

Gastrointestinal fate of food allergens and its relationship with allergenicity

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Abstract: Food allergens are closely related to their gastrointestinal digestion fate, but the changes in food allergens during digestion and related mechanisms are quite complicated. This review presents in detail digestion models for predicting allergenicity, the fates of food allergens in oral, gastric and duodenal digestion, and the applications of digestomics in mapping IgE-binding epitopes of digestion-resistant peptides. Moreover, this review highlights the structure–activity relationships of food allergens during gastrointestinal digestion. Digestion-labile allergens may share common structural characteristics, such as high flexibility, rendering them easier to be hydrolyzed into small fragments with decreased or eliminated allergenicity. In contrast, the presence of disulfide bonds, tightly wound α -helical structures, or hydrophobic domains in food allergens helps them resist gastrointestinal digestion, stabilizing IgE-binding epitopes, thus maintaining their sensitization. In rare cases, digestion leads to increased allergenicity due to exposure of new epitopes. Finally, the action of the food matrix and processing on the digestion and allergenicity of food allergens as well as the underlying mechanisms was overviewed. The food matrix can directly act on the allergen by forming complexes or new epitopes to affect its gastrointestinal digestibility and thereby alter its allergenicity or indirectly affect the allergenicity by competing for enzymatic cleavage or influencing gastrointestinal pH and microbial flora. Several processing techniques attenuate the allergenicity of food proteins by altering their conformation to improve susceptibility to degradation by digestive enzymes. Given the complexity of food components, the food itself rather than a single allergen should be used to obtain more accurate data for allergenicity assessment.

KEYWORDS

allergenicity, epitopes, food allergen, food matrix, food processing, gastrointestinal digestion

Practical Application

The review article will help to understand the relationship between food protein digestion and allergenicity, and may provide fundamental information for evaluating and reducing the allergenicity of food proteins.

1 | INTRODUCTION

Food allergy is an important public health problem affecting people all over the world. In the past few years, the prevalence of food allergy has increased significantly, affecting approximately 10% of the population (Seth et al., 2020). Allergic reactions to food manifest in a variety of allergic symptoms, including vomiting, diarrhea, flushing, urticaria, angioedema, acute bronchospasm, hypotension, dizziness, and sometimes fatal manifestations, such as anaphylactic shock (Florsheim et al., 2021; Renz et al., 2018). Most food allergens are proteins, and the priority food allergens are cereals containing gluten, crustacea, eggs, fish, milk, peanuts, sesame, and specific tree nuts (FAO/WHO, 2021). Food intake is the main approach for food allergens to cause allergies. After ingestion, most food allergens are primarily hydrolyzed by digestive enzymes in the gastrointestinal tract; subsequently, the remaining intact food allergens and peptides are transported from the lumen to the mucosa by intestinal epithelial cells (Sampson et al., 2018). As they enter the mucosal immune system, allergens and peptides containing specific epitopes bind to immune cells such as antigen-presenting cells (APCs) and B cells triggering a series of immune processes such as the production of immunoglobulin E (IgE) and the secretion of interleukin, which is a sensitization phase. With a second intake of the same allergen, they interact with specific IgE binding to high-affinity Fc receptor (FcεRI) on mast cells and basophils, leading to degranulation of these cells and the occurrence of allergic symptoms, which is an elicitation phase (Figure 1) (Renz et al., 2018; Sampson et al., 2018; Wai et al., 2017).

Generally, dietary allergenic proteins can be divided into two categories: digestion-resistant and digestion-labile proteins. Astwood et al. (1996) proved that many dietary allergenic proteins showed significant resistance to pepsin digestion compared with nonallergenic proteins. Evaluating the digestive stability of proteins through in vitro digestion is considered one of the important methods to evaluate the allergenic potential of proteins (Bøgh & Madsen, 2016; Sun et al., 2021). However, as research continues, the idea that food allergens are stable for digestion is being questioned by other researchers. Proteins unstable to digestive enzymes are still considered responsible for triggering severe allergic reactions. Several major food allergens, such as milk Bos d 8, egg Gal d 1, shrimp Pen a 1, apple Mal d 1, hazelnut Cor a 1.04, and celery Api g 1, were quite labile during digestion (Boddakayala et al., 2021; Souza, 2020). In fact, there are potent allergens that do not share the commonly attributed physicochemical properties. The classical definition of food allergens should probably be revised considering the latest findings about the impact of different physicochemical parameters on protein allergenicity, which is assessed by sensitizing and/or eliciting capacity (Bøgh & Madsen, 2016; Costa, Bavaro, et al., 2022; Costa, Villa, et al., 2022). Digestion can lead to rupture or exposure in conformational and/or linear epitopes of food proteins, resulting in changes in food sensitizing and allergenic capacity. This may also be the underlying reason why digestion-labile proteins remain allergenic after digestion.

A variety of factors can affect the digestion of food allergens and thus change their IgE-binding capacity and/or eliciting capacity. The food matrix influences the structural

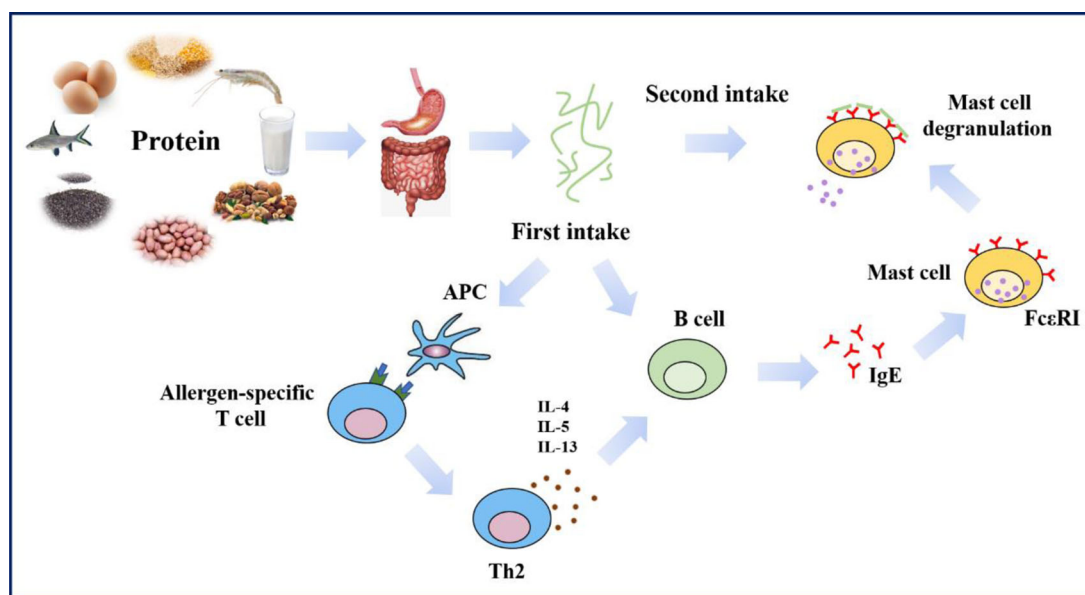


FIGURE 1 Schematic diagram of IgE-mediated allergic reaction

stability of food allergens (e.g., Gal d 1, Gal d 2, Mal d 1, Bos d 5, Cor a 8, and Ber e 1), which in turn affects their gastrointestinal digestion, epithelial transport, and ability to sensitize and/or elicit allergic reactions (Benedé et al., 2015; Pekar et al., 2018; Schulten et al., 2011). In addition, different processing processes, including heat treatment represented by cooking and baking and nonthermal treatment represented by high pressure and ultrasound, can lead to changes in the physicochemical properties and structure of food proteins, thus affecting the digestion and allergenic characteristics of food allergens (Costa, Bavaro, et al., 2022; Costa, Villa, et al., 2022). Thus, it is necessary to discuss the underlying mechanisms by which the food matrix and food processing affect food digestion and allergenicity.

Despite the fact that food allergens are closely related to their gastrointestinal digestion fate, the changes in food allergens during digestion and the related mechanisms of action are quite complicated. This review presents in detail gastrointestinal digestion models for predicting allergenicity, the fates of food allergens in oral, gastric and duodenal digestion, and the applications of digestomics in mapping IgE-binding epitopes of digestion-resistant peptides. Moreover, this review also highlights the structure–activity relationships of food allergens during gastrointestinal digestion as well as the underlying mechanisms by which the food matrix and food processing affect the digestion and allergenicity of food allergens.

2 | GASTROINTESTINAL FATE OF FOOD ALLERGENS

2.1 | Gastrointestinal digestion models for predicting allergenicity

At present, the European Food Safety Authority (EFSA), Codex Alimentarius Commission (CAC), Food and Agriculture Organization of the United Nations (FAO), and World Health Organization (WHO) have established different guidelines to evaluate the allergenicity of proteins (EFSA Panel on Dietetic Products et al., 2016; EFSA Panel on Genetically Modified Organisms, 2011; Ladics, 2008; Pali-Schöll et al., 2019). As one of the important steps, gastrointestinal digestion models have been widely used in the potential allergenicity evaluation of proteins, such as enzymatic cross-linked proteins, processed proteins, and recombinant proteins. For example, X. Li, Bai, et al. (2020) used simulated gastrointestinal digestion to evaluate the digestibility of polyphenol oxidase cross-linked bovine α -lactalbumin polymer and found that the cross-linked α -lactalbumin showed a higher digestive stability and lower IgE-binding capacity than α -lactalbumin. In

addition, M. Liu et al. (2019) subjected pressure-treated shrimp (*Litopenaeus vannamei*) to simulated gastrointestinal digestion and found that pressure treatment reduced the digestive stability and the immunoreactivity of shrimp.

Several in vivo digestion studies have been conducted on humans (Polovic et al., 2007; Troost et al., 2001). However, in vivo digestion tests are rarely used due to ethical limitations and poor repeatability, although such tests can accurately reflect physiological processes, allowing a more realistic and accurate assessment of allergens (Alegría et al., 2015; Bohn et al., 2018; Thuenemann, 2015). As a result, several attempts have been made to develop in vitro digestion models, which have the characteristics of simple operation; rapid, low cost, short experiment period; and high repeatability (Guerra et al., 2012; C. Li, Yu, et al., 2020). In vitro digestion models can be divided into static simulated digestion models and dynamic simulated digestion models according to the difference in digestion conditions. In the dynamic simulated digestion models, the physical and chemical conditions (digestive enzyme concentrations, pH, ionic strength, emptying rate, etc.) at different digestion stages will evolve with time; however, static simulated digestion models do not take into account these evolutions over time (Dupont & Mackie, 2015). Recently, a semidynamic simulated gastrointestinal digestion model, which builds upon a static model that simplifies the dynamic digestion conditions (e.g., acidification, gastric fluid and enzyme secretion and emptying) related to the gastric phase of digestion, has also been used as a simulated digestion model (Mulet-Cabero et al., 2020).

Most studies use static simulated digestion models as food digestion tools because they are easy to use, cheap, and do not require specific equipment (Feunteun et al., 2018). These static simulated digestion models consist of two or three digestive steps (oral, gastric, and intestinal) and use a series of stirred vessels to simulate a bioreactor. A single set of biochemical conditions (e.g., temperature, enzymes, pH, and bile salts) were simultaneously reproduced in these vessels. In addition, these in vitro static models usually specify a number of parameters such as pH and duration of digestion, amount and type of digestive enzymes used, stirring/agitation speed, and amount of food sample. Although the static simulated digestion model is widely used, it also has obvious disadvantages, such as the significant differences in the use of digestion parameters in different individual models and difficulty in the control of digestive conditions, which hinder the possibility of comparing results across research teams (Minekus et al., 2014). For this reason, a general standardized and practical static digestion method based on physiologically relevant conditions was proposed by Infogest (Minekus et al., 2014), which can help minimize some of these disadvantages and can be used in the allergenicity assessment

of proteins. Villa et al. (2021) used this static digestion method to investigate the effect of autoclaving and in vitro digestion on the allergenicity of milk proteins incurred in sausage and found that autoclaving induced a higher digestibility and eliminated the IgE-binding capacity of milk proteins following digestion. Mattar et al. (2021) digested the muffins containing eggs and peanuts in vitro following the protocol of this standardized static digestion and found that the immunoreactivity of egg and peanut allergens disappeared after digestion.

Dynamic in vitro digestion models have been developed over the past few decades. These systems are composed of different devices that best mimic physiological conditions in the human or animal digestive tract. Compared to static models, these dynamic models allow simulation of dynamic aspects of digestion, such as transportation of digested food, continuous secretion of digestive juices, different enzyme concentrations, and changes in pH over time. A dynamic gastrointestinal system (Bionic Rat Model II+) composed of an artificial silicone stomach and duodenum was constructed to simulate digestion (Chen et al., 2013; Huang et al., 2020; Qing et al., 2019). Gastric digestion was initiated by pouring the oral digesta into the artificial stomach through the esophagus model, and the gastric digesta was passed through the artificial pylorus to initiate duodenal digestion. During digestion, the in vivo movement of the stomach and duodenum was mimicked using rolling extrusion plates, and the artificial gastric and intestinal fluids were continuously delivered with a syringe pump. Huang et al. (2020) used this dynamic gastrointestinal system to simulate the digestion of soybean protein isolate (SPI) and fermented soybean protein isolate (FSPI) and found that the IgE-binding capacity of FSPI was significantly lower than that of SPI at 30 min of gastric and intestinal digestion. In addition, Guo et al. (2021) set up a simplified dynamic digestion system, which consists of two consecutive compartments simulating the stomach and small intestine; the sensors are equipped to control the temperature and pH, and the micro peristaltic pumps are equipped to control the flow rate and time. This dynamic digestion system was applied by Guo et al. (2021) to compare the digestibility and potential allergenicity (reflected in IgG/IgE-binding ability and activation of basophils) of raw shrimp extracts in static and dynamic digestion systems. The results showed that tropomyosin exhibited better digestive stability and potential allergenicity in the dynamic digestive system than in the static digestive system. Although there are still few studies on allergen digestion using dynamic digestion models, it is the future trend of food allergen digestion research because it has irreplaceable advantages compared with the static digestion model.

2.2 | Digestive process of food allergens

2.2.1 | Oral digestion

Food digestion is a continuous and dynamic process in the human body (Figure 2). It starts in the mouth, where chewing and salivation are two complementary oral mechanisms (Sahbaz et al., 2017). Especially for solid foods, oral processing can reduce the size of food and facilitate its absorption (Tamura et al., 2017). Some researchers have overlooked the significance of oral digestion studies because of the short duration of the oral phase during food digestion, but recent research suggests that this idea may be challenged (Peyron et al., 2021). The mouth contains saliva, which is a complex viscous aqueous medium containing 99.5% water, 0.3% protein/enzymes, and various electrolytes, such as sodium, potassium, calcium, magnesium, phosphate, and bicarbonate (Salles et al., 2010). Meanwhile, approximately 30 different enzymes have been found in human saliva (C. Li, Yu, et al., 2020). Among them, human salivary α -amylase may degrade food glycoproteins by cleaving their 1,4-glycosidic bond and affects allergenicity, as some allergens are glycoproteins (Pekar et al., 2018). Researchers found that oral digestion may affect food allergenicity in the following ways: (a) α -amylase may lead to epitopes modification of plant food allergens or reveal new epitopes and (b) glycoproteins and other food matrix compounds may form stable complexes during food processing, which reduces the degradation of glycoproteins by α -amylase and affects food allergenicity (Pali-Schöll et al., 2018; Rao et al., 2020).

2.2.2 | Gastric digestion

After oral digestion, the ingested proteins are swallowed. After passing quickly through the esophagus, the proteins enter the stomach and denature under the action of gastric acid. On average, the stomach secretes 2–3 L of gastric juice (pH 2) per day, which contains gastric acid, salts, and digestive enzymes, mainly pepsin and lipase (Bornhorst & Paul Singh, 2014). In the process of gastric digestion, many internal and external factors, such as the amount and activities of pepsin, the food matrix (e.g., fat, protein and carbohydrate) and the protein origin, can affect protein digestion and allergenicity (Dima et al., 2020; Somaratne et al., 2020).

During gastric digestion, the amount and activities of pepsin can significantly affect the digestive stability of allergens, leading to changes in sensitizing and eliciting capacity. Gámez et al. (2015) found significant differences in the IgE-binding ability of tropomyosin after 60 min treatment with pepsin of different activities; the

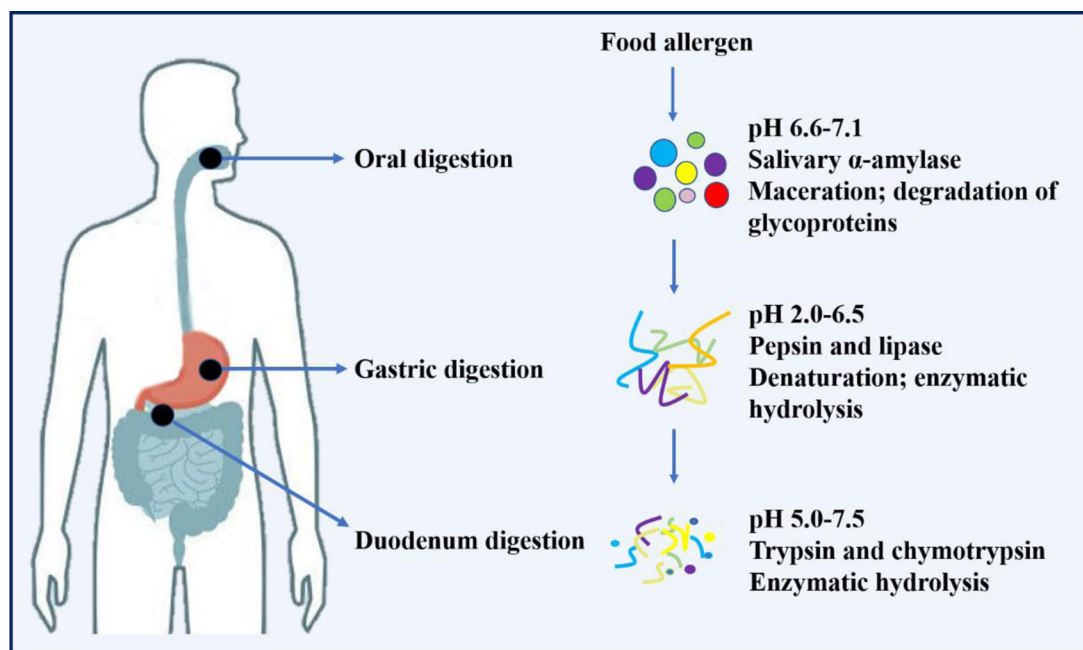


FIGURE 2 Digestive process of food allergens in the gastrointestinal tract

IgE-binding ability of tropomyosin decreased under the treatment of 0.1 U/ μ g pepsin, while it almost disappeared under 10 U/ μ g pepsin treatment. Moreover, changes in pH during food intake can also affect protein digestion and then influence protein allergenicity (Pekar et al., 2018). The optimal pH of pepsin is between 1.8 and 3.2, but the gastric pH can rise from 2 during fasting to 6.5 with food intake and then decrease again with time (Gan et al., 2018; Lu et al., 2010). Rao et al. (2018) found that digested peanuts at pH 3 showed a lowering IgE-binding capacity after 120 min of digestion. However, peanut proteins were not digested and had no effect on IgE reactivity when gastric digestion was performed at pH 6.5 (Rao et al., 2020). In addition, Untersmayr et al. (2005) conducted an interesting study on the effects of gastric digestion on codfish allergenicity. By increasing the pH value during gastric digestion from 1.25 to 5, they found that the IgE-binding capacity of digested codfish protein was 10,000-fold reduced. It was also clearly indicated that in the effector phase of food allergy, when IgE has been formed and fixed to effector cells via high-affinity IgE receptors, gastric digestion can significantly alter the response pattern of the immune system to allergens (Untersmayr & Jensen-Jarolim, 2006; Untersmayr et al., 2005). Surprisingly, the digestive stability to pepsin and IgE-binding capacity of allergens from different origins are different. For example, the digestive stability of tropomyosin depends on its origin: shrimp tropomyosin was stable during in vitro gastric digestion under the condition of 1 U/ μ g pepsin and pH 3, while chicken tropomyosin degraded quickly. As a result, shrimp tropomyosin has significantly higher IgE-binding capacity than chicken

tropomyosin (Klueber et al., 2020). Therefore, the above factors should be considered when evaluating the gastric digestive stability and allergenicity of food allergens.

2.2.3 | Duodenum digestion

After gastric digestion, the digestion of food is continued in the small intestine. Most of the protein digestion occurs in the duodenum. Pancreatic enzymes work with other digestive enzymes produced by the lining of the small intestine together to breakdown food components, with trypsin and chymotrypsin playing a major role in protein digestion (Joye, 2019; Sedighi et al., 2019). Previous studies only considered the allergenicity of proteins during gastric digestion (Keshavarz et al., 2020; Plundrich et al., 2015), but proteins may be further hydrolyzed by trypsin and chymotrypsin once they enter the small intestine (Macierzanka et al., 2012). Gastrointestinal models involving intestinal proteolysis have been developed specifically to assess protein allergenicity (Dupont & Mackie, 2015). For example, peach lipid transfer protein, which is the main allergen in peach, is mainly hydrolyzed by trypsin and is resistant to pepsin and chymotrypsin; intact proteins and some high molecular weight peptides can be recognized by the patient's serum (Cavatorta et al., 2010). Toomer et al. (2015) conducted a simulated gastric (0.8 U/ μ g pepsin; pH 2; 37°C; 60 min), intestinal (32 U/ μ g pancreatin; pH 7.5; 37°C; 60 min), and gastrointestinal digestion (60 min of gastric digestion and 30 min intestinal digestion) of total shrimp proteins, which

found that only proteins that were stable to pepsin, trypsin, and chymosin simultaneously might trigger an immune response. Since both the stomach and intestine contain digestive enzymes that may hydrolyze allergens, it is also important to further study the changes in digestive characteristics and potential allergenicity of allergens during intestinal digestion.

2.3 | Digestomics of food allergens

Protein resistance to gastrointestinal digestion has been discussed as an important factor in allergenicity. Most of the previous reports on gastrointestinal digestion of allergens have focused on the fate of intact proteins and their IgE-binding potential (Lang et al., 2015). Moreover, food allergens digested in the stomach and/or intestines do not necessarily eliminate their allergenicity (Di Stasio, d'Acerno, et al., 2020; Mamone et al., 2015). Notably, most of the current studies evaluating the digestive stability of allergens only monitored the degradation of allergens using protein electrophoresis and western blot experiment, while the immunologically active peptide fragments generated during protein digestion were analyzed in only a few studies (Di Stasio, Tranquet, et al., 2020; Pfeifer et al., 2015). Mass spectrometry (MS)-based digestomics can be used to characterize the digestion-resistant peptides of food allergens and compare them with truly known linear IgE epitopes to further clarify the immunodominant allergen epitopes of food proteins (De Angelis et al., 2017; Mattison et al., 2014). Di Stasio et al. (2017) identified nearly 800 peptides from peanut digestive products and found that GNIFSGFTPEFLEQA, IETWNPNNQEFECAG, DEDEYEYD, and VTVRGGLRILSPDRK could bind to IgE, resulting in allergic reactions. In addition, Korte et al. (2017) identified 1183 peptides from hazelnut digestive products; of these, 130 peptides carried known IgE-binding epitopes that may represent sensitizers for hazelnut allergy. Recently, Radosavljević et al. (2020) first identified digestion-resistant peptides released from whole cow's milk by pepsin digestion and found that 97% of peptides were derived from casein and overlapped with the known IgE epitopes of milk allergens. Therefore, the use of digestomics makes it possible to monitor the IgE-binding epitopes that are released sequentially after the digestion of allergens. Since the key to food allergy is the presence of IgE-binding epitopes in digestion products, the identification of allergens containing IgE-binding epitopes by digestomics can improve the understanding of allergenic determinants and provide a theoretical basis for the analysis of food allergens.

3 | STRUCTURE–ACTIVITY RELATIONSHIPS OF FOOD ALLERGENS DURING GASTROINTESTINAL DIGESTION

Evaluating the digestive stability of proteins is considered one of the important methods to predict the allergenic potential of proteins (Bøgh & Madsen, 2016). However, some studies have shown that proteins unstable to digestive enzymes can still possess sensitizing and eliciting capacity (Bannon et al., 2003; Bøgh & Madsen, 2016; Herman & Roper, 2021). This phenomenon suggests that digestive stability of food allergens is not necessary to trigger an allergic reaction. The allergenic potential of proteins cannot be evaluated only by their tolerance to digestion but may be related to the structural changes of proteins during digestion. To further explore the underlying mechanisms responsible for the sensitizing and eliciting capability of food allergens, it is particularly important to overview the structural changes and allergenic properties of food proteins during digestion as well as their structure–activity relationships (Table 1).

3.1 | Structural characteristics of food allergens that are susceptible to reduce or even loss the allergenicity during digestion

Food allergens are mostly proteins or glycoproteins with molecular weights between 3 and 90 kDa, thereby enabling immune recognition (Untersmayr & Jensen-Jarolim, 2006). However, after food allergens enter the gastrointestinal environment through the oral route, they will be hydrolyzed to different degrees due to different inherent structures and exposure sites under the action of digestive enzymes such as pepsin, trypsin, and chymotrypsin. Some food allergens are hydrolyzed by digestive enzymes into small peptide fragments with decreased sensitizing and allergenic capacity (Figure 3a). Takagi et al. (2005) found that chicken egg white ovomucoid (OVM) was degraded into many peptides with sizes ranging from 4.5 to 6.0 kDa after gastric digestion; these small OVM peptides produced by pepsin were detected to bind to serum IgE in only one-fifth of OVM allergic patients, and their IgE-binding capacity was significantly reduced compared with that of intact OVM (Takagi et al., 2005). In other cases, food allergens undergo substantial structural changes in the gastrointestinal tract and are hydrolyzed by digestive enzymes into a series of peptide fragments with small molecular weight, which will not react with structures involved in antigen recognition or presentation. This means that it can trigger neither an

TABLE 1 Changes in the structure and allergenicity of food allergens during gastrointestinal digestion

Food source	Allergen	Digestion conditions	Structure changes	Sensitizing and allergenic changes	References
Chicken egg white	Ovomucoid	Gastric digestion: 100 U pepsin/mg protein; pH 2.0; 37°C; 1 h.	Degraded into many small peptides.	Decreased egg white-specific IgE level.	Takagi et al. (2005)
Cow milk	α -Lactalbumin	Digestion in 3-week-old Brown Norway rats by oral administration (200 μ g protein/rat/time).	Damaged conformational epitopes.	Decreased the specific IgG1 and IgE-binding ability.	Madsen et al. (2014)
Cow milk	α -Lactalbumin	Gastric digestion: 22.75 U pepsin/mg protein; pH 3.0; 37°C; 2 h. Intestinal digestion: 3.45 U trypsin/mg protein; 0.04 U chymotrypsin/mg protein; pH 7.0; 37°C; 2 h.	Exposed linear epitopes.	Reduced IgG IC ₅₀ values; increased IgE-binding rates and IgG-binding abilities; increased degranulation ability and β -Hex release of KU812 cell.	X. Wang, Tu, Liu, et al. (2021)
Cow milk	β -Lactoglobulin	Gastric digestion: 180 U pepsin/mg protein; pH 2.5; 37°C; 2 h. Intestinal digestion: 34.5 U trypsin/mg protein; 0.44 U chymotrypsin/mg protein; pH 6.5; 37°C; 2 h.	Digested into peptide fragments with smaller molecular weight.	No specific IgG and IgE responses.	Bøgh et al. (2013)
Cow milk	Caseins	Gastric digestion: 2375 U pepsin/ml protein solution; pH 3.6; 37°C; 1 h.	Aggregation of IgE epitopes in short digestion-resistant peptides.	Retained IgE-binding epitopes.	Radosavljević et al. (2020)
Peanut	Ara h 1	Gastric digestion: 182 U pepsin/mg protein; pH 2.5; 37°C; 2 h. Intestinal digestion: 34.5 U trypsin/mg protein; 0.44 U chymotrypsin/mg protein; pH 6.5; 37°C; 15 min.	Aggregation of IgE epitopes in digests.	Retained both sensitizing, IgE-binding and eliciting capacity.	Bøgh et al. (2012)
Peanut	Ara h 1, Ara h 3	Oral digestion: 75 U salivary amylase/ml protein solution; pH 7; 37°C; 2 min. Gastric digestion: 2000 U pepsin/ml protein solution; pH 3; 37°C; 2 h. Intestinal digestion: 100 U trypsin/ml protein solution; 25 U chymotrypsin/ml; pH 7; 37°C; 2 h.	Hydrolyzed into digestion-resistant fragments with the preserved core structure.	Retained the IgE reactivity.	Prodic et al. (2018)
Peanut	Ara h 3	Gastric digestion: substrate: pepsin ratio 500:1; pH 2.5; 37°C; 2 h.	Hydrolyzed into peptide fragments with small molecular weight.	No IgE-binding capacity.	van Bostel et al. (2008)

(Continues)

TABLE 1 (Continued)

Food source	Allergen	Digestion conditions	Structure changes	Sensitizing and allergenic changes	References
Peanut	Ara h 2, Ara h 6	Intestinal digestion: substrate: trypsin ratio 1000: 1.36; pH 8; 37°C; 90 min.	Tightly coiled helical structures connected by disulfide bonds.	Retained the IgE-binding potency and allergenic capacity.	Apostolovic et al. (2016) and Prodic et al. (2018)
Hazelnut	Cor a 14, Cor a 8	Oral digestion: 75 U α -amylase/ml protein solution; pH 7; 37°C; 2 min. Gastric digestion: 1950 U pepsin/ml protein solution; pH 3; 37°C; 2 h. Intestinal digestion: 100 U trypsin/ml protein solution; pH 7; 37°C; 2 h.	Tightly wound α -helical structure connected by disulfide bonds.	Retained the IgE epitopes and immunogenicity.	Korte et al. (2017)
Hazelnut	Cor a 12, Cor a 13	Oral digestion: 75 U α -amylase/ml protein solution; pH 7; 37°C; 2 min. Gastric digestion: 1950 U pepsin/ml protein solution; pH 3; 37°C; 2 h. Intestinal digestion: 100 U trypsin/ml protein solution; pH 7; 37°C; 2 h.	The existence of hydrophobic central domain.	Hindered the digestion and hydrolysis; retained IgE-binding for proteins.	Korte et al. (2017)
Apple, peach, and hazelnut	Bet v 1 homologs	Gastric digestion: 10.56 U pepsin/ml SGF; pH 2.5; 37°C; 1 h.	Partially expanded the protein spatial structure due to structural flexibility.	Eliminated histamine release capacity and reduced allergenic activity.	Sancho et al. (2011)
Peach	Lipid transfer protein	Gastric digestion: substrate: pepsin ratio 60.5: 1; pH 2; 37°C; 3 h. Intestinal digestion: substrate: trypsin ratio 60.5: 1; substrate: α -chymotrypsin ratio 60.5: 1; pH 7.8; 37°C; 4 h.	The core of Pru p 3 linked by the disulfide bridges.	Potential to be recognized by IgE.	Cavatorta et al. (2010)
Kiwi	Kiwifruit protein	Gastric digestion: 10 U pepsin/ μ g protein; pH 2, 2.5, 3, 5, 7; 37°C; 1 h.	Expanded the protein folding structure and exposed new epitopes.	Increased IgE reactivity and sensitization capacity.	Lucas et al. (2008)
Tomato peel/pulp	Sola 1 7	Gastric digestion: 182 U pepsin/mg protein; pH 2; 37°C; 1 h. Intestinal digestion: 24.7 U pancreatic porcine lipase/mg protein; 34.5 U trypsin/mg protein; 34.5 U α -chymotrypsin/mg protein; pH 6.5; 37°C; 1 h.	Partially unfolded the structure and unmasked IgE epitopes.	Increased IgE-reactivity.	Martin-Pedraza et al. (2021)

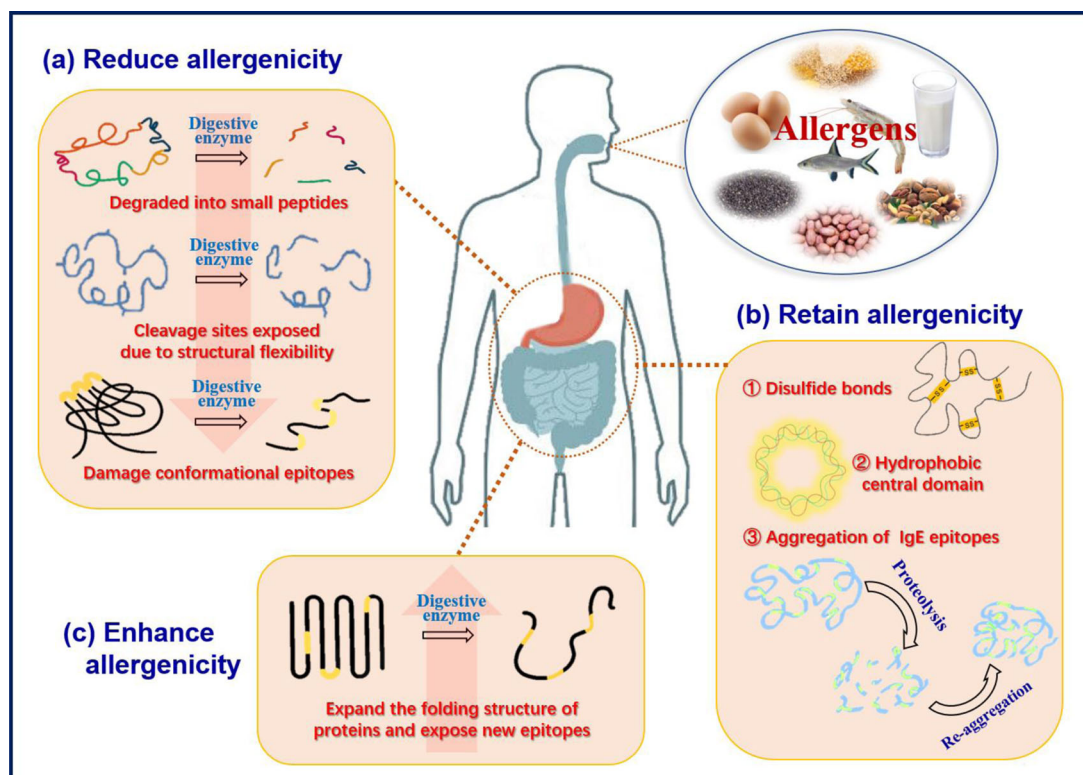


FIGURE 3 Structure–activity relationships of food allergens during gastrointestinal digestion. (a) Structural characteristics of food allergens that are susceptible to reduction or even loss of allergenicity during digestion; (b) Structural characteristics of food allergens that retain allergenicity during digestion; (c) Structural characteristics of food allergens that enhance allergenicity during digestion

immunogenic nor an allergic response. van Boxtel et al. (2008) showed that the legumin allergen from peanuts (Ara h 3) was degraded into peptide fragments with molecular weight less than 9 kDa after pepsin digestion for 2 h and that these short peptides no longer retained any IgE-binding ability. Similarly, gastroduodenal digestion of β -lactoglobulin resulted in smaller peptide fragments with molecular weight less than 4.5 kDa and succeeded in completely abolishing the sensitizing capacity (Bøgh et al., 2013).

These digestion-labile allergens may share common structural characteristics (Figure 3a). First, the flexibility of the protein structure makes the cleavage sites easily exposed to digestive enzymes (Pekar et al., 2018), rendering it more susceptible to be hydrolyzed into small fragments with decreased or eliminated allergenic potential. Mapping of the digestion products of an allergenic lipid transfer protein from peach revealed three chymotryptic sites and one tryptic site existing in loop regions on the protein surface (Abdullah et al., 2016). Allergenic homologs of Bet v 1 in apple, peach, and hazelnut were also found to partially expand the protein spatial structure due to their structural flexibility under acidic gastric conditions, and at the same time, their exposed IgE-binding sites were rapidly degraded by

pepsin, which contributes to the loss of histamine release and the reduced allergenic capacity (Sancho et al., 2011). These results suggest that the flexibility of the protein structure facilitates the access of digestive enzymes to peptide bonds, which may destroy allergenic epitopes and thus induce a reduction in allergenicity or even immune ignorance.

Furthermore, some studies have shown that conformational epitopes are more easily damaged than linear epitopes during digestion (Bøgh et al., 2013; Martín-Pedraza et al., 2021; Wu et al., 2017). Conformational epitopes are susceptible to acidic and proteolytic environments during gastrointestinal digestion due to changes in protein conformation, whereas linear epitopes are only destroyed by proteolysis due to the location of a cleavage site (Bøgh & Larsen, 2021; Madsen et al., 2014). Cow's milk allergen (α -lactalbumin) was found to lose its conformational epitopes due to acidic and proteolytic environments during gastrointestinal digestion, which induced a decrease in its specific IgG1- and IgE-binding ability (Madsen et al., 2014). Likewise, the loss of linear epitopes induced by proteolysis during gastrointestinal digestion could also reduce the sensitizing and allergenic capacity of some allergens (T. Li et al., 2021; Villa et al., 2021).

3.2 | Structural characteristics of food allergens that retain allergenicity during digestion

There are also a considerable number of food allergens that are highly resistant to digestion. Most studies have confirmed that when food allergens have strong resistance to digestion, they will not only increase the probability of encountering cells that induce the mucosal immune system but also retain adequate structure and size to be recognized by immune cells, thereby maintaining their inherent allergenicity (Bøgh & Madsen, 2016; Pekar et al., 2018), as depicted in Figure 3b.

The presence of disulfide bonds within protein molecules may help them resist gastrointestinal digestion by stabilizing the three-dimensional structure of food allergens in extreme gastrointestinal environments or by preventing the dislocation of digestive fragments and stabilizing IgE-binding epitopes, thus maintaining their sensitizing capacity (Pekar et al., 2018). Peanut allergens Ara h 2 and Ara h 6 are known to possess four tightly coiled helical structures connected by disulfide bonds and are resistant to proteolysis. The resulting digestion-resistant peptides form a tight digestion-resistant core maintained by disulfide bonds and produce a comparable IgE-binding capacity to intact allergens (Apostolovic et al., 2016). The importance of disulfide bonds for the digestion resistance and sensitizing capacity of Ara h 2 and Ara h 6 was confirmed by another study (Prodic et al., 2018). Similar to Ara h 2 and Ara h 6, prolamin superfamily allergens, such as 2S albumins, cereal prolamins, nonspecific lipid transfer proteins (nsLTP), and cereal α -amylase trypsin inhibitors, displayed high structural stability during gastric digestion and preserved their allergenicity after passing the digestion process due to their tightly wound α -helical structure, which was connected by 4–5 intramolecular stable disulfide bonds (Costa, Bavaro, et al, 2022; Korte et al., 2017). It is thus likely that the steric hindrance around disulfide bonds in allergens makes it inaccessible for digestive enzymes to access the cleavage sites, thus allowing allergens to retain their allergenicity after digestion.

In addition, the hydrophobic domains of some food allergens can protect the core structure of proteins from being damaged during gastrointestinal digestion, thus maintaining the allergenicity of allergens. Korte et al. (2017) found that the core structure of oil globulin Cor a 12 and Cor a 13 was located in the hydrophobic central domain within the oil droplet during gastric digestion, which can hinder the digestion and hydrolysis of pepsin and maintain the sensitizing capacity of allergens. Prodic et al. (2018) found that the N-terminal and C-terminal

noncore flanking regions of peanut allergens Ara h 1 and Ara h 3 were prone to be hydrolyzed into high molecular weight digestion-resistant fragments with the preserved core structure of allergens, which retained the IgE reactivity.

It is worth noting that some food allergens are hydrolyzed into a large number of small molecular peptides after gastrointestinal digestion, but their digestion products retain both sensitizing and eliciting capacity after digestion, almost comparable to intact allergens (Prodic et al., 2018). This was suggested to be a result of the survival of IgE-binding epitopes during digestion. Some epitopes are even aggregated to complexes of larger sizes in the gastrointestinal tract and then trigger the immune response in susceptible individuals. Bøgh et al. (2012) found that the IgE epitopes in Ara h 1 digests were in an aggregated state resembling the original folding of the intact Ara h 1, making the survival of conformational epitopes possible. Similarly, the short digestion-resistant peptides of cow's milk allergens caseins can aggregate and re-form functional IgE-binding epitopes (Radosavljević et al., 2020). The survival and even aggregation of IgE-binding epitopes during gastrointestinal digestion are a prerequisite for B-cell recognition and antibody production (Untersmayr & Jensen-Jarolim, 2006). Hence, it is critical for the sensitizing and eliciting capacity of allergens.

3.3 | Structural characteristics of food allergens that enhance allergenicity during digestion

Gastrointestinal digestion usually reduces or retains the allergenicity of food proteins, but in rare cases, proteolysis may also lead to increased allergenicity due to exposure of new epitopes that are not accessible prior to digestion (Figure 3c). Lucas et al. (2008) found that gastrointestinal digestion expanded the original protein folding structure of kiwi allergens, thus obtaining a great deal of hydrolyzed peptides with new epitopes (Lucas et al., 2008); these digested hydrolysates can combine with more IgE to enhance their allergenicity. Moreover, tomato peel/pulp nsLTP (Sola l 3) showed increased immunoreactivity after gastrointestinal digestion with an IgE-binding value of 185% compared to the undigested protein, suggesting that the partial unfolding of Sola l 3 under acidic gastric conditions might unmask IgE epitopes (Martín-Pedraza et al., 2021). Similar results have been described for α -lactalbumin, where some linear epitopes retained on the antidigestive stable peptides were exposed after gastroduodenal digestion and played a more important role in triggering allergic reactions than conformational

epitopes, resulting in increased allergenicity after digestion (X. Wang, Tu, Liu, et al., 2021).

The formation of aggregates is generally considered to be the main factor for increasing the IgE-binding capacity of allergens when new epitopes are formed in the aggregates; in the aggregated forms of some allergens (e.g., parvalbumins and lipocalins), new conformational epitopes may become accessible (Costa, Villa, et al., 2022). In the case of parvalbumins, the formation of amyloid fibers increases their IgE-binding capacity by facilitating passage through the intestinal epithelial barrier (Martinez et al., 2015; Sánchez et al., 2016). Likewise, the formation of aggregates in lipocalins impedes their digestion, alters the transport mechanism through the epithelial barrier, and increases their allergenicity (Costa, Villa, et al., 2022).

4 | FOOD MATRIX INFLUENCES DIGESTION AND ALLERGENICITY OF FOOD ALLERGENS

A food matrix is a complex system that contains all the components that make up the food. Allergens are usually ingested by the body as one of the food components, and the food matrix has a vital influence on the digestion of allergens. Figure 4 shows the approaches by which the food matrix influences the digestion and allergenicity of food allergens, which is mainly reflected in two aspects. On the one hand, the food matrix directly acts on the allergen to further affect its gastrointestinal digestibility, mucosal absorption kinetics and performance in the immune system, thereby affecting its allergenicity; on the other hand, the food matrix can act on the digestive environment and further affect the digestion and allergenicity of allergens.

4.1 | Food matrix acts directly on allergens to affect their digestion and allergenicity

Food matrix components, including nonallergenic proteins, carbohydrates, lipids, and other components, can act directly on allergens to affect their digestion and allergenicity, but their modes of action are varied (Table 2).

The protein-rich food matrix (e.g., hazelnut and peanut extract) delays gastrointestinal digestion and epithelial transport of food allergens through the Caco-2 monolayer, thereby reducing their IgE-binding capacity (Schulten et al., 2011). This is mainly because nonallergenic proteins can create a competitive environment for enzymatic cleavage and delay the hydrolysis of food allergens by digestive enzymes. Simultaneously, nonallergenic proteins compete with allergens for active epithelial transport, reducing the

epithelial transport rates of allergens and their IgE-binding capacity (Rahaman et al., 2016; Schulten et al., 2011).

The effect of carbohydrates in the matrix on allergens differs from that of nonallergenic proteins. Jiménez-Saiz et al. (2013) studied the IgE-binding ability and *in vitro* gastrointestinal digestibility of egg allergens in the presence of pectin, gum arabic, and xylan. The results showed that allergens interacted with polysaccharides to form complexes that were strongly recognized by IgE, increased their IgE-binding ability, and hampered their digestibility. However, glycation involving carbohydrates occurring during heat treatment will not only change the conformation of allergens but also affect their biological parameters, such as digestibility and allergenicity (Costa, Bavaro, et al., 2022). A very typical consequence of conformational changes in allergens is related to the formation of aggregates (complex macrostructures), which may contribute not only to masking existing epitopes but also to generating new epitopes that can activate the IgE response (Costa, Bavaro, et al., 2022; Costa, Villa, et al., 2022). The allergens Ara h 1 in peanuts form higher order structures corresponding to trimer molecular weight once they have experienced the Maillard reaction in the presence of various sugars (incubation at 55°C for 10 days). They were found to bind higher levels of IgE and be more resistant to heat and digestion by gastrointestinal enzymes (Maleki, Chung, et al., 2000). Moreover, the modification of β -lactoglobulin with arabinose (incubation at 55°C for 1 h) not only enhanced the aggregation degree of allergens but also increased resistance to digestive enzymes and reduced allergies in the human body (X. Wang, Ye, et al., 2021).

In addition, the food matrix can also regulate allergic potential by forming ligands with allergens. It has been proven that the interaction between food allergens and their ligands leads to structural changes that affect their thermostability, digestive digestion, and allergenicity (Costa, Villa, et al., 2022; Finkina et al., 2020). Lipid ligands change the degradation process of lipid-bound food allergens in the human gastrointestinal tract, affect their passage through the epithelial barrier, and reduce or increase the efficiency of their interaction with IgE (Jappe et al., 2019). For example, the presence of lipid ligands reduced the degradation rate of the lentil allergen Len c3, and its allergenic capacity can be retained after gastroduodenal digestion (Finkina et al., 2020). Conversely, ligand binding can increase the susceptibility of allergenic nonspecific lipid transfer proteins to gastroduodenal proteolysis (Abdullah et al., 2016), which may reduce the sensitizing and/or eliciting capacity. Furthermore, natural compounds such as catecholamines, flavonoids, metal ions, and stilbenoids in the food matrix can form ligands with allergens (Chruszcz et al., 2021).

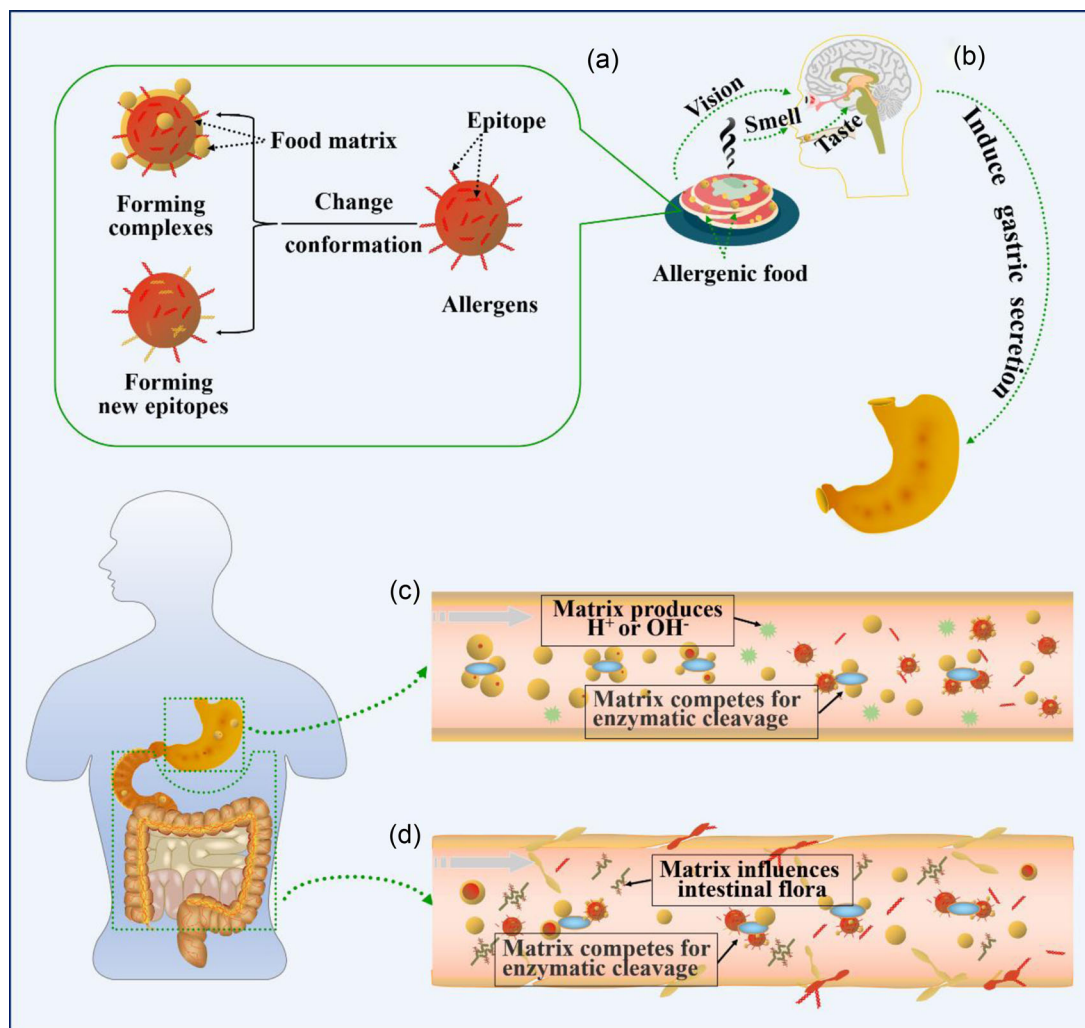


FIGURE 4 Approaches by which the food matrix influences the digestion and allergenic properties of food allergens. (a) The food matrix changes the conformation of allergens by forming complexes or new epitopes; (b) the food matrix induces the secretion of digestive juice through sensory organs; (c) the food matrix competes with allergens for enzymatic cleavage or changes the pH value of gastric juice in the gastric phase; (d) the food matrix competes with allergens for enzymatic cleavage and epithelial transport or influences the intestinal flora in the intestinal phase

Taken together, the food matrix acts on allergens in unique ways, thereby affecting the digestion and allergenicity of allergens. The way in which the food matrix affects allergens can be roughly divided into two aspects: one is that the food matrix (mainly carbohydrates and lipids) changes the conformation of allergens by forming complexes or new epitopes (Figure 4a); the other is that the food matrix (mainly nonallergenic proteins) competes with allergens for enzymatic cleavage (Figure 4c,d).

4.2 | Food matrix acts indirectly on allergens by influencing digestive environment

It is worth noting that the food matrix also directly affects the digestive environment of the human body, and the

degree of digestion can change the structure and molecular weight of proteins to affect their allergenicity. The most widespread is the effect of the food matrix on gastric pH (Figure 4b), intestinal pH (Figure 4c), and microbial flora (Figure 4d).

Proteins are digested and broken down into smaller fragments at a low pH of gastric juice. This greatly reduces the potential of food protein to bind IgE and increases the threshold dose (i.e., minimum effective dose) of allergens required to elicit symptoms with food allergy (Armentia et al., 2010; Pali-Schöll et al., 2018). Gastric juice with a higher pH will hinder the normal digestion of foods such as hazelnuts, milk, and casein. The resulting larger fragments or proteins are more likely to be recognized by the immune system, which increases the risk of sensitization or allergic reactions (Pali-Schöll et al., 2018). It has been proven that antacids (e.g., calcium carbonate, glycine, sodium

TABLE 2 The influence of the food matrix on digestion and allergenic properties of food allergens

Allergen	Matrix	Matrix effect	Digestion conditions	Digestibility	Allergenicity/antigenicity	References
Cor a 8 (hazelnut)	Nonallergenic proteins	Creating a competitive environment with allergens.	Gastric digestion: 2.5 mg/ml pepsin; substrate: pepsin ratio 1:1.25; pH 1.5; 37°C; 2 h. Intestinal digestion: 1.6 mg/ml pancreatin; substrate: pancreatin ratio 1:5; pH 7; 37°C; 45 min.	Delayed gastrointestinal degradation.	Reduced IgE-binding capacity.	Schulten et al. (2011)
β -Lactoglobulin	Phycocyanobilin	Covalent modification	Gastric digestion: pepsin activity 2800 U/mg; substrate: pepsin ratio 1:10; pH 2.5; 37°C; 6 h. Intestinal digestion: 0.4 mg/ml pancreatin; substrate: pancreatin ratio 1:1; pH 7.2; 37°C; 4 h.	Higher resistance to pepsin and pancreatic digestion; improved digestion stability.	IgE-binding properties remain unaltered.	Radomirovic et al. (2022)
β -Lactoglobulin	Galactose, tagatose	Glycation	Gastric digestion: pepsin activity 3300 U/mg; substrate: pepsin ratio 20:1; pH 2.5; 37°C; 2 h. Intestinal digestion: trypsin activity 300 U/mg; chymotrypsin activity 62 U/mg; substrate: trypsin: chymotrypsin ratio 400:1:4; pH 6.5; 37°C; 2 h	Enhanced resistance to gastric degradation.	Reduced IgG/IgE reactivity.	Corzo-Martínez et al. (2010)
Ara h 1, Ara h 2	Dextrose, fructose	Maillard reaction	Gastric secretions are obtained from the stomach of a fasting individual; substrate: gastric secretions ratio 1:10; pH 2; 37°C; 15 h.	More resistant to digestion by gastrointestinal enzymes.	Increased IgE-binding level.	Maleki, Chung, et al. (2000)
β -Lactoglobulin	Arabinose	Glycation	Gastric digestion: 284 U pepsin/mg protein; substrate: pepsin ratio 20:1; pH 2.5; 37°C; 2 h. Intestinal digestion: pancreatin including trypsin, amylase, and lipase; substrate: pancreatin ratio 25:1; pH 7; 37°C; 2 h	Increased resistance to digestive enzymes and having a lower hydrolysis value.	Decreased IgG/IgE-binding rate and antigenicity.	X. Wang, Ye, et al. (2021)
Tropomyosin	Glucose	Maillard reaction	Gastric digestion: pepsin activity 3411 U/mg; substrate: pepsin ratio 50:1; pH 1.2; 37°C; 1 h. Intestinal digestion: trypsin activity 13,165 U/mg; substrate: trypsin ratio 100:1; pH 7; 37°C; 3 h	Reduced digestibility.	Inhibited Caco-2 proliferation and interleukin-8 release; reduced allergenicity.	Z. Zhang, Xiao, et al. (2019)

(Continues)

TABLE 2 (Continued)

Allergen	Matrix	Matrix effect	Digestion conditions	Digestibility	Allergenicity/antigenicity	References
Ovalbumin, ovomucoid	Pectin, gum arabic, xylan	Interaction with proteins, producing complexes which are strongly recognized by IgE.	Gastric digestion: 172 U pepsin/mg protein; pH 2; 37°C; 1 h. Intestinal digestion: trypsin activity 10,100 U/mg; chymotrypsin activity 55 U/mg; pH 7; 37°C; 30 min.	Reduced digestive sensitivity.	Significantly increased IgE reactivity.	Jiménez-Saiz et al. (2013)
Len c3	Fatty acids	Forming lipid ligands	Gastric digestion: final protein concentration 0.05 mM; substrate: pepsin ratio 20:1; pH 2; 37°C; 2 h. Intestinal digestion: substrate: trypsin: chymotrypsin ratio is 400:1:4; pH 8; 37°C; 24 h.	More resistant to digestion.	Retained the ability to bind to IgE after gastroduodenal digestion.	Finkina et al. (2020)
Parvalbumin	N-Hexadecane	Lipid emulsion	Gastric digestion: final protein concentration 2.8 µg/ml; pepsin: substrate ratio 0.0007:1; pH 1.2; 37°C; 3 h.	Reduced digestibility; increased resistance to gastrointestinal digestion.	Increased IgE-binding capacity.	Luo et al. (2020)
Ara h 8	Peanut matrix	Maillard reactions, lipid oxidations, and lipophilic associations	Gastric digestion: 2.5 mg/ml pepsin; substrate: Enzynorm f®: Kreon® ratio 10: 8:0.067: 0.57; pH 2.0; 37°C; 2 h.	Enhanced proteolytic stability; reduced digestibility.	Increased IgE reactivity.	Petersen et al. (2014)
Gal d 2 (egg), Ara h 1, and Ara h 3	Muffin matrix	Maillard reaction, interaction between proteins and lipids	Gastric digestion: 63 U pepsin/mg protein; pH 2.5; 37°C; 2 h. Intestinal digestion: 34.5 U trypsin/mg protein; 11.8 U chymotrypsin/mg protein; 1.7 U amylase/mg carbohydrate; pH 6.5; 37°C; 2 h.	Highly resistant to digestion.	Increased IgE reactivity.	Mattar et al. (2021)
Ara h 1, Ara h 2, and Ara h 6,	Chocolate dessert, cookie matrix	Changing the progressive release of allergens, interaction between matrix components and protein.	Gastric digestion: 63 U pepsin/mg protein; pH 2.5; 37°C; 2 h. Intestinal digestion: 34.5 U trypsin/mg protein; 11.8 U chymotrypsin/mg protein; 1.7 U amylase/mg carbohydrate; 8.4 U lipase/mg fat; pH 6.5; 37°C; 2 h.	Increased digestibility for Ara h 1; highly resistant to digestion for Ara h 2 and Ara h 6.	Decreased IgE reactivity of Ara h 1, Ara h 2, and Ara h 6.	Rao et al. (2020)
Prunin (almond)	Chocolate mousse, Victorian sponge cake	Interference with protease-substrate protein interaction, interaction between matrix components and proteins.	Gastric digestion: 146 U pepsin/ml; pH 2.5; 37°C; 2 h. Intestinal digestion: 5.9 U chymotrypsin/ml, 104 U trypsin/ml, 3.2 µg colipase/ml, and 54 pancreatic lipase/ml; pH 6.5; 37°C; 1 h.	Reduced pepsin degradation rate.	Better retention of immunoreactivity was detected by dot blots and sandwich ELISA.	Mandalari et al. (2014)

carbonate, sodium bicarbonate) can partially neutralize gastric acid or increase gut permeability, which leads to increased exposure to intact proteins, thereby enhancing sensitization and allergic reactions (Sakai et al., 2000; Sathe et al., 2016). A recent study showed that children who received acid-suppressive medications had a higher risk of developing allergies to food, such as peanuts, milk, and eggs (Mitre et al., 2018). In addition, Armentia et al. (2010) added vinegar that can reduce gastric pH during cooking, and it was concluded that this measure reduced allergic responses to lentils and chicken through skin prick test and immunoblotting. Therefore, gastric digestion may interfere with the development of food allergies and may protect against food allergic reactions (Samadi et al., 2021). Before any contact of food with the stomach, gastric secretion is induced through sense organs such as taste, smell, and vision (Figure 4b) (Fine & Riera, 2019). The flavor components in the food matrix should also be considered in the research scope. Due to the complex effects of the food matrix on gastric juice changes, the effect of the food matrix on allergic reactions by influencing gastric juices should be considered comprehensively.

It should not be overlooked that the food matrix can not only reduce or promote the digestion of food protein by the body but also regulate or destroy the balance of microorganisms in the intestine, thereby affecting the allergenicity of proteins. Therefore, food matrix components (e.g., prebiotics, probiotics, dietary fiber, etc.) that can optimize intestinal flora and promote digestion have been proposed to prevent and treat allergic symptoms (Carlson et al., 2018; Tan-Lim & Esteban-Ipac, 2018). Among them, dietary fiber is considered by researchers to interfere with food allergies by affecting the digestion of allergens and intestinal microbiota. Pectin, as a typical representative of dietary fiber in a food matrix, was demonstrated by Polovic et al. (2007) to reduce the digestibility of food (e.g., kiwi, banana, apple, and cherry) allergens. In addition, pectin can alter the ratio of Firmicutes to Bacteroidetes in intestinal and pulmonary microbiota, resulting in increased local and systemic concentrations of short-chain fatty acids and inhibiting the inflammatory function of dendritic cells (Blanco-Pérez et al., 2021). All of these factors will affect the allergic sensitization process in atopic individuals and suggest that food allergies can be prevented or alleviated through targeted dietary interventions.

Since food allergens are unlikely to be presented to the human immune system in their natural state, it is particularly important to consider the food matrix effects (Costa, Villa, et al., 2022). In short, the food matrix not only alters the conformation of allergens, thus affecting their binding to immune cells but also alters their digestion in the gastrointestinal tract, thereby affecting the number of complete allergens that enter the immune system. The per-

formance of allergens in the immune system will further alter their allergenicity. With the diversification of the food matrix, the interactions between the matrix and allergens become more complex. Therefore, research on food allergenicity should be based on the food itself rather than on a single allergen, and the food matrix effects should be fully analyzed to obtain a more comprehensive and systematic evaluation of food allergenicity.

5 | FOOD PROCESSING INFLUENCES DIGESTION AND ALLERGENICITY OF FOOD ALLERGENS

Food processing is an important factor affecting the digestion and allergenic properties of food allergens. It is believed that many food allergens are stable proteins that can survive the strong acid and proteolytic environment of the gastrointestinal tract and then reach the intestinal mucosal immune system (Polovic et al., 2007) or can be digested into high molecular weight peptide fragments that retain IgE-binding and T-cell stimulation capabilities (Jiménez-Saiz et al., 2014). Food processing can reduce immune responses by making allergens more susceptible to gastrointestinal enzymes or by producing hypoallergenic hydrolysates (Jiménez-Saiz et al., 2015). A summary of the effects of food processing on the digestion and allergenicity of food allergens is shown in Table 3.

5.1 | Thermal processing influences the digestion and allergenicity of food allergens

Studies have shown that heat treatment can disinfect foods to ensure food safety, improve sensory and nutritional quality, and increase the diversity of food products (Vanga et al., 2017) and may also have a positive, negative, or sometimes no effect on allergies (Rahaman et al., 2016). Heat treatment can disrupt the secondary or tertiary structures of food allergens. These structural changes can obscure, destroy, or expose the linear or conformational epitopes of allergens to affect allergenicity (Di Stasio, Tranquet, et al., 2020; Ekezie et al., 2018). Structural changes and conformational epitopes are more susceptible to processing (e.g., heat treatment, ultrasound, irradiation, and hydrostatic high pressure) (Jiménez-Saiz et al., 2015; Ma et al., 2020; Tong et al., 2012; Zhu et al., 2018), while linear epitopes are more susceptible to enzymatic hydrolysis (Kasera et al., 2015) or the Maillard reactions (Toda et al., 2014). Structural changes in food proteins caused by thermal processing may further affect gastrointestinal digestibility and thus change their allergenicity (Rahaman et al., 2016). Thermal treatment can be divided into two types: moist

TABLE 3 Summary of the effects of food processing on the digestion and allergenicity of food allergens

Food processing	Treatment	Food allergens	Digestion conditions	Digestibility and allergenicity changes	Reference
Steaming	100°C; 20 min	Tropomyosin	Gastric digestion: 3.75 U pepsin/mg protein; pH 1.2; 37°C; 1 h. Intestinal digestion: 0.6 U trypsin/mg protein; pH 7.5; 37°C; 4 h.	Difficult to promote digestion, and no significant effect on allergenicity.	Cheng et al. (2020)
Back pressure cooking	Backpressure sterilizer; 120°C; 20 min	Tropomyosin		Improved digestion and reduced IgE-binding ability.	Cheng et al. (2020)
High temperature and high pressure	Autoclave; 120°C; 20 min	Tropomyosin		Improved digestion and reduced IgE-binding ability.	Cheng et al. (2020)
Extrusion	100°C; 15 min	Ara h 1 subunits (4, 17, and 22 kDa)	Gastric digestion: substrate: pepsin ratio 8:25; pH 1.2; 37°C; 1 h.	Increased susceptibility to peptic hydrolysis and reduced IgE-binding ability.	Chen and Phillips (2005)
Frying	150–160°C; 3 min	35 ku	Gastric digestion: 10,000 U pepsin/mg protein; pH 1.2; 37°C; 1 h.	Unaffected antienzyme ability and high IgE/IgG-binding ability.	Y. Liu, Lin, et al. (2011)
Roasting	170°C; 15 min	Walnuts/Hazelnuts/Almonds crude protein	Oral digestion: 75 U salivary amylase/ml protein; pH 7.0; 37°C; 2 min. Gastric digestion: 2000 U pepsin/ml protein; pH 3.0; 37°C; 2 h. Intestinal digestion: 100 U pancreatin/ml protein; pH 7.0; 37°C; 2 h. Jejunal brush border membrane digestion: 13 U intestinal BBM aminopeptidase N/ml protein; pH 7.2; 37°C; 6 h.	Enhanced digestibility, reduction or destruction of epitopes and reduced allergenicity.	Di Stasio, Tranquet, et al. (2020)
Roasting	170°C; 15 min	Peanut proteins	Gastric digestion: 1 M pepsin solution pH 1.2; 37°C; 1 h.	Greater stability in simulated gastric juice, high degranulated basophils and mast cells and high concentration of TH2-type serological indexes.	T. Zhang, Shi, et al. (2018)
Maillard reaction	Glucose glycation; 60°C; 48 h	Tropomyosin	Gastric digestion: substrate: pepsin ratio 50:1; pH 1.2; 37°C; 1 h. Intestinal digestion: substrate: trypsin ratio 100:1; pH 7.5; 37°C; 3 h.	Weakened digestibility, weakened degranulation, decreased histamine level, and decreased allergenicity.	Z. Zhang, Xiao, et al. (2019)

(Continues)

TABLE 3 (Continued)

Food processing	Treatment	Food allergens	Digestion conditions	Digestibility and allergenicity changes	Reference
High hydrostatic pressure	200 MPa; 25°C; 20 min	Cod protein	Gastric digestion: substrate: pepsin ratio 100:1; pH 1.9; 37°C; 0.5 h. Intestinal digestion: substrate: trypsin ratio 30:1; pH 8.0; 37°C; 2 h.	Enhanced digestibility and reduced IgE/IgG-binding ability.	Y. Zhang, Ren, et al. (2019)
High hydrostatic pressure	600 MPa; 40°C; 5 min	Tropomyosin	Oral digestion: 75 U salivary amylase/ml protein; pH 7.0; 37°C; 2 min. Gastric digestion: 2000 U pepsin/ml protein pH 3.0; 37°C; 2.5 h. Intestinal digestion: 100 U pancreatin/ml protein pH 7.0; 37°C; 2.5 h.	Improved pepsin digestion and reduced IgE-binding ability.	Faisal et al. (2019)
Pulsed light	0.27 J/cm ² per pulse	Shrimp extracts	Gastric digestion: 330 U pepsin/mg protein; substrate: pepsin ratio 50:1; pH 1.2; 37°C; 2 h. Intestinal digestion: 200 U trypsin/mg protein; substrate: trypsin ratio 50:1; 40 U α -chymotrypsin/mg protein; substrate: α -chymotrypsin ratio 50:1; pH 6.8; 37°C; 2 h.	Reduced IgE-binding ability.	W. W. Yang et al. (2012)
Pulsed light	0.4 J/cm ² per pulse	β -Lactoglobulin	Gastric digestion: substrate: pepsin ratio 40:1; pH 2.0; 37°C; 1 h.	More susceptible to protease and decreased IgE-binding ability.	Orcajo et al. (2019)
Ultrasound	100, 200, 300, 400, 500, 600, 700, 800 W; 15 min	Tropomyosin	Gastric digestion: substrate: pepsin ratio 50:1; pH 1.2; 37°C; 1 h. Intestinal digestion: substrate: trypsin ratio 100:1; pH 8.0; 37°C; 2 h.	More susceptible to hydrolysis and decreased IgE-binding ability.	Z. Zhang, Zhang, et al. (2018)
Ultrasound	120 W/cm ² ; 15 min	β -Lactoglobulin	Gastric digestion: substrate: pepsin ratio 50:1; pH 2.5; 37°C; 1 h. Intestinal digestion: substrate: trypsin ratio 25:1; pH 7.0; 37°C; 2 h.	Increased susceptibility to peptic hydrolysis and reduced IgG/IgE-binding activity.	Shao et al. (2020)
Fermentation	3% (v/v) <i>L. plantarum</i> B1-6; 2% (w/v) glucose; 37°C; 48 h	Fermented soy protein isolate	Dynamic gastric and duodenal parts. Oral digestion: 75 U α -amylase/ml protein; pH 7.0; 37°C; 3 min. Gastric digestion: 250 U pepsin/ml protein; pH 1.6; 26 μ /min; 3 h. Intestinal digestion: 200 U pancreatin/ml protein; pH 7.0; 26 μ /min; 3 h.	Enhanced digestibility and reduced IgE-binding ability.	Huang et al. (2020)
Fermentation	1% (v/v) <i>Lactobacillus casei</i> LeY; 37°C; 12 h	Fermented sweet buttermilk	Oral digestion: pH 6.5–7.4, 37°C, 5 min. Gastric digestion: pepsin; pH 3.0; 37°C; 1 h. Intestinal digestion: pancreatin and bile extract porcine; pH 7.0; 37°C; 2 h.	Reduced IgE/IgG-binding ability.	Wróblewska et al. (2016)

(Continues)

TABLE 3 (Continued)

Food processing	Treatment	Food allergens	Digestion conditions	Digestibility and allergenicity changes	Reference
Fermentation	2% (v/v) <i>Lactobacillus delbrueckii</i> subsp. <i>bulgaricus</i> ; 37°C	α -Lactalbumin, β -lactoglobulin	Gastric digestion: substrate: pepsin ratio 20:1 pH 2.5, 37°C; 15 min. Intestinal digestion: 10 mg trypsin/ml protein; pH 7.5; 37°C; 2 h.	More susceptible to hydrolysis and decreased IgG-binding activity.	Zheng et al. (2014)
Enzymatic cross-linking and heat treatment	Tyrosinase; 52°C; 30 min	Arginine kinase	Gastric digestion: substrate: pepsin ratio 4000:1; pH 1.2; 37°C; 1 h. Intestinal digestion: substrate: trypsin ratio 50:1; pH 7.5; 37°C; 4 h.	Resistant to gastrointestinal digestion, mitigated IgE-binding activity, inhibited antigen-induced histamine release in RBL-2H3 cells.	Fei et al. (2016)
Enzymatic cross-linking and heat treatment	Polyphenol oxidase; 100°C; 5 min	Ovalbumin	Gastric digestion: 2000 U pepsin/ml protein pH 1.2; 37°C; 1 h. Intestinal digestion: 100 U pancreatin/ml protein; pH 7.0; 37°C; 2 h.	Enhanced digestibility, reduced IgG/IgE-binding activity and degranulation capacity of KU812.	Tong et al. (2021)
Ultrasound combined cooking	200 W; 30°C	Tropomyosin	Gastric digestion: 160 U pepsin/mg protein; substrate: pepsin ratio 200:1; pH 1.2, 37°C, 1 h. Intestinal digestion: 32 U trypsin/ml protein; substrate: trypsin ratio 2000:1; 132 U chymotrypsin/ml protein; substrate: chymotrypsin ratio 5000:1; pH 7.5; 37°C; 4 h.	More susceptible to hydrolysis and decreased IgE/IgG-binding ability.	G. Liu, Yu, et al. (2011)
Ultrasound-assisted glycosylation	D-(+)-Mannose glycosylated for 3 h at 65°C and 0, 400, 600 W, 15 min	Ovalbumin	Gastric digestion: substrate: pepsin ratio 20:1; pH 2.0; 37°C; 1 h. Intestinal digestion: substrate: trypsin ratio 25:1; substrate: chymotrypsin ratio 100:1; pH 8.0; 37°C; 1 h.	Slight decrease of peptic digestibility but decreased IgE/IgG-binding ability.	W. W. Yang et al. (2021)
Ultrasound-assisted glycosylation	D-Galactose glycosylated at 55°C for 3.5 h, 100 W/cm ²	α -Lactalbumin	Gastric digestion: 22.75 U pepsin/mg protein; pH 3.0; 37°C; 2 h. Intestinal digestion: 3.45 U trypsin/ml protein; 3.45 U chymotrypsin/ml protein; pH 7.0; 37°C; 2 h.	Relatively high stability to pepsinolysis, drastically felled IgE-binding ability and decreased histamine release.	X. Wang, Tu, Ye, et al. (2021)

and dry heat processing. Moist-heat processing includes steaming, boiling, frying, extrusion, microwaving, high temperature, and high-pressure sterilization, whereas dry-heat processing encompasses roasting and baking (Moore et al., 1980; Shriver & Yang, 2011).

5.1.1 | Moist-heat processing

Processing (heating) of food in the presence of liquid can be considered “moist-heat processing.” Cheng et al. (2020) treated Chinese mitten crab with the ordinary cooking method (100°C, 20 min) and found that the digestive stability and IgE-binding capacity of tropomyosin were not significantly changed, while reverse pressure cooking (120°C, 20 min) or high temperature and pressure treatment (120°C, 20 min) induced a significant decrease in the IgE-binding capacity of tropomyosin and its digestion products. It is important to note that immunoreactive proteins of 23 and 29 kDa were still present in legumes even when autoclaved at 138°C for 20 min, which could cause IgE reactivity to these processed legumes. Nevertheless, autoclaving for 30 min abolished the binding of IgE to both components while producing a new IgE-binding protein with a molecular weight of 70 kDa (Álvarez-Álvarez et al., 2005).

Extrusion reduces the IgE-binding potential of peanut proteins by making the allergen insoluble and eliminating the immune activity of antigenic epitopes. Ara h 1 subunits (4, 17, and 22 kDa) showed some resistance to in vitro gastric digestion, but they were sensitive to pepsin hydrolysis after extrusion, which reduced their IgE-binding ability (Chen & Phillips, 2005). However, frying may have different effects on the IgE-binding ability of proteins. A report showed that frying had no effect on the digestion resistance of soluble proteins in prawn (*Metapena eusensis*) and that the main allergen (35 ku) still showed strong IgE-binding activity (Y. Liu, Lin, et al., 2011).

5.1.2 | Dry-heat processing

Roasting, one of the dry-heat processing methods, has contradictory effects, since it can contribute to increasing, maintaining, or decreasing the allergenic potential depending on the target allergen (Costa, Bavaro, et al., 2022). Roasted nuts are more digestible than raw nuts, and roasting results in a reduction or destruction of known allergen epitopes, reducing the immunogenicity of nut allergens, but several peptides retain intact IgE-binding sequences (Di Stasio, d'Acierno, et al., 2020). In contrast, T. Zhang, Shi, et al. (2018) found that roasted peanut proteins had greater stability in simulated gastric juice than

raw peanut proteins and boiled peanut proteins in simulated gastric fluid, and this high stability may be the reason for their high allergenicity, as reflected by changes in ethology (diarrhea and weight loss), pathology (splenomegaly and jejunum breakage), and relevant serological indexes (specific IgG1 and IgG2a, IL-4, IFN- γ , histamine, and MCP-1). Similarly, studies have shown that after roasting, Ara h 1 monomers are intermolecularly cross-linked to form covalently bound trimers and hexamers, which protect allergens from gastrointestinal digestion (Maleki & Hurlburt, 2004). The formation of trimers protects the molecule from protease digestion and deformation to a certain extent and theoretically allows several fragments of Ara h 1 that contain intact IgE-binding sites to pass through the small intestinal lumen, thereby causing it to be recognized by immune cells and contributing to its allergies (Maleki, Kopper, et al., 2000).

5.1.3 | The Maillard reaction

Thermal processing may be used to modify allergenic proteins via interactions with other food components or may alter allergen reactivity by masking IgE-binding epitopes. A typical example of such a reaction is the Maillard reaction. After the Maillard reaction with galactose, tropomyosin from *Scylla paramamosain* had poor digestive stability and could be degraded by digestive protease after 30 min to generate small peptide segments with no IgG-binding activity (Han et al., 2018). Similarly, glucose glycation was also reported to reduce the digestibility and weaken the allergenicity of tropomyosin from *Exopalaemon modestus*, which was analyzed by western blot using sera from shrimp food allergy patients, while deglycosylation showed the opposite effect; gastric digestion can partially weaken the allergenicity of glycosylated tropomyosin, while subsequent intestinal digestion can effectively hydrolyze glycosylated tropomyosin and reduce its allergenicity (Z. Zhang, Xiao, et al., 2019). However, it has been reported that a diet rich in the Maillard reaction products limits protein digestion. In healthy males, it is manifested by increased fecal nitrogen excretion, decreased apparent nitrogen absorption, and decreased nitrogen digestibility (Seiquer et al., 2006). In addition, dendritic cells preferentially recognize proteins modified by advanced glycation end products, upregulate the expression of AGE receptors, and then activate mast cells and basophils to secrete allergy signaling mediators such as histamine, ultimately aggravating food allergy symptoms (Mueller et al., 2013; Toda et al., 2014). As the Maillard reaction acting on the digestibility and allergenicity of allergens is affected by the types of reducing sugars, ongoing scientific efforts are seeking suitable reducing sugars

to counteract food allergies through the Maillard reactions (Costa, Bavaro, et al., 2022; Costa, Villa, et al., 2022).

Although heat treatment methods can reduce the allergenicity of food, they may have a negative impact on sensory properties and nutrients, especially thermally unstable compounds such as ascorbic acid and polyphenols (Dong et al., 2021). In addition, some food allergens can withstand heat treatment due to their abnormally stable α -helical coiled-coil secondary structure or the presence of intra/inter molecular cystine that defines their structural integrity (Ekezie et al., 2018). Therefore, it is imperative to find other nonthermal food processing methods to reduce allergenicity.

5.2 | Nonthermal processing influences the digestion and allergenicity of food allergens

With the development of nonthermal processing techniques, such as high hydrostatic pressure (HHP), pulsed ultraviolet light, ultrasound, and fermentation, minimally processed products have received more attention (Siddiqui & Rahman, 2015). Nonthermal processing technology can change the conformation of proteins (Ekezie et al., 2018) and then affect the digestion and absorption of allergens in the gastrointestinal tract, thus affecting their allergenicity. Compared with thermal processing, nonthermal processing technology may reduce the allergenicity of food while preserving the original characteristics of food materials. Therefore, the researchers explored the effects of nonthermal processing on allergenic proteins and the possibility of producing foods with low allergens.

5.2.1 | High hydrostatic pressure processing

HHP is a nonthermal food processing technology with a pressure between 100 and 800 MPa that has been proven to be very effective in reducing the IgE-binding ability of allergens. HHP leads to protein denaturation and aggregation (Gharbi & Labbafi, 2018; Johnson et al., 2010), which might reduce the IgE-binding ability of allergens by increasing gastrointestinal digestibility. Y. Zhang, Bi, et al. (2019) found that HHP treatment improved the gastrointestinal digestibility of cod protein and significantly reduced the IgE- and IgG-binding ability (Y. Zhang, Bi, et al., 2019). The digestibility of tropomyosin Tod p1 in fresh squid was increased by HHP treatment, in which 400 and 600 MPa treatments were more effective in reducing allergenicity than 200 MPa based on indirect ELISA (Jin et al., 2015). Another study showed that HHP processing at 600 MPa and 40°C for 5 min increased the antigenicity

(IgG-binding capacity) of tropomyosin by almost double, and further digestion of the HHP sample induced a noticeable reduction (Faisal et al., 2019). The higher antigenicity after HHP processing may be because HHP treatment of tropomyosin at 600 MPa may disrupt the gestalt-binding interactions and expose the internal binding epitopes; simultaneously, this structural change makes tropomyosin more readily hydrolyzed by digestive enzymes.

5.2.2 | Pulsed light processing

Pulsed light processing is considered to be an effective way to inactivate microorganisms during food processing (Ekezie et al., 2018). Conformational changes caused by pulsed light lead to more open structures that expose hydrophobic amino acids, which may facilitate protein aggregation but also make enzyme cleavage sites more accessible (del Castillo-Santaella et al., 2014). Orcajo et al. (2019) reported that pulsed light could alter the configuration of β -lactoglobulin, improving the susceptibility to be hydrolyzed by pepsin and reducing the immune reactivity of β -lactoglobulin to both IgG and IgE. Instead, pulsed light-treated tropomyosin remained stable during gastric digestion, and gastric digestion did not alter the IgE-binding capability of pulsed light-treated tropomyosin, which might be due to the role of disulfide bonds in resisting digestion (W. W. Yang et al., 2012). Unlike in simulated gastric digestion, shrimp tropomyosin was rapidly degraded in simulated intestinal fluid, irrespective of whether the protein was treated with pulsed light. However, the pulsed light treatment reduced shrimp allergens remained at a low level under the in vitro simulated gastric and intestinal digestive conditions (W. W. Yang et al., 2012). Therefore, pulsed light treatment may affect the sensitizing capacity of food proteins to varying degrees by changing their digestion while inactivating microorganisms during food processing.

5.2.3 | Ultrasound

Ultrasound can induce conformational changes in proteins, loosen the protein structure, and even destroy the peptide chain of proteins, resulting in the exposure of enzyme cleavage sites, further improving digestibility and thus changing allergenicity (Shao et al., 2020; J. Wang, Wang, et al., 2021; Z. Zhang, Zhang, et al., 2018). Tropomyosin from *E. modestus* was resistant to gastric digestion, but high-intensity ultrasound combined with gastrointestinal digestion hydrolyzed tropomyosin most effectively and reduced the allergenicity of its digestive products, as suggested by the immunoblotting and ELISA

data (Z. Zhang, Zhang, et al., 2018). A recent study reported that the allergenicity of ultrasonicated β -lactoglobulin after gastric digestion was increased. However, ultrasonicated β -lactoglobulin digested by the gastrointestinal tract presents a completely opposite result. Ultrasound increased the hydrolysis of β -lactoglobulin by trypsin and produced more small peptides, which caused a decrease in IgG/IgE-binding ability (Shao et al., 2020). Hence, ultrasonic pretreatment might make allergens more easily degraded by digestive enzymes and then destroy or expose the epitopes, thus affecting their allergenic potential to varying degrees.

5.2.4 | Fermentation

Fermentation is one of the traditional processes of food processing, and many studies suggest that fermentation is an efficient approach for alleviating food allergenicity (Pi et al., 2021). Interestingly, studies have found that, along with the reduction in allergenicity, the digestibility of food is improved after fermentation (J. Li et al., 2019; Seo & Cho, 2016). Fermentation by lactic acid bacteria has been reported to promote the digestibility rate of soy proteins as well as reduce or eliminate their IgE-binding capacity (Huang et al., 2020). Similar results were found in milk proteins (Wróblewska et al., 2016). Moreover, fermentation facilitates digestion of different proteins via different approaches. Fermentation promoted hydrolysis of α -lactalbumin by trypsin, whereas β -lactoglobulin from fermented milk was more vulnerable to pepsin than the one from unfermented milk. Nevertheless, the antigenicity of α -lactalbumin and β -lactoglobulin was effectively reduced (Zheng et al., 2014).

Further studies revealed that fermentation changed the conformation and aggregation state of allergens, which prolonged the gastric transit time, resulting in improved hydrolysis and reduced exposure of intact epitopes in the duodenum, thus decreasing allergenicity (Huang et al., 2020).

5.3 | Combined processing treatment influences the digestion and allergenicity of food allergens

The combined processing treatment generally shows a better performance in reducing food immunoreactivity compared to the single processing technique. Enzymatic cross-linking, which utilizes the enzyme to catalyze the polymerization of proteins primarily through the formation of intramolecular and intermolecular cross-links (Heck et al., 2013; Tong et al., 2018), can affect

the digestibility of proteins in the gastrointestinal tract, thereby reducing allergenicity (Y. Li & Damodaran, 2017; X. Li, Bai, et al., 2020; G. Liu et al., 2017; Tantoush et al., 2011). In recent years, enzymatic cross-linking combined with heat treatment has become a new method to reduce food allergenicity. Fei et al. (2016) found that the arginine kinase in crabs after enzymatic cross-linking and heat treatment was more resistant to gastrointestinal digestion than the native arginine kinase, and the IgG- and IgE-binding activity of digested products was reduced. Another study showed that cross-linking of polyphenol oxidase on ovalbumin (OVA) after heating or denaturant pretreatment changed the secondary structure of OVA, promoted its gastrointestinal digestion, and significantly reduced OVA-specific IgG and IgE levels (competitive inhibition ELISA data) as well as OVA-induced degranulation capacity of human basophilic KU812 cells; moreover, enzymatic cross-linking after heating pretreatment was more effective in reducing the potential allergenicity of OVA than enzymatic cross-linking after denaturant pretreatment (Tong et al., 2021). Hence, a combination of enzymatic cross-linking with heating pretreatment may be a new strategy to develop hypoallergenic foods.

Combining ultrasound with other methods may be a potential application in industrial food production (Ekezie et al., 2018). Ultrasound combined with cooking treatment markedly reduced the digestive stability and IgE-binding capacity of tropomyosin from crab (*S. paramamosain*) when compared to the single ultrasound treatment (G. Liu, Yu, et al., 2011). The reason may be that ultrasound treatment destroys the structure of tropomyosin to a certain extent, and further cooking can lead to continuous degradation of tropomyosin, which is conducive to gastrointestinal digestion and thus reduces its IgE-binding capacity (G. Liu, Yu, et al., 2011). A recent study showed that sonication combined with glycation only caused a small decrease in OVA digestibility under simulated gastric and small intestine conditions but that OVA-specific IgG and IgE levels were exceedingly low after digestion (W. Yang et al., 2021). Similar phenomena were found in sonication-assisted glycated α -lactalbumin (X. Wang, Tu, Ye, et al., 2021), which can be attributed to the shielding effect of the linear epitopes caused by the greater degree of glycation. The allergenicity of β -lactoglobulin was also significantly reduced by ultrasound combined with glycation modification and subsequent digestion. Digestion led to a decrease in some peptides with complete immunogenicity, and glycosylation had a masking effect on allergen epitopes of β -lactoglobulin (Shao et al., 2021).

Above all, a combination of thermal and nonthermal processing can reduce the allergenicity of various foods by affecting the digestive process.

6 | CONCLUSION AND FUTURE TRENDS

This review outlines current developments associated with the gastrointestinal fate of food allergens and its relationship with allergenicity. In recent decades, various digestion models *in vivo* and *in vitro* have been widely developed for evaluating the potential allergenicity of proteins. Among them, dynamic *in vitro* digestion models will become the new method of food allergen studies due to a more realistic simulation of the digestive environment *in vivo* and no ethical limitations.

Food allergens may undergo structural changes during oral-gastric-duodenal digestion and even rupture or exposure of conformational and/or linear epitopes, resulting in reduced, retained, or enhanced sensitizing and eliciting capacity. Digestion-labile allergens may share common structural characteristics, such as high flexibility of protein structure, rendering it more susceptible to being hydrolyzed into small fragments with decreased or eliminated allergenic potential. In contrast, the presence of disulfide bonds, tightly wound α -helical structures, or hydrophobic domains in food allergens helps them resist gastrointestinal digestion, stabilizing IgE-binding epitopes and thus maintaining their allergenicity. More dramatically, in rare cases, digestion leads to increased allergenicity due to exposure of new epitopes that are not accessible prior to digestion. Current research has mainly focused on monitoring the degradation and structural changes of food allergens during *in vitro* digestion. More data on the mapping of IgE-binding epitopes in digestion-resistant peptides using digestomics and bioinformatics are necessary, which would be of particular value for evaluating the potential allergenicity of proteins.

It should not be overlooked that a variety of factors can affect the digestion of food allergens, thus changing their allergenicity. One factor is the food matrix: it can directly act on the allergen by forming complexes or new epitopes to further affect its gastrointestinal digestibility, mucosal absorption kinetics, and performance in the immune system, thereby affecting its allergenicity. Moreover, it may also compete with allergens for enzymatic cleavage or influence gastrointestinal pH and microbial flora, further changing the allergenicity of allergens. Another factor is food processing: several processing techniques, including high temperature and high pressure, extrusion, the Maillard reaction, pulsed light, ultrasound, and fermentation, can be beneficial for attenuating the sensitizing and allergenic capability of food proteins by increasing their digestibility; in comparison to the single treatment, the combination of processing provides better performance in most cases. In view of the complexity of food compo-

nents, the food itself rather than a single allergen should be used to obtain more accurate data for evaluating the allergenicity of food proteins. This review will provide useful information for evaluating the effectiveness of food matrix and food processing in reducing the allergenicity of food proteins.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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