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REVIEW



Sesame allergy: mechanisms, prevalence, allergens, residue detection, effects of processing and cross-reactivity

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ABSTRACT

Sesame allergy is a serious public health problem and is mainly induced by IgE-mediated reactions, whose prevalence is distributed all over the world. Sesame has been included on the priority allergic food list in many countries. This review summarizes the mechanism and prevalence of sesame allergy. The characteristics, structures and epitopes of sesame allergens (Ses i 1 to Ses i 7) are included. Moreover, the detection methods for sesame allergens are evaluated, including nucleic-acid, immunoassays, mass spectrometry, and biosensors. Various processing techniques for reducing sesame allergenicity are discussed. Additionally, the potential cross-reactivity of sesame with other plant foods is assessed. It is found that the allergenicity of sesame is related to the structures and epitopes of sesame allergens. Immunoassays and mass spectrometry are the major analytical tools for detecting and quantifying sesame allergens in food. Limited technologies have been successfully used to reduce the antigenicity of sesame, involving microwave heating, high hydrostatic pressure, salt and pH treatment. More technologies for reducing the allergenicity of sesame should be widely investigated in future studies. The reduction of allergenicity in processed sesames should be ultimately confirmed by clinical studies. What's more, sesame may exhibit cross-reactivity with peanut and tree nuts.

KEYWORDS

Sesame allergy; sesame allergen; mechanisms; prevalence; processing for reducing allergenicity

Introduction

Sesame (*sesamum indicum* L.) is a global agricultural crop with an increased harvested area (5.0 million ha in 1961 to 12.8 million ha in 2019) and production (1.4 million tonnes in 1961 to 6.5 million tonnes in 2019) (Figure 1A) (FAO 2021). At present, sesame is mainly cultivated in non-developed countries such as Brazil, China, India, Nigeria, Sudan, Uganda, in which Sudan had the highest yield (1,210,000 tonnes) and planting area (4,243,680 ha) according to FAO (Figure 1B) (FAO 2021). Additionally, sesame has been used in many foods (e.g., breads, cakes, snacks, biscuits, dishes, burgers, dressings, and edible oil) (Torricelli et al. 2020). However, sesame has become a new major food allergen according to the risk assessment of food allergens from FAO/WHO on 10 May 2021. Additionally, sesame has been included as a priority/major food allergen in some countries such as Canada prior to the FAO/WHO consultation. Sesame allergy was reported to affect 0.1–0.2% of the general population (Touma, La Vieille, et al. 2021; Ziegler and Aalberse 2020). Similar to peanut, shellfish, tree nuts and fish, sesame allergy is likely to persist throughout life (Pi, Yang, Sun, Wang, et al. 2021; Ziegler and Aalberse

2020). As shown in Figure 1C, sesame allergy has been reported in many countries such as the Canada and United States, and its incidence is on the rise (Ben-Shoshan et al. 2010; Ben-Shoshan et al. 2012; Du Toit et al. 2008; Gupta et al. 2018; Osborne et al. 2011; Protudjer and Abrams 2019; Sicherer et al. 2010; Soller et al. 2015). At present, sesame allergy has attracted more attention, which is reflected by the increase in published articles about sesame allergy (Figure 1D).

Sesame seeds provide nearly 44–57% lipid, 18–25% protein, 13–14% carbohydrates, 2.46% minerals, and 0.088% polyphenols (Mujtaba et al. 2020; Pal, Chandra, and Sachan 2020), demonstrating many health-promoting effects or properties such as anti-oxidative, anti-inflammatory, anti-cancer, antihypertensive, mitigation of neurodegeneration, regulation of intestinal microbial (Liu et al. 2021; Majdalawieh and Mansour 2019; Mohamed et al. 2021; Pal, Chandra, and Sachan 2020; Figure 2). Therefore, due to their great bioactive and nutritional components, sesame seeds have been widely used in many industries such as pharmaceuticals, foods, cosmetics, and biodiesel (Segla Koffi Dossou et al. 2022). To avoid serious health problems (e.g., anaphylactic shock and death) during its application, an

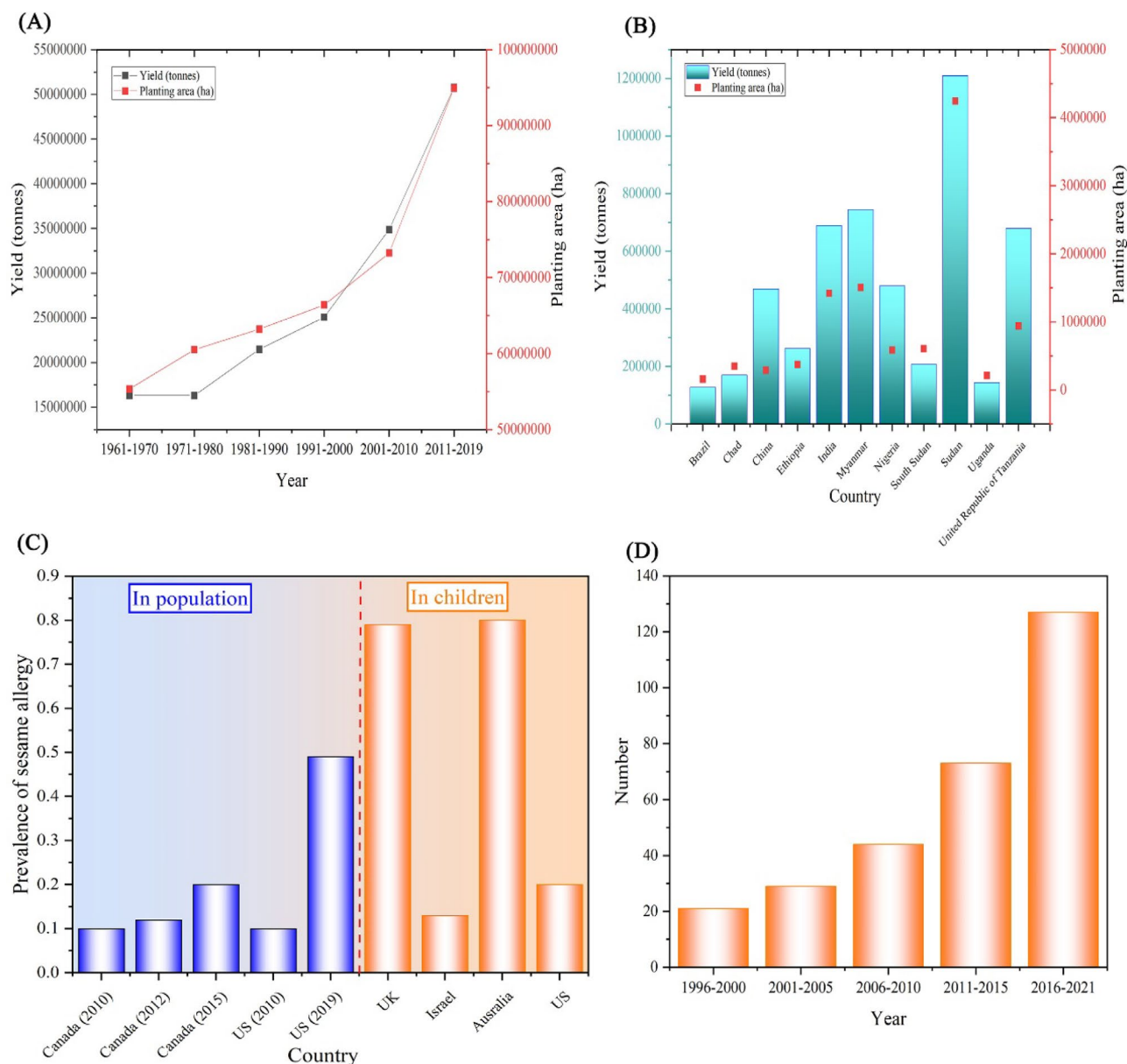


Figure 1. The situation of sesame planting and sesame allergy. (A) The changes in sesame planting area and its yield from 1961 to 2019 around the world. The data was from FAO (2021). (B) High planting area and yield of sesame among some countries in 2019. The data was from FAO (2021). (C) The prevalence of sesame allergy in population and children among some countries, respectively. The data was from Ben-Shoshan et al. (2010), Ben-Shoshan et al. (2012), Du Toit et al. (2008), Gupta et al. (2018), Osborne et al. (2011), Protudjer and Abrams (2019), Sicherer et al. (2010) and Soller et al. (2015). (D) The number of published papers about sesame allergy. The dates are from the Web of science.

assessment of sesame allergy and sesame allergens is needed. At present, several reviews (Adatia et al. 2017; Gangur, Kelly, and Navuluri 2005; Orruno and Morgan 2006; Patel and Bahna 2016) have evaluated sesamum allergy involving diagnosis and prevention. However, the mechanism and prevalence of sesame allergy, characteristics and detection of sesame allergens, and the reduced allergenicity effect of processing have not been reported or well explained. Thus, we provide a comprehensive and up-to-date overview on these contents after reviewing the published literature about sesame allergy and sesame allergen by Web of Science, ScienceDirect, PubMed and Google Scholar, which may provide references for future research on sesame allergy and

provide the foundation for producing hypoallergenic sesame products.

The mechanism of sesame allergy

Sesame allergy is classified into immunoglobulin (IgE) mediated, non-IgE-mediated and occupational reactions (Chen, Wu, and Deng 2015), in which IgE-mediated reactions are mainly responsible for sesame allergy (Nemni et al. 2021). As shown in Figure 3, sesame allergens were carried to local lymph nodes and presented to CD4+ T cells, resulting in the TH2 cell differentiation of naive CD4+ T cells and activation of Th2 cell-related allergic responses.

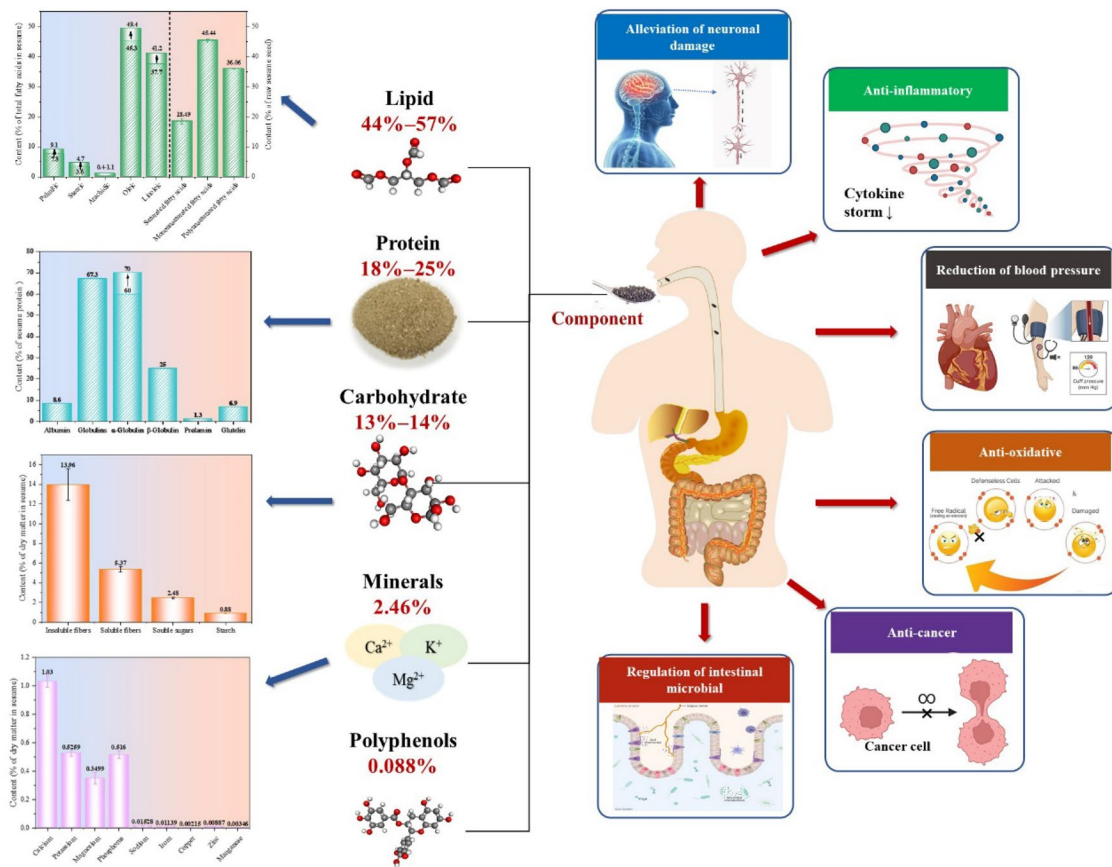


Figure 2. The composition and function of sesame. The composition data was from Mujtaba et al. (2020), and Pal, Chandra, and Sachan (2020). The figure was edited through biorender.

Specific IgE antibodies produced from B cells bind to sesame allergen to result in the release of mediators induced by degranulation of mast cells, which induces issues in the cardiovascular, integumentary, respiratory, and nervous systems. In addition, IL-4, IL-5, IL-9 and IL-13 produced by Th2 cells and type 2 innate lymphoid cell (ILC2) induce the accumulation of eosinophil and basophil and suppression of Th1 and Treg to result in the increase of mediator for allergic reactions (Pi, Yang, Sun, Cui, et al. 2021; Renz et al. 2018; Yu, Freeland, and Nadeau 2016). The IgE-mediated symptoms usually manifest within 2 hours of exposure to sesame allergens (Manuyakorn and Tanpowpong 2019). In contrast, non-IgE mediated symptoms usually manifest 2–24 hours after exposure to allergens (Manuyakorn and Tanpowpong 2019), including food protein-induced enterocolitis, enteropathy, proctocolitis and allergic eosinophilic gastroenteritis (Chen, Wu, and Deng 2015; Ovadia et al. 2019). In contrast to IgE-mediated sesame allergy, non-IgE-mediated sesame allergy is rare to lead to a life-threatening ailment, such as trouble in breathing and anaphylaxis (Ahmed et al. 2021). For occupational reactions, inhalation and skin contact may be the main reason, and allergenic reactions (bronchospasm) usually manifest when non-working (Patel and Bahna 2016). Overall, sesame allergy can be triggered by 1.02 mg of sesame protein (Adatia et al. 2017), corresponding to two raw sesame seeds (Dano et al. 2015).

Prevalence of sesame allergy

Sesame allergy has been a global issue that affects human health, and the prevalence of sesame allergy has been reported in various countries such as Britain, Israel, US, Canada, Australia, Kuwait and Lebanon, etc (Aaronov et al. 2008; Ali 2017; Derby, Gowland, and Hourihane 2005; Irani and Maalouly 2015; Nachshon et al. 2019; Saf et al. 2020; Soller et al. 2015; Table 1). In Israel, sesame allergy is the 2nd most common food allergy in children (Nemni et al. 2021), accounting for 43% of allergic cases in children (Adatia et al. 2017). The prevalence rates of 0.13–0.93% for sesame allergy in Israel children were observed by Dalal et al. (2002), Du Toit et al. (2008) and Garkaby et al. (2021). Carla Irani et al. (2011) conducted the 1842 population survey in Lebanon and found that the prevalence of sesame allergy was 3.79% in infants with food allergy, followed by 2.65% in children and 1.91% in adults. In addition, sesame allergy is the 3rd most common food allergy in Lebanon children behind milk (1st) and egg (2nd) (Baz 2016). For Australian children, sesame allergy is the 5th most common allergen responsible for food allergy (Dalal et al. 2002). Sesame is also the 3rd most common allergen responsible for food allergy in Saudi Arabia (Nemni et al. 2021; Touma, Dominguez, et al. 2021). Interestingly, the prevalence of sesame allergy was increased from 0.1% to 0.2% ranging from 2010 to 2015 in Canada (Ben-Shoshan et al. 2010; Soller

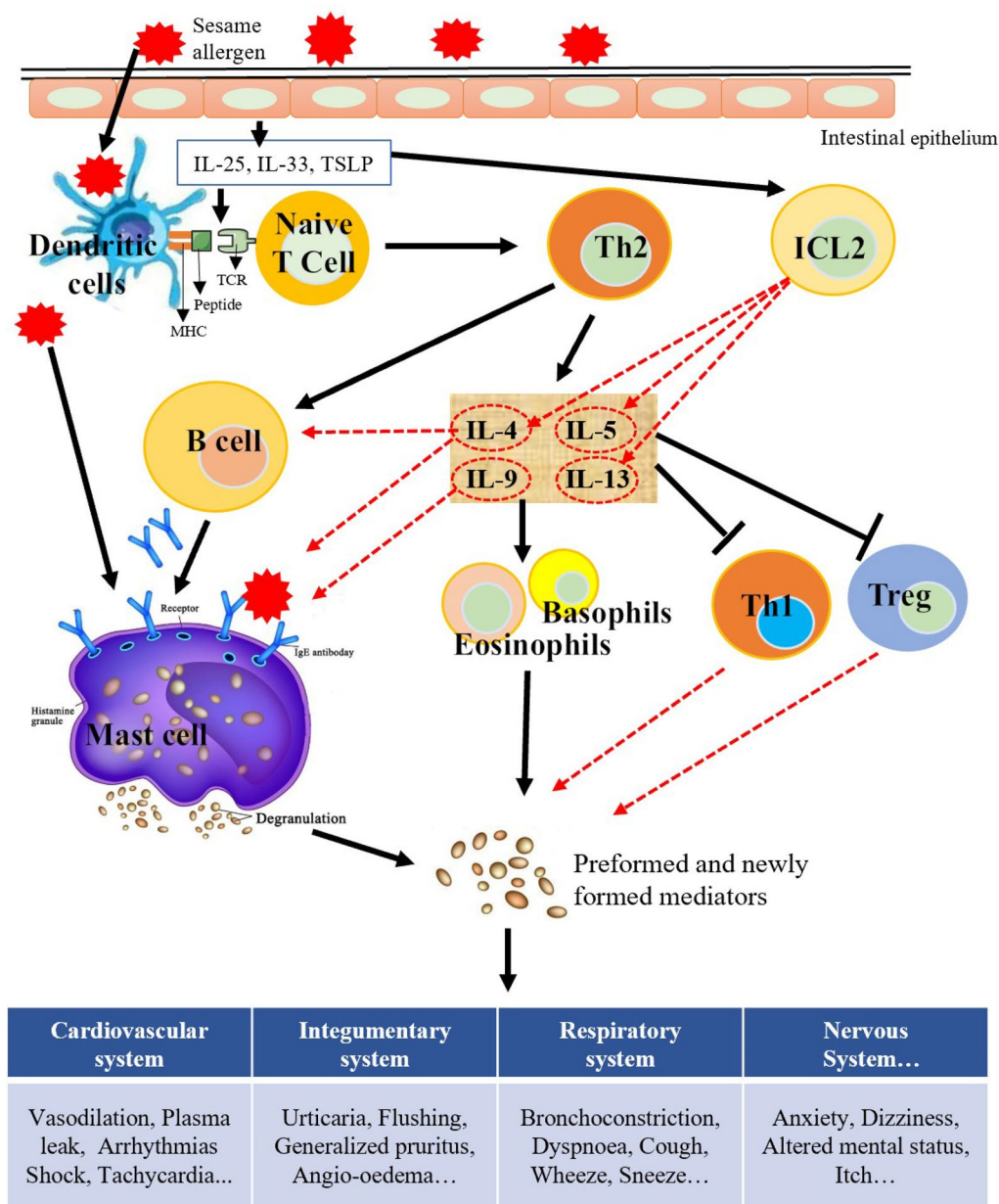


Figure 3. The mechanism of IgE-mediated sesame allergy. → and → indicates the facilitation or conversion effects, — represents the inhibition effects.

et al. 2015) and from 0.1% to 0.49% ranging from 2010 to 2019 in the US (Protudjer and Abrams 2019; Sicherer et al. 2010; Warren et al. 2019), which indicated that the prevalence of sesame allergy was on the rise in some countries.

The prevalence of sesame allergy is related to the survey method and population. Sasaki et al. (2018) found that the prevalence of sesame allergy in adolescents was 0.3% by questionnaire but was 0.2% by oral food challenge (OFC). Thus, the prevalence of sesame allergy is usually over-estimated by questionnaires because the response of the questionnaire is not confirmed clinical symptoms. Similar results were shown in Warren et al. (2019), who reported that the high prevalence of sesame allergy was observed in US adults and children through the self-report method, followed by the history of convincing symptoms or physician diagnosis, and physician diagnosis. Significant different prevalence was also observed in different

population ages (Warren et al. 2019), and different population numbers (Ben-Shoshan et al. 2012; Soller et al. 2012). Therefore, to obtain the accurate prevalence, great respondents, reasonable age distribution and confirmed allergenic criteria are necessary for surveys. The diagnosis of sesame allergy can be achieved in many ways, including DBPCFC (double-blind, placebo-controlled food challenge), skin prick test (SPT), serum-specific IgE level, oral food challenge (OFC), basophil activation test (BAT) (Orruno and Morgan 2006; Patel and Bahna 2016; Salari et al. 2020; Santos et al. 2021; Teodorowicz et al. 2016). The DBPCFC is the gold standard for the diagnosis of sesame allergy (Orruno and Morgan 2006), and OFC is essential for diagnosis and should be carried out with caution under experienced supervision (Li et al. 2017). However, DBPCFC and OFC might be inappropriate in some cases for extensive surveys due to their time-consuming, expensive and risk of serious

Table 1. Summary of studies addressing the prevalence of sesame allergy.

Author, year	Population	Basis	Country/region	Prevalence of sesame allergy
Dalal et al. (2002)	9070 infants and young children (0–2 years)	Questionnaire and SPT	Central Israel	0.18%
Venter et al. (2006)	798 children (6 years)	Questionnaire and SPT	Isle of Wight (UK)	0.60%
Du Toit et al. (2008)	5171 Jewish children	Questionnaire, SPT and slgE	UK	0.79%
Sicherer et al. (2010)	13,534 subjects	Questionnaire	US	0.10%
Ben-Shoshan et al. (2010)	3613 subjects	Questionnaire, SPT and clinical records	Canada	0.10%
Osborne et al. (2011)	2848 infants (12-month-old)	SPT	Australia	0.80%
Ben-Shoshan et al. (2012)	4169 subjects	Telephone survey, self-report	Canada	0.12%
Irani and Maaloully (2015)	506 subjects	Telephone survey and questionnaire	Lebanon	5.0%
Soller et al. (2015)	4026 subjects	Telephone survey	Canada	0.20%
Peters et al. (2017)	3142 children age 4-year	OFC and SPT	Melbourne, Australia	0.40%
Peters et al. (2017)	5276 children age 1 year	OFC and SPT	Melbourne, Australia	0.60%
(Ali 2017)	865 Young Adult	Self-Report	Kuwait	0.46%
	Students at Kuwait University			
Sasaki et al. (2018)	5016 adolescents	OFC	Melbourne in Australia	0.20%
Sasaki et al. (2018)	4800 adolescents	Questionnaire	Melbourne in Australia	0.30%
Gupta et al. (2018)	38,408 children	Questionnaire	US	0.20%
Warren et al. (2019)	78,851 individuals (40,453 adults and 38,408 children)	Questionnaires	US	0.49%
Protudjer and Abrams (2019)	40,453 adults and 38,408 children	Questionnaires	US	0.49%
Nachshon et al. (2019)	12,592 Adults	Self-Report and slgE	Israeli	0.09%
Garkaby et al. (2021)	1932 young children ranged 18–30 months	Questionnaire, SPT and OFC	North Israel	0.93%

SPT=skin prick test. slgE=serum-specific IgE test. OFC=oral food challenge, usually not blinded.

health problems (e.g., anaphylactic shock and death). Additionally, vitro techniques (SPT, specific IgE, BAT) may be unsatisfactory because they cannot simulate the “real life” situation of sesame allergens in the body, which may be because sesame allergens generally cause an allergic reaction in the intestines (Goto et al. 2008; Orruno and Morgan 2006). Therefore, the combination of Vitro techniques (SPT, specific IgE, BAT), clinical history and cautious OFC may be an effective and suitable way to diagnose sesame allergy for extensive surveys. This combination method has been used by Garkaby et al. (2021), Nachshon et al. (2019) and Peters et al. (2017), presenting the most reliable prevalence for sesame in Australia and Israel. Overall, sesame allergy has spread all over the world at a high prevalence. The prevalence of sesame allergy is not generally compared unless under the same survey method and a similar population number. Results of many studies can't be expanded to the general population due to the

creation of selection bias in surveys. Therefore, the prevalence of sesame allergy still needs further evaluation.

Characteristics of sesame allergens

At present, the World Health Organization and International Union of Immunological Societies (WHO/IUIS) Allergen Nomenclature Subcommittee has identified 7 sesame allergens, namely Ses i 1 to Ses i 7 (Sub-Committee., 2022). Among these sesame allergens (Table 2), Ses i 1 and Ses i 2 (from the 2S albumin, 15–25% of total sesame proteins), Ses i 3 (from 7S globulin, 5%), and Ses i 6 and Ses i 7 (from 11S globulin, 60–70%) are mainly responsible for serious allergenic reactions to sesame (Hsiao et al. 2006; Ma et al. 2020; Orruno and Morgan 2007; Patel and Bahna 2016). 2S albumin is typically a heterodimeric protein composed of a single polypeptide chain, consisting of a small subunit (4kDa) and a large subunit (9kDa) connected by

Table 2. Sesame allergens.

Allergen (Sub-Committee., 2022)	Biochemical name (Sub-Committee., 2022)	MW/kDa (SDS-PAGE) (Sub-Committee., 2022)	Isoelectric point (Bouakkadia et al. 2015)	Recognition by sesame-allergic patients (Sub-Committee., 2022)	Length of peptide chain (Xiuli et al. 2019)	Uniprot number (Xiuli et al. 2019)	Biological function (Agne, Rancé, and Bidat 2003; Xiuli et al. 2019)	Contents (% of sesame proteins) (Hsiao et al. 2006)
Ses i 1	2S albumin	9	8.1	100% (10 of 10)	153	Q9AUD1	Seed storage protein	15–25
Ses i 2	2S albumin	7	6.1	66.7% (24 of 36) (Maruyama et al. 2016)	148	Q9XHP1	Seed storage protein	
Ses i 3	7S vicilin-like globulin	45	7.6	60% (12 of 20)	585	Q9AUD0	Seed storage protein	1–2
Ses i 4	Oleolin	17	9.8	100% (32 of 32)	166	Q9FUJ9	Carrier protein	1–2
Ses i 5	Oleolin	15	10.1	100% (32 of 32)	153	Q9XHP2	Carrier protein	
Ses i 6	11S globulin	52	7.7	52% (13 of 25)	459	Q9XHP0	Seed storage protein	60–70
Ses i 7	11S globulin	57	8.6	40% (10 of 25)	497	Q9AUD2	Seed storage protein	

The references marked in the first line of the table are responsible for the contents of the table, unless otherwise noted.

two disulfide bonds (Beyer et al. 2002; Hsiao et al. 2006; Estibalitz Orruño and Morgan 2011). However, the disulfide bond is not observed in 7S globulin, and it is composed of at least eight polypeptide chains (12.4 to 65.5 kDa) and is considered a minor constituent of the total storage proteins in sesame (Orruño and Morgan 2011). The 11S globulin has a hexamer structure composed of six non-covalently interacting subunits (Orruño and Morgan 2011). Each 11S globulin subunit contains an acidic polypeptide (30–34 kDa) and a basic polypeptide (20–25 kDa) linked by a disulfide bond (Hsiao et al. 2006; Orruño and Morgan 2011), in which the basic subunit plays an important role in sesame allergy (Magni et al. 2010). It was reported that the 2S albumin was extremely or relatively stable to hydrolysis of pepsin or trypsin and chymotrypsin, respectively (Orruño and Morgan 2011). In contrast, both 7S and 11S proteins were relatively labile to pepsin but extremely labile to trypsin and chymotrypsin (Orruño and Morgan 2011). In addition, basic peptides from 11S protein are less susceptible to proteolysis than acidic peptides (Orruño and Morgan 2011), which is probably responsible for a more critical role in sesame allergy compared to acidic peptides (Magni et al. 2010).

Ses i 1

Ses i 1, a storage protein, is stable for acid conditions, thermal processing and digestion with trypsin and proteolytic enzyme, resulting from the firm compaction by disulfide bonds and loss of the restriction enzyme site (Achouri and Boye 2013; Honjoya et al. 2021; Moreno et al. 2005). In general, the Ses i 1 is stable up to 90°C at neutral and acid pH, showing minimal and reversible changes (mainly α -helical secondary structure) (Moreno et al. 2005). In addition, it retains the intact structure within 2 h of gastric digestion and only loss the small subunit within 2 h of subsequent duodenal digestion so that many of the IgE epitope regions of the protein remain intact (Moreno et al. 2005), resulting in the absorption of immunologically active form and the elicitation of allergic reactions (Javier Moreno et al. 2006). Therefore, linear and conformational epitopes in Ses i 1 might retain after treatment with acid conditions, thermal processing and enzyme, resulting in an essential alteration of the ability to trigger an allergic reaction. Moreover, Ses i 1-sIgE (specific IgE antibodies) is promising for diagnosing sesame allergy (Maruyama et al. 2016; Saf et al. 2020; Yanagida et al. 2019) because Ses i 1 can be recognized by 100% (10 of 10) patients allergic to sesame (Beyer et al. 2002). Additionally, Ses i 1-sIgE has its superior diagnostic accuracy over the whole sesame-sIgE and Ses i 2-sIgE (Goldberg et al. 2021; Lemoine-Courcelles et al. 2021; Saf et al. 2020).

Ses i 2

Ses i 2 is also a storage protein and has some sequence similarity (50%) and identity (35%) with Ses i 1 (Maruyama et al. 2016). Although the structure of Ses i 2 is similar to

that of Ses i 1 (Figure 4A, B), Ses i 2 was less allergenic than Ses i 1 (Maruyama et al. 2016). Ses i 2 was reported to be recognized by 30% of the patients with sesame allergy (Beyer et al. 2002). As shown in Table 3, at least 9 different epitopes are identified, in which epitopes 1 (AA46-55, SRQCQMRHCM), 2 (AA48-57, QCQMRHCMQW), 5 (AA76-86, NQGQFEHFREC) are immunodominant IgE-binding epitopes, which was all recognized by 93.3% (14 of 15) patients with sesame allergy (Wolff et al. 2004).

Ses i 3

Ses i 3 has a trimer structure (Figure 3C) (Ma et al. 2021) and consist of various polypeptides, but not contains a disulfide bond (Magni et al. 2010). The main forces of holding the polypeptides together are hydrogen bonding, hydrophobic and electrostatic forces (Orruño and Morgan 2007). Therefore, Ses i 3 can be dissociated in an alkaline environment (Orruño and Morgan 2007). Ses i 3 was reported to be recognized by 75% of the patients with sesame allergy (Beyer et al. 2002). Compared to Ses i 1 and Ses i 2, Ses i 3 is a minor constituent in sesame seeds (Beyer et al. 2002; Leduc et al. 2006). In contrast to 11S globulin (Ses i 6 and 7) and 2S albumin (Ses i 1 and 2), Ses i 3 has a potential N-glycosylation site (Maruyama et al. 2016). As shown in Figure 4C, there is 36.24% α -helix, 19.32% β -sheets, 10.09% β -turns and 34.36% random coils based on SOPMA prediction, in which β -turns and random coils are the dominant regions of the epitopes (Table 3) (Ma et al. 2021).

Ses i 4 to Ses i 7

Ses i 4 and Ses i 5 are derived from oleosins and considered transmembrane protein (Ma et al. 2021). Oleosins represents only 1–2% of total seed proteins, and corresponds to 80–90% of total oil body proteins (Leduc et al. 2006). Ses i 4 and Ses i 5 was reported to be recognized by all 32 patients allergic to sesame, suggesting that oleosins were major allergens in sesame seed (Leduc et al. 2006). However, Ehlers et al. (2019) demonstrated that sesame oleosins are minor allergens because low levels of specific IgE to sesame oleosins were detected in 17% of sesame allergic and 15% of tolerant patients with sIgE sensitization. Therefore, whether Ses i 4 and Ses i 5 are considered major sesame allergens needs to be investigated and confirmed in future studies. Notably, Ses i 4 and Ses i 5 can also cause severe reactions (Patel and Bahna 2016; Wallowitz et al. 2007).

Ses i 6 and Ses i 7 are 11S globulin, and there is a 36% identity between Ses i 6 and Ses i 7 (Beyer et al. 2007b). It was reported that the expressed recombinant Ses i 6 and Ses i 7 was recognized by 54.2% and 41.7% of patients with sesame seed allergy, respectively (Beyer et al. 2007a). 11S globulins consist of a group of acidic and basic polypeptide chains (Magni et al. 2010). The acidic and, mostly, basic subunits of 11S globulins may actually represent the major sesame seed allergens (Magni et al. 2010). Compared to the acidic subunits, the basic subunits are less accessible to

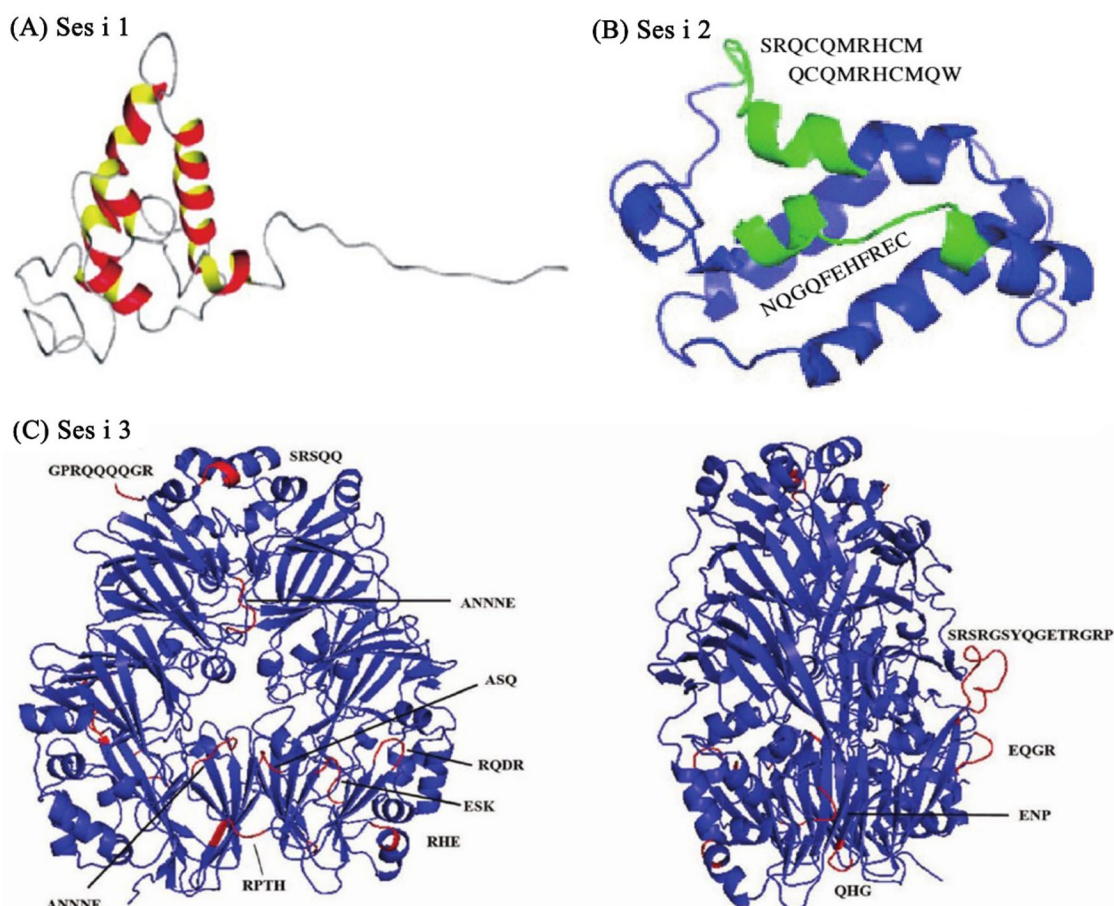


Figure 4. The structure of sesame allergens and their some epitopes, including Ses i 1 (A), Ses i 2 (B), Ses i 3 (C) (Xiuli et al. 2019; Ma et al. 2021).

Table 3. Epitopes in sesame allergens.

Sesame allergens	Peptide	Amino acid sequence	Positions	Reference
Ses i 2	1	SRQCQMRHCM	46–55	(Wolff et al. 2004)
	2	QCQMRHCMQW	48–57	
	3	CMQWMRSMRG	54–63	
	4	EANQGQFEHF	74–83	
	5	NQGQFEHFREC	76–86	
	6	GQFEHFRECC	78–87	
	7	FEHFRECCNE	80–89	
	8	HFRECCNEIR	82–91	
	9	RECCNEIRDVK	84–94	
Ses i 3	1	SESKDP	23–28	(Ma et al. 2021)
	2	RQKHQGEHG	60–68	
	3	NRKSP	81–85	
	4	QHG	99–101	
	5	YQREKGRQDDNPTDPEKQY	115–134	
	6	RRQG	142–145	
	7	KYREQQGREGGRGE	162–175	
	8	EGR	178–180	
	9	EQGR	188–191	
	10	QHG	210–212	
	11	RQDR	270–273	
	12	ENP	328–330	
	13	RHE	378–380	
	14	ESK	390–392	
	15	RPTH	401–404	
	16	ASQ	416–418	
	17	SRSRGSYQGETRGRP	469–483	
	18	ANNNE	525–529	
	19	SRSQQ	563–567	
	20	GPRQQQGR	574–582	

endogenous and exogenous proteolytic enzymes, resulting in its transition of the gastrointestinal tract without major cleavage events, which may trigger remarkable allergic reactions (Magni et al. 2010).

The detection of sesame allergens

Sesame labeling as an allergenic food is an important measure to reduce exposure to sesame and protect the health of patients allergic to sesame (Bianchi et al. 2019; Touma, La Vieille, et al. 2021). The detection of sesame residues in food products contributes to accurating allergen labeling for sesame, thus making wise decisions for sesame-allergic patients. It was reported that a 15-year-old girl died due to eating a prepackaged sandwich without allergen labeling for sesame in a London airport in July 2018 (Pistiner, Hernandez-Trujillo, and Davis 2018), which could be avoided by allergen labeling. Currently, various technical approaches have been successfully used to detect the sesame allergens in processed food products, involving nucleic-acid based methods (end-point PCR, multiplex ligation-dependent probe amplification (MLPA), real-time PCR), immunoassays (enzyme-linked immunosorbent assay (ELISA), western blot), mass spectrometry (LC/MS-MS and UHPLC-Q-TOF-MS/MS), and biosensors (colometric LAMP microfluidic chip) (Figure 5).

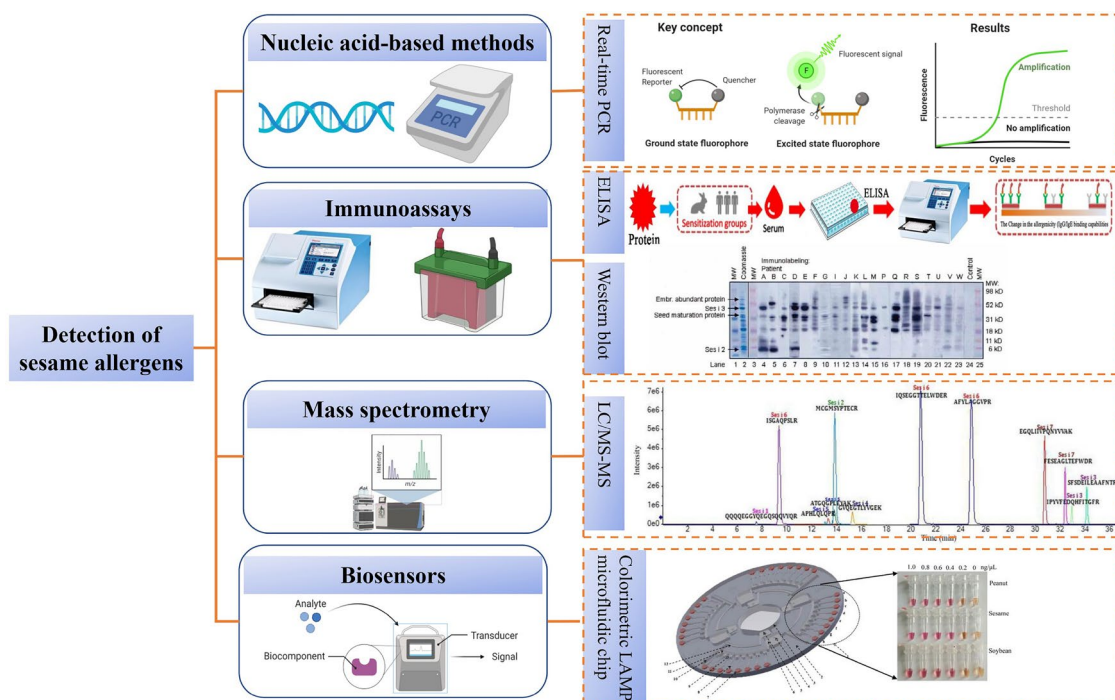


Figure 5. The detection of sesame allergen. Western bolt is from Beyer et al. (2002); lanes 4 to 23: immunolabeling with sera from 20 patients with sesame seed allergy, lane 24: labeling with control sera. LC/MS-MS is from Ma et al. (2020); the extracted ion chromatogram of sesame allergen signature peptides was obtained using scheduled LC-MRM analysis. Colorimetric LAMP microfluidic chip is from Yuan et al. (2018). The figure is also edited through biorender.

Nucleic-acid based methods

Nucleic-acid based methods are used to detect sesame allergens by detecting the coding genes of allergic protein. DNA molecules are more stable than protein in the processing so that nucleic-acid based methods are less affected by matrix (Torricelli et al. 2020). Nucleic acid-based methods are divided into end-point PCR, real-time PCR, multiplex ligation-dependent probe amplification, droplet digital PCR, Loop-mediated isothermal amplification (Sena-Torralba et al. 2020), in which end-point PCR and real-time PCR are reported to detect sesame allergens. The end-point PCR was used to detect sesame allergens, whose sensitivity was improved by microchip capillary electrophoresis (Lab-on-chip) (Coisson et al. 2010). At present, the detection of sesame allergens is mainly reported in multiple real-time PCR (López-Calleja et al. 2015; Torricelli et al. 2020; Waiblinger et al. 2014; Zhang et al. 2018). As shown in Figure 5 (real-time PCR, qPCR), qPCR is based on PCR technology together with the addition of fluorescence substance, in which the amplification of target DNA is reflected by the accumulation of fluorescence signal (Zhang et al. 2019). In contrast with the end-point PCR, qPCR can give a quantitative account (Linacero et al. 2020). Compared to simplex PCR reaction whose amplification efficiency is affected by many factors (e.g., the size of the amplicon, primer concentration and GC content of the primer), the dominant factor of multiplex PCR is the preference for the amplification of a specific amplicon due to the competition in individual PCR amplification (Zhang et al. 2018). Generally, the qPCR methods include the Taqman and SYBR-Green assays. It was reported that a dual-labelled

TaqMan real-time PCR was used to detect sesame and flaxseed in processed food products with detection limits of 1.3 mg/kg for sesame and 1.4 mg/kg for flaxseed, respectively, which has many advantages such as save-time, reduced costs and low probability of cross-contamination (López-Calleja et al. 2015). Similar results were shown by Torricelli et al. (2020), who found that a triplex-labeled TaqMan real-time PCR is fast, specific and robust to detect sesame, pistachio, and macadamia nut allergens with detection limits of 0.005% for sesame, 0.004% for pistachio and 0.006% for macadamia nut. Zhang et al. (2018) also found that a triplex-labeled SYBR Green qPCR was efficient to detect peanut, soybean and sesame in foods when the concentration of the primer pairs for peanut, soybean and sesame were 0.3, 0.2, and 0.25 μ M, respectively. Overall, the Taqman assay shows higher sensitivity than SYBR-Green assays, but is more expensive than SYBR-Green assays. Additionally, multiplex ligation-dependent probe amplification (MLPA) was also to simultaneously detect the sunflower, poppy, flaxseed, sesame and soybean allergenic ingredients in commercial food products (López-Calleja et al. 2017). Overall, the most important control point for PCR is a suitable DNA clean-up procedure, improving amplification efficiency and reducing interference from other substances (e.g., PCR inhibitors)

Immunoassays

Immunoassay methods rely on the use of specific and high-affinity antibodies to detect allergic components in food samples, including enzyme-linked immunosorbent assay (ELISA), western blot and Lateral flow immunoassay

(Sena-Torralba et al. 2020). ELISA and western blot have been widely used to detect sesame allergens, exhibiting many advantages such as high sensitivity, low cost, ease of use, and rapid result acquisition. It was reported that a noncompetitive, sandwich-type ELISA using a commercial sesame protein test kit was used to detect the sesame residues in γ -irradiated white sesame seeds (Zoumpoulakis et al. 2012) and thermal processed, salt and high pressure treated sesame protein (Achouri and Boye 2013). Kishikawa et al. (2018) also used indirect ELISA to find the least content of albumin (8.6 $\mu\text{g}/\text{grain}$) in Acc. No. 526 among different sesame cultivars based on 14-kDa albumin antibodies. Koppelman et al. (2015) developed a sandwich ELISA with a low limit of quantification (0.5 ppm), showing essentially no cross-reactivity with other foods or food ingredients (92 tested). A similar sandwich ELISA was also developed by Redl et al. (2010). The western blot is another common immunoassay that combines SDS-PAGE electrophoresis with antibody recognition. Compared to ELISA, the western blot exhibits low sensitivity, but it can show the protein profile of sesame. Beyer et al. (2002), Kishikawa et al. (2018), and Teodorowicz et al. (2016) have used western blot to identify allergic ingredients and their molecular weight distributions in sesame. What's more, an antibody from a patient or animal with sesame allergy was used to conduct ELISA and western blot, which can directly evaluate the IgE or IgG binding ability and in turn indicates the potential allergenicity in sesame (Figure 5 ELISA and western blot). However, immunoassay methods (ELISA and western blot) also exhibit some disadvantages such as the occurrence of false positives (the antibody quality and cross-reactivity due to homology between the antibody recognition sites of different proteins) and negative results (matrix effect and protein denaturation or degradation in food processing), which needs to be addressed in future studies.

Mass spectrometry

Mass spectrometry (MS) is an alternative to immunoassays for the detection of allergens in the last decade. Compared to immunoassays, the disadvantage such as the existence of false positives and negatives have been overcome by MS due to the no-require of antibodies, exhibiting the profiles of protein/peptides (Sena-Torralba et al. 2020). In addition, MS detects and directly quantifies multiple allergens in foods at the same time (Torricelli et al. 2020). It was reported that the content of Ses i 1-Ses i 8 in different sesame products (e.g., hotpot dipping sauce, spicy chili beer sauce, cookie, cake and candy) was determined through LC/MS-MS, in which the content of Ses i 6 was the highest among all sesame allergens for all food products (Ma et al. 2020). In addition, the differences in peptide profiles were observed in different sesame cultivars (Figure 5, LC/MS-MS) (Ma et al. 2020). Six sesame allergens (Ses i 1, Ses i 2, Ses i 3, Ses i 4, Ses i 6, and Ses i 7) was also confirmed in cold-pressed oils through UHPLC-Q-TOF-MS/MS (Kotecka-Majchrzak et al. 2020). Although MS is a promising technique to increase specificity and reproducibility

compared to immunoassay and nucleic-acid based technologies, it cannot detect the allergenicity directly, and requires expensive equipment and well-trained analysts.

Biosensors

Biosensors are also used to detect sesame allergens due to their excellent versatility in bioreceptors, materials and transduction modes terms, including optical electrochemical and magnetic biosensors (Sena-Torralba et al. 2020). There were limited reports about biosensors to detect sesame allergens. As shown in Figure 5 (colorimetric LAMP microfluidic chip), an optical-based biosensor, colorimetric loop-mediated isothermal amplification (LAMP) microfluidic chip was used to detect peanut, sesame and soybean allergens with detection limits of 0.4 ng/ μL , in which in the presence of peanut, sesame, or soybean in the samples, the corresponding reaction well of the microfluidic chip will appear pink, or otherwise remain light brown (Yuan et al. 2018). Therefore, biosensors to detect sesame allergens need to be investigated in the future.

The processing to reduce the allergenicity of sesame

The avoidance of sesame is the most effective measure to prevent allergic reactions for allergic patients, but it may consequently affect the nutritional intake of the body, resulting in various nutritional deficiencies (Pi et al. 2019; Rahaman, Vasiljevic, and Ramchandran 2016; Wang et al. 2020). In addition, the avoidance of sesame is almost impossible because sesame has been widely used as a source of processing foods. Moreover, medical treatments (e.g., antihistamines, adrenaline, steroid and non-steroid drugs) are usually limited by some factors such as side effects and expensive (Wang et al. 2020; Wiparat and Pornthep 2019). Similar to peanut allergy (Pitt et al. 2018; Togias et al. 2017), prevention should be about actions that can be taken during pregnancy, breastfeeding, formula feeding, and weaning in infancy to hinder the development of allergies to sesame seeds. However, this aspect is not well studied for sesame seeds (Hsu et al. 2013). Thus, processing to reduce the allergenicity of sesame appears to be an effective and promising approach for preventing sesame allergy.

Heat treatments (e.g., blanching, boiling, autoclaving, roasting or frying) are common processes for sesame products. Heat treatment usually induces structural changes in protein, cleavage and re-arrangement of disulfide bonds, protein-aggregation, and chemical interaction with other ingredients (e.g., carbohydrates and lipids) to lead to the masking/destruction or exposure/generation of epitopes, resulting in the reduction or increase of allergenicity in sesame (Pi, Sun, et al. 2021; Pi et al. 2022; Pi et al. 2019). It was reported that the antigenicity of sesame seeds was significantly increased after boiling at 100°C for 5 min, but was not time-dependent (i.e., no further increased antigenicity was observed when boiling time was increased to 10 min) (Achouri and Boye 2013). However, the opposite results were

shown in dry roasted sesame seeds, appearing the increased antigenicity with time-dependent (i.e., the antigenicity of sesame seeds was increased after dry roasting at 150°C for 7.5 min, and was furtherly increased when the dry roasting time was increased to 15 min) (Achouri and Boye 2013). In addition, a significant ($P < 0.05$) reduction of antigenicity was observed in the microwave heated sesame seeds at 1000 W for 3 min, whereas there were no significant ($P < 0.05$) changes in antigenicity in the microwave heated sesame seeds at 1000 W for 1 min (Achouri and Boye 2013). These results demonstrated that the changes in antigenicity are related to the heating method, temperature, and time. Moist heating (boiling) and dry heating (microwave heating and dry roasting) may cause different reactions and structural changes in sesame seeds, which have been elaborated in the thermal treatment soybeans (Pi, Sun, et al. 2021). Moreover, different sesame proteins also exhibited different changes in protein profile after heat treatment based on SDS-PAGE (Achouri and Boye 2013; Ahmadian-Kouchaksaraei et al. 2014). These results resulted in different changes in the antigenicity of sesame after different heat treatments, but its mechanism needs to be investigated in future studies. It is worth noting that heat treatment may produce the advanced glycation end products which contribute to the increase of IgE binding ability (Chung and Champagne 2001), and the effects of other ingredients (lipid and carbohydrate) in sesame allergenicity should also be noted.

Several studies have also investigated the effect of γ -irradiation and high hydrostatic pressure on the antigenicity of sesame seed and sesame protein solution, respectively (Achouri and Boye 2013; Zoumpoulakis et al. 2012). There were no significant ($P < 0.05$) changes in the antigenicity of sesame proteins after white sesame seeds were γ -irradiated at 2.5, 5.0 and 10.0 kGy (Zoumpoulakis et al. 2012). Additionally, the safe dose of irradiation for food products is generally below 10 kGy (Pi, Yang, Sun, Wang, et al. 2021). Therefore, irradiation to reduce the allergenicity of sesame should be concentrated in its protein solution rather than seeds, which is based on the reduced antigenicity in γ -irradiated Ara h 2 and Ara h 6 solutions with the increase of irradiation dose (Luo and Hu 2019; Luo et al. 2013). High hydrostatic pressure is an emerging technology and affects non-covalent bonds (e.g., hydrophobic, hydrogen, ionic bonds and salt bridges) rather than covalent bonds to induce the protein denaturation and structural changes, resulting in the masking or destruction of epitopes and the reduction of allergenicity (Chizoba Ekezie, Cheng, and Sun 2018; Pi, Sun, et al. 2021; Pi et al. 2019). It was reported that the antigenicity of sesame protein solution was reduced after treatment with high hydrostatic pressure (100, 200, 300, 400, 500 MPa) at all tested pH for 10 min, which was because high hydrostatic pressure caused conformational changes to force the protein into a tightly packed structure for masking the allergen epitopes (Achouri and Boye 2013). This reduction of antigenicity in the sesame protein solution might be achieved by the reduced allergenicity in other sesame allergens rather than Sei i 1 and Sei 2 because Sei i 1 and Sei 2 may be resistant to high hydrostatic pressure due to their disulfide bonds.

During the processing to reduce the allergenicity of sesame, the influence of solvent cannot be ignored. Achouri and Boye (2013) reported that there was the lowest allergenicity in sesame proteins extracted with higher salt (0.6, 1 M NaCl), compared to other extraction solvents, resulting from the differences in the types of allergens and the changes in protein structure. A high NaCl concentration improved the solubilization of the 11S globulin and some 7S proteins rather than 2S albumin, and the salt introduction could prevent epitopes from reacting with the IgG antibodies (Achouri and Boye 2013). Achouri and Boye (2013) further found the lower allergenicity in sesame proteins solution at pH2 due to the absence of 7S and 11S globulin, compared to sesame proteins solution at pH10. Therefore, solvents play an important role in processing to reduce the allergenicity of sesame.

Overall, current studies have demonstrated that the antigenicity of sesame can be reduced through microwave heating, high hydrostatic pressure, salt and pH treatment.

However, antigenicity and allergenicity can be quite different as IgG and IgE binding epitopes are not necessarily identical. Our previous studies have demonstrated that the allergenicity in many plant foods (e.g., soybean and peanut) were reduced by various technologies, including boiling, glycosylation, magnetic-bead adsorption, microbial fermentation, enzyme catalysis (Pi, Fu, et al. 2021; Pi, Sun, et al. 2021; Pi et al. 2022; Pi et al. 2019; Pi, Yang, Sun, Cui, et al. 2021). Further studies should pay attention to seeking suitable processing for reducing the allergenicity of sesame. In addition to ELISA and western blot using serum from patients or animals allergic to sesame, cell and animal experiments are also used to evaluate the allergenicity, and clinical human testing is used to definitively confirm the reduction of allergenicity of sesame.

Cross-reactivity between sesame and other foods

In general, over 170 foods can induce the allergic reaction, but 90% of the incidence is provoked by eight major food allergens, namely shellfish, soybean, peanut, milk, tree nut, egg, wheat and fish (Chizoba Ekezie, Cheng, and Sun 2018; Pi, Yang, Sun, Cui, et al. 2021; Pi, Yang, Sun, Wang, et al. 2021). Additionally, sesame allergy altogether with peanut and tree nut allergies is responsible for most life-threatening food-induced allergic reactions (Brough et al. 2020). As shown in Table 4, sesame allergens are divided into five groups (2S albumin, 7S vicilin-like globulin, 11S globulin, oleosin, and profilin), which are also found in other plant major food allergens such as soybean, wheat, peanut and tree nut. Therefore, certain homology might be observed in Ses i 1 and Ses i 2 with Ber e 1, Jug r 1 and Ara h 2 (Agne, Rancé, and Bidat 2003; Beyer et al. 2002), in Ses i 3 with Ara h 1 (Mahlab-Guri et al. 2021), and in Ses i 6 and Ses i 7 with Ara h 3, Jug r 4 and Cor a 9 (Beyer et al. 2007a). Could this degree of homology be responsible for the cross-reactivity between sesame and other plant foods?

Several studies have demonstrated the cross-sensitization between sesame and peanuts or tree nuts (e.g., cashew,

Table 4. Comparison of sesame and plant allergens in various classes.

Allergenic foods		2S albumin	7S vicilin-like globulin	11S globulin	Oleosin	Profilin
Sesame		Ses i 1 Sei i 2	Sei i 3	Sei i 6 Sei i 7	Sei i 4 Sei i 5	Sei i 8
Soybean		Gly m 8	Gly m 5	Gly m 6	–	Gly m 3
Peanut		Ara h 2 Ara h 6 Ara h 7	Ara h 1	Ara h 3	Ara h 10 Ara h 11 Ara h 14 Ara h 15	Ara h 5
Wheat	Common buckwheat	Fag e 2	Fag e 3 Fag e 5	–	–	–
	Tartarian buckwheat	Fag t 2	–	–	Fag t 6	–
Tree nuts	Cashew	Ana o 3	Ana o 1	–	–	–
	Black walnut	Jug n 1	Jug n 2	Jug n 4	–	–
	English walnut	Jug r 1	Jug r 2 Jug r 6	Jug r 4	–	Jug r 7
	Almond	–	–	Pru du 6	–	Pru du 4
	Pistachio	Pis v 1	Pis v 2 Pis v 3	Pis v 5	–	–
	Pecan	Car i 1	Car i 2	Car i 4	–	–
	Hazelnut	Cor a 14	Cor a 11	Cor a 9	Cor a 12 Cor a 13 Cor a 15	Cor a 2
	Macadamia	–	Mac i 1	–	–	–
	Brazil nut	Ber e 1	–	Ber e 2	–	–

The symbol “–” demonstrated that the allergen did not be published by the World Health Organization and International Union of Immunological Societies (WHO/IUIS) Allergen Nomenclature Subcommittee.

hazelnut, walnut and almond) based on SPT and specific serum IgE results (Baker et al. 2019; Stutius et al. 2010; Stutius et al. 2009). Evidence for co-sensitization between sesame and peanuts or tree nuts has also been shown by electronic medical records from Middle Eastern/North African patients (Joseph et al. 2021) and a retrospective medical record from Texas Children’s Hospital Allergy (Tuano et al. 2016). This implies that patients with sesame allergy are more likely sensitized to peanuts or tree nuts. Therefore, patients with sesame allergy are suggested to avoid peanuts or tree nuts. Clinical cross-reactivity between sesame and peanuts or tree nuts may exist in some cases. Stutius et al. (2010) found that children with a clinical history of both peanut allergy and tree nut allergy were more likely to have an allergic reaction to sesame. Based on recent clinical history, SPT and oral food challenges, Mahlab-Guri et al. (2021) reported that 14.2%, 12.6%, 10%, 7.4% of patients with sesame allergy were allergic to eggs, peanuts, tree nuts, milk, respectively. Similar results were shown in Brough et al. (2020), who found the cross-reactivity between nut and sesame based on SPT, specific IgE, and OFC tests. Teodorowicz et al. (2016) also reported that 2 of 6 patients with sesame allergy had oral allergy syndrome to tree nuts. A survey in US also demonstrated that nearly 50%, 33%, 25% and 20% of patients with sesame allergy are allergic to peanuts, tree nuts, eggs, and milk allergy based on our convincing allergic symptom-report criteria (Warren et al. 2019). Additionally, several studies have demonstrated the cross-reactive IgE binding between Ses i 3 and Ara h 1 as well as Ses i 6 and Jug r 4 (Tuano et al. 2016; Wallowitz et al. 2007). The high homology (~80%) between an epitope (AA294-303, TPGEFELFFG) of Ara h 1 and the corresponding area (AA315-324 TPGEFELFEG) of the Ses i 3 might be responsible for the cross-reactive IgE binding between peanut and sesame (Beyer et al. 2002). The homology was also shown in the epitopes of Ses i 2

and Ber e 1 as well as Ses i 3 and Jug r 6, which was probably responsible for the cross-reactive IgE binding between sesame and Brazil nut as well as sesame and walnut (Dubiel et al. 2018; Wolff et al. 2004). Therefore, the homology in epitopes of allergens may be responsible for the cross-reactive IgE binding between sesame and other foods. It can be speculated that the recognition of this epitope in one patient might result in clinical reactivity between other foods and sesame or that recognition of this epitope might explain the presence of measurable IgE levels without clinical cross-reactivity. It is desirable and necessary to confirm the clinical cross-reactivity between sesame and other foods and its reason.

Conclusion and future perspective

Sesame allergy has been a global public health problem due to its persistence throughout the lifetime, severity of symptoms and relatively high prevalence, which suggests the potential to be a major food allergen. At present, the allergen labeling for sesame is only found in some countries such as US, Canada, European Union and Australia (Table 5). The allergen labeling and manufacturing control measures for sesame should be taken seriously, especially in many countries that have not included sesame on the lists of priority allergenic foods. Although the issues in cardiovascular, integumentary, respiratory, and nervous systems are induced by sesame allergens, the information about epitopes and structure of sesame allergens are limited, which need to be investigated in the future. Cross-reactivity might exist between sesame and other foods, which needs to be confirmed by clinical trials. Based on the cross-sensitization between sesame and peanuts or tree nuts, patients with sesame allergy should try to avoid peanuts and tree nuts. For the detection method for sesame allergens, every method

Table 5. Standards for allergenic labeling in some countries.

Allergens	US	Canada	European Union	Australia	China	Singapore	Saudi, Arabia, UAE, Kuwait, Bahrain, Oman, Qatar, Yemen	Philippines, India, Marancia	Iceland, Liechtenstein, North Malton, Norway, Switzerland, Sweden, Scotland, Ukraine, Turkey	Brazil
Sesame	✓	✓	✓	✓			✓		✓	
Shellfish	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Egg	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Fish	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Milk	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Peanut	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Soybean	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
tree nut	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
wheat	✓	✓	✓	✓					✓	✓
Cereals		✓	✓	✓	✓	✓	✓	✓	✓	
Buckwheat										
Celery			✓				✓		✓	
Lupin			✓	✓			✓		✓	
Mollusk		✓	✓	✓		✓	✓		✓	
Mustard		✓	✓				✓		✓	
Sulfite (>10ppm)	✓	✓	✓	✓		✓	✓	✓	✓	✓
Bee pollen				✓						
Mango				✓						

The symbol “✓” represented the allergenic labeling for certain foods in the country. The blank demonstrated that the country did not include certain foods as priority/major food allergens.

has its advantages and disadvantages. All detection methods cannot measure the IgG and IgE binding ability, except for ELISA and western blot using serum from patients or animals allergic to sesame. MS can simultaneously and quantitatively detect multiple allergen components by analyzing the content of characteristic peptides. The MS method is developed in a short time and does not require synthetic antibodies. Therefore, the combination of the immunoanalytical method with MS technology might be an effective way to detect sesame allergens. More attention should be paid to processing for reducing the allergenicity of sesame based on clinical studies. Further studies should also seek more processing methods to reduce the allergenicity in sesame without sacrificing its nutritional value, providing a theoretical basis and practical guide for the development of low-allergenic sesame foods. Notably, multi-technology is a promising way to achieve the purpose.

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Author contributions

Xiaowen Pi designed the manuscript, performed preliminary data analysis, and wrote the initial review. Ph.D Zeyu Peng, Jiarong Wang and Yuanqing Jiang helped “Xiaowen Pi” to modify manuscripts. Professor Guiming Fu and Yili Yang suggested some amendments to the initial review. Professor YuXue Sun supervised the project and edited the final version of the manuscript.

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