



Review

Processes for reducing egg allergenicity: Advances and different approaches

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ABSTRACT

Egg is a versatile ingredient and ubiquitous food. Nevertheless, egg proteins are a common cause of allergy mainly in childhood. Until now, egg eviction has been the best way to prevent this disorder, however, processed food can contribute to mitigate allergies and to guarantee life quality of allergic individuals. This review focuses on discussing and highlighting recent advances in processes to reduce egg allergenicity as well as new approaches to egg allergy management. In recent times, different methods have been developed to reduce egg allergies, by hiding the epitopes or changing the native or conformational structure of the proteins. Despite processing food has not yet been a solution to completely remove the allergenic potential of egg proteins, innovative strategies, such as addition of phenolic compounds, have been developed with promising results.

1. Introduction

The egg is a versatile and ubiquitous food used in the diets worldwide and in processed foods, with nutritional properties that generate important health benefits, such as antioxidant activity (Miranda et al., 2015). Nevertheless, egg consumption has also been considered as the trigger of certain disorders such as food allergy, mainly in childhood (Xepapadaki et al., 2016). Although egg allergy may result from different avian species, the most studied and also the most impactful is the hen's egg allergy. However, in this review we will use the term usually employed, egg allergy. Given the health, social and economic impact of this disease, many efforts have been made to find methods for reducing egg allergenicity using different approaches. Therefore, this review will discuss and highlight the recent advances in processes to reduce egg allergenicity as well as new developments in its management.

2. Egg allergy

Allergy is an overreaction by the immune system to harmless environmental substances which it recognizes as antigens (Dhanapala, De Silva, Doran & Suphioglu, 2015). Food allergy is an abnormal reaction to food constituents, caused by anomalous immune responses. This reaction can appear in sensitized individuals after dietary exposure to specific food allergens (Verhoeckx et al., 2015). The development of food

allergy involves two phases: the sensitization, that results from the interaction between an allergen and an antigen-presenting cell, leading to the production of immunoglobulin E (IgE) specific to the allergen; the second phase, the elicitation, consists of the interaction of the allergen with the specific IgE on the surface of the mast cells or basophils, leading to the release of mediators of the immune response (Pelz and Bryce, 2015). Researchers have thought that food allergy results from alterations in immune tolerance mechanisms, determined by gut microbiota, and microbiome variations (Canani et al., 2019; Fazlollahi et al., 2019).

Food allergy is considered a public health issue, since its prevalence has been increasing in the last few decades affecting 4–11% of children less than 5 years of age (Sicherer & Sampson, 2018; Ma et al., 2021). Despite the main prevalence of food allergy in younger people, adult cases have also been reported (Mahdavinia, 2020).

Among food allergies in babies and children, egg allergy is the most frequent after cow's milk allergy (Praticò et al., 2014). Global data indicate that the prevalence of egg allergy is about 2% in children under 5 years (Xepapadaki et al., 2016; Peters et al., 2017).

Most of the egg allergic reactions involve an immediate immunological response with overproduction of an antibody, such as IgE, against linear and conformational epitopes of egg allergens (Ehlers et al. 2020). During allergic reactions, distinct factors can contribute to threshold variation in an individual exposed to an allergen. Some of these factors are intrinsic, such as age, race and genetics, others may be predicted but not easily controlled, such as asthma (Sicherer & Sampson, 2018). The

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use of eggs in many processed foods reinforces the need for the development of strategies for reducing and controlling egg allergenicity (Dhanapala et al., 2015)

3. Egg protein allergens

The egg consists of approximately 8–11% shell, 56–61% white and 27–32% yolk (Zhu, Vanga, Wang, & Raghavan, 2018a). Egg white is considerably more allergenic than egg yolk (Dang et al. 2019). In fact, egg white contains numerous different proteins and glycoproteins which can trigger allergic reactions, and includes: ovomucoid (Gal d 1), about 11% of egg white, with 28KDa; ovalbumin (Gal d 2), about 54% of egg white, with 42.7KDa; Ovotransferrin (Gal d 3), about 12% of egg white, with 76.6KDa; and lysozyme (Gal d 4) about 3–4% of egg white, with 14KDa (Dhanapala et al., 2015; Lin, Wu, Huang, Cheng & Yeh, 2016; Park, Yoon, Kim, Han, & Choi, 2017) (Table 1). Gal d 1 and Gal d 2 are the major allergens of egg white (Martorell et al., 2013). Initially, research on egg allergy had been more focused on Gal d 2 due to its high abundance in egg white. However, studies on Gal d 1 have shown that despite initially being considered a minor allergen, now it is postulated to be the dominant egg allergen due to its resistance to heat and high allergenic potential (Ognjenović et al., 2014; Wai, Leung, Leung & Chu, 2019). Although avidin is not considered an allergen, this egg white protein is widely studied, since it forms a complex with biotin which prevents its absorption (Zhu et al., 2018a). The egg yolk has two minor allergens: Alpha-livetin or chicken serum albumin (Gal d 5), that can cause an egg syndrome to avian, and the YGP42 protein (Gal d 6) (Table 1) (Wai et al., 2019). It is important to highlight that there are minor food allergens that have not yet been thoroughly studied, which can limit the full understanding of its effect on protein allergenicity.

Another relevant issue is the cross-reactivity with different avian eggs allergens that must be taken in account among children with hen's egg allergy. In fact, and despite the low consume of eggs of other avian species, compared to chicken eggs, the elimination of all type of avian eggs allergens in the diet of these children should to be performed (Moghtaderia, Nabavizadehb, & Teshnizic, 2020).

4. Egg protein allergy diagnosis

Different techniques have been used for egg allergy diagnosis (Sicherer & Sampson, 2018). The evaluation of patients' clinical history, followed by a physical examination, is the first approach to study egg allergy (Sicherer & Sampson, 2018). To make an accurate diagnosis it is important to consider all the symptoms and factors that cause allergy (Mahdavinia, 2020). The following steps usually involve *in vivo* Skin Prick Testing (SPT) and *in vitro* tests, such as ImmunoCAP specific IgE blood tests to evaluate the presence of egg allergen-specific antibodies (Muraro et al., 2014). The combination of egg specific serum IgE levels and SPT has been used to guide clinical decisions and to monitor the

evolution of egg allergy in children (Graham, Bégin, Paradis, Lacombe-Barrios, Paradis & Des Roches, 2016). In addition, combined ImmunoCAP test and oral food challenge (OFC) improve the diagnosis and the treatment approaches (Graham et al., 2016). Kim et al. (2019) concluded that the levels of specific IgE to egg white can be utilized as a predictor of tolerance in egg allergic children. Moreover, the specific IgE against to linear epitopes of Gal d 1 showed to be highly specific for identification of hen's egg allergic adults, and can be an additional value in egg allergy diagnosis (Ehlers et al. 2020). Basophil activation tests (BATs) were also considered a crucial tool in the diagnosis of food allergy due to a superior specificity than SPT and specific IgE (Sato, Yanagida & Ebisawa, 2018). Component-resolved diagnostics (CRD) appears to provide additional information to determine if OFCs should be performed to diagnose allergies (Sato et al., 2018; Dona & Suphioglu, 2020). Recently, a new molecular based diagnostic, termed precision allergy molecular diagnostic applications (PAMD@), was described as an important tool in the management of the allergic patients (Ansotegui et al., 2020). PAMD@ allows mapping the sensitization profile and assessing the food allergy risk and the cross-reactivities between different combinations of food and inhalant allergens. Thus, PAMD@ can contribute to understanding the molecular mechanisms underlying allergic sensitization and cross-reactivities of food allergens (Ansotegui et al., 2020).

5. Processes for reducing egg allergenicity

The production of safe and innovative food products, without losing nutrients, has been the goal of food technicians during the last years. Food processing techniques can be applied to transform raw products into consumables and can provide many beneficial effects (Mattarozzi & Careri, 2019). Given that processing may affect the capacity of proteins to promote allergic sensitisation, it is important to control the allergenicity of processed food (Verhoeckx et al., 2015). The protein changes depend on different factors like the type of food, allergen levels and processing requirements (Cabanillas & Novak, 2019). Among the allergenic foods, the egg is the one in which the processing or cooking most alters the allergenicity. In fact, the allergic potential of egg can be reduced or increased due to protein unfolding upon specific treatment, which leads to structural alterations that can hide or destruct the epitopes of binding IgE (Jiménez-Saiz, Bénéde, Molina & López-Expósito, 2015; Pablos-Tanarro, Ojalvo, Blanco, Fandiño, & Molina, 2017; Cabanillas & Novak, 2019).

The evaluation of the effect of the food processing on the physico-chemical properties of egg proteins and its impact on eggs allergenicity has been performed using different strategies, including assays for IgE-binding capacity, and *in vitro* (mast cell, basophil granulocyte and basophil) and *in vivo* (animal models such as BALB/c mouse, C3H/HeJ mouse, and BN rat) experiments where an elicitation of an allergic response is induced (Huang et al. 2018). The SPT and food challenges, such as OFC and double-blind placebo-controlled food challenges (DBPCFC), despite being the best methods to assess the potential sensitising capacity of food proteins to the patients, are difficult to implement due to the economic and ethical limitations (Costa et al., 2021).

Despite the determination of specific IgE only informs about sensitization, it has been widely used to assess the allergenic potential of food proteins, although sensitization does not always culminate in the elicitation phase. The IgE-binding capacity of the allergens is usually determined by Immunoblotting, ELISA (enzyme-linked immunosorbent assay) and enzyme allergosorbent test (EAST)/ImmunoCap using human sera or plasma of sensitised or allergic patients. These techniques are also applied to perform immunoreactivity assays using animal antibodies for measure of the immune reaction caused by an antigen. On the other hand, the allergenicity and the allergenic potential are assessed by a simulation of allergic reactions using *in vitro* or *in vivo* assays with cellular and animal models, respectively (Verhoeckx et al., 2015; Huang et al., 2018; Costa et al., 2021).

Table 1
Egg allergenic proteins.

Egg proteins	Allergen name	Molecular weight	Percentage content	Observations
Ovomucoid (OVM)	Gal d1	28KDa	11% egg white	Dominant egg allergen Heat resistant
Ovalbumin (OVA)	Gal d2	42,7 KDa	54% egg white	Most abundant protein
Ovotransferrin (OVT)	Gal d3	76,6 KDa	12% egg white	–
Lysozyme (LYS)	Gal d4	14 KDa	3–4% egg white	–
Chicken serum albumin	Gal d5	69 KDa	40–60% egg yolk	The main egg yolk protein
YGP42	Gal d6	35 KDa		Egg yolk protein

In the last years, there has been a great investment in the development of new processing techniques to produce hypoallergenic foods. Thermal and non-thermal techniques (Fig. 1 and Table 2) have been shown to alter sensitization and allergenicity potential of egg proteins, however such methods have not yet been able to completely eliminate egg allergenicity (Zhu et al., 2018a; Ma et al., 2020).

5.1. Heat treatment

Thermal processing has been applied on foods to improve microbial safety, detoxification, texture and digestibility. In addition, the heat treatments cause modifications in the physical-chemical and functional properties of proteins. The effect of heating on allergic food components can decrease the allergenicity or increase it by promoting structure and conformational alterations in the native protein (Verhoeckx et al., 2015; Vanga, Singh & Raghavan, 2017). Egg products can be used after extensive heating, such as cakes, egg pasta and bread or with less heating such as fresh mayonnaise. Curiously, it was observed that eggs cooked with wheat or other substances are less IgE reactive than eggs heated on their own (Bloom et al., 2015). Thus, the patients allergic to eggs may present lower reactivity to foods like cakes, than to cooked eggs alone (Dhanapala et al., 2015). Heating by destroying or modifying conformational epitopes can decrease the allergenicity of diverse foods. Moreover, the heat induces protein denaturation, rearranging or forming novel intra and/or intermolecular bonds, which prevent epitopes from being recognized by IgE (Ekezie, Cheng & Sun, 2018).

Different studies have shown that heating Gal d 2 decreases the binding to IgE compared to unheated Gal d 2 (Leonard, 2016). Thus, it is important to find out how heat treatments promote a change in the structure of food proteins and how it influences their digestibility, since both factors can affect their allergenicity (Ekezie et al. 2018). Pablos-Tanarro et al. (2017) applied moderate heat treatments to egg white and found a reduction of its allergenic potential in a BALB/c model of egg allergy. After heat treatment at specific pH, temperature, time, and concentration conditions, the egg white can aggregate and denature; however, the processing parameters could be monitored to control the

protein aggregation (Gharbi & Labbafi, 2018). Claude et al. (2017) studied the effect of pH and ionic strength in Gal d 2 allergenicity during the aggregation process by thermal treatments. In fact, the aggregates formed at low ionic strength and near pH of stored egg, in which electrostatic repulsions compensate for hydrophobic attractions, exhibit a reduced allergenicity compared to the aggregates formed when electrostatic repulsions are minimal, at pH near the isoelectric point and high ionic strength. Moreover, the morphology and the structure of aggregates are relevant factors to take into account in the immune response during the sensitization, since they can induce differences in the development phase of allergy. Posteriorly, Claude et al. (2019) also studied the capacity of Gal d 2 and thermal aggregates, to promote degranulation of a humanized rat cell line that was sensitised with sera from children with egg allergy. They concluded that the aggregates had significantly lower ability to trigger degranulation than native Gal d 2.

Contrarily to Gal d 2, Gal d 1 is more resistant to heat and to proteolytic digestion due to the disulphide bonds that link the three sub-domains. The principal responsible for the high allergenicity of Gal d 1 is the domain 3 which has a great stability and also the most dominant binding epitope (Verhoeckx et al., 2015). Nevertheless, recently it was described over 90% reduction of Gal d 1 antigenicity after a treatment at pH 9.5 and temperature of 100 °C, due to the change in linear epitopes exposure and position of the conformational epitopes (Stănciuc, Cretu, Banu & Aprodu, 2018). Curiously, it was found that high levels of IgE towards Gal d 1 can suggest an incapability to tolerate extensively heated eggs (Chokshi & Sicherer, 2015).

The efficacy of a graduated exposure to extensively heated and baked egg to promote tolerance in egg allergic children, under 2 years, was evaluated and a significant decrease in time to resolve the allergy in these children was observed (Gotesdyner et al., 2019). The authors suggested an action mechanism involving a gradual decrease in egg specific IgE and an increase in protective IgG and cellular regulatory pathways. Brossard et al. (2019) performed SPT in egg-allergic children and showed that all of them had reactive SPTs to raw egg white and 72% to raw egg yolk. It was also observed that SPT-reactivity for some children decreased after heating, but hard-boiling was more effective than

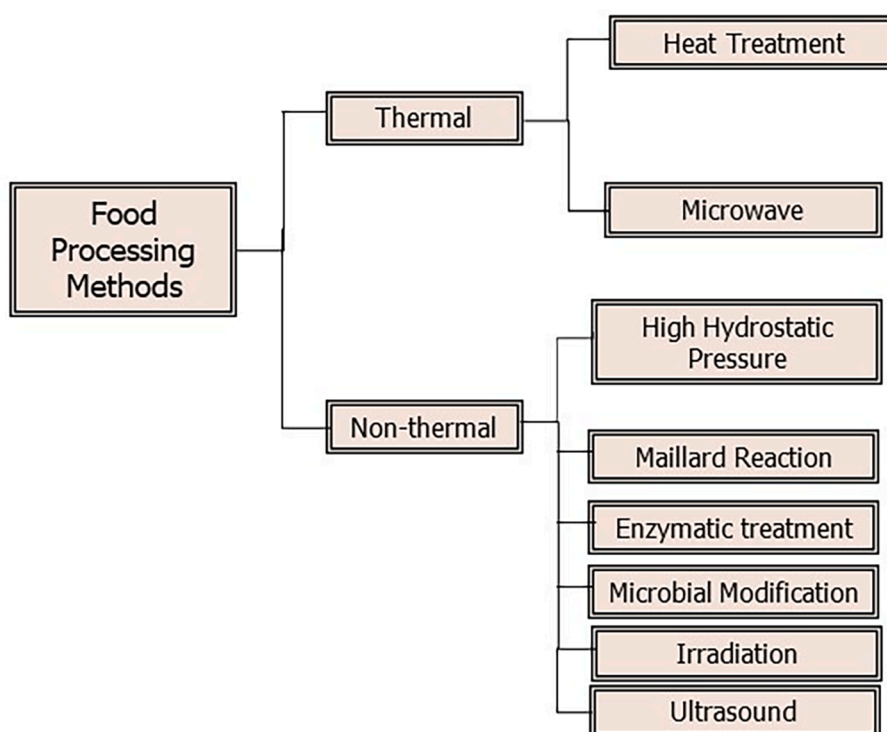


Fig. 1. Thermal and non-thermal food processing methods.

Table 2
Methods for reducing egg allergenicity.

Methods	Goal	Results		References
		Advantages	Disadvantages	
Heat treatment	Modification of physical–chemical and functional properties Changing structural conformation Reducing allergenicity through structured graduate exposure protocol	Partial decrease in allergenicity Reduced intestinal absorption Early eat introduction	Ovomucoid is heat resistant Denaturation Hiding of epitopes Need of trained and experienced teams Not completely effective Mask or unmask epitopes in the allergen Expose buried amino acids producing neoallergens, increasing the allergenicity	Bloom et al. (2015); Brossard et al. (2019); Claude et al. (2017, 2019); Gotesdyner et al. (2019); Horino et al. (2019); Leonard (2016); Martorell et al. (2013); Pablos-Tanaro et al. (2017); Pérez-Quintero et al. (2020); Shin et al. (2013); Stănciuc et al. (2016, 2018)
Microwave	Changing structural conformation	Reduce allergenicity potential Increase protein digestibility Rapid heating High energy efficiency Reduce the drying time Faster and efficient heating Improve product quality Better nutritional/sensory properties	Not completely effective Mask or unmask epitopes in the allergen Expose buried amino acids producing neoallergens, increasing the allergenicity Degradation of the products by dry heating Food dehydrating	Ekezie et al. (2017); Hu et al. (2019); Li et al. (2018, 2020); Zhu et al. (2018b)
High hydrostatic pressure	Improve microbial safety Changes structure Modify egg white foaming	Foods with no allergenic components Reduce allergenicity Increase profitability Functionality and bioactive properties of food products, without affecting their organoleptic properties Microbial food safety	Induction of denaturation and aggregation Minimal deterioration of colour, flavour, texture, and nutritional value Physical changes in food components Changes in food nutrition and functionality IgE-binding can decrease, remain unchanged or increase Aggregation Formation of new allergenic compounds Decrease of nutritional value Development of chronic inflammation	Huang et al. (2014); López-Expósito et al. (2008); Naderi et al. (2017); Pablos-Tanarro et al. (2017); Panozzo et al. (2014); Patrignani & Lanciotti (2016); Rahaman et al. (2016)
Maillard reaction	Reducing sugars and compounds with free amino acids	Changes in immunoreactivity of linear and conformational epitopes	IgE-binding can decrease, remain unchanged or increase Aggregation Formation of new allergenic compounds Decrease of nutritional value Development of chronic inflammation	Ma et al. (2013); Rahaman et al. (2016); Teodorowicz et al. (2017); Toda et al. (2019); Wang et al. (2020)
Enzymatic treatment	Hydrolysis with enzymes Breaking polypeptide sequences	Production of bioactive peptides Cleavage of conformational and linear epitopes Significant reduction in IgG and IgE binding capacity Regulation Th2	Partial IgE binding capacity Formation of immunoreactive peptides	Chang et al. (2018); Gazme et al. (2020); Liu et al. (2018); Lozano-Ojalvo et al. (2016); Park et al. (2017); Tong et al. (2018); Yang et al. (2018)
Food radiation	Triggering oxygen radical generating radialysis	Reduction of IgE-binding Products with longer shelf life	Changes in color, flavour, taste, and pH Increase the potential allergenicity Fragmentation, aggregation No difference in IgE-binding capacity Increase the risk of allergenic reactions Enhanced IgG and IgE binding capacity	Manzocco et al. (2012); Manzocco and Nicoli (2012); Rahaman et al. (2016)
Ultrasound	Reduction of food allergenicity	Lead to changes in both conformational and physical properties of proteins which can affect the allergenicity Reduced IgG and IgE binding capacity	Enhanced IgG and IgE binding capacity	Nayak et al. (2017); Sheng et al. (2018); Stefanović et al. (2014); Yang et al. (2017, 2018); Zhu et al. (2018b)
Microbial modification	Modify properties in food products: the hydrophobicity, solubility, gelation, emulsification, foaming and viscosity	Provide fermented foods Improved gastro-intestinal digestibility	Do not reduce potential allergenicity	Canani et al. (2019); Fazlollahi et al. (2019); Giosafatto et al. (2012); Huang et al. (2017); Jiménez-Saiz et al. (2015); Ma et al. (2015)

pasteurization. Another study concluded that children with hyper-responsiveness to heated egg yolk in childhood can exhibit egg allergy for longer (Horino, Kitazawa, Satou & Miura, 2019). Recently, it was demonstrated that egg allergic children who eat regularly baked eggs are more likely to overcome allergy than egg allergic children who followed a strict diet without eggs. Additionally, they concluded that eat baked eggs daily seems to improve the tolerance to raw eggs (Pérez-Quintero, Martínez-Azcona, Balboa, & Vila, 2020).

5.2. Microwave

The thermal treatments using new technologies, such as microwave, have increasing over the last years. The microwave generates heat instantly and significantly reduces the processing time and operational cost when compared to the conventional dry-heating methods (Vanga et al., 2017; Ekezie, Sun, Han & Cheng, 2017; Li, Sun, Ma, Jin & Sheng, 2018). The main advantages of microwaves are the less time to start and

the fast and efficient heating, with reduced drying time, which can improve the product quality and food nutritional and sensory qualities. However, microwaves also show disadvantages, such as degradation of the products by dry heating and food dehydration. Since microwave heat induce alterations in the conformational structures and physical properties of food, different studies have been performed aiming the decrease of egg allergenicity (Cabanillas & Novak, 2019). Nevertheless, the microwave treatments can promote an increase as well as a decrease of the allergenicity, by changing the native structure of the proteins, which can mask or unmask epitopes in the allergen, expose buried amino acids or generate neoallergens (Cabanillas & Novak, 2019).

Recently, a study analysed an allergen threshold data from OFC given to children allergic to cooked egg and cow's milk, where the egg was heated in a microwave 600 W, 2×30 s. The results showed that the dose-distribution curves for reaction thresholds to mildly baked eggs at microwave do not exhibited significant differences, comparing to OFC using hard heated egg (Remington, Westerhout, Campbell & Turner, 2017). A ATR-FTIR and CD spectroscopy were used to evaluate the result of microwave treatment on the secondary structure of the egg white proteins and observed a reduction of α -helices levels and an increment of β -sheets (Zhu, Vanga, Wang, & Raghavan, 2018b). Moreover, it was found that microwaves can remarkably inactivate the egg white avidin, probably due to changes in the secondary structure. Modifications in the secondary and tertiary structures with aggregation of Gal d 2 were also found after glycation and microwave treatment (Hu et al., 2019). The changes affected the potential allergenicity of egg white, however additional analyses should be performed. Findings from a recent study (Li, Jin & Sheng, 2020) showed that microwave heating affects negatively the rehydration of egg white powder, nonetheless its modification by phosphorylation was able to inhibit this effect to some extent. The described studies analysed the structural and/or the physicochemical properties of egg proteins after microwave treatment, however additional experiments must be performed to verify the impact of this processing method in allergenicity of egg proteins.

5.3. High hydrostatic pressure

High hydrostatic pressure (HHP) has become an alternative to thermal treatment since it can improve microbial safety, physical changes in food components, nutrition and functionality, as well as bioactive properties without affecting organoleptic characteristics (Naderi, House, Pouliot & Doyen, 2017). On the other hand, high pressure can modify the structure of allergenic proteins in foods and reduce their allergenicity (Huang, Hsu, Yang & Wang, 2014). Current high-pressure homogenizers permit pressures 10–15 times higher than conventional ones, with ranges between 300 and 400 MPa, without deterioration of colour, flavour, texture, and nutritional value, since HHP does not break covalent bonds (Patrignani & Lanciotti, 2016). In fact, both high pressure processing and high-pressure homogenization can affect the digestibility and allergenicity of proteins, by modification of the secondary and tertiary structures due to the breakage of the non-covalent interactions (Rahaman, Vasiljevic & Ramchandran, 2016). A 10% decrease of immunoreactivity, analysed by an ELISA method, was observed after egg white high-pressure homogenization (Panozzo et al., 2014). The authors suggested that protein epitopes became bury during the unfolding and aggregation of the protein, which promotes a reduction of immune response. Egg protein denaturation and aggregation can occur depending on the specific pressure range of the HHP and on factors, such as protein concentration, duration of treatment, temperature and pH. Contrarily to pressures above 150 MPa, pressures below 100 MPa did not cause egg white protein aggregation (Gharbi & Labbafi, 2018). On the other hand, an improve in the allergenic potential of egg white, with increased Th2-biased response, was observed in a BALB/c model of egg allergy after heat and high-pressure treatments of egg white (Pablos-Tanarro et al., 2017). Despite some controversial results, the use of high-pressure processing technology, as a pre-treatment

procedure for food products, seems to afford the production of hypoallergenic foods, (Huang et al., 2014), however more studies based on mice allergy models, and also clinical trials, have to be performed to validate this approach (Costa et al., 2021).

5.4. Maillard reaction

The non-enzymatic reaction of amino acids or proteins with reducing sugars during thermal processing is named Maillard reaction (MR) (Gupta et al., 2018; Toda, Heliwig, Henle & Vieths, 2019). The initial process involves the formation of a Schiff base, by the reaction between the carbonyl group of the reducing sugar and an amine group of the protein that is converted in a stable product, a ketimine termed the Amadori product. The protein glycation finally can result in advanced glycation end-products (AGEs) that are present in thermal processed foods. The MR compounds are applied in the industrial food processing to confer functional characteristics to foods such as appearance, smell, taste and texture (Teodorowicz, van Neerven & Savelkoul, 2017). The AGE products have different sizes and chemical structures and can include compounds with adverse effects to human health, such as acrylamide and heterocyclic amines, known as carcinogens (Zhang, Wang, & Fu, 2020a). Since glycation can change the structures of allergenic proteins, different studies have been performed regarding the effects of AGEs formation on food allergenicity (Gupta et al., 2018; Zhang et al., 2020a).

An increase of Gal d 2 IgE binding after glycation was observed which can indicate the exposure of the epitopes initially buried (Ma et al., 2013). Different studies have concluded that the effects of the MR are varied (Teodorowicz et al., 2017; Gupta et al., 2018; Toda et al., 2019; Wang et al., 2020), and depend on different factors, such as type and concentration of reducing sugars, allergens thermal stability, the presence of basic amino acids residues in allergens, and processing conditions (e.g. temperature, pH, time). It is important to refer that glycation affects both linear and conformational structures of allergenic proteins and can hide the epitopes or form neoallergens which can result in a decrease, increase or even unchanged immunoreactivity (Rao, Jiang, Li, Samiwala, & Labuza, 2018). Thus, further research must be developed, in special *in vivo* studies, to confirm the impact of glycation in allergenicity of egg proteins.

Moreover, recently, it was suggested that MR products, like AGEs, when present in the diet, may act as inflammatory agents that affect the gut microbiome, and trigger the development of various pathologies, namely the allergic reactions (Toda et al., 2019; Zhang et al., 2020a).

5.5. Enzymatic treatment

Enzymatic hydrolysis is an efficient process for modification of food proteins allergenicity. Depending on the type of enzyme and the extent of hydrolysis, the enzymatic hydrolysis may break polypeptide sequences producing bioactive peptides and modifying their allergenicity by cleavage of conformational and linear epitopes (Rahaman et al., 2016; Chang, Lahti, Tanaka & Nickerson, 2018). Hypoallergenic pepsin hydrolysates of Gal d 2 down control the Th2 responses promoted by egg allergens and increase Th1 responses, thus being a potential candidate for peptide-based immunotherapy of egg allergic patients (Lozano-Ojalvo, Molina & López-Fandiño, 2016). Findings of Park et al. (2017) revealed that the deglycosylation of Gal d 2 after *N*-acetylglucosaminidase treatment reduced the degree of Gal d 2 antigenicity and allergenicity, after the analysis using a competitive indirect ELISA performed with both egg-allergic sera of children and rabbit antiserum to Gal d 2, respectively. In another study by Tong et al. (2018), a polyphenol oxidase catalysed cross-linking of Gal d 2 with caffeic acid significantly reduced the allergenicity potential of this allergen in a mouse model of Balb/, however it was not completely eliminated. Liu, Chen, Chen, Tong and Gao (2018) also found that enzymatic cross-linking of Gal d 2 with a polyphenol oxidase, in the presence of caffeic acid, decreased the

antigenicity, as a result of changes in the Gal d 2 conformation. In fact, it was observed a significant reduction in IgG and IgE binding to Gal d 2 epitopes after enzymatic treatment. These results are according to [Tong et al. \(2018\)](#) and suggest a new potential approach for producing hypoallergenic egg products. Nevertheless, since the reduction of allergenicity has been only partial, other strategies must be developed. Recently, [Gazme, Rezaei, and Udenigwe \(2020\)](#) studied the hydrolysis of egg white proteins by immobilized and free enzymes Neutrase and Thermolysin and concluded that proteolysis promotes a significant reduction in the immunoreactivity of egg white proteins, compared to *in vitro* digestion. However, IgE-binding capacities were not completely eliminated due to the presence of intact proteins, and also due to the several immunoreactive peptides from egg white proteins. Moreover, the epitopes more resistant to enzymatic hydrolysis were from Gal d 1.

5.6. Food irradiation

Radiation has been used for food conservation and to prevent changes in its nutritional and sensorial characteristics. Radiation can alter the immunoreactivity of certain food proteins by promoting structural and conformational modifications, such as cleavage of bonds, aggregation, crosslinking and amino acid alterations ([Dong, Wang, & Raghavan, 2021](#)). These effects are caused by free radicals produced due to water radiolysis during proteins irradiation ([Rahaman et al., 2016](#)). Despite some interesting studies using pulsed UV have been performed to reduce allergens in foods, such as soy, peanut and milk, there are still some contradictory results for eggs ([Dong et al., 2021](#)). In fact, it was observed that UV-C exposure of egg proteins promoted denaturation with a decrease in IgG-binding capacity ([Manzocco & Nicoli, 2012](#)). On the other hand, in another study by [Manzocco, Panozzo and Nicoli \(2012\)](#), no difference was found in IgE-binding capacity between irradiated and untreated egg white.

The effect of γ -radiation on Gal d 2 also promotes contradictory effects on IgE-binding capacity, with an increase at low levels of radiation and a decrease at higher ones. In fact, when submitted to γ -radiation (≥ 10 kGy), the IgE-binding to Gal d 2 is greatly reduced, as well as the secretion of cytokines (ILs-4 and -5) suppressing Th2 dominant immune response in a Gal d 2-allergic mouse model ([Seo et al. 2007](#)).

In conclusion, although food irradiation seems to be a potential technique to reduce the allergenicity of eggs, further studies should be carried out for its application in the food industry ([Dong et al., 2021](#))

5.7. Ultrasound

In the last years, ultrasound has been studied as potential alternative non-thermal process to decrease food allergenicity ([Nayak, Li, Ahmed, & Lin, 2017](#)). Ultrasound can promote changes in both conformational and physical features of proteins, affecting emulsification and solubility properties which can alter its allergenicity ([Zhu et al., 2018a](#)). Nevertheless, different results have been found since the effect of ultrasound differs with distinct food proteins ([Nayak et al., 2017](#)). [Stefanović et al. \(2014\)](#) obtained hydrolysates of egg white with lower molecular weight and potentially with decreased allergenicity, after combining ultrasound pre-hydrolysis treatment with proteases to improve functional properties of the proteins. On the other hand, [Yang, Tu, Wang, Li and Tian \(2017\)](#) showed a significant enhance in the IgG and IgE binding of Gal d 2 after high-intensity ultrasound. However, it was also considered a potential reduction in antigenicity since the protein unfolding and display of IgG and IgE epitopes can permit its alteration by the combination of other methods with ultrasound. In fact, glycation with mannose, after ultrasound pretreatment at 0–600 W, significantly reduced the IgG and IgE binding capacities of Gal d 2, due to the marked changes in its tertiary and secondary structures ([Yang, Tu, Wang, Zhang & Song, 2018](#)). [Sheng et al. \(2018\)](#) observed that high-intensity ultrasound has a significant effect on the egg white foaming properties by modification of the protein structure, however no immunoreactivity

experiments were performed to confirm the reduction in allergenicity. It has been suggested that ultrasound treatments seem to be more efficient when combined with other methods, such as heat or glycation, despite being considered an alternative non-thermal processing in the reduction of food allergenicity ([Dong et al. 2021](#)),

5.8. Microbial modification

Microbial transglutaminase (MTGase) is a transferase that can modify the functional and structural properties of food proteins by crosslinking and also by covalent conjugation of polyamines, lipid esterification, or deamidation of glutamine. MTGase has a high potential in food processing, since shows crosslinking efficiency as mammalian transglutaminases (TGases) in a great variety of food proteins, such as egg proteins ([Reddy, Singh, Sofi & Reddy, 2013](#)).

Despite the wide application of enzymatic crosslinking in the food industry, MTGase has not shown a great impact on the decrease of allergenicity of food proteins ([Jiménez-Saiz et al., 2015](#)). Nevertheless, a reduction in allergenicity of the major allergen of peanuts ([Wu et al. 2017](#)) or tofu ([Zhu et al., 2019](#)) was observed to a certain extent.

Most of the studies that applied MTGase to egg proteins have described changes in protein structure and an improvement in its digestibility; however, there has been no noticeable reduction in allergenicity. [Giosafatto et al. \(2012\)](#) proposed the use of TGase-modified Gal d 2 as a potential component to improve functional and mechanical properties, such as digestibility, and viscoelasticity, respectively. Despite the observation that MTGase crosslinking can modulate the gastric and duodenal digestibility of Gal d 2, its allergenic properties were not analysed in this study. A high pressure-assisted MTGase-induced Gal d 2 and egg white cross-linking was applied to improve gastroduodenal digestion, but no reducing in protein allergenicity was observed due the formation of high amounts of monomeric proteins, in addition to high-molecular weight polymers ([Ma, Ojalvo, Chen, Fandiño & Molina, 2015](#)). Nevertheless, it is important to refer the potential of enzyme crosslinking on gastroduodenal digestion of processed allergens, which in some cases can affect directly their allergenicity.

Besides the transglutaminases, the microbial fermentation has also a significant role in the nutritional and organoleptic properties of foods as well as in its preservation ([Ross, Hill, Stanton, Sugrue, Hill & Arendt, 2017](#)). Since is thought that food allergy results from a deficiency in mechanisms of immune tolerance, which are regulated by gut microbiota, different researchers have associated gut microbiota dysbiosis with the emergence of food allergies. Thus, it has been suggested that certain probiotic strains can be used to prevent allergy, due to its action in immune responses. However, more studies should be carried out to confirm and to characterize the interrelation between probiotics ingestion, the microbiome and the immune response mechanisms in allergy ([Canani et al., 2019; Fazlollahi et al., 2019](#)).

The gut microbial community has also been recognised as bringing a health benefit. New terms are emerging, such as paraprobiotics or postbiotics, showing that microbial fractions, or cell lysates, can also allow health benefits, providing additional bioactivity ([Huang et al., 2017](#)). In a recent study, [Song et al. \(2020\)](#) found that a new strain of *Lactobacillus rhamnosus* (Lr-0601) modulates gut microbiota and shows a potent immunoregulatory activity in mice sensitized to Gal d 2, which can be used as a potential approach against immune-related diseases.

6. Phenolic compounds: A new approach for reducing egg allergenicity?

Phenolic compounds are natural antioxidants and chemoprotective agents, originated from secondary metabolites, that are found in vegetables, fruits, grains, essential oils, tea, beverages and derived foods, widely used in food and medicine ([Ozdal, Capanoglu & Altay, 2013](#)). Their structure can have an aromatic ring bearing one hydroxyl group, named "phenolic", or one or more aromatic rings bearing more than one

hydroxyl group, designed “polyphenol” (Chu, Bao & Wu, 2018).

Phenolic compounds can bind to proteins by noncovalent interactions and also by stable covalent interactions (Chu et al., 2018, Perusko et al. 2017). Polyphenolic compounds can interact with food proteins forming complexes (Ozidal et al., 2013; He et al., 2019) that exhibit distinct physicochemical properties (Ulrich, 2015). These interactions promote modifications in the tertiary and secondary protein structures, and the formation of aggregates, depending on the type and size of the proteins (Ozidal et al., 2013).

It has been shown that interactions by phenolic compounds, such as gallic, coumaric, caffeic, ferulic, chlorogenic, tannic acids, resveratrol, and quercetin, can influence protein structure, functionality, and characteristics. The reaction between phenolic compounds and proteins can alter the solubility, thermal stability, foaming, emulsifying and gel properties (Chu et al., 2018). There are important characteristics that affect phenolic-protein interactions, such as molecular weight, structural flexibility, and abundance of hydroxyl groups (Buitimea-Cantúa, Gutiérrez-Urbe & Serna-Saldívar, 2018).

During the last years, different phenolic compounds have been tested to decrease or to eliminate the allergenic capacity of food proteins by changing their native conformation (He et al., 2019). Chung & Champagne (2009) conducted one of the first studies to verify the effect of phenolic compounds on food proteins. Results showed that addition of the caffeic, chlorogenic and ferulic acids to peanut extracts and liquid peanut butter promoted the irreversible precipitation of most of the major peanut allergens, Ara h 1 and Ara h 2 and, consequently, a 10- to 16-fold reduction of IgE binding in the soluble material. In a recent study, it was shown that complexation of polyphenols to peanut flour used in animal diet formulations can potentially lower plasma IgE of peanut-sensitized C3H/HeJ mice (Bansode, Randolph, Plundrich, Lila & Williams, 2019). The binding affinity between tannic acid and Gal d 2, bovine serum albumin and bovine β -lactoglobulin was evaluated by the analysis of intrinsic fluorescence of these proteins and it was observed that the binding affinities varied among the three proteins and depend on its structural differences (Xie, Wehling, Ciftci, & Zhang, 2017). Moreover, according to CD spectra, all the three proteins showed modifications in secondary and tertiary structures after binding with tannic acid, however no immunoreactivity studies were performed. Curiously, Zhang, Liu, Su, Roux & Sathe (2018) observed a stabilizing effect of tannic acid, tannin, ellagic acid, tea tannin, and walnut tannin on amandin against heat denaturation, which prevents the reduction of its immunoreactivity, as demonstrated by dot blot, Western blot and ELISA. On the other hand, a recent study (Wu et al., 2018) provided a novel strategy to produce hypoallergenic food, with reduced β -lactoglobulin IgE-binding capacity, due to structural change by promoting

covalent conjugation of this protein with the phenolic compounds epigallocatechin 3-gallate (EGCG) and chlorogenic acid. Pessato et al. (2018) also suggested an approach to diminish the allergenicity of whey proteins by complexation with EGCG involving non-covalent interactions that induced secondary and tertiary structure modifications.

In addition to above mentioned food proteins, different phenolic compounds, such as caffeic, chlorogenic and tannic acids, EGCG, quercetin and tea polyphenol, also form complexes with egg proteins and have been tested for reduction of its allergenicity (Table 3). Ognjenović et al. (2014) showed that the catechin EGCG binds to the major allergen of egg white, Gal d 2, promoting modifications in conformation of the protein. Nevertheless, the study reveals that EGCG-binding site does not fully overlap with the dominant epitope to which IgE binds. In this way, it is possible the interaction between Gal d 2 and IgE and also basophils degranulation. Shen et al. (2014) concluded that the strong conformational changes of Gal d 2 and Gal d 4, in presence of tea polyphenol, can promote and also inhibit digestion of these two egg white proteins. In fact, the structure of the polyphenol-protein complexes is affected by pH changes, resulting in different degrees of Gal d 2 and Gal d 4 unfolding and distinct digestibility. Li & Yan (2017) demonstrated the binding of Gal d 2 to five dietary antioxidants, with structural and thermodynamic changes observed by spectroscopic techniques that affect the allergen secondary structure and the folding. As previously mentioned, Tong et al. (2018) analyzed the OVA crosslinking by polyphenol oxidase in the presence of caffeic acid. On the other hand, a promising method for OVA hyposensitization by using the chlorogenic acid-OVA interaction showed that

changes in the protein structure resulted in a reduction of IgE-binding capacity (Lu et al., 2018). Tong et al. (2018) analyzed the Gal d 2 crosslinking by polyphenol oxidase, in the presence of caffeic acid, and observed a partial reduction of allergenicity of Gal d 2 in a mouse model, due to intermolecular aggregation and formation of polymers which affected the digestibility of this allergen. On the other hand, a promising method for Gal d 2 hyposensitization using the chlorogenic acid-OVA interaction showed a reduction in the capacity of IgE binding due to the hide of the linear IgE epitope by the binding of chlorogenic acid to the allergen (Lu et al., 2018). Moreover, when Gal d 2 was crosslinked with caffeic acid as intermediary, marked structural changes in epitopes were observed, with a reduction of antigenicity and potential allergenicity. The decrease in binding to IgE and IgG result from the alteration of the linear epitope due to the crosslinking restriction site being positioned in the allergic epitope. In addition, crosslinking promotes secondary structure disorder and exposure of hydrophobic regions in the surface of the protein, leading to conformational changes with destruction or alteration of conformational epitopes (Liu et al.

Table 3
Application of phenolic compounds for egg reducing allergenicity.

Phenolic compounds	Protein	Results	Changes	References
Caffeic Acid	OVA	Partial reduced allergenicity in a mouse model	Conformational changes and adjustment in epitopes	Liu et al. (2018); Tong et al. (2018)
Chlorogenic Acid	OVA	Decreased IgE binding	Conformational changes	Lu et al. (2018)
EGCG	OVA LYZ	Reduced allergenicity Decreased IgE binding	OVA unfold Conformational changes	He et al. (2019); Ognjenović et al. (2014)
Quercetin	OVA	Change in protein structure, functionality, and characteristics Reduced allergenicity <i>in vitro</i> and <i>in vivo</i> , in a mouse model. Reduced ability for IgE-binding Th1/Th2 modulation	Conformational changes and destruction or mask of the epitopes	Zhang et al. (2020)
Tannic Acid	OVA	–	Formation of complexes to use in nanoencapsulation systems for oral drug delivery	Xie et al. (2017)
Tea Polyphenol	OVA LYZ	Reduced allergenicity Improves pepsin digestion and prevents pancreatin digestion	Conformational changes Structural change of substrate affects the proteins digestion	Shen et al. (2014)

Glossary: EGCG - (-)-epigallocatechin 3-gallate; OVA – ovalbumin; LYZ – Lysozyme.

2018). The unfolding of Gal d 2 was analysed by spectroscopic methods after the covalent binding with EGCG. Besides the increase of digestibility and antioxidant activity, it was observed a lower IgE binding capacity compared with native Gal d 2, with a potential reducing of allergenicity (He et al., 2019). Recently, Zhang et al. (2020b) showed the binding of quercetin to Gal d 2 can diminish its allergenicity *in vitro* and *in vivo*, in a mouse model. It was observed a change in structure of Gal d 2 with destruction or mask of the epitopes, leading to a reduced capacity for binding to IgE and triggering cell degranulation. Also, the levels of specific IgE, IgG1, IgG and the expression of the high-affinity IgE receptor on sensitized mast cells surface were decreased. Moreover, a modulation of the Th1/Th2 immune response was observed, suggesting the suppressing of the allergic reaction promoted by Gal d 2 (Zhang et al. (2020b)).

The promising results obtained in different studies suggest that phenolic compounds, in addition to their well-known antioxidant activity, show a considerable potential for future use as agents or food additives to reduce eggs allergenicity or to prepare hypoallergenic products with adequate functional properties in the food industry.

7. What needs to be done in egg allergy? Challenges and perspectives

Currently, there are no treatments approved for egg allergy, although significant research is being developed to find potential therapeutic modalities. In fact, the treatment of egg allergy is based on avoiding foods with eggs in the composition until tolerance has been acquired. New approaches, such as microarray analysis and epitope mapping, are being made to follow up the implemented strategies in food processing for eliminating or reducing egg allergenicity (Chokshi & Sicherer, 2015). In this respect, IgE epitope mapping has arising as a novel process for diagnosis and prognosis of egg allergy, that can contribute to elucidate the mechanisms underlying the pathogenesis and tolerance development in allergy (Liu & Sathe, 2018).

Different experimental strategies have been developed using hypoallergens generated by site-directed mutagenesis within the IgE-binding epitopes, sequence restructuring, disruption of allergen conformation and digestion of allergen extracts (Wai et al., 2019). Site-directed mutagenesis was used to decrease the allergenicity of the major egg allergen Gal d 1 by breaking two disulfide bonds in domain 3. This mutant Gal d 1 with reduced IgE reactivity can be potentially used in immunotherapy for inducing tolerance to Gal d 1 and also for diagnostic purposes (Dhanapala, Withanage-Dona, Tang, Doran & Suphioglu, 2017). These new promising strategies are still restricted to animal models and preclinical characterization, so further studies in human subjects will be necessary to confirm safety and efficacy (Wai et al., 2019). Nevertheless, Yang & Kulis (2019) examined current evidence of safety and efficacy of hypoallergenic proteins in the treatment of food allergies and concluded that these new therapies could offer safer treatment alternatives. If the current research on egg allergy proves successful in the future, it will be highly beneficial since eggs are present in a wide variety of processed foods (Pablos-Tanarro et al., 2017).

A crescent number of studies on therapies for egg allergy have been performed with egg extracts, but there are no standardized protocols regarding the allergen load, treatments duration and the inclusion of control groups (Praticò et al., 2014; Wai et al., 2019). Also, a lack of standardized outcome measures to be applied in immunotherapy studies limits its evaluation. In fact, the success in allergen-specific immunotherapy trials can be assessed not only by desensitization or sustained irresponsive, but also by improved health related quality of life (Schoos et al., 2020). Future research with a larger sample of population is needed to study the effects of modified egg allergens from processed food in patients IgE reactivity and egg tolerance (Dhanapala et al., 2015). It is important to refer that most studies with processed eggs are *in vitro* and focus on the IgE-binding capacity instead on their allergenicity, whereas systematic research on the impact of processing methods

on eggs allergenicity under controlled conditions is less frequent (Rao et al., 2018). Since the efficient avoidance of egg allergens or immunotherapy are not always possible, it is fundamental to develop new processing methods that definitely eliminate the eggs allergenic potential (Stănciuc, Banu, Turturică, & Aprodu, 2016).

Additionally, the improvement of specificity and sensitivity of analytical methods for egg allergens detection is important not only to identify relevant allergens as food ingredients, but also for the risk assessment of the presence of unintended allergens resulted from cross-contact during manufacturing. A recent review of current analytical methodologies to verify the Voluntary Incidental Trace Allergen Labeling (VITAL®) concluded that the available methods, such as ELISA, PCR and mass spectrometry, present some problems for detection of egg allergens due to the range of detected single proteins and also due to matrix incompatibility of the method (Holzhauser et al., 2020). Nevertheless, high resolution mass spectrometry has emerging as an additional technique for egg allergen detection and quantification, as well as for identification of amino acid changes in allergens from processed foods (Gavage et al., 2019).

Recently, the researchers have been studying the ability of the gut microbiome to influence food allergy control (Canani et al., 2019). It was demonstrated that environmental factors, including a low-fat, high-fibre diet, and medications, can trigger intestinal microbiome dysbiosis, and were related with food allergy. Thus, the gut microbiome may be a future therapeutic target in egg allergy. However, the investigative approach to the gut microbiome is not considered enough, and more scientific evidence is needed to be brought into clinical practice (Canani et al., 2019).

Much research is being conducted on the role of metabolites and information is being derived from the intestinal microbiota, such as butyrate, which is thought to contribute to finding the way to a post-biotic approach to stimulate allergy tolerance (Paparo et al., 2019). Despite the mechanisms are not yet completely elucidated, there is increasing evidence that choosing the ideal bacterial strain, dosage, and time interval, is the best way forward (Sindher, Long, Acharya, Sampath & Nadeau, 2018; Paparo et al., 2019). In a recent study, it was found that the microbiota is related to individual food allergies and may vary according to food allergen, which led researchers to think that the distinct intestinal microbiota in allergic babies is associated with egg allergy and may serve to achieve preventive or therapeutic strategies (Fazlollahi et al., 2019).

8. Conclusions

Different processes have been applied to mitigate the allergenic potential of proteins and to reduce egg allergy. Unfortunately, the studies show that the allergenicity of egg proteins cannot be completely eliminated by the described methods, even when combined. Thus, the development of egg allergens with low allergenicity is demanding to be applied in immunotherapy to desensitize allergic patients and also for diagnostic purposes. It is also necessary to develop robust methods for the evaluation of allergenicity risk of egg foods. New approaches are needed to determine strategies for reducing food allergies related to the hen egg and to define worldwide standards for allergen extracts.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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