

Review

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Review

Engineering Allergenicity: A Review of Non-Thermal Processing Approaches to Reduce Immune Reactivity in Foods

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Abstract

Food allergies are a rising global health concern, influenced by complex interactions among genetic predisposition, environmental exposures, dietary habits, and gut microbiota. Sensitization typically occurs through dermal, respiratory, or gastrointestinal routes, with epithelial barrier dysfunction and Th2-skewed immune responses playing key roles. Understanding the mechanisms and pathways of sensitization is critical to developing effective mitigation strategies. Both thermal and non-thermal food processing technologies are being explored for their potential to reduce the allergenicity of common foods such as milk, egg, peanut, tree nuts, and seafood. Thermal methods can denature allergenic proteins but may also compromise nutritional and sensory quality. In contrast, non-thermal technologies—including high-pressure processing, pulsed light, cold plasma, and ultrasound—offer milder alternatives that modify protein structures, mask or degrade IgE-binding epitopes, and reduce immunoreactivity while preserving food quality. However, outcomes are highly context-dependent, influenced by food matrix, processing parameters, and assessment methods. Limitations in current in vitro and in vivo models, lack of standardized allergenicity testing protocols, and insufficient clinical validation remain key barriers. This review synthesizes current knowledge of allergy mechanisms with technological approaches for allergen reduction, highlighting promising interventions, existing constraints, and the need for integrated research to develop safe, hypoallergenic foods.

Keywords: food allergy non-thermal processing; allergenicity reduction; pulsed electric fields; high hydrostatic pressure; ultraviolet; ultrasonication; cold plasma

1. Food Allergy and Sensitization: Mechanisms, Pathways, and Risk Factors

Food allergy is defined as an adverse immune response to specific food proteins and affects approximately 6% of children and 3%–4% of adults. Clinical manifestations vary widely but most commonly involve the skin, gastrointestinal tract, and respiratory system. Immunologically, food allergies are classified into IgE-mediated and non-IgE-mediated (cellular) responses [1,2].

Under normal circumstances, the immune system maintains tolerance to dietary antigens—a process known as oral tolerance. Food allergy represents a failure of this immunological tolerance. Although a wide range of foods can elicit allergic reactions, a limited number of foods account for most clinically significant cases. These include milk, eggs, peanuts, tree nuts, fish, and shellfish [2–4].

Diagnosis of food allergy requires a structured, evidence-based approach. The process typically begins with a thorough clinical history and is followed by diagnostic tools such as serologic testing, skin prick tests, elimination diets, and, when indicated, oral food challenges. Advances in molecular allergology have led to the characterization of many food allergens, enhancing the understanding of underlying immune mechanisms and paving the way for novel diagnostic and therapeutic strategies.



Nevertheless, the current mainstay of management remains strict avoidance of known allergens, comprehensive patient education, and readiness to manage accidental exposures—primarily through the use of emergency epinephrine [2].

Food allergies can develop through various routes of sensitization. Class 1 food allergies result from oral exposure to food proteins and are commonly associated with proteins that are resistant to heat, acid, and enzymatic degradation [5–7]. These allergens are often introduced during infancy or early childhood, a period when the immune system is particularly susceptible to dysregulation. In contrast, class 2 food allergies result from primary sensitization to inhaled allergens, such as pollens, that share structural similarity with proteins in raw fruits or vegetables. This can lead to cross-reactivity and symptoms consistent with pollen–food allergy syndrome [5,6].

Research suggests that sensitization to certain class 1 allergens—such as peanuts and eggs—may also occur through the skin, especially in individuals with impaired skin barrier function [8,9]. Many class 1 food allergens are water-soluble glycoproteins ranging from 10 to 70 kDa in size and demonstrate resistance to digestion and thermal processing. Examples include caseins in milk, ovomucoid in eggs, vicilins in peanuts, and nonspecific lipid transfer proteins found in apples (*Mal d 3*) and corn (*Zea m 14*) [5,6]. *Bet v 1*, the major birch pollen allergen, exemplifies a class 2 allergen. It can elicit respiratory sensitization and cause oral symptoms when cross-reactive proteins such as *Mal d 1* (apple) or *Dau c 1* (carrot) are ingested. Most food allergens fall into a limited number of protein families, including the Cupin and Prolamin superfamilies, and pathogenesis-related proteins [5,6].

The clinical relevance of specific sensitizations varies. For instance, peanut allergens *Ara h 1*, *Ara h 2*, and *Ara h 3* are often implicated in severe IgE-mediated allergic reactions, whereas *Ara h 8*—a *Bet v 1* homolog—is usually associated with milder symptoms and oral allergy syndrome [10]. Despite structural similarities between proteins, true clinical cross-reactivity is often less common than laboratory tests suggest [1,6].

Food allergies can result in a range of clinical disorders affecting one or more organ systems. Many gastrointestinal disorders attributed to food allergies exhibit overlapping symptoms, but they can often be distinguished through careful clinical evaluation and diagnostic testing [11–13]. Additionally, some pediatric gastrointestinal conditions—such as colic, constipation, and reflux—are occasionally suspected to have allergic etiologies (Figure 1).

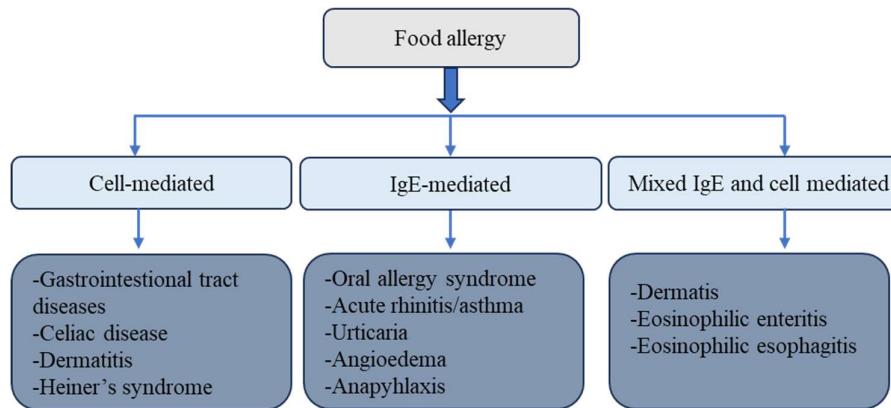


Figure 1. Classification of food allergy (adapted from [169]).

Anaphylaxis represents one of the most severe outcomes of food allergy, with foods being the leading cause of anaphylactic episodes in outpatient settings [14]. Fatal cases often involve peanut or tree nut exposure in adolescents or young adults with pre-existing food allergies and asthma, and typically occur in the absence of prompt epinephrine administration [12,15].

Adverse food reactions more broadly, termed food intolerances, arise from a variety of mechanisms. These reactions are categorized as toxic or non-toxic. Non-immune-mediated intolerances—such as those due to enzymatic deficiencies (e.g., lactose intolerance) or sensitivity to

biogenic amines—are more common than immune-mediated food allergies. Nonetheless, immune-mediated food allergies, though less prevalent, affect millions globally and pose significant medical and economic burdens. In their most severe form, these allergies can cause life-threatening anaphylaxis [2,16,17]. The National Institute of Allergy and Infectious Diseases (NIAID) defines food allergy as “a specific immune response to a food that results in reproducible adverse health effects” [18,19], encompassing both adaptive and innate immune pathways.

The concept of allergy was introduced by Clemens von Pirquet in 1906, who described hypersensitivity reactions such as serum sickness in children receiving antiserum therapies [20,21]. Later, hypersensitivity reactions were classified into four immunological types [22]. The most common food allergy mechanism is Type I hypersensitivity, mediated by IgE antibodies against food allergens. These reactions involve complex immune cascades, including T cell activation and eosinophil recruitment [16]. Diagnosis often includes detection of specific IgE antibodies or IgE-related cellular responses [2].

Although there has been speculation regarding the involvement of food-specific IgG antibodies in Type II or Type III hypersensitivity reactions, current scientific evidence does not support a pathogenic role. Accordingly, professional societies discourage the use of IgG-based food allergy testing [23–25]. Type IV hypersensitivity reactions, mediated by T cells, contribute to conditions such as celiac disease, in which gluten proteins trigger autoimmune inflammation in the gut [26]. Another T cell-mediated disorder is food protein-induced enterocolitis syndrome (FPIES), which typically affects infants and is not associated with IgE [27].

Recent studies also implicate the innate immune system in food-induced inflammation. Molecules such as wheat amylase-trypsin inhibitors and certain milk oligosaccharides activate Toll-like receptor 4 (TLR4), initiating intestinal inflammation [4,28]. Such mechanisms may underlie disorders like non-celiac gluten sensitivity [4,29,30].

In industrialized nations, IgE-mediated food allergies affect 3%–8% of children and 1%–3% of adults [2,17,31]. These conditions impose not only physical health risks but also emotional and social burdens due to dietary limitations and lifestyle adjustments. The most common allergenic foods include milk, eggs, wheat, peanuts, tree nuts, sesame, fish, fruits, and vegetables [24,31]. Allergies to milk, eggs, and wheat often resolve in childhood, while allergies to peanuts, tree nuts, and seafood tend to persist [2].

Estimating the true prevalence of food allergies remains challenging due to variability in diagnostic methodologies and reliance on self-reported versus clinically confirmed cases [32]. Nevertheless, evidence suggests that both the incidence and severity of food allergies are increasing, driven by a complex interplay of genetic and environmental factors, including diet and lifestyle [9,33–35].

Epigenetic research has revealed that children with IgE-mediated food allergies exhibit distinct DNA methylation patterns in CD4+ T cells, suggesting a role for gene–environment interactions in allergy pathogenesis [36]. The “hygiene hypothesis,” first proposed by Strachan [37], posits that reduced microbial exposure—due to smaller family sizes and improved sanitation—impairs immune system development, increasing susceptibility to allergic disease. Supporting this, children raised in anthroposophic environments—with minimal antibiotic or vaccine exposure and adherence to organic diets—show lower rates of allergies [38,39].

Limited dietary and microbial diversity in early life may impede immune tolerance, contributing to the growing prevalence of allergic and inflammatory conditions in developed societies [40]. Allergic sensitization refers to the immune system’s initial response upon first exposure to an allergen [4,41]. Two primary routes of sensitization have been described. Class 1 allergens—such as milk, egg, and peanut—induce sensitization through the gastrointestinal tract [42]. Class 2 allergens, such as Bet v 1 from birch pollen, sensitize via the respiratory tract and can cross-react with homologous food proteins (e.g., Mal d 1 in apples), resulting in oral allergy syndrome [4,43–46].

Epicutaneous sensitization—where allergens enter through inflamed or damaged skin—has also been proposed as a sensitization route. In murine models, such exposure leads to intestinal mast cell expansion and systemic anaphylaxis [47–49].

Multiple factors influence the likelihood of sensitization:

- **Allergen structure and stability:** Resistance to gastrointestinal degradation enhances allergenicity [5,6,50].
- **Epithelial barrier integrity:** Mutations (e.g., in the *filaggrin* gene) and environmental factors (e.g., alcohol, NSAIDs, pathogens) compromise mucosal barriers, facilitating allergen penetration [51–53].
- **Adjuvant effects of food matrices:** Nonallergenic components and microbial products in foods may act as immunological adjuvants, promoting sensitization [6].

Conversely, secretory immunoglobulins—particularly SIgA and SIgM—strengthen mucosal defenses and promote oral tolerance. Mice deficient in SIgA transport exhibit increased intestinal permeability and greater vulnerability to allergen-induced anaphylaxis, which can be reversed by the induction of regulatory T cells [54,55].

2. Mitigation Strategies for Food Allergens

2.1. Allergen Elimination and Control Strategies

Elimination or reduction of allergens in the food supply chain requires a multifaceted and preventive approach. Genetic modification or selective breeding is one strategy used to remove or silence genes encoding allergenic proteins, such as the reduction or knockout of Ara h 2 and Ara h 6 in peanuts [56]. Enzymatic hydrolysis is another promising approach, in which proteolytic enzymes cleave allergenic epitopes to decrease immunoreactivity. This method has proven effective in hydrolyzed milk and wheat products [57,58]. However, proteolysis may not fully eliminate allergenic potential. For example, Sen et al. [59] observed that the peanut allergen Ara h 2 retained IgE-binding epitopes post-hydrolysis, especially when disulfide bonds were intact. This highlights the importance of linear epitopes in allergen stability, and suggests that reducing disulfide bonds alone may not sufficiently degrade allergenic regions.

In addition to ingredient-level interventions, allergen control measures begin with careful raw material management. This includes supplier verification and traceability systems to ensure allergen-free inputs [60]. In manufacturing, dedicated lines, validated sanitation, and equipment separation are necessary to avoid cross-contact [61–63]. Hazard Analysis and Critical Control Points (HACCP), ingredient monitoring, and accurate food labeling are central to allergen risk management. Finally, workforce training and allergen awareness programs are vital for maintaining safety throughout the supply chain [64].

2.2. Effects of Food Processing on Allergen Control

Food processing plays a critical role in modifying allergenic properties while enhancing safety, shelf life, and nutritional value. Physical, chemical, and biochemical processing methods can influence allergenicity based on food type and processing conditions [65–67]. The structural integrity and allergenic potential of proteins are significantly influenced by processing. Changes in physicochemical properties and protein stability can alter immunogenicity [57,68,69]. The food matrix can modulate these effects, at times enhancing allergenic responses [70,71]. These treatments may reduce, increase, or have no effect on allergenicity. Notably, some techniques can lead to the formation of neoallergens—new antigenic compounds created during processing—which may intensify allergic reactions [72–74].

Thermal and non-thermal food processing can alter epitope structures, reducing allergenicity by disrupting existing immunodominant epitopes or creating neoallergens. The phenomenon of

neoallergen formation has been recognized since the 1970s, when it was reported that processed foods could elicit allergic responses even when raw forms did not [75]. Subsequent findings identified neoallergens in processed pecans [76] and wheat flour [77]. Processing typically reduces allergenicity in many foods. Fermentation not only enhances nutritional quality and preservation but also affects allergenicity. Lactic acid bacteria, for example, degrade IgE-binding epitopes in milk proteins, such as β -lactoglobulin, thus reducing allergenicity [78]. However, fermentation's effects are product-specific. Soy sauce, a fermented product, retains allergenicity despite microbial activity [79], while fermented dairy products such as yogurt often show reduced immunogenicity due to acid denaturation and proteolysis [80,81].

2.3. Thermal Processing and Its Effects on Allergenicity

Thermal treatment is one of the most commonly used technologies in food processing and can significantly alter the structure and immunoreactivity of food allergens. Heat-induced denaturation leads to unfolding of proteins, disruption of disulfide bonds, and potential destruction of IgE-binding epitopes. For example, heating egg proteins such as ovomucoid or ovalbumin at 100°C for extended periods reduces their IgE-binding capacity [81]. Similarly, roasting or boiling peanuts can modify allergenic proteins (e.g., Ara h 1, Ara h 2) and reduce or sometimes enhance allergenicity depending on the conditions (Table 1) [82,83].

Table 1. Influence of thermal processing on various food allergen types (adapted from [57]).

Allergen Type	Response to Thermal Processing
Bet v 1-like proteins (e.g., Mal d 1 in apple, Pru av 1 in cherry)	Highly sensitive to heat; prone to unfolding. Susceptible to chemical changes such as Maillard reaction products in high-sugar foods and interactions with polyphenols, leading to decreased allergenic potential.
Prolamin superfamily proteins (e.g., non-specific lipid transfer proteins [nsLTPs], 2S albumins like Mal d 3; tropomyosin; parvalbumin)	Moderately heat stable; proteins unfold to a limited extent but tend to regain their structure upon cooling. Maillard reactions may still enhance allergenic potential.
Cupin family proteins (e.g., Ara h 1 in peanut); Lipocalins (e.g., β-lactoglobulin and α-lactalbumin in milk)	Partially resistant to denaturation; undergo partial unfolding and tend to aggregate. Can form structural networks (e.g., in emulsions or gels). Heat can also lead to Maillard reactions, which may increase allergenicity.
Flexible proteins (e.g., caseins in milk, gluten storage proteins in wheat, ovomucoid in egg)	Structurally dynamic and heat-resistant; maintain mobility and do not exhibit classic denaturation behavior under thermal conditions. Their allergenicity remains largely unchanged.

Baking and extrusion may reduce the allergenicity of wheat and soy by Maillard reactions and protein aggregation, although new allergenic determinants can sometimes be formed [84]. However, in some cases, thermal processing increases the resistance of certain allergens to digestion, potentially enhancing their allergenic potential. Thus, heat treatments must be carefully optimized based on food type and target allergen.

Studies have demonstrated that moist heat can significantly reduce the allergenic potential of certain foods. For instance, sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) revealed a marked loss of protein bands in canned tuna and salmon extracts compared to raw or

conventionally cooked samples. Immunoblotting further showed minimal IgE-specific binding in the canned extracts. ELISA inhibition assays and oral challenges with canned salmon in allergic individuals confirmed reduced allergenicity, suggesting that some fish allergens are more heat-labile than previously thought [60,85].

Similarly, kiwi fruit allergy provides a compelling case of heat-mediated allergenicity reduction. Variability in patient responses has been attributed to protein heterogeneity and cross-reactivity with other allergens, such as pollens. However, steam cooking kiwi at 100°C for 5 minutes followed by homogenization effectively eliminated sensitivity in certain allergic children [86–88].

In the case of milk allergens, the IgE-binding capacity of β -lactoglobulin, whether as an isolated protein or within whole milk, was assessed using FEIA-CAP inhibition. While mild heating at 74°C caused only slight reductions, significant decreases in IgE binding were observed at 90°C. Despite reduced binding, a sufficiently high concentration of β -lactoglobulin could still inhibit a similar total amount of IgE antibodies across all heat treatments [80].

Allergic reactions are triggered by IgE antibody binding to specific protein epitopes. Cross-linking of IgE on mast cells or basophils leads to the release of histamine and other mediators [89]. Thermal sensitivity varies by epitope type: conformational epitopes are more easily denatured, while linear epitopes are more heat-resistant [57,90]. As a result, heating may reduce allergenicity in some foods like lentils, enhance it in others like peanuts, or have no effect, as observed in boiled peas [91,92].

Pollen-related allergens in fruits and vegetables often become less immunogenic after heating. However, allergens in foods like shrimp can remain heat-stable and retain immunogenicity post-cooking. The type of epitope also affects stability: conformational epitopes, reliant on three-dimensional protein folding, are more susceptible to denaturation during processing, whereas linear epitopes may resist heat but are subject to enzymatic or chemical alteration. Genetic engineering allows precise modification of such epitopes to reduce allergenicity.

Protein structures respond differently to thermal conditions: mild heat (70–80°C) disrupts secondary structures, moderate heat (80–90°C) affects disulfide bonding, and intense heat (90–100°C) induces aggregation [90,93]. Heat may also initiate Maillard reactions, where lysine residues form covalent bonds with sugars, generating advanced glycation end products that could increase allergenicity [90].

Heating can enhance digestibility and reduce allergenicity in legumes such as chickpeas, lentils, lupins, and black gram [94]. Conversely, it may reduce digestibility in peanut allergens like Ara h 1 and Ara h 2 [83,95]. Thermal processing may also produce neoantigens, which elicit stronger immune responses [69,83]. The Maillard reaction is a key mechanism behind this neoantigen formation, where heat-induced protein-sugar interactions yield glycation products with heightened immunogenic potential [96]. In a study by [97], sera from 57 patients with suspected meat allergy showed stronger IgE binding to raw meat extracts than to those heated at 140°C for 20 minutes, suggesting thermal degradation of most allergens. However, chicken was an exception: six of 24 sera reacted more strongly to heated chicken meat. Common allergenic proteins in raw and cooked chicken were identified at 17–66 kDa, while heat-labile proteins (45 and 150 kDa) disappeared and neoallergens emerged in the 14–90 kDa range.

The IgE-binding capacity of wheat proteins significantly decreases with increasing temperature and heating time. When wheat flour and dough (flour mixed with 50% water) were subjected to heat treatments at 80°C, 100°C, and 120°C for 10, 20, and 60 minutes, both neutral and acidic protein extracts showed reduced IgE reactivity in skin prick tests (SPT) and radioallergosorbent tests (RAST) using sera from cereal-sensitive adults. No further reduction in allergenicity was observed beyond 10 minutes at 120°C, indicating a thermal stability threshold. Pooled sera RAST scores dropped from class 4 (untreated flour) to class 2 following heat treatment. Notably, heated dough demonstrated lower allergenic potential than heated flour at 80°C and 100°C, though this difference was no longer evident at 120°C [98].

Heat treatment by microwave heating of kiwi fruit to 40, 60, 80, and 90°C resulted in a progressive reduction in allergenicity, as assessed by skin prick testing (SPT) in three kiwi-allergic individuals. At 90°C, SPT responses were negative in two patients and markedly reduced in the third, indicating significant thermal degradation of allergenic proteins [99].

Protein solubility in minced beef decreases with extended heat treatment. Following heating at 85°C for up to 2 hours, SDS-PAGE revealed faint bands at 17.8, 19, 14, 20, 45, and >60 kDa, which were also detectable in well-cooked samples (80°C, 20 min) via immunoblotting. Among these, the 17.8 kDa protein showed the highest IgE-binding activity in patients with confirmed allergy to cooked beef (positive DBPCFC). Bovine serum albumin and gamma-globulin were undetectable in minced beef heated at 80°C for 10 and 3 minutes, respectively. However, isolated serum albumin remained stable at 95°C for 15 minutes, whereas isolated gamma-globulin was fully denatured at 65°C within 15 min [100].

Dry heat processing can influence the allergenic potential of foods through complex chemical reactions such as the Maillard reaction and enzymatic browning. These processes can irreversibly alter or destroy conformational epitopes. For example, Gruber et al. [101] demonstrated that cherry allergen Pru av 1 loses its IgE-binding capacity due to the Maillard reaction and polyphenol oxidase-catalyzed oxidation. Similarly, Hansen et al. [102] reported that roasting hazelnuts reduced their allergenicity, particularly among individuals sensitized to birch pollen-related allergens such as Cor a 1.04 and Cor a 2. However, five out of seventeen birch pollen-allergic individuals still reacted to roasted hazelnuts in double-blind placebo-controlled food challenge tests, indicating that roasting does not eliminate allergenicity for all patients. These findings suggest that individual sensitivity to conformational versus linear epitopes is a critical consideration in evaluating the allergenic potential of thermally processed foods. Conversely, Maleki et al. [103] found that thermal processing actually increased the IgE-binding capacity of major peanut allergens Ara h 1 and Ara h 2, indicating that heating may enhance peanut allergenicity in some cases.

Because processing alone may not eliminate all allergens, integrating multiple strategies is more effective [104]. Thermal techniques such as blanching, pasteurization, canning, and roasting offer accessible and cost-effective allergen mitigation and microbial control [105]. Freezing inhibits microbial growth below -9.5°C (15°F), contributing to food stability [60,79]. Drying enhances shelf life and lowers storage costs, though its allergen-modifying effects vary. Edible crickets with three major allergens identified: tropomyosin, actin, and hexamerin-like protein 2, particularly *Gryllus bimaculatus* (two-spotted cricket), are gaining attention as a high-protein food source; however, knowledge about how processing affects their allergenicity is limited. It was proven that tray drying led to a more pronounced reduction in the allergenicity of heat-labile proteins [106].

Fiocchi et al. [107] investigated the allergenicity of freeze-dried and homogenized beef in ten children with confirmed beef allergy, all of whom had positive skin prick tests (SPT) to both raw and heated beef and positive DBPCFC responses to 180 g of heated beef (5 min, 100°C). All children showed positive SPT reactions to untreated bovine serum albumin, and five reacted positively to it in DBPCFC. In contrast, only one child had a positive SPT to freeze-dried beef, and none reacted in DBPCFC. Homogenized beef also elicited no positive responses in either test. In a related study, the same group [106] reported weak allergenic potential of freeze-dried and homogenized beef, as well as freeze-dried sheep meat, in just two of 12 children with clinically confirmed beef allergy [88].

2.4. Non-Thermal Processing for Allergen Reduction

Non-thermal food processing technologies have gained considerable attention as promising strategies to reduce the allergenicity of food proteins without compromising nutritional value, sensory quality, or functional properties. Unlike traditional thermal treatments, non-thermal methods such as high-pressure processing (HPP), pulsed electric fields (PEF), cold plasma, ultrasound, and ultraviolet (UV) treatments offer more targeted approaches for modifying allergenic proteins. These techniques can disrupt protein structures, mask or cleave IgE-binding epitopes, and trigger biochemical changes that reduce immunoreactivity. As the prevalence of food allergies

continues to rise globally, non-thermal interventions provide a compelling alternative for developing hypoallergenic food products while maintaining consumer acceptability and regulatory compliance (Table 2).

Table 2. Overview of nonthermal methods for allergen reduction (adapted from [169]).

Technology	Mechanism of Action	Limitations
High-Pressure Processing	Disrupts non-covalent bonds within proteins; alters protein conformation through aggregation and gelation, affecting epitope exposure; enhances enzymatic hydrolysis.	Dual effects of pressure require accurate control; combining with other treatments may be necessary to optimize results.
Pulsed Electric Fields	Alters the secondary structure of allergenic proteins.	Often used alongside heat treatments to improve efficacy.
Pulsed Light	UV Delivers high-intensity UV pulses that cause photochemical modifications in proteins, including structural changes and epitope destruction	Limited penetration depth; potential degradation of sensitive nutrients; treatment uniformity can be challenging depending on food surface characteristics.
Cold Plasma	Reactive oxygen and nitrogen species (ROS and RNS) interact with antigens, altering protein configurations.	High equipment costs; limited understanding of how cold plasma mitigates food allergens; potential cytotoxic effects of treated liquids warrant further investigation.
Ultrasound	Cavitation generated by ultrasonic waves breaks peptide bonds, leading to irreversible unfolding and structural disruption of allergenic proteins.	Can negatively impact product color, flavor, and nutritional quality.
Gamma Irradiation	Allergenic proteins absorb radiation, altering their 3D structures; free radical formation leads to water radiolysis and modification of amino acid side chains.	Effective dose levels are not clearly established; not all protein-rich foods are currently approved for irradiation in the EU; concerns remain regarding food irradiation safety.

2.4.1. High Hydrostatic Pressure and Allergenicity in Foods

High hydrostatic pressure (HHP) processing is a non-thermal food preservation method that typically subjects food products to pressures between 100 and 600 MPa, often at ambient or refrigerated temperatures. This treatment is particularly impactful on protein molecules, as it disrupts non-covalent interactions such as hydrogen bonds, ionic bonds, hydrophobic forces, and van der Waals interactions [108,109]. These interactions are fundamental to maintaining the secondary, tertiary, and quaternary structures of proteins. However, unlike thermal processing, HHP generally does not cleave covalent bonds such as peptide bonds or disulfide bridges unless extremely high pressures or extended treatment durations are applied [110]. As a result, while the primary amino acid sequence typically remains intact, HHP can lead to significant unfolding and denaturation of proteins, altering their structural and functional properties [111].

One of the most critical implications of HHP-induced protein denaturation is its effect on allergenicity. Food allergens are proteins or glycoproteins that possess immunologically active regions—known as epitopes—that are recognized by Immunoglobulin E (IgE) antibodies in sensitized individuals [112]. These epitopes can be either conformational, depending on the three-dimensional folding of the protein, or linear, comprising a continuous stretch of amino acids. HHP has the potential to disrupt these epitopes, especially conformational ones, by unfolding the protein structure and eliminating the spatial arrangements necessary for epitope recognition. Consequently, the IgE-binding capacity of many food allergens is reduced after HHP treatment [84].

In addition to epitope disruption, HHP can also cause protein aggregation. During unfolding, reactive groups become exposed, leading to intermolecular interactions and the formation of protein aggregates. This aggregation can result in the masking of linear epitopes or the creation of neoepitopes—new epitopic structures that may be more or less allergenic depending on the protein and processing conditions [113]. Furthermore, HHP-treated proteins often become more susceptible to proteolysis. The unfolding of the protein enhances accessibility for digestive enzymes such as pepsin and trypsin, promoting more effective breakdown during gastrointestinal digestion. This reduced stability and increased enzymatic degradation decrease the likelihood of allergenic epitopes surviving digestion and triggering immune responses [112].

The efficacy of HHP in reducing allergenicity is not uniform across all food proteins and is influenced by several factors, including pressure intensity, exposure time, temperature, pH, and the composition of the surrounding food matrix. For instance, pressures exceeding 400 MPa are generally required to significantly reduce allergenicity in robust proteins like β -lactoglobulin (from milk), tropomyosin (from shellfish), or ovomucoid (from egg) [114]. Additionally, the presence of other food components—such as lipids, carbohydrates, or salts—can stabilize protein structures or shield epitopes, thereby diminishing the effectiveness of HHP [115,116]. These matrix effects must be considered when designing HHP-based allergen control strategies.

HHP can lead to structural alterations in allergenic proteins, potentially reducing their immunoreactivity by destroying conformational epitopes. However, in some cases, HHP can expose hidden epitopes or modify existing ones, resulting in unchanged or even increased allergenicity. The outcome is dependent on the specific protein, the pressure level, and whether other treatments (e.g., heat) are combined with HHP. In the case of β -lactoglobulin (BLG), a major milk allergen, treatment at 600 MPa caused irreversible changes in secondary and tertiary structures, including the release of free thiol groups and surface hydrophobicity [117]. These structural changes enhanced the protein's IgE-binding capacity, indicating increased allergenicity post-treatment.

Kato et al. [118] demonstrated that HHP, when combined with 8 M urea, significantly reduced rice allergen levels. The proposed mechanism involved structural damage to allergens caused by pressure, followed by enhanced extraction with urea to remove these proteins. Egg allergenicity was shown to decrease when pressure was applied in combination with heat. A study reported that the synergistic application of pressure and heat significantly reduced the allergenic response to hen's egg, compared to either treatment alone [119]. HHP applied to soybean sprouts at 400 MPa resulted in significant reductions in the levels of Gly m 1, a key soybean allergen [120]. The treatment also reduced antigenicity of soybean protein isolates, with modifications in protein structure likely responsible for the lowered immunoreactivity. Overall, HHP is a promising tool for allergen mitigation in food systems. However, the effects are protein-specific and process-dependent. When combined with thermal treatments or other chemical agents, HHP may significantly reduce allergenicity, making it an important strategy in the development of hypoallergenic foods (Table 3).

Table 3. Effects of high hydrostatic pressure on allergenicity of various foods.

Food Variety	Treatment Conditions	Key Findings	Reference
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Soybean	300 MPa, 40°C, 15 min	HHP notably reduced allergenicity in soybean sprouts, with only an 18% decrease in essential amino acids and overall nutritional value. HHP may offer a viable method for producing low-allergen soybean sprouts.	[2]
Soybean	400 MPa	Treatment improved protein solubility and hydrophobicity, while decreasing β -sheet content.	[3]
Soy protein isolate (infant formula)	300 MPa, 15 min	Allergenicity reduced by 46.8% due to structural and interaction changes in SPI, suggesting enhanced safety in allergic individuals.	[4]
Peanut	150–800 MPa, 20–80°C, 10 min; 60–180 MPa	No major changes observed in allergen secondary structure under HHP. However, high-pressure microfluidization reduced Ara h 2 allergenicity by modifying its structure and increasing UV absorption and hydrophobicity.	[5,6]
Tofu	300 MPa, 40°C, 15 min	HHP did not change tofu protein composition but lowered intensity of some protein bands. Allergenicity remained unchanged.	[2]
Rice	100–400 MPa, 10–120 min; 300 MPa, 30 min + Protease N	Pressure facilitated allergen release into surrounding solution; with protease, allergens were nearly eliminated from rice grains.	[7]
Almond	600 MPa, 4–70°C, 5–30 min	No significant change in allergen concentration or IgE-binding capacity as per SDS-PAGE, WB, and ELISA.	[8]
Whey protein isolate	200–600 MPa, 30–68°C, 10–30 min	Antigenicity of β -lactoglobulin increased with pressure, temperature, and duration.	[9]
Skim milk	200–600 MPa, 30–68°C, 10–30 min	β -lactoglobulin levels rose post-treatment; thermal addition mitigated allergenicity, but HHP-treated samples retained higher β -lg than controls.	[9]
Sweet whey	200–600 MPa, 30–68°C, 10–30 min	β -lg antigenicity rose at moderate temperatures and pressures; higher temperatures reduced but did not eliminate antigenicity.	[9]

Milk	>100 MPa	+	Proteolysis of β -lg was accelerated under chymotrypsin/trypsin, HHP, suggesting potential for hypoallergenic food production.	[10]
Apple	400–800 MPa, 80°C, 10 min		Mal d 3 allergen lost α -helical structure, becoming a random coil; immunoreactivity declined at \geq 400 MPa.	[6]
Apple	700 MPa, 115°C, 10 min		Mal d 1 showed minimal changes at 20°C, but more pronounced at 80°C; Mal d 3 IgE reactivity dropped by ~30%.	[11]
Apple	600 MPa, 5 min		Mal d 1 immunoreactivity decreased by >50% with combined high pressure and heat.	[11]
Apple	600 MPa, 5 min; repeated consumption		Daily intake of HHP-treated apple gel for 3 weeks led to desensitization in highly allergic individuals; 90% negative skin tests post-treatment.	[12]
Carrot	500 MPa, 50°C, 10 min		Slight increase in β -sheet structure of Dau c 1; no change in immunoreactivity observed.	[13]
Carrot juice	400–550 MPa, 3–10 min; 500 MPa, 30–50°C, 10 min		HHP had no observable effect on the allergenic potential of carrot juice.	[13]
Celeriac	700 MPa, 118°C, 10 min		Allergenicity of Api g 1 was significantly reduced through combined pressure and thermal processing.	[11]
Celery	500 MPa, 50°C, 10 min		Api g 1 structural changes were pressure-dependent but did not impact allergenicity.	[14]

2.4.2. Pulsed Electric Fields (PEF) Technology and Its Impact on Food Allergenicity

Pulsed electric field (PEF) technology represents a cutting-edge, non-thermal processing method that applies short bursts of high-voltage pulses—typically between 1 and 50 kV/cm—to biological materials such as tissues or fluids. This approach results in electroporation, a temporary increase in cell membrane permeability caused by dielectric breakdown, facilitating improved mass transfer and promoting the release of internal components such as proteins, lipids, and bioactive molecules [121–124]. PEF has gained broad acceptance across multiple domains within the food industry. Its applications range from microbial inactivation and juice extraction to drying pre-treatment, seed enhancement, detoxification of mycotoxins, and starch transformation [125–128]. Fundamentally, PEF's mechanism involves inducing electroporation in cell membranes through high-intensity, short-duration pulses. These pulses lead to reversible or irreversible structural modifications in the membrane, thereby enhancing the transfer of substances and aiding in the recovery of intracellular compounds [123,124].

The performance of PEF systems is closely tied to the electrical behavior of cell membranes, which are largely composed of lipid bilayers acting as insulators. These membranes isolate the conductive environments inside and outside the cell, making each cell resemble a microscopic capacitor [122]. When placed in a conductive solution and exposed to an electric field, the cell disrupts

the uniformity of the field, concentrating the intensity at the poles of the membrane aligned with the field [124].

A typical PEF setup includes a high-voltage pulse generator (ranging from 10 to 80 kV/cm), a treatment chamber with insulated electrodes, a cooling system, and a flow system for uniform exposure [122,125]. The system design is tailored through parameters like pulse duration, waveform, frequency, and electrode configuration. Pulse modes can be exponential decay, sinusoidal, monopolar, or bipolar. For instance, monopolar pulses have a constant polarity, while bipolar ones alternate it, minimizing polarization effects on electrodes. Different waveforms—such as square, decaying exponential, logarithmic, or oscillatory—offer varying benefits. Square waves, for example, ensure consistent membrane disruption, whereas decaying pulses can reduce energy use and thermal damage. The choice of pulse configuration is critical for achieving the desired effects—whether microbial inactivation, compound extraction, or textural modification—while preserving the nutritional and sensory quality of food products. Advanced control and safety systems are incorporated into industrial PEF equipment to ensure continuous, hygienic, and reliable processing [122,125,129,130]. Upon the application of the electric field, the cell—functioning as a dielectric sphere in a conductive environment—undergoes enhanced localized electric field intensity at its poles. These intensified regions are key sites for electroporation, often experiencing a field strength far exceeding the average applied to the bulk medium [124].

Although research on the influence of PEF on protein structure remains relatively limited, several studies have reported notable structural and functional changes depending on the protein type [131] and evidences suggest that PEF can disrupt the secondary and tertiary structures of proteins. These alterations are likely due to ionization of specific chemical groups and the disruption of electrostatic interactions [132,133]. Initially, protein molecules become polarized, leading to the exposure of hydrophobic amino acid residues to the surrounding solvent. This process subsequently results in protein unfolding and aggregation under the influence of high-intensity electric fields [134]. PEF processing has gained considerable interest in the food industry because of its energy efficiency, ability to preserve nutritional quality, and its suitability for liquid food matrices [135]. For instance, treatment of soybean protein isolates with PEF has demonstrated alterations in physicochemical properties, including denaturation and aggregation behaviors [136]. Similarly, investigations involving purified enzymes such as horseradish peroxidase and pectin esterase revealed a decline in enzymatic activity post-treatment, which was primarily attributed to conformational changes in protein structure [137]. However, it is important to consider that these changes may not result solely from the electric field itself; thermal effects due to associated Ohmic heating could also contribute to the observed outcomes [137]. The study conducted by Johnson et al. [138] explored the effects of PEF processing on the structural integrity of selected food allergens, including peanut allergens Ara h 2 and Ara h 6, and apple allergens Mal d 3 and Mal d 1b, all expressed heterologously. Structural changes were assessed using circular dichroism spectroscopy and gel-filtration chromatography. The findings showed that PEF treatment did not lead to any significant alterations in the secondary structure or aggregation state of the allergens. These results suggest that PEF is a structurally non-invasive food processing method with minimal impact on the conformation of purified food allergens.

A study investigating the effect of pulsed electric field (PEF) treatment at 25 kV/cm and 50 °C on *Pru p 3*, the major allergenic protein in peach, revealed that PEF induced structural denaturation of the protein, as determined by ELISA using rabbit IgG. However, the PEF treatment did not affect the IgE-binding capacity of *Pru p 3*, as shown by a competitive fluorescent immunoassay with sera from peach-allergic patients. Additionally, skin prick test results varied among individuals; more than 50% of participants exhibited increased skin reactivity following PEF treatment, indicating that patient-specific sensitization patterns may persist despite structural alterations in the allergen [139].

Experimental studies have demonstrated that high-intensity PEF treatments, particularly at 25–35 kV/cm for durations ranging from 60 to 180 μs, significantly impact the structural conformation of ovalbumin, including the α-helix content, thereby altering its immunogenic properties. The most

substantial reduction in immunoreactivity was observed at 35 kV/cm for 180 μ s [140], indicating PEF's potential to lower the allergenicity of egg proteins.

In a molecular dynamics simulation study, Vanga et al. [141] explored the effects of oscillating and static electric fields (2450 MHz, 0.05 V/nm) at various temperatures (300, 380, and 425 K) on the structure of Ara h 6, a major peanut allergen. The simulations revealed significant conformational modifications under all tested conditions, implying potential impacts on the allergen's functional properties. Subsequently, Vanga et al. [142] experimentally treated peanut flour with electric field intensities of 10, 15, and 20 kV for 60–180 minutes. Results indicated time-dependent increases in α -helix conformational changes, likely attributed to the emergence of new random coil structures and protein aggregates during processing.

However, not all findings confirm a consistent reduction in allergenicity. For instance, Johnson et al. [138] reported no significant structural changes in Ara h 2 and Ara h 6 (peanut 2S albumins), Mal d 1, and Mal d 3 (apple allergens) following PEF treatment at electric field strengths ranging from 0 to 35 kV/cm, with 2 Hz frequency and up to 130 kJ/kg energy input. Similarly, Paschke [143] found no notable reduction in celery allergen content when treated with a 10 kV PEF at 50 Hz.

A recent study investigated the modulation of ovalbumin (OVA) allergenicity using PEF treatment, highlighting structural changes linked to reduced immunoreactivity. PEF treatment at 6 kHz inhibited IgE and IgG1 binding by 30.41%, accompanied by visible microstructural surface cracks and unfolding of the protein's secondary structure. Spectroscopic analyses revealed a blue shift in the amide I band, reductions in α -helix and β -sheet content, and conformational changes in disulfide bonds. Increased fluorescence intensity suggested exposure of hydrophobic residues such as tryptophan and tyrosine. Molecular dynamics simulations further confirmed reduced structural stability and hydrogen bonding. These findings suggest that PEF disrupts allergenic epitopes by altering protein conformation, supporting its potential application in developing hypoallergenic egg products [144]. In comparison to thermal and other non-thermal techniques, the impact of PEF on the structural modification and immunoreactivity of food allergens appears to be relatively limited. These inconsistent outcomes highlight the need for further optimization of PEF parameters to achieve reliable and reproducible allergen mitigation.

2.4.3. Pulsed Ultraviolet (PUV) Light and Its Impact on Food Allergenicity

Pulsed light (PL) technology utilizes a series of extremely brief, high-intensity bursts of broad-spectrum white light, composed primarily of ultraviolet (UV) light (54%), followed by visible light (26%) and infrared radiation (20%) [145]. The PUV light spans wavelengths from 200 nm to 1000 nm, allowing it to deliver intense light energy within a very short duration [146]. As a result, PUV light can achieve energy intensities up to a thousand times greater than those of traditional continuous UV systems (Shriver and Yang 2011). The technology utilizes xenon flash lamps to generate short-duration (typically <1 ms), high-energy light bursts at a frequency ranging from 1 to 20 Hz. These pulses result in rapid microbial inactivation via photochemical, photothermal, and photophysical mechanisms, primarily targeting nucleic acids and protein structures. In addition to microbial control, PUV has been investigated for its potential to alter food allergens, degrade toxins, and induce structural and functional changes in biomolecules such as proteins and lipids, without significantly elevating product temperature or compromising sensory and nutritional qualities [147–150].

In food applications, PUV light has been explored for its ability to modify the structural configuration of allergenic proteins. This includes altering conformational epitopes and promoting protein aggregation, which may reduce allergenicity [146,150]. However, post-treatment re-association of peptide fragments can lead to the development of neo-epitopes—new structures that could increase the allergenic potential of the food [151].

The functional mechanisms of PUV light inactivation can be grouped into photochemical, photothermal, and photophysical processes. These effects contribute to chemical transformations and modifications in protein structure, influenced by rapid heating and the intermittent delivery of high-energy pulses [146,152].



When applied to peanut samples—including raw, roasted, and peanut butter extracts—PUV light at distances of 10.8, 14.6, and 18.2 cm for 1–6 minutes caused a marked reduction in the intensity of allergenic proteins Ara h 1, Ara h 2, and Ara h 3, as evidenced by SDS-PAGE analysis. Increased energy doses (111.6 to 223.2 J/cm²) and longer exposure times further enhanced this reduction, while greater distance from the light source diminished the effect. ELISA results revealed that IgE binding decreased approximately 3-fold in raw peanut extracts and 7-fold in peanut butter slurry compared to untreated controls. These effects are attributed to changes in protein solubility and the formation of insoluble aggregates due to PUV treatment [153].

PUV light treatment of soy extracts for 2, 4, and 6 minutes led to a time-dependent decline in major allergens such as glycinin and β -conglycinin. Indirect ELISA using sera from soy-allergic individuals showed that IgE binding was reduced by 20%, 44%, and 50%, respectively. The observed reduction is likely associated with aggregation of allergenic proteins under PUV exposure [146]. PUV light also reduced the immunoreactivity of Gly m5 and Gly m6 allergens in soy when applied at a distance of 8–10 cm for up to 6 minutes. Gel bands corresponding to Gly m5 disappeared after just 2 minutes of treatment, while Gly m6 bands remained visible even after 6 minutes, indicating differential susceptibility to degradation or precipitation [154].

Similarly, ultraviolet-C (UV-C) treatment has shown promising effects in reducing the allergenic potential of milk proteins. Significant reductions in IgE binding were also observed in milk allergens including α -casein, α -lactalbumin, and β -lactoglobulin after 15 minutes of UV-C exposure. The decrease in immunoreactivity is likely due to alterations in discontinuous epitope structures. The enhanced effect in whey solutions has been linked to the greater pulse intensity and energy associated with PUV treatment [155]. The enhanced allergen reduction observed in whey proteins subjected to PUV treatment could be linked to the higher energy and pulse rate involved in the process [156].

For egg white proteins, ultraviolet exposure caused both aggregation and backbone cleavage; however, no substantial changes in immunoreactivity were observed compared to untreated controls. This suggests that the structural changes induced by UV light may not significantly affect allergenic epitopes in egg proteins [157].

Exposure of raw and boiled shrimp extracts (5 mg/mL) to pulsed ultraviolet (PUV) light at a pulse width of 360 μ s, frequency of 3 pulses per second, and a distance of 10 cm led to a notable and irreversible reduction in allergenic reactivity. This reduction has been attributed to the formation of high molecular weight protein complexes, likely due to cross-linking between tropomyosin and other heat-sensitive proteins [145,146]. This effect was attributed to the formation of high molecular weight compounds via cross-linking between tropomyosin and other heat-sensitive proteins during the treatment [145].

Overall, PUV light has shown the capacity to lower allergenic potential in soy, peanut, milk, and shrimp products, though it appears ineffective for modifying egg allergens. Despite these promising results, especially for producing hypoallergenic food items, further investigations—including clinical and *in vivo* studies—are necessary to confirm its broader applicability in food processing [142].

However, not all studies report a reduction in allergenicity with UV processing. For instance, Manzocco et al. [157] found that although ultraviolet exposure led to aggregation and backbone cleavage in egg white proteins, these structural changes did not significantly affect their immunoreactivity compared to untreated samples, suggesting that the epitope structures remained largely unchanged.

Overall, the evidence suggests that PUV light may be effective in reducing allergenicity in foods such as soy, milk, shrimp, and peanuts, while it appears to have limited impact on egg allergens (Table 4). Although the technology shows potential for producing hypoallergenic food products, further investigation—particularly clinical and *in vivo* studies—is essential before broader adoption in the food industry [104].

Table 4. Effect of UVC treatment on allergenicity of various foods (adapted from [169]).

Food material	Target allergen	Treatment	Effect on immunoreactivity	References
Milk	α -casein, α -lactalbumin	UVC treatment (15 min)	25% reduction	α -casein [166]
	β -lactoglobulin	UVC treatment (15 min)	27.7% whey fractions reduction	[166]
Egg	Ovalbumin	UV processing (0.61 kJ/m ²)	No effect	[168]
	Ovomucoid	UV processing (63.7 kJ/m ²)	No effect	[168]
Shrimp	Tropomyosin	PUV sterilization (4 min)	Reduced	[170]
Peanut	Ara h 1, Ara h 2, Ara h 3	PUV treatment on butter slurry (1–3 min); raw and roasted peanuts (2–6 min)	67% reduction binding of peanut butter slurry; 12.5 folds reduction, 100% reduction total extracts	IgE [164]
Soy	Gly m5	PUV treatment (1–6 min)	100% reduction Gly m5 reduced	[165]
	Gly m6	PUV treatment (1–6 min)	Gly m6 retained	[165]
	Soy extracts (e.g., glycinin, β -conglycinin)	PUV treatment 2 min	20% reduction	[164]
		PUV treatment 4 min	40% reduction	[164]
		PUV treatment 6 min	50% reduction	[164]

2.4.4. Gamma Irradiation and Its Impact on Food Allergenicity

Radiation refers to the transfer or emission of energy through space or a material medium in the form of waves or particles. It is broadly classified into two types: nonionizing and ionizing radiation. Nonionizing radiation lacks the energy required to remove electrons from atoms or molecules and is typically considered non-harmful, causing little to no chemical changes. This category includes ultraviolet light, visible light, infrared radiation, microwaves, and radio waves—all of which are lower in energy and generally not used for food processing. In contrast, ionizing radiation carries sufficient energy to dislodge electrons, resulting in the formation of ions. This form includes energetic electromagnetic waves and subatomic particles capable of altering molecular structures. Among ionizing methods, gamma irradiation is considered one of the most straightforward techniques [164,165]. The reduction in immunoreactivity was linked to protein denaturation, assessed through parameters such as turbidity, surface hydrophobicity, and chromogenic reactivity. These findings suggest that coagulation of allergenic proteins may play a crucial role in minimizing allergenicity post-irradiation [166]. Irradiation of wheat germ agglutinin (WGA) was found to initially cause polypeptide chain fragmentation, followed by the formation of large, insoluble amorphous aggregates, ultimately leading to a decrease in allergenicity [167].

Radiation has proven to be an effective method for preserving food while maintaining its nutritional value and sensory qualities. It induces structural modifications in food proteins—including fragmentation, aggregation, cross-linking, and alterations to amino acids—that can influence their immunogenic properties [168]. These changes are primarily driven by reactive oxygen species formed during the radiolysis of water when proteins are irradiated in aqueous environments.

Exposure to ionizing radiation at doses of 10 and 50 kGy (applied at 10 °C with a rate of 10 kGy/h) altered the conformational epitopes in peanuts, leading to a significant reduction in IL-4 cytokine production by splenocytes from sensitized mice [169]. Similarly, Luo et al. [168] demonstrated that irradiation of purified peanut allergen Ara h 6 and whole peanut extract (at 1, 3, 5, and 10 kGy, 10 °C) resulted in a notable decline in IgG binding, as detected by ELISA, with higher radiation doses enhancing the effect. Interestingly, up to 5 kGy, the IgG response to whole peanut extract was greater than that of Ara h 6 alone, potentially due to the presence of other components in the extract that shielded Ara h 6 epitopes.

A comparable pattern was reported by Zhenxing et al. [170] in shrimp, where protein extracts irradiated at doses between 3 and 15 kGy (10 °C, 1 kGy/h) showed reduced IgE binding. However, intact shrimp muscle initially exhibited increased IgE reactivity up to 5 kGy, which then declined at higher doses.

A dose-dependent response to irradiation was observed in a study on cow milk allergy by Lee et al. [156], where IgE binding to isolated β -lactoglobulin (β -lg) increased up to a dose of 5 kGy. Beyond this level, protein agglomeration occurred, likely masking specific epitopes and resulting in reduced allergenic potential. In contrast, Kaddouri et al. [171] reported enhanced recognition of anti- β -lg IgG antibodies following irradiation (3–10 kGy at 13 Gy/min) of both liquid and freeze-dried cow milk and whey. These differing results may be attributed to the sample form—whether β -lg was isolated or present within a milk matrix—and the type of antibodies used in detection. These findings suggest that the allergenic response of purified proteins and whole food extracts to irradiation can vary, which holds relevance for food industry applications. Furthermore, differences in dose rate among studies indicate that the impact of varying dose rates at a constant radiation dose on protein allergenicity remains unclear.

In other research, irradiation of whole almonds, cashews, and walnuts did not result in structural changes to allergenic proteins or alter their allergenic potential [172]. Conversely, studies have shown that irradiation may increase the immune reactivity of gliadin and wheat flour [173]. These opposing results may stem from the physical state of the samples—solid versus solution—which can influence how effectively irradiation reduces allergenicity. Overall, applying irradiation to food allergens in liquid form appears to be the most promising approach for minimizing their immunoreactivity.

Seo et al. [174] observed a decrease in the presence of the egg allergen ovalbumin when exposed to gamma radiation using cobalt-60 at a dose of 100 kGy, while treatment at 10 kGy showed no significant impact. This reduction was believed to result from alterations in the protein's molecular weight. Gamma irradiation is known to promote protein crosslinking—such as disulfide bond formation—and enhance hydrophobic interactions, both of which can lead to protein aggregation [175]. However, a 100 kGy dose exceeds levels typically considered safe for food processing, as doses up to around 10 kGy are generally recognized as safe for consumption [176]. In a separate study, Seo et al. [177] also reported reduced ovalbumin immunoreactivity in white cake samples irradiated at 10–20 kGy.

In studies involving crustacean allergens, such as shrimp tropomyosin, gamma irradiation at doses of 7 kGy and higher resulted in the disappearance of the characteristic 36 kDa tropomyosin band on SDS-PAGE, indicating structural degradation. Additionally, IgE binding was significantly diminished at the highest doses tested [178]. Multiple studies have demonstrated the effectiveness of gamma irradiation in modifying allergenic proteins. For instance, Seo et al. [174] reported that ovalbumin, a principal allergen. Gamma irradiation can enhance protein crosslinking through the

formation of disulfide bonds and intensified hydrophobic interactions, which promote aggregation and possible loss of immunoreactive epitopes (Table 5) [166].

Table 5. Mechanisms by which PUV affects protein structure and allergenicity.

Mechanism	Details	Impact on Allergenicity	Citations
Photo-oxidation	PUV emits intense UV-C light (200–280 nm) that causes oxidative modifications, particularly in amino acids like tryptophan, tyrosine, and methionine.	Oxidative damage to amino acid residues alters the structure of allergenic epitopes.	[158]
Disruption of Disulfide Bonds	High-energy UV pulses can break disulfide bridges that maintain protein conformation.	Destabilization of tertiary structure reduces IgE-binding ability.	[160]
Epitope Modification	PUV alters conformational and linear epitopes through structural denaturation.	IgE-binding is reduced due to loss of native allergenic regions.	[68,101]
Protein Aggregation / Fragmentation	UV treatment may lead to cross-linking or fragmentation, depending on exposure time and intensity.	Aggregation can mask epitopes; fragmentation may eliminate allergenic potential.	[101,160,161]
Surface Effects	PUV has limited penetration depth (~microns); primarily impacts food surface proteins.	Effective for surface allergens; limited impact on allergens embedded within the food matrix.	[162,163]
Dose- and Matrix-Dependent Effects	Allergen reduction is influenced by pulse energy, duration, distance, and the optical properties (color, opacity) of the food.	Matrix composition may shield proteins or influence energy absorption, thus modulating allergenicity outcomes.	[164]

2.4.5. High-Intensity Ultrasound and Its Impact on Food Allergenicity

Ultrasound technology has gained considerable attention in food processing due to its non-thermal and energy-efficient nature. It involves the application of sound waves with frequencies above the range of human hearing, typically between 20 kHz and 100 kHz in food systems [180].

When ultrasound is applied at high intensity, it induces a phenomenon known as acoustic cavitation—the formation, growth, and implosive collapse of microbubbles within a liquid medium [181]. The core mechanism involves cavitation, wherein alternating compression and rarefaction cycles form microbubbles that collapse violently, generating localized temperatures up to 5000 K and pressures reaching 1000 atm [182]. These extreme conditions facilitate protein denaturation, potentially altering allergenic structures and epitopes. This collapse generates localized hot spots with extremely high temperatures (up to 5000 K) and pressures (up to 1000 atm), although these effects are confined to the microscopic scale and last for only a few microseconds [183]. Alongside thermal effects, cavitation leads to intense shear forces, microjetting, turbulence, and the production of free radicals (e.g., hydroxyl radicals from water sonolysis), all of which can contribute to physical and chemical transformations in food matrices [184].

High-intensity ultrasound (HIU) has been explored for various food processing operations, including peeling of fruits and vegetables [185], reduction of oil content and shelf-life extension of fried products [186], and shortening of parboiling time in rice processing [187]. More recently, its potential to alter protein structure and reduce food allergenicity has attracted scientific interest. The primary mechanism by which HIU affects allergens lies in its capacity to alter the three-dimensional structure of allergenic proteins. During sonication, proteins can undergo unfolding, aggregation, or fragmentation due to mechanical stress and localized heating, leading to changes in epitope exposure and antigenicity. Additionally, free radicals generated during cavitation may oxidize specific amino acid residues, contributing further to conformational changes [58,166].

In a study by Li et al. [187], shrimp samples were subjected to high-intensity ultrasound at a frequency of 30 kHz for durations ranging from 130 to 180 minutes. This treatment significantly reduced IgE-binding capacity in both isolated tropomyosin (the major shrimp allergen) and in crude shrimp protein extracts. Specifically, IgE-binding to the isolated tropomyosin was reduced by 81.3–88.5%, whereas binding in the shrimp extract decreased by approximately 68.9%, based on ELISA assays. Immunoblotting also revealed that prolonged ultrasound exposure led to the formation of new, lower-molecular-weight protein bands, suggesting fragmentation of the allergenic protein. This structural disruption likely contributed to the observed decrease in allergenic reactivity. Interestingly, the treatment duration was relatively long, yet no significant temperature rise or quality deterioration of the shrimp product was reported. This highlights one of the advantages of HIU as a non-thermal method for allergen mitigation. Zhenxing et al. [170] further confirmed that shrimp allergenicity decreased more significantly at elevated temperatures (50 °C) during ultrasound treatment. In another study, Zhang et al. [188] subjected shrimp tropomyosin (TM) to 15 minutes of ultrasound (100–800 W), reporting a substantial degradation of TM and associated reduction in allergenicity, as evidenced by ELISA and immunoblotting using sera from allergic patients. However, some shellfish allergens appear more resistant to ultrasound. Chen et al. [189] found minimal degradation and unchanged IgE-binding activity of arginine kinase (AK) in crayfish even after ultrasound treatment at 200 W and 30 °C for up to 180 minutes. Dairy proteins also showed limited response; Tammineedi et al. [155] observed no significant changes in SDS-PAGE profiles of α -casein, β -lactoglobulin, and α -lactalbumin after treatment with 500 W ultrasound at 20 kHz for up to 30 minutes. Similar findings were reported in other milk allergen studies [155,190].

In soy protein, Tammineedi et al. [155] demonstrated a 24% decrease in immunoreactivity following treatment with high-intensity ultrasound at 37 kHz for 10 minutes. The observed reduction is attributed to alterations in secondary and tertiary structures. Similarly, significant allergen reduction has been observed in roasted peanuts; Li et al. [187] reported decreases of 84.8% in Ara h 1 and 4.88% in Ara h 2 after exposure to 50 Hz ultrasound for two hours. Structural modifications in the α -helical IgE-binding regions of these proteins are believed to account for this change [191,192]. Zhenxing et al. [170] further confirmed that shrimp allergenicity decreased more significantly at elevated temperatures (50 °C) during ultrasound treatment. In another study, Zhang, He et al. (2018b) subjected shrimp tropomyosin (TM) to 15 minutes of ultrasound (100–800 W), reporting a substantial

degradation of TM and associated reduction in allergenicity, as evidenced by ELISA and immunoblotting using sera from allergic patients.

The efficiency of ultrasound appears to increase when combined with thermal treatment, suggesting a synergistic effect. Ultrasound processing offers several benefits, including reduced energy consumption, minimal chemical usage, enhanced mass transfer, and better retention of sensory qualities [193]. Given these advantages and its proven potential in reducing immunoreactivity in soy, peanuts, and shellfish, ultrasound is a compelling alternative to conventional processing methods. Nevertheless, optimization of key parameters—such as frequency, treatment duration, and temperature—is essential to maximize its efficacy in allergen reduction across various food types. Overall, high-intensity ultrasound offers a promising approach to reduce the allergenic potential of food proteins through a combination of physical and chemical effects (Table 6). While more data is needed to understand optimal parameters and food matrix-specific responses, current evidence supports its utility as part of an integrated strategy for allergen control in food systems [165].

Table 6. Effects of gamma irradiation on food allergens.

Food Matrix	Irradiation Dose (kGy)	Effect on Allergen	Mechanism/Observation	Reference
Egg (Ovalbumin)	10–100	Reduced allergenicity	Change in molecular weight; protein aggregation and cross-linking (disulfide bonds)	[174,177]
White Cake (with egg)	10–20	Reduced ovalbumin reactivity	Reduction in IgE binding	[174]
Shrimp (Tropomyosin)	7–10	Undetectable tropomyosin band; reduced IgE binding	Protein denaturation, aggregation; turbidity and surface hydrophobicity changes	[145]
Shrimp (Tropomyosin)	1–15 + heat (100°C)	5–30-fold reduction in IgE binding	Synergistic effect with heat treatment	[170]
Egg (Ovomucoid)	10 + heat	Almost undetectable levels of ovomucoid	Irradiation more effective than heat alone due to ovomucoid heat stability	[156]
Tree Nuts (Almonds, Cashews, Walnuts)	1–25 ± heat	Minimal change in allergenicity	Allergens stable under irradiation and heat	[179]

2.4.6. Cold Plasma and Its Impact on Food Allergenicity

Cold plasma is primarily used for microbial inactivation and decontamination of food due to its lower energy consumption and reduced temperature requirements compared to traditional methods [199]. Ionized gas, often referred to as the fourth state of matter, consists of a mixture of reactive species such as UV photons, ions, electrons, free radicals, molecules, and excited atoms. These

components are formed through the excitation and ionization of gases and are capable of interacting with proteins, resulting in conformational changes. Since most food allergens are proteins, it is hypothesized that cold plasma treatment could similarly alter their structures through these reactive agents [165,199]. Multiple studies have shown the potential of plasma treatment in reducing food allergenicity. For example, Venkataratnam et al. [200] applied cold atmospheric plasma (80 kV) for different durations (0 to 60 minutes) to dry, defatted peanut flour and whole peanuts. Competitive ELISA using bovine serum albumin showed up to a 43% reduction in antigenicity, accompanied by secondary structure changes detected through circular dichroism. In another investigation, direct dielectric discharge cold plasma treatment for 5 minutes at 30 kV and 60 Hz led to a 76% decrease in shrimp allergen tropomyosin's immunoreactivity [166].

In one study, the impact of both direct and remote cold atmospheric pressure plasma (CAPP) on the immunoreactivity of soy protein isolate was examined [165]. Researchers measured factors such as sample weight, surface temperature, pH, and hydrogen peroxide content. SDS-PAGE analysis revealed a noticeable reduction in the intensity of protein bands corresponding to the primary soy allergens β -conglycinin (Gly m5) and glycinin (Gly m6). The most substantial decrease in immunoreactivity—ranging from 91% to 100%—was observed in the soluble protein fraction following direct CAPP treatment. Remote CAPP exposure also reduced immunoreactivity, though to a slightly lesser extent, with reductions of up to 89%. These reductions in immunoreactivity are attributed to the disruption or masking of conformational epitopes by free radicals produced during plasma exposure, which hinders IgE antibody recognition [201]. Meinlschmidt et al. [154] reported that CAPP treatment of soy protein extracts for up to 10 minutes at 9, 10, and 11 kVpp (3.0 kHz) nearly eliminated Gly m5 allergen reactivity. This was likely due to alterations in conformational and linear epitopes or destruction of antibody binding sites, as shown by sandwich ELISA using human sera and monoclonal antibodies.

On the other hand, Tammineedi et al. [155] treated milk α -casein with cold atmospheric plasma at 13.56 MHz radiofrequency and 30.7 L/min argon gas flow for 5, 10, and 15 minutes. They found no significant reduction in immunoreactivity, possibly due to limited plasma exposure or insufficient treatment intensity. These varied findings across food types suggest that cold plasma's effectiveness in allergen reduction is not uniform and depends on factors such as sample composition and processing conditions. To date, reductions in allergen levels have been observed in soy, peanuts, shrimp, and wheat after cold plasma treatment, while no notable changes have been reported in milk proteins. Furthermore, concerns remain regarding the quality degradation associated with this method. Several studies have linked cold plasma processing to undesirable effects, including accelerated lipid oxidation, nutrient loss (such as vitamins), and compromised sensory qualities [202–204]. Therefore, while cold plasma holds potential, its limitations highlight the need for continued research and the development of alternative food processing technologies.

2.4.7. Genetic Modification and Its Role in Reducing Allergenicity

Genetic modification (GM) refers to the deliberate alteration of an organism's genetic material using biotechnology, allowing for the insertion, deletion, or silencing of specific genes to achieve desired traits. In the context of food production, GM is employed to enhance crop yield, resistance to pests or diseases, and improve nutritional or functional characteristics. Over recent years, its potential to reduce food allergenicity has become a growing area of research, although concerns regarding safety, stability, and consumer perception remain significant. One strategy to reduce allergenicity in foods through GM involves silencing the expression of specific allergenic proteins by employing post-transcriptional gene silencing or co-suppression mechanisms. This approach aims to prevent the production of allergenic proteins during gene expression. However, uncertainties persist regarding the long-term stability of these modifications. Incomplete suppression or loss of gene silencing could reintroduce allergens, posing potential health risks to sensitized individuals. Additionally, removing key proteins may affect the structural and functional integrity of food products, as many allergenic proteins play vital roles in the metabolism and development of the source organism [79].

Public skepticism also surrounds the possibility that modifying protein structures may inadvertently result in the emergence of new allergenic determinants or epitopes that the immune system may fail to recognize as harmless. Therefore, a more targeted strategy—such as altering specific IgE-binding epitopes while maintaining the overall structure and functionality of the protein—may offer a safer and more effective route [205].

Experimental studies provide insights into these strategies. For instance, Rupa et al. [206] modified the IgE-binding sites of ovomucoid, a major egg allergen, by introducing glycosylation at known epitope locations. This post-translational modification significantly reduced IgE-mediated immune responses in a mouse model, demonstrating the feasibility of epitope-focused interventions. However, since the modified proteins were expressed in yeast cells rather than in the natural egg matrix, it remains unclear how such changes would impact the final food product. In a study targeting peanut allergens, Chu et al. [207] applied RNA interference to suppress the expression of Ara h 2 and Ara h 6, two major peanut allergens. Although this intervention significantly decreased IgE binding to these allergens, the whole peanut extract still retained immunoreactivity, likely due to the presence of other allergenic proteins. Interestingly, the silencing of these genes did not lead to any noticeable morphological changes in the peanut plants. Similarly, Dodo et al. [56] reported reduced IgE binding following genetic silencing of Ara h 2. In another example, Herman et al. [208] demonstrated that silencing Gly m Bd 30, a key soybean allergen, nearly eliminated IgE binding. Detailed protein analyses and microscopic evaluations confirmed that the modified soybeans were structurally and compositionally similar to their non-GM counterparts and did not produce any new allergens. Although these findings highlight the potential of GM approaches to reduce allergenicity (Table 7), broader questions concerning consumer acceptance, regulatory approval, and long-term safety must still be addressed.

Table 7. Overview of recent studies on the impact of ultrasound processing on food allergenicity (adapted from [194]).

Food	Target Allergen	Treatment	Immunoreactivity	References
Soy	Proteins	37 kHz, 10 min	Reduced 24%	[195]
Milk	α-casein	500 W and 20 kHz (10–30 min)	No effect	[155]
	β-lactoglobulin	500 W and 20 kHz (10–30 min)	No effect	[195]
	α-lactalbumin	500 W and 20 kHz (10–30 min)	No effect	[190]
Peanut	Ara h1	50 Hz for 5 h	Reduced 84.8%	[196]
	Ara h2	50 Hz for 5 h	Reduced 4.88%	[197]
Shrimp (boiled)	Proteins	30 kHz, 800 W (0–50 °C, 0–30 min)	Reduced 40%–50%	[197]
Shrimp (raw)	Proteins	30 kHz, 800 W (0–50 °C, 0–30 min)	Reduced up to 8%	[197]
Crayfish	Tropomyosin	100–800 W, 15 min	Reduced	[198]
Shrimp and allergens	Multiple (including tropomyosin)	30 Hz, 800 W (30–180 min)	Reduced up to 75%	[170]
Crayfish	Arginine kinase	200 W, 30 °C (10–180 min)	No effect	[189]

3. Conclusions

The rising prevalence of food allergies necessitates the development of effective mitigation strategies that ensure both consumer safety and food quality. A growing body of evidence highlights the complex interplay between the molecular characteristics of food allergens, processing conditions, and the surrounding food matrix in determining allergenic potential. Different processing technologies—thermal and non-thermal—induce distinct physicochemical modifications in food proteins, thereby influencing their digestibility, bioavailability, and IgE-binding capacity.

Thermal treatments such as moist heat generally reduce allergenicity by disrupting protein conformation and enhancing proteolytic susceptibility, while dry heat methods (e.g., roasting and baking) may increase allergenicity through the formation of neo-epitopes via Maillard reactions. Non-thermal technologies, including HPP, PEF, cold plasma, PUV, US, and gamma irradiation, offer promising alternatives for allergen mitigation by inducing conformational changes without compromising nutritional and sensory attributes. Additionally, microbial fermentation and enzymatic hydrolysis can effectively target linear epitopes, further reducing allergenic potential.

Despite these advances, translating reductions in IgE reactivity observed *in vitro* to clinically meaningful outcomes remain a significant challenge. The variability in digestive stability, structural resilience of allergenic proteins, and individual immune responses necessitates the use of complementary *in vivo* assessments such as skin prick tests, oral food challenges, and mediator release assays to validate hypoallergenic claims. Furthermore, a comprehensive understanding of both conformational and linear epitope modifications is essential for the design of processing strategies that minimize elicitation thresholds without compromising safety.

Future research should focus on standardizing allergenicity assessment protocols, integrating multi-hurdle approaches for simultaneous allergen and microbial risk reduction, and expanding studies to encompass emerging alternative proteins. Ultimately, a multidisciplinary approach that bridges food processing technology, immunology, and clinical validation is crucial for developing safe, effective, and industry-relevant solutions to mitigate food allergenicity and improve public health outcomes.

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