypress pollen is lower, and other allergenic families, such as PR-10 proteins and profilins, dominate. A study from Japan observed that 65% of patients allergic to fruits were sensitized to GRPs [158]. The geographic variability of GRP sensitization reflects the regional distribution of cypress trees and the consumption patterns of GRP-containing foods.

In addition to peaches (Pru p 7) and Japanese apricots (Pru m 7), GRP allergens have been identified in a wide range of fruits, vegetables, and pollens. Notable examples include sweet cherry (Pru av 7), orange (Cit s 7), pomegranate (Pun g 7), and bell pepper (Cap a 7). Further GRPs have been described in raspberries (Rub i 7), kiwi (Act d 7), apples (Mal d 7), tomatoes (Lyc e 7), melons (Cuc m 7), and strawberries (Fra a 7). In pollens, GRP allergens seem to be confined to the Cupressaceae tree family, with key examples being Cup s 7 (cypress), Cry j 7 (Japanese cedar), and Jun a 7 (juniper) [118,158,163].

Clinical symptoms of GRP-related allergies range from mild to severe and can affect multiple organ systems. Localized symptoms, such as oral itching, tingling, and swelling, often occur after consuming GRP-containing foods like peaches, oranges, or apricots [163]. While these reactions are typically mild and self-limiting, the heat and digestion stability of GRPs can lead to systemic symptoms, including gastrointestinal distress (nausea, vomiting, and abdominal pain), urticaria, and, in rare cases, anaphylaxis [158,163]. Additionally, respiratory symptoms such as allergic rhinitis and asthma may arise in individuals sensitized to GRPs in cypress pollen, particularly during the pollen season [120,164].

6.5. Thaumatin-like Proteins (TLPs)

Thaumatococcal proteins (TLPs) are a family of pathogenesis-related (PR) proteins involved in plant defense mechanisms. TLPs are named for their structural resemblance to thaumatin, a sweet-tasting protein first isolated from miracle berry arils (*Thaumatococcus daniellii*) [165]. Their discovery as allergens in both pollens and plant-derived foods has highlighted their role in PFAS.

TLPs are small proteins, typically ranging between 20 and 30 kDa, characterized by a conserved structure that includes 16 conserved cysteine residues forming eight disulfide bridges [166]. These disulfide bonds confer remarkable stability to heat, enzymatic digestion, and acidic conditions, allowing TLPs to retain their allergenic properties even after cooking or processing [167]. Their structural resilience, combined with their ability to

bind sugars and other small molecules, makes them effective in defending plants against pathogens, such as fungi and bacteria. TLPs are often classified as PR-5 proteins [168] and play a critical role in protecting plants during stress conditions like infection, drought, or cold [169].

In allergology, TLPs have been identified as significant contributors to sensitization, particularly through exposure to certain pollens. Among these, the Cupressaceae tree family, including species like Japanese cedar (*Cry j 3*) and cypress (*Cup s 3*), serves as the primary source of sensitization [170]. Sensitization to these pollen-derived TLPs can lead to cross-reactivity with homologous TLPs in foods, triggering PFAS symptoms. While cypress pollen is the most well-documented source, emerging research suggests that other pollens may also contain TLP allergens, although their clinical significance remains underexplored [117].

The prevalence of TLP-related allergies is closely tied to geographic and environmental factors. In regions like Japan and the Mediterranean basin, where Cupressaceae trees are abundant, sensitization to pollen-derived TLPs is more common [171]. The prevalence of food allergies related to TLPs is less well-documented but is likely higher in areas where dietary staples include TLP-rich foods like apples, peaches, and tomatoes. In Northern Europe and North America, where PR-10 proteins dominate allergen profiles, TLPs are less frequently implicated in allergic diseases [172]. However, their global prevalence may be underestimated due to the limited availability of diagnostic tools specifically targeting TLPs [117].

Notable examples in fruits include Mal d 2 in apples, Pru av 2 in sweet cherries, Pru p 2 in peaches, Act d 2 in kiwi, and Mus a 4 in banana. In vegetables, TLP allergens such as Sola l 2 in tomatoes, Cap a 1 in pepper, and Api g TLP in celery have been reported [117].

Clinically, TLP allergy manifests as OAS, where affected individuals experience itching, tingling, or mild swelling of the lips, mouth, and throat after consuming TLP-containing foods like certain fruits (e.g., apples, kiwis, or peaches) or nuts [169]. More severe reactions, though less common, include urticaria, gastrointestinal symptoms (nausea, abdominal pain, or diarrhea), and respiratory distress. In rare cases, anaphylaxis may occur, especially in sensitized individuals with high exposure [173,174]. Symptoms are often seasonal, coinciding with the pollination periods of tree or grass species that express TLP, and are exacerbated by co-factors like exercise or alcohol consumption [171].

6.6. β -1,3-Glucanases

β -1,3-glucanases are hydrolytic enzymes that catalyze the breakdown of β -1,3-glucan, a polysaccharide component of fungal cell walls and other structural carbohydrates [175]. These enzymes are part of the glycoside hydrolase family and exhibit a conserved β -barrel structure typical of hydrolytic enzymes. These enzymes are widely present in plants, fungi, bacteria [176], and also some invertebrates such as house dust mites (*Dermatophagoides* spp.) [177]. β -1,3-glucanases belong to the PR-2 protein family and are induced in response to biotic stresses such as fungal infections. β -1,3-glucanases are also involved in developmental processes, such as cell wall remodeling during growth and germination [175].

Pollen is a significant source of β -1,3-glucanase allergens, particularly from grass species (e.g., timothy grass, Bermuda grass) and certain trees, such as birch and olive. The prevalence of sensitization to β -1,3-glucanases varies geographically and depends on regional flora [178]. In temperate regions, grass pollen β -1,3-glucanases are common sensitizers, contributing to the high rates of seasonal allergic rhinitis and asthma. In Mediterranean areas, olive pollen β -1,3-glucanases play a prominent role, while birch pollens are significant allergens in Northern and Central Europe [179]. The prevalence of

cross-reactivity with fungal allergens may also be higher in areas with humid climates, where fungal spores are abundant [180].

Allergens from the β -1,3-glucanase protein family are found in both pollens and plant-based foods, contributing to respiratory and food-related allergic reactions [44]. Notable examples from pollens include Phl p 2 from timothy grass and Cyn d 2 from Bermuda grass, as well as tree pollen allergens like Ole e 9 from olive, Hev b 2 from the rubber, Bet v 2 from birch, Fra e 9 from ash, and Cup a 2 from Arizona cypress. In foods, β -1,3-glucanases are represented by Mus a 5 from banana, Act d 3 from kiwi, and Sol t 3 from tomato, among others [44,181].

Allergy to β -1,3-glucanases typically manifests as respiratory symptoms, including allergic rhinitis, sneezing, nasal congestion, and asthma; these reactions are particularly prominent during pollen seasons when exposure to allergenic pollens is highest [120]. Ingested β -1,3-glucanases can lead to oral itching, mild swelling, and discomfort. Systemic reactions, such as urticaria or even anaphylaxis, though rare, may occur in highly sensitized individuals or when cofactors like exercise or alcohol are involved [182]. β -1,3-glucanases are also involved in latex-banana (or latex-fruit) syndrome, a cross-reactivity phenomenon where individuals allergic to latex may react to foods like bananas, avocados, and kiwis due to shared allergenic proteins [183].

6.7. Isoflavonoid Reductases (IFRs)

Isoflavonoid reductases (IFRs) are a group of enzymes belonging to the short-chain dehydrogenase/reductase (SDR) family [184]. These enzymes play a critical role in the biosynthesis of isoflavonoids and related compounds, which are vital secondary metabolites in plants [185]. Isoflavonoids contribute to plant defense by acting as phytoalexins, antimicrobial compounds synthesized in response to pathogen attack [184].

PFAS caused by IFRs is most prevalent in temperate regions where exposure to pollen allergens such as Bet v 6 (birch) and Ole e 12 (olive) is high. In Northern and Central Europe, birch pollen is a major trigger, leading to frequent cross-reactivity with foods like apple, carrot, and peach. The Mediterranean region sees significant sensitization to olive and ash pollens, with related reactions to persimmon, citrus fruits, and tomatoes [100]. In East Asia, birch pollen contributes to PFAS alongside regional foods like litchi and citrus, while South America and Africa experience lower birch exposure but report PFAS due to olive and cypress pollens in Mediterranean-like climates [55].

The IFRs from pollens include Bet v 6 from birch, Cor a 6 from hazel, and Ole e 12 from olive. In foods, IFR allergens include Cit s IFR from orange, Lit c IFR from litchi, Pyr c 5 from pear, and Dau c 5 from carrot [44]. Additional sources include peach, apple, persimmon, bell pepper, potato, and tomato, which are associated with PFAS, particularly in individuals sensitized to IFRs in pollens like birch or ash [127].

IFR allergens can trigger respiratory symptoms such as allergic rhinitis, nasal congestion, and asthma when inhaled as pollen particles [44]. Food sources of IFR-like proteins, such as soybeans, peanuts, and other legumes, can induce symptoms ranging from OAS to systemic reactions like urticaria, gastrointestinal distress, and anaphylaxis in sensitized individuals. Cross-reactivity with other legumes or foods containing similar proteins may exacerbate allergic responses, particularly in individuals with a primary sensitization to peanut or soybean allergens [186].

7. PFAS Diagnosis

Diagnosis of PFAS involves a combination of clinical history, physical examination, and confirmatory testing. A thorough patient history is the cornerstone of diagnosis and should focus on the timing and nature of symptoms, the specific foods involved, and

any seasonal patterns that suggest pollen sensitization [44]. Commonly implicated foods include apples, peaches, cherries, carrots, celery, and nuts, depending on the pollen to which the patient is sensitized.

Skin prick testing (SPT) and serum-specific IgE testing are valuable tools for identifying pollen sensitization. Extracts from pollens and suspected foods can be used to confirm cross-reactivity. However, in some cases, commercial food extracts may not contain the heat-labile proteins responsible for PFAS symptoms, necessitating testing with fresh food preparations (the “prick-to-prick” method) [187].

The advent of component-resolved diagnostics (CRD) has revolutionized the diagnosis of PFAS by allowing for the detection of IgE to specific allergenic proteins rather than whole extracts [119]. For example, testing for sensitization to Bet v 1, the major birch allergen, can help identify individuals at risk for PFAS to related foods like apples and carrots. Similarly, testing for profilins (e.g., Phl p 12, a grass pollen profilin) or isoflavonoid reductases (e.g., Bet v 6) can provide insights into the patient’s cross-reactivity profile.

Figure 4 illustrates a flowchart outlining a structured step-by-step diagnosis algorithm for PFAS, designed to guide clinicians through the evaluation process, ensuring accurate diagnosis and differentiation from other conditions [98,188].

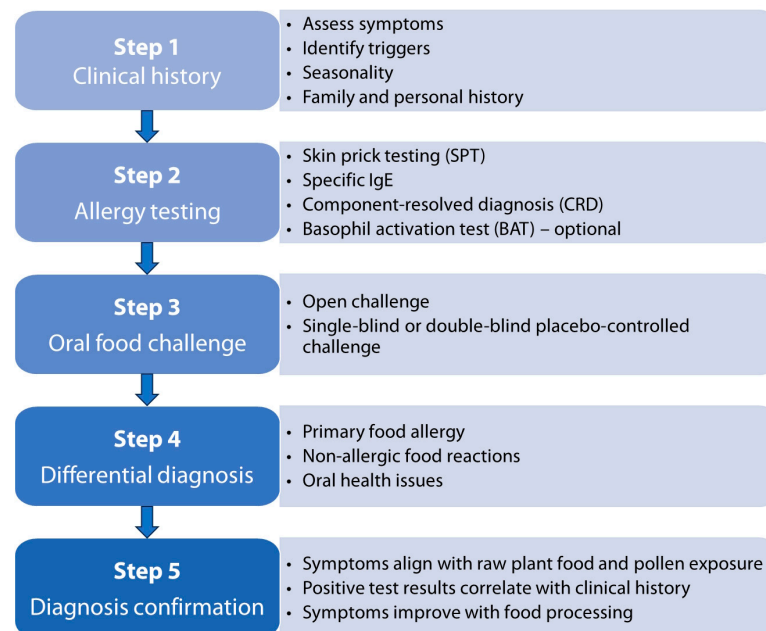


Figure 4. PFAS diagnosis flowchart. The flowchart illustrates a structured approach for clinicians to evaluate and confirm the diagnosis of pollen–food allergy syndrome (PFAS).

7.1. Skin Prick Testing (SPT)

Skin prick testing (SPT) is a key diagnostic tool for identifying immunoglobulin E (IgE)-mediated allergic reactions, including PFAS [98]. SPT provides a reliable, minimally invasive method to confirm sensitization to specific pollens and foods in patients presenting with symptoms like oral itching, swelling, or systemic reactions following ingestion of certain foods [189]. The technique is particularly valuable in PFAS cases because it can identify the primary pollen allergen responsible for cross-reactivity and assess the patient’s risk profile for food allergens. The European Academy of Allergy and Clinical Immunology (EAACI) strongly recommends skin prick testing and/or serum-specific IgE measurement as first-line diagnostic tools for patients with a history suggestive of IgE-mediated food allergy [98].

SPT involves introducing a small amount of allergen extract into the superficial layers of the skin, typically on the forearm or back, using a sterile lancet. The procedure begins with the application of control solutions: a positive control (histamine) to confirm the skin’s reactivity and a negative control (saline or glycerin) to rule out non-specific skin irritation. Allergen extracts from relevant pollens (e.g., birch, grass, ragweed) and foods (e.g., apple, peach, hazelnut) are then applied in separate spots. After 15–20 min, the wheal and flare are measured. A positive result is indicated by a wheal diameter of at least 3 mm larger than the negative control [189,190]. In PFAS, SPT often reveals sensitization to pollens with corresponding reactions to related food extracts, confirming the cross-reactivity underlying the syndrome [191].

In PFAS diagnosis, commercial food extracts used in SPT may not always contain the heat-labile proteins responsible for allergic reactions, such as PR-10 proteins or profilins [192,193]. These proteins are easily degraded during food processing and storage, making the extracts less reliable for identifying food-related allergies. To address this limitation, fresh food testing, also known as the “prick-to-prick” method, is commonly employed. In this technique, a sterile lancet is first pricked into a piece of the suspected fresh food (e.g., raw apple or peach) and then applied to the patient’s skin [187]. Fresh food testing is particularly effective for detecting PFAS-related allergens, as it ensures that the relevant proteins remain intact and available for testing [192]. This method complements testing with commercial extracts and improves diagnostic accuracy, especially in cases where patients report symptoms but commercial extracts yield negative results [187].

SPT results for PFAS must be interpreted carefully to differentiate between primary food allergies and cross-reactive sensitivities. For example, a positive test to birch pollen (Bet v 1) accompanied by reactions to apple, carrot, or hazelnut suggests PFAS rather than a primary food allergy. Similarly, sensitization to grass pollen (Phl p 12) with reactions to melon or tomato points to profilin cross-reactivity. Conversely, strong reactions to specific foods without associated pollen sensitization may indicate a primary food allergy unrelated to PFAS.

In some cases, component-resolved diagnostics (CRD) may be used alongside SPT to measure specific IgE to individual allergenic proteins, such as Bet v 1 (birch), Mal d 1 (apple), or Api g 1 (celery). This approach provides detailed insights into the cross-reactivity mechanisms driving PFAS and helps tailor management strategies [98].

The strengths and limitations of skin prick testing (SPT) are summarized in Table 2, providing a clear comparison of its advantages and challenges in diagnosing PFAS.

Table 2. Strengths and limitations of skin prick testing for PFAS [115,187,190,194–196].

Category	Description	Details/Insights
Strengths		
<i>Rapid results</i>	SPT provides immediate feedback, allowing clinicians to correlate findings with the patient’s clinical history during the same visit.	Results are available within 15–20 min, making it an efficient diagnostic tool.
<i>Minimally invasive</i>	The test is simple, safe, and well-tolerated by most patients.	Requires only a small lancet and allergen extract, with minimal discomfort for the patient.
<i>Broad applicability</i>	SPT can assess sensitization to a wide range of pollens and foods in a single session, making it a comprehensive diagnostic tool for PFAS.	Ideal for identifying multiple allergens simultaneously, including pollens and related foods.
<i>High sensitivity</i>	When combined with fresh food testing, SPT achieves high sensitivity for detecting relevant allergens in PFAS.	Fresh food testing helps identify heat-labile proteins like PR-10 proteins and profilins not always detected by extracts.
<i>Cost-effective</i>	SPT is a relatively low-cost diagnostic tool compared to molecular diagnostics or in vitro IgE testing.	Widely available in clinical settings.
<i>Non-invasive follow-up</i>	Enables ongoing monitoring of sensitization patterns without invasive procedures.	Can track allergen changes in response to therapy or environmental shifts.

Table 2. Cont.

Category	Description	Details/Insights
Limitations		
<i>False negatives</i>	Heat-labile proteins in PFAS, such as PR-10 proteins and profilins, may degrade in commercial extracts, leading to false negatives.	Fresh food testing is essential to overcome this limitation.
<i>Non-specific reactivity</i>	Non-specific skin reactions or dermographism can complicate interpretation, necessitating careful control comparisons.	Negative and positive controls are critical for accurate interpretation.
<i>Requires expertise</i>	Accurate interpretation of SPT results demands expertise to distinguish between primary sensitizations and cross-reactive allergies.	Specialized training is needed to correlate results with clinical history and dietary triggers.
<i>Limited specificity</i>	Positive SPT results indicate sensitization but do not always confirm clinical allergy, as some sensitized individuals may remain asymptomatic.	Additional diagnostics, such as oral food challenges, may be needed to confirm clinical relevance.
<i>Risk of systemic reactions</i>	Rarely, SPT may trigger systemic allergic reactions, especially in highly sensitized individuals.	Emergency medications (e.g., epinephrine) should be readily available during testing.
<i>Geographic variability</i>	Allergen extracts may not represent local or regional allergen sources accurately, leading to incomplete diagnostic coverage.	Custom extracts may be needed for certain endemic allergens.

A negative SPT or specific IgE result is typically associated with high sensitivity and strong negative predictive value (NPV), making these tests essential tools for ruling out food allergies [98]. This is especially true when high-quality allergen extracts are used and the patient has no history of clinical reactions to the suspected food. However, these tests are not infallible, and their results must always be considered in the context of the patient’s clinical history and overall presentation. Therefore, in patients with a strongly suggestive history of food allergy, a negative test result should not be relied upon to exclude the diagnosis outright [98]. Factors such as the age of the patient, the specific food allergen, and the presence of co-factors (e.g., exercise or alcohol) that might modulate allergic responses need to be taken into account [82]. The diagnostic performance of tests also varies depending on the allergen and the patient’s age. For instance, younger children often have lower levels of allergen-specific IgE that still correlate with clinical allergy, while older individuals may show greater cross-reactivity due to conditions like pollen–food allergy syndrome. For example, peanut-specific IgE tests have been found to have higher specificity in younger children, whereas Ara h 2-specific IgE tests are more accurate in adults [197]. This difference may stem from the higher prevalence of primary peanut allergy in children compared to the greater occurrence of cross-reactive pollen–food allergy syndrome in older individuals [60]. Such variability underscores the importance of age-specific considerations when interpreting test results.

Moreover, while diagnostic cutoffs for IgE levels or wheal sizes in SPT have been developed based on research studies and meta-analyses, these thresholds should not be applied rigidly in clinical practice [194,197,198]. They are better used as guidance to inform the likelihood of an allergy rather than as definitive decision points. Extrapolating cutoffs across different patient populations or clinical scenarios requires caution, as variations in local allergens, individual immune responses, and test protocols can influence diagnostic accuracy [98].

In summary, while negative SPT or specific IgE results are valuable for excluding food allergy in many cases, they are not absolute. The interpretation of these results requires careful consideration of the clinical history, patient-specific factors, and the broader diagnostic context. Clinicians should use diagnostic thresholds as flexible tools rather than definitive answers, ensuring that allergy evaluations remain patient-centered and adaptable to individual needs [98].

The results of SPT play a critical role in guiding dietary recommendations and allergen avoidance strategies for PFAS patients. For example, individuals with confirmed birch pollen sensitivity and positive SPT to apple, hazelnut, and carrot may be advised to avoid these foods in raw form but tolerate them when cooked, as heat denatures PR-10

proteins [98,188]. Patients with profilin sensitivity may need broader dietary modifications due to profilins' widespread presence in plants. Additionally, SPT results can inform decisions regarding allergen immunotherapy (AIT), targeting the primary pollen allergen to reduce cross-reactive food symptoms.

7.2. Component-Resolved Diagnostics (CRD)

Component-resolved diagnosis (CRD) is a cutting-edge diagnostic tool that can identify specific allergenic proteins to which a patient is sensitized. Unlike traditional diagnostic methods, such as whole allergen extracts used in SPT or specific IgE tests, CRD focuses on individual allergenic molecules. This approach is particularly valuable in PFAS, where cross-reactivity between structurally similar proteins in pollens and plant-based foods is a key feature [138]. By identifying the precise protein responsible for sensitization, CRD provides greater diagnostic accuracy, enabling personalized management strategies for patients.

CRD relies on advanced molecular diagnostic platforms that measure specific IgE against individual allergenic components, enabling precise identification of sensitizations that traditional methods using whole allergen extracts may miss. While there are several platforms available for component-resolved diagnostics, ImmunoCAP, ISAC, and ALEX are among the most widely used. These platforms employ advanced technologies to offer valuable insights into the mechanisms of allergic responses and cross-reactivity [119,137,138].

ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden) is a singleplex diagnostic assay that tests for specific IgE to a single allergen or allergenic component per test [199]. It uses a solid-phase system where allergens are immobilized on a cellulose sponge matrix. This platform provides quantitative results expressed in kU/L, allowing clinicians to assess the degree of sensitization and its clinical significance. ImmunoCAP is highly sensitive and specific, making it ideal for targeted testing and long-term monitoring of IgE levels [200]. However, its singleplex nature means it is less efficient for patients with complex allergy profiles requiring multiple tests [190].

ISAC (Immuno Solid-Phase Allergen Chip; ThermoFisher Scientific, Waltham, MA, USA) is a multiplex diagnostic platform that tests for IgE to over 100 allergenic components simultaneously [201]. It uses a microarray chip with purified allergens immobilized on its surface. Requiring only a small amount of serum, ISAC provides a semi-quantitative profile of sensitizations, making it particularly useful for patients with polysensitization or unclear allergic triggers. Its ability to test for panallergens like PR-10 proteins, profilins, and LTPs helps identify cross-reactivity patterns. However, ISAC results are semi-quantitative, meaning they are less precise than ImmunoCAP's fully quantitative measurements [202].

ALEX (Allergy Xplorer, MacroArray Diagnostics GmbH (MADx), Vienna, Austria) is another multiplex diagnostic platform that tests for IgE against more than 300 allergens, combining whole allergen extracts and molecular components. Unlike ISAC, ALEX includes cross-reactivity inhibition, which minimizes false positives from panallergens like profilins and CCDs (cross-reactive carbohydrate determinants) [201]. This feature enhances specificity and makes ALEX particularly valuable for distinguishing primary sensitizations from cross-reactivity [203]. While results are semi-quantitative, ALEX integrates comprehensive allergen profiling with user-friendly data presentation, making it a powerful tool for complex allergy cases [204].

These diagnostic methods, each with its distinct strengths and limitations, play a complementary role in the comprehensive evaluation of allergies. By leveraging their unique features, clinicians can achieve a more accurate and tailored approach to diagnosis. For an in-depth comparison of their characteristics, practical applications, and limitations, please refer to Table 3 below.

Table 3. Comparison of ImmunoCAP, ISAC, and ALEX [98,119,138,190,202,205].

Heading	ImmunoCAP	ISAC (Immuno Solid-Phase Allergen Chip; ThermoFisher Scientific, Waltham, MA, USA)	ALEX (Allergy Xplorer)
How It Works	Singleplex assay that measures IgE to one allergen or component per test.	Multiplex assay testing IgE to > 100 allergenic components on a microarray chip.	Multiplex assay testing IgE to > 300 whole allergens and molecular components on an allergen array.
	Uses a solid-phase system with allergens immobilized on a cellulose sponge matrix.	Uses purified allergens immobilized on a chip, requiring minimal serum (20–30 µL).	Integrates whole extracts and components with cross-reactivity inhibition for higher specificity.
	Results are quantitative (kU/L).	Results are semi-quantitative (fluorescence intensity levels).	Results are semi-quantitative and integrate cross-reactivity adjustments.
Advantages			
Quantitative results	Provides precise measurements of IgE levels, helping assess sensitization and risk.	Semi-quantitative results allow broad allergen screening and cross-reactivity insights.	Semi-quantitative results combined with inhibition testing improve specificity for genuine sensitization.
Comprehensive testing	Wide library of allergens, including region-specific ones.	Simultaneous testing for > 100 allergenic components across pollens, foods, and other sources.	Tests > 300 allergens, covering both whole extracts and components for comprehensive profiling.
Sensitivity and specificity	High sensitivity and specificity for targeted allergens.	Ideal for identifying cross-reactivity due to panallergens like PR-10, profilins, and LTPs.	High specificity through cross-reactivity inhibition technology.
Ease of use	Widely available, standardized, and reproducible across labs.	Requires minimal serum and provides a complete sensitization overview.	User-friendly data presentation with clear insights into primary and cross-reactive sensitizations.
Limitations			
Cost	Can be expensive for multiple allergens or components.	Expensive but cost-effective for complex allergy cases.	Relatively expensive but efficient for patients with complex or multiple suspected allergies.
Result format	Quantitative results are easy to interpret.	Semi-quantitative results require experienced interpretation to correlate with clinical relevance.	Semi-quantitative results may lack the precision needed for exact risk assessment.
Component limitations	Limited to clinician-selected allergens or components; rare ones may be unavailable.	Does not include all region-specific allergens, limiting coverage in some cases.	Some rare or region-specific allergens may be absent.
Serum requirement	Requires a larger volume of serum for testing multiple allergens.	Requires minimal serum (20–30 µL).	Requires a low volume of serum (100 µL).
Applications in PFAS			
Identifying panallergens	Effective for targeted testing of panallergens like PR-10 proteins, profilins, and LTPs.	Simultaneously identifies sensitization to multiple panallergens like PR-10 proteins, profilins, and LTPs.	Covers a wide range of panallergens, integrating whole extracts and components for detailed insights.
Primary vs. cross-reactivity	Differentiates primary food allergies from cross-reactivity with pollens.	Broad allergen panel helps identify patterns of cross-reactivity across multiple allergen sources.	Combines whole extracts and components to distinguish primary sensitization from cross-reactivity.
Risk stratification	Quantitative results enable detailed risk assessment (e.g., <i>Ara h 2</i> for severe peanut allergy).	Helps determine risk based on allergen stability (e.g., PR-10 for mild symptoms, LTPs for systemic reactions).	Identifies risk by combining sensitization profiles with cross-reactivity inhibition for stability insights.
Guiding dietary advice	Ideal for providing specific advice based on IgE levels to individual allergens.	Identifies panallergen sensitization, enabling tailored dietary recommendations (e.g., raw vs. cooked tolerance).	Integrates sensitization profiles to guide personalized dietary and exposure advice.
Supporting immunotherapy	Identifies primary allergens for allergen immunotherapy (e.g., <i>Bet v 1</i> for birch).	Helps guide allergen immunotherapy decisions by clarifying primary sensitization patterns.	Assists in AIT decisions by revealing sensitization to multiple relevant allergens.
Insights/Observations			
Special use cases	Ideal for monitoring sensitization over time or tracking therapy response.	Best for initial screening of complex cases or polysensitization.	Excellent for broad sensitization profiling in patients with multiple or unclear triggers.
Comparative edge	Best for precise, targeted testing and long-term tracking of IgE levels.	Ideal for comprehensive overviews in patients with complex allergic profiles.	Combines extract- and component-based testing with cross-reactivity inhibition for higher specificity.

7.3. Basophil Activation Test (BAT)

The Basophil Activation Test (BAT) is an advanced in vitro diagnostic tool used to assess allergic reactions mediated by IgE. BAT measures the activation of basophils in response to allergen exposure [206,207]. It involves exposing the patient's basophils, isolated from whole blood, to specific allergens under controlled laboratory conditions. Upon recognition of an allergen by IgE bound to the basophil surface, the cells become

activated and express markers such as CD63 and CD203c. The degree of basophil activation is quantified using flow cytometry, providing a clear indication of whether the allergen triggers a reaction. BAT can be used with both whole allergen extracts and purified molecular components, making it a versatile tool for assessing allergen-specific reactivity. BAT is particularly valuable in conditions like PFAS, where distinguishing between primary food allergies and cross-reactivity caused by pollens is essential [207].

BAT is particularly useful for differentiating cross-reactivity in PFAS from genuine primary food allergies [207]. For example, basophil activation in response to PR-10 proteins like Bet v 1 (birch pollen) may explain cross-reactivity with apple (Mal d 1), while no activation to primary food allergens indicates a lower likelihood of systemic reactions. BAT also provides insights into the potential severity of allergic reactions. Strong basophil activation in response to stable allergens like LTPs (e.g., Pru p 3 in peach) correlates with a higher risk of severe systemic reactions, while weaker activation to labile proteins like PR-10 typically reflects mild, localized symptoms [206]. By testing multiple allergens simultaneously, BAT can also map patterns of cross-reactivity in PFAS. For example, a patient sensitized to grass profilins (Phl p 12) may show basophil activation to profilins in foods like melon or tomato, supporting a diagnosis of PFAS. BAT offers greater specificity and higher negative predictive values compared to prick tests and specific IgE measurements, without compromising sensitivity or positive predictive values [194,207]. Therefore, BAT results can guide tailored dietary recommendations. For instance, a patient with significant basophil activation to raw apple but none to cooked apple may safely consume the cooked form, as heat denatures PR-10 proteins.

Despite its utility, BAT has several limitations that restrict its widespread use [208]. It requires specialized equipment, such as flow cytometers, and trained personnel, making it technically complex and less accessible than standard tests like ImmunoCAP or skin prick testing. Moreover, approximately 10% to 15% of individuals are “nonresponders”, meaning their basophils respond to non-IgE-mediated stimulants but not to IgE-mediated controls or allergens, rendering the test results uninterpretable [209]. The cost of BAT is also relatively high, which may limit its availability in routine clinical practice. Furthermore, BAT depends on fresh blood samples, as basophils are short-lived, presenting logistical challenges in sample collection and processing [210]. Another significant limitation is the lack of full standardization across laboratories, with varying protocols and thresholds, which can lead to inconsistent results and complicate interpretation [208].

7.4. Oral Food Challenge (OFC)

The oral food challenge (OFC) is a gold standard diagnostic procedure for confirming food allergies, including PFAS [98]. While diagnostic tests such as SPT and specific IgE measurements provide valuable insights into sensitization, they may not always correlate with clinical allergy.

OFC is designed to confirm whether a specific food triggers an allergic reaction, differentiating between clinically relevant allergies and asymptomatic sensitization. In PFAS, OFC can help:

- Verify clinical reactions: it determines whether symptoms like oral itching, tingling, or swelling occur after consuming a suspected food [211].
- Differentiate between allergies: OFC distinguishes PFAS, typically caused by labile proteins like PR-10 or profilins, from primary food allergies associated with stable proteins like storage proteins [212].
- Guide dietary management: by identifying tolerable foods, OFC helps avoid unnecessary dietary restrictions, improving patients' quality of life [98].

Oral food challenges (OFC) are categorized into three main types, each with unique advantages and limitations [212]. The open food challenge involves the patient consuming the suspected food in an unblinded manner under medical supervision. This approach is particularly suitable for PFAS, where subjective symptoms like oral itching are expected, and the risk of severe reactions is low. It is simple and cost-effective but may be influenced by patient or clinician bias due to the lack of blinding. In contrast, the single-blind food challenge conceals from the patient whether the food provided is the allergen or a placebo, reducing patient bias and yielding more objective results. The most rigorous method, the double-blind, placebo-controlled food challenge (DBPCFC), ensures that neither the patient nor the clinician knows whether the administered food is the allergen or a placebo. This approach is highly reliable for confirming PFAS and distinguishing it from primary food allergies. However, DBPCFC is time-intensive, resource-demanding, and typically reserved for cases where diagnostic uncertainty remains high [31,98,211].

The procedure for an OFC involves the controlled introduction of the suspected food in gradually increasing amounts while closely monitoring the patient for any symptoms. It begins with a pre-challenge evaluation, where a detailed clinical history and prior test results, such as SPT or specific IgE levels, are reviewed to confirm the necessity and safety of the challenge [213]. Contraindications, including uncontrolled asthma or recent severe allergic reactions, are ruled out. Baseline assessments of vital signs, such as heart rate, blood pressure, and oxygen saturation, along with an oral cavity examination, are conducted [213,214]. Foods are then prepared in their raw form, especially when PFAS is suspected, as heat-labile allergens like PR-10 proteins are often denatured during cooking. Standardized portions are used to ensure accurate dosing. During the incremental dosing phase, the patient consumes small, progressively larger amounts of the food at intervals of 15–30 min under medical supervision. This continues until either a typical serving size is reached or symptoms develop. After the final dose, the patient is observed for 1–2 h to monitor for delayed reactions. Throughout the procedure, symptoms such as oral itching, swelling, or gastrointestinal discomfort are carefully documented to assess the clinical relevance of the suspected food allergen [98].

The outcomes of an OFC in PFAS can vary depending on the patient's response to the suspected food allergen. A positive challenge occurs when symptoms are reproduced, confirming PFAS to the specific food. These symptoms typically include oral itching, mild swelling, and discomfort, characteristic of oral allergy syndrome, and are usually localized without systemic involvement. A negative challenge, where no symptoms are observed, indicates that the food is tolerable, providing reassurance to the patient and potentially expanding dietary options, especially in cases where unnecessary avoidance was previously practiced [194]. However, in rare cases, unexpected reactions such as systemic or severe responses may occur, particularly in patients sensitized to more stable allergens like LTPs or those with undiagnosed primary food allergies [215]. Therefore, emergency treatment must always be readily available during an OFC [55,216]. The main advantages and limitations of OFC in PFAS are summarized in Table 4.

The OFC not only confirms PFAS diagnosis but also plays a critical role in long-term management. By identifying foods that cause symptoms and those that are tolerable, OFC reduces dietary restrictions and improves patient confidence in managing their condition. It is particularly useful for reassuring patients about cooked or processed foods when reactions are limited to heat-labile allergens [98].

Therefore, the oral food challenge remains the definitive diagnostic tool for PFAS. While it is resource-intensive and requires meticulous planning, its ability to confirm clinical relevance, guide personalized dietary advice, and improve patient outcomes makes

it invaluable in PFAS care. When combined with molecular diagnostics like CRD, OFC ensures a comprehensive approach to diagnosing and managing food allergies [98,213].

Table 4. Advantages and limitations of OFC in PFAS [98,188,194,217,218].

Category	Details	Additional Insights
Advantages of OFC		
<i>High diagnostic accuracy</i>	OFC directly confirms the clinical relevance of sensitization detected through other diagnostic tests, making it the gold standard for PFAS.	Particularly valuable when SPT or specific IgE results are inconclusive.
<i>Personalized management</i>	Results guide tailored dietary recommendations, allowing patients to safely consume tolerable foods while avoiding problematic ones.	Reduces patient anxiety by clarifying which foods are safe in raw or cooked forms.
<i>Minimizing dietary restrictions</i>	OFC helps prevent unnecessary avoidance of foods, improving nutrition and quality of life.	Expands dietary options and supports balanced nutrition, especially in children and individuals with multiple food restrictions.
<i>Clarity in complex cases</i>	In polysensitized patients, OFC identifies specific triggers among cross-reactive allergens.	Essential for differentiating between cross-reactivity and primary food allergies.
Limitations of OFC		
<i>Resource-intensive</i>	OFC requires trained personnel, controlled environments, and significant time, making it less accessible in routine practice.	Requires specialized facilities, which may not be available in all healthcare settings.
<i>Risk of reactions</i>	Although PFAS reactions are typically mild, the risk of unexpected systemic reactions necessitates close medical supervision.	Emergency treatments such as epinephrine must be readily available.
<i>Subjectivity</i>	Open challenges may introduce bias, particularly for subjective symptoms like itching or tingling.	Blinded challenges (e.g., single- or double-blind) can help reduce bias.
<i>Patient anxiety</i>	The prospect of consuming a suspected allergen can cause anxiety, which may complicate interpretation of symptoms.	Proper counseling and reassurance can help mitigate patient concerns before the challenge.

7.5. Exploratory Approaches in Food Allergy Testing

These exploratory and emerging methods complement traditional diagnostics, offering new avenues for understanding and managing food allergies, particularly in complex and polysensitized patients. While many approaches require further validation, they highlight the potential for personalized and precise diagnostic solutions in the future.

7.5.1. Mast Cell Activation Test (MAT)

Similar to the Basophil Activation Test (BAT), MAT measures in vitro activation of mast cells, either derived from mast cell lines or generated from peripheral blood hematopoietic stem cells, using flow cytometry to determine allergic responses. A key distinction is that MAT uses patient serum or plasma to sensitize the mast cells, enabling retrospective testing of stored samples, unlike BAT, which requires fresh blood. However, challenges include difficulty in isolating mast cells, high variability of primary cells, and lower sensitivity than BAT, making MAT particularly useful only as a secondary diagnostic option for basophil non-responders [197,217,219,220].

7.5.2. Allergen-Specific IgG₄ and IgA

Elevated levels of IgG₄ and IgA have been increasingly recognized as markers associated with immunological tolerance and the efficacy of oral immunotherapy (OIT) in managing food allergies. IgG₄, a unique subclass of IgG, plays a pivotal role in immune reg-

ulation. Unlike IgE, IgG₄ exhibits low affinity for Fc receptors on effector cells, preventing the activation of mast cells and basophils, and thereby mitigating allergic responses. IgG₄ is thought to act as a “blocking antibody” [221], competing with IgE for allergen binding and neutralizing allergens before they trigger an immune response. Increased levels of allergen-specific IgG₄ observed during successful OIT indicate a shift toward tolerance, with patients often experiencing reduced symptoms or complete desensitization [222,223].

Similarly, IgA, particularly secretory IgA (sIgA), is integral to mucosal immunity and has been implicated in the pathophysiology of food allergy tolerance. Found predominantly in mucosal tissues such as the gastrointestinal tract, sIgA can form immune complexes with allergens, reducing their ability to cross the epithelial barrier and trigger an allergic response [224]. Elevated sIgA levels have been linked to protective effects against food allergy development and improved outcomes in OIT. For instance, studies have shown that salivary IgA levels correlate with positive therapeutic responses in peanut allergy OIT [224,225].

The potential utility of measuring IgG₄ and IgA levels lies in their ability to serve as biomarkers for predicting and monitoring OIT success. By tracking the rise in these immunoglobulins during treatment, clinicians can assess the progression toward tolerance and adjust therapy accordingly. Furthermore, their presence may provide insights into the underlying mechanisms of immunological tolerance, offering avenues for developing novel therapeutic strategies [226].

However, it is important to note that elevated IgG₄ and IgA levels are not always definitive markers of tolerance. For example, IgG₄ can also be a bystander product of allergen exposure without directly contributing to desensitization [222,227]. Therefore, despite the potential role of IgG₄ in immunological tolerance and OIT response, EAACI does not recommend IgG₄ testing for the diagnosis of food allergy [228]. This stance reflects the fact that elevated IgG₄ levels are not specific to allergic conditions and may also be seen in individuals with frequent allergen exposure or tolerance. More research is needed to fully understand the interplay between these immunoglobulins and immune responses in food allergies. Nonetheless, their potential as diagnostic and therapeutic tools makes them promising candidates for improving allergy diagnosis and management.

7.5.3. Bead-Based Epitope Assays (BBEA)

BBEA represents a scalable, high-throughput platform for detecting IgE and IgG₄ binding to allergen epitopes [217]. By coupling allergen peptides to beads, this technology allows simultaneous testing of multiple allergens with minimal serum volumes. Sensitivity and specificity are high, particularly for well-characterized allergies like peanut. BBEA offers advantages in phenotypic stratification and severity prediction, but its reliance on precise prior knowledge of allergen epitopes and its limitation to sequential (not conformational) epitopes constrain its broader applicability. Combining BBEA with cellular assays and clinical history may enhance its utility [208,229].

7.5.4. Glycosylation Analysis

Glycosylation of allergens and IgE may influence cross-reactivity and allergy severity. For instance, cross-reactive carbohydrate determinants (CCDs) have been implicated in IgE cross-reactivity without clinical relevance [32]. However, for cases such as bee venom allergy, glycosylation of the major allergen Api m 1 increases its IgE epitopes, thereby increasing its allergenic activity [230]. Conversely, IgE glycosylation has been linked to allergen potency, but its role in distinguishing allergic from tolerant individuals remains unclear [231].

7.5.5. Microbiome Analysis

Altered compositions of the oral and gut microbiota have been increasingly associated with the development and persistence of food allergies, influencing immune responses and allergic disease trajectories. The gut microbiome plays a pivotal role in immune system development and regulation, with microbial metabolites like short-chain fatty acids (e.g., butyrate) shown to promote regulatory T-cell (Treg) differentiation and tolerance [232,233]. In food allergy, disruptions to microbial diversity—known as dysbiosis—have been linked to a skewed Th2 immune response, which promotes the production of IgE and the development of allergic sensitization [234].

Specific microbiome profiles have been observed in food-allergic individuals compared to non-allergic controls. For example, reduced abundances of beneficial genera such as *Prevotella* and *Bifidobacterium*, alongside an overrepresentation of potentially pro-inflammatory species like *Neisseria*, have been implicated in allergic conditions [235]. These findings highlight the potential for microbiome analysis to identify biomarkers of food allergy and possibly stratify patients based on disease severity or reaction thresholds. Moreover, variations in microbiota composition between high- and low-threshold allergic patients suggest that microbial profiles may influence the clinical manifestation of food allergies [236].

Despite these promising insights, significant challenges remain in applying microbiome analysis as a diagnostic tool. The complexity and variability of the microbiome, influenced by factors such as diet, age, ethnicity, medication use (e.g., antibiotics), and environmental exposures, make standardization difficult [237]. These variables introduce noise into microbiome studies, complicating the interpretation of findings and reducing reproducibility across populations and settings [238]. Additionally, the interdependent mechanisms between microbiota, host immune responses, and external factors are not yet fully understood, further limiting the clinical utility of microbiome analysis.

While microbiome analysis offers a fascinating avenue for understanding food allergies and exploring potential therapeutic targets, its role in diagnosis remains exploratory. Future advancements in technology, standardization protocols, and large-scale longitudinal studies will be crucial for unlocking its diagnostic and predictive potential. Until then, microbiome analysis is better suited as an adjunct to traditional diagnostic methods, providing complementary insights rather than serving as a stand-alone tool [217].

7.5.6. Artificial Intelligence (AI)

Artificial intelligence (AI) and machine learning (ML) are transforming the field of allergy diagnostics by leveraging their ability to analyze complex and multidimensional data sets with speed and precision [239]. Traditional diagnostic methods, while effective, often rely on linear relationships and predefined algorithms, which can be limiting when addressing the multifaceted nature of allergic diseases. AI, on the other hand, excels at identifying hidden patterns, integrating data from diverse sources, and making predictions that go beyond conventional approaches [240].

AI has demonstrated remarkable accuracy in identifying food allergies and predicting tolerance, making it a valuable tool for improving diagnostic precision and patient outcomes [241]. By analyzing data sets from omics technologies (e.g., genomics, proteomics, metabolomics), specific IgE profiles, and clinical histories, AI models can differentiate between primary sensitizations, cross-reactivity, and clinically irrelevant sensitizations [242]. This capability is particularly useful in complex cases, such as those involving polysensitized individuals or overlapping allergic conditions.

AI-powered clustering algorithms can categorize patients into distinct phenotypes based on their allergic profiles, reaction severities, and immunological markers [239]. For

instance, clustering techniques can separate patients with true peanut allergy from those with cross-reactive sensitization to birch pollen. This stratification not only aids in diagnosis but also informs personalized treatment plans, such as selecting candidates for AIT or tailoring dietary recommendations [243].

AI models are proving invaluable in predicting patient responses to interventions like OIT or elimination diets. By analyzing baseline variables such as cytokine levels, allergen-specific IgE concentrations, and microbiome composition, these models can identify individuals who are more likely to achieve tolerance or experience adverse effects. This predictive capability reduces trial and error in treatment, improving safety and efficiency [240].

AI is seamlessly integrating with advanced diagnostic platforms such as CRD, BAT, and epitope profiling. For example, machine learning algorithms have been applied to bead-based epitope assays to analyze allergen epitopes and predict severity of reactions [208]. Similarly, AI models can analyze data sets from microbiome studies to explore host-microbe interactions in allergy development.

Despite its potential, the implementation of AI in allergy diagnostics faces several challenges. High-quality data sets are essential for training robust models, yet data variability, limited sample sizes, and incomplete records can hinder performance [244]. Additionally, AI models require interpretability to ensure clinicians understand the reasoning behind predictions, fostering trust and reliability in clinical practice.

In the future, AI is expected to play a central role in allergy care, from early diagnosis to personalized management and monitoring of treatment outcomes. As more data becomes available and algorithms improve, AI-driven approaches will become an indispensable component of modern allergology.

8. PFAS Management

Managing PFAS requires a comprehensive and personalized approach, as this condition arises from complex cross-reactive mechanisms between pollen and food allergens. While PFAS symptoms are typically mild and localized, some patients may experience more severe reactions, particularly those sensitized to stable allergens like LTPs. The variability in symptom severity and the broad range of implicated allergens necessitate tailored strategies to ensure effective management and improve patients' quality of life.

Management of PFAS focuses on accurate diagnosis, symptom relief, and risk reduction. This includes strategies such as dietary modifications, pharmacotherapy, and in select cases, AIT. Advances in CRD have enhanced the precision of PFAS diagnosis, enabling clinicians to provide clearer guidance on safe food consumption. Education and counseling play an equally critical role, empowering patients to navigate their condition confidently and avoid unnecessary dietary restrictions that may lead to nutritional deficiencies or reduced quality of life.

By integrating current knowledge and best practices on PFAS management, this discussion aims to provide a roadmap for clinicians to optimize care for PFAS patients, addressing their unique needs and promoting long-term health and well-being.

8.1. Food Avoidance

Food avoidance is essential in managing food allergies, including PFAS. The primary goal of avoidance is to prevent the onset of allergic symptoms. However, unlike other food allergies, PFAS often involves heat-labile allergens such as PR-10 proteins and profilins, which are denatured by cooking. This makes the approach to avoidance in PFAS more nuanced, balancing the prevention of symptoms with maintaining a diverse and nutritionally adequate diet.

Approaches to food avoidance in PFAS involve tailoring strategies to the nature of the allergens and the patient's specific sensitivities [44,96,133,188]. For example, individuals sensitized to birch pollen who react to raw apples may tolerate baked apples or apple juice, while those reacting to raw carrots can consume them safely when cooked. This approach minimizes unnecessary dietary restrictions and helps maintain a diverse diet. Selective avoidance of trigger foods is also essential, with patients advised to avoid specific foods that elicit symptoms while continuing to eat those they tolerate. For instance, a patient reacting to peaches but tolerating pears and cherries can restrict peach consumption while keeping other stone fruits in their diet. It has also been shown that fruit peels contain a higher concentration of allergens than the pulp, so peeled fruit may be tolerated [245]. Detailed food diaries can help identify patterns and refine avoidance strategies. Patients with multiple pollen sensitivities may experience broader cross-reactivity, such as those allergic to birch, grass, and ragweed pollen reacting to a wider range of fruits and vegetables [97]. These cases may require more extensive avoidance plans informed by diagnostic tools like (AI-enhanced) CRD. However, for those sensitized to heat-stable allergens such as lipid transfer proteins (e.g., Pru p 3 in peach or Jug r 3 in walnut), both raw and cooked forms of the food can trigger systemic reactions. For such patients, strict avoidance is necessary as cooking does not neutralize these stable proteins.

Food avoidance in PFAS presents several challenges, with over-avoidance being a common issue. Patients may unnecessarily eliminate large food groups out of fear of symptoms, which can lead to nutritional deficiencies, particularly in vitamins and minerals like vitamin C and fiber that are abundant in fruits and vegetables. This over-restriction can also negatively impact quality of life, contributing to anxiety around eating or fear of public dining [246]. Education and reassurance are crucial to preventing over-avoidance and fostering a balanced approach. Another challenge involves hidden allergens in processed foods, such as fruit juices, purees, or salads, which may contain raw trigger foods like celery or apples [247]. Patients must be educated on reading labels and inquiring about ingredients, especially when dining out. Cultural and social factors further complicate food avoidance, as certain foods central to cultural traditions or social gatherings may be difficult to avoid or substitute. Supporting patients in navigating these situations is essential for maintaining their dietary needs and social participation while managing their condition effectively.

Therefore, the ultimate goal of food avoidance in PFAS is not complete elimination of foods but rather symptom management with minimal impact on quality of life. Avoidance strategies should be tailored to each patient's needs, accounting for symptom severity, cultural preferences, and nutritional requirements. Patients who can safely consume cooked or processed foods should be encouraged to do so, reducing unnecessary restrictions [246]. Additionally, introducing AIT for pollen allergies may reduce cross-reactivity over time, further alleviating the need for strict avoidance.

8.2. Pharmacological Treatment

Pharmacological treatment for PFAS primarily aims to manage symptoms and improve quality of life, particularly for patients experiencing frequent or severe reactions. However, even though PFAS symptoms are generally mild and localized, pharmacological interventions can be helpful in mitigating discomfort, especially when food avoidance alone is insufficient or impractical.

Oral antihistamines are the mainstay of pharmacological management in PFAS, similar to their role in other allergic conditions. Antihistamines primarily act as H1 receptor inverse agonists to block the effects of histamine at H1 receptors. Unlike traditional antagonists, which simply block a receptor from being activated by an agonist, an inverse agonist

actively reduces the receptor's intrinsic activity even in the absence of a natural ligand (like histamine) [248]. By blocking H1 histamine receptors, these medications effectively reduce symptoms such as itching, tingling, or mild swelling associated with OAS. They are fast-acting, widely available, and generally well-tolerated. Non-sedating second-generation antihistamines, such as loratadine, cetirizine, or fexofenadine, are preferred due to their favorable side effect profiles [31]. These medications are typically used on an as-needed basis before consuming known trigger foods or during peak pollen seasons when cross-reactivity tends to be heightened. Antihistamines are broadly classified into first-generation (sedating) and second-generation (non-sedating) agents, with the latter being preferred for PFAS due to their favorable safety and side-effect profiles. Table 5 provides an overview of commonly used H1 antihistamines, including their generation, receptor specificity, pharmacokinetics, sedation potential, and clinical applications in allergic diseases including PFAS.

Table 5. Overview of antihistamines acting on H1 receptors used in allergy management [249].

Drug Name	Generation	Formulation	Onset of Action	Duration of Action	Sedation Potential	Common Uses in Allergies
Diphenhydramine	First	Oral, Injectable	15–30 min	4–6 h	High	Acute allergic reactions, anaphylaxis adjunct
Chlorpheniramine	First	Oral	30 min	4–6 h	Moderate	Allergic rhinitis, mild allergic reactions
Hydroxyzine	First	Oral, Injectable	15–30 min	4–6 h	High	Anxiety-related itching, urticaria
Cetirizine	Second	Oral	1 h	24 h	Low	PFAS, allergic rhinitis, urticaria
Levocetirizine	Second	Oral	1 h	24 h	Very Low	PFAS, chronic urticaria, allergic rhinitis
Loratadine	Second	Oral	1–3 h	24 h	Minimal	PFAS, allergic rhinitis
Desloratadine	Second	Oral	1–3 h	24 h	Minimal	PFAS, chronic idiopathic urticaria
Fexofenadine	Second	Oral	1 h	24 h	None	PFAS, seasonal allergic rhinitis
Rupatadine	Second	Oral	1–2 h	24 h	Very Low	PFAS, chronic urticaria, allergic rhinitis
Bilastine	Second	Oral	1 h	24 h	None	PFAS, allergic rhinoconjunctivitis
Ebastine	Second	Oral	1–3 h	24 h	Low	Chronic urticaria, allergic rhinitis

For patients with persistent or more severe symptoms, short courses of topical corticosteroids may be considered to reduce inflammation and provide symptomatic relief, particularly when oral antihistamines alone are insufficient. These include corticosteroid mouth rinses (e.g., dexamethasone or betamethasone solutions) or corticosteroid sprays (e.g., fluticasone or budesonide), which can target inflammation directly in the oral cavity. These formulations are generally well-tolerated, with minimal systemic absorption when used as directed, making them a suitable option for managing localized symptoms such as oral itching, burning, or swelling [250]. Systemic corticosteroids, on the other hand, are rarely required in the management of PFAS because the symptoms are typically mild, transient, and limited to the oral cavity. The use of systemic corticosteroids, such as oral prednisolone, is generally reserved for more severe presentations, such as cases where reactions extend beyond the oral cavity, such as gastrointestinal symptoms (e.g., abdominal pain, nausea), significant angioedema, or systemic discomfort [251]. In these rare situations, a short course of systemic corticosteroids may help to rapidly reduce inflammation and alleviate symptoms. However, the risks of systemic side effects, including weight gain,

hyperglycemia, and adrenal suppression with prolonged use, must be carefully weighed against the benefits [252]. In clinical practice, systemic corticosteroids should only be used under close supervision, with particular attention to patients with comorbidities such as diabetes, osteoporosis, or hypertension, where corticosteroid use can exacerbate existing conditions. Furthermore, it is essential to counsel patients on the appropriate use of topical and systemic corticosteroids to minimize adverse effects and ensure effective symptom control [249]. Overall, while corticosteroids—both topical and systemic—play a limited role in PFAS management, they remain valuable adjuncts in specific clinical scenarios where inflammation leads to persistent discomfort or when severe allergic symptoms require more aggressive intervention.

Although systemic reactions are rare in PFAS, certain patients are at an increased risk and may require additional precautions. Individuals sensitized to heat-stable allergens, such as LTPs, are particularly vulnerable, as these allergens can remain intact even after food is cooked. Therefore, LTPs can trigger more severe and systemic reactions, including gastrointestinal distress, generalized urticaria, or anaphylaxis [141]. For patients with a history of systemic reactions or more severe allergic symptoms, the provision of an epinephrine auto-injector for emergency use is strongly recommended. This precaution is essential not only for individuals with LTP sensitivity but also for those with overlapping food allergies (e.g., to nuts, seeds, or shellfish) or conditions that place them at a higher risk of anaphylaxis, such as mast cell disorders or poorly controlled asthma [98]. In these cases, the potential for a systemic reaction escalates, necessitating preparedness for immediate intervention [98,188]. Epinephrine auto-injectors should be prescribed alongside thorough patient education on their proper use [253]. Patients should be instructed to recognize the early signs of anaphylaxis, such as widespread hives, angioedema, difficulty breathing, dizziness, or gastrointestinal symptoms, and to use the auto-injector promptly if these symptoms occur. Clinicians should emphasize the importance of carrying the auto-injector at all times, particularly when consuming raw plant-based foods that are known to trigger PFAS or in situations where access to emergency medical care may be delayed [98]. In addition to LTP-related risk, patients with PFAS who experience worsening symptoms over time or those with comorbid conditions that exacerbate allergic responses (e.g., exercise-induced food allergy or alcohol consumption) may also benefit from an individualized emergency action plan. Such a plan outlines specific steps to take during a reaction, including the administration of epinephrine, antihistamines, and seeking immediate medical attention [81]. Overall, while systemic reactions in PFAS remain uncommon, identifying at-risk individuals and ensuring appropriate preventive measures—such as prescribing epinephrine auto-injectors—are crucial for patient safety. This proactive approach helps mitigate the risk of severe reactions and equips patients to respond effectively to potentially life-threatening symptoms [254].

Omalizumab, a monoclonal antibody that targets IgE, has been explored as a potential treatment for PFAS, particularly in patients with severe or persistent symptoms. While direct studies on omalizumab for PFAS are limited, its efficacy in reducing IgE-mediated allergic responses suggests potential benefits [31]. In cases where cross-reactivity between pollens and foods results in systemic reactions or chronic symptoms, omalizumab may help by dampening the overall allergic response. Additionally, anecdotal and case-report-level evidence indicates that omalizumab can alleviate persistent PFAS symptoms in highly sensitized individuals [60,255].

However, managing PFAS with pharmacological options can be challenging due to the variability in symptom presentation and patient response. One of the primary challenges is ensuring adherence to treatment regimens, particularly with as-needed antihistamine use. Patients may underuse medications due to misconceptions about the severity of

their condition or overestimate their ability to avoid triggers [256,257]. Additionally, pharmacological treatments do not address the underlying sensitization or cross-reactivity driving PFAS, limiting their role to symptomatic relief.

8.3. Allergen Immunotherapy (AIT)

Allergen Immunotherapy (AIT) is a well-established treatment for allergic conditions such as allergic rhinitis, asthma, and insect venom allergies [258,259]. In recent years, its role in managing PFAS has gained attention, particularly for individuals whose symptoms significantly impact their quality of life. AIT offers the potential to address the underlying sensitization by modulating immune responses, reducing the severity of pollen-induced reactions, and potentially alleviating associated food allergies.

AIT involves exposing the patient to gradually increasing doses of the allergen, either subcutaneously (SCIT) or sublingually (SLIT), over time. It works by gradually desensitizing the immune system to specific allergens, altering the underlying immune response and inducing long-term tolerance [260]. The core mechanism involves a controlled exposure to increasing doses of allergens, which modulates the immune system in several stages:

1. **Shift in immune response:** during an allergic reaction, the immune system predominantly produces IgE antibodies, which bind to mast cells and basophils, triggering the release of histamine and other inflammatory mediators. AIT induces a class-switch in antibody production from allergen-specific IgE to IgG₄, a blocking antibody that prevents allergen-IgE binding, shifting the balance from a Th2-dominant response, characterized by IgE production, to a Th1-dominant response and Treg activation. This reduces the activation of mast cells and basophils. The production of blocking antibodies, such as IgG₄, plays a key role in neutralizing allergens before they can trigger IgE-mediated reactions [261,262].
2. **T-cell modulation:** AIT promotes the development of regulatory T cells (Tregs), which suppress allergic inflammation by releasing anti-inflammatory cytokines such as IL-10 and TGF- β . These cytokines reduce the activity of effector T-helper 2 (Th2) cells, which are responsible for producing IgE and driving allergic inflammation [260].
3. **Dendritic cell modulation:** dendritic cells exposed to allergens in the presence of AIT shift their cytokine production profile to favor tolerance rather than sensitization. This further supports the suppression of Th2 responses and enhances the induction of Tregs [262].
4. **Long-term tolerance:** over time, AIT leads to the reprogramming of the immune system, resulting in long-lasting tolerance to allergens even after discontinuation of treatment. This effect distinguishes AIT from symptomatic treatments like antihistamines [263].

In PFAS, AIT targeting the primary pollen allergen (e.g., birch or grass pollen) can desensitize the immune system to the cross-reactive proteins in foods, reducing both respiratory and food-related symptoms. Beyond its impact on respiratory symptoms, AIT has also been effective in reducing the severity of oral symptoms caused by cross-reactive food allergens, which is particularly beneficial for patients with significant dietary restrictions or persistent symptoms despite avoidance strategies [264].

Applications of AIT in PFAS primarily focus on addressing the underlying pollen sensitization that drives cross-reactivity with food allergens. Pollen-specific AIT, such as for birch or grass, is the most common approach. By targeting the immune response to pollens, AIT reduces reactivity to related food allergens. For instance, birch pollen AIT can alleviate symptoms triggered by PR-10 proteins found in foods like apples (Mal d 1), hazelnuts (Cor a 1), and carrots (Dau c 1) [265], while grass pollen AIT has been shown to reduce reactions to profilins in melons, tomatoes, and bananas [266]. Another study

demonstrated the effectiveness of SCIT with Japanese cedar pollen extract in patients allergic to Japanese cedar pollen and tomatoes. This treatment improved symptoms of both Japanese cedar pollen and tomato allergies. The beneficial effects were associated with a significant reduction in basophil activation [267]. However, a recent systematic review on SLIT and SCIT in birch pollen-allergic patients has not provided enough evidence to draw firm conclusions about its beneficial effects on birch pollen-related food allergy [264]. However, its efficacy in alleviating food-related symptoms caused by stable allergens is less established compared to its success with labile proteins like PR-10 or profilins [268].

Oral immunotherapy (OIT) offers a potential approach for managing PFAS, particularly in patients with persistent symptoms or systemic reactions to cross-reactive food allergens [269]. By gradually introducing small, controlled amounts of the allergenic food, OIT aims to desensitize the immune system, reducing symptom severity and reaction thresholds [270]. OIT can complement pollen-specific AIT by directly targeting problematic foods, expanding dietary options and improving quality of life [97,271]. However, challenges include the risk of allergic reactions during desensitization, the long-term commitment required for maintenance, and variable efficacy in PFAS-specific cases [60]. Despite these limitations, OIT represents a promising adjunctive therapy for select PFAS patients, with ongoing research needed to refine its application.

9. Conclusions

PFAS is a complex condition rooted in cross-reactivity between pollen allergens and structurally similar proteins in plant-based foods. While its symptoms are typically mild and localized, PFAS poses significant challenges for diagnosis and management due to the diverse range of implicated allergens and varying clinical presentations. Advances in diagnostic tools, such as CRD, OFC, and emerging techniques like BAT, have enhanced our ability to identify specific sensitizations and predict clinical relevance. These tools, combined with innovations like ImmunoCAP, ISAC, and ALEX, provide clinicians with a comprehensive understanding of patient-specific allergen profiles, improving diagnostic precision and guiding tailored management strategies.

The implicated allergens in PFAS belong to well-defined protein families, including PR-10 proteins, profilins, LTPs, TLPs, and IFRs. Each family contributes distinct biochemical properties influencing allergen stability and clinical reactivity. Labile proteins like PR-10 and profilins primarily cause localized oral symptoms, while stable proteins such as LTPs are more likely to induce systemic reactions. Understanding these protein families and their cross-reactivity with pollens is essential for accurate diagnosis, risk assessment, and management planning, particularly in tailored strategies.

The management of PFAS requires a multifaceted approach. Food avoidance remains an essential component of care, with emphasis on selective avoidance strategies that balance symptom prevention with the maintenance of nutritional adequacy and quality of life. Pharmacological treatments, including antihistamines and corticosteroids, play a crucial role in alleviating symptoms, while biologics like omalizumab hold promise for refractory or severe cases. AIT, particularly targeting primary pollen sensitizations, has emerged as an effective method to reduce both respiratory and food-related symptoms, offering hope for patients with significant dietary restrictions or persistent symptoms.

Despite these advancements, challenges persist. Over-avoidance of foods, the variability of patient responses to treatment, and the need for long-term adherence to therapies such as AIT highlight the importance of patient education and individualized care. Furthermore, emerging technologies, such as epitope mapping, microbiome analysis, and artificial intelligence, are reshaping our understanding of PFAS, offering opportunities for more precise diagnostics and personalized interventions.

Future research on PFAS should explore innovative management strategies tailored to improve patient outcomes and quality of life. One promising avenue is the development of personalized treatment plans that integrate allergen immunotherapy with dietary guidance, leveraging advances in molecular allergy diagnostics. Such approaches could help refine cross-reactivity risk assessment and enhance therapeutic effectiveness. Additionally, novel delivery methods for immunotherapy, including sublingual and epicutaneous routes, warrant further investigation for their potential to increase patient adherence and reduce adverse effects.

Raising awareness among healthcare providers is another critical focus area. Comprehensive training programs and continuing education initiatives can equip clinicians with the knowledge and tools to better diagnose and manage PFAS. These efforts should emphasize the importance of recognizing subtle clinical presentations and understanding the impact of regional and seasonal variations in allergen exposure. Enhanced awareness and education will not only improve patient care but also foster multidisciplinary collaborations, paving the way for more holistic and innovative approaches to managing this complex syndrome.

As research continues to uncover the immunological mechanisms driving PFAS, there is potential to develop more targeted therapies and predictive tools. Collaborative efforts between clinicians, researchers, and patients are essential to improve outcomes and reduce the burden of PFAS on individuals' health and well-being. This comprehensive approach underscores the importance of integrating current knowledge with evolving innovations, ensuring that PFAS management continues to advance in both effectiveness and accessibility.

Author Contributions: Conceptualization, L.H., C.F.B. and C.P.; Methodology, L.H. and C.F.B.; Resources, C.P.; Writing—original draft preparation, L.H., C.F.B., C.U., S.I.M., E.-L.Z., R.-I.Z., E.C. and M.G.; Writing—review and editing, L.H., C.F.B., C.U., S.I.M., E.-L.Z., R.-I.Z., E.C. and M.G.; Visualization, L.H., C.F.B. and E.C.; Supervision, L.H. and C.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: We would like to acknowledge Victor Babeş University of Medicine and Pharmacy Timișoara for their support in covering the costs of publication for this research paper.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Douwes, J.; Pearce, N. Epidemiology of Respiratory Allergies and Asthma. In *Handbook of Epidemiology*; Springer: New York, NY, USA, 2014; pp. 2263–2319. [[CrossRef](#)]
2. Bousquet, J.; Anto, J.M.; Bachert, C.; Baiardini, I.; Bosnic-Anticevich, S.; Walter Canonica, G.; Melén, E.; Palomares, O.; Scadding, G.K.; Togias, A.; et al. Allergic Rhinitis. *Nat. Rev. Dis. Prim.* **2020**, *6*, 95. [[CrossRef](#)]
3. Suanno, C.; Aloisi, I.; Fernández-González, D.; Del Duca, S. Pollen Forecasting and Its Relevance in Pollen Allergen Avoidance. *Environ. Res.* **2021**, *200*, 111150. [[CrossRef](#)]
4. Raith, M.; Swoboda, I. Birch Pollen-The Unpleasant Herald of Spring. *Front. Allergy* **2023**, *4*, 1181675. [[CrossRef](#)] [[PubMed](#)]
5. Bastl, M.; Bastl, K.; Dirr, L.; Berger, M.; Berger, U. Variability of Grass Pollen Allergy Symptoms throughout the Season: Comparing Symptom Data Profiles from the Patient's Hayfever Diary from 2014 to 2016 in Vienna (Austria). *World Allergy Organ. J.* **2021**, *14*, 100518. [[CrossRef](#)]
6. Chen, K.-W.; Marusciac, L.; Tamas, P.T.; Valenta, R.; Panaitescu, C. Ragweed Pollen Allergy: Burden, Characteristics, and Management of an Imported Allergen Source in Europe. *Int. Arch. Allergy Immunol.* **2018**, *176*, 163–180. [[CrossRef](#)]

7. Oh, J.-W. Pollen Allergy in a Changing Planetary Environment. *Allergy Asthma Immunol. Res.* **2022**, *14*, 168–181. [[CrossRef](#)] [[PubMed](#)]
8. D'Amato, G.; Annesi-Maesano, I.; Urrutia-Pereira, M.; Del Giacco, S.; Rosario Filho, N.A.; Chong-Neto, H.J.; Solé, D.; Ansotegui, I.; Cecchi, L.; Sanduzzi Zamparelli, A.; et al. Thunderstorm Allergy and Asthma: State of the Art. *Multidiscip. Respir. Med.* **2021**, *16*, 806. [[CrossRef](#)]
9. Bonini, M.; Monti, G.S.; Pelagatti, M.M.; Ceriotti, V.; Re, E.E.; Bramè, B.; Bottero, P.; Tosi, A.; Vaghi, A.; Martelli, A.; et al. Ragweed Pollen Concentration Predicts Seasonal Rhino-Conjunctivitis and Asthma Severity in Patients Allergic to Ragweed. *Sci. Rep.* **2022**, *12*, 15921. [[CrossRef](#)]
10. Tameeris, E.; Bohnen, A.M.; Bindels, P.J.E.; Elshout, G. Clinical Response to Varying Pollen Exposure in Allergic Rhinitis in Children in The Netherlands. *BMC Pediatr.* **2023**, *23*, 258. [[CrossRef](#)] [[PubMed](#)]
11. D'Amato, G.; Murrieta-Aguttes, M.; D'Amato, M.; Ansotegui, I.J. Pollen Respiratory Allergy: Is It Really Seasonal? *World Allergy Organ. J.* **2023**, *16*, 100799. [[CrossRef](#)]
12. D'Amato, G.; Chong-Neto, H.J.; Monge Ortega, O.P.; Vitale, C.; Ansotegui, I.; Rosario, N.; Haahtela, T.; Galan, C.; Pawankar, R.; Murrieta-Aguttes, M.; et al. The Effects of Climate Change on Respiratory Allergy and Asthma Induced by Pollen and Mold Allergens. *Allergy* **2020**, *75*, 2219–2228. [[CrossRef](#)] [[PubMed](#)]
13. Weber, R.W. Current and Future Effects of Climate Change on Airborne Allergens. *Curr. Allergy Asthma Rep.* **2024**, *24*, 373–379. [[CrossRef](#)] [[PubMed](#)]
14. Von Hertzen, L.C.; Haahtela, T. Asthma and Atopy—The Price of Affluence? *Allergy* **2004**, *59*, 124–137. [[CrossRef](#)] [[PubMed](#)]
15. Asher, M.I.; García-Marcos, L.; Pearce, N.E.; Strachan, D.P. Trends in Worldwide Asthma Prevalence. *Eur. Respir. J.* **2020**, *56*, 2002094. [[CrossRef](#)]
16. Murrison, L.B.; Brandt, E.B.; Myers, J.B.; Hershey, G.K.K. Environmental Exposures and Mechanisms in Allergy and Asthma Development. *J. Clin. Investig.* **2019**, *129*, 1504–1515. [[CrossRef](#)] [[PubMed](#)]
17. Ozoh, O.B.; Aderibigbe, S.A.; Ayuk, A.C.; Desalu, O.O.; Oridota, O.E.; Olufemi, O.; Egbagbe, E.; Babashani, M.; Shopeyin, A.; Ukwaja, K.; et al. The Prevalence of Asthma and Allergic Rhinitis in Nigeria: A Nationwide Survey among Children, Adolescents and Adults. *PLoS ONE* **2019**, *14*, e0222281. [[CrossRef](#)]
18. Nathan, R.; Meltzer, E.; Derebery, J.; Campbell, U.; Stang, P.; Corrao, M.; Allen, G.; Stanford, R. Prevalence of Nasal Symptoms in the United States: Findings from the Burden of Allergic Rhinitis in America Survey. *Allergy Asthma Proc.* **2008**, *29*, 600–608. [[CrossRef](#)] [[PubMed](#)]
19. Silva, D.L.; de Barayazarra, S.; Valero, A.; Garcia, E.; Uriarte, S.; Peñaranda, A.; Chapman, E.; Garcia, M.B.; Ocampo, J.; Valencia, V.; et al. Control of Allergic Rhinitis in Four Latin American Countries: Rinola Study. *Front. Allergy* **2022**, *3*, 980515. [[CrossRef](#)] [[PubMed](#)]
20. Katelaris, C.H.; Lai, C.K.W.; Rhee, C.-S.; Lee, S.H.; De Yun, W.; Lim-Varona, L.; Quang, V.T.; Hwang, J.; Singh, H.; Kim, J.; et al. Nasal Allergies in the Asian-Pacific Population: Results from the Allergies in Asia-Pacific Survey. *Am. J. Rhinol. Allergy* **2011**, *25* (Suppl. 1), S3–S15. [[CrossRef](#)] [[PubMed](#)]
21. Ha, J.; Lee, S.W.; Yon, D.K. Ten-Year Trends and Prevalence of Asthma, Allergic Rhinitis, and Atopic Dermatitis among the Korean Population, 2008–2017. *Clin. Exp. Pediatr.* **2020**, *63*, 278–283. [[CrossRef](#)] [[PubMed](#)]
22. Bauchau, V.; Durham, S.R. Prevalence and Rate of Diagnosis of Allergic Rhinitis in Europe. *Eur. Respir. J.* **2004**, *24*, 758–764. [[CrossRef](#)] [[PubMed](#)]
23. Katelaris, C.H.; Sacks, R.; Theron, P.N. Allergic Rhinoconjunctivitis in the Australian Population: Burden of Disease and Attitudes to Intranasal Corticosteroid Treatment. *Am. J. Rhinol. Allergy* **2013**, *27*, 506–509. [[CrossRef](#)] [[PubMed](#)]
24. Peat, J.K.; Haby, M.; Spijker, J.; Berry, G.; Woolcock, A.J. Prevalence of Asthma in Adults in Busselton, Western Australia. *BMJ* **1992**, *305*, 1326–1329. [[CrossRef](#)]
25. Savouré, M.; Bousquet, J.; Jaakkola, J.J.K.; Jaakkola, M.S.; Jacquemin, B.; Nadif, R. Worldwide Prevalence of Rhinitis in Adults: A Review of Definitions and Temporal Evolution. *Clin. Transl. Allergy* **2022**, *12*, e12130. [[CrossRef](#)] [[PubMed](#)]
26. Urrutia-Pereira, M.; Mocelin, L.P.; Ellwood, P.; Garcia-Marcos, L.; Simon, L.; Rinelli, P.; Chong-Neto, H.J.; Solé, D. Prevalence of Rhinitis and Associated Factors in Adolescents and Adults: A Global Asthma Network Study. *Rev. Paul. Pediatr.* **2023**, *41*, e2021400. [[CrossRef](#)] [[PubMed](#)]
27. Ng, P.P.-L.C.; Tham, E.H.; Lee, B.-W. Primary Prevention of Allergy—Is It Feasible? *Allergy Asthma Immunol. Res.* **2023**, *15*, 419–436. [[CrossRef](#)]
28. Wong, G.W.-K. Food Allergies around the World. *Front. Nutr.* **2024**, *11*, 1373110. [[CrossRef](#)]
29. Elghoudi, A.; Narchi, H. Food Allergy in Children—the Current Status and the Way Forward. *World J. Clin. Pediatr.* **2022**, *11*, 253–269. [[CrossRef](#)] [[PubMed](#)]
30. Lee, E.C.K.; Trogen, B.; Brady, K.; Ford, L.S.; Wang, J. The Natural History and Risk Factors for the Development of Food Allergies in Children and Adults. *Curr. Allergy Asthma Rep.* **2024**, *24*, 121–131. [[CrossRef](#)] [[PubMed](#)]

31. Kato, Y.; Morikawa, T.; Fujieda, S. Comprehensive Review of Pollen-Food Allergy Syndrome: Pathogenesis, Epidemiology, and Treatment Approaches. *Allergol. Int.* **2024**. [\[CrossRef\]](#) [\[PubMed\]](#)
32. Sharma, E.; Vitte, J. A Systematic Review of Allergen Cross-Reactivity: Translating Basic Concepts into Clinical Relevance. *J. Allergy Clin. Immunol. Glob.* **2024**, *3*, 100230. [\[CrossRef\]](#) [\[PubMed\]](#)
33. Carlson, G.; Coop, C. Pollen Food Allergy Syndrome (PFAS): A Review of Current Available Literature. *Ann. Allergy Asthma Immunol.* **2019**, *123*, 359–365. [\[CrossRef\]](#) [\[PubMed\]](#)
34. Chong, K.W.; Ruiz-Garcia, M.; Patel, N.; Boyle, R.J.; Turner, P.J. Reaction Phenotypes in IgE-Mediated Food Allergy and Anaphylaxis. *Ann. Allergy Asthma Immunol.* **2020**, *124*, 473–478. [\[CrossRef\]](#) [\[PubMed\]](#)
35. Shin, M. Food Allergies and Food-Induced Anaphylaxis: Role of Cofactors. *Clin. Exp. Pediatr.* **2021**, *64*, 393–399. [\[CrossRef\]](#) [\[PubMed\]](#)
36. Tuft, L.; Blumstein, G.I. Studies in Food Allergy: II. Sensitization to Fresh Fruits: Clinical and Experimental Observations. *J. Allergy* **1942**, *13*, 574–582. [\[CrossRef\]](#)
37. Amlot, P.L.; Kemeny, D.M.; Zachary, C.; Parkes, P.; Lessof, M.H. Oral Allergy Syndrome (OAS): Symptoms of IgE-mediated Hypersensitivity to Foods. *Clin. Exp. Allergy* **1987**, *17*, 33–42. [\[CrossRef\]](#)
38. Kim, J.H. Insights into Pediatric Pollen Food Allergy Syndrome. *Clin. Exp. Pediatr.* **2020**, *63*, 483–484. [\[CrossRef\]](#) [\[PubMed\]](#)
39. Gupta, N.; Mapondela, K. Allergy Testing in Lower Middle Income Countries. *Clin. Exp. Allergy* **2024**, *54*, 4–6. [\[CrossRef\]](#) [\[PubMed\]](#)
40. Valenta, R.; Hochwallner, H.; Linhart, B.; Pahr, S. Food Allergies: The Basics. *Gastroenterology* **2015**, *148*, 1120–1131.e4. [\[CrossRef\]](#) [\[PubMed\]](#)
41. Koidl, L.; Gentile, S.A.; Untersmayr, E. Allergen Stability in Food Allergy: A Clinician’s Perspective. *Curr. Allergy Asthma Rep.* **2023**, *23*, 601–612. [\[CrossRef\]](#) [\[PubMed\]](#)
42. Popescu, F.-D. Cross-Reactivity between Aeroallergens and Food Allergens. *World J. Methodol.* **2015**, *5*, 31–50. [\[CrossRef\]](#) [\[PubMed\]](#)
43. Jeon, Y.H. Pollen-Food Allergy Syndrome in Children. *Clin. Exp. Pediatr.* **2020**, *63*, 463–468. [\[CrossRef\]](#) [\[PubMed\]](#)
44. Poncet, P.; Sénéchal, H.; Charpin, D. Update on Pollen-Food Allergy Syndrome. *Expert Rev. Clin. Immunol.* **2020**, *16*, 561–578. [\[CrossRef\]](#) [\[PubMed\]](#)
45. Özdemir, E.; Damadoğlu, E.; Karakaya, G.; Kalyoncu, A.F. Prevalence and Clinical Features of Pollen-Food Allergy Syndrome in Adults with Seasonal Allergic Rhinitis. *Eur. Rev. Med. Pharmacol. Sci.* **2023**, *27*, 103–109. [\[CrossRef\]](#) [\[PubMed\]](#)
46. Tham, E.H.; Leung, D.Y.M. How Different Parts of the World Provide New Insights Into Food Allergy. *Allergy Asthma Immunol. Res.* **2018**, *10*, 290–299. [\[CrossRef\]](#)
47. Biedermann, T.; Winther, L.; Till, S.J.; Panzner, P.; Knulst, A.; Valovirta, E. Birch Pollen Allergy in Europe. *Allergy* **2019**, *74*, 1237–1248. [\[CrossRef\]](#) [\[PubMed\]](#)
48. Breiteneder, H.; Kraft, D. The History and Science of the Major Birch Pollen Allergen Bet v 1. *Biomolecules* **2023**, *13*, 1151. [\[CrossRef\]](#) [\[PubMed\]](#)
49. Hwang, Y.; Motomura, C.; Fukuda, H.; Kishikawa, R.; Watanabe, N.; Yoshihara, S. Relationship among Airborne Pollen, Sensitization, and Pollen Food Allergy Syndrome in Asian Allergic Children. *PeerJ* **2022**, *10*, e14243. [\[CrossRef\]](#) [\[PubMed\]](#)
50. Grijincu, M.; Tănăsie, G.; Zbîrcea, L.-E.; Buzan, M.-R.; Tamaş, T.-P.; Cotarcă, M.-D.; Huţu, I.; Babaev, E.; Stolz, F.; Dorofeeva, Y.; et al. Non-Specific Lipid Transfer Protein Amb a 6 Is a Source-Specific Important Allergenic Molecule in Ragweed Pollen. *Int. J. Mol. Sci.* **2024**, *25*, 6513. [\[CrossRef\]](#) [\[PubMed\]](#)
51. Skjøth, C.A.; Sun, Y.; Karrer, G.; Sikoparija, B.; Smith, M.; Schaffner, U.; Müller-Schärer, H. Predicting Abundances of Invasive Ragweed across Europe Using a “Top-down” Approach. *Sci. Total Environ.* **2019**, *686*, 212–222. [\[CrossRef\]](#) [\[PubMed\]](#)
52. Hrabovský, M.; Kubalová, S.; Kanka, R. The Impact of Changing Climate on the Spread of the Widely Expanding Species Ambrosia Artemisiifolia in Slovakia. *Theor. Appl. Climatol.* **2024**, *155*, 6137–6150. [\[CrossRef\]](#)
53. Wang, W.; Wang, Q.; Lu, S.; Lin, Y.; Suzuki, M.; Saito, Y. Behavior of Autumn Airborne Ragweed Pollen and Its Size-Segregated Allergens (Amb a 1): A Study in Urban Saitama, Japan. *Atmosphere* **2023**, *14*, 247. [\[CrossRef\]](#)
54. Barni, S.; Caimmi, D.; Chiera, F.; Comberiati, P.; Mastorilli, C.; Pelosi, U.; Paravati, F.; Marseglia, G.L.; Arasi, S. Phenotypes and Endotypes of Peach Allergy: What Is New? *Nutrients* **2022**, *14*, 998. [\[CrossRef\]](#) [\[PubMed\]](#)
55. Krikeerati, T.; Rodsaward, P.; Nawiboonwong, J.; Pinyopornpanish, K.; Phusawang, S.; Sompornrattanaphan, M. Revisiting Fruit Allergy: Prevalence across the Globe, Diagnosis, and Current Management. *Foods* **2023**, *12*, 4083. [\[CrossRef\]](#) [\[PubMed\]](#)
56. Sasaki, M.; Morikawa, E.; Yoshida, K.; Fukutomi, Y.; Adachi, Y.; Odajima, H.; Akasawa, A. The Prevalence of Oral Symptoms Caused by Rosaceae Fruits and Soybean Consumption in Children; a Japanese Population-Based Survey. *Allergol. Int.* **2020**, *69*, 610–615. [\[CrossRef\]](#) [\[PubMed\]](#)
57. Mastorilli, C.; Cardinale, F.; Giannetti, A.; Caffarelli, C. Pollen-Food Allergy Syndrome: A Not so Rare Disease in Childhood. *Medicina* **2019**, *55*, 641. [\[CrossRef\]](#)

58. Gargano, D.; Appanna, R.; Santonicola, A.; De Bartolomeis, F.; Stellato, C.; Cianferoni, A.; Casolaro, V.; Iovino, P. Food Allergy and Intolerance: A Narrative Review on Nutritional Concerns. *Nutrients* **2021**, *13*, 1638. [\[CrossRef\]](#) [\[PubMed\]](#)
59. Rennie, G.H.; Zhao, J.; Camus-Ela, M.; Shi, J.; Jiang, L.; Zhang, L.; Wang, J.; Raghavan, V. Influence of Lifestyle and Dietary Habits on the Prevalence of Food Allergies: A Scoping Review. *Foods* **2023**, *12*, 3290. [\[CrossRef\]](#) [\[PubMed\]](#)
60. Sicherer, S.H.; Warren, C.M.; Dant, C.; Gupta, R.S.; Nadeau, K.C. Food Allergy from Infancy Through Adulthood. *J. Allergy Clin. Immunol. Pract.* **2020**, *8*, 1854–1864. [\[CrossRef\]](#)
61. Yasudo, H.; Yamamoto-Hanada, K.; Yang, L.; Saito-Abe, M.; Sato, M.; Miyaji, Y.; Shimada, M.; Hirai, S.; Toyokuni, K.; Ishikawa, F.; et al. Pollen Food Allergy Syndrome in Allergic March. *Nutrients* **2022**, *14*, 2658. [\[CrossRef\]](#) [\[PubMed\]](#)
62. Skypala, I.J. Can Patients with Oral Allergy Syndrome Be at Risk of Anaphylaxis? *Curr. Opin. Allergy Clin. Immunol.* **2020**, *20*, 459–464. [\[CrossRef\]](#) [\[PubMed\]](#)
63. Kim, M.; Ahn, Y.; Yoo, Y.; Kim, D.K.; Yang, H.J.; Park, H.S.; Lee, H.J.; Kim, M.A.; Jeong, Y.Y.; Kim, B.S.; et al. Clinical Manifestations and Risk Factors of Anaphylaxis in Pollen-Food Allergy Syndrome. *Yonsei Med. J.* **2019**, *60*, 960–968. [\[CrossRef\]](#)
64. Hossny, E.; Ebisawa, M.; El-Gamal, Y.; Arasi, S.; Dahdah, L.; El-Owaidy, R.; Galvan, C.A.; Lee, B.W.; Levin, M.; Martinez, S.; et al. Challenges of Managing Food Allergy in the Developing World. *World Allergy Organ. J.* **2019**, *12*, 100089. [\[CrossRef\]](#)
65. Ramsey, N.; Berin, M.C. Pathogenesis of IgE-Mediated Food Allergy and Implications for Future Immunotherapeutics. *Pediatr. Allergy Immunol.* **2021**, *32*, 1416–1425. [\[CrossRef\]](#)
66. Wang, J.; Zhou, Y.; Zhang, H.; Hu, L.; Liu, J.; Wang, L.; Wang, T.; Zhang, H.; Cong, L.; Wang, Q. Pathogenesis of Allergic Diseases and Implications for Therapeutic Interventions. *Signal Transduct. Target. Ther.* **2023**, *8*, 138. [\[CrossRef\]](#) [\[PubMed\]](#)
67. Gigon, L.; Fettelet, T.; Yousefi, S.; Simon, D.; Simon, H.-U. Eosinophils from A to Z. *Allergy* **2023**, *78*, 1810–1846. [\[CrossRef\]](#)
68. Miyake, K.; Shibata, S.; Yoshikawa, S.; Karasuyama, H. Basophils and Their Effector Molecules in Allergic Disorders. *Allergy* **2021**, *76*, 1693–1706. [\[CrossRef\]](#) [\[PubMed\]](#)
69. Zhang, Z.; Kurashima, Y. Two Sides of the Coin: Mast Cells as a Key Regulator of Allergy and Acute/Chronic Inflammation. *Cells* **2021**, *10*, 1615. [\[CrossRef\]](#) [\[PubMed\]](#)
70. Francis, O.L.; Wang, K.Y.; Kim, E.H.; Moran, T.P. Common Food Allergens and Cross-Reactivity. *J. Food Allergy* **2020**, *2*, 17–21. [\[CrossRef\]](#)
71. Geng, Q.; Zhang, Y.; Song, M.; Zhou, X.; Tang, Y.; Wu, Z.; Chen, H. Allergenicity of Peanut Allergens and Its Dependence on the Structure. *Compr. Rev. Food Sci. Food Saf.* **2023**, *22*, 1058–1081. [\[CrossRef\]](#) [\[PubMed\]](#)
72. Zhou, E.; Li, Q.; Zhu, D.; Chen, G.; Wu, L. Characterization of Physicochemical and Immunogenic Properties of Allergenic Proteins Altered by Food Processing: A Review. *Food Sci. Hum. Wellness* **2024**, *13*, 1135–1151. [\[CrossRef\]](#)
73. Pekar, J.; Ret, D.; Untersmayr, E. Stability of Allergens. *Mol. Immunol.* **2018**, *100*, 14–20. [\[CrossRef\]](#)
74. Verhoeckx, K.C.M.; Vissers, Y.M.; Baumert, J.L.; Faludi, R.; Feys, M.; Flanagan, S.; Herouet-Guicheney, C.; Holzhauser, T.; Shimojo, R.; van der Bolt, N.; et al. Food Processing and Allergenicity. *Food Chem. Toxicol.* **2015**, *80*, 223–240. [\[CrossRef\]](#) [\[PubMed\]](#)
75. Silva, Y.P.; Bernardi, A.; Frozza, R.L. The Role of Short-Chain Fatty Acids From Gut Microbiota in Gut-Brain Communication. *Front. Endocrinol.* **2020**, *11*, 25. [\[CrossRef\]](#) [\[PubMed\]](#)
76. Huang, M.-T.; Chiu, C.-J.; Tsai, C.-Y.; Lee, Y.-R.; Liu, W.-L.; Chuang, H.-L.; Huang, M.-T. Short-Chain Fatty Acids Ameliorate Allergic Airway Inflammation via Sequential Induction of PMN-MDSCs and Treg Cells. *J. Allergy Clin. Immunol. Glob.* **2023**, *2*, 100163. [\[CrossRef\]](#) [\[PubMed\]](#)
77. Devonshire, A.; Gautam, Y.; Johansson, E.; Mersha, T.B. Multi-Omics Profiling Approach in Food Allergy. *World Allergy Organ. J.* **2023**, *16*, 100777. [\[CrossRef\]](#) [\[PubMed\]](#)
78. Dubois, A.E.J.; Turner, P.J.; Hourihane, J.; Ballmer-Weber, B.; Beyer, K.; Chan, C.-H.; Gowland, M.H.; O'Hagan, S.; Regent, L.; Remington, B.; et al. How Does Dose Impact on the Severity of Food-Induced Allergic Reactions, and Can This Improve Risk Assessment for Allergenic Foods?: Report from an ILSI Europe Food Allergy Task Force Expert Group and Workshop. *Allergy* **2018**, *73*, 1383–1392. [\[CrossRef\]](#) [\[PubMed\]](#)
79. Bartra, J.; Turner, P.J.; Muñoz-Cano, R.M. Cofactors in Food Anaphylaxis in Adults. *Ann. Allergy Asthma Immunol.* **2023**, *130*, 733–740. [\[CrossRef\]](#)
80. Samadi, N.; Klems, M.; Untersmayr, E. The Role of Gastrointestinal Permeability in Food Allergy. *Ann. Allergy Asthma Immunol.* **2018**, *121*, 168–173. [\[CrossRef\]](#) [\[PubMed\]](#)
81. Srisuwatthari, W.; Kanchanaphoomi, K.; Nawiboonwong, J.; Thongngarm, T.; Sompornrattanaphan, M. Food-Dependent Exercise-Induced Anaphylaxis: A Distinct Form of Food Allergy—An Updated Review of Diagnostic Approaches and Treatments. *Foods* **2023**, *12*, 3768. [\[CrossRef\]](#) [\[PubMed\]](#)
82. Cardona, V.; Luengo, O.; Garriga, T.; Labrador-Horrillo, M.; Sala-Cunill, A.; Izquierdo, A.; Soto, L.; Guilarte, M. Co-Factor-Enhanced Food Allergy. *Allergy* **2012**, *67*, 1316–1318. [\[CrossRef\]](#)
83. Shiratsuki, R.; Chinuki, Y.; Fukushima, S.; Morita, E. A Case of Pork-Cat Syndrome That Developed as Food-Dependent Exercise-Induced Anaphylaxis. *Acta Derm. Venereol.* **2020**, *100*, adv00233. [\[CrossRef\]](#)

84. Liu, Z.; Trifonova, D.; Tulaeva, I.; Riabova, K.; Karsonova, A.; Kozlov, E.; Elisyutina, O.; Khaitov, M.; Focke-Tejkl, M.; Chen, T.-H.; et al. Albumins Represent Highly Cross-Reactive Animal Allergens. *Front. Immunol.* **2023**, *14*, 1241518. [[CrossRef](#)] [[PubMed](#)]
85. Kim, C.; Kim, S.W.; Hwang, Y.H. Recurrent Urticaria Caused by Specific Cat Serum Albumin IgE Cross-Reacting with Pork Serum Albumin. *Clin. Exp. Pediatr.* **2020**, *63*, 451–453. [[CrossRef](#)] [[PubMed](#)]
86. Popescu, F.-D.; Ganea, C.S.; Panaitescu, C.; Vieru, M. Molecular Diagnosis in Cat Allergy. *World J. Methodol.* **2021**, *11*, 46–60. [[CrossRef](#)]
87. Abel-Fernández, E.; Martínez, M.J.; Galán, T.; Pineda, F. Going over Fungal Allergy: *Alternaria Alternata* and Its Allergens. *J. Fungi* **2023**, *9*, 582. [[CrossRef](#)]
88. Xing, H.; Wang, J.; Sun, Y.; Wang, H. Recent Advances in the Allergic Cross-Reactivity between Fungi and Foods. *J. Immunol. Res.* **2022**, *2022*, 7583400. [[CrossRef](#)] [[PubMed](#)]
89. German-Sanchez, A.; Alonso-Llamazares, A.; Garcia-Gonzalez, F.; Matala-Ahmed, B.; Bartolome-Zavala, B.; Antepara-Ercoreca, I. Allergy to Beer and Wine Caused by *Saccharomyces Cerevisiae* in a Patient Sensitized to Fungi. *J. Investig. Allergol. Clin. Immunol.* **2022**, *32*, 311–313. [[CrossRef](#)] [[PubMed](#)]
90. Dauby, P.-A.L.; Whisman, B.A.; Hagan, L. Cross-Reactivity between Raw Mushroom and Molds in a Patient with Oral Allergy Syndrome. *Ann. Allergy Asthma Immunol.* **2002**, *89*, 319–321. [[CrossRef](#)] [[PubMed](#)]
91. Hernandez-Ramirez, G.; Barber, D.; Tome-Amat, J.; Garrido-Arandia, M.; Diaz-Perales, A. *Alternaria* as an Inducer of Allergic Sensitization. *J. Fungi* **2021**, *7*, 838. [[CrossRef](#)]
92. Mandallaz, M.M.; de Weck, A.L.; Dahinden, C.A. Bird-Egg Syndrome: Cross-Reactivity between Bird Antigens and Egg-Yolk Livetins in IgE-Mediated Hypersensitivity. *Int. Arch. Allergy Appl. Immunol.* **2009**, *87*, 143–150. [[CrossRef](#)]
93. Hemmer, W.; Klug, C.; Swoboda, I. Update on the Bird-Egg Syndrome and Genuine Poultry Meat Allergy. *Allergo J. Int.* **2016**, *25*, 68–75. [[CrossRef](#)] [[PubMed](#)]
94. Varshney, P.; Pongracic, J.A. Clinical Manifestations of Immunoglobulin E-Mediated Food Allergy, Including Pollen-Food Allergy Syndrome. *J. Food Allergy* **2020**, *2*, 22–25. [[CrossRef](#)] [[PubMed](#)]
95. Kanikowska, A.; Janisz, S.; Mańkowska-Wierzbička, D.; Gabryel, M.; Dobrowolska, A.; Eder, P. Management of Adult Patients with Gastrointestinal Symptoms from Food Hypersensitivity—Narrative Review. *J. Clin. Med.* **2022**, *11*, 7326. [[CrossRef](#)]
96. Lloyd, M. Pollen-Food Allergy Syndrome (PFAS). *Curr. Allergy Clin. Immunol.* **2022**, *35*, 213–222.
97. Giovannini, M.; Skypala, I.J.; Caubet, J.C.; Du Toit, G.; Nowak-Węgrzyn, A. Diagnosis and Management of Pollen Food Allergy Syndrome to Nuts. *J. Allergy Clin. Immunol. Pract.* **2024**, *12*, 599–604. [[CrossRef](#)]
98. Santos, A.F.; Riggioni, C.; Agache, I.; Akdis, C.A.; Akdis, M.; Alvarez-Perea, A.; Alvaro-Lozano, M.; Ballmer-Weber, B.; Barni, S.; Beyer, K. EAACI Guidelines on the Management of IgE-mediated Food Allergy. *Allergy* **2023**, *78*, 3057–3076. [[CrossRef](#)]
99. Meyer, R.; Venter, C. Food Hypersensitivity. In *Clinical Paediatric Dietetics*; Shaw, V., Ed.; John Wiley & Sons Ltd.: Chichester, UK, 2020; pp. 315–318. [[CrossRef](#)]
100. Andersen, M.-B.S.; Hall, S.; Dragsted, L.O. Identification of European Allergy Patterns to the Allergen Families PR-10, LTP, and Profilin from Rosaceae Fruits. *Clin. Rev. Allergy Immunol.* **2011**, *41*, 4–19. [[CrossRef](#)]
101. Westwell-Roper, C.; To, S.; Andjelic, G.; Lu, C.; Lin, B.; Soller, L.; Chan, E.S.; Stewart, S.E. Food-allergy-specific Anxiety and Distress in Parents of Children with Food Allergy: A Systematic Review. *Pediatr. Allergy Immunol.* **2022**, *33*, e13695. [[CrossRef](#)]
102. Jonsson, M.; Ekström, S.; Protudjer, J.L.P.; Bergström, A.; Kull, I. Living with Food Hypersensitivity as an Adolescent Impairs Health Related Quality of Life Irrespective of Disease Severity: Results from a Population-Based Birth Cohort. *Nutrients* **2021**, *13*, 2357. [[CrossRef](#)] [[PubMed](#)]
103. Protudjer, J.L.P.; Golding, M.; Salisbury, M.R.; Abrams, E.M.; Roos, L.E. High Anxiety and Health-Related Quality of Life in Families with Children with Food Allergy during Coronavirus Disease 2019. *Ann. Allergy Asthma Immunol.* **2021**, *126*, 83–88. [[CrossRef](#)] [[PubMed](#)]
104. Greiwe, J. Quality of Life and Psychological Issues Associated with Food Allergy. *J. Food Allergy* **2023**, *5*, 43–48. [[CrossRef](#)] [[PubMed](#)]
105. Kachru, R. Psychosocial Issues and Quality of Life Associated with Food Allergy. *J. Food Allergy* **2020**, *2*, 95–98. [[CrossRef](#)] [[PubMed](#)]
106. Sampige, R.; Frankel, L.A. The Relationship between Children's Food Allergies and Family Mealtimes: A Systematic Review. *J. Child Health Care* **2023**. [[CrossRef](#)]
107. Abrams, E.M.; Simons, E.; Roos, L.; Hurst, K.; Protudjer, J.L.P. Qualitative Analysis of Perceived Impacts on Childhood Food Allergy on Caregiver Mental Health and Lifestyle. *Ann. Allergy Asthma Immunol.* **2020**, *124*, 594–599. [[CrossRef](#)] [[PubMed](#)]
108. Chooniedass, R.; Soller, L.; Hsu, E.; To, S.; Cameron, S.B.; Chan, E.S. Parents of Children with Food Allergy: A Qualitative Study Describing Needs and Identifying Solutions. *Ann. Allergy Asthma Immunol.* **2020**, *125*, 674–679. [[CrossRef](#)] [[PubMed](#)]
109. Dupuis, R.; Kinsey, E.W.; Spergel, J.M.; Brown-Whitehorn, T.; Graves, A.; Samuelson, K.; Epstein, C.; Mollen, C.; Cannuscio, C.C. Food Allergy Management at School. *J. Sch. Health* **2020**, *90*, 395–406. [[CrossRef](#)]

110. Caner, N.; Efe, Y.S.; Söyünmez, S.; Bayat, M. Managing Food Allergies at School: A Qualitative Study. *J. Pediatr. Nurs.* **2023**, *73*, 58–66. [\[CrossRef\]](#) [\[PubMed\]](#)
111. Santos, A.F.; Worm, M.; Kurita, S.; Wong, T.; Contato, D.; Pirillo, E.; Esteban, A.E.; Tassinari, P.; Perna, F.; Chinthrajah, R.S. Living with Food Allergies: The Experiences of Adult Patients and Caregivers. *Front. Allergy* **2023**, *4*, 1272851. [\[CrossRef\]](#)
112. Cook, E.E. Anthropological and Sociological Perspectives on Food Allergy. *Clin. Exp. Allergy* **2023**, *53*, 989–1003. [\[CrossRef\]](#)
113. Rocheleau, B.N.; Rocheleau, G.C. Bullying Victimization among Children with Food Allergies and Parental Mental Health. *J. Fam. Issues* **2021**, *42*, 2319–2334. [\[CrossRef\]](#)
114. Muraro, A.; Worm, M.; Alviani, C.; Cardona, V.; DunnGalvin, A.; Garvey, L.H.; Riggioni, C.; de Silva, D.; Angier, E.; Arasi, S.; et al. EAACI Guideline: Anaphylaxis (2021 Update). *Allergy* **2022**, *77*, 357–377. [\[CrossRef\]](#) [\[PubMed\]](#)
115. Skypala, I.J.; Hunter, H.; Krishna, M.T.; Rey-Garcia, H.; Till, S.J.; du Toit, G.; Angier, E.; Baker, S.; Stoenchev, K.V.; Luyt, D.K. BSACI Guideline for the Diagnosis and Management of Pollen Food Syndrome in the UK. *Clin. Exp. Allergy* **2022**, *52*, 1018–1034. [\[CrossRef\]](#) [\[PubMed\]](#)
116. Breiteneder, H.; Radauer, C. A Classification of Plant Food Allergens. *J. Allergy Clin. Immunol.* **2004**, *113*, 821–830. [\[CrossRef\]](#) [\[PubMed\]](#)
117. Palacín, A.; Rivas, L.A.; Gómez-Casado, C.; Aguirre, J.; Tordesillas, L.; Bartra, J.; Blanco, C.; Carrillo, T.; Cuesta-Herranz, J.; Bonny, J.A.C.; et al. The Involvement of Thaumatin-like Proteins in Plant Food Cross-Reactivity: A Multicenter Study Using a Specific Protein Microarray. *PLoS ONE* **2012**, *7*, e44088. [\[CrossRef\]](#)
118. Iizuka, T.; Barre, A.; Rougé, P.; Charpin, D.; Scala, E.; Baudin, B.; Aizawa, T.; Sénéchal, H.; Poncet, P. Gibberellin-Regulated Proteins: Emergent Allergens. *Front. Allergy* **2022**, *3*, 877553. [\[CrossRef\]](#) [\[PubMed\]](#)
119. Panaitescu, C.; Haidar, L.; Buzan, M.R.; Griju, M.; Spanu, D.E.; Cojanu, C.; Laculiceanu, A.; Bumbacea, R.; Agache, I. Precision Medicine in the Allergy Clinic: The Application of Component Resolved Diagnosis. *Expert Rev. Clin. Immunol.* **2022**, *18*, 145–162. [\[CrossRef\]](#)
120. Kiguchi, T.; Yamamoto-Hanada, K.; Saito-Abe, M.; Sato, M.; Irahara, M.; Ogita, H.; Miyagi, Y.; Inuzuka, Y.; Toyokuni, K.; Nishimura, K.; et al. Pollen-Food Allergy Syndrome and Component Sensitization in Adolescents: A Japanese Population-Based Study. *PLoS ONE* **2021**, *16*, e0249649. [\[CrossRef\]](#)
121. WHO/IUIS Allergen Nomenclature Sub-Committee. Available online: <http://www.allergen.org/> (accessed on 20 November 2024).
122. Global Biodiversity Information Facility. Available online: <https://www.gbif.org> (accessed on 20 November 2024).
123. Islam, M.M.; El-Sappah, A.H.; Ali, H.M.; Zandi, P.; Huang, Q.; Soaud, S.A.; Alazizi, E.M.Y.; Wafa, H.A.; Hossain, M.A.; Liang, Y. Pathogenesis-Related Proteins (PRs) Countering Environmental Stress in Plants: A Review. *S. Afr. J. Bot.* **2023**, *160*, 414–427. [\[CrossRef\]](#)
124. Zribi, I.; Ghorbel, M.; Brini, F. Pathogenesis Related Proteins (PRs): From Cellular Mechanisms to Plant Defense. *Curr. Protein Pept. Sci.* **2021**, *22*, 396–412. [\[CrossRef\]](#) [\[PubMed\]](#)
125. Dos Santos, C.; Franco, O.L. Pathogenesis-Related Proteins (PRs) with Enzyme Activity Activating Plant Defense Responses. *Plants* **2023**, *12*, 2226. [\[CrossRef\]](#) [\[PubMed\]](#)
126. Li, L.; Chang, C.; Guan, K. Birch Pollen Allergens. *Curr. Protein Pept. Sci.* **2022**, *23*, 731–743. [\[PubMed\]](#)
127. Wang, X.; Chen, L.; Ding, J.; Wang, H.; Wang, X. Profiles of Birch Allergen Component Sensitization and Its Association with Pollen Food Allergy Syndrome in Northern China. *J. Asthma Allergy* **2023**, *16*, 1241–1250. [\[CrossRef\]](#) [\[PubMed\]](#)
128. Aglas, L.; Soh, W.T.; Kraiem, A.; Wenger, M.; Brandstetter, H.; Ferreira, F. Ligand Binding of PR-10 Proteins with a Particular Focus on the Bet v 1 Allergen Family. *Curr. Allergy Asthma Rep.* **2020**, *20*, 25. [\[CrossRef\]](#) [\[PubMed\]](#)
129. Führer, S.; Unterhauser, J.; Zeindl, R.; Eidelpes, R.; Fernández-Quintero, M.L.; Liedl, K.R.; Tollinger, M. The Structural Flexibility of PR-10 Food Allergens. *Int. J. Mol. Sci.* **2022**, *23*, 8252. [\[CrossRef\]](#)
130. 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. [\[CrossRef\]](#) [\[PubMed\]](#)
131. Kapingidza, A.B.; Pye, S.E.; Hyduke, N.; Dolamore, C.; Pote, S.; Schlachter, C.R.; Commings, S.P.; Kowal, K.; Chruszcz, M. Comparative Structural and Thermal Stability Studies of Cuc m 2.0101, Art v 4.0101 and Other Allergenic Profilins. *Mol. Immunol.* **2019**, *114*, 19–29. [\[CrossRef\]](#)
132. García-Ramírez, B.; Mares-Mejía, I.; Rodríguez-Hernández, A.; Cano-Sánchez, P.; Torres-Larios, A.; Ortega, E.; Rodríguez-Romero, A. A Native IgE in Complex with Profilin Provides Insights into Allergen Recognition and Cross-Reactivity. *Commun. Biol.* **2022**, *5*, 748. [\[CrossRef\]](#)
133. Hauser, M.; Roulias, A.; Ferreira, F.; Egger, M. Panallergens and Their Impact on the Allergic Patient. *Allergy Asthma Clin. Immunol.* **2010**, *6*, 1. [\[CrossRef\]](#) [\[PubMed\]](#)
134. Lyons, S.A.; Clausen, M.; Knulst, A.C.; Ballmer-Weber, B.K.; Fernandez-Rivas, M.; Barreales, L.; Bieli, C.; Dubakiene, R.; Fernandez-Perez, C.; Jedrzejczak-Czechowicz, M.; et al. Prevalence of Food Sensitization and Food Allergy in Children Across Europe. *J. Allergy Clin. Immunol. Pract.* **2020**, *8*, 2736–2746.e9. [\[CrossRef\]](#) [\[PubMed\]](#)

135. Lipp, T.; Acar Şahin, A.; Aggelidis, X.; Arasi, S.; Barbalace, A.; Bourgoïn, A.; Bregu, B.; Brighetti, M.A.; Caeiro, E.; Caglayan Sozmen, S. Heterogeneity of Pollen Food Allergy Syndrome in Seven Southern European Countries: The@ IT. 2020 Multicenter Study. *Allergy* **2021**, *76*, 3041–3052. [[CrossRef](#)] [[PubMed](#)]
136. Zbircea, L.-E.; Buzan, M.-R.; Grijincu, M.; Babaev, E.; Stolz, F.; Valenta, R.; Păunescu, V.; Panaitescu, C.; Chen, K.-W. Relationship between IgE Levels Specific for Ragweed Pollen Extract, Amb a 1 and Cross-Reactive Allergen Molecules. *Int. J. Mol. Sci.* **2023**, *24*, 4040. [[CrossRef](#)]
137. Barber, D.; Diaz-Perales, A.; Escribese, M.M.; Kleine-Tebbe, J.; Matricardi, P.M.; Ollert, M.; Santos, A.F.; Sastre, J. Molecular Allergology and Its Impact in Specific Allergy Diagnosis and Therapy. *Allergy Eur. J. Allergy Clin. Immunol.* **2021**, *76*, 3642–3658. [[CrossRef](#)] [[PubMed](#)]
138. Ansotegui, I.J.; Melioli, G.; Canonica, G.W.; Gómez, R.M.; Jensen-Jarolim, E.; Ebisawa, M.; Luengo, O.; Caraballo, L.; Passalacqua, G.; Poulsen, L.K.; et al. A WAO—ARIA—GA2LEN Consensus Document on Molecular-Based Allergy Diagnosis (PAMD@): Update 2020. *World Allergy Organ. J.* **2020**, *13*, 100091. [[CrossRef](#)] [[PubMed](#)]
139. Gómez Torrijos, E.; Gratacós Gómez, A.R.; González Jimenez, O.M.; Joyanes Romo, J.B.; Palacios Cañas, A.; García Rodríguez, R. Profilins and Food-Dependent Exercise-Induced Anaphylaxis. *J. Investig. Allergol. Clin. Immunol.* **2021**, *31*, 349–350. [[CrossRef](#)] [[PubMed](#)]
140. Alvarado, M.I.; Jimeno, L.; De La Torre, F.; Boissy, P.; Rivas, B.; Lázaro, M.J.; Barber, D. Profilin as a Severe Food Allergen in Allergic Patients Overexposed to Grass Pollen. *Allergy* **2014**, *69*, 1610–1616. [[CrossRef](#)] [[PubMed](#)]
141. Mota, I.; Gaspar, Â.; Benito-Garcia, F.; Correia, M.; Arêde, 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. [[CrossRef](#)]
142. Deng, S.; Yin, J. Mugwort Pollen-Related Food Allergy: Lipid Transfer Protein Sensitization and Correlation with the Severity of Allergic Reactions in a Chinese Population. *Allergy Asthma Immunol. Res.* **2019**, *11*, 116–128. [[CrossRef](#)] [[PubMed](#)]
143. D’Aiuto, V.; Mormile, I.; Granata, F.; Napolitano, F.; Lamagna, L.; Della Casa, F.; de Paulis, A.; Rossi, F.W. Worldwide Heterogeneity of Food Allergy: Focus on Peach Allergy in Southern Italy. *J. Clin. Med.* **2024**, *13*, 3259. [[CrossRef](#)] [[PubMed](#)]
144. Liccardi, G.; Mistrello, G.; Noschese, P.; Falagiani, P.; D’Amato, M.; D’Amato, G. Oral Allergy Syndrome (OAS) in Pollinosis Patients after Eating Pistachio Nuts: Two Cases with Two Different Patterns of Onset. *Allergy* **1996**, *51*, 919–922. [[CrossRef](#)]
145. Liccardi, G.; Russo, M.; Mistrello, G.; Falagiani, P.; D’Amato, M.; D’Amato, G. Sensitization to Pistachio Is Common in Parietaria Allergy. *Allergy* **1999**, *54*, 643–645. [[CrossRef](#)] [[PubMed](#)]
146. Lyons, S.A.; Burney, P.G.J.; Ballmer-Weber, B.K.; Fernandez-Rivas, M.; Barreales, L.; Clausen, M.; Dubakiene, R.; Fernandez-Perez, C.; Fritsche, P.; Jedrzejczak-Czechowicz, M.; et al. Food Allergy in Adults: Substantial Variation in Prevalence and Causative Foods Across Europe. *J. Allergy Clin. Immunol. Pract.* **2019**, *7*, 1920–1928.e11. [[CrossRef](#)]
147. Aruanno, A.; Urbani, S.; Frati, F.; Nucera, E. LTP Allergy/Sensitization in a Pediatric Population. *Allergol. Immunopathol.* **2020**, *48*, 763–770. [[CrossRef](#)] [[PubMed](#)]
148. Giménez-Campillo, C.; Arroyo-Manzanares, N.; Pastor-Belda, M.; Campillo, N.; Viñas, P. Discrimination of the Geographical Origin of Peaches by the Monitoring of Volatile Organic Compounds by Gas Chromatography with Mass Spectrometry and Chemometric Tools. *J. Food Compos. Anal.* **2024**, *129*, 106125. [[CrossRef](#)]
149. Schwingshackl, L.; Morze, J.; Hoffmann, G. Mediterranean Diet and Health Status: Active Ingredients and Pharmacological Mechanisms. *Br. J. Pharmacol.* **2020**, *177*, 1241–1257. [[CrossRef](#)]
150. Penedos, C.; Salamanca, G.; Tavares, B.; Fonseca, J.; Carreiro-Martins, P.; Rodrigues-Alves, R.; Moral de Gregorio, Á.; Valero, A.; Branco Ferreira, M. Aerobiology of Olive Pollen (*Olea europaea* L.) in the Atmosphere of the Iberian Peninsula. *Atmosphere* **2024**, *15*, 1087. [[CrossRef](#)]
151. Lara, B.; Rojo, J.; Fernández-González, F.; González-García-Saavedra, A.; Serrano-Bravo, M.D.; Pérez-Badia, R. Impact of Plane Tree Abundance on Temporal and Spatial Variations in Pollen Concentration. *Forests* **2020**, *11*, 817. [[CrossRef](#)]
152. Decuyper, I.I.; Faber, M.A.; Sabato, V.; Bridts, C.H.; Hagendorens, M.M.; Rihs, H.-P.; De Clerck, L.S.; Ebo, D.G. Where There’s Smoke, There’s Fire: Cannabis Allergy through Passive Exposure. *J. Allergy Clin. Immunol. Pract.* **2017**, *5*, 864–865. [[CrossRef](#)] [[PubMed](#)]
153. Jiang, N.; Guan, K.; Xiang, L. Food-Dependent Exercise-Induced Anaphylaxis (FDEIA) Suspected Triggered by Lipid Transfer Protein in a Chinese Child: A Case Report. *Asia Pac. Allergy* **2024**, *14*, 148–150. [[CrossRef](#)] [[PubMed](#)]
154. San Bartolomé, C.; Muñoz-Cano, R.; Rius, J.; Casas-Saucedo, R.; Balsells, S.; Egri, N.; Ruano-Zaragoza, M.; de la Cruz, C.; Bartra, J.; Pascal, M. Detection of Wheat Lipid Transfer Protein (Tri a 14) Sensitization: Comparison between Currently Available Diagnostic Tools. *Int. Arch. Allergy Immunol.* **2022**, *183*, 75–79. [[CrossRef](#)]
155. Ritonga, F.N.; Zhou, D.; Zhang, Y.; Song, R.; Li, C.; Li, J.; Gao, J. The Roles of Gibberellins in Regulating Leaf Development. *Plants* **2023**, *12*, 1243. [[CrossRef](#)] [[PubMed](#)]

156. Carreras-Katcheff, S.; Bartolomé, B.; Labrador-Horrillo, M.; Garriga Baraut, T. Allergy to Gibberellin-Regulated Proteins in an Adolescent: A Case of Orange-Induced Anaphylaxis Mediated by Cofactors. *Allergol. Immunopathol.* **2024**, *52*, 48–50. [[CrossRef](#)] [[PubMed](#)]
157. Sénéchal, H.; Šantrůček, J.; Melčová, M.; Svoboda, P.; Zídková, 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. [[CrossRef](#)] [[PubMed](#)]
158. Inomata, N. Gibberellin-Regulated Protein Allergy: Clinical Features and Cross-Reactivity. *Allergol. Int.* **2020**, *69*, 11–18. [[CrossRef](#)] [[PubMed](#)]
159. Sénéchal, H.; Keykhosravi, S.; Couderc, R.; Selva, M.A.; Shahali, Y.; Aizawa, T.; Busnel, J.M.; Arif, R.; Mercier, I.; Pham-Thi, N.; et al. Pollen/Fruit Syndrome: Clinical Relevance of the Cypress Pollen Allergenic Gibberellin-Regulated Protein. *Allergy Asthma Immunol. Res.* **2019**, *11*, 143–151. [[CrossRef](#)] [[PubMed](#)]
160. Poncet, P.; Aizawa, T.; Sénéchal, H. The Subtype of Cupressaceae Pollinosis Associated with Pru p 7 Sensitization Is Characterized by a Sensitization to a Cross-Reactive Gibberellin-Regulated Protein in Cypress Pollen: BP14. *Clin. Exp. Allergy J. Br. Soc. Allergy Clin. Immunol.* **2019**, *49*, 1163–1166. [[CrossRef](#)] [[PubMed](#)]
161. Klingebiel, C.; Chantran, Y.; Arif-Lusson, R.; Ehrenberg, A.E.; Östling, J.; Poisson, A.; Liabeuf, V.; Agabriel, C.; Birnbaum, J.; Porri, F.; et al. Pru p 7 Sensitization Is a Predominant Cause of Severe, Cypress Pollen-Associated Peach Allergy. *Clin. Exp. Allergy J. Br. Soc. Allergy Clin. Immunol.* **2019**, *49*, 526–536. [[CrossRef](#)]
162. Cecchi, L.; Poncet, P.; Maltagliati, L.; Carli, G.; Macchia, D.; Maggi, L.; Meucci, E.; Parronchi, P.; Mazzoni, A.; Salvati, L.; et al. Optimization of the Diagnosis and Characterization of Gibberellin-Regulated Protein Sensitization: An Italian Cohort Study. *Ann. Allergy Asthma Immunol.* **2024**, *132*, 82–90.e1. [[CrossRef](#)] [[PubMed](#)]
163. Biagioni, B.; Tomei, L.; Valleriani, C.; Liccioli, G.; Barni, S.; Sarti, L.; Citera, F.; Giovannini, M.; Mori, F. Allergy to Gibberellin-Regulated Proteins (Peamaclein) in Children. *Int. Arch. Allergy Immunol.* **2021**, *182*, 1194–1199. [[CrossRef](#)]
164. Pahus, L.; Gouitaa, M.; Sofalvi, T.; Alagha, K.; Gras, D.; Chanez, P.; Charpin, D. Cypress Pollen Allergy Is Responsible for Two Distinct Phenotypes of Allergic Rhinitis Different from Other Pollinosis. *Eur. Ann. Allergy Clin. Immunol.* **2018**, *50*, 28–35. [[CrossRef](#)]
165. van der Wel, H.; Loeve, K. Isolation and Characterization of Thaumatin I and II, the Sweet-Tasting Proteins from *Thaumatococcus Daniellii* Benth. *Eur. J. Biochem.* **1972**, *31*, 221–225. [[CrossRef](#)]
166. Sharma, A.; Sharma, H.; Rajput, R.; Pandey, A.; Upadhyay, S.K. Molecular Characterization Revealed the Role of Thaumatin-Like Proteins of Bread Wheat in Stress Response. *Front. Plant Sci.* **2021**, *12*, 807448. [[CrossRef](#)] [[PubMed](#)]
167. Wang, L.; Xu, Z.; Yin, W.; Xu, K.; Wang, S.; Shang, Q.; Sa, W.; Liang, J.; Wang, L. Genome-Wide Analysis of the Thaumatin-like Gene Family in Qingke (*Hordeum vulgare* L. var. *nudum*) Uncovers Candidates Involved in Plant Defense against Biotic and Abiotic Stresses. *Front. Plant Sci.* **2022**, *13*, 912296. [[CrossRef](#)]
168. Jain, A. Seed Storage Protein, Functional Diversity and Association with Allergy. *Allergies* **2023**, *3*, 25–38. [[CrossRef](#)]
169. Feng, L.; Wei, S.; Li, Y. Thaumatin-like Proteins in Legumes: Functions and Potential Applications—A Review. *Plants* **2024**, *13*, 1124. [[CrossRef](#)] [[PubMed](#)]
170. Osada, T.; Okano, M. Japanese Cedar and Cypress Pollinosis Updated: New Allergens, Cross-Reactivity, and Treatment. *Allergol. Int.* **2021**, *70*, 281–290. [[CrossRef](#)]
171. Barre, A.; Sénéchal, H.; Nguyen, C.; Granier, C.; Poncet, P.; Rougé, P. Structural Basis for the IgE-Binding Cross-Reacting Epitopic Peptides of Cup s 3, a PR-5 Thaumatin-like Protein Allergen from Common Cypress (*Cupressus sempervirens*) Pollen. *Allergies* **2023**, *3*, 11–24. [[CrossRef](#)]
172. Charpin, D.; Pichot, C.; Belmonte, J.; Sutra, J.-P.; Zidkova, J.; Chanez, P.; Shahali, Y.; Sénéchal, H.; Poncet, P. Cypress Pollinosis: From Tree to Clinic. *Clin. Rev. Allergy Immunol.* **2019**, *56*, 174–195. [[CrossRef](#)] [[PubMed](#)]
173. Esteves-Caldeira, L.; Neto, M.; Labrador-Horrillo, M.; Pedro, E. Identification of a Thaumatin-like Protein as a New Allergen in Persimmon (*Diospyros kaki*) with Cross-Reactivity with Banana (*Musa acuminata*). *Arq. Asma Alerg. Immunol.* **2021**, *5*, 203–207.
174. Yakhlef, M.; Giangrieco, I.; Ciardiello, M.A.; Fiume, I.; Mari, A.; Souiki, L.; Pocsfalvi, G. Potential Allergenicity of Medicago Sativa Investigated by a Combined IgE-binding Inhibition, Proteomics and in Silico Approach. *J. Sci. Food Agric.* **2021**, *101*, 1182–1192. [[CrossRef](#)]
175. Perrot, T.; Pauly, M.; Ramírez, V. Emerging Roles of β -Glucanases in Plant Development and Adaptive Responses. *Plants* **2022**, *11*, 1119. [[CrossRef](#)]
176. Caseiro, C.; Dias, J.N.; de Andrade Fontes, C.M.; Bule, P. From Cancer Therapy to Winemaking: The Molecular Structure and Applications of β -Glucans and β -1, 3-Glucanases. *Int. J. Mol. Sci.* **2022**, *23*, 3156. [[CrossRef](#)] [[PubMed](#)]
177. Waldron, R.; McGowan, J.; Gordon, N.; Mitchell, E.B.; Fitzpatrick, D.A.; Doyle, S. Characterisation of Three Novel β -1,3 Glucanases from the Medically Important House Dust Mite *Dermatophagoides pteronyssinus* (Airmid). *Insect Biochem. Mol. Biol.* **2019**, *115*, 103242. [[CrossRef](#)]

178. Pablos, I.; Wildner, S.; Asam, C.; Wallner, M.; Gadermaier, G. Pollen Allergens for Molecular Diagnosis. *Curr. Allergy Asthma Rep.* **2016**, *16*, 31. [\[CrossRef\]](#) [\[PubMed\]](#)
179. Torres, M.; Palomares, O.; Quirarte, J.; Pauli, G.; Rodríguez, R.; Villalba, M. An Enzymatically Active β -1,3-Glucanase from Ash Pollen with Allergenic Properties: A Particular Member in the Oleaceae Family. *PLoS ONE* **2015**, *10*, e0133066. [\[CrossRef\]](#)
180. Liu, H.; Lu, X.; Li, M.; Lun, Z.; Yan, X.; Yin, C.; Yuan, G.; Wang, X.; Liu, N.; Liu, D.; et al. Plant Immunity Suppression by an Exo- β -1,3-Glucanase and an Elongation Factor 1 α of the Rice Blast Fungus. *Nat. Commun.* **2023**, *14*, 5491. [\[CrossRef\]](#) [\[PubMed\]](#)
181. Vassilopoulou, E.; Zuidmeer, L.; Akkerdaas, J.; Tassios, I.; Rigby, N.R.; Mills, E.N.C.; van Ree, R.; Saxoni-Papageorgiou, P.; Papadopoulos, N.G. Severe Immediate Allergic Reactions to Grapes: Part of a Lipid Transfer Protein-Associated Clinical Syndrome. *Int. Arch. Allergy Immunol.* **2007**, *143*, 92–102. [\[CrossRef\]](#)
182. Callero, A.; Perez, E.; Ledesma, A.; Martinez-Tadeo, J.A.; Hernandez, G.; Rodríguez-Plata, E.; Garcia-Robaina, J.C. A Case Report of Bell Pepper Anaphylaxis: Could 1, 3- β -Glucanase Be the Culprit Allergen? *Ann. Allergy Asthma Immunol.* **2012**, *109*, 474–475. [\[CrossRef\]](#) [\[PubMed\]](#)
183. Gromek, W.; Kołdej, N.; Świtała, S.; Majsiak, E.; Kurowski, M. Revisiting Latex-Fruit Syndrome after 30 Years of Research: A Comprehensive Literature Review and Description of Two Cases. *J. Clin. Med.* **2024**, *13*, 4222. [\[CrossRef\]](#)
184. Bhinija, K.; Huehne, P.S.; Mongkolsuk, S.; Sitthimonchai, S.; Satayavivad, J. A Short-Chain Dehydrogenase/Reductase (SDR) Detection for the Isoflavone Reductase Gene in Bulbophyllum and Other Orchids. *S. Afr. J. Bot.* **2022**, *144*, 295–304. [\[CrossRef\]](#)
185. Moummou, H.; Kallberg, Y.; Tonfack, L.B.; Persson, B.; van der Rest, B. The Plant Short-Chain Dehydrogenase (SDR) Superfamily: Genome-Wide Inventory and Diversification Patterns. *BMC Plant Biol.* **2012**, *12*, 219. [\[CrossRef\]](#) [\[PubMed\]](#)
186. Gellrich, D.; Eder, K.; San Nicoló, M.; Berghaus, A.; Gröger, M. The Clinical Impact of Bet v 6 in Birch Pollen-Sensitized Patients. *Int. Arch. Allergy Immunol.* **2017**, *173*, 34–43. [\[CrossRef\]](#)
187. Terlouw, S.; van Boven, F.E.; Borsboom-van Zonneveld, M.; de Graaf-In 't Veld, T.; Gerth van Wijk, R.; van Daele, P.L.A.; van Maaren, M.S.; Kuijpers, J.H.S.A.M.; Veenbergen, S.; de Jong, N.W. Comparison of Skin Prick Test and Prick-to-Prick Test with Fruits and Vegetables in the Diagnosis of Food Allergy. *Clin. Transl. Allergy* **2024**, *14*, e12375. [\[CrossRef\]](#)
188. Muraro, A.; Werfel, T.; Hoffmann-Sommergruber, K.; Roberts, G.; Beyer, K.; Bindslev-Jensen, C.; Cardona, V.; Dubois, A.; duToit, G.; Eigenmann, P.; et al. EAACI Food Allergy and Anaphylaxis Guidelines: Diagnosis and Management of Food Allergy. *Allergy* **2014**, *69*, 1008–1025. [\[CrossRef\]](#)
189. Heinzerling, L.; Mari, A.; Bergmann, K.-C.; Bresciani, M.; Burbach, G.; Darsow, U.; Durham, S.; Fokkens, W.; Gjomarkaj, M.; Haahtela, T.; et al. The Skin Prick Test—European Standards. *Clin. Transl. Allergy* **2013**, *3*, 3. [\[CrossRef\]](#) [\[PubMed\]](#)
190. Ansotegui, I.J.; Melioli, G.; Canonica, G.W.; Caraballo, L.; Villa, E.; Ebisawa, M.; Passalacqua, G.; Savi, E.; Ebo, D.; Gómez, R.M.; et al. IgE Allergy Diagnostics and Other Relevant Tests in Allergy, a World Allergy Organization Position Paper. *World Allergy Organ. J.* **2020**, *13*, 100080. [\[CrossRef\]](#) [\[PubMed\]](#)
191. Osterballe, M.; Hansen, T.K.; Mortz, C.G.; Bindslev-Jensen, C. The Clinical Relevance of Sensitization to Pollen-Related Fruits and Vegetables in Unselected Pollen-Sensitized Adults. *Allergy* **2005**, *60*, 218–225. [\[CrossRef\]](#) [\[PubMed\]](#)
192. Macchia, D.; Melioli, G.; Pravettoni, V.; Nucera, E.; Piantanida, M.; Caminati, M.; Campochiario, C.; Yacoub, M.-R.; Schiavino, D.; Paganelli, R. Guidelines for the Use and Interpretation of Diagnostic Methods in Adult Food Allergy. *Clin. Mol. Allergy* **2015**, *13*, 27. [\[CrossRef\]](#) [\[PubMed\]](#)
193. Pitsios, C.; Iliopoulou, A.; Kontogianni, M.; Papagregoriou, G. Detection of Profilin in SPT Extracts That Are Supposed to Contain It. *Allergol. Immunopathol.* **2019**, *47*, 12–15. [\[CrossRef\]](#) [\[PubMed\]](#)
194. Foong, R.-X.; Dantzer, J.A.; Wood, R.A.; Santos, A.F. Improving Diagnostic Accuracy in Food Allergy. *J. Allergy Clin. Immunol. Pract.* **2021**, *9*, 71–80. [\[CrossRef\]](#) [\[PubMed\]](#)
195. Muthupalaniappen, L.; Jamil, A. Prick, Patch or Blood Test? A Simple Guide to Allergy Testing. *Malays. Fam. Physician* **2021**, *16*, 19. [\[CrossRef\]](#) [\[PubMed\]](#)
196. Terlouw, S.; van Boven, F.E.; Borsboom-van Zonneveld, M.; de Graaf-in 't Veld, C.; van Splunter, M.E.; van Daele, P.L.A.; van Maaren, M.S.; Schreurs, M.W.J.; de Jong, N.W. Homemade Food Allergen Extracts for Use in Skin Prick Tests in the Diagnosis of IgE-Mediated Food Allergy: A Good Alternative in the Absence of Commercially Available Extracts? *Nutrients* **2022**, *14*, 475. [\[CrossRef\]](#) [\[PubMed\]](#)
197. Riggioni, C.; Ricci, C.; Moya, B.; Wong, D.; van Goor, E.; Bartha, I.; Buyuktiryaki, B.; Giovannini, M.; Jayasinghe, S.; Jaumdally, H.; et al. Systematic Review and Meta-Analyses on the Accuracy of Diagnostic Tests for IgE-Mediated Food Allergy. *Allergy* **2024**, *79*, 324–352. [\[CrossRef\]](#) [\[PubMed\]](#)
198. Çigerci Günaydın, N.; Eren Akarcan, S.; Gülen, F.; Bal, C.M.; Tanaç, R.; Atasever, M.; Demir, E. Cut-Off Values of Specific IgE and Skin Prick Test to Predict Oral Food Challenge Positivity in Children with Cow's Milk Allergy. *Turkish Arch. Pediatr.* **2022**, *57*, 603–610. [\[CrossRef\]](#) [\[PubMed\]](#)
199. van Hage, M.; Hamsten, C.; Valenta, R. ImmunoCAP Assays: Pros and Cons in Allergology. *J. Allergy Clin. Immunol.* **2017**, *140*, 974–977. [\[CrossRef\]](#) [\[PubMed\]](#)

200. Popescu, F.-D.; Vieru, M. Precision Medicine Allergy Immunoassay Methods for Assessing Immunoglobulin E Sensitization to Aeroallergen Molecules. *World J. Methodol.* **2018**, *8*, 17–36. [[CrossRef](#)] [[PubMed](#)]
201. Nösslinger, H.; Mair, E.; Oostingh, G.J.; Ahlgrimm-Siess, V.; Ringauf, A.; Lang, R. Multiplex Assays in Allergy Diagnosis: Allergy Explorer 2 versus ImmunoCAP ISAC E112i. *Diagnostics* **2024**, *14*, 976. [[CrossRef](#)]
202. Lis, K.; Bartuzi, Z. Selected Technical Aspects of Molecular Allergy Diagnostics. *Curr. Issues Mol. Biol.* **2023**, *45*, 5481–5493. [[CrossRef](#)] [[PubMed](#)]
203. Chen, H.; Jiang, Q.; Yang, Y.; Zhang, W.; Yang, L.; Zhu, R. Cross-Reacting Carbohydrate Determinants Inhibitor Can Improve the Diagnostic Accuracy in Pollen and Food Allergy. *J. Asthma Allergy* **2022**, *15*, 713–725. [[CrossRef](#)] [[PubMed](#)]
204. Platteel, A.C.M.; van der Pol, P.; Murk, J.-L.; Verbrugge-Bakker, I.; Hack-Steemers, M.; Roovers, T.H.W.M.; Heron, M. A Comprehensive Comparison between ISAC and ALEX(2) Multiplex Test Systems. *Clin. Chem. Lab. Med.* **2022**, *60*, 1046–1052. [[CrossRef](#)] [[PubMed](#)]
205. Luengo, O.; Labrador-Horrillo, M. Molecular Allergy Diagnosis in Clinical Practice: Frequently Asked Questions. *J. Investig. Allergol. Clin. Immunol* **2022**, *32*, 1–12. [[CrossRef](#)]
206. Eberlein, B. Basophil Activation as Marker of Clinically Relevant Allergy and Therapy Outcome. *Front. Immunol.* **2020**, *11*, 1815. [[CrossRef](#)]
207. Bergmann, M.M.; Santos, A.F. Basophil Activation Test in the Food Allergy Clinic: Its Current Use and Future Applications. *Expert Rev. Clin. Immunol.* **2024**, *20*, 1297–1304. [[CrossRef](#)] [[PubMed](#)]
208. Santos, A.F.; Kulis, M.D.; Sampson, H.A. Bringing the Next Generation of Food Allergy Diagnostics Into the Clinic. *J. Allergy Clin. Immunol. Pract.* **2022**, *10*, 1–9. [[CrossRef](#)] [[PubMed](#)]
209. Santos, A.F.; Alpan, O.; Hoffmann, H.-J. Basophil Activation Test: Mechanisms and Considerations for Use in Clinical Trials and Clinical Practice. *Allergy* **2021**, *76*, 2420–2432. [[CrossRef](#)]
210. Bourgoin, P.; Dupont, T.; Agabriel, C.; Carsin, A.; Verles, A.; Cabanski, M.; Vitaliti, A.; Busnel, J.-M. Possible Alternative Strategies to Implement Basophil Activation Testing in Multicentric Studies. *Cytom. Part B Clin. Cytom.* **2024**, *106*, 392–404. [[CrossRef](#)]
211. Bird, J.A.; Leonard, S.; Groetch, M.; Assa'ad, A.; Cianferoni, A.; Clark, A.; Crain, M.; Fausnight, T.; Fleischer, D.; Green, T.; et al. Conducting an Oral Food Challenge: An Update to the 2009 Adverse Reactions to Foods Committee Work Group Report. *J. Allergy Clin. Immunol. Pract.* **2020**, *8*, 75–90.e17. [[CrossRef](#)] [[PubMed](#)]
212. Onyimba, F.; Crowe, S.E.; Johnson, S.; Leung, J. Food Allergies and Intolerances: A Clinical Approach to the Diagnosis and Management of Adverse Reactions to Food. *Clin. Gastroenterol. Hepatol.* **2021**, *19*, 2230–2240.e1. [[CrossRef](#)] [[PubMed](#)]
213. Calvani, M.; Bianchi, A.; Reginelli, C.; Peresso, M.; Testa, A. Oral Food Challenge. *Medicina* **2019**, *55*, 651. [[CrossRef](#)]
214. Wasserman, S.; Bégin, P.; Watson, W. IgE-Mediated Food Allergy. *Allergy Asthma Clin. Immunol.* **2018**, *14*, 55. [[CrossRef](#)]
215. Gawryjółek, J.; Wycech, A.; Smyk, A.; Krogulska, A. Difficulties in Interpretation of Oral Food Challenge Results. *Postep. Dermatol. Alergol.* **2021**, *38*, 721–726. [[CrossRef](#)] [[PubMed](#)]
216. Sampath, V.; Abrams, E.M.; Adlou, B.; Akdis, C.; Akdis, M.; Brough, H.A.; Chan, S.; Chatchatee, P.; Chinthrajah, R.S.; Cocco, R.R. Food Allergy across the Globe. *J. Allergy Clin. Immunol.* **2021**, *148*, 1347–1364. [[CrossRef](#)] [[PubMed](#)]
217. Wong, D.S.H.; Santos, A.F. The Future of Food Allergy Diagnosis. *Front. Allergy* **2024**, *5*, 1456585. [[CrossRef](#)] [[PubMed](#)]
218. Skypala, I.J.; Bartra, J.; Ebo, D.G.; Antje Faber, M.; Fernández-Rivas, M.; Gomez, F.; Luengo, O.; Till, S.J.; Asero, R.; Barber, D.; et al. The Diagnosis and Management of Allergic Reactions in Patients Sensitized to Non-Specific Lipid Transfer Proteins. *Allergy* **2021**, *76*, 2433–2446. [[CrossRef](#)] [[PubMed](#)]
219. Ebo, D.G.; Bahri, R.; Tontini, C.; Van Gasse, A.L.; Mertens, C.; Hagendorens, M.M.; Sabato, V.; Elst, J. Mast Cell versus Basophil Activation Test in Allergy: Current Status. *Clin. Exp. Allergy J. Br. Soc. Allergy Clin. Immunol.* **2024**, *54*, 378–387. [[CrossRef](#)]
220. Piletta-Zanin, A.; Ricci, C.; Santos, A.F.; Eigenmann, P.A. BAT and MAT for Diagnosis of Peanut Allergy: A Systematic Review and Meta-Analysis. *Pediatr. Allergy Immunol.* **2024**, *35*, e14140. [[CrossRef](#)] [[PubMed](#)]
221. Rispens, T.; Huijbers, M.G. The Unique Properties of IgG4 and Its Roles in Health and Disease. *Nat. Rev. Immunol.* **2023**, *23*, 763–778. [[CrossRef](#)]
222. Qin, L.; Tang, L.-F.; Cheng, L.; Wang, H.-Y. The Clinical Significance of Allergen-Specific IgG4 in Allergic Diseases. *Front. Immunol.* **2022**, *13*, 1032909. [[CrossRef](#)]
223. Barshow, S.M.; Kulis, M.D.; Burks, A.W.; Kim, E.H. Mechanisms of Oral Immunotherapy. *Clin. Exp. Allergy J. Br. Soc. Allergy Clin. Immunol.* **2021**, *51*, 527–535. [[CrossRef](#)]
224. Scheurer, S.; Junker, A.-C.; He, C.; Schülke, S.; Toda, M. The Role of IgA in the Manifestation and Prevention of Allergic Immune Responses. *Curr. Allergy Asthma Rep.* **2023**, *23*, 589–600. [[CrossRef](#)] [[PubMed](#)]
225. Smeekens, J.M.; Baloh, C.; Lim, N.; Larson, D.; Qin, T.; Wheatley, L.; Kim, E.H.; Jones, S.M.; Burks, A.W.; Kulis, M.D. Peanut-Specific IgG4 and IgA in Saliva Are Modulated by Peanut Oral Immunotherapy. *J. Allergy Clin. Immunol. Pract.* **2022**, *10*, 3270–3275. [[CrossRef](#)] [[PubMed](#)]

226. Sahiner, U.M.; Giovannini, M.; Escribese, M.M.; Paoletti, G.; Heffler, E.; Alvaro Lozano, M.; Barber, D.; Canonica, G.W.; Pfaar, O. Mechanisms of Allergen Immunotherapy and Potential Biomarkers for Clinical Evaluation. *J. Pers. Med.* **2023**, *13*, 845. [[CrossRef](#)] [[PubMed](#)]
227. O'Shea, K.; Hogan, S.P. IgG4 in Eosinophilic Esophagitis: Perpetrator, Accomplice or Bystander? *Ann. Esophagus* **2018**, *1*, 14. [[CrossRef](#)]
228. Stapel, S.; Asero, R.; Ballmer-Weber, B.; Knol, E.; Strobel, S.; Vieths, S.; Kleine-Tebbe, J. Testing for IgG4 against Foods Is Not Recommended as a Diagnostic Tool: EAACI Task Force Report. *Allergy* **2008**, *63*, 793–796. [[CrossRef](#)] [[PubMed](#)]
229. Suprun, M.; Getts, R.; Raghunathan, R.; Grishina, G.; Witmer, M.; Gimenez, G.; Sampson, H.A.; Suárez-Fariñas, M. Novel Bead-Based Epitope Assay Is a Sensitive and Reliable Tool for Profiling Epitope-Specific Antibody Repertoire in Food Allergy. *Sci. Rep.* **2019**, *9*, 18425. [[CrossRef](#)] [[PubMed](#)]
230. Gattinger, P.; Bidovec-Stojkovic, U.; Zidarn, M.; Korosec, P.; Valenta, R.; Mittermann, I. Glycosylation Enhances Allergenic Activity of Major Bee Venom Allergen Api m 1 by Adding IgE Epitopes. *J. Allergy Clin. Immunol.* **2021**, *147*, 1502–1504.e5. [[CrossRef](#)]
231. Shade, K.-T.C.; Conroy, M.E.; Washburn, N.; Kitaoka, M.; Huynh, D.J.; Laprise, E.; Patil, S.U.; Shreffler, W.G.; Anthony, R.M. Sialylation of Immunoglobulin E Is a Determinant of Allergic Pathogenicity. *Nature* **2020**, *582*, 265–270. [[CrossRef](#)]
232. Kim, C.H.; Park, J.; Kim, M. Gut Microbiota-Derived Short-Chain Fatty Acids, T Cells, and Inflammation. *Immune Netw.* **2014**, *14*, 277–288. [[CrossRef](#)]
233. Ohnmacht, C.; Park, J.-H.; Cording, S.; Wing, J.B.; Atarashi, K.; Obata, Y.; Gaboriau-Routhiau, V.; Marques, R.; Dulauroy, S.; Fedoseeva, M. The Microbiota Regulates Type 2 Immunity through ROR γ t⁺ T Cells. *Science* **2015**, *349*, 989–993. [[CrossRef](#)]
234. Kim, C.H. Complex Regulatory Effects of Gut Microbial Short-Chain Fatty Acids on Immune Tolerance and Autoimmunity. *Cell. Mol. Immunol.* **2023**, *20*, 341–350. [[CrossRef](#)] [[PubMed](#)]
235. Komaki, S.; Sahoyama, Y.; Hachiya, T.; Koseki, K.; Ogata, Y.; Hamazato, F.; Shiozawa, M.; Nakagawa, T.; Suda, W.; Hattori, M.; et al. Dimension Reduction of Microbiome Data Linked Bifidobacterium and Prevotella to Allergic Rhinitis. *Sci. Rep.* **2024**, *14*, 7983. [[CrossRef](#)]
236. Zhang, L.; Chun, Y.; Ho, H.-E.; Arditi, Z.; Lo, T.; Sajja, S.; Rose, R.; Jones, D.; Wang, J.; Sicherer, S.; et al. Multiscale Study of the Oral and Gut Environments in Children with High- and Low-Threshold Peanut Allergy. *J. Allergy Clin. Immunol.* **2022**, *150*, 714–720.e2. [[CrossRef](#)] [[PubMed](#)]
237. Hou, K.; Wu, Z.-X.; Chen, X.-Y.; Wang, J.-Q.; Zhang, D.; Xiao, C.; Zhu, D.; Koya, J.B.; Wei, L.; Li, J.; et al. Microbiota in Health and Diseases. *Signal Transduct. Target. Ther.* **2022**, *7*, 135. [[CrossRef](#)] [[PubMed](#)]
238. Ahn, J.; Hayes, R.B. Environmental Influences on the Human Microbiome and Implications for Noncommunicable Disease. *Annu. Rev. Public Health* **2021**, *42*, 277–292. [[CrossRef](#)] [[PubMed](#)]
239. van Breugel, M.; Fehrmann, R.S.N.; Bügel, M.; Rezwan, F.I.; Holloway, J.W.; Nawijn, M.C.; Fontanella, S.; Custovic, A.; Koppelman, G.H. Current State and Prospects of Artificial Intelligence in Allergy. *Allergy* **2023**, *78*, 2623–2643. [[CrossRef](#)]
240. MacMath, D.; Chen, M.; Khoury, P. Artificial Intelligence: Exploring the Future of Innovation in Allergy Immunology. *Curr. Allergy Asthma Rep.* **2023**, *23*, 351–362. [[CrossRef](#)]
241. Kuniyoshi, Y.; Tokutake, H.; Takahashi, N.; Kamura, A.; Yasuda, S.; Tashiro, M. Machine Learning Approach and Oral Food Challenge with Heated Egg. *Pediatr. Allergy Immunol.* **2021**, *32*, 776–778. [[CrossRef](#)] [[PubMed](#)]
242. Zhang, J.; Lee, D.; Jungles, K.; Shaltis, D.; Najarian, K.; Ravikumar, R.; Sanders, G.; Gryak, J. Prediction of Oral Food Challenge Outcomes via Ensemble Learning. *Inform. Med. Unlocked* **2023**, *36*, 101142. [[CrossRef](#)]
243. Cafarotti, A.; Giovannini, M.; Begìn, P.; Brough, H.A.; Arasi, S. Management of IgE-Mediated Food Allergy in the 21st Century. *Clin. Exp. Allergy J. Br. Soc. Allergy Clin. Immunol.* **2023**, *53*, 25–38. [[CrossRef](#)]
244. Chen, P.; Wu, L.; Wang, L. AI Fairness in Data Management and Analytics: A Review on Challenges, Methodologies and Applications. *Appl. Sci.* **2023**, *13*, 10258. [[CrossRef](#)]
245. Fernández-Rivas, M.; Cuevas, M. Peels of Rosaceae Fruits Have a Higher Allergenicity than Pulps. *Clin. Exp. Allergy J. Br. Soc. Allergy Clin. Immunol.* **1999**, *29*, 1239–1247. [[CrossRef](#)] [[PubMed](#)]
246. Leone, L.; Mazzocchi, A.; Maffei, L.; De Cosmi, V.; Agostoni, C. Nutritional Management of Food Allergies: Prevention and Treatment. *Front. Allergy* **2022**, *3*, 1083669. [[CrossRef](#)] [[PubMed](#)]
247. Skypala, I.J. Food-Induced Anaphylaxis: Role of Hidden Allergens and Cofactors. *Front. Immunol.* **2019**, *10*, 673. [[CrossRef](#)] [[PubMed](#)]
248. Church, D.S.; Church, M.K. Pharmacology of Antihistamines. *World Allergy Organ. J.* **2011**, *4*, S22–S27. [[CrossRef](#)]
249. Brunton, L.L.; Knollmann, B.C.; Hilal-Dandan, R. *Goodman & Gilman's the Pharmacological Basis of Therapeutics*; McGraw Hill Medical: New York, NY, USA, 2018; ISBN 1259584739.
250. Yuliana; Zakiawati, D. A Rare Case of Allergic Stomatitis Due to the Consumption of Boiled Cassava. *J. Asthma Allergy* **2024**, *17*, 863–869. [[CrossRef](#)] [[PubMed](#)]
251. Iglesia, E.G.A.; Kwan, M.; Virkud, Y.V.; Iweala, O.I. Management of Food Allergies and Food-Related Anaphylaxis. *JAMA* **2024**, *331*, 510–521. [[CrossRef](#)]

252. Noetzelin, S.; Breville, G.; Seebach, J.D.; Gastaldi, G. Short-Term Glucocorticoid-Related Side Effects and Adverse Reactions: A Narrative Review and Practical Approach. *Swiss Med. Wkly.* **2022**, *152*, w30088. [\[CrossRef\]](#)
253. Weir, A.; Arg  ez, C. *Epinephrine Auto-Injectors for Anaphylaxis: A Review of the Clinical Effectiveness, Cost-Effectiveness, and Guidelines*; Canadian Agency for Drugs and Technologies in Health: Ottawa, ON, USA, 2020.
254. Golden, D.; Wang, J.; Wasserman, S.; Akin, C.; Campbell, R.; Ellis, A.; Greenhawt, M.; Lang, D.; Ledford, D.; Lieberman, J.; et al. Anaphylaxis: A 2023 Practice Parameter Update. *Ann. Allergy Asthma Immunol.* **2023**, *132*, 124–176. [\[CrossRef\]](#) [\[PubMed\]](#)
255. Sakamoto, D.; Hamada, S.; Kobayashi, Y.; Shimono, M.; Shimamura, A.; Kanda, A.; Asako, M.; Iwai, H. Omalizumab Is Effective for a Patient with Pollen-Food Allergy Syndrome Who Experienced Intractable Lip Edema. *Auris Nasus Larynx* **2023**, *50*, 805–810. [\[CrossRef\]](#)
256. Baharudin, A.; Abdul Latiff, A.H.; Woo, K.; Yap, F.B.-B.; Tang, I.P.; Leong, K.F.; Chin, W.S.; Wang, D.Y. Using Patient Profiles To Guide The Choice Of Antihistamines In The Primary Care Setting In Malaysia: Expert Consensus And Recommendations. *Ther. Clin. Risk Manag.* **2019**, *15*, 1267–1275. [\[CrossRef\]](#)
257. Prince, B.T.; Mikhail, I.; Stukus, D.R. Underuse of Epinephrine for the Treatment of Anaphylaxis: Missed Opportunities. *J. Asthma Allergy* **2018**, *11*, 143–151. [\[CrossRef\]](#)
258. Roberts, G.; Pfaar, O.; Akdis, C.A.; Ansotegui, I.J.; Durham, S.R.; Gerth van Wijk, R.; Halken, S.; Larenas-Linnemann, D.; Pawankar, R.; Pitsios, C. EAACI Guidelines on Allergen Immunotherapy: Allergic Rhinoconjunctivitis. *Allergy* **2018**, *73*, 765–798. [\[CrossRef\]](#) [\[PubMed\]](#)
259. Dhami, S.; Zaman, H.; Varga, E.-M.; Sturm, G.J.; Muraro, A.; Akdis, C.A.; Antol  n-Am  rigo, D.; Bil  , M.B.; Bokanovic, D.; Calderon, M.A.; et al. Allergen Immunotherapy for Insect Venom Allergy: A Systematic Review and Meta-Analysis. *Allergy* **2017**, *72*, 342–365. [\[CrossRef\]](#)
260. Alvaro-Lozano, M.; Akdis, C.A.; Akdis, M.; Alviani, C.; Angier, E.; Arasi, S.; Arzt-Gradwohl, L.; Barber, D.; Bazire, R.; Cavkaytar, O.; et al. EAACI Allergen Immunotherapy User’s Guide. *Pediatr. Allergy Immunol.* **2020**, *31* (Suppl. 2), 1–101. [\[CrossRef\]](#) [\[PubMed\]](#)
261. L  pez, J.-F.; Imam, M.B.; Satitsuksanoa, P.; Lems, S.; Yang, M.; Hwang, Y.-K.; Losol, P.; Choi, J.-P.; Kim, S.-H.; Chang, Y.-S. Mechanisms and Biomarkers of Successful Allergen-Specific Immunotherapy. *Asia Pac. Allergy* **2022**, *12*, e45. [\[CrossRef\]](#)
262. Koml  si, Z.I.; Kov  cs, N.; Sokolowska, M.; van de Veen, W.; Akdis, M.; Akdis, C.A. Mechanisms of Subcutaneous and Sublingual Aeroallergen Immunotherapy: What Is New? *Immunol. Allergy Clin.* **2020**, *40*, 1–14. [\[CrossRef\]](#)
263. Kucuksezer, U.C.; Ozdemir, C.; Cevhertas, L.; Ogulur, I.; Akdis, M.; Akdis, C.A. Mechanisms of Allergen-Specific Immunotherapy and Allergen Tolerance. *Allergol. Int.* **2020**, *69*, 549–560. [\[CrossRef\]](#) [\[PubMed\]](#)
264. Kallen, E.J.J.; Welsing, P.M.J.; L  wik, J.M.; Van Ree, R.; Knulst, A.C.; Le, T.M. The Effect of Subcutaneous and Sublingual Birch Pollen Immunotherapy on Birch Pollen-Related Food Allergy: A Systematic Review. *Front. Allergy* **2024**, *5*, 1360073. [\[CrossRef\]](#) [\[PubMed\]](#)
265. Hamada, M.; Kagawa, M.; Tanaka, I. Evaluation of Subcutaneous Immunotherapy with Birch Pollen Extract for Pollen-Food Allergy Syndrome. *Asia Pac. Allergy* **2021**, *11*, e39. [\[CrossRef\]](#)
266. Furci, F.; Ricciardi, L. Plant Food Allergy Improvement after Grass Pollen Sublingual Immunotherapy: A Case Series. *Pathogens* **2021**, *10*, 1412. [\[CrossRef\]](#) [\[PubMed\]](#)
267. Inuo, C.; Kondo, Y.; Tanaka, K.; Nakajima, Y.; Nomura, T.; Ando, H.; Suzuki, S.; Tsuge, I.; Yoshikawa, T.; Urisu, A. Japanese Cedar Pollen-Based Subcutaneous Immunotherapy Decreases Tomato Fruit-Specific Basophil Activation. *Int. Arch. Allergy Immunol.* **2015**, *167*, 137–145. [\[CrossRef\]](#)
268. Werfel, T.; Asero, R.; Ballmer-Weber, B.K.; Beyer, K.; Enrique, E.; Knulst, A.C.; Mari, A.; Muraro, A.; Ollert, M.; Poulsen, L.K. Position Paper of the EAACI: Food Allergy Due to Immunological Cross-reactions with Common Inhalant Allergens. *Allergy* **2015**, *70*, 1079–1090. [\[CrossRef\]](#) [\[PubMed\]](#)
269. Dijkema, D.; Ruitenbeek, M.C.; Weerstand-Noor, K.; Oude Elberink, H.N.G.; van de Ven, A.A.J.M. Outcomes of Apple Oral Immunotherapy in Pollen Food Allergy Syndrome. *J. Allergy Clin. Immunol. Glob.* **2024**, *3*, 100271. [\[CrossRef\]](#) [\[PubMed\]](#)
270. Mori, F.; Barni, S.; Liccioli, G.; Novembre, E. Oral Immunotherapy (OIT): A Personalized Medicine. *Medicina* **2019**, *55*, 684. [\[CrossRef\]](#)
271. Block, W.; Shapiro, B.; Neeno, T. Non-Daily OIT Dose Frequency May Be Safe and Effective. *J. Allergy Clin. Immunol.* **2021**, *147*, AB107. [\[CrossRef\]](#)

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.