Nut Allergenicity

Nut allergenic proteins are characterized by their resistance to denaturation and proteolysis. Food processing is proposed as a tool to modify the allergenicity of nuts, to ensure their safety and to improve their organoleptic properties. The effect of processing (conventional and novel methods) on nut allergenicity is variable by abolishing existing epitopes or generating neoallergens.

Keywords: allergens ; food hypersensitivity ; nuts ; thermal processing ; pressure processing ; enzymatic digestion

1. Introduction

Currently, the main cause of anaphylactic reactions in Western countries is food allergies. It has been estimated that food allergies affect between 1 and 3% of the general population and up to 8% of children. Food allergies cause more than 30,000 anaphylactic reactions in the US [1]. In Europe, food allergies are the leading cause of anaphylaxis, and between 10 and 18% of anaphylactic reactions occur at school [2]. The list containing the 14 most allergenic foods in the European Union includes peanuts and tree nuts. In accordance with Regulation (EU) No. 1169/2011, the presence of nuts must be indicated on food labels [3]. After fruit, peanuts and tree nuts are the most prevalent cause of allergic reactions in Spain (26%) [4]. However, nuts are increasingly consumed in the last years due to their health benefits, which are attributable to their high content of protein, unsaturated fatty acids, vitamins and antioxidants [5].

Nut allergen proteins belong to seed storage proteins, such as legumin (11–13S globulin composed of acidic subunits of 30–40 kDa and basic 15–20 kDa), vicilin (7S globulin of approximately 50–60 kDa) and 2S albumin (15 kDa) [6]. Nut allergenic proteins are characterized by their resistance to denaturation and proteolysis [7]. Other nut allergens, such as pathogenesis-related (PR) proteins, profilins and lipid transfer proteins (LTP), are considered to be panallergens because they contribute to the allergenicity of a large group of seeds, pollen, nuts, fruit and other plants [8].

Food processing is used in the industry to ensure safety and to enhance organoleptic properties, in addition to altering food allergenicity. Food processing can modify the structure, properties and function of proteins, and as a result, the IgE-binding capacity of allergens can be affected. As some processing treatments have been shown to decrease the allergenicity of certain foods, food processing may play an important role in developing hypoallergenic foods and using them for food tolerance induction. Other processes, however, can increase the allergenicity of some foods [9]. Heat treatment modifies the structure of proteins, and therefore, epitopes and their immunogenic potential can be affected. This effects depends on both technological parameters and the type of matrix [10][11]. The effect of processing on allergenicity is variable and, as such, new allergenic compounds can be generated, while existing reactive epitopes can also be damaged or destroyed [12][13][14][15]. The structural changes produced using treatments such as boiling, microwave heating and pressure-cooking, and their effects on legume and nut allergenicity, have been evaluated. Importantly, findings indicate that heat- or pressure-based processing reduces IgE-binding capacity [12][13][14][15][16][17][18].

2. Most Prevalent Allergenic Nuts and Their Predominant Allergens

Nuts are a rich source of protein and other nutritional compounds with functional properties. This promotes their presence in manufactured foods. In Europe, tree nut allergies are common [19], with a hazelnut allergy being the most prevalent tree nut allergy. In the US, peanuts and tree nuts, such as almonds, walnuts or cashews, seem to be more common allergenic sources [20].

Table 1 summarizes the main nut allergens. Several hazelnut proteins have been described as allergens: Cor a 1 (Bet v 1 homologue), Cor a 2 (profilin), Cor a 8 (lipid transfer protein (LPT)), Cor a 9 (11S legumin), Cor a 11 (7S vicilin), Cor a 14 (2S albumin) and the oleosins Cor a 12, Cor a 13 and Cora a 15 [21]. Ana o 1 (7S vicilin) [22], Ana o 2 (11S legumin) [23] and Ana o 3 (2S albumin) have been identified and characterized as cashew allergens [24]. Pistachios are also well characterized for their allergenic potential and display high cross-reactivity with cashews and mangoes [25]. The five major

allergens in pistachios are one 2S albumin (Pis v 1), two 11S legumins (Pis v 2 and 5), one 7S vicilin (Pis v 3) and one superoxide dismutase (Pis v 4) [25][26][27][28]. Most of the epitopic regions of Pis v 1 and Pis v 3 showed a high degree of similarity with the Ana o 1, Ana o 2 and Ana o 3 epitopes. This is considered to be the molecular basis for the IgE-binding cross-reactivity observed between pistachios and cashews [29]. In almonds, six allergenic proteins have been characterized: Pru du 3 (LTP), Pru du 4 (profilin), Pru du 5 (60S ribosomal protein), Pru du 6 (11S legumin), Pru du 8 (antimicrobial seed storage protein) and Pru du 10 (mandelonitrile lyase 2) [30]. Thus far, five allergenic proteins have been identified in walnuts: Jug r 1 (2S albumin), Jug r 2 (7S vicilin), Jug r 3 (LTP), Jug r 4 (11S legumin) and Jug r 5 (profilin) [31]. The major allergen in walnuts is Jug r 4, which is highly homologous with other 11S globulin allergens, such as Cor a 9 (hazelnut), Ana o 2 (cashew) and Ara h 3 (peanut), explaining their IgE cross-reactivity [31].

Table 1. Allergens in nuts (WHO/IUIS Allergen Nomenclature Subcommittee).

Source	Allergen	Protein Family	MW* (kDa)
Hazelnut *(Corylus avellana)*	Cor a 1	Pathogen-related protein (PR10)	17
	Cor a 2	Profilin	14
	Cor a 8	Non-specific lipid transfer protein (LTP)	9
	Cor a 9	11S globulin/legumin	40
	Cor a 11	7S globulin/vicilin	47
	Cor a 12	Oleosin	17
	Cor a 13	Oleosin	14–16
	Cor a 14	2S albumin	16
	Cor a 15	Oleosin	17
Cashew *(Anacardium occidentale)*	Ana o 1	Vicilin-like protein	50
	Ana o 2	Legumin-like protein	55
	Ana o 3	2S albumin	14
Pistachio *(Pistachia vera)*	Pis v 1	2S albumin	7
	Pis v 2	11S globulin/legumin	32
	Pis v 3	7S globulin/vicilin	55
	Pis v 4	Manganese Superoxide dismutase	25.7
	Pis v 5	11S globulin/legumin	36
Almond *(Prunus dulcis)*	Pru du 3	Non-specific lipid transfer protein 1(LTP) Profilin	9
	Pru du 4	60S acidic ribosomal protein P2	14
	Pru du 5	11S globulin/legumin	10
	Pru du 6	Antimicrobial seed storage protein	60
	Pru du 8	Mandelonitrile lyase 2	31
	Pru du 10		60
Walnut *(Juglans regia)*	Jug r 1	2S albumin	15
	Jug r 2	7S globulin/vicilinNon-specific lipid transfer protein (LTP)	44
	Jug r 3	11S globulin/legumin	9
	Jug r 4	Profilin	36
	Jug r 5		20
Brazil nut *(Bertholletia excelsa)*	Ber e 1	2S sulfur-rich albumin	9
	Ber e 2	11S globulin	29
Chestnut *(Castanea sativa)*	Cas s 5	Chitinase	
	Cas s 8	Non-specific lipid transfer protein 1	12–13
	Cas s 9	Cytosolic class I small heat shock protein	17

MW*: molecular weight.

A study reported that the prevalence of tree nut allergies in the US was greater than 1.1% and was more common in individuals under 18 years of age [20]. In 2005, the European Commission funded a large Europe-wide research project (EuroPrevall) designed to evaluate and provide a broad overview of the prevalence, basis and cost of food allergies. For this project, 56 partners from 19 European countries collaborated [32]. Studies involved community surveys, birth cohort studies and clinical studies using double-blind placebo-controlled food challenges (DBPCFC) and SPT. The project provided knowledge about the prevalence of food allergies, as well as the ranking of allergenic foods (food groups) as a function of the number of reactions they provoke both in the overall population and in specific population groups (regarding age and geographic location). In this context, Lyons et al. [33] reported that the highest prevalence of nut allergies was estimated for hazelnut (4%) in accordance with challenge tests and sensitization assessed by SPT. Nut allergies appear to affect adults and adolescents more, probably due to their late introduction into the diet [34]. Hazelnuts are widely consumed in Europe and presented a high prevalence of positive reactions in a double blind, placebo-controlled food challenge (DBPCFC) [19]. In the US, 7.5% of the total of 188 participants were found to be allergic to hazelnuts in a 11-year follow-up study [35]. The effects of variety showed no influence on the allergenicity of hazelnuts,

with Cor a 9 and Cor a 1 being the predominant IgE-binding proteins in 13 European varieties [36]. Cashews are the second most allergic nut and a significant health problem in the US [37]. The anaphylactic reactions to cashew are, often, severe clinical manifestations, and even more dangerous than with peanuts. Cashew nuts are consumed all over the world due to their beneficial effects on human health, but they have also been reported to cause allergic reactions in sensitized patients [38]. In a study by Rance et al. [39], it was concluded that 2-year-old infants are more at risk among children sensitive to cashew nuts. The reactions were triggered in three-quarters of cases at first exposure. A possible explanation for this finding is that there is a correlation between earlier exposure to cashew nuts and a greater cashew nut allergy [40]. The symptoms upon the ingestion of cashews were also reported to be more severe compared to those caused due to exposure to other food allergens, such as nuts and peanuts [38]. Pistachio nuts are widely consumed all over the world and primarily produced in Iran and the United States. However, they have also been observed to cause significant allergic reactions in people sensitive to the allergens Pis v 1, Pis v 2 and Pis v 3 [41]. Sicherer et al. [35] estimated an allergy to pistachios in approximately 10% of the individuals evaluated. Almonds can provide many health benefits due to their low glycemic index and being a source of vitamin E and energy, manganese, fiber, protein and various polyphenolic components [5]. Almonds are ranked third after walnuts and cashews in eliciting allergic reactions [35], although some almond-allergic patients tend to pass oral food challenges, probably because many profilin-sensitized patients do not exhibit symptoms [30]. Amandin, or Almond Major Protein, is primarily responsible for IgE-mediated immunoreactivity. Walnuts are considered to be responsible for the highest number of allergic reactions in sensitized subjects [31], but they have health benefits, such as reducing the risk of diabetes and cardio-vascular diseases [5].
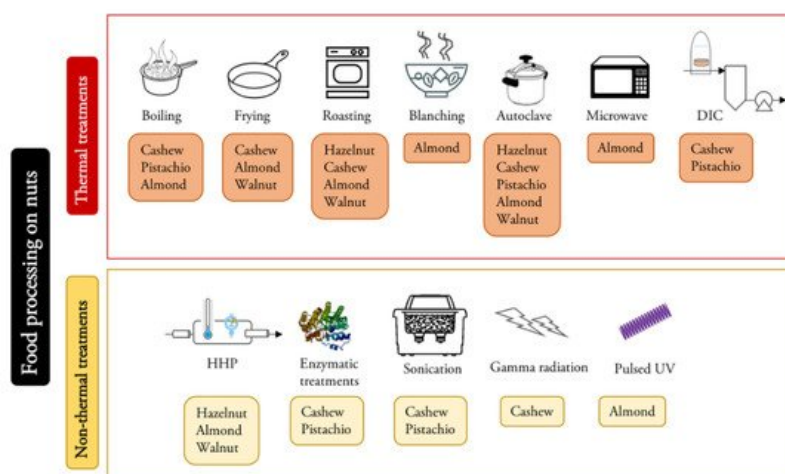
3. Food Processing

The reasons for consuming processed foods include ensuring preservation and safety; improving quality, such as flavor, color and taste; convenience; variety; out of season availability; and lack of equipment, time or skills needed for home food preparation of certain foods. A significant quantity of food is processed at home by consumers, in addition to industrial food processing and in institutional settings. The type of processing method can be chosen by product type, scale of processing, available infrastructure, consumer preferences and product sensory qualities. These reasons explain that the same raw food can be often processed differently [42]. As the majority of foods are usually consumed after processing, it was also relevant to understand the protein characteristics which are influenced by processing, such as stability against heat and pressure, as well as mechanical and chemical activities [43]. Thermal processing methods, such as boiling, frying, roasting, baking, pressure cooking or microwave heating, are applied to certain food products before consumption to improve their suitability for specific applications [44]. Non-thermal food processing, such as high hydrostatic pressure (HHP) or enzymatic treatment, can be applied to some foods. These processing treatments can modify the biochemical characteristics of proteins or generate chemical reactions within the food matrix components.

4. Effect of Thermal Processing on Food Allergens

Thermal and non-thermal processing methods are applied to foods to improve their preservation, quality, safety and suitability for specific product applications. The processing can affect the solubility, digestibility and other related parameters. Through thermal treatments, proteins can form oligomers, or become aggregated, denatured, fragmented or re-assembled, and these modifications can produce a decreased solubility [45]. The overall IgE-binding capacity of a particular extract can be more or less antigenic or result in new allergens (neoallergens) as a consequence of heat processing [46]. Thermal processing analysis is, therefore, necessary for assessing the allergenicity of existing and newly introduced foods [11]. The influence of heat processing mainly depends on the temperature and time conditions used. In addition, interactions with other food matrix constituents can affect the structure of a protein. Generally, the loss of a secondary structure occurs when the temperature is around 70–80 °C, while at 80–90 °C, rearrangements of disulfide bonds and the formation of new bonds take place. Aggregation occurs at higher temperatures (90–100 °C) [47].

The influence of a wide variety of treatments on the allergenicity of nuts has been studied (**Figure 1**, **Table 2**) [44][48][49]. Thermal treatments in walnuts [17]; HHP in hazelnuts [50]; and roasting, blanching, autoclaving and microwave heating in almonds [51] have been analyzed, and the results differ depending on the material and the conditions of the treatments studied. Studies with walnuts have indicated that the digestibility of protein probably increases after heat treatment, so the absorption of the protein can also increase in the gastrointestinal tract, and due to this, the possibility of allergens eliciting an allergenic response decreases [52]. However, in some cases, thermal processing may cause some neoantigens that were not originally present to form or the digestibility of a particular allergen may be reduced. These neoantigens may present an additional problem, and these facts can enhance the allergenic manifestation in sensitized patients. The formation of some neoantigens can be produced by the Maillard reaction when sugar residues interact with proteins during heating, generating sugar-conjugated protein derivatives, which enhance the allergenicity of some proteins, such

as 2S albumins [53]. However, glycation and aggregation from the Maillard reaction reduced the Ig E binding capacity of legumins and did not affect the IgE-binding capacity of vicilins and nsLTP [43]

Figure 1. Summary of food processing methods and their applications in the reviewed nuts.

Table 2. Effects of processing on IgE immunoreactivity of nut allergens.

Source	Processing Conditions	IgE Reactivity *	Reference
Hazelnut	Roasting 140 °C, 40 min	↓	Hansen et al. [54]
	Roasting 144 °C, time not indicated	↓	Worm et al. [55]
	Autoclaving 138 °C, 15 and 30 min	↓↓	Lopez et al. [56]; Cuadrado et al. [57]
	HHP 300–600 MPa, 15 min	=	Prieto et al. [50]; Cuadrado et al. [57]
Cashew	Boiling, 100 °C, 30 and 60 min	= (~↓)	Cuadrado et al. [14]; Sanchiz et al. [15]
	Boiling, 100 °C, 15 min + sodium sulfite	~↓	Mattison et al. [58]
	Frying, 191 °C, 1 min	= (~↓)	Su et al. [59]
	Roasting 200 °C, 15 min	~↑	Venkatachalam et al. [60]
	Autoclaving 138 °C, 15 and 30 min	↓	Cuadrado et al. [14]; Sanchiz et al. [15]
	Autoclaving 138 °C, 30 min + Amano 3DS 120 min	↓↓	Cuadrado et al. [14]
	DIC 7 bar, 2 min	↓↓	Vicente et al. [61]
Pistachio	Boiling, 100 °C, 30 and 60 min	= (~↓)	Cuadrado et al. [14]; Sanchiz et al. [15]
	Steaming	~↓	Noorbakhsh et al. [62];
	Autoclaving 138 °C, 15 and 30 min	↓	Cuadrado et al. [14]; Sanchiz et al. [15]
	Autoclaving 138 °C, 30 min + Amano SD 60 min	↓↓	Cuadrado et al. [14]
	DIC 7 bar, 2 min	↓↓	Vicente et al. [61]
Almond	Boiling, 100 °C, 5 and 10 min	=	Su et al. [59]
	Frying, 191 °C, 1 min	= (~↓)	Su et al. [59]
	Roasting 180 °C, 15 min	=	Su et al. [59]
	Autoclaving 121 °C, 30 min	=	Venkatachalam et al. [51]
	Autoclaving 138 °C, 15 and 30 min	↓↓	Cuadrado et al. [57]
	HHP 300–600 MPa, 15 min	=	Cuadrado et al. [57]

Source	Processing Conditions	IgE Reactivity *	Reference
Walnut	**Frying, 191°C, 1 min**	**= (~↓)**	**Su et al. [59]**
	Roasting 160 °C, 30 min; 177 °C, 12 min	**=**	**Su et al. [59]**
	Autoclaving 138 °C, 15 and 30 min	**↓↓**	**Cabanillas et al. [17].**
	HHP 300–600 MPa, 15 min	**=**	**Cabanillas et al. [17].**

* IgE reactivity determined by different techniques and conditions. Pictography: =, ↓, ↑, ~, are a symbolic representation of the global effect of the specific treatment on the IgE reactivity of a given food (=, similar; ↑, increase; ↓, decrease; ~ ↑, slight increase; ~↓, slight decrease).

The IgE recognizes and interacts with epitopes belonging to allergenic proteins.

Two types of IgE binding epitopes are possible, either linear or conformational ones. In linear epitopes, amino acid is arranged in linear order in the polypeptide chain, while in the conformational epitopes, amino acids are far apart in the primary sequence but may come together during the folding of the polypeptide chain. Linear epitopes may be more problematic as compared to the conformational ones, as they are mostly resistant to heat treatment. Thermal processing mainly affects conformational epitopes as the bonds can be broken down due to heat. Refolding allows the formation of native conformational epitopes, but few new allergens may be formed, which requires further efforts to minimize the risk associated with neoantigens [63]. Thus, thermal processing can strongly alter the structure, function and allergenicity of foods.

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