allergies

Review

Mitigating Food Protein Allergenicity with Biopolymers, Bioactive Compounds, and Enzymes

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Abstract: This review explores strategies for mitigating food allergies by treating foods with biopolymers, bioactive compounds, and food-grade enzymes. Biopolymers like chitosan, alginate, and pectin show potential in reducing the allergenic properties of food. Polyphenols such as quercetin, resveratrol, curcumin, and epigallocatechin gallate demonstrate promise as anti-inflammatory molecules that can lessen the symptoms and severity of allergic reactions. Enzymes, including proteases such as pepsin, papain, and bromelain, and transferases like transglutaminase, offer the potential to reduce the allergenic potency of proteins by various mechanisms, though more research is needed for the optimization and assessment of the safety and palatability of treated foods. Overall, this review offers insights into potential strategies to alleviate allergic reactions by reducing the allergenic properties of food proteins.

Keywords: food protein allergy; mitigation strategies; biopolymers; bioactive compounds; enzymes

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1. Introduction

Allergenic proteins, found in certain foods, plants, animals, or substances, can trigger immune responses in susceptible individuals. These proteins are typically harmless to non-allergic individuals but can cause symptoms ranging from mild (itching, hives) to severe (anaphylaxis) in those who are allergic. Examples of food allergens include peanut protein Ara h 1, cow's milk protein, casein, ovalbumin (OVA), ovomucoid (OM) in eggs, and gliadin (G) in wheat, which can lead to allergic reactions and digestive issues [1–4].

Allergic reactions can affect individuals of any age, sex, or ethnicity, with susceptibility varying by geographic region and environmental exposure [5]. At the American College of Allergy, Asthma, and Immunology's Annual Scientific Meeting, studies showed that preadolescent males have higher incidences of food allergies than females, although susceptibility increases in females as they reach adulthood [6]. Wang et al. (2021) reported that female mice sensitized with OVA exhibited more severe food allergies than males, linked to hormonal mechanisms, which could inform personalized treatment strategies [7]. Geographic differences also affect allergy prevalence, with environmental factors, access to healthcare, and local diets contributing to regional variations [8,9]. Globally, food allergies affect up to 10% of people, with higher rates in developed countries [10–12].

The most effective strategy for managing food allergies is avoiding the allergen, which involves reading food labels carefully, inquiring about ingredients when dining out, and avoiding cross-contaminated foods. Immunotherapy, such as oral immunotherapy (OIT), sublingual (SLIT), or subcutaneous immunotherapy (SCIT), can also be used to desensitize individuals to allergens gradually. Palforzia®, an OIT for peanut allergies, is the first FDA-approved treatment for food allergies [13].

Medications can manage allergic symptoms but do not cure allergies. Antihistamines address mild symptoms like itching, while epinephrine is critical for severe reactions such

as anaphylaxis. Carrying an epinephrine auto-injector (e.g., EpiPen) is recommended for those at risk of severe reactions, as it works by maintaining blood pressure and opening airways during anaphylaxis. Corticosteroids may reduce inflammation but are not long-term solutions [14,15].

Food scientists play a key role in reducing the allergenic potential of proteins by modifying their structures through heat treatment, enzymatic hydrolysis, fermentation, or chemical modification, such as glycation or acetylation, which can lower the protein's ability to bind to IgE antibodies. Additionally, biopolymers like polysaccharides and bioactive compounds such as polyphenols can interact with allergens to mask or reduce their immunogenicity. These interactions are promising for developing hypoallergenic foods, but further research is needed to fully understand their mechanisms and impacts on allergenicity [16–18]. Enzymatic hydrolysis is another promising technique to reduce allergenicity by breaking down allergenic proteins into smaller, less reactive peptides. However, incomplete hydrolysis or the variability of enzymatic efficiency across different food matrices presents challenges. Furthermore, these treatments may impact the texture, flavor, and nutritional quality of foods, posing difficulties in balancing reduced allergenicity with food quality.

This manuscript reviews protein allergy, including its prevalence, causes, and symptoms, while also examining biopolymer–allergen and bioactive–allergen interactions and enzymatic strategies for modifying allergenic proteins.

2. Current Research and Knowledge on Managing Allergic Reactions to Foods, Biopolymers, Bioactive Compounds, or Enzymes

2.1. Managing Food Allergies: Mechanisms, Symptoms, and Identification

Effective management of food allergies relies on prevention strategies and identifying allergens. For example, individuals with milk allergies should opt for dairy-free alternatives like soy or almond milk, while those with peanut or tree nut allergies must avoid these nuts and high-risk foods such as baked goods and sauces. Early introduction of peanuts to infants at high risk has been shown to reduce the likelihood of peanut allergies by over 80% [19]. Shellfish and tree nut allergies require vigilance, especially when dining out, due to the risk of cross-contamination [20–24]. Food allergies occur when the immune system produces IgE antibodies against specific proteins in food (See Figure 1). Food allergies occur when the immune system produces IgE antibodies in response to specific proteins in food (see Figure 1 for an overview of this immune response). Upon exposure to an allergen, antigen-presenting cells process the protein and present it to helper T cells, which activate B cells. B cells then differentiate into plasma cells and memory B cells. Upon re-exposure, memory B cells rapidly produce antibodies, triggering allergic reactions via mast cell activation and mediator release [25]. The most common allergenic foods—peanuts, tree nuts, shellfish, milk, eggs, soy, and wheat cause IgE-mediated immune responses, leading to symptoms like wheezing, tingling in the mouth, facial swelling, abdominal pain, and chest tightness [21–24,26–28]. Accurate identification of food allergies involves methods such as skin prick tests, blood tests measuring IgE levels, and elimination diets. In some cases, an oral food challenge (OFC), considered the gold standard for diagnosing food allergies, is conducted under medical supervision. Healthcare professionals will also assess an individual's medical history and symptoms following the consumption of suspected allergenic foods to form a diagnosis [4,29,30].

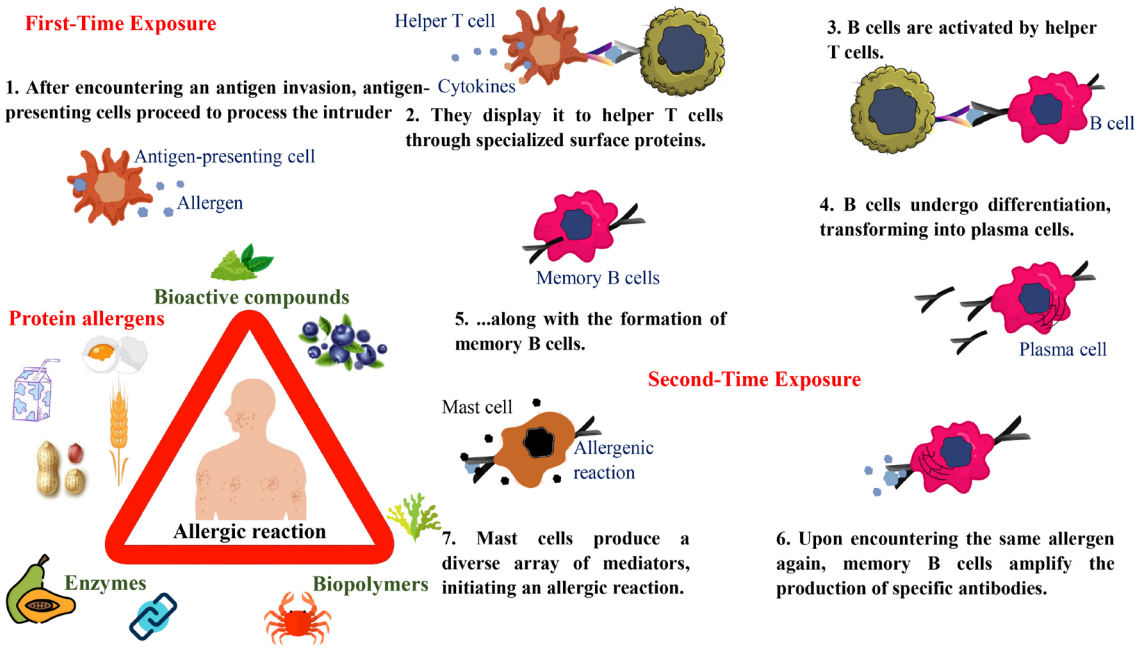

Figure 1. Graphic representation of the immune response to allergens or other perceived intruding molecules.

2.2. The Importance of Understanding the Molecular and Structural Characteristics of Food Allergens and the Compounds That Influence Them

Understanding the molecular and structural characteristics of food allergens is crucial for developing strategies to reduce allergenicity and improve food safety. Compounds such as biopolymers, enzymes, and bioactive substances have demonstrated significant potential in influencing these characteristics. One notable example is the potential of chitosan (CS) derivatives, obtained through a Maillard reaction, as a natural food preservative. Chitosan, a biopolymer derived from chitin, possesses antimicrobial properties that can extend food shelf life. Studies highlight the improved functional properties of CS derivatives, including enhanced solubility and antioxidant activity. However, while these functional properties are discussed, the structural changes in CS derivatives, such as altered molecular weight, charge distribution, and polymer chain configuration, require further elaboration, as these factors affect their interactions with food components. Additionally, although CS originates from shellfish, making it a potential allergen, it is suggested that CS derivatives may have reduced allergenicity. Further research is needed to better understand these properties and assess their safety as food preservatives [31]. Polyphenolics, naturally occurring compounds found in fruits, vegetables, and herbs, have also gained attention for their ability to reduce allergenicity through various mechanisms. For example, quercetin has been shown to reduce allergic airway inflammation in mice, isoquercitrin inhibits chemokine production by neutrophils, and genistein suppresses basophil degranulation in allergic individuals. The molecular structures of these compounds, particularly the multiple hydroxyl groups in quercetin, contribute to their antioxidant activity and ability to stabilize reactive oxygen species (ROS), which play a role in reducing inflammation and allergic responses. These polyphenolics have shown potential in modulating the immune system and reducing allergic reactions, though further research is needed to optimize their use in allergy treatments [32]. Curcumin (Cn), a polyphenol found in turmeric, also exhibits strong anti-inflammatory properties by reducing inflammatory cytokines and histamines while promoting anti-inflammatory cytokines. Its unique structure, featuring two phenolic groups and a diketone structure, plays a key role in inhibiting inflammation. These findings support the potential of natural compounds like curcumin as safe alternatives or enhancements to conventional allergy treatments, but additional research is necessary to explore their full therapeutic potential [33,34]. Another area of interest is protease resistance

in food proteins, as discussed by Akkerdaas et al. (2018). Proteins that resist breakdown by digestive enzymes are often linked to higher allergenicity, as seen in studies by Maleki et al. Structural features such as disulfide bonds or folded domains contribute to this resistance. However, Akkerdaas et al. argue that protease resistance alone is not a definitive predictor of allergenicity, and other factors like protein structure, food processing methods, and individual immune responses also play critical roles. They propose that while protease resistance can be useful in assessing allergenic potential, a comprehensive, multifactorial approach is necessary for accurate risk assessment [35,36]. In conclusion, understanding the molecular and structural characteristics of food allergens and the compounds that influence them is essential for developing effective treatments and improving food safety. While natural compounds show promise, further research is required to fully comprehend their functional properties, interactions with food matrices, and impact on allergenicity.

2.3. Novel Approaches to Mitigating Allergic Reactions: Biopolymer–Allergen and Bioactive–Allergen Interactions and Enzymatic Strategies

Allergic reactions can be mitigated through various strategies, which can be broadly categorized into two approaches: (1) Compounds that interact with specific allergenic proteins, leading to structural modifications that diminish their IgE-binding capacity. (2) Compounds that reduce the severity of allergic reactions, which act to modulate the body's immune response without directly altering allergenic proteins.

2.3.1. Structural Modification of Allergen Proteins to Reduce Allergenicity

Both biopolymers and enzymes have been shown to reduce the allergenicity of food proteins by altering their structure. These modifications reduce the IgE-binding capacity of allergenic proteins, thereby decreasing their potential to trigger immune responses.

Biopolymer–Allergen Interactions

Biopolymers are known to reduce allergenicity by interacting with allergenic proteins through mechanisms such as encapsulation or altering their conformation. These interactions can help prevent allergens from interacting with the immune system, thereby mitigating symptoms or reducing the severity of allergic reactions. By forming protective barriers, particularly at the intestinal level, biopolymers limit the immune system's exposure to allergens and reduce the risk of triggering an immune response. However, certain enzymes, like papain-like proteases, can disrupt this protective barrier by breaking down tight junctions in the intestinal lining, potentially increasing the passage of allergens and the risk of sensitization. This interaction between biopolymers and enzymes must be taken into account when evaluating the effectiveness of biopolymer-based approaches to reduce allergenic potential.

1. Chitosan

Chitosan (CS) is derived from the deacetylation of chitin, a polymer composed of N-acetyl-D-glucosamine and D-glucosamine units linked via glycosidic bonds. Chitin is typically extracted from aquatic organisms, making their waste a primary source for CS production. CS has garnered significant attention for its potential to bind allergenic proteins, alter their conformation, and reduce their ability to elicit immune responses. When administered, CS forms a gel-like barrier in the intestine, blocking allergens from interacting with immune cells, thereby decreasing sensitization and allergic reactions [37]. One notable method involves the immunization of mice against peanut allergies by orally administering CS-DNA nanoparticles. These nanoparticles, formed by combining plasmid DNA and CS, induced the production of secretory IgA and serum IgG2a in mice, reducing allergen-induced anaphylaxis, IgE levels, plasma histamine, and vascular leakage. This demonstrates the potential of CS-DNA nanoparticles as a prophylactic treatment for food allergies [38]. In another study, CS oligosaccharide (COS) was tested for its effects on shrimp tropomyosin (TM)-induced allergy. COS, with different polymerization degrees, was administered to shrimp-allergic mice presensitized with TM. The results show that COS

treatment improved severe food allergy symptoms by regulating Th1 and Th2 cytokines, reducing serum IgE, IgG1, and histamine levels while increasing IgG2a and Th1 cytokine levels [39]. Furthermore, CS nanoparticles were explored as delivery vehicles for a DNA vector encoding transforming growth factor-beta (TGF-beta) in the treatment of ovalbumin (OVA)-induced allergy. Oral administration of CS-encapsulated TGF-beta DNA resulted in a sustained increase in TGF-beta protein in the intestinal tissue of mice, which alleviated allergic symptoms caused by OVA. This highlights the potential of CS-encapsulated DNA for gene therapy in food allergies [40]. The Maillard reaction, a process where reducing sugars react with proteins, has been investigated for its ability to reduce the allergenicity of shrimp TM, the main shellfish allergen. In one study, ribose, galacto-oligosaccharide, and COS were used in the Maillard reaction, with COS showing the highest efficacy in reducing IgE binding by altering TM's conformation and allergenic epitopes [41,42]. Similarly, a Maillard reaction between soy protein and CS produced a conjugate with improved functional properties, showing potential for use in food preservation, processing, and the development of hypoallergenic food products for individuals with soy allergies [43]. Additionally, the anti-inflammatory properties of low-molecular-weight COS (LM-COS) were studied in an allergic inflammation model in mice induced by OVA. Oral administration of LM-COS significantly reduced levels of interleukin (IL)-4, 5, 13, and tumor necrosis factor (TNF)-α in lung tissue and bronchoalveolar lavage fluid, indicating its potential as a therapeutic agent for allergic inflammation [44]. In summary, CS has shown promising results in mitigating allergic reactions through various mechanisms, including the use of CS-DNA nanoparticles, COS treatments, and CS-encapsulated DNA to deliver TGF-beta. The Maillard reaction with reducing sugars, particularly COS, also offers a method to reduce the allergenicity of shrimp TM and soy proteins while enhancing their functional properties. However, caution must be exercised, as CS may induce immediate-type allergies in susceptible individuals.

2. Alginate (ALG)

Alginate (ALG), a soluble dietary fiber extracted from brown algae such as *Laminaria japonica*, has demonstrated potential as an antiallergic therapy. ALG is known for its ability to form gels or encapsulate proteins, limiting their availability for absorption in the digestive tract. This encapsulation reduces immune cell exposure to allergenic proteins, thus decreasing the likelihood of sensitization. Additionally, ALG has been shown to interact with various proteins, reducing their bioactivity. In a study using a mouse model of egg allergy, ALG effectively reduced allergic reactions by inhibiting mast cell degranulation and improving the integrity of intestinal epithelial villi. Furthermore, ALG decreased levels of allergic mediators, such as IgE, histamine, and IL-4, while increasing IFN-γ levels. These results suggest that ALG could be employed as a functional food ingredient or additive to alleviate food protein-induced allergic responses [45]. Another study focused on *Sargassum graminifolium* (SG), a marine brown alga rich in fucoidans and alginic acid polysaccharides, and its potential for treating food allergies. In this study, SG fucoidans and ALGs were shown to significantly reduce allergy symptoms, diarrhea, and injury to the jejunum in mice. Fucoidans down-regulated OVA-specific IgE and TNF-α levels and had a more pronounced effect on regulating intestinal microbiota richness and diversity than ALGs at the same dose. Fucoidans also regulated the abundance of Firmicutes, Lactobacillus, and Alistipes in food-allergic mice. These findings suggest that fucoidans and ALGs may work through different regulatory pathways to treat food allergies, offering insights into the development of alga-derived polysaccharides for therapeutic purposes [46]. In another study, the efficacy of cyanidin-3-O-glucoside (C3G) in mitigating food allergies was enhanced by delivering it via enteric sodium ALG, specifically targeting the rectal and colonic regions. This targeted delivery improved intestinal microecological homeostasis, enhanced intestinal epithelial barrier function, and promoted a better balance between Th1 and Th2 immune responses. Encapsulating C3G in sodium ALG also protected the polyphenol from degradation in the upper gastrointestinal tract, delivering a larger quantity to the intestine for more substantial biological effects [47]. Overall, ALG shows great potential as an effective treatment for food protein-induced allergies. It can attenuate allergic reactions and regulate intestinal

microbiota. Targeted delivery of bioactive compounds, such as polyphenols, via enteric sodium ALG, enhances intestinal epithelial barrier function and improves the balance of Th1/Th2 immune responses.

3. Pectin

Pectin is another biopolymer with strong gelling properties that can encapsulate allergens, reducing their interaction with the immune system. By forming protective barriers in the gastrointestinal tract, pectin can help prevent allergens from crossing the intestinal barrier, thus lowering the risk of allergic responses. However, there is currently limited research on the use of pectin to mitigate food protein allergies. Peyron et al. (2005) examined the effects of heat treatment and the addition of low/high-methylated pectin (LMP/HMP) on the allergenicity and digestibility of β-lactoglobulin (β-Lg) and its hydrolysis products. In their study, β-Lg was first hydrolyzed by pepsin and then by a trypsin/chymotrypsin (T/C) mixture, with digestion products analyzed using SDS-PAGE electrophoresis and immunoblotting. The results show that heat denaturation significantly increased β-Lg's susceptibility to pepsin and T/C digestion, thus reducing its immunoreactivity. This effect was modulated by LMP and HMP, which interacted with β-Lg, affecting cleavage site accessibility and epitope masking. LMP decreased β-Lg's immunoreactivity by altering peptide conformation or masking IgG epitopes, while HMP reduced digestibility by masking cleavage sites. These findings emphasize the potential of process optimization and formulation to modulate food allergenicity [48]. Another study investigated the impact of biopolymers such as pectin, gum arabic, and xylan, commonly used in the food industry, on the allergenicity of ovalbumin (OVA) and ovomucoid (OM), the primary egg allergens. In vitro digestion under simulated physiological conditions revealed that these polysaccharides increased the reactivity of OVA and OM with human IgE while concurrently reducing their susceptibility to digestion. The observed resistance to digestion is a classic characteristic of food allergens. This study demonstrates that interactions between OVA and OM with these biopolymers enhance IgE binding while reducing digestibility, emphasizing the importance of considering the food matrix in allergenicity assessments [49]. Although research on the use of pectin to mitigate food protein allergies is limited, these studies suggest that pectin has the potential to reduce allergic reactions. However, the results are not yet conclusive, and more research is required to confirm the effectiveness of pectin as a treatment for food protein allergies. The studies highlight the importance of susceptibility to proteolysis and the food matrix in the digestibility of food allergens and their potential to trigger an immune response.

Table 1 provides a summary of studies focused on using biopolymers for the purpose of mitigating or preventing allergenic reactions triggered by food allergen proteins.

Table 1. Summary of studies related to the use of biopolymers to mitigate or prevent allergenic reactions caused by food allergen proteins.

Biopolymer	Study/Experiment	Results	Target	Ref.
CS	Oral administration of CS DNA nanoparticles synthesized by combining plasmid DNA and CS in mice	Reduced levels of allergen-induced anaphylaxis, IgE, plasma histamine, and vascular leakage.	Peanut	[38]
CS	Treatment of a mouse model of food allergy with chitosan COS	Improved severe food allergy symptoms and reduced serum IgE and IgG1 levels, while increasing IgG2a levels.	Shrimp	[39]
CS	Oral administration of TGF-beta-expressing DNA vector in CS nanoparticles in mice	Sustained increase in TGF-beta protein in mouse intestinal tissue and improved food allergy symptoms induced by OVA.	Egg	[40]

Table 1. *Cont.*

Biopolymer	Study/Experiment	Results	Target	Ref.
CS	Use of Maillard reaction with reducing sugars to eliminate allergenicity of TM	All three sugars significantly reduced allergenicity, with COS showing the highest efficiency.	Shellfish	[41,42]
CS	Maillard-type soy protein–CS conjugate	Enhanced antimicrobial activity, improved emulsifying properties, and reduced allergenicity.	Soybean	[43]
CS	Anti-inflammatory effects of LM-COS in allergic inflammatory	LM-COS reduced levels of pro-inflammatory cytokines in OVA-sensitized/challenged allergic inflammatory model mice.	Egg	[44]
ALG	Use in a mouse model	ALG effectively reduced allergic reactions, inhibited mast cell degranulation, and improved intestinal epithelial villi integrity.	Egg	[45]
SG fucoidans and ALGs	Study on mice with food allergies	Reduced allergy symptoms, diarrhea, and jejunum injury. Down-regulated OVA-specific IgE and TNF-α levels.	Egg	[46]
C3G	Study on targeted rectal and colonic delivery via enteric sodium ALG in ameliorating OVA allergies	Enhanced intestinal microecological homeostasis, improved intestinal epithelial barrier function, and balanced Th1/Th2 immune responses.	Egg	[47]
Pectin	Effects of heat treatment and pectin addition on allergenicity of BLG	Heat denaturation increased protein's susceptibility to proteolysis, reducing immunoreactivity. Pectin addition reduced accessibility to cleavage sites/epitope sequences via nonspecific interactions.	Milk	[48]
Pectin, gum arabic, and xylan	Effect of pectin, gum arabic, and xylan on reactivity of OVA and OM with human IgE	Polysaccharides increased reactivity of OVA and OM with human IgE while reducing susceptibility to digestion. Pectin showed highest resistance to digestion and could potentially hinder allergen's reaction with human IgE.	Egg	[49]

ALG: alginate; C3G: cyanidin-3-O-glucoside; chitosan: CS; chitosan oligosaccharide: COS; DNA: deoxyribonucleic acid; IgE: immunoglobulin E; IgG1: immunoglobulin G1; IgG2a: immunoglobulin G2a; LM-COS: low-molecular-weight COS; OVA: ovalbumin; ovomucoid: OM; sargassum graminifolium: SG; TGF-beta: transforming growth factor beta; Th1: T-helper 1; Th2: T-helper 2; TNF-α: tumor necrosis factor alpha.

Protease–Enzyme Interactions

Proteases, such as pepsin and bromelain, modify allergen structures by breaking down proteins or altering their shape, making them less likely to provoke allergic reactions. These enzymes act by cleaving allergenic proteins into smaller fragments or changing their conformation, which can reduce their ability to bind to IgE antibodies and trigger immune responses. Proteases like pepsin, papain, bromelain, and transglutaminase have been explored for their ability to reduce the allergenicity of food proteins. However, the role of proteases is multifaceted. For instance, papain-like proteases can play a dual role. While they can reduce the allergenicity of proteins by breaking them down, they also have the ability to break down tight junctions at the intestinal level. Tight junctions are critical for maintaining the integrity of the intestinal barrier, which prevents the passage of harmful substances, including allergens, into the bloodstream. When papain-like proteases break these junctions, they can enhance the passage of allergenic proteins through the intestinal lining, thereby promoting sensitization and increasing the risk of allergic reactions. The research by Kopper et al. (2004) investigated the gastric digestion of peanut protein allergens using in vitro assays. The researchers found that the digestion of peanut proteins is primarily carried out by the enzyme pepsin, which is present in the stomach.

The study suggests that pepsin plays a crucial role in the breakdown of peanut proteins during digestion and may have implications for the development of allergenic reactions in individuals with peanut allergies [50] Yu and Mikiashvili (2020) study evaluated the efficacy of different proteases in decreasing the allergen content and IgE-binding of raw peanuts. The researchers treated peanut samples with papain, bromelain, Alcalase, and trypsin and measured the levels of Ara h 1, 2, and 6 allergens, as well as IgE-binding activity. All proteases significantly decreased the intact allergen content and IgE-binding, with papain being the most effective. The study suggests that protease treatment could be a useful strategy in reducing peanut allergenicity and potentially aid in preventing and treating peanut allergies [51]. Piersma et al. (2005) studied the proteolytic processing of Ara h 3, a major allergen in peanuts. In vitro assays were used to investigate the cleavage of Ara h 3 by proteases such as trypsin, chymotrypsin, and pepsin. Results indicate that Ara h 3 was cleaved by all tested proteases, resulting in smaller fragments. The study also investigated the IgE-binding activity of these fragments and found that some retained their IgE-binding capacity, while others did not. These findings suggest that the proteolytic processing of Ara h 3 may contribute to peanut allergies and have implications for the development of allergen-reducing strategies. Overall, the study provides insights into the effects of digestion on IgE binding to a peanut allergen [52].

Papain is a protease enzyme extracted from papaya fruit and is widely used in food processing as a meat tenderizer and in the production of cheese, beer, and other food products. Here are some case studies that highlight the potential role of papain enzymes in mitigating allergenic reactions of proteins: In 2020, Feng et al. developed a new catalytic material called papain-Cu3(PO_4)$_2$•3H_2O-magnetic nanoflowers that effectively hydrolyzes cow's milk allergenic proteins. The papain in the non-selective catalytic material breaks down proteins, including the allergenic proteins, while the magnetic nanoflowers help to remove the hydrolyzed products. The researchers optimized the conditions for the hydrolysis process, including pH, temperature, and the amount of catalytic material used. The results demonstrate that the papain-Cu3(PO_4)$_2$•3H_2O-magnetic nanoflowers effectively reduced IgE binding under specific conditions. The research sheds light on the potential of papain as a catalyst for mitigating protein allergy in food products such as cow's milk allergenic proteins. The researchers propose that their catalytic material may lead to the development of allergen-reduced food products in the future [53]. The potential of papain to mitigate protein allergy by studying the effects of pH, temperature, enzyme-to-substrate ratio, and reaction time on the antigenicity of casein hydrolysates is further explored and showed that all these parameters significantly affected the antigenicity of the hydrolysates. The investigators found that the optimal conditions for reducing antigenicity were a pH of 8.0, temperature of 37 °C, enzyme-to-substrate ratio of 1:100 (w/w), and reaction time of 6 h. Papain effectively hydrolyzed the casein under these conditions, resulting in a reduction in antigenicity. The researchers suggest that papain has the potential to reduce the risk of protein allergies in food products [54]. The potential use of papain in mitigating soy protein allergy was explored by analyzing the hydrolysis on antioxidant and antiangiotensin activities, antigenicity, and digestibility of soybean milk protein. The study showed that papain hydrolysis improved antioxidant and antiangiotensin activities while reducing antigenicity and enhancing digestibility. The researchers suggest that the hydrolyzed soybean milk protein may be utilized to develop new food products with improved health benefits and decreased allergenicity. Thus, they conclude that papain has the potential to reduce protein allergy by decreasing antigenicity while simultaneously enhancing other beneficial properties of food proteins [55]. The combined enzymatic digestion with papain and ultrafiltration on whey protein concentrate was studied. The results reveal that papain was effective in reducing the antigenicity of whey protein concentrate when used for enzymatic digestion. The subsequent ultrafiltration of the hydrolysates further decreased the antigenicity, suggesting that the combined enzymatic digestion and ultrafiltration approach might effectively mitigate the allergenicity of whey protein concentrate. The researchers also identified the optimal conditions for the enzymatic digestion of whey protein concen-

trate by papain. The research concludes that papain has the potential to play a crucial role in mitigating protein allergy by reducing the antigenicity of whey protein concentrate, and this approach can be used to develop new food products with improved health benefits and decreased allergenic potential [56]. Meinlschmidt et al. (2016) used papain to debitter soy protein hydrolysates and analyzed its effects on protein allergy. Debittering led to reduced major soy allergen levels, and fermentation further mitigated allergenicity while improving safety and sensory qualities. The researchers concluded papain could play a significant role in reducing soy allergens in debittered soy protein hydrolysates, and fermentation can enhance safety and sensory qualities [57].

Bromelain is a protease enzyme extracted from pineapples and is widely used in food processing, particularly in the meat industry as a tenderizer. Here are some case studies that highlight the potential role of bromelain enzymes in mitigating allergenic reactions of proteins: Vera Medeiros et al. (2014) used bromelain to partially hydrolyze caseins in bovine milk formula, aiming to improve its digestibility and angiotensin-converting enzyme (ACE)-inhibitory properties. They found that bromelain significantly reduced casein fragment size, improving digestibility and increasing ACE-inhibitory activity. Bromelain treatment may also decrease the allergenicity of the formula, making it potentially beneficial for infants with cow's milk protein allergy. The study concluded that partial hydrolysis of caseins using bromelain can improve formula properties [58]. The study by Villas-Boas et al. (2015) aimed to investigate the effects of two-step enzymatic modification on the resistance of BLG epitopes to simulated gastrointestinal digestion and to assess the potential of bromelain in mitigating protein allergy. Results show that the two-step enzymatic modification of BLG led to a significant reduction in its overall immunoreactivity and resistance to simulated gastrointestinal digestion. Combination use of trypsin and chymotrypsin was found to be more effective than the use of each enzyme alone. Additionally, the study demonstrated the effectiveness of bromelain in mitigating the allergic response to BLG in mice, which could be attributed to the proteolytic activity of bromelain breaking down allergenic epitopes into smaller fragments [59]. Arteaga et al. (2020) reported the effects of enzymatic hydrolysis on the molecular weight distribution, techno-functional properties, and sensory perception of pea protein isolates (PPIs), with a focus on the potential of bromelain to reduce protein allergy. The study found that enzymatic hydrolysis improved the techno-functional properties of the PPIs, and higher degrees of hydrolysis led to better properties. Additionally, bromelain was effective in reducing the allergenicity of the hydrolyzed PPIs, as shown by the significant decrease in IgE-binding capacity of the hydrolyzed samples. The results suggest that enzymatic hydrolysis can enhance the techno-functional properties of PPIs and bromelain and thus reduce the possibility of allergic reactions associated with pea protein consumption [60]. Another study aimed to produce hypoallergenic wheat flour through enzymatic fragmentation of allergens and investigate its application in food processing, with a focus on bromelain's potential to mitigate protein allergy. They determined that a combination of bromelain and papain effectively reduced the allergenicity of wheat flour by breaking down major allergens into smaller fragments. The resulting hypoallergenic wheat flour was used to make bread and cookies with good sensory and textural properties. The study suggests that enzymatic fragmentation, particularly with the use of bromelain, can effectively reduce the allergenicity of wheat flour, which may help individuals with wheat allergies in the future [61].

In conclusion, proteases like pepsin, papain, and bromelain offer promising avenues for reducing the allergenic properties of food proteins. These enzymes can break down allergenic proteins under controlled conditions, potentially leading to the development of safer food products for individuals with food allergies. However, the digestion of proteins within different food matrices may vary, and further research is needed to optimize enzyme use and ensure long-term safety.

Transglutaminase (TG) Interactions

Transglutaminase (TG) has been studied for its potential to reduce the allergenicity of food proteins through its cross-linking activity. By catalyzing protein cross-linking, TG can alter the structure of allergenic proteins, decreasing their IgE-binding capacity and making them less likely to trigger immune responses in individuals with food allergies.

TG is commonly used in food processing to enhance texture and flavor. Several studies highlight its potential to mitigate allergenic reactions. For example, Fotschki et al. (2020) demonstrated that microbial TG (mTG) treatment reduced the immunoreactivity of horse milk proteins, suggesting an alternative for cow milk allergy management. The study found that horse milk, having half the protein content of cow milk, exhibited significantly lower IgE and IgG reactivity post-digestion, implying TG-induced polymerization could be beneficial for cow milk allergy sufferers, pending clinical validation [62]. Meng et al. (2020) explored enzymatic hydrolysis combined with TG crosslinking to reduce peanut allergenicity. They found that TG crosslinking not only reduced allergenicity but also improved the functional properties of peanut proteins, offering promise for safer peanut-based products [63]. TG's effect on wheat flour proteins was also studied, showing reduced immunoreactivity and structural changes, potentially making it useful for individuals with wheat allergies or celiac disease. However, further research is needed to determine the optimal conditions and assess its safety in humans [64]. Villas-Boas et al. (2010) investigated TG-induced polymerization of BLG, a key cow milk allergen, and found that it reduced IgE binding from milk-allergic patient sera. This suggests TG could improve the safety of cow milk-based products for allergic individuals [65]. Yuan et al. (2017) examined TG-catalyzed glycosylation of shrimp tropomyosin (TM), a major allergen, which reduced its antigenicity and allergenicity through structural modifications. TG-catalyzed glycosylation offers a mild, site-specific method for reducing shrimp allergenicity, with potential for wider food processing applications [66]. Additionally, mTG was used to crosslink recombinant Ara h 1, a major peanut allergen, reducing its allergenicity without compromising structural integrity. This crosslinked protein showed reduced IgE binding and allergenicity in skin prick tests, making it a potential candidate for immunotherapy [67].

Overall, TG shows promise as a tool for reducing the allergenic properties of proteins while maintaining their structural and functional properties. It may be applied to improve the safety of allergenic food products and develop new immunotherapies for allergic diseases. However, more research is required to fully understand its effects on various allergenic proteins and its safety and efficacy in human applications. Table 2 provides a summary of studies focused on using enzymes for the purpose of mitigating or preventing allergenic reactions triggered by food allergen proteins.

Table 2. Summary of studies related to the use of enzymes to mitigate or prevent allergenic reactions caused by food allergen proteins.

Enzyme	Study/Experiment	Results	Target	Ref.
Pepsin	Investigated the gastric digestion of using in vitro assays.	Pepsin plays a crucial role in digestion, with implications for allergenic reactions.	Peanut	[50]
Papain	Evaluated the efficacy of different proteases.	IgE-binding, showing potential in reducing allergenicity.	Peanut	[51]
Trypsin	Proteolytic processing of Ara h 3 using trypsin, chymotrypsin, and pepsin.	Ara h 3 was cleaved by all tested proteases; some fragments retained IgE-binding, impacting allergenicity.	Peanut	[52]
Papain	Developed papain-$Cu_3(PO_4)_2{\cdot}3H_2O$-magnetic nanoflowers.	Papain reduced IgE binding.	Milk	[53]
Papain	Casein hydrolysis under varying conditions.	Optimal conditions reduced protein allergies.	Milk	[54]

Table 2. *Cont.*

Enzyme	Study/Experiment	Results	Target	Ref.
Papain	Effects on protein digestibility and antigenicity.	Reduced antigenicity and enhanced its health benefits.	Soybean	[55]
Papain	Combined enzymatic digestion and ultrafiltration	Papain significantly reduced the antigenicity.	Whey protein concentrate	[56]
Papain	Enzymatic Debittering and fermentation	led to reduced major allergen levels, and mitigated allergenicity	Soy protein	[57]
Bromelain	Analyzed enzymatic hydrolysis.	Improved digestibility and decreased allergenicity.	Milk Casein	[58]
Bromelain	Two-step enzymatic modification.	Reduced immunoreactivity and allergenicity.	BLG	[59]
Bromelain	Analyzed enzymatic hydrolysis.	Improved techno-functional properties and reduced allergenicity.	PPIs	[60]
Bromelain	Study on enzymatic fragmentation.	Reduced allergenicity, producing hypoallergenic flour.	wheat flour	[61]
TG	Enzymatic treatment on proteins.	Reduced immunoreactivity; lower IgE and IgG reactivity post digestion.	Milk (horse and cow)	[62]
TG	Enzymatic hydrolysis and crosslinking.	Reduced allergenicity; improved functional properties.	Peanut	[63]
TG	Enzymatic treatment on proteins.	Reduced immunoreactivity and altered protein structure; potential for improving safety in allergy management.	Wheat flour	[64]
TG	Enzyme-induced polymerization	Reduced BLG antigenicity; decreased IgE binding from allergic patient sera.	BLG	[65]
TG	Enzyme-catalyzed glycosylation	Induced structural unfolding of TM; reduced antigenicity and allergenicity.	Shrimp	[66]
TG	Crosslinking of recombinant Ara h 1.	Significant decrease in IgE-binding activity; potential candidate for immunotherapy.	Peanut	[67]

BLG: β-lactoglobulin; G: gliadin; IgE: immunoglobulin E; PPIs: pea protein isolates; TM: tropomyosin.

2.3.2. Interaction of Bioactive Compound with Allergen Proteins to Lessen Symptoms

Bioactive compounds from natural sources provide significant advantages over conventional medications for allergy relief. First, they are generally recognized as safe (GRAS) and cause fewer side effects, making them suitable for long-term use. These compounds, such as polyphenols, offer multiple health benefits, including anti-inflammatory and antioxidant properties, while conventional medicines typically target specific symptoms. Furthermore, bioactive compounds are derived from renewable plant sources, ensuring sustainability and accessibility, especially in developing regions. Their preventive potential allows for dietary incorporation to reduce the risk of allergic sensitization over time. Some examples of bioactive compounds and their effects on allergens include:

Quercetin (QU)

A flavonoid found in various fruits, vegetables, and herbs, such as onions, apples, and parsley. QU has been shown to reduce the allergic response to food proteins by inhibiting the release of histamine and other inflammatory molecules. The study examined the impact of conjugating OVA with QU on the allergenicity of OVA using a mouse model. QU conjugation changed the protein structure, potentially masking OVA epitopes, and reduced the IgE-binding and mediator release capacity of OVA. In vivo, conjugation reduced levels of IgE, IgG1, IgG, plasma histamine, and mast cell protease-1 on sensitized mast cells.

Conjugation also modulated the Th1/Th2 immune response by decreasing Th2-related cytokines (IL-4, 5, 13) and increasing a Th1-related cytokine (IFN-γ). These findings suggest that conjugating OVA with QU could reduce OVA allergenicity and may offer insights into reducing food allergenicity through polyphenol conjugation [68]. The study by Wang et al. (2019) investigated the binding of QU to wheat gliadin at different pH levels. Results show that QU binds to gliadin (G) through different mechanisms at different pH levels, leading to changes in the structure of G and potentially reducing its allergenicity. These findings suggest the potential use of modified wheat G products enriched with QU under different pH conditions, although further research is needed to evaluate their effect on other functionalities of G for food industry applications [69]. Shishehbor et al. (2010) investigated the effects of QU on peanut-induced anaphylactic reactions in a rat model of peanut allergy. QU treatment for four weeks completely abrogated anaphylactic reactions in sensitized rats following challenges. The study suggested that QU may protect against IgE-mediated wheat allergy by inhibiting mast-cell-mediated anaphylactic reactions, reducing inflammatory enzyme activity, modulating the expression of high-affinity immunoglobulin E receptors (FcεRIs) on basophils and mast cells, and repairing damaged gut epithelial cells. The study also proposed that the rat model may be more predictive of human peanut-induced allergic responses than the Brown Norway rats [70].

In summary, the studies reviewed suggest that QU, a polyphenol found in fruits and vegetables, has potential as a natural alternative medicine for the prevention and treatment of food allergies. It can reduce the allergenicity of food allergens by modifying their protein structure and inhibiting the release of immune cells responsible for allergic reactions. QU also shows promise in modulating the Th1/Th2 immune response and repairing damaged gut epithelial cells. However, more research is needed to evaluate the efficacy and safety of QU as a therapeutic agent for food allergies in humans.

Resveratrol

A polyphenol found in grapes, red wine, and peanuts, resveratrol has been shown to reduce allergic reactions by inhibiting the production of inflammatory cytokines and promoting the production of anti-inflammatory cytokines. One study aimed to prepare resveratrol-enriched peanut sprouts with reduced levels of allergic proteins using ultrasound-treated peanut seeds. The study found that ultrasound treatment increased resveratrol levels in the sprouts while reducing the levels of allergic proteins, making them less likely to cause allergic reactions. In vitro studies using immune cells from individuals with peanut allergies showed that resveratrol could reduce the production of inflammatory molecules, suggesting its potential as a therapeutic agent for peanut allergies. The study suggests that the use of ultrasound treatment to prepare resveratrol-enriched peanut sprouts may provide a way to reduce the allergenic potential of peanuts while also providing potential health benefits through the increased levels of resveratrol [71]. A different study explored the potential of resveratrol, a natural compound with anti-inflammatory and antioxidant properties, as a therapeutic agent for allergic diseases. These researchers found that resveratrol treatment was able to attenuate anaphylactic responses and inhibit the activation of IgE-mediated mast cells, both of which are involved in allergic reactions. In vitro studies using human mast cells further supported the potential of resveratrol to inhibit the release of inflammatory molecules in response to allergens. These findings suggest that resveratrol may have important implications for the development of new treatments for allergic diseases such as asthma and allergic rhinitis [72]. The study investigated the potential of dietary resveratrol to prevent food allergies in mice. Resveratrol reduced allergic response, IgE antibodies, mast cell degranulation, and cytokines in resveratrol-fed mice. Resveratrol inhibited the activation of inflammatory cells and the release of inflammatory molecules in response to allergens in human mast cells. Results suggest resveratrol may be a useful therapeutic agent for individuals with food allergies [73]. A study investigated the potential of resveratrol to treat allergic rhinitis in mice. Resveratrol has anti-inflammatory and antioxidant properties and shows promise as a therapeutic agent for allergic diseases. The study found that

resveratrol treatment reduced symptoms of allergic rhinitis in mice, such as sneezing and mucus secretion. Resveratrol inhibited the activation of inflammatory cells and reduced pro-inflammatory cytokine expression and thus mitigated allergy symptoms in mice. The study suggests resveratrol may be a useful therapeutic agent for allergic rhinitis and other allergic diseases [74].

The studies suggest that resveratrol, a natural compound found in grapes, red wine, and peanuts, may reduce allergic reactions and provide health benefits through its anti-inflammatory and antioxidant properties. Resveratrol-enriched peanut sprouts prepared using ultrasound treatment may also reduce the allergenic potential of peanuts. Resveratrol has been found to attenuate anaphylactic responses, inhibit the activation of IgE-mediated mast cells, prevent the development of food allergies, and attenuate allergic rhinitis in mice. These findings suggest that resveratrol may be a useful therapeutic agent for individuals with asthma, allergic rhinitis, and food allergies.

Curcumin (Cn)

A polyphenol found in turmeric, Cn has been shown to have anti-inflammatory properties and inhibit the release of histamine and other inflammatory molecules [75]. One article explores the effects of Cn on mastocytosis and intestinal anaphylaxis in a mouse model of food allergy. Cn ingestion significantly inhibited mastocytosis and suppressed intestinal anaphylaxis in mice, as evidenced by a decrease in the number of mast cells and a reduction in the severity of allergic reactions. The study suggests that Cn may be a potential therapeutic agent for the treatment of food allergies and other mast cell-related disorders, but further research is needed to determine the optimal dose and duration of Cn supplementation for maximum benefit [76]. A different study investigated the role of protein disulfide isomerases (PDIs) in mast cell responses during food allergy and the potential protective effects of Cn. The study found that inhibiting PDI-induced mast cell degranulation and cytokine production with Cn led to a decrease in allergic symptoms in mice. The study suggests that Cn may be a potential therapeutic agent for the treatment of food allergies and other mast cell-related disorders by inhibiting PDIs [77]. The effects of hot alkali modifications on peanut protein secondary structure and Cn's embedding rate were also studied. They found that the extent of modification and reaction time are critical factors in determining the changes in the secondary structure of peanut protein. The embedding rate of Cn is highest under the conditions of 1% NaOH modification at 80 °C for 3 h. Hot alkali modification can improve the embedding rate of Cn and may have potential applications for delivering bioactive compounds. Further research is needed to determine optimal modification conditions of peanut protein and evaluate potential health benefits [78].

Cn may have therapeutic effects for food allergies and mast cell-related disorders. Cn inhibits the release of histamine and reduces mast cell degranulation and cytokine production in mouse models. Cn can also be used as a carrier for delivering other bioactive compounds. However, more research is needed to determine the optimal dosage, duration, and modification conditions for maximum Cn embedding efficiency into protein carriers.

Epigallocatechin Gallate (EGCG)

A catechin found in green tea, EGCG has been shown to have anti-inflammatory and antioxidant properties and to reduce the severity of allergic reactions. The enzymatic and non-enzymatic conjugates of lactoferrin and EGCG were examined with a focus on their formation, structure, functionality, and allergenicity. The researchers discuss various techniques for forming these conjugates and how the resulting structures can differ. They also explore the antioxidant and antibacterial properties of these conjugates. The researchers note that while lactoferrin and EGCG are generally safe, conjugation may increase the risk of allergic reactions, which is an important consideration for their use in food products [79]. EGCG and β-lactoglobulin (βLg) were conjugated to form EGCG–βLg conjugates, altering βLg's structure and bioactivity for potential allergen

desensitization. Temperature affected conjugation by reducing EGCG's binding affinities and numbers. This conjugation decreased βLg's IgE-binding capacity and introduced antioxidant properties. In vivo, EGCG–βLg conjugates significantly reduced serum IgE levels, inflammatory cytokines, and anaphylaxis symptoms, effectively suppressing allergic responses [80]. The effects of EGCG and proanthocyanidins (PACs) on the functionality and allergenicity of soybean protein isolate (SPI) were assessed. The investigators describe how SPI can be modified using EGCG and PACs and how the resulting modifications can affect protein properties. They found that both EGCG and PACs can improve functional properties, such as the emulsifying activity of SPI, while reducing allergenicity. However, the researchers note that there are some differences between the effects of EGCG and PACs on SPI, with EGCG being more effective at improving emulsifying properties, while PACs are more effective at reducing allergenicity [81]. The anti-inflammatory effects of EGCG were investigated in a mouse model of OVA-induced allergic rhinitis. The investigators describe how the mice were sensitized to OVA to induce allergic rhinitis and how EGCG was administered to the mice. They found that EGCG is able to reduce the symptoms of allergic rhinitis in mice, including nasal rubbing and sneezing, as well as reducing the levels of inflammatory cytokines in the nasal mucosa [82]. A study of SPI-EGCG conjugate investigated the covalent binding sites of a soy protein isolate SPI-EGCG conjugate and evaluated its IgE-binding ability. The researchers describe how the SPI-EGCG conjugate was synthesized using a covalent binding method and how the conjugate was then characterized using a variety of techniques, including SDS-PAGE, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS), and FTIR. They found that the EGCG was covalently bound to the SPI at specific amino acid residues, primarily lysine and cysteine residues. The study also evaluates the IgE-binding ability of the SPI-EGCG conjugate using ELISA assays. The researchers found that the conjugate has reduced IgE-binding ability compared with unmodified SPI, suggesting that it may have reduced allergenicity [83]. Assessment of the synergistic effects of l-theanine and EGCG demonstrated that OVA allergy was alleviated by regulating intestinal immunity through inhibition of mast cell degranulation. The investigators describe how mice were sensitized to OVA to induce an allergic reaction and how l-theanine and EGCG were administered to the mice. They found that the combination of l-theanine and EGCG is able to reduce the symptoms of OVA allergy in the mice, including reduced serum levels of OVA-specific IgE and reduced mast cell degranulation in the intestine [84]. The therapeutic effects of epigallocatechin (EGC) and EGCG on the allergic reaction to αs1-casein sensitized mice were assessed. The researchers describe how mice were sensitized to αs1-casein to induce an allergic reaction and how EGC and EGCG were administered to the mice. They found that both EGC and EGCG were effective in reducing the symptoms of αs1-casein allergy in the mice, including reduced serum levels of αs1-casein-specific IgE and reduced histamine release from mast cells. The manuscript also describes the potential mechanisms of action for the therapeutic effects of EGC and EGCG, including their ability to inhibit the production of inflammatory cytokines and to regulate the expression of regulatory T cells. Overall, the study suggests that EGC and EGCG may have potential as therapeutic agents for the treatment of food allergies, particularly in cases where αs1-casein is the allergen [85].

These bioactive compounds, through immune modulation and structural interactions with allergens, offer promising alternative therapies for reducing food allergy symptoms. However, more research is necessary to optimize their usage and determine their long-term safety and efficacy in human subjects. Table 3 provides a summary of studies focused on using bioactive compounds for the purpose of mitigating or preventing allergenic reactions triggered by food allergen proteins.

Table 3. Summary of studies related to the use of bioactive compounds to mitigate or prevent allergenic reactions caused by food allergen proteins.

Bioactive Compound	Study/Experiment	Results	Target	Ref.
QU	Mouse model study	Conjugation with OVA reduced IgE-binding and release capacity of OVA, modulated Th1/Th2 immune response, and reduced levels of IgE, IgG1, IgG, plasma histamine, and mast cell protease-1 on sensitized mast cells.	Egg	[68]
QU	In vitro study	QU binds to G through different mechanisms at different pH levels, leading to changes in the structure of G and potentially reducing its allergenicity.	Wheat	[69]
QU	Rat model study	QU treatment completely abrogated anaphylactic reactions in sensitized rats.	Peanut	[70]
Resveratrol	In vitro study using immune cells	Resveratrol reduced the production of inflammatory molecules in response to peanut allergens.	Peanut	[71]
Resveratrol	In vitro study using human mast cells	Resveratrol treatment was able to attenuate anaphylactic responses and inhibit the activation of IgE-mediated mast cells, both of which are involved in allergic reactions.	Allergenic Foods	[72]
Resveratrol	Mouse model study	Resveratrol reduced allergic response, IgE antibodies, mast cell degranulation, and cytokines in resveratrol-fed mice. Resveratrol inhibited the activation of inflammatory cells and release of inflammatory molecules in response to allergens in human mast cells.	Egg	[73]
Polyphenols	Resveratrol as a therapeutic agent for allergic rhinitis in mice	Resveratrol reduced symptoms of allergic rhinitis, inhibited activation of inflammatory cells, and reduced pro-inflammatory cytokine expression in nasal tissues.	Egg	[74]
Cn	Mouse model study	Cn ingestion significantly inhibited mastocytosis and suppressed intestinal anaphylaxis in mice, as evidenced by a decrease in the number of mast cells and a reduction in the severity of allergic reactions.	Egg	[76]
Cn	In vitro study using human mast cells	Inhibiting PDIs reduced mast cell degranulation and cytokine production, leading to a decrease in allergic symptoms in mice. Cn was also found to inhibit PDIs and reduce allergic symptoms in mice.	Allergenic Foods	[77]
Cn	In vitro study	The embedding rate of Cn was highest under the conditions of 1% NaOH modification at 80 °C for 3 h.	Peanut	[78]
EGCG	In vitro study	Lactoferrin and EGCG are generally safe, but conjugation may increase the risk of allergic reactions.	Milk	[79]
EGCG	Mouse model study	EGCG- BLG conjugate significantly reduces allergic reactions in a mouse model of food allergy.	Milk	[80]
EGCG	In vitro study	Both EGCG and PACs can improve the functional properties of SPI while reducing its allergenicity.	SPI	[81]
EGCG	Mouse model study	EGCG showed anti-inflammatory effects in a mouse model of OVA -induced allergic rhinitis.	Egg	[82]
EGCG conjugate	Covalent binding sites identified and IgE-binding ability evaluated	Conjugation had reduced IgE-binding ability compared with unmodified SPI, suggesting reduced allergenicity.	SPI	[83]
EGCG	Synergistic effects in alleviating OVA allergy	Combination of l-theanine and EGCG reduced serum levels of OVA -specific IgE and reduced allergic reaction	Egg	[84]
EGC and EGCG	Therapeutic effects on the allergic reaction of αs1-casein sensitized mice	Both EGC and EGCG reduced serum levels of αs1-casein-specific IgE and reduced histamine release from mast cells in αs1-casein sensitized mice.	Milk	[85]

Cn: curcumin; EGCG: epigallocatechin gallate; EGC: epigallocatechin; G: gliadin; IgE: immunoglobulin E; IgG: immunoglobulin G; IgG1: immunoglobulin G1; OVA: ovalbumin; PACs: proanthocyanidins; PDIs: protein disulfide isomerases; QU: quercetin; RES: resveratrol; SPI: soybean protein isolate; Th1: T-helper 1; Th2: T-helper 2.

2.4. New Insights and Recommendations for Preventing Food Allergies

A promising theoretical framework for preventing food allergies combines both structural and immunomodulatory approaches. The "Dual Action Allergy Mitigation Model" proposes that effective food allergy prevention requires (1) reducing allergenicity by modifying the allergenic protein structure using enzymatic or biopolymer-based methods and (2) modulating the immune response using bioactive compounds, such as polyphenols, to reduce inflammation and hypersensitivity reactions. By targeting both the allergen and the immune response, this dual approach could significantly reduce allergic reactions and potentially prevent sensitization in at-risk populations.

2.5. Future Prospects for Preventing Food Allergy

The future of food allergy prevention lies in a multifaceted approach that combines dietary, technological, and biotechnological innovations. Ongoing research into bioactive compounds, such as polyphenols, and their incorporation into functional foods shows promise for reducing allergic sensitization and symptoms. Advances in enzymatic treatments, biopolymer-based packaging, and biosensors in smart packaging for real-time detection of protein allergens could further limit exposure to allergenic proteins. Additionally, personalized nutrition, informed by genetic and immunological profiling, may enable tailored dietary interventions that prevent allergies before they develop. Collectively, these strategies suggest a future where food allergies can be more effectively managed or even prevented through natural, sustainable, and personalized approaches.

3. Conclusions

In conclusion, the collection of studies reviewed here suggests that foods can be treated with various compounds, such as biopolymers and polyphenolic compounds of digestive enzymes, to reduce their allergenic potential by different mechanisms. Biopolymers such as chitosan, alginate, and pectin can serve as additives that bind or intercalate into proteins to alter their structure and possibly their allergenic potential. Natural polyphenolic compounds like quercetin, resveratrol, curcumin, and epigallocatechin gallate, derived from fruits and vegetables, are believed to have anti-inflammatory properties that show promise in reducing allergic reactions and providing health benefits. Enzymes, including proteases such as pepsin, papain, and bromelain, and transferases like transglutaminase, modify the structure of proteins in foods through degradation, cross-linking, and oligomerization, with the potential for altering the allergenic properties of food proteins. While all of these hold promise, further research is imperative to comprehensively understand the safety and efficacy of these strategies in human subjects. The findings of this review offer insights into potential strategies to reduce the allergic potential of foods.

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Abbreviations

ACE: Angiotensin-converting enzyme; ALG: Alginate; BLG: β-lactoglobulin; C3G: Cyanidin-3-O-glucoside; CD: Circular dichroism spectroscopy; Cn: Curcumin; COS: Chitosan oligosaccharide; CS: Chitosan; DGP: Deamidated gliadin peptide; DNA: Deoxyribonucleic acid; EGC: Epigallocatechin; EGCG: Epigallocatechin gallate; ELISA: Enzyme-linked immunosorbent assay; EPIT: Epidermal immunotherapy; FcεRIs: High-affinity immunoglobulin E receptors; FTIR: Fourier transform infrared spectroscopy; G: Gliadin; IgE: Immunoglobulin E; IgG1: Immunoglobulin G1; IgG2a: Immunoglobulin G2a; IFN-γ: Interferon-gamma; IL: Interleukin; LM-COS: Low-molecular-weight chitosan oligosaccharides; MALDI-TOF-MS: Matrix-assisted laser desorption/ionization time-of-flight mass spectrom-

etry; Mtg: Microbial transglutaminase; OFC: Oral food challenge; OIT: Oral immunotherapy; OM: Ovomucoid; OVA: Ovalbumin; PAC: Proanthocyanidin; PDI: Protein disulfide isomerase; PPI: Pea protein isolate; QU: Quercetin; RES: Resveratrol; RBL-2H3: Rat basophilic leukemia-2H3; SCIT: Subcutaneous immunotherapy; SDS-PAGE: Sodium dodecyl sulfate–polyacrylamide gel electrophoresis; SG: Sargassum graminifolium; SIRT1: Sirtuin 1; SLIT: Sublingual immunotherapy; SPI: Soybean protein isolate; SPR: Surface plasmon resonance; Tgf: Transforming growth factor beta; Th1: T-helper 1; Th2: T-helper 2; TM: Tropomyosin; Tnf-α: Tumor necrosis factor alpha; Ttg: Tissue transglutaminase; USFDA: U.S. Food and Drug Administration; LMP: Low-methylated pectin; HMP: High-methylated pectin; T/C: Trypsin/chymotrypsin; TM: Tropomyosin.

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