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Review

Engineering Food Allergenicity: Mechanisms and Applications of Thermal and Non-Thermal Processing Technologies

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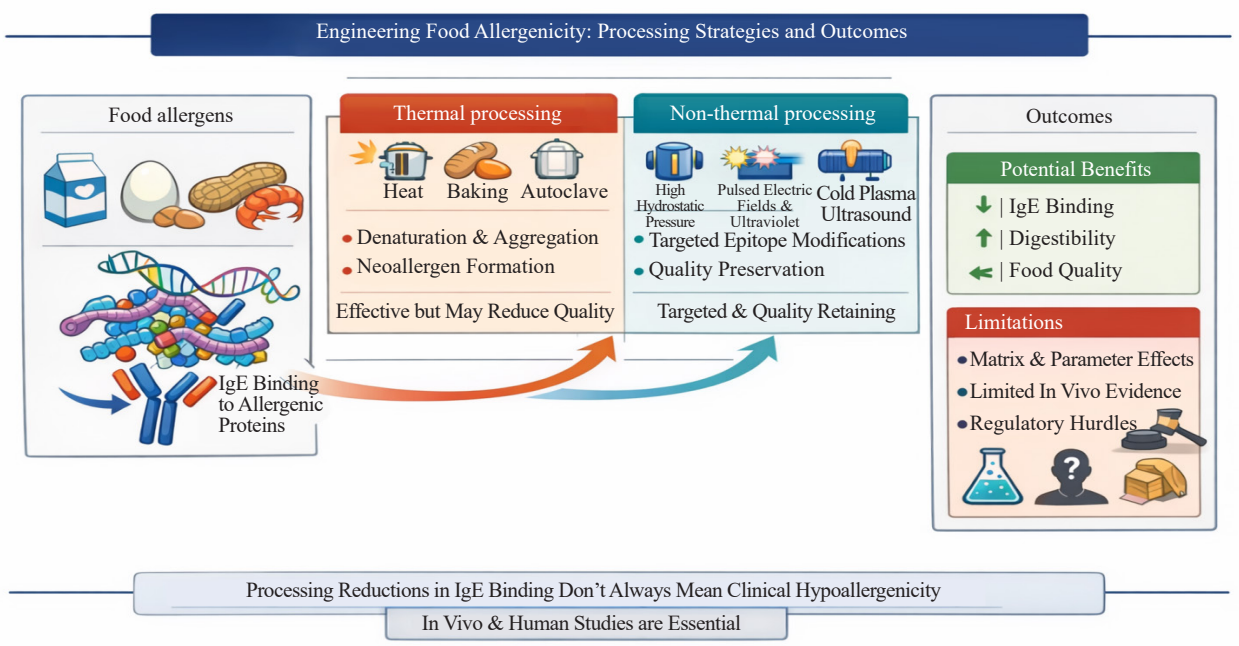
Graphical Abstract:



Abstract: Food allergies represent a growing global public health challenge arising from complex interactions among genetic predisposition, environmental exposures, dietary habits, and gut microbiota. Sensitization may occur through dermal, respiratory, or gastrointestinal routes and is strongly influenced by epithelial barrier dysfunction and Th2-skewed immune responses. A detailed understanding of allergen structure, immune recognition, and sensitization pathways is therefore essential for the development of effective mitigation strategies. Both thermal and non-thermal food processing technologies have been investigated for their ability to reduce the allergenicity of common foods, including milk, egg, peanut, tree nuts, and seafood. Conventional thermal processing can denature allergenic proteins and enhance

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digestibility, but may also adversely affect nutritional value and sensory quality. In contrast, emerging non-thermal technologies—such as High Hydrostatic Pressure (HHP), Pulsed Ultraviolet (PUV) light, cold plasma, ultrasound, pulsed electric fields, and gamma irradiation—offer alternative approaches that induce targeted structural modifications in allergenic proteins while better preserving product quality. However, the effectiveness of these technologies is highly context-dependent, varying with the food matrix, processing parameters, and allergen type; moreover, reductions in Immunoglobulin E (IgE) reactivity observed in vitro do not always translate into clinically meaningful outcomes. Limitations in standardized allergenicity assessment, insufficient in vivo and clinical validation, and challenges related to scalability and regulatory acceptance remain significant barriers. This review integrates immunological mechanisms with food engineering perspectives to critically evaluate thermal and non-thermal processing strategies, highlighting the translational potential of non-thermal technologies as promising, scalable tools for developing safe, quality-preserving, and clinically relevant hypoallergenic foods.

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

1. Introduction

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 as Immunoglobulin E (IgE)-mediated and non-IgE-mediated (cellular) responses [1, 2] (Figure 1).

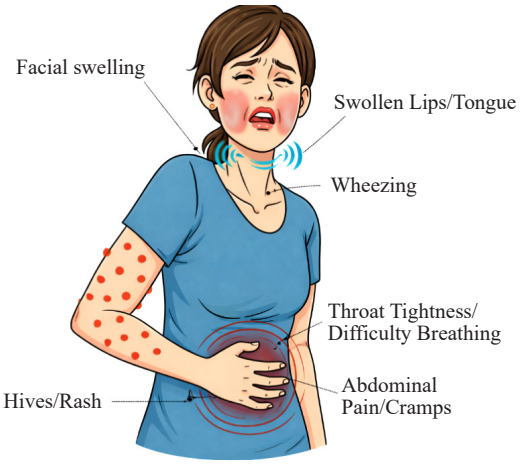

Figure 1. Overview of the most common clinical manifestations of food allergy, including cutaneous, gastrointestinal, and respiratory symptoms observed in IgE-mediated reactions

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 [3-5] (Figure 2). The food allergy diagnostic 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 [5-8].

Food group	Key allergens/Notes
Milk	Allergens: Caseins (α-, β-, κ-casein); Whey proteins (β-lactoglobulin, α-lactalbumin) Notes: Whey proteins are generally heat-labile.
Egg	Egg white: Ovomucoid, Ovotransferrin Notes: Egg white proteins are heat-stable and often the primary allergen.
Peanut	Allergen: Ara h 1, Ara h 2, Ara h 6 (storage proteins) Notes: Highly stable proteins; resistant to heat and digestion.
Tree Nuts	Almond: Pru u 6 Cashew: Ana o 1 Walnut: Jug r 1, Jug r 2
Seafood	Fish allergens: Parvalbumins Shellfish allergens: Tropomyosin Notes: Heat-stable; strong cross-reactivity across crustaceans and mollusks.
Soy	Allergens: Glycinin (Gly m 5), β-conglycinin (Gly m 6)
Wheat	Allergens: Gluten proteins (Gliadin, Glutenin) Notes: Associated with wheat allergy or celiac disease (distinct mechanisms).
Sesame	Allergens: Ses i 1, Ses i 2 Notes: Increasingly recognized as a major allergen.

Figure 2. Major food groups responsible for the majority of clinically relevant food allergies worldwide, including milk, eggs, peanuts, tree nuts, fish, and shellfish

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. This structural stability facilitates the persistence of allergenic epitopes and can lead to cross-reactivity with homologous proteins from other sources [9-11]. This can lead to cross-reactivity and symptoms consistent with pollen-food allergy syndrome [12-15]. Food allergies can result in a range of clinical disorders affecting one or more organ systems. Additionally, some pediatric gastrointestinal conditions—such as colic, constipation, and reflux—are occasionally suspected to have allergic etiologies [13-18]. 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 [15, 19-21].

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" [22, 23], encompassing both adaptive and innate immune pathways. Historically, allergy was described as a hypersensitivity reaction, such as serum sickness observed in children receiving antiserum therapies [24-28], and later classified into four immunological types [29-32]. More recent evidence highlights a role for the innate immune system in food-induced inflammation, which may underlie conditions such as non-celiac gluten sensitivity [33-36]. Estimating the true prevalence of food allergy remains challenging due to variability in diagnostic criteria and reliance on self-reported versus clinically confirmed cases [37-41]. Early-life factors, including limited dietary and microbial diversity, may impair immune tolerance and contribute to the rising prevalence of allergic disease in industrialized societies [42-46].

Epicutaneous sensitization through a compromised skin barrier has also been shown to promote intestinal mast cell expansion and systemic anaphylaxis [47-53]. Beyond the route of initial exposure, increasing evidence indicates that the immunological outcome of food allergen contact is critically shaped by the site, timing, and inflammatory context of antigen encounter. Early-life environmental factors, including reduced microbial diversity, skin inflammation, and altered dietary exposures, have been shown to impair immune education and favor Th2-skewed sensitization rather than tolerance [54-56]. Studies using both human cohorts and experimental models demonstrate that epithelial barrier

dysfunction facilitates allergen penetration and promotes the release of epithelial-derived alarmins such as Thymic Stromal Lymphopoietin (TSLP), IL-33, and IL-25, which amplify type 2 immune responses and enhance mast cell and basophil activation [57-59]. In parallel, gastrointestinal exposure to food antigens does not uniformly result in tolerance; rather, outcomes depend on antigen dose, protein digestion stability, microbiota-derived signals, and dendritic cell programming within gut-associated lymphoid tissue [60-62]. Collectively, these findings highlight the coordinated role of cutaneous and intestinal barrier-immune crosstalk in shaping systemic allergic susceptibility. Sensitization is influenced by protein stability, epithelial barrier integrity, and food matrix effects, whereas Secretory Immunoglobulin A (SIgA) and Secretory Immunoglobulin M (SIgM) support oral tolerance and limit allergen-induced immune responses [63-66].

The prevalence and severity of food allergies continue to rise globally, driven by genetic, environmental, and lifestyle factors. Consequently, effective prevention and mitigation strategies are urgently needed, including allergen avoidance, improved labeling, and processing-based approaches that reduce allergenic potential through thermal and non-thermal treatments.

1.1 *Terminology clarification*

Throughout this review, specific terminology is used to distinguish between different levels of allergen assessment. IgE-binding refers strictly to the interaction between allergenic proteins and IgE antibodies, as measured by immunochemical assays such as Enzyme-Linked Immunosorbent Assay (ELISA), immunoblotting, or inhibition tests. Immunoreactivity is used as a broader term encompassing IgE-binding together with functional cellular responses, including basophil activation, mediator release, skin prick testing, or other immune effector outcomes. Antigenicity denotes the general ability of a protein to be recognized by antibodies (often IgG-based) or immune components, particularly in experimental or animal models, and does not necessarily imply clinical allergenicity. These distinctions are maintained throughout the manuscript to avoid overinterpretation of in vitro findings as direct indicators of clinical relevance.

This review integrates mechanistic insights with practical processing strategies to control food allergenicity, highlighting how diverse thermal and non-thermal technologies can modulate allergenic risk while preserving food quality.

2. Mitigation strategies for food allergens

2.1 *Allergen elimination and control strategies*

As illustrated in Figure 1, food allergy manifestations can involve multiple organ systems, underscoring the clinical importance of effective allergen mitigation strategies across diverse food matrices. 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 [52]. 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 [54, 55]. However, proteolysis may not fully eliminate allergenic potential. For example, Sen et al. [56] 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 (Figure 3).

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 [53]. In manufacturing, dedicated lines, validated sanitation, and equipment separation are necessary to avoid cross-contact [57-59]. 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 [60].

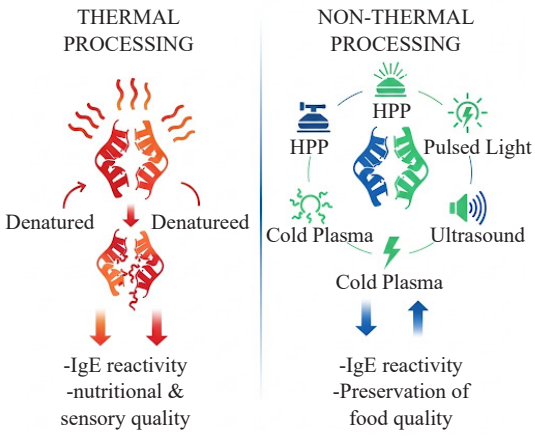

Figure 3. Allergen mitigation by thermal and non-thermal technologies

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 [21, 61-63]. The structural integrity and allergenic potential of proteins are significantly influenced by processing. Changes in physicochemical properties and protein stability can alter immunogenicity [54, 64, 65]. The food matrix can modulate these effects, at times enhancing allergenic responses [66, 67]. 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 [68-70]. The major allergenic food sources most frequently implicated in clinical reactions, including milk, egg, peanut, tree nuts, and seafood, are summarized in Figure 2 and form the primary focus of processing-based allergen mitigation approaches discussed in this review.

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 [71]. Subsequent findings identified neoallergens in processed pecans [72] and wheat flour [73]. 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 [74]. However, the effects of fermentation on allergenicity vary depending on the food product. For example, soy sauce—a fermented product—retains allergenicity despite microbial activity [75]. In contrast, fermented dairy products such as yogurt often exhibit reduced immunogenicity due to acid denaturation and proteolysis [76, 77].

2.3 *Thermal processing and its effects on allergenicity*

Thermal processing is among the most widely used food technologies and can substantially alter the structure and immunoreactivity of food allergens. Heat-induced denaturation affects proteins through unfolding, disruption of disulfide bonds, aggregation, and Maillard-type chemical modifications, which may reduce, preserve, or enhance IgE-binding depending on allergen type, food matrix, and processing intensity [77, 78].

Milk allergens exemplify the complexity of thermal effects. Whey proteins such as β-lactoglobulin and α-lactalbumin denature progressively with heating, whereas caseins remain largely heat-stable due to their flexible structure [78-80]. Pasteurization (50-90 °C) has been reported to increase IgE binding to whey proteins compared with unheated milk [79], while higher temperatures ($\geq$ 90 °C) may reduce IgE binding without eliminating allergenicity [77]. Epidemiological data suggest lower milk allergy prevalence among raw milk consumers [80-82], although controlled clinical comparisons with pasteurized milk are lacking [83]. Sterilization and high-temperature treatments further induce aggregation and Maillard reactions, which can expose or mask epitopes in an allergen-specific manner [76, 84-86]. Data

on UHT-treated milk allergenicity remain limited [78].

Extensive clinical evidence supports reduced egg allergenicity following prolonged heating. Approximately 50-85% of egg-allergic children tolerate baked or extensively heated egg products [44, 87, 88]. Ovomucoid (OVO) is the dominant heat-stable egg allergen, whereas ovalbumin is more heat-labile [89, 90]. Animal and in vitro studies further demonstrate reduced IgE binding, enhanced digestibility, and attenuated allergic responses after heating [91-94].

In contrast, peanut allergens show strongly processing-dependent and sometimes opposing responses. Boiling generally reduces allergenicity by leaching low-molecular-weight allergens into cooking water and enhancing digestibility [62, 95-99], whereas roasting consistently increases IgE binding, largely through Advanced Glycation End product (AGE) formation [95, 96, 100, 101]. Autoclaving can reduce allergenicity of roasted peanuts, although major allergens such as Ara h 2 and Ara h 6 remain highly protease-resistant [102]. Animal studies suggest that roasting may enhance sensitization [66, 103].

Thermal responses of tree nut allergens are similarly allergen-specific. Roasting reduces IgE binding of birch pollen-related allergens (e.g., Cor a 1) but has limited impact on heat-stable lipid transfer proteins and seed storage proteins [104-109]. Comparable heat resistance has been reported for cashew, walnut, pistachio, pecan, and Brazil nut allergens, with reductions generally restricted to extreme processing conditions [62, 110-116].

Soy and wheat allergens exhibit variable responses to heat. Heating and extrusion can reduce IgE binding in soy proteins [117-120], although outcomes depend on processing intensity and assessment method. In wheat, cooking does not substantially alter clinical reactivity in adults, as shown by Double-Blind Placebo-Controlled Food Challenge (DBPCFC) studies [121]. Heat-stable allergens such as α-amylase/trypsin inhibitors retain IgE reactivity, whereas wheat lipid transfer proteins are heat-labile [107]. Baking and pasta processing induce protein aggregation that can either reduce allergenicity or generate digestion-resistant structures, depending on temperature and moisture conditions [122-125].

Table 1. Influence of thermal processing on various food allergen types

Allergen type	Impact of 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., 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, 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.
Seed storage proteins (e.g., Gly m 5 and Gly m 6 in soy; Cor a 9 in hazelnut)	Generally, more resistant to thermal denaturation due to compact structures. However, prolonged heating can induce aggregation or chemical modifications, with variable effects on allergenicity depending on the matrix.
Shellfish allergens (e.g., tropomyosin, arginine kinase)	Tropomyosin is heat-stable and often retains allergenicity even after boiling or frying. Arginine kinase is more heat-sensitive, showing reduced allergenicity upon thermal treatment.
Fish allergens (e.g., parvalbumin)	Highly stable against heat; retains allergenicity after cooking. Denaturation may occur at high temperatures, but refolding often restores IgE-binding capacity.
Egg proteins (e.g., ovomucoid, ovalbumin)	Ovomucoid is highly heat-resistant and maintains allergenicity after prolonged heating. Ovalbumin is more heat-sensitive and loses allergenicity with sufficient denaturation and aggregation.
Milk proteins (e.g., caseins, β-lactoglobulin)	Caseins are heat-stable and maintain allergenicity, while β-lactoglobulin is sensitive to unfolding and aggregation. Heat-induced Maillard products can either reduce or enhance allergenicity depending on processing conditions.

Additional food systems further illustrate the allergen-specific nature of thermal effects. Mustard allergens exhibit high heat stability due to compact, disulfide-rich structures [126-131], whereas moist heat significantly reduces allergenicity in selected fish species [131]. Heat treatment also lowers allergenicity in kiwi fruit [77, 132, 133], legumes [134, 135], and certain meats [136], although exceptions—such as chicken—highlight the formation of neoallergens under specific conditions [136].

Overall, thermal processing affects allergenicity in an epitope-and matrix-dependent manner summarized in Table 1 [100, 104, 137]. While extensive heating can reduce clinical reactivity for certain foods (e.g., egg and boiled peanut), thermal treatments may also preserve or enhance allergenicity through aggregation and Maillard-driven neoepitope formation [65, 100, 137]. Consequently, although thermal processing remains one of the most clinically substantiated allergen mitigation strategies, its effects cannot be generalized across allergen types and require careful optimization and clinical validation.

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 HHP, 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 non-thermal methods for allergen reduction (adapted from [13])

Technology	Mechanism of action	Limitations
High hydrostatic pressure	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 UV light	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*

Mechanism: 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. Two key scientific principles are particularly important in understanding the application of HHP technology in food processing. According to Le Chatelier's principle, reactions associated with a reduction in volume are favored under high-pressure conditions. In addition, the isostatic rule ensures that pressure is transmitted instantaneously and uniformly throughout

the food matrix, regardless of product size or shape. Specifically, interactions such as hydrogen bonds, ionic interactions, hydrophobic forces, and van der Waals interactions—critical for maintaining secondary, tertiary, and quaternary protein structures—are affected [138, 139]. 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 [140]. 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 [141].

Efficacy: 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 [142]. 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 [78].

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 [143]. HHP-treated proteins often become more susceptible to proteolysis. Protein unfolding increases accessibility for digestive enzymes such as pepsin and trypsin, promoting more efficient gastrointestinal breakdown and reducing the likelihood that allergenic epitopes survive digestion and trigger immune responses. This reduced stability and increased enzymatic degradation decrease the likelihood of allergenic epitopes surviving digestion and triggering immune responses [142].

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) [144]. 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 [145, 146]. 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 [147]. These structural changes enhanced the protein's IgE-binding capacity, indicating increased allergenicity post-treatment.

Kato et al. [148] 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 [149]. HHP applied to soybean sprouts at 400 MPa resulted in significant reductions in the levels of Gly m 1, a key soybean allergen [150]. 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 allergenity of various foods

Food variety	Treatment conditions	Key findings	Reference
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.	[151]
Soybean	400 MPa	Treatment improved protein solubility and hydrophobicity, while decreasing β-sheet content.	[152]
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.	[153]
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.	[154, 155]
Tofu	300 MPa, 40 °C, 15 min	HHP did not change tofu protein composition but lowered intensity of some protein bands. Allergenicity remained unchanged.	[151]
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.	[148]
Almond	600 MPa, 4-70 °C, 5-30 min	No significant change in allergen concentration or IgE-binding capacity as per Sodium Dodecyl Sulfate-Polyacrylamide Gel Electrophoresis (SDS-PAGE), Western Blot (WB), and ELISA.	[156]
Whey protein isolate	200-600 MPa, 30-68 °C, 10-30 min	Antigenicity of β-lactoglobulin increased with pressure, temperature, and duration.	[147]
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.	[147]
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.	[147]
Milk	> 100 MPa + chymotrypsin/trypsin, 20 min	Proteolysis of β-lg was accelerated under HHP, suggesting potential for hypoallergenic food production.	[157]
Apple	400-800 MPa, 80 °C, 10 min	Mal d 3 allergen lost α-helical structure, becoming a random coil; immunoreactivity declined at ≥ 400 MPa.	[155]
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%.	[158]
Apple	600 MPa, 5 min	Mal d 1 immunoreactivity decreased by > 50% with combined high pressure and heat.	[158]
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.	[159]
Carrot	500 MPa, 50 °C, 10 min	Slight increase in β-sheet structure of Dau c 1; no change in immunoreactivity observed.	[160]
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.	[160]
Celeriac	700 MPa, 118 °C, 10 min	Allergenicity of Api g 1 was significantly reduced through combined pressure and thermal processing.	[158]
Celery	500 MPa, 50 °C, 10 min	Api g 1 structural changes were pressure-dependent but did not impact allergenicity.	[161]

Limitations: Although high hydrostatic pressure primarily disrupts non-covalent interactions while generally preserving covalent bonds, the resulting structural modifications do not uniformly translate into predictable or clinically meaningful reductions in allergenic potential [161, 162]. HHP has demonstrated the capacity to alter allergenic protein structures; however, its clinical relevance is highly dependent on processing conditions and protein-specific responses. Although selected studies—such as repeated consumption of HHP-treated apple products—suggest potential clinical benefits, including reduced skin reactivity and partial desensitization, these effects remain allergen-and matrix-specific. In contrast, several allergens, including β-lactoglobulin and certain nut proteins, have exhibited unchanged or even

increased immunoreactivity following HHP treatment, underscoring the risk of extrapolating in vitro reductions in IgE binding to meaningful clinical outcomes. Consequently, while HHP represents a promising non-thermal strategy for allergen mitigation, its clinical efficacy should be interpreted cautiously and confirmed through well-designed human challenge studies, particularly when applied as a standalone technology rather than in combination with complementary processing approaches.

2.4.2 *Pulsed electric field technology and its impact on food allergenicity*

Mechanism: 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 [163-166]. 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 [167-170]. 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 [165, 166].

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 [164]. 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 [166].

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 [164, 167]. 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 [164, 167, 171, 172]. 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 [166].

Efficacy: 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 [173] 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 [174, 175]. 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 [176]. 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 [177]. For instance, treatment of soybean protein isolates with PEF has demonstrated alterations in physicochemical properties, including denaturation and aggregation behaviors [178]. 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 [179]. 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 [179]. The study conducted by Johnson et al. [155] 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 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 [180].

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 μs [181], indicating PEF's potential to lower the allergenicity of egg proteins.

In a molecular dynamics simulation study, Vanga et al. [182] explored the effects of oscillating and static electric fields (2,450 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. [183] 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.

Limitations: However, not all findings confirm a consistent reduction in allergenicity following PEF treatment. For instance, Johnson et al. [155] 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) under the applied PEF conditions. These discrepancies across studies likely arise from multiple factors. These include differences in protein state (purified versus matrix-embedded), electric field strength, pulse duration, and energy input, as well as variability in analytical methods used to assess structural and immunological changes. Similarly, Paschke [184] 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 [185]. 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.

Current evidence suggests that the clinical significance of PEF-induced allergen modification is highly variable and remains insufficiently substantiated. Most studies evaluating PEF-induced allergen modification are limited to in vitro analyses, relying primarily on structural characterization and IgE-binding assays, with only limited in vivo validation and virtually no controlled human challenge data. Moreover, several reports indicate that PEF induces minimal structural changes in purified allergens or yields matrix-and parameter-dependent outcomes, and patient-level responses (e.g., skin reactivity) may not decrease even when conformational alterations are observed. These limitations underscore that reductions in IgE binding or observed structural modifications should not be interpreted as definitive indicators of reduced clinical allergenicity. Consequently, although PEF offers attractive industrial advantages—such as energy efficiency and compatibility with liquid food matrices—its true clinical impact on allergenicity requires confirmation through standardized protocols and well-designed in vivo and human studies, ideally within combined or multi-hurdle processing frameworks.

2.4.3 *Pulsed UV light and its impact on food allergenicity*

Mechanism: Pulsed UV Light (PUV) technology utilizes a series of extremely brief, high-intensity bursts of broad-spectrum white light, composed primarily of UV light (54%), followed by visible light (26%) and infrared radiation (20%) [186]. The PUV light spans wavelengths from 200 nm to 1,000 nm, allowing it to deliver intense light energy within a very short duration [101]. As a result, PUV light can achieve energy intensities up to a thousand times greater than those of traditional continuous UV systems [186]. 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 (Table 4) [187-190].

Table 4. 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.	[191]
Disruption of Disulfide Bonds	High-energy UV pulses can break disulfide bridges that maintain protein conformation.	Destabilization of tertiary structure reduces IgE-binding ability.	[192]
Epitope modification	PUV alters conformational and linear epitopes through structural denaturation.	IgE-binding is reduced due to loss of native allergenic regions.	[64, 193]
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.	[93, 192, 193]
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.	[194, 195]
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.	[196]

Efficacy: 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 [101, 190]. 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 [197].

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 [101, 198]. 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/cm^2) 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 [199].

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 [101]. PUV light also reduced the immunoreactivity of Gly m 5 and Gly m 6 allergens in soy when applied at a distance of 8-10 cm for up to 6 minutes. Gel bands corresponding to Gly m 5 disappeared after just 2 minutes of treatment, while Gly m 6 bands remained visible even after 6 minutes, indicating differential susceptibility to degradation or precipitation [200].

Similarly, 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 [201]. 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 [202].

For egg white proteins, UV 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 [203].

Exposure of raw and boiled shrimp extracts (5 mg/mL) to PUV light at a pulse width of 360 µs, 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 [101, 186]. 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 [186]. 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 [183]. However, not all studies report a reduction in allergenicity with UV processing. For instance, Manzocco et al. [203] found that although UV 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 a limited impact on egg allergens, as summarized in Table 5. 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 [204].

Table 5. Effect of UV-C treatment on allergenicity of various foods (data summarized from [13, 205])

Food material	Target allergen	Treatment	Effect on immunoreactivity	References
Milk	α-casein, α-lactalbumin	UVC treatment (15 min)	25% α-casein reduction	[201]
	β-lactoglobulin	UVC treatment (15 min)	27.7% whey fractions reduction	[201]
Egg	Ovalbumin	UV processing (0.61 kJ/m^2)	No effect	[203]
	Ovomucoid	UV processing (63.7 kJ/m^2)	No effect	[203]
Shrimp	Tropomyosin	PUV sterilization (4 min)	Reduced	[206]
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 IgE binding of peanut butter slurry; 12.5 folds reduction, 100% reductiom total extracts	[199]
Soy	Gly m 5	PUV treatment (1-6 min)	100% reduction Gly m 5 reduced	[200]
	Gly m 6	PUV treatment (1-6 min)	Gly m 6 retained	[200]
	Soy extracts (e.g., glycinin, β-conglycinin)	PUV treatment 2 min	20% reduction	[199]
		PUV treatment 4 min	40% reduction	[199]
		PUV treatment 6 min	50% reduction	[199]

Limitations: Despite promising reductions in IgE reactivity observed in vitro, the clinical relevance of PUV-induced allergen modification remains largely unvalidated, as the majority of available evidence is derived from in vitro structural characterization and IgE-binding assays, with scarce in vivo validation and no controlled human challenge studies. Although substantial reductions in IgE reactivity have been reported for allergens in soy, peanut, milk, and shrimp, these outcomes are strongly influenced by treatment dose, exposure geometry, and food surface accessibility. In addition, the limited penetration depth of PUV light confines its effectiveness primarily to surface-associated proteins, thereby restricting its applicability in complex or opaque food systems. Accordingly, laboratory-scale reductions in immunoreactivity should be interpreted cautiously until corroborated by standardized in vivo and clinical investigations. Future studies should prioritize clinically meaningful endpoints and evaluate the integration of PUV into combined or multi-hurdle processing strategies to enhance translational potential.

2.4.4 *Gamma irradiation and its impact on food allergenicity*

Mechanism: 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 [197, 198, 202].

Efficacy: Among ionizing methods, gamma irradiation is considered one of the most straightforward techniques [207, 208]. The reduction in immunoreactivity was linked to protein denaturation, assessed through parameters such as turbidity, surface hydrophobicity, and chromogenic reactivity. The findings suggest that coagulation of allergenic proteins may play a crucial role in minimizing allergenicity post-irradiation [209]. Gamma irradiation generates free radicals that cleave peptide bonds and oxidize amino acid side chains. These reactions disrupt the secondary and tertiary structures of allergenic proteins, thereby altering their conformational epitopes. While gamma irradiation can markedly decrease allergenic potential, its application may also lead to partial losses in nutritional quality, such as degradation of sulfur-containing amino acids, and, in rare cases, the formation of novel antigenic determinants. Therefore, although gamma irradiation represents a promising strategy for mitigating food allergenicity through protein structural modification, careful optimization of treatment parameters is required to balance allergen reduction with nutritional retention and product safety. 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 [210-213]. These changes are primarily driven by reactive oxygen species formed during the radiolysis of water when proteins are irradiated in aqueous environments. These structural modifications have been shown to reduce IgE-binding capacity in several major allergens, including Ara h 1 and Ara h 2 in peanuts, β-lactoglobulin in milk, and ovomucoid in egg proteins, with the degree of reduction being strongly dose-dependent, typically requiring doses above 5-10 kGy [202, 211-213]. Multiple studies have demonstrated the effectiveness of gamma irradiation in modifying allergenic proteins [214]. 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 6) [215].

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)	[214, 216]
White Cake (with egg)	10-20	Reduced ovalbumin reactivity	Reduction in IgE binding	[214]

Table 6. (cont.)

Food matrix	Irradiation dose (kGy)	Effect on allergen	Mechanism/Observation	Reference
Shrimp (Tropomyosin)	7-10	Undetectable tropomyosin band; reduced IgE binding	Protein denaturation, aggregation; turbidity and surface hydrophobicity changes	[186]
Shrimp (Tropomyosin)	1-15 + heat (100 °C)	5-30-fold reduction in IgE binding	Synergistic effect with heat treatment	[207]
Egg (Ovomucoid)	10 + heat	Almost undetectable levels of ovomucoid	Irradiation more effective than heat alone due to ovomucoid heat stability	[202]
Tree Nuts (Almonds, Cashews, Walnuts)	1-25 ± heat	Minimal change in allergenicity	Allergens stable under irradiation and heat	[217]

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 [218]. 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 [13]. Similarly, Luo et al. [210] 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. In other research, irradiation of whole almonds, cashews, and walnuts did not result in structural changes to allergenic proteins or alter their allergenic potential [113]. Conversely, studies have shown that irradiation may increase the immune reactivity of gliadin and wheat flour [219]. 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.

A comparable pattern was reported by Zhenxing et al. [207] 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. 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 [220].

A dose-dependent response to irradiation was observed in a study on cow milk allergy by Lee et al. [202], 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. [221] 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.

Seo et al. [214] 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 [222]. 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 [213]. In a separate study, Seo et al. [216] also reported reduced ovalbumin immunoreactivity in white cake samples irradiated at 10-20 kGy.

Limitations: Although gamma irradiation has demonstrated measurable immunochemical effects in experimental

models, its translation into clinically meaningful allergen reduction remains limited. Several studies report dose-dependent decreases in IgE or IgG binding—particularly at doses ≥ 5-10 kGy—yet these reductions do not consistently translate into diminished clinical allergenicity, especially when allergens are embedded within complex food matrices. Moreover, the narrow margin between doses required for effective allergen modification and those that may compromise nutritional quality or approach regulatory limits presents a major challenge for industrial implementation. These constraints underscore the need for carefully optimized dose regimes and for additional in vivo and controlled clinical studies to determine whether irradiation-induced structural changes result in clinically relevant reductions in allergic responses among sensitized individuals. Consequently, gamma irradiation is likely to be most effective when incorporated into combined or multi-hurdle processing strategies rather than applied as a standalone allergen mitigation approach.

2.4.5 *High-intensity ultrasound and its impact on food allergenicity*

Mechanism: 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 [223]. 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 [208]. The core mechanism involves cavitation, wherein alternating compression and rarefaction cycles form microbubbles that collapse violently, generating localized temperatures up to 5,000 K and pressures reaching 1,000 atm [209]. These extreme conditions facilitate protein denaturation, potentially altering allergenic structures and epitopes. This collapse generates localized hot spots with extremely high temperatures (up to 5,000 K) and pressures (up to 1,000 atm), although these effects are confined to the microscopic scale and last for only a few microseconds [224]. 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 [225].

High-Intensity Ultrasound (HIU) has been explored for various food processing operations, including peeling of fruits and vegetables [226], reduction of oil content and shelf-life extension of fried products [227], and shortening of parboiling time in rice processing [228]. 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 [55, 215].

Efficacy: In a study by Li et al. [228], 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. [207] further confirmed that shrimp allergenicity decreased more significantly at elevated temperatures (50 °C) during ultrasound treatment. In another study, Zhang et al. [229] 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. [230] 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. [201] 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 [201, 231].

In soy protein, Tammineedi et al. [201] 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. [228] 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 [232, 233]. 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 [234]. 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.

Limitations: Despite its promise, the efficacy of high-intensity ultrasound for allergen mitigation is highly dependent on processing parameters (e.g., frequency, power density, treatment duration) and food matrix composition, limiting reproducibility and scalability. From a clinical relevance perspective, supporting evidence remains largely confined to in vitro IgE-binding assays and immunoblot analyses, with limited validation in animal models and a near absence of controlled human challenge studies. Although ultrasound can induce substantial structural modifications in certain allergens—particularly in shellfish, soy, and selected peanut proteins—these effects are strongly protein- and matrix-dependent and do not consistently translate into clinically meaningful reductions in allergenicity. Moreover, the prolonged treatment times or high energy inputs often required may constrain industrial feasibility when ultrasound is applied as a standalone technology [235]. Current evidence therefore indicates that ultrasound is most effective when integrated into multi-hurdle processing strategies, where synergistic effects with mild heat or complementary treatments enhance epitope disruption while preserving product quality. Representative studies and treatment conditions are summarized in Table 7.

Table 7. Overview of recent studies on the impact of high-intensity ultrasound processing on food allergenicity (adapted from [205])

Food	Target allergen	Treatment	Immunoreactivity	References
Soy	Proteins	37 kHz, 10 min	Reduced 24%	[236]
Milk	α-casein	500 W and 20 kHz (10-30 min)	No effect	[201]
	β-lactoglobulin	500 W and 20 kHz (10-30 min)	No effect	[236]
	α-lactalbumin	500 W and 20 kHz (10-30 min)	No effect	[231]
Peanut	Ara h 1	50 Hz for 5 h	Reduced 84.8%	[237]
	Ara h 2	50 Hz for 5 h	Reduced 4.88%	[238]
Shrimp (boiled)	Proteins	30 kHz, 800 W (0-50 °C, 0-30 min)	Reduced 40%-50%	[238]
Shrimp (raw)	Proteins	30 kHz, 800 W (0-50 °C, 0-30 min)	Reduced up to 8%	[238]
Crayfish	Tropomyosin	100-800 W, 15 min	Reduced	[239]
Shrimp and allergens	Multiple (including tropomyosin)	30 Hz, 800 W (30-180 min)	Reduced up to 75%	[207]
Crayfish	Arginine kinase	200 W, 30 °C (10-180 min)	No effect	[230]

2.4.6 *Cold plasma and its impact on food allergenicity*

Mechanism: 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 [240]. 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 [235, 240].

Efficacy: Multiple studies have shown the potential of plasma treatment in reducing food allergenicity. For example, Venkataratnam et al. [112] 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 [215].

In one study, the impact of both direct and remote Cold Atmospheric Pressure Plasma (CAPP) on the immunoreactivity of soy protein isolate was examined [235]. 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 m 5) and glycinin (Gly m 6). 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 [241]. Meinlschmidt et al. [200] 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 m 5 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. [201] treated milk a-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 [242-244]. Therefore, while cold plasma holds potential, its limitations highlight the need for continued research and the development of alternative food processing technologies.

Limitations: From a clinical relevance perspective, the allergen-modifying effects of cold plasma have been demonstrated predominantly through in vitro immunochemical assays, with only limited confirmation from in vivo models and a lack of controlled human clinical studies. Although substantial reductions in IgE-binding capacity have been reported for allergens in soy, peanut, and shrimp, the clinical significance of these structural and immunochemical changes remains uncertain. The persistence of allergenic responses in certain protein systems, such as milk, together with concerns regarding oxidative damage and potential quality deterioration, further complicates translation to real food applications. Consequently, while cold plasma represents a promising non-thermal approach for allergen mitigation, its practical implementation will require careful optimization of treatment conditions and, critically, validation through animal models and well-controlled human challenge studies to establish meaningful reductions in allergic reactivity.

2.4.7 *Genetic modification and its role in reducing allergenicity*

Mechanism: 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 [75].

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 [245].

Efficacy: Experimental studies provide insights into these strategies. For instance, Rupa et al. [246] 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. [247] applied Ribonucleic Acid (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. [52] reported reduced IgE binding following genetic silencing of Ara h 2. In another example, Herman et al. [248] 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, broader questions concerning consumer acceptance, regulatory approval, and long-term safety must still be addressed. Representative genetic modification strategies aimed at reducing food allergenicity, together with their target allergens and reported outcomes, are summarized in Table 8.

Table 8. Genetic modification and allergenicity reduction

Method	Target allergen(s)	Key findings	Citation
Post-translational glycosylation	Ovomucoid (egg allergen)	Attachment of carbohydrate moieties to IgE-binding sites suppressed allergic reactions in mice by decreasing both IgE production and its reactivity.	[246]
RNA interference (RNAi)	Ara h 2 and Ara h 6 (peanut allergens)	Silencing specific allergens led to a significant reduction in IgE binding; however, overall IgE binding remained due to the presence of other peanut allergens.	[247]
Gene silencing	Ara h 2 (peanut allergen)	A reduction in IgE binding was observed.	[52]
Gene silencing	Gly m Bd 30 (soybean allergen)	IgE binding was nearly completely inhibited, with no alterations in structure or composition and no formation of new allergens.	[248]

Limitations: Despite the growing body of mechanistic and immunochemical evidence, the translation of processing-induced allergen modification into clinically meaningful risk reduction remains uncertain. Most studies reporting reduced IgE binding or structural alteration rely on in vitro assays, which provide valuable mechanistic insight but do not reliably predict allergic outcomes in sensitized individuals. Limited in vivo animal data and the near absence of controlled human challenge studies further constrain the interpretation of these findings. In several cases, residual allergenicity, matrix-dependent shielding effects, or protein-specific resistance have been observed despite measurable reductions in immunoreactivity. Therefore, processing-induced decreases in IgE binding should not be equated with

clinical hypoallergenicity without corroborating evidence from standardized in vivo models and well-designed clinical trials. Establishing clinically relevant endpoints and integrating processing technologies into rational, multi-hurdle frameworks will be essential to advance allergen mitigation strategies from experimental observations toward practical and safe applications.

3. Advantages, disadvantages, and limitations of food processing technologies for allergen mitigation

Thermal processing affects allergenicity in an epitope-dependent manner. Conformational epitopes, which rely on native three-dimensional protein folding, are generally more susceptible to heat-induced denaturation, whereas linear epitopes tend to be more heat-stable but may undergo chemical or enzymatic modification. All processing approaches reviewed in this study influence the physicochemical properties of food proteins in distinct ways. These changes, in turn, modulate gastrointestinal digestion, bioavailability, and allergenic potential. Thermal processing is one of the most extensively applied methods, where exposure to heat generally reduces allergenicity by altering protein conformation, disrupting IgE-binding epitopes, and enhancing enzymatic digestibility. Nevertheless, these benefits are often counterbalanced by undesirable consequences for product quality, including changes in texture, flavor, and nutrient retention [201, 220].

Despite their potential advantages, non-thermal food processing technologies present several important limitations. Their effectiveness in reducing allergenicity is highly dependent on the food matrix, processing parameters, and the structural characteristics of the target allergen. In many cases, non-thermal treatments result in only partial modification or masking of IgE-binding epitopes. As a result, residual allergenic activity may persist. In addition, inconsistent outcomes across different studies reflect the lack of standardized processing conditions and allergenicity assessment protocols. Limited penetration depth, scalability challenges, and insufficient clinical validation further restrict the widespread industrial adoption of these technologies. Consequently, optimization of process parameters and integration with complementary approaches are often required to achieve reliable and reproducible allergen reduction.

Beyond these technical constraints, several additional factors hinder the broader adoption of non-thermal techniques in industrial settings. First, the capital investment required for advanced processing equipment can be substantial, raising concerns regarding cost-effectiveness for manufacturers. Second, certain technologies, such as ultrasonication, offer limited control over critical operational parameters when applied at scale. This limitation reduces treatment efficiency and contributes to inconsistent outcomes. This has led to growing interest in combined or hurdle-based approaches, for example, coupling ultrasound with other methods to enhance reproducibility and scalability. Third, there remains a scarcity of long-term toxicological and safety assessments concerning structural modifications induced by novel technologies, which poses regulatory and consumer acceptance challenges. Finally, a critical barrier to adoption is the lack of standardized protocols for assessing allergenicity, which makes it difficult to compare results across studies or establish clear guidelines for industrial implementation [185, 196].

Taken together, these factors highlight both the potential and the limitations of current allergen mitigation strategies. Non-thermal technologies, in particular, hold promise for balancing allergen reduction with preservation of product quality, yet their effectiveness is highly context-dependent and requires further optimization. Moving forward, efforts should focus on standardizing allergenicity assessment methods and conducting comprehensive safety evaluations to support the safe and effective implementation of non-thermal processing technologies [201, 212]. In parallel, the development of cost-effective, multi-hurdle processing strategies that integrate allergen reduction with microbial control represents a promising direction for industrial application [220].

From a comparative perspective, many apparent contradictions in the literature regarding processing-induced changes in allergenicity can be rationalized. These discrepancies arise from several key influencing factors. First, allergen responses are highly protein-specific; for example, heat-stable allergens such as Ara h 2 may retain or even enhance immunoreactivity following thermal treatment, whereas heat-labile proteins such as Ara h 1 are more susceptible to denaturation and degradation. Second, the food matrix plays a critical role, as isolated proteins often respond differently to processing compared to proteins embedded within complex food systems containing lipids, carbohydrates, and other interacting components. Third, processing parameters—including temperature-time combinations, pressure intensity,

electric field strength, and treatment duration—substantially influence structural modifications and epitope accessibility. Discrepancies are further amplified by differences in allergenicity assessment methods. In vitro IgE-binding assays, cell-based tests, and in vivo challenge models often yield non-equivalent outcomes. Integrating these factors provides a more coherent framework for interpreting divergent findings and underscores the importance of standardized experimental designs when evaluating processing-induced changes in food allergenicity.

To further integrate and systematically benchmark non-thermal allergen mitigation strategies, it is useful to consider these technologies within a unified comparative framework. HHP and PEF treatments generally show greater efficacy in liquid and semi-liquid food systems, where uniform energy transfer facilitates protein structural modification, whereas ultraviolet and cold plasma technologies are better suited for surface-associated allergens but are constrained by limited penetration depth. Ultrasound-based approaches offer process flexibility and lower capital cost but often exhibit variable effectiveness when applied alone. From a benchmarking perspective, no single non-thermal technology consistently outperforms others across all allergen types, food matrices, and processing conditions. Instead, their relative performance is determined by allergen stability, matrix complexity, and achievable process intensity under industrial constraints. These considerations underscore the importance of rational process design, where technologies are selected and combined based on complementary mechanisms rather than evaluated in isolation.

When considered comparatively, non-thermal processing technologies exhibit distinct strengths and limitations that depend on allergen type, food matrix, and application context. Technologies such as HHP and pressure-or thermal-based treatments are generally more effective against heat-labile allergens, where protein unfolding and denaturation readily disrupt IgE-binding epitopes. In contrast, heat-stable allergens, including 2S albumins such as Ara h 2, often show limited responsiveness to both thermal and certain non-thermal treatments, necessitating higher processing intensities or combined approaches. Among non-thermal technologies, HHP and PEF treatments demonstrate greater potential for modifying allergen structure in liquid or semi-liquid matrices, whereas UV-C and cold plasma technologies are more suitable for surface-associated allergens but exhibit limited penetration depth. From an application standpoint, HHP offers relatively high efficacy but is constrained by equipment cost and batch processing, while PEF provides energy-efficient continuous processing but shows variable effectiveness across different proteins and matrices. Ultrasound and UV-based approaches are comparatively lower in cost but often require integration with complementary treatments to achieve consistent allergen reduction. Collectively, these comparisons underscore that no single technology is universally optimal; rather, the selection of processing strategies should be tailored to allergen stability, food matrix complexity, and practical considerations related to cost and scalability.

Given the inherent limitations of single processing technologies, synergistic or combined processing strategies have increasingly emerged as a promising approach for enhancing allergen mitigation while minimizing adverse effects on food quality. By integrating complementary mechanisms, such as structural unfolding induced by thermal or pressure-based treatments with enhanced mass transfer or surface disruption achieved through ultrasound, pulsed electric fields, or ultraviolet irradiation, combined approaches can achieve greater allergen reduction at lower individual treatment intensities. For example, coupling high hydrostatic pressure with mild heat has been shown to improve protein denaturation efficiency, while ultrasound-assisted thermal or pressure treatments can enhance treatment uniformity and reproducibility. Importantly, synergistic processing also offers opportunities to address multiple objectives simultaneously, including allergen reduction, microbial inactivation, and quality preservation. As such, multi-hurdle and synergistic processing frameworks represent a critical future direction for overcoming the limitations of single technologies and enabling more effective, scalable, and application-specific allergen mitigation strategies.

Across food processing technologies, allergen mitigation outcomes are influenced by dose-effect relationships, which are often complex and technology-specific. For thermal treatments and gamma irradiation, dose dependence is typically expressed as temperature-time combinations or absorbed radiation dose, respectively. In non-thermal technologies, analogous dose-effect relationships exist but are defined by different operational variables. For HHP processing, allergenic modifications are primarily governed by pressure intensity and holding time, whereas for PEF treatments, electric field strength, pulse frequency, and total energy input play critical roles. Similarly, UV and cold plasma treatments exhibit dose-dependent effects determined by irradiation intensity and exposure duration. Importantly, increasing processing intensity does not always result in proportional reductions in allergenicity and may lead to diminishing returns or adverse quality changes. These nonlinear dose-effect relationships underscore the need for careful optimization of processing parameters to balance allergen reduction with product quality and safety.

Although reductions in in vitro IgE reactivity are frequently reported following food processing, such outcomes do not necessarily translate into clinically meaningful reductions in allergenicity. In vitro assays provide valuable mechanistic insight but cannot fully capture the complexity of immune responses in vivo. Evidence from animal models and human clinical or challenge studies remains limited and sometimes inconsistent, yet these approaches offer more direct indicators of clinical relevance. Variations in study design, exposure routes, immune endpoints, and population characteristics further complicate cross-study comparisons. Therefore, while processing-induced structural modifications may attenuate IgE binding, their true clinical significance should be interpreted cautiously until supported by robust in vivo and well-controlled clinical investigations.

4. 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. Together, these factors determine overall 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, whereas dry heat methods (e.g., roasting and baking) may increase allergenicity through the formation of neo-epitopes via Maillard reactions. Non-thermal technologies, including HHP, PEF, cold plasma, PUV light, US, and gamma irradiation, offer promising alternatives by inducing conformational changes without extensive losses in sensory or nutritional quality. Microbial fermentation and enzymatic hydrolysis can further complement these methods by targeting linear epitopes, thereby reducing allergenic potential at the peptide level.

While these strategies present clear advantages, important limitations must be acknowledged. Thermal methods are widely accessible and cost-effective, but can negatively affect texture, flavor, and nutritional value. Non-thermal techniques preserve sensory quality and are often scalable for industrial use; however, they require high capital investment, may have limited penetration in heterogeneous food matrices, and exhibit variable efficacy across different allergenic proteins. Fermentation and enzymatic hydrolysis are effective at reducing linear epitopes but can be difficult to standardize due to microbial variability and may produce off-flavors or alter product acceptability. Moreover, a critical challenge across all approaches is that reductions in IgE reactivity observed in vitro do not always translate into clinically meaningful reductions in allergenicity.

Regulatory approval and consumer acceptance represent additional critical barriers to the implementation of allergen mitigation technologies. Processing-induced allergen reduction must be evaluated within existing regulatory frameworks, which often require clear demonstration of safety, nutritional equivalence, and clinically relevant reductions in allergenicity. For emerging non-thermal and genetic modification-based approaches, regulatory uncertainty persists regarding labeling requirements, risk communication, and long-term safety assessment. In parallel, consumer acceptance is strongly influenced by perceptions of “naturalness”, processing intensity, and trust in novel technologies, which may limit market adoption even when technical efficacy is demonstrated. Addressing these challenges will require transparent risk assessment, standardized validation protocols, and effective communication strategies that align scientific evidence with regulatory expectations and consumer concerns.

Future research should prioritize standardized allergenicity assessment protocols, multi-hurdle processing strategies that simultaneously reduce allergenic and microbial risks, and evaluations in real-world food systems. The limitations of current approaches in industrial applications—such as cost, scalability, product heterogeneity, and regulatory uncertainty—underscore the need for interdisciplinary collaboration. Advances in enzyme-assisted processing, fermentation, and emerging non-thermal methods hold potential for producing hypoallergenic alternatives for high-risk foods such as peanuts, milk, and wheat, while also supporting the safe integration of novel protein sources, including plant-based and insect-derived ingredients. Ultimately, linking mechanistic insights with practical processing outcomes will enable the development of standardized, safe, and consumer-accepted products that meaningfully reduce the burden of food allergies worldwide.

Despite substantial progress in understanding processing-induced modifications of food allergens, several critical gaps remain that must be addressed to advance clinical translation and industrial implementation:

Clinical validation: Most allergen mitigation strategies are supported primarily by in vitro IgE-binding assays and animal models. Well-designed human clinical trials and controlled oral food challenge studies are urgently needed to establish clinically meaningful reductions in allergenicity.

Standardization of assessment methods: The lack of harmonized protocols for allergenicity testing including digestion models, immunoassays, and clinical endpoints—limits cross-study comparability and regulatory evaluation.

Matrix- and dose-dependent effects: Greater mechanistic insight is required to understand how the food matrix composition, processing intensity, and allergen structure jointly influence treatment efficacy, particularly for heat-stable and structurally compact allergens.

Combined and multi-hurdle strategies: Future work should focus on rationally designed combinations of thermal, non-thermal, enzymatic, and fermentation-based approaches to overcome the limitations of single technologies while preserving product quality.

Industrial scalability and safety: Long-term safety assessments, cost-benefit analyses, and regulatory considerations must be integrated early in technology development to facilitate real-world adoption.

Addressing these challenges through interdisciplinary research that integrates food engineering, immunology, clinical allergy, and regulatory science will be essential for translating mechanistic advances into safe, effective, and consumer-accepted hypoallergenic foods.

Author contributions

Gulsun Akdemir Evrendilek: Literature review, writing original manuscript; Alper Güven: writing formatting.

Conflicts of interest

The authors declare no conflicts of interest.

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