allergies

Review

The Role of Bacterial Toxins and Environmental Factors in the Development of Food Allergies

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Abstract: Food allergies (FAs) represent a significant and growing global health issue, with increasing prevalence across different age groups. This review provides a comprehensive analysis of the epidemiology, mechanisms, and risk factors involved in FA development. Currently, FAs are estimated to affect 2% of the general population, with higher rates in children (~8%). However, these figures may be inaccurate because of the reliance on self-reported data and immunoglobulin E (IgE) testing, which may not reflect clinically confirmed cases. Environmental and genetic factors, including exposure to bacterial toxins, dietary habits, and the gut microbiota, play critical roles in FA development. Specifically, Staphylococcus aureus enterotoxins are implicated in disrupting intestinal barriers and enhancing immune sensitization to allergenic proteins. This immune dysregulation promotes Th2 responses and compromises regulatory T cell function, crucial elements in allergy pathogenesis. As the prevalence of FAs continues to rise, there is a pressing need for accurate diagnostic tools, heightened public awareness, and effective prevention strategies. Further research is needed to elucidate the specific role of bacterial toxins and other environmental factors in FA development to advance clinical management approaches.

Keywords: food allergies; epidemiology; prevalence; mechanisms; food additives; hypersensitivity; anaphylaxis; public health

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1. Introduction

The increasing prevalence of food allergies (FAs) is a significant public health concern, as evidenced by numerous epidemiological studies that highlight a troubling rise in reported cases. Current estimates suggest that approximately 2% of the general population is affected by FAs, although self-reported figures often indicate higher prevalence rates. For instance, a survey conducted in Saudi Arabia reported a self-reported prevalence of FAs among adults at 13%, while physician-diagnosed cases were only 6.5% [1]. Similarly, a study in Canada found that 12.1% of participants self-reported FAs, contrasting with national data that suggested a lower prevalence of 9.3% [2]. This discrepancy between self-reported and clinically confirmed cases raises critical questions regarding the reliability of these statistics, as they often rely on subjective reporting methods and specific IgE antibody tests, which may not accurately reflect true allergic responses [3]. While adults generally exhibit lower rates of FAs, children are particularly vulnerable, with food additives identified as a notable cause of hypersensitivity, affecting an estimated 1.2% of this population [4]. The most common allergens include cow milk, eggs, peanuts, tree

nuts, fish, and shellfish, with factors such as maternal heredity and early feeding practices playing a role in the development of food hypersensitivity [5].

FAs are complicated phenomena that involve both IgE-mediated and non-IgE-mediated immune responses and are influenced by genetic and environmental factors [6,7]. Understanding the mechanisms that contribute to FAs is essential, as these conditions not only impact the quality of life of affected individuals but also impose significant healthcare costs and societal burdens [8]. This comprehensive review aims to critically evaluate the current understanding of the mechanisms underlying FAs and assess the effectiveness of existing management strategies. Despite intensive research, the precise factors driving the increasing prevalence of FAs remain only partially understood, highlighting the need for further investigations into genetic predispositions and environmental triggers, including the role of the gut microbiota and death habits [9,10].

The aim of this review is to summarize current findings on FA epidemiology, analyze the multifactorial mechanisms involved in FA development, and evaluate the effects of FA on the quality of life of affected individuals. Recent advances in gene–environment interactions in FAs highlight the importance of this synthesis for future research and clinical practice. To address the increasing prevalence of FAs, accurate diagnosis, patient education, and effective treatment are needed to prevent life-threatening reactions. Raising awareness among healthcare professionals and the general public is crucial for improving the quality of life of those affected. Elucidating the role of food additives in allergic reactions, especially in children, is crucial for effective prevention and treatment. In addition, studying the interactions between food additives and environmental factors such as pollen levels and air pollution is crucial to understanding the development of allergies and identifying high-risk populations.

2. Prevalence and Epidemiology of FAs

2.1. Prevalence of FAs

The prevalence of FAs varies across different age groups and populations, reflecting a complex interplay of genetic, environmental, and methodological factors. Approximately 8% of children are affected by FAs, with peanuts, milk, and eggs being the most common allergens [11]. The prevalence of symptoms in Korean children aged 6–12 years is 19.7% [12]. In contrast, the prevalence in adults is approximately 2%, with self-reported adverse reactions in Lithuania schoolchildren being 16.4% [13]. A study in Istanbul reported a self-reported lifetime prevalence of 9.5% for FAs and nonallergic food hypersensitivity (FA/NAFH), but the percentage of clinically confirmed cases was only 0.3% [14]. Discrepancies between self-reported and clinically confirmed cases highlight the challenges in accurately determining FA prevalence.

2.2. Epidemiological Factors

The epidemiology of FAs is influenced by various factors, including sex and age. Self-reported adverse food reactions range from 5 to 33%, with women reporting higher frequencies [6,13]. The prevalence of stringent testing methods, such as double-blind placebo-controlled challenges, is estimated to be approximately 2% in the general population [15]. Pregnancy increases the risk of FAs in women, with approximately 20% of women being affected [6,13].

2.3. Global Perspective

FAs are more common in developed countries, affecting up to 5% of adults and 8% of children [10,16]. In Canada, the self-reported prevalence of FAs is 12.1%, with a household prevalence of 14.9%, in contrast to the national estimate of 9.3% [2]. In the United States, the prevalence of FAs in adults is between 10% and 13%, with physician-diagnosed cases accounting for approximately 6% of FAs [17]. These discrepancies between self-reported and clinically diagnosed cases highlight the tendency of self-reported data to overestimate prevalence [18] . The prevalence of FAs varies widely around the world. A systematic review reported rates ranging from 1% in Thailand to 10% in Australia among children [19].

In Europe, a meta-analysis revealed significant differences in the prevalence of FAs between countries and populations [20]. In South Africa, 2.5% of children aged 12 to 36 months suffer from FAs, whereas in China, 3.8% of infants suffer from FAs [21]. Reliance on self-reported data complicates the epidemiological landscape and often leads to inflated prevalence estimates. For example, some studies reported a self-reported prevalence of up to 17% for milk allergies [22]. This inconsistency highlights the need for objective diagnostic measures such as double-blind placebo-controlled food testing to accurately determine prevalence [23]. The increasing prevalence of FAs is not limited to only children; recent studies have shown an increasing trend in FAs occurring in adults and increasing in the affected population [24]. This shift requires a comprehensive understanding of the epidemiology of FAs, including the identification of risk factors and the development of effective management strategies.

3. Gene–Environment and Molecular Mechanisms in FA Development

Gene–environment interactions are crucial in the development of FAs and involve a complex relationship between genetic predispositions and environmental factors. Both genetic and environmental influences are essential for understanding the causes of FAs. Specific genetic polymorphisms, such as those in the SPINK5, STAT6, HLA, and FOXP3 genes, are linked to an increased susceptibility to FAs, as these genes play key roles in immune regulation and inflammatory responses [25].

Environmental factors encompass a range of influences, including dietary habits, exposure to pollutants, and early-life microbiota. Maternal nutrition during pregnancy, particularly the intake of omega-3 fatty acids and vitamin D, is associated with a lower risk of FAs in children [25]. Additionally, exposure to allergens and pollutants during critical periods of immune development can increase genetic vulnerability, leading to a greater incidence of FAs [26]. The impact of the outdoor environment on FA risk involves complex interactions among factors such as vitamin D, air pollution, greenery, and pollen (Figure 1).

UVB radiation, which varies by latitude, influences vitamin D production, whereas vegetation levels affect outdoor activity, UVB exposure, and pollen or mold exposure. Dense greenery can block UVB radiation. Environmental microbiota diversity is correlated with vegetation levels and pollen exposure is linked to greenery. Air pollution can increase pollen allergenicity and stimulate IgE responses [27–29]. Vegetation can modulate pollution levels and pollution can damage vegetation [30,31]. Allergy development may involve pollution, chemicals, inflammation, infection, microbiome changes, allergen exposure, and genetics [32]. Animal studies suggest that peanut sensitization via the respiratory route potentially explains higher urban FA rates [33]. A systems approach considering interrelationships among environmental factors may be crucial for understanding their links to FAs and human health [32,34–37].

The microbial exposure and biodiversity hypotheses examine how microbial exposure influences immune system development and allergy risk. The microbial exposure hypothesis posits that insufficient early microbial exposure can impair immune system development and increase allergy risk. In contrast, the biodiversity hypothesis asserts that exposure to diverse environments, which introduce a variety of microbes, supports a healthy immune system and a balanced gut microbiome [34,35]. Skin and gut microbes are essential for shaping immune responses, and disruptions in these microbial communities can lead to allergic reactions and increased IgE production [38–40]. Research indicates that children with FAs often possess different gut microbiotas than those without allergies [41,42]. For example, children raised on farms with regular animal contact exhibit lower allergy rates than urban-raised children do [40].

Industrialization has increased air pollution exposure from vehicles, diesel exhaust, and bushfires, increasing pollutants such as particulate matter (PM) and nitrous oxide (NO). While the link between air pollution and respiratory allergies, such as asthma, is well documented, its impact on FAs remains unclear. Air pollution may affect allergic disease through several mechanisms. Epithelial cells in the skin, gut, and respiratory tract serve as

barriers against pollutants. Exposure can trigger inflammation and disrupt the epithelial barrier, allowing allergens to penetrate deeper into tissues and enter the bloodstream [32,43]. Studies regarding air pollution and food sensitization yield mixed results, with some suggesting that increased PM2.5 exposure is correlated with increased risk [44–46]. Urban expansion has reduced natural green spaces. Environmental greenness, including that of trees, shrubs, and grasses, supports microbial diversity and overall health [47]. Green spaces are linked to improved mental and cardiovascular health and reduced mortality [48–52]. The biodiversity hypothesis suggests that exposure to green environments enhances microbial diversity and supports immune health [35,53]. Green environments can mitigate the adverse effects of environmental factors such as air pollution, enhance air quality, and reduce health issues related to pollution exposure. However, research on greenness and allergies is limited. A German study revealed no strong link between residential greenness and food sensitization but noted that exposure to allergenic trees increased food sensitization [54], possibly because of the cross-reactivity between pollen and food allergens [55,56]. The HealthNuts study indicated that increased exposure to environmental greenness was correlated with a greater risk of peanut and egg allergies [57]. While some studies suggest that more green space might protect against conditions such as asthma and allergic rhinitis [58–61], others indicate an increased risk [62–64]. Pollen affects the immune system and can trigger allergies. Pollen proteins and lipids influence immune cells and damage the airway epithelial barrier, potentially increasing allergen uptake [65]. Research indicates that high pollen levels may facilitate food sensitization by damaging the epithelial barrier and increasing allergen exposure [33]. The Australian HealthNuts study revealed that exposure to grass pollen during pregnancy and the first year of life increased the risk of food sensitization in infants at 12 months, especially in those with a family history of FAs [66]. Cross-reactivity between food and pollen allergens, such as peanuts and birch or plane tree pollen, also contributes to this risk [67,68]. Increased environmental allergen exposure may prime the immune system to react more strongly to related food allergens.

Gene–environment interactions inform public health initiatives aimed at reducing the prevalence of FAs. Identifying specific environmental triggers that interact with genetic predispositions can guide targeted interventions, such as dietary recommendations for pregnant women and infants, to mitigate the risk of FAs [25]. Recognizing the role of early-life exposure in shaping immune responses can inform strategies to promote healthy microbiota development, which is crucial for immune system maturation [26].

The global rise in FAs is significantly influenced by bacterial and environmental factors. Research by Berni Canani and colleagues [69] emphasized that early-life microbial dysbiosis is crucial in the onset of FAs, suggesting that a balanced gut microbiome may prevent such allergies. Similarly, Ling et al. [70] reported that alterations in the composition of the fecal microbiota are associated with FAs in infants, suggesting that specific bacterial communities influence immune responses related to food hypersensitivity. The role of interleukin-10 (IL-10) in regulating immune responses against commensal bacteria indicates that a healthy microbiota can modulate immune tolerance and reduce allergic reactions. Furthermore, the administration of probiotics, such as Bifidobacterium breve, has been shown to alter the gut microbiota and alleviate FAs through specific signaling pathways, supporting the role of the microbial composition in FA management.

Environmental factors significantly contribute to FA incidence. Nonoral food allergens in house dust are linked to food sensitization and allergy development [71,72]. Genetic predispositions, such as HLA polymorphisms, interact with environmental exposures, including dietary habits, pollution, and infections, to influence FA likelihood. Rural settlement and early microbial exposure associated with high-microbial environments may protect against FAs by modulating the infant microbiome [72,73], whereas urbanization and reduced microbial exposure may increase the risk [72]. Geographical variation in seafood allergy prevalence suggests that local dietary practices and environmental exposures influence allergic reactions. Prenatal exposure to environmental tobacco smoke is

linked to increased allergy susceptibility in offspring. Marrs et al. [40] highlighted the complex relationship between microbial exposure and FAs, with certain bacterial exposures either mitigating or exacerbating allergy risk. Early-life exposure to diverse microbial environments, such as rural settings, correlates with lower FA incidence than exposure to urban environments with reduced microbial diversity. The impacts of air pollution and climate change on development remain unclear because of inconsistent findings in cohort studies [72,73]. The protective role of endotoxin exposure against food sensitization is debated, with conflicting evidence on its effectiveness [71]. The complexity of external exposomes and genetic factors necessitates further research to develop effective interventions [72]. FA incidence in the Chinese population, highlighting the importance of specific IgE sensitization and food challenges in diagnosing FAs and revealing significant geographic and environmental variations in prevalence [74]. Pursey et al. [75] reported that food addiction, which is influenced by environmental factors, is common among those with FAs. Additionally, Hulin et al. [76] demonstrated that indoor air pollution in urban areas is correlated with increased respiratory issues, potentially extending to FAs, especially in children. The authors Kostara et al. [77] noted that genetic factors, such as HLA polymorphisms, interact with environmental exposures, complicating the understanding of FA incidence. Table 1 summarizes the key factors, mechanisms, and research directions related to FAs, highlighting the need for continued research.

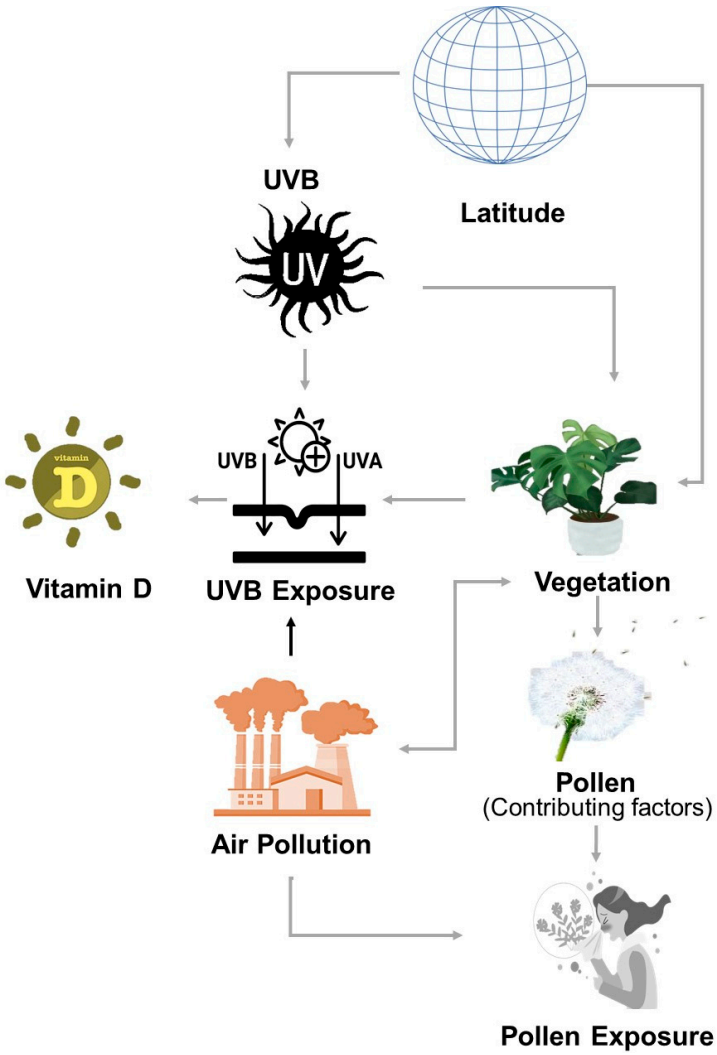

Figure 1. Interplay of environmental factors in FA development. This figure illustrates the complex interrelationships among vitamin D, air pollution, environmental greenness, and pollen exposure, highlighting their potential roles as contributing factors in the development of FAs.

Table 1. Overview of immune and molecular mechanisms and epithelial barrier dysfunction in FA pathogenesis.

Immunological Process	Key Mechanistic Components	Mechanistic Overview	Description
Induction of Allergic Immune Responses	Food Allergen Processing	Breakdown and recognition of food allergens by hydrolytic enzymes in the gastrointestinal tract. Processed by antigen-presenting cells (APCs) and recognized by antigen-specific T cells.	Upon ingestion, food allergens encounter digestive enzymes like proteases and lipases that break them down into smaller peptides. These peptides are processed by dendritic cells (DCs) and macrophages, which present them to T cells, initiating an immune response.
	Th2 Cell Differentiation	Naïve T helper cells differentiate into Th2 cells under the influence of IL-4, promoting IL-4, IL-5, IL-10, and IL-13 secretion, leading to IgE production by B cells.	IL-4 plays a crucial role in shifting immune responses toward a Th2 phenotype. The secretion of IL-4 and IL-13 promotes class switching in B cells, resulting in the production of allergen-specific IgE, which is central to allergic reactions.
	Mast Cell Activation	IgE binds to FcεRI receptors on mast cells and basophils, triggering degranulation and mediator release (e.g., histamine) during antigen re-exposure.	Upon re-exposure to the allergen, cross-linking of IgE molecules on mast cells and basophils leads to the release of histamine, leukotrienes, and prostaglandins, causing symptoms like vasodilation, bronchoconstriction, and mucus production in allergic individuals.
	Influence of Cooking on Allergenicity	Cooking can reduce (e.g., peanut allergens Ara h 1 in fried or boiled peanuts) or increase allergenicity (e.g., shellfish allergens increase post-heating).	Cooking methods, such as boiling, can denature food proteins, making them less recognizable by the immune system and thus reducing allergenicity. However, in some cases like with shellfish, heat can enhance allergenicity by exposing IgE-binding epitopes that are normally hidden.
Oral Tolerance	Development of Tolerance	Occurs in the gut-associated lymphoid tissue (GALT), where a breakdown leads to allergic responses.	Oral tolerance involves the immune system becoming desensitized to food antigens that are consistently encountered in the diet. When oral tolerance is lost, the immune system instead mounts an allergic response, characterized by the production of allergen-specific IgE.
	Mechanisms	Involves antigen recognition by dendritic cells, followed by the induction of T regulatory cells (Tregs) and B regulatory cells (Bregs). The gut environment, such as metabolites, modulates responses.	The gut microbiome and its metabolites (e.g., SCFAs) play a crucial role in maintaining immune homeostasis. Tregs induced in response to dietary antigens help suppress aberrant Th2 responses, maintaining tolerance. Disruptions to this environment lead to allergy.
Dendritic Cells (DCs)	Antigen Uptake and Migration	Antigens are taken up by M cells and GAPs, transferred to dendritic cells. Tolerogenic CD103 $^{+}$ CX3CR1^{-} DCs promote Treg development, while CX3CR1 $^{+}$ DCs are inflammatory.	DCs in the gut sample food antigens through specialized epithelial cells like M cells or goblet cell-associated passages (GAPs). Tolerogenic DCs promote immune tolerance, whereas inflammatory DCs contribute to sensitization and allergic inflammation.
	Treg Induction	Tolerogenic CD103^{+} DCs migrate to mesenteric lymph nodes, promoting Treg induction via TGF-β and RALDH2.	Tolerogenic DCs express the enzyme RALDH2, which converts vitamin A into retinoic acid, crucial for the differentiation of Tregs. These cells produce immunosuppressive cytokines like IL-10, which are essential for the suppression of allergic responses.
T Regulatory Cells (Tregs)	Role in Allergy and Tolerance	Th2 cells drive allergic inflammation, while Tregs (FOXP3^{+} and Th3 cells) regulate immune tolerance, maintaining the balance between allergy and tolerance.	Tregs are central to maintaining peripheral tolerance to food antigens. They inhibit effector Th2 responses through the production of IL-10 and TGF-β, thereby preventing the activation of the allergic cascade. The disruption of Treg function can lead to allergic diseases.
	Mechanisms of Treg Function	Tregs secrete IL-10 and TGF-β to inhibit APCs and suppress effector T cell proliferation, crucial for maintaining tolerance. Dysfunction results in allergic inflammation.	Tregs exert their regulatory effects by directly suppressing antigen presentation by DCs and macrophages and by dampening the activity of effector T cells. This prevents excessive immune responses, helping maintain immune homeostasis in the gut and peripheral tissues.

Table 1. *Cont.*

Immunological Process	Key Mechanistic Components	Mechanistic Overview	Description
B Regulatory Cells (Bregs)	Suppression of Allergic Responses	Bregs suppress effector T cells by producing IL-10, TGF-β, and IL-35. They contribute to tolerance by producing IgG4, which inhibits the IgE-mediated degranulation of mast cells and basophils.	Bregs support immune tolerance by secreting anti-inflammatory cytokines and producing IgG4 antibodies that block allergen–IgE interactions. Their regulatory role extends to suppressing T cell proliferation and dampening DC activation, further preventing allergic responses.
	Mucosal Tolerance	Bregs maintain mucosal tolerance, involving IL-10-producing $CD5^+$ Bregs and interaction with $CD40L^+$ ILC3s.	Bregs are essential for mucosal tolerance, particularly in the gut. Their production of IL-10 and interaction with innate lymphoid cells (ILC3s) help preserve barrier integrity and prevent excessive immune activation against food antigens.
Epithelial Barrier Dysfunction	Impaired Barrier Integrity	The disruption of epithelial tight junctions by pro-inflammatory cytokines (e.g., IL-4, IL-13) increases permeability, allowing allergen penetration and immune system exposure.	Epithelial cells form a physical barrier that prevents allergens from entering the systemic circulation. Th2 cytokines like IL-4 and IL-13 weaken this barrier by disrupting tight junctions, increasing the likelihood of allergen translocation and subsequent immune activation.
	Molecular Mechanisms of Barrier Loss	IL-33, TSLP, and IL-25 released by epithelial cells activate ILC2s and Th2 cells, enhancing allergic inflammation and contributing to barrier breakdown.	Epithelial damage leads to the release of danger signals like IL-33 and TSLP, which activate innate and adaptive immune responses. This further weakens the barrier, perpetuating inflammation and increasing allergen penetration, aggravating the allergic response.
Molecular Pathways	JAK-STAT Signaling Pathways	IL-4/IL-13-mediated signaling through JAK-STAT pathways promotes Th2 differentiation, IgE class switching in B cells, and epithelial barrier dysfunction.	The JAK-STAT pathway is a critical signaling mechanism for Th2 cytokines. In allergic individuals, this pathway is hyperactive, promoting the overproduction of IgE and impairing epithelial function. Targeting this pathway is a therapeutic strategy in allergic diseases.
	MAPK and NF-κB Pathways	These pathways drive the inflammatory response in allergic reactions, regulating cytokine production (e.g., TNF-α, IL-6) and promoting epithelial barrier dysfunction.	MAPK and NF-κB are key transcriptional pathways that regulate the expression of pro-inflammatory cytokines during allergic responses. Their activation contributes to tissue inflammation, airway remodeling, and the breakdown of the epithelial barrier.

Abbreviations: IL: Interleukin; IgE: immunoglobulin E; TGF-β: transforming growth factor beta; Treg: regulatory T cells; Breg: regulatory B cells; FOXP3: Forkhead box P3; DCs: dendritic cells; GALT: gut-associated lymphoid tissue; M Cells: microfold cells; GAPs: goblet-associated Paneth cells; ILC3s: innate lymphoid cells type 3; CD: cluster of differentiation; RA: retinoic acid; SCFAs: short-chain fatty acids.

3.1. The Role of Epigenetic Modifications in FAs

Epigenetic modifications, especially DNA methylation and histone modifications, play pivotal roles in the development and regulation of FAs by influencing gene expression and immune responses, thereby affecting susceptibility. DNA methylation involves adding a methyl group to cytosine bases, leading to gene silencing and regulating immune responses related to FAs. Abbring et al. (2019) reported that raw cow milk consumption increases DNA demethylation of the FoxP3 gene, which is essential for regulatory T cells (Tregs) that maintain immune tolerance, highlighting the influence of diet on immune tolerance through epigenetic mechanisms [78]. Krajewski et al. (2018) reported that curcumin in turmeric suppresses mast cell responses and modulates histone acetylation, which is crucial for managing mast cell-mediated allergic reactions [79]. These findings underscore the need to understand the environmental impacts of FA susceptibility on DNA methylation and gene–environment interactions.

Histone modifications, which involve chemical changes to histone proteins around DNA, affect chromatin structure and gene accessibility, influencing gene expression. The authors [80] reported decreased histone acetylation at Th1 and regulatory loci after FA induction, indicating the role of histone modifications in immune responses to allergens [80]. Martino et al. (2018) reported specific DNA methylation patterns in naïve $CD4^+$ T cells from allergic children linked to dysregulated immune responses, suggesting that epigenetic alterations contribute to FA development through modified T cell activation [81]. This interplay between histone modifications and immune cell function highlights the complexity of epigenetic regulation in FA pathogenesis.

The interaction between DNA methylation and histone modifications is crucial in FAs. Zhou et al. (2021) emphasized that dietary components can regulate these mechanisms, altering immune gene development and function [82]. Early dietary exposure may influence the epigenetic regulation of immune responses, suggesting that diet can modulate epigenetic mechanisms involved in allergy susceptibility. Neeland et al. (2021) noted that FA prevalence disparities among demographic groups might be due to genetic and environmental factors, underscoring the need for studies considering these interactions [83].

3.2. Mechanisms of Cross-Reactivity and Sensitization

Cross-reactivity and sensitization in FAs involve complex immune responses to structurally similar proteins from different sources, notably in individuals with pre-existing allergies. Contact with cross-reactive allergens can cause severe reactions due to structural homology between allergens, as documented in the scientific literature. For example, those allergic to bananas may react to other fruits with similar protein structures. Research indicates that the degree of homology, allergen stability, and augmentation factors influence the severity of allergic reactions, potentially triggering anaphylaxis in those with banana allergies [84]. Latex–fruit syndrome exemplifies this, where individuals with latex allergies react to fruits that share allergenic structures such as profilins and lipid transfer proteins [85].

Pollen complicates FAs via cross-reactivity. Cuesto et al. reported that certain pollen allergens can cross-react with food proteins, causing allergies in pollen-sensitized individuals [86]. Skypala et al. reported that oral allergy syndrome (OAS) is often triggered by IgE cross-reactivity between pollen and food proteins, especially in raw fruits and vegetables [87]. Pollen–food syndromes (PFSs), which can be more severe than typical OASs, explain these reactions [88]. Thaumatin-like proteins (TLPs) are allergens in various plant foods and pollens that contribute to cross-reactivity [89]. Peach TLPs, identified as major allergens, further highlight these complex mechanisms [90].

The clinical implications of cross-reactivity include potential misdiagnosis or underestimation of FA severity. Ribeiro et al.'s review revealed allergic risks from edible insects and noted that shellfish-allergic individuals may react to insects because they share allergenic proteins such as tropomyosin [91]. Comprehensive allergen assessments are crucial, particularly for novel foods, as evidenced by a severe crocodile meat allergy in a child, necessitating further research into cross-reactivities [92]. Effective management and patient education require the classification of food allergens and their cross-reactivity. Francis et al. noted that while immunologic cross-sensitization is common, some food allergen groups, such as tree nuts and shellfish, have high clinical cross-reactivity rates and require careful

dietary management [93]. Ebo et al. reported severe reactions to fruits and vegetables in cannabis-sensitized patients, further complicating the FA landscape [88].

Comparing peanut allergies with other tree nut allergies provides insights into cross-reactivity and sensitization mechanisms. Research has shown that peanut-allergic individuals often exhibit sensitization to various tree nuts, complicating their diagnosis and management. A study indicated that specific kiwi seed allergens cross-react with peanuts and tree nuts, with many patients sensitized to these kiwi allergens also showing IgE reactivity to peanuts and tree nuts [94]. This aligns with Odijk et al., who documented immunological cross-reactivity between homologous storage proteins in nuts, seeds, and legumes, highlighting the complexity of cross-reactivity among these food groups [26]. Approximately 20–40% of peanut-allergic individuals also have concomitant allergies to related tree nuts [95]. This is supported by findings that children allergic to Brazil nuts often have more severe reactions than those with peanut allergies [96].

The allergenic profiles of tree nuts significantly contribute to cross-reactivity. For example, a study revealed that cashew nut-allergic patients often cross-react with pistachio nuts, with many also being sensitized to peanuts [97]. Understanding the allergenic similarities between tree nuts and peanuts is crucial, as patients may react to multiple allergens because of their shared protein structures. Furthermore, 11S globulins and 2S albumins play a significant role in cross-reactivity, as these proteins contribute to the cross-reactive potential between peanuts and tree nuts such as almonds, hazelnuts, and walnuts [7,94]. This information is particularly relevant in clinical settings, where patients with a single nut allergy are often advised to avoid all nuts to prevent severe allergic reactions.

3.3. Cross-Reactivity and Sensitization Mechanisms in Peanut Allergies

Peanut allergies involves cross-reactivity with other legumes and tree nuts, facilitated by various allergens and sensitization mechanisms. IgE cross-reactivity between peanut allergens and those from other legumes and tree nuts has been demonstrated, although specific allergens have not been fully identified [98]. Patterns of cross-reactivity are noted between peanuts and lupines, peanuts and soy, and certain tree nuts, but the clinical relevance of these patterns varies [99]. Sensitization to peanut allergens can occur through nonoral exposure, likely via the respiratory tract [100]. The bronchial epithelium reacts to the major peanut allergens Ara h 1 and Ara h 2, which cross the epithelial barrier and trigger pro-inflammatory mediators, whereas peanut lipids may enhance barrier function and reduce allergen transport [100]. Clinically, cross-reactivity between peanuts and other nuts is relatively low, with an estimated 30% cross-reactivity rate [101]. These findings suggest that many peanut allergy cases arise independently of cross-reactivity. For example, despite high cross-reactivity between walnuts and pecans, these nuts do not significantly cross-react with peanuts, indicating sensitization without cross-reactive responses [101]. The structural similarities between peanut allergens and those in other legumes complicate diagnosis and management, but component-resolved diagnostics and targeted immunotherapy offer promising improvements [55,102]. Component-resolved diagnostics have shown that specific peanut allergens, such as Ara h 2 and Ara h 6, share structural similarities with allergens in other legumes, leading to cross-reactive sensitization [55]. Ara h 8, which is homologous to the birch pollen allergen Bet v 1, is linked with pollen–food allergy syndrome, causing reactions to both birch pollen and peanuts [55]. Approximately 50% of peanut-allergic individuals also show sensitization to other legumes, such as soybeans and lentils [103]. These findings highlight the importance of component-resolved diagnostics to distinguish true peanut allergies from cross-reactive responses, aiding in the development of more effective treatment strategies [104,105]. The Learning Early About Peanut Allergy (LEAP) study revealed that the early introduction of peanut-containing foods to high-risk infants (4–11 months) reduced the relative risk of developing a peanut allergy by 81% by age five compared with the risk in those who avoided peanuts [106–108]. This highlights the role of oral exposure in fostering tolerance rather than sensitization. Conversely, a delayed introduction of allergenic foods correlates with increased rates of FAs [109,110], emphasizing that cross-reactivity alone does not account for the increasing prevalence of peanut allergies (Table 2).

Table 2. Factors contributing to peanut sensitization in infants and their mechanistic pathways.

Factor	Mechanism of Sensitization	Clinical and Research Implications	References
Immune System Immaturity	Immature neonatal immune responses skew toward Th2 dominance, promoting IgE production. Deficient regulatory T cell (Treg) activity fails to induce oral tolerance. Dendritic cell function remains suboptimal, reducing antigen presentation efficiency. Immaturity of the mucosal immune system, including limited secretory IgA, further hampers tolerance induction.	Exploring early immunomodulatory interventions, such as Treg-boosting therapies, could support the development of oral tolerance. Early introduction of allergens should be evaluated in high-risk infants, especially those with family histories of atopy.	[25,111–113]
Genetic Susceptibility	Mutations in *FLG* (filaggrin) impair skin barrier function, promoting allergen penetration and sensitization. HLA class II alleles (*HLA-DQ2/DQ8*) are strongly associated with FAs. Epigenetic mechanisms, including DNA methylation changes, may further modulate immune responses in genetically predisposed infants.	Genetic screening in early infancy can identify high-risk groups. Targeted interventions, such as barrier-enhancing treatments or early allergen exposure, may be particularly effective for infants with *FLG* mutations. Gene–environment interactions should be a focus of future research.	[112,114–119]
Gut Microbiome Alterations	Reduced diversity in gut microbiota, especially the loss of *Bifidobacterium* and *Lactobacillus* species, impairs oral tolerance by altering regulatory cytokine production (e.g., IL-10, TGF-β). Changes in the gut-associated lymphoid tissue (GALT) and microbial metabolites like short-chain fatty acids (SCFAs) disrupt immune homeostasis.	Probiotic and prebiotic interventions in early infancy could modulate gut microbiota to restore immune homeostasis. Clinical trials should evaluate the role of specific microbial strains in preventing sensitization.	[120–127]
Environmental Exposures	Epicutaneous exposure to peanut allergens, particularly in infants with impaired skin barriers (e.g., eczema), sensitizes via Langerhans cells, promoting Th2-driven IgE responses. Household and environmental allergens, such as dust mites, may further exacerbate this process by acting as adjuvants.	Research should define the threshold levels of environmental allergen exposure required for sensitization. Topical interventions, such as emollients or barrier creams, may prevent sensitization in infants with atopic dermatitis (AD) or eczema. Studies should also assess combined exposures to multiple allergens.	[128–132]
Atopic Dermatitis (AD)	AD leads to chronic skin inflammation and impaired epidermal barrier function, facilitating allergen entry and sensitization. Skin immune cells, particularly epidermal dendritic cells and Th2 cytokines (e.g., IL-4, IL-13), drive IgE-mediated responses. The filaggrin deficiency associated with AD further exacerbates this barrier dysfunction.	Preventive strategies focusing on early skin care, including the regular use of emollients and topical anti-inflammatory agents, may reduce allergen penetration and sensitization. Emerging therapies targeting the Th2 cytokine axis (e.g., anti-IL-4/IL-13 agents) could be evaluated for their role in reducing peanut sensitization in infants with AD.	[133–138]
Impact of Early Feeding Practices	Early introduction of peanut proteins via oral routes (by 4–6 months) promotes oral tolerance through Treg activation and reduced Th2 cytokine responses. Delayed introduction, especially in infants with eczema, increases the risk of sensitization due to a lack of early immune priming.	Current guidelines recommending early peanut introduction should be rigorously followed, particularly in infants with AD or a family history of atopy. Further research should explore dose–response relationships for oral tolerance induction, particularly in high-risk populations.	[106,139–147]
Prenatal and Perinatal Factors	Maternal diet during pregnancy and breastfeeding, as well as in utero allergen exposure, can influence infant immune responses. Epigenetic modifications, such as changes in DNA methylation and histone acetylation, may impact Th1/Th2 balance and immune programming in the fetus.	Maternal dietary interventions during pregnancy, such as controlled exposure to allergens, may modulate fetal immune responses. Epigenetic biomarkers could help identify infants at risk for sensitization and guide preventive strategies.	[114,148]
Animal Models in Peanut Sensitization	Murine models highlight key sensitization pathways, including disrupted Treg function and gut epithelial barrier dysfunction. These models also show that environmental and oral exposures play critical roles in the loss of oral tolerance. The role of specific microbial communities in sensitization pathways is increasingly studied.	Advances in murine models that mimic human peanut sensitization should continue to inform therapeutic development, including allergen immunotherapy and oral tolerance strategies. Translational research focusing on the microbiome's role in sensitization is critical for future interventions.	[149–154]

Abbreviations: IL-10: Interleukin-10; IgE: immunoglobulin E; IgA: immunoglobulin A; FLG: Filaggrin; HLA: Human Leukocyte Antigen; TGF-β: transforming growth factor beta; Treg: regulatory T cells; GALT: gut-associated lymphoid tissue; Th-2: T helper-2; AD: Atopic Dermatitis; SCFAs: short-chain fatty acids.

4. Bacterial Contamination in Food and Its Role in Allergy Sensitization

The increased consumption of animal products such as meat, milk, and eggs due to rapid population growth; urbanization; higher per capita incomes; globalization; and changes in consumption habits (high protein dietary preferences) has led to a higher demand for foods of animal origin, as well as intensive animal production and processing of products, especially large-scale production and the global movement of products. During this period, flawed processing practices may be present at any point on the farm, increasing the chances of contamination and transmission [97], while the risk of food contamination depends largely on health status, personal hygiene, knowledge of food hygiene, and the operational practices of food handlers. Bacterial foodborne diseases are infectious or virulent diseases caused by the consumption of food or water and can be categorized as poisoning (food poisoning caused by toxins produced by pathogens), infection (ingestion of food containing pathogens), or toxic infection (toxins produced during growth in the human gut). Foodborne illnesses pose a considerable public health burden globally, with 600 million cases of diarrheal disease attributable to contaminated food in 2010, according to the World Health Organization [98], and approximately 217 million cases occurring in children under 5 years of age [99].

4.1. Contamination of Food with Staphylococcus Aureus and Its Enterotoxins

Staphylococcus aureus (*S. aureus*) is one of the most common foodborne pathogens worldwide, with a prevalence second only to that of Salmonella [155,156]. The contamination of food with *S. aureus* can occur through various routes, including direct contact with infected food animals and inadequate hygiene practices during food production, retail, and storage. Notably, *S. aureus* is a commensal organism found in the nasal passages, throat, and skin of approximately 50% of healthy individuals, complicating efforts to eliminate its presence in food environments, even those with stringent hygiene protocols [157]. *S. aureus* contamination is particularly common in protein-rich foods, such as milk, dairy products, meats (pork, beef, lamb, poultry), and eggs [158].

These food items serve as common carriers for enterotoxin-producing strains of *S. aureus*. The bacterium is characterized as a Gram-positive, catalase-positive, coagulase-positive coccobacillus capable of thriving at a wide range of temperatures (7–48 °C, with an optimum of 30–37 °C) and pH values (4.2–9.3, with an optimum of 7.0–7.5). Its ability to tolerate high sodium chloride concentrations (up to 15%) further enhances its survival in various food matrices, particularly those subjected to extensive handling.

The enterotoxins produced by *S. aureus* are a primary concern in food safety, as they are responsible for numerous food poisoning incidents. For example, in 2000, the contamination of low-fat milk with *S. aureus* resulted in 13,420 cases of food poisoning in Japan; similar incidents occurred in 2009 in France and Japan and were linked to cooked food and raw cheese, respectively. These events often involve the presence of 0.5–10 μg of enterotoxin per 100 g of food, with toxic symptoms manifesting after the ingestion of 10–20 μg, and sensitive individuals require less than 1 μg for adverse effects [159]. Notably, staphylococcal enterotoxin B (SEB) exhibits significant heat resistance, allowing it to persist in food even after cooking processes that eliminate bacteria [160].

The pathogenesis of *S. aureus* enterotoxins, particularly their role in causing gastrointestinal symptoms such as vomiting and diarrhea, has not been fully elucidated. However, the mechanism is hypothesized to resemble that of the cholera toxin, which disrupts ionic homeostasis in the intestinal barrier. The heat and gastric acid resistance of these enterotoxins exacerbates the health risks associated with *S. aureus* infections. While *S. aureus* is typically a harmless commensal organism, it can become pathogenic under certain conditions, such as a compromised immune system or breaches in the skin or mucosal barriers. Jorde et al. [161] elucidated the significant role of *S. aureus* and its toxins in the pathogenesis of allergic asthma, noting that *S. aureus* produces various toxins, particularly enterotoxins, which can exacerbate airway inflammation and hyper-responsiveness. These toxins may function as superantigens, leading to an imbalanced immune response that contributes

to the worsening of asthma symptoms. Furthermore, they emphasize the importance of understanding the mechanisms by which *S. aureus* colonization influences asthma development, suggesting that targeting these toxins could offer new therapeutic avenues for managing asthma exacerbations linked to microbial factors.

S. aureus possesses multiple virulence factors that contribute to its pathogenicity, including coagulases, hemolysins, nucleases, and enterotoxins. These factors facilitate adherence to host tissues, damage host cells, and evade the immune response. Importantly, enterotoxins are produced when *S. aureus* proliferates in food stored at room temperature, and these toxins remain in food even after the bacteria are killed, highlighting the critical need for proper food handling and storage practices [162–164].

4.2. Toxicological Effects of S. aureus Enterotoxins

The first evidence linking staphylococci to food poisoning was presented by Barber in 1914. He positively demonstrated that staphylococci were capable of causing poisoning when he consumed unrefrigerated milk from a cow suffering from mastitis (inflammation caused by staphylococci); however, it was not until other examples of food poisoning occurred in the late twentieth century that a correlation between staphylococcal-containing foods and symptomatology was recognized [105]. SEs and enterotoxin-like (SEls) proteins have been implicated in the toxicology of *Staphylococcus aureus*. The SEls protein superfamily shares many characteristics; they are nonglycosylated, antigenically distinct, low-molecular-weight (19–29 kDa), single-chain proteins that fold into globular structures [165]. Only enterotoxins that have shown emetic potential in primates are designated as "SEs", whereas enterotoxins that fail to do so or have not been evaluated in nonhuman primate models of vomiting are referred to as enterotoxin-like [110]. Animal studies have shown that SEs stimulate mast cell degranulation to release 5-hydroxytryptamine (5-HT), which is essential for SEs to induce vomiting [111].

The mechanism by which 5-hydroxytryptamine triggers vomiting has been investigated. 5-Hydroxytryptamine stimulates 5-hydroxytryptamine receptors on adjacent vagal afferent nerves in the small intestine, which triggers depolarization of the vagal afferent nerves, transmits signals to the vomiting center in the medulla oblongata, and ultimately induces the vomiting reflex [112]. In addition, animal experiments have demonstrated that severing the vagus nerve in animals can terminate SE as a trigger for the vomiting response [113]. The specific receptor for SEs to stimulate the release of 5-HT from mast cells is not yet known and SEs, as superantigenic proteins, have a high affinity for the MHC-II molecule; however, animal experiments have demonstrated that the receptor for SEs to interact with mast cells is independent of the MHC-II molecule [114].

In addition to mast cells, SEs also show high affinity for epithelial cells [115] and cuprocytes [116], which may be one of the reasons why SEs can rapidly cross the intestinal epithelial barrier, and the process of SEs crossing the intestinal epithelial barrier is dependent on the presence of glycolipids [117]. The clinical signs of diarrhea tend to be less pronounced in gold–glucan food poisoning than in strong vomiting induction, which may be partly due to the weak ability of some SEs to cause leakage and dilatation of the intestinal segments [166]. A strong correlation between SEB pairs and diarrhea has only been observed, which may be related to the inhibition of the small intestinal reabsorption of electrolytes and water by SEBs [167].

4.3. S. aureus Enterotoxin B Superantigenic Effects and Immune Response Mechanisms

S. aureus and its toxins are considered a class of superantigens; in particular, the production of 11 enterotoxins (staphylococcal enterotoxins, SEA-SEE, SEG-SEI, and SER-SET) and 10–12 or even 10–15 M enterotoxins can trigger the activation of oligoclonal T cells, leading to the release of relevant immune factors [168]. In general, invading antigens are first phagocytosed and processed by antigen-presenting cells (APCs) and then presented to T cells via MHC-II molecules, which are recognized by the α and β chains of T cell surface receptors (TCRs) and receive antigenic information, further generating specific immune

responses. However, SEs can reduce or not activate the presentation of antigen-presenting cells and directly activate the binding of MHC-II and TCR, resulting in the activation of T cells without receiving antigen information and the rapid proliferation and release of a large number of immune factors [169,170]. Moreover, SEs, as the most common antigen, can be specifically recognized by B cells and produce specific antibodies, which activate MHC-II on the surface of B cells and TCRs on the surface of T cells and further stimulate T cells to express CD40L receptors, which constitute another important signaling molecule for Th cell activation [171]. In addition, TSST-1 and SEB further promote Th cell differentiation by enhancing the interaction of T cell CD28 with CD86 on the surface of APCs [172,173].

The molecular details of the superantigenic activity of SEs have been dissected via extensive X-ray crystallographic, structural, and mutational analyses. Unlike conventional antigens, the nonspecific activation of T cells by SEs is independent of antigen processing and T cell presentation by antigen-presenting cells (APCs). In most cases, SEs bind first to MHC-II-like molecules expressed on APCs and then to one or more variable Vb chains of T cell receptors (TCRs) [174]. SEs share a common overlapping binding region on HLA-DR, known as the MHC-II-like binding site involving the α-chain, and a higher-affinity binding site is found at the C-terminus [175,176]. Other cell surface molecules, such as CD2, CD11a/ICAM-1, and ELAM, promote the better binding of SEBs to endothelial cells and T cells [177]. SEs promote the binding of TCRs to their receptors, followed by the activation of protein tyrosine kinases (PTKs), LCKs, and ZAP-70, leading to the activation of phospholipase C gamma (PLCγ), the release of intracellular second messengers, and the subsequent activation of protein kinase C (PKC) [178,179]. SEA, SED, and SEH bind to the HLA-DRβ chain in a Zn^{2+}-dependent manner. Additionally, SEB has stronger superantigenic activity, a possible mechanism by which SEB stimulation, as described above, enhances the costimulation of T cells with the APC surface receptors CD28 and B7-2 (CD86) [180]. Such superantigenic effects of Aureus toxins, which potentially contribute to APC recognition and the presentation of allergenic proteins, the activation and differentiation of Th cells, and the subsequent promotion of specific B cell proliferation and the production of specific IgEs, may constitute the immunological mechanism by which Aureus and its toxins are positively associated with the development of allergic diseases [181].

4.4. Role of S. aureus in FA Sensitization and Immune Dysregulation

S. aureus plays a complex role in FAs through immune interactions and enterotoxin production. Early colonization by *S. aureus* in infants is linked to a reduced risk of FAs by 18 months, likely due to immune stimulation and enhanced oral tolerance [182,183]. Conversely, *S. aureus* can exacerbate FAs, especially in children with atopic dermatitis, with a significant correlation between *S. aureus* colonization and allergies to milk, eggs, and peanuts. Enterotoxins from *S. aureus* increase systemic IgE production when co-applied with food allergens, facilitating allergic sensitization [184].

The hygiene hypothesis posits that reduced microbial exposure in early life increases allergy risk, suggesting *S. aureus* may protect against allergies through immune modulation [185,186]. *S. aureus* in the nasal mucosa is linked to heightened allergic responses, indicating its active role in influencing the immune landscape [187,188].

S. aureus commonly colonizes the skin in individuals with atopic dermatitis (AD), increasing FA risk through immune dysregulation driven by superantigens, which enhance allergic sensitization [184,189]. *S. aureus* is frequently found in the nasal passages and skin of allergic individuals, correlating with exacerbated allergic responses. Patients with allergic rhinitis and asthma have higher *S. aureus* colonization rates, up to 87.5% in asthmatics [190,191]. The association between *S. aureus* and FAs likely involves superantigens produced by the bacterium, which activate T cells and foster a Th2-skewed immune response, a key feature of allergic reactions [192,193]. Superantigens such as staphylococcal enterotoxin B (SEB) exacerbate allergic inflammation, particularly in FAs [186,194]. These superantigens may disrupt immune tolerance, increasing sensitivity to food allergens. Additionally, *S. aureus* affects the microbiome and skin barrier function, facilitating allergen

penetration and sensitization through dysbiosis [186,195]. *S. aureus* colonization and its link to immune dysregulation and food allergen sensitization is increasingly recognized. *S. aureus* colonizes the skin of atopic dermatitis (AD) patients at significantly higher rates (60% to 100%) compared to healthy individuals (5% to 30%) [196,197]. This colonization is associated with an overactive Th2 immune response, characteristic of allergic conditions [198,199]. Experimental models show that *S. aureus* enterotoxins, particularly SEB, enhance dendritic cells (DCs) and T cell activation, leading to heightened immune responses to food allergens, such as ovalbumin, promoting sensitization [200].

Moreover, *S. aureus* colonization combined with exposure to food allergens significantly increases allergen-specific IgE production, linking *S. aureus* to FA sensitization. Clinical studies show that AD children colonized by *S. aureus* have higher levels of specific IgE against common food allergens like peanuts, eggs, and milk, independent of eczema severity. The presence of IgE antibodies against *S. aureus* enterotoxins is associated with severe allergic responses, underscoring the role of *S. aureus* in immune dysregulation.

4.5. The Role of S. aureus in Atopic Dermatitis and Its Implications for FAs

S. aureus is a significant contributor to the exacerbation of atopic dermatitis (AD) and its association with FAs. Research indicates that *S. aureus* is a predominant colonizer in patients with AD, with colonization rates reaching as high as 90% in lesional skin [201]. This colonization is not incidental; it correlates with an increased severity of AD and the development of FAs [202]. A systematic review has confirmed a strong association between the severity of AD and food sensitization, suggesting that more severe cases of AD are particularly linked to FAs [190]. The mechanisms underlying this relationship involve immune dysregulation and the impact of *S. aureus* superantigens. Studies have shown that superantigens produced by *S. aureus* can enhance Th2 immune responses, which are implicated in allergic reactions, including FAs [203]. Specifically, the co-application of *S. aureus* enterotoxins with food allergens has been demonstrated to increase systemic IgE production, indicating that *S. aureus* may facilitate sensitization to food allergens through skin exposure [204]. Moreover, early exposure to *S. aureus* in infancy has been associated with a lower risk of developing FAs, highlighting a complex interplay between immune system maturation and allergen exposure [205]. Clinical observations further support the connection between *S. aureus* colonization and FAs. For instance, a study found that children with AD who were colonized by *S. aureus* had a higher incidence of FAs, particularly to common allergens such as milk, eggs, and peanuts [202]. This suggests that *S. aureus* not only exacerbates skin inflammation but also predisposes individuals to systemic allergic responses. Environmental factors, including household peanut consumption, significantly influence sensitization. Higher concentrations of peanut dust correlate with an increased sensitization risk in infants [201]. Infants with AD and filaggrin (FLG) gene mutations are particularly vulnerable to peanut allergies under these conditions [201]. T helper (Th) cell-mediated immune responses, especially Th2 responses, also affect the likelihood of developing peanut allergies. Infants with strong Th2 responses in atopic conditions like eczema are at higher risk [206].

The concept of oral tolerance, as evidenced by the LEAP study, underscores the importance of early and regular exposure to peanuts in reducing the risk of sensitization and subsequent allergic reactions [207]. This suggests that factors such as the timing and nature of allergen exposure are crucial in preventing peanut allergies rather than cross-reactivity alone. Atopic dermatitis significantly impacts peanut sensitization due to compromised skin barrier integrity, which facilitates allergen penetration. Studies show that severe eczema increases the risk of peanut allergies, with odds ratios indicating a strong correlation between eczema severity and peanut sensitization [208]. Additionally, mutations in the filaggrin gene (FLG) are associated with both AD and an increased risk of FAs [209]. Future research should focus on developing targeted therapies, such as Treg-enhancing treatments, microbiome modulation, and novel immunotherapies, to mitigate peanut sensitization risk and improve allergic disease outcomes.

5. The Role of Gut Microbiota in FA Pathogenesis

Dysbiosis, or an imbalance in gut microbial communities, has been linked to the pathogenesis of FAs. A healthy gut microbiota promotes a Th1 immune response, which protects against allergies, whereas dysbiosis shifts the immune response toward a Th2 phenotype associated with allergic reactions [210,211]. Factors such as the mode of delivery at birth (e.g., cesarean section) and antibiotic use can disrupt normal microbial communities, increasing susceptibility to FAs [148,212,213]. Specific microbial metabolites, particularly short-chain fatty acids (SCFAs) produced by gut bacteria, increase immune tolerance and protect against FAs. The composition of the gut microbiota and SCFA production influence the differentiation and function of regulatory T cells (Tregs), which are essential for maintaining immune homeostasis and preventing allergic responses [214,215]. Certain bacterial species, such as *Akkermansia muciniphila*, have been associated with protective effects against FAs, suggesting that promoting a diverse and balanced gut microbiome may be a viable prevention strategy [216,217]. Recent studies have also highlighted the impact of the maternal gut microbiota on the development of FAs in offspring. Alterations in the maternal microbiota before and during pregnancy can influence a child's gut microbiota and susceptibility to FAs [218,219]. Additionally, the timing of exposure to specific allergens and the microbial environment during early life are critical factors shaping immune responses and tolerance development [213,220]. Innovative therapeutic approaches are being explored to manipulate the gut microbiota and enhance immune tolerance in individuals at risk for FAs. Probiotics and prebiotics are gaining attention for their potential to restore microbial balance and improve immune function, with clinical trials underway to evaluate their efficacy in preventing or alleviating FAs [211,212,221]. Understanding the interplay between dietary factors, the gut microbiota, and immune responses is essential for developing personalized strategies for managing FAs [222,223].

The Th2 immune response, characterized by IgE antibody production, is a key pathway in the development of FAs. Genetic factors, particularly polymorphisms in genes such as STAT6, significantly influence this process by promoting IgE class switching in B cells and activating mast cells and eosinophils, exacerbating allergic reactions [224,225]. The role of alarmins, cytokines released by epithelial cells during allergic responses, has also been emphasized as a potential biomarker for FAs and a target for therapeutic intervention [226].

Recent advancements in oral immunotherapy (OIT) have shown promise in modifying the immune response in food-allergic individuals. OIT can reverse the Th2 cell-like programming of Tregs, restoring their function and promoting a more balanced immune response [227,228]. Identifying cellular and molecular biomarkers predictive of treatment response has become a significant focus, with ongoing research aimed at understanding the innate and adaptive immune mechanisms involved in FAs [225,228]. The influence of the microbiome on FAs has garnered attention, with studies indicating that the gut microbiota composition significantly affects immune responses. For example, germ-free mice exhibit impaired mast cell functionality and do not develop FAs, suggesting that specific gut bacteria are essential for allergic response development [228]. Interventions aimed at modulating the gut microbiota, such as probiotics, have shown potential in preventing or alleviating FAs by enhancing immune tolerance [229].

Epigenetic factors, particularly histone acetylation, significantly influence immune responses in FAs. Alterations in histone acetylation at regulatory loci, such as decreased levels, are associated with susceptibility [80] and B cell dysfunction [230] in FAs. Histone acetylation facilitated by histone acetyltransferases (HATs) opens chromatin, promoting gene transcription, while histone deacetylases (HDACs) compact chromatin, reducing gene expression. This balance is crucial for modulating the immune response, particularly in allergic diseases such as FAs. Key cytokine genes involved in T helper cell differentiation (Th1, Th2, Th9), immune tolerance, and inflammatory pathways are influenced by histone acetylation. The acetylation of H3K9 and H3K27 at specific sites is associated with promoting or suppressing immune responses, contributing to allergic sensitization. Defective acetylation disrupts immune tolerance and leads to the distorted Th2 responses typical of

FAs. The modulation of histone acetylation, for example, by HDAC inhibitors, may help alleviate FA symptoms by restoring immune balance. Histone H4 acetylation is particularly associated with anti-allergic effects and supports regulatory T cell differentiation. Therefore, therapeutic strategies targeting histone acetylation hold promise for the treatment of FAs [231].

FAs are characterized by inappropriate immune responses to normally harmless food proteins, leading to a range of clinical manifestations ranging from mild symptoms to life-threatening anaphylaxis. The cellular and molecular mechanisms underlying FAs involve a complex interplay between immune cell activation, molecular pathways such as IgE binding and cytokine production, and epithelial barrier dysfunction. Recent research has provided insights into these mechanisms, enhancing our understanding of FA pathogenesis and potential therapeutic approaches.

6. The Impact of Food Processing and Immune Mechanisms on Allergenicity

The influence of cooking on allergenicity is significant, as cooking can alter the structure of food proteins, impacting their potential to cause allergic reactions. Thermal processing methods such as boiling, roasting, frying, and baking can denature proteins, potentially reducing their allergenicity [96]. The allergenic potential of food proteins is often determined by their stability and resistance to digestion. Cooking can modify epitopes, the part of the antigen recognized by the immune system, thereby affecting their binding to IgE antibodies and the subsequent allergic response [161,162]. Antigen uptake involves dendritic cells (DCs), which are key antigen-presenting cells that capture, process, and present food allergens to T cells. Different subsets of DCs play distinct roles in immune responses. After capturing antigens, DCs migrate to lymph nodes, where they interact with T cells and can induce the differentiation of regulatory T cells (Tregs) [163]. Tregs are crucial for maintaining immune tolerance and preventing allergies. DCs play a pivotal role in determining whether an immune response to a food antigen results in tolerance (nonreactivity) or an allergic response, with the balance between Tregs and Th2 cells (which promote allergic responses) being critical. Mast cell activation involves the induction of allergic responses through the release of histamine and other inflammatory mediators [164]. When activated by allergens through IgE antibodies bound to their surface receptors, MCs cause allergic symptoms such as hives, asthma, and anaphylaxis. In addition to their role in immediate allergic reactions, MCs can influence other immune cells, contributing to the chronicity and severity of allergic diseases. Understanding how MCs might contribute to immune tolerance involves studying their interactions with other immune cells and their responses to chronic allergen exposure [164–166]. Mucosal tolerance refers to the immune system's ability to remain unresponsive (tolerant) to harmless antigens, such as food proteins, encountered through mucosal surfaces such as the gut. This process involves several immune cells, including DCs, Tregs, and mucosal epithelial cells. The induction of tolerance is mediated by a complex network of signaling pathways and immune interactions that prevent overreactive immune responses. Effective mucosal tolerance mechanisms are essential for preventing FAs [163,167]. When these mechanisms fail or are dysregulated, they can lead to the development of FAs and other immune-mediated diseases. Table 1 presents a comprehensive overview of the immune response to food allergens, emphasizing the importance of understanding the development, regulation, and potential treatment options for FAs.

7. Conclusions

FAs are a multifactorial health burden driven by complex interactions between genetic susceptibility factors and environmental exposures. Bacterial toxins, particularly those produced by *S. aureus*, have emerged as significant contributors to the disruption of the intestinal barrier and immune tolerance. These insights into the pathophysiology of FAs underscore the importance of preventive measures, including early intervention strategies targeting high-risk populations, improved hygiene standards, and dietary management. Additionally, advancing

diagnostic accuracy through immunological markers and refining therapeutic approaches can reduce the incidence of life-threatening allergic reactions. To address the increasing prevalence of FAs effectively, future research must prioritize the mechanistic roles of bacterial and environmental factors in immune sensitization and cross-reactivity, which will ultimately inform evidence-based guidelines for FA prevention and treatment.

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