

A Comprehensive Review on Kiwifruit Allergy: Pathogenesis, Diagnosis, Management, and Potential Modification of Allergens Through Processing

Jin Wang , Sai Kranthi Vanga , Christine McCusker, and Vijaya Raghavan

Abstract: Kiwifruit is rich in bioactive components including dietary fibers, carbohydrates, natural sugars, vitamins, minerals, omega-3 fatty acids, and antioxidants. These components are beneficial to boost the human immune system and prevent cancer and heart diseases. However, kiwifruit is emerging as one of the most common elicitors of food allergies worldwide. Kiwifruit allergy results from an abnormal immune response to kiwifruit proteins and occur after consuming this fruit. Symptoms range from the oral allergy syndrome (OAS) to the life-threatening anaphylaxis. Thirteen different allergens have been identified in green kiwifruit and, among these allergens, Act d 1, Act d 2, Act d 8, Act d 11, and Act d 12 are defined as the “major allergens.” Act d 1 and Act d 2 are ripening-related allergens and are found in abundance in fully ripe kiwifruit. Structures of several kiwifruit allergens may be altered under high temperatures or strong acidic conditions. This review discusses the pathogenesis, clinical features, and diagnosis of kiwifruit allergy and evaluates food processing methods including thermal, ultrasound, and chemical processing which may be used to reduce the allergenicity of kiwifruit. Management and medical treatments for kiwifruit allergy are also summarized.

Keywords: cross-reactivity, kiwifruit allergy, nonthermal processing, secondary structure, thermal processing

Introduction

Kiwifruit (*Actinidia deliciosa*) are wild plants that were first found in China and named “Chinese gooseberry.” There are approximately 55 species cultured including green kiwifruit (*A. deliciosa*), golden kiwifruit (*A. chinensis*), hardy kiwifruit (*A. arguta*), Chinese egg gooseberry (*A. coriacea*), and hearty red kiwifruit (*A. purpurea*; Burdon & Lallu, 2011; Huang & Tan, 1988). At their commercial harvesting stages, the fruits have a soft texture and a pleasant flavor. In 2018, United States Dept. of Agriculture (USDA) Nutrient Database reported that kiwifruit is an excellent source of dietary fiber, carbohydrates, sugars, vitamin C and E, minerals (calcium, magnesium, potassium, and phosphorus), omega-3 fatty acids, and antioxidants (for example, phenols) as outlined in Table 1. In 2016, Food and Agriculture Organization of the United Nations (FAO) reported that the total worldwide kiwifruit production was 4,274,870 tons. Kiwifruit is generally consumed in fresh form. However, the shelf life of fresh kiwifruit is very short because of tissue softening and senescence (Wang, Shan,

Yuan, & Yue, 2016). To avoid the food loss, kiwifruit is made into different products including juice, dried kiwifruit slices, and frozen products; which can further be used as an ingredient in ice creams, baked goods, and fruit jam (Cassano, Donato, & Drioli, 2007).

Studies suggest that bioactive compounds such as vitamins and polyphenols present in kiwifruit may contribute to the prevention of cancer and cardiovascular diseases (Shu et al., 2008; Vissers, Carr, Pullar, & Bozonet, 2013). Immune activity may also be influenced by ingestion of kiwi fruit. Iwasawa, Morita, Ueda, and Yamazaki (2010) and Skinner, Loh, Hunter, and Zhang (2011) reported that the production of specific cytokines (for example, IL-12) in mice was significantly increased after oral administration of kiwifruit juice when compared to the control group that received the same quantity of water. Studies have also observed that consumption of 0.5 L of kiwifruit juice (about eight kiwifruits) was associated with decreased DNA damage in human cells compared to the cells from the water consuming control group (Collins, Horská, Hotten, Riddoch, & Collins, 2001). Oxidative DNA damage is positively correlated with some cancers (Skinner et al., 2011). Thus, consuming kiwifruit may potentially reduce the risk of cancers due to its antioxidant effect. Furthermore, in one study of 43 volunteers with hyperlipidemia, a significant decrease in high-density lipoprotein cholesterol content was observed after 8-week consumption of two kiwifruits per day. Vitamin C and

CRF3-2018-0192 Submitted 8/24/2018, Accepted 1/5/2019. Authors Wang, Vanga, and Raghavan are with Dept. of Bioresource Engineering, Faculty of Agricultural and Environmental Sciences, McGill Univ., Sainte-Anne-de-Bellevue, Quebec, Canada. Author McCusker is with Meakins-Christie Laboratories, Research Inst. of the McGill Univ. Health Centre, Montreal, Quebec, Canada. Direct inquiries to author Wang (E-mail: jin.wang6@mail.mcgill.ca).

Table 1–Nutrients in 100 grams (g) raw green kiwifruit (Source: USDA Nutrient Database, 2018).

Nutrients		Amount
Proximates	Energy	61 kcal
	Water	83%
	Carbohydrate	14.66 g
	Fiber	3.0 g
	Sugar	8.99 g
	Protein	1.14 g
Minerals	Calcium	34 mg
	Magnesium	17 mg
	Potassium	312 mg
	Phosphorus	34 mg
Vitamins	Vitamin C	92.7 mg
	Vitamin E	1.46 mg
Lipids	Fatty acids	363 mg

vitamin E levels in the blood were also increased (Chang & Liu, 2009).

In 1981, the first report on kiwifruit allergy was published (Fine, 1981) and kiwifruit is increasingly recognized as a common elicitor causing allergic reactions worldwide. In Sweden and Denmark, nearly half of food allergic individuals reported kiwifruit allergy in self-reported surveys (Eriksson et al., 2004). In Spain, approximately 1.8% of the total population are allergic to kiwifruit (Mills et al., 2007). In France, in a study of 182 children (2 to 14 years of age), 9% of the population reported hypersensitivity to kiwifruit (Rance, Grandmottet, & Grandjean, 2005). For many patients, symptoms associated with kiwifruit ingestion may be a form of food pollen syndrome (FPS). Kiwifruit FPS occurs in patients with allergic sensitization to plant pollen proteins which are sharing similar protein structures to those found in the kiwifruit (Wang, Vanga, & Raghavan, 2017). Pollen allergy is estimated to occur in 20% to 40% of the population worldwide (Asam, Hofer, Wolf, Aglas, & Wallner, 2015). In European countries, approximately 40% of individuals reported hypersensitive to tree and/or weed pollens (D'Amato et al., 2007), while in North America, pollen allergies are reported in >20% of the population (Schmidt, 2016). Thus, the potential for a high frequency of FPS after exposure to kiwifruit is significant. In one study of 55 patients (female: male = 39:16) with oral food challenge diagnosed kiwifruit allergy, 22% had isolated kiwifruit allergy with no cross-reactivity to pollens, although the majority had demonstrable cross-reactivity with other plant proteins, especially from foods belonging to the Rosaceae family (50%), peanuts (31%), and tree nuts (42%; Sirvent et al., 2014b).

Studies have shown that conformational epitopes of some protein allergens can be altered by heating or enzymatic hydrolysis (Caubet & Wang, 2011). Modification of these secondary and tertiary structures can lead to the loss of their potential IgE-binding sites in these proteins as IgE-binding is essential for triggering allergic symptoms. This modification suggests that kiwifruit allergic individuals might safely consume appropriately altered proteins from kiwifruit (Okolie, Aryee, & Udenigwe, 2018). Studies have reported that thermal processing (for example, steam cooking) and chemical treatments could modify the structures of the proteins present in kiwifruit, which in turn results in a reduction of kiwifruit allergenicity (Bublin et al., 2008; Fiocchi et al., 2004). Further application and validation of novel techniques in processing are needed to demonstrate reductions in the kiwifruit allergenicity in food industries.

In this review, we describe the pathogenesis and clinical characteristics of kiwifruit allergy. Diagnostic methods based on in vivo

reactivity to protein (for example, skin prick test) and DNA (for example, polymerase chain reaction [PCR]), their advantages and disadvantages are also described. Further, 13 kiwifruit allergens are recognized, and some of their secondary protein structures are analyzed. Several ripening-related kiwifruit allergenic proteins (for example, Act d 1, 2, 5, and 11) are reviewed. We also discuss three potential processing methods: thermal processing (for example, steam cooking), nonthermal processing (ultrasound treatment), and chemical treatment (for example, enzymatic hydrolysis) that may reduce the allergenicity of kiwifruit.

Pathogenesis, Clinical Features, Diagnosis, and Epidemiology of Kiwifruit Allergy

Pathogenesis

Kiwifruit allergy is an abnormal immune response following consumption. As shown in Figure 1, food allergies develop when proteins present in kiwifruit or other foods are recognized by the immune system, and an inappropriate type of immune response is generated. This response leads to the formation of allergen-specific antibodies (for example, IgE isotype), a process known as sensitization. The newly formed IgE antibodies then link to specific effector immune cells known as mast cells. When there is a subsequent exposure to kiwifruit or related products, the allergens attach to the specific IgE antibodies and activate the high-affinity IgE receptors on the surface of mast cells (Yu, Freeland, & Nadeau, 2016). Mast cell activation results in the release of histamine and other inflammatory mediators which lead to the initial symptoms of kiwifruit allergy (Lin & Sampson, 2009). Kiwifruit, and pollen or plant-derived foods such as birch and grass pollen (Bublin et al., 2010), avocado (Lee, Jeon, & Lee, 2013), banana (Sakai et al., 2010), peanut, and tree nuts (Sirvent et al., 2014b) share homologous allergens and thus sensitization to one may result in symptoms following kiwifruit ingestion due to the presence of cross-reactive protein allergens. For example, individuals who are sensitized to tree pollen have pollen-specific IgE. This IgE molecule may also recognize proteins with similar structures present in kiwifruit leading to the activation of the IgE bound-mast cell, which causes symptoms of food allergy (Oberhuber et al., 2008). Thus, clinically significant reactions to kiwifruit follow direct sensitization to the kiwifruit or through cross-sensitization with other allergens of similar structures. The severity of symptoms is, in part, dependent upon the route of sensitization with the highest risk of severe anaphylactic reactions in those patients sensitized directly to kiwifruit.

Clinical features

Kiwifruit allergy has been identified as the most common fruit-induced allergies and represents the fourth most common food allergy in France, after milk, egg, and peanuts (Alemán et al., 2004; Mattila et al., 2003). Kiwifruit allergy is associated with a range of symptoms including oral allergy syndrome (OAS), which results from cross-sensitization to life-threatening anaphylaxis, a result of direct sensitization (Kerzl, Simonowa, Ring, Ollert, & Mempel, 2007). As shown in Table 2, mild kiwifruit allergic symptoms, related to the OAS, include swelling, itching, tingling, or burning reactions in or around mouth, lips, tongue, and throat (Lucas, Lewis, & Hourihane, 2003). Skin symptoms include rashes, itching, hives and eczema, erythema, and angioedema (Fine, 1981). More significant systemic symptoms (Scurlock, Vickery, Hourihane, & Burks, 2010) include wheezing, nasal congestion, shortness of breath, abdominal pain, nausea, or vomiting

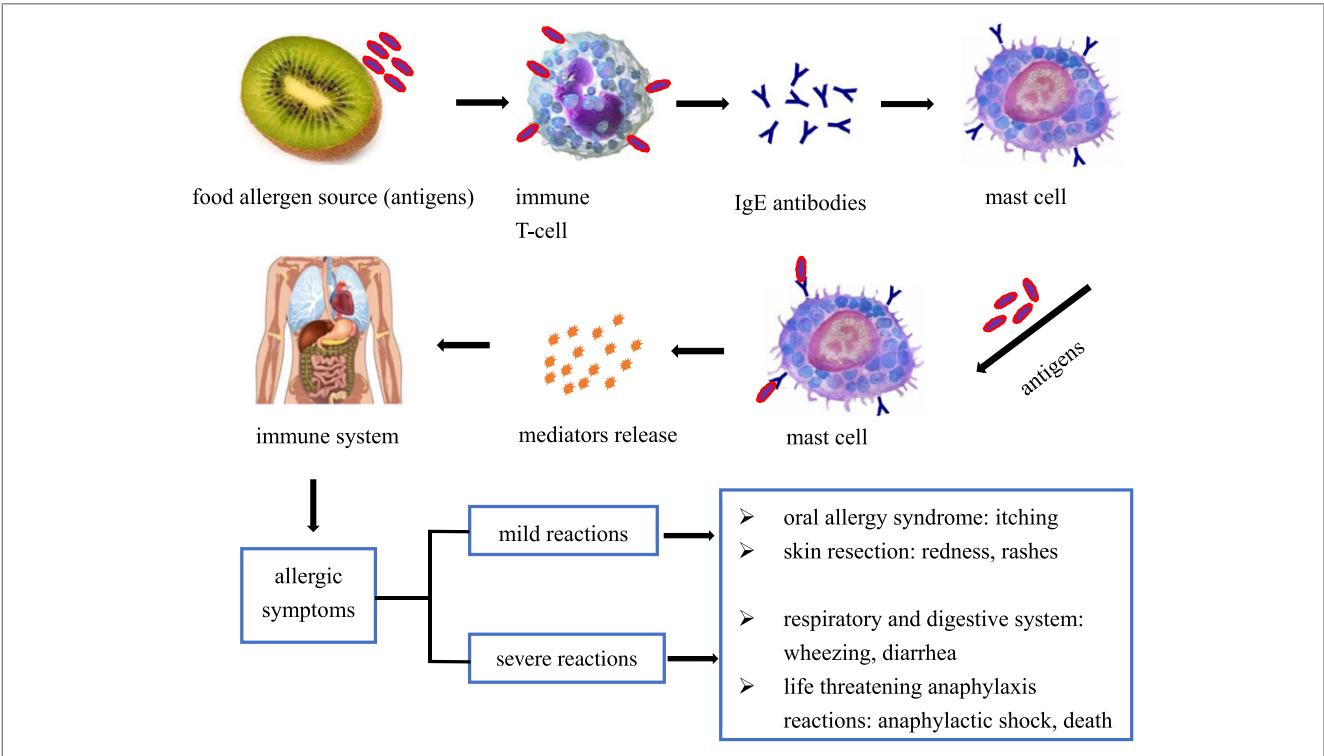


Figure 1–Overview of allergic sensitization to kiwifruit and related allergic reactions.

Table 2–Allergic symptoms on consumption of kiwifruit.

Allergen sources	Type of reactions	Symptoms	References
<i>Actinidia deliciosa</i> (Kiwifruit)	Oral allergy syndrome (OAS)	Swelling, itching, tingling, or burning sensation in and around mouth, lips, tongue, and throat	Lucas et al., 2003
	Skin reactions	Itching and redness of skin, skin rashes, hives, and eczema	Fine, 1981
	Respiratory and digestive system reactions	Wheezing, nasal congestion, troubled breathing coupled with shortness of breath, abdominal pain, nausea, or vomiting, diarrhea	Scurlock et al., 2010; Waserman & Watson, 2011
	Life threatening anaphylaxis reactions	Shortness of breath, heart rate increase, blood pressure decreases, anaphylactic shock, dizziness, fainting, or loss of consciousness	Kerzl et al., 2007

(Waserman & Watson, 2011). Severe, life-threatening reactions may lead to increasing heart rate, decreasing blood pressure, lightheadedness, respiratory failure, and anaphylactic shock. Coma or death may ensue unless medical treatment is administered promptly (Ciardiello et al., 2009). In one study 55 kiwifruit-allergic volunteers (female:male = 39:16) were challenged with kiwifruit. Sixty-two percent of the volunteers developed the local OAS, whereas 38% had systemic allergenic reactions after kiwifruit consumption (Sirvent et al., 2014b).

Diagnosis and detection

The major types of diagnostic and detection methods are shown in Table 3. Clinical diagnostic tools include double-blind placebo-controlled food challenge (DBPCFC), skin prick test (SPT), enzyme-linked immunosorbent assay (ELISA), and immunoCAP (Ahn, 2011). The DBPCFC is considered the gold standard diagnostic tool. Patients are given foods to consume, and both the patient and the treating physician are blind as to whether to food consumed contains any relevant allergens or is a placebo. This procedure ensures an objective assessment of outcomes without operator-specific preconceptions or bias (Lieberman & Sicherer, 2011). If patients develop clear objective signs and symptoms of an

allergic response, the test is considered positive. However, the food challenge generally needs several days to complete because the allergic reactions can be only triggered after ingesting sufficient doses of allergen and placebo. SPT is, therefore, a more accessible diagnostic tool. SPT involves placing small amounts of protein extract from kiwifruit pulp on the patient’s skin (arm) which is scratched or pricked by using a needle (Moreno Álvarez, Sexto, Bardina, Grishina, & Sampson, 2015). In this way, small amounts of protein allergen are exposed to the mast cells of the patient’s skin. In allergic individuals, allergen binding to kiwifruit-specific IgE on these cutaneous mast cells results in the release of histamine and a localized allergic reaction (Heinzerling et al., 2013). After 10 to 15 min, the skin is examined for redness (flare) and inflammation (wheal). The wheal sizes are 3 mm or bigger than the negative control (0.9% saline solution), which is considered as a positive test (Heinzerling et al., 2013). SPT is therefore quick and easy to perform. Further, it is also less expensive than DBPCFC, and multiple allergens can be tested at the same time (Heinzerling et al., 2013; Sicherer & Wood, 2012). This test is particularly useful in identifying IgE-specific sensitization to allergens (95%) (Siles & Hsieh, 2011). The sensitivity (the true positive rate) of SPT of kiwifruit allergy ranges from 60% to 93%, but there is an overall poor specificity (the

Table 3—Common diagnosis and detection methods for kiwifruit allergy.

Types	Method	Target analyte	Advantages	Disadvantages	References
Clinical diagnostic methods	DBPCFC	Proteins	Gold standard for a specific allergy	It needs several days to obtain the results	Ahn, 2011
	SPT	Proteins	A brief time; Low cost; high sensitivity (93%)	High “false positive” results (50% to 60%) and low specificity (33% to 45%)	Asha’ari et al., 2011; Heinzerling et al., 2013; Lucas et al., 2003
	ELISA	Proteins	A brief time; High specificity (99%) and sensitivity (71%)	Complex protocol; High cost with side effects (for example, pain and bleeding)	Griffiths et al., 2017; Pedersen et al., 2012; Poms et al., 2004
	ImmunoCAP	Proteins	A brief time; High specificity (98%) and sensitivity (60%); Easy to operate	Side effects (for example, pain and bleeding)	Griffiths et al., 2017; Pedersen et al., 2012
DNA-based detecting methods	PCR	DNA	High specificity; Stable DNA level	Equipment is expensive	Hindson et al., 2011; Poms et al., 2004
	Rt-PCR	DNA	High specificity; Stable DNA level	Equipment is expensive	Hindson et al., 2011; Poms et al., 2004

true negative rate) ranging from 33% to 45%. Further, SPT has a significant false positive rate up to 50% to 60% (Asha’ari, Suhaimi, Yusof, Rushdan, & Maraina, 2011), which limits the utility of SPT.

ELISA and immunoCAP (a commercial ELISA) are two similar blood test methods based on the detection of specific IgE present in the blood of patients. They can be used to diagnose if the individual is sensitized to kiwifruit or other commercial extracts (food products) and are used in various sectors including laboratories, food industry, and regulatory agencies (van Hengel, 2007). The specific allergens are measured through a colorimetric reaction after binding to specific enzyme-labeled antibodies and quantified using standard curves (Poms, Klein, & Anklam, 2004). These IgE-based diagnostic methods have a high sensitivity (60% to 71%) and specificity (98% to 99%) and are relatively rapid to perform compared to other methods (Griffiths et al., 2017; Pedersen et al., 2012). However, similar to SPT, these diagnostic methods are characterized by a high rate of false positive or negative results when used to predict clinical disease, especially in patients with a high total serum IgE concentration (Rusznak & Davies, 1998; Sinclair & Peters, 2004). These methods have a potential application in the detection of allergenicity of kiwifruit or related products. Le et al. (2011) evaluated the IgE-binding capacity of kiwifruit allergens present in six varieties by ELISA. The results showed that “Hayward” had the highest allergenicity (82%), followed by “Eriantha 96” of 55%, “Eriantha 114” of 55%, and “Summer 3373” of 45%. The lowest rate of allergenicity was observed in “Jintao” of 19%. However, the use of this type of test is limited by cost to develop and perform the assay as the required biological reagents (for example, primary and secondary detection antibodies) are derived from the animals (for example, rabbit). Similar methods include Western blotting and dot blotting of the IgE, but these have similar limitations.

DNA-based detecting methods including PCR and real-time PCR (Rt-PCR) are used to detect specific allergen concentrations in food products in the research setting. In comparison to clinical diagnostic methods, DNA-based methods including PCR and Rt-PCR are used to test the concentrations of allergens present in food (Hindson et al., 2011). Detection of DNA has been shown to be more stable under different processing conditions (for example, high temperature) compared to proteins that are potentially modified during processing (Poms et al., 2004). When the protein content present in fruit (for example, kiwifruit) is low, DNA-based methods can be used to detect minute contaminations from the fruit. PCR or Rt-PCR detection methods have been used to

detect the concentrations of allergens present in citrus fruits (Gabriel et al., 2017), peaches (Graziano, Gulli, & Marmiroli, 2018), and strawberries (Ishibashi, Yoshikawa, & Uno, 2017), and is highly specific and sensitive compared to the traditional detection methods (Holzhauser & Röder, 2015). As kiwifruit allergy is not as common as the “Big Eight” allergies (peanut, tree nut, milk, egg, soy, sesame, fish, and wheat allergies), there are very limited reports regarding the detection of kiwifruit or related commercial products. Taguchi et al. (2007) developed a PCR method targeting ITS-1 region in kiwifruit by designing two primer pairs (F123 and R178). The results showed that this method is able to detect amounts ranging from 5 to 50 fg of kiwifruit allergens. Further, Graziano et al. (2018) have developed a quantitative real-time PCR to quantify the concentrations of kiwifruit allergens in complex food matrices. The results represented a specific and sensitive method for the rapid detection of allergens levels in mixed foods. However, the practical applications in food industries of these DNA-based methods like PCR are limited due to the complexity of the protocols and expense of related equipment. Therefore, development of novel diagnostic and detecting methods with improved sensitivity, specificity, ease of operation, and low cost are needed.

Global epidemiology of kiwifruit allergy

Kiwifruit (*Actinidia*) is native to the North Eastern parts of China, specifically the Yangtze River valley, identified at the beginning of the 1900s (Nishiyama, 2007). It was first introduced in New Zealand in 1904 and exported to Europe and the United States started in 1962 (Lucas et al., 2003). Currently, kiwifruits are produced worldwide in countries including China, New Zealand, France, Italy, United States, Spain, and Australia (Ward & Courtney, 2013). The first publication on kiwifruit allergy was in 1981 (Fine, 1981), and following that more patients living with kiwifruit allergy were reported. In the last decade, the data obtained from the Web of Science (April 2018) shows that the total number of publications on kiwifruit allergy has risen to 135, reflecting the increasing prevalence of kiwifruit allergy. In some European countries, for example, in Spain, approximately 1.8% of the total population are allergic to kiwifruit (Mills et al., 2007). In France, among 182 children (2 to 14 years of age) with a history of allergies to one or more food, 9% were allergic to kiwifruit (Rance et al., 2005). Currently, the global statistics regarding the distribution of kiwifruit allergy is limited. The database of Web of Science shows that the majority of the publications (95%) on kiwifruit allergy are from Europe and USA. In contrast only 5%

of publications are from Asian countries (for example, India and Japan). There is a higher concentration of researchers working on kiwifruit allergy in Europe possibly reflecting the prevalence of the disease in these regions (Bublin et al., 2004; Le et al., 2013). Further, a large amount of birch trees located in European countries may be also contributing to the frequency of kiwifruit allergy through cross-reactivity between birch pollen and homologous structures found in kiwifruit proteins (Gall, Kalveram, Forck, & Sterry, 1994; Pastorello et al., 1996; Wang et al., 2017).

Main Kiwifruit Allergens

The World Health Organization and International Union of Immunological Societies (WHO/IUIS) Allergen Nomenclature Sub-committee have identified 13 key allergenic proteins present in green kiwifruit (*Actinidia deliciosa*) and three in gold kiwifruit (*Actinidia chinensis*; Table 4). Among these allergens, Act d 1 and Act d 2 are the first two kiwifruit allergens identified by Pastorello et al. (1998). Act d 1 is one of main kiwifruit allergens with a 30 kDa molecular weight belonging to the papain-like family of cysteine proteases (Merima Bublin et al., 2010). Act d 2 is a 20 to 26 kDa member of thaumatin-like proteins (TLP) with 200 amino acid residues (Misra, Kamthan, Kumar, & Ghosh, 2016). These proteins are expressed in fruit tissues when the plants are stressed (for example, by drought) or when infectious pathogens activate the defense system (Acharya et al., 2013; Muoki, Paul, & Kumar, 2012; Singh, Kumar, Kumar, Shukla, & Kirti, 2013). Act d 3 is a 40 kDa protein attached to complex glycans (cross-reactive carbohydrate determinants; Palacin et al., 2008). Act d 4 is a 12 to 16 kDa phytocystatin and is considered a cysteine proteinase inhibitor (Ahmed, Shamsi, & Bano, 2016; Bublin et al., 2010).

Act d 5 (kiwellin) is a cysteine-rich 26 to 28 kDa protein, which is abundantly presented in green and gold kiwifruit (Maddumage et al., 2013). It consists of two domains belonging to the expansin, N-terminal domain family (Tuppo et al., 2008). In general, Act d 6 (18 kDa) is expressed in ripe fruits involving the synthesis of pectin methylesterase (Jolie et al., 2010). Fewer patients are allergic to Act d 7 which belongs to pectin methylesterase with a 50 kDa molecular weight (Bublin et al., 2011). Act d 8 (15–18 kDa) is one of pathogenesis-related (PR-10) proteins that is found to be homologous to birch pollen (Agarwal & Agarwal, 2014; Oberhuber et al., 2008). They are unstable proteins which can be eliminated through thermal processing (for example, cooking or steaming; Kashyap & Kashyap, 2015). Act d 11 has been recognized as one of the main ripening-related proteins present in kiwifruit (D'Avino et al., 2011). Both Act d 11 and Act d 8 belong to the Bet v 1 family and have been implicated in allergic reactions normally linked to the OAS (Sussman, Sussman, & Sussman, 2010). Act d 9 (profilin) and Act d 10 (nsLTP) are two other minor allergens present in kiwifruit (Bublin et al., 2010). In 2014, two novel allergens: Act d 12 (a 50.2 kDa 11S globulin) and Act d 13 (a 12 kDa 2S albumin) were extracted from green kiwifruit seeds (Sirvent et al., 2014b). Studies found that these proteins have cross-reactivity with allergens present in peanuts and tree nuts (Sirvent et al., 2014a; Sirvent et al., 2014b).

As shown in Table 4, there are also three allergens, Act c 5, Act c 8, and Act c 10 extracted from *Actinidia chinensis* (gold kiwifruit). Act c 5 (kiwellin) is the main allergen and is a 28-kDa protein representing approximately 30% of the total protein found in gold kiwifruit (Tamburrini et al., 2005). The 17-kDa Act c 8 belongs to the PR-10 family and is considerably less abundant in gold kiwifruit (Popović, Grozdanović, & Gavrović-Jankulović, 2013). This protein is encoded by open reading frames (ORFs) of

474 nucleotides, corresponding to 158 amino acid residues. There are six ORF sequences related to Act c 8 isoforms which were detected in gold kiwifruit (Oberhuber et al., 2008). Act c 10 is a 10-kDa protein belonging to the ns-LTP involved in the defense mechanisms of the plant (Bernardi et al., 2011).

Structural Properties of Kiwifruit Allergens

There are four main kiwifruit allergen families including PR-10, TLPs, nsLTPs, and profilins which can induce allergic reactions (Wang et al., 2017). PR-10 (pathogenesis-related) proteins consist of 151 to 162 amino acids (Breiteneder & Radauer, 2004), and are presented in many fruits such as cherry, peach, and apple. These proteins are associated with symptoms of OAS reactions. LTPs are approximately 200 amino acid proteins and are significantly produced when the plant suffers from external stressors, like viral or bacterial infections (Salcedo, Sanchez-Monge, Barber, & Diaz-Perales, 2007). The ns-LTPs are generally found in the plant-based food sources (for example, strawberry, peach) and have a 7 to 9 kDa molecular mass (Wang et al., 2017). Profilins are a 12 to 15 kDa protein family considered as functional proteins to regulate the polymerization of the actin filament (Breiteneder & Radauer, 2004). Profilins are the most common allergens presented in many fruits including orange, mango, sweet cherry, strawberry, pineapple, and melon (Asero, Monsalve, & Barber, 2008).

The kiwifruit allergen, Act d 2 consists of a chain with 201 residues (PDB database, 2013). It is made up of 13% helical (6 helices; 28 residues) and 38% beta sheets (18 strands; 77 residues) in the form of the secondary structure (Figure 2). Act d 5 is a two-chain protein of 189 residues (PDB database, 2015). 10% helical (5 helices; 19 residues) and 26% beta sheets (12 strands; 50 residues) are observed in the secondary structure of this protein. Act d 11 is a 17-kDa protein which is found abundantly in ripe kiwifruit (Chruszcz et al., 2013). The secondary structure of Act d 11 is made up of 22% of helical (4 helices; 33 residues) and 46% of beta sheets (7 strands; 70 residues) containing 150 residues and 1299 atoms (PDB database, 2013). Studies have reported that 10% of all kiwifruit-allergic patients produce IgE specific to Act d 11 (D'Avino et al., 2011). The related data regarding the secondary structure of other kiwifruit allergens are not available from PDB.

As shown in Table 5, Act d 8 present in kiwifruit is from PR-10 family and shows high sequence similarities to those proteins present in different fruits, vegetables, and pollens. These plant sources include cherry (Pru av 1), apricot (Pru ar 1), tomato (Sol al 4), pear (Pyr c 1), strawberry (Fra a 1), peach (Pru p 1), apple (Mal d 1), carrot (Dau c 1), celery (Api g 1), birch pollen (Bet v 1), and beech pollen (Fag s 1). These allergens share four similar amino acid sequences: FKAFVLD, LEGDGGVGTIK, TFGEGS, and VKHRIDG with kiwifruit allergen (data source: GenBank database). Many studies have reported that these sequence similarities in proteins may cause significant cross-reactivity (Aalberse, Akkerdaas, & Van Ree, 2001; Ferreira, Hawranek, Gruber, Wopfner, & Mari, 2004). Cross-reactivity between kiwifruit allergens and birch pollen was reported in 1994, where the cross-reactivity was evaluated through the use of immunoblot and radioallergosorbent techniques (Gall et al., 1994). Clinical cross-reactivities of 55 kiwifruit allergic individuals were tested by oral food challenge. Fifty percent of patients tested showed clinical cross-reactivity with the fruits from Rosaceae family such as peach and pear (Sirvent et al., 2014b).

Another kiwifruit allergen, Act d 10 belonging to nsLTP family also has a homologous sequences to the allergens present in apricot (Pru ar 3), mulberry (Mor n 3), peach (Pru p 3), orange (Cit s 3),

Table 4–Main allergens present in kiwifruit (data source: WHO/IUIS Allergen Nomenclature Sub-Committee, 2010 to 2017).

Species	Allergen	MW	Biochemical name	Property	References
Green Kiwifruit (<i>Actinidia deliciosa</i>)	Act d 1	30 kDa	Cysteine protease (actinidin)	Major allergen	Bublin et al., 2010
	Act d 2	24 kDa	Thaumatin-like protein	Major allergen	Misra et al., 2016
	Act d 3	40 kDa	NA	Minor allergen	Palacin et al., 2008)
	Act d 4	11 kDa	Phytocystatin (cysteine proteinase inhibitors)	Minor allergen	Bublin et al., 2010
	Act d 5	26 kDa	Kiwellin	Minor allergen	Maddumage et al., 2013
	Act d 6	18 kDa	Pectin methylesterase inhibitor	Minor allergen	Jolie et al., 2010
	Act d 7	50 kDa	Pectin methylesterase	Minor allergen	Bublin et al., 2011
	Act d 8	17 kDa	Pathogenesis-related protein (PR-10)	Major allergen	Agarwal et al., 2014
	Act d 9	14 kDa	Profilin	Minor allergen	Bublin et al., 2010
	Act d 10	10 kDa	Non-specific lipid transfer protein (nsLTP)	Minor allergen	Bublin et al., 2010
	Act d 11	17 kDa	Major latex protein/ripening-related protein (MLP/RRP)	Major allergen	Sussman et al., 2010
	Act d 12	50.2 kDa	Cupin, 11S globulin	Major allergen	Sirvent et al., 2014a
	Act d 13	113.6 kDa	2S albumin	Minor allergen	Sirvent et al., 2014a
Gold Kiwifruit (<i>Actinidia chinensis</i>)	Act c 5	28 kDa	Kiwellin	Major allergen	Tamburrini et al., 2005
	Act c 8	17 kDa	PR-10	Minor allergen	Popović et al., 2013
	Act c 10	10 kDa	nsLTP	Minor allergen	Bernardi et al., 2011

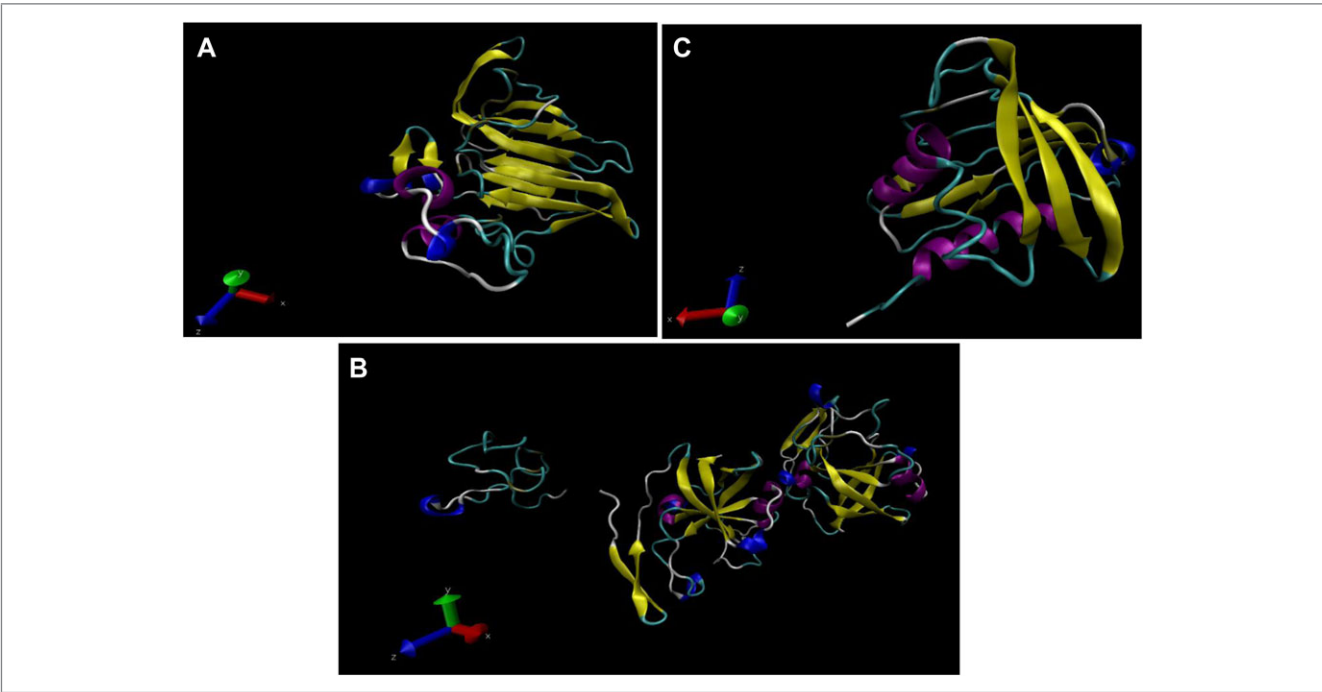


Figure 2–Secondary structure of Act d 2 (A), Act d 5 (B), and Act d 11 (C) allergens present in kiwifruit. (Source: protein data bank, α -helix: Purple, 3/10 helix: Blue, η -helix: Red, β -sheets: Yellow, Turns: Cyan, coils: White).

peanut (Ara h 9), and hemp pollen (Can s 3; as shown in Table 5). These similar sequences include KCGV, CGQV, PDRQAACN-CLKQ, AAAL, and ISRSTDCSK, which are potentially cross-reactive. There are no studies reported to examine whether linear conformations (the sequences causing cross-reactivity between fruits) exist in nsLTPs, and further studies are required. Recently, a new allergen, Act d 12 has been recognized in kiwifruit belonging to 11S globulin protein family. As shown in Table 5, Act d 12 shares significant similar sequences, including FQCAGVA, PGCPPE, and OPQQ, with proteins present in plant seeds such as tree nuts, peanuts, and soybean. This plant-based protein is also found in walnut (Jug r 4), pistachio (Pis v 5), almond (Pru du 6), brazil nut (Ber e 2), and hazelnut (Cor a 9). Similar IgE-binding

epitopes present in kiwifruit seeds (for example, storage protein, Act d 12) are also found in nuts (for example, hazelnut, peanut, and walnut) and peanut proteins (Barre, Delplanque, Simplicien, Benoist, & Rouge, 2017; Sirvent et al., 2014b). This spectrum of potentially cross-reactive proteins across a wide range of fruits, vegetables, nuts, and seeds may explain why many varied food sources induce allergic symptoms in highly sensitized individuals. One study of 59 adolescents and adults with peanut allergy showed that 39% of these patients had allergic symptoms after consuming kiwifruit. This same study reported that 46% of these peanut allergic patients also had an almond allergy, although 22% were soybean, and 54% were hazelnut allergic (Odijk, Sjölander, Brostedt, Borres, & Englund, 2017).

Table 5—Amino acid sequence similarities between different allergens (data source: WHO/IUIS Allergen Nomenclature Sub-Committee).

Protein types	Amino acid sequences	Allergen sources
Pathogenesis-related protein (PR-10)	KFAFVLD LEGDGGVGTIK TFGECS VKHRIDG	Kiwifruit (Act d 8); Apricot (Pru ar 1); Cherry (Pru av 1); Tomato (Sol al 4); Pear (Pyr c 1); Strawberry (Fra a 1); Apple (Mal d 1); Peach (Pru p 1); Celery ^a (Api g 1); Carrot (Dau c 1); Birch pollen (Bet v 1); Beech pollen ^b (Fag s 1);
11S globulin	FQCAGVA PGCPE OPQQ	Kiwifruit (Act d 12); Pistachio (Pis v 5); Peanut (Ara h 3); Soybean (Gly m 6); Walnut (Jug r 4); Hazelnut (Cor a 9); Brazil nut ^c (Ber e 2); Almond ^d (Pru du 6)
Non-specific lipid transfer protein (nsLTP)	KCGV CGQV PDRQAACNCLKQ AAAL ISRSTDCSK	Kiwifruit (Act d 10); Apricot (Pru ar 3); Mulberry ^e (Mor n 3); Peach (Pru p 3); Orange (Cit s 3); Peanut ^f (Ara h 9); Hemp pollen ^g (Can s 3)

Note:

^aThe amino sequences of Api g 1 is FQGFVID, IKGDGGPGTLK, MTLRIDG;^bIEGSGGPGTIK, VKHRIDE;^cFRCAGVAA, SGCPE, ESQQ;^dFECAGVA, QSQQ, PGCPR;^eAAGL, ISPSTDCSK;^fRCCV, ISTSTNCAT;^gRCCV, ISTSTNCAT.**Table 6—Ripening-related allergens present in a variety of fruits.**

Species	Ripening- related allergen	MW	Biochemical name	References
Kiwifruit	Act d 1	30 kDa	Cysteine protease (actinidin)	Ciardiello et al., 2009
	Act d 2	24 kDa	Thaumatin-like protein	
	Act d 5	26 kDa	Kiwellin	
	Act d 11	17 kDa	Major latex protein/ripening-related protein (MLP/RRP)	
Peach	Pru p 3	9 kDa	Lipid transfer protein (LTP)	Brenna et al., 2004
Apple	Mal d 1	17 kDa	Pathogenesis-related protein (PR-10)	Schmitz-Eiberger & Matthes, 2011
	Mal d 3	9 kDa	Non-specific lipid transfer protein (nsLTP)	Sancho et al., 2006

Ripening-Related Allergens

After harvest, many fruits need a period of ripening prior to consumption. This ripening improves color, flavor, and nutrients content, enhancing the quality of the fruit (Bron & Jacomino, 2006; Kyriacou, Soteriou, Roupheal, Siomos, & Gerasopoulos, 2016). However, studies have shown that maturity related allergens, present in kiwifruit, significantly increase during this storage period. During the ripening stages, total protein content has been shown to dramatically increase from 20 to 300 mg/100 grams in both green and gold kiwifruit (Ciardiello et al., 2009). The three allergenic proteins actinidin (Act d 1), TLP (Act d 2), and kiwellin (Act d 5), concentrations present in the kiwifruit, picked after commercial harvest (42 days), reached a higher level compared to those picked before commercial harvest (104 days; Table 6). The WHO/IUIS Allergen Nomenclature Sub-committee has described that Act d 11 is also a ripening-related allergen present in kiwifruit (D'Avino et al., 2011). Thus, there are four ripening-related allergenic proteins abundantly synthesized during the period of postharvest ripening.

Other fruit species such as peaches have similar-type ripening-related allergens like Pru p 3, a 9-kDa lipid transfer protein (LTP; Brenna, Pastorello, Farioli, Pravettoni, & Pompei, 2004). During the ripening period, SDS-PAGE and immunoblotting analyses showed that the protein bands intensity corresponding to Pru p 3 in fully ripened peaches increased compared to the fruits harvested 15 days before commercial ripening dates. In the ripening stage, peaches undergo significant stressors such as high temperatures, pests, and diseases which may enhance the synthesis of Pru p 3 allergen as the first line of defense. In apples, Mal d 1 (17 kDa) and Mal d 3 (9 kDa) are two major ripening-related apple allergens. Studies have reported that Mal d 1 belongs to pathogenesis-related proteins (PR-protein) and is present in

unripe “Golden Delicious” and “Topaz” apples. This allergen sharply increased after an 8-week storage time (Schmitz-Eiberger & Matthes, 2011). Mal d 1 is upregulated by internal (for example, polyphenol oxidase activity) and external factors (for example, temperatures), resulting in its increased synthesis in stored apples and is specifically increased by 125% in “Golden Delicious” apples and by 750% in “Topaz” apples (Schmitz-Eiberger & Matthes, 2011). Similarly, the concentration of Mal d 3, a 9-kDa nsLTP is two times higher in fully matured apples compared to immature stages (Sancho et al., 2006). This significant increase is attributed to the increase of respiration rate and ethylene biosynthesis. These two factors are associated with ripening and softening of apples. Altogether these data suggest that the expressions of fruit allergens differ significantly in various fruits during their ripening stages and highlights the need to fully elucidate the relationship between the concentrations of fruit allergens and ripening stages of fruits.

Effect of Processing Techniques in Kiwifruit Allergens Reduction

Thermal processing

In the food industry, thermal processing is a primary technique widely used to destroy bacteria and enzymes through the combination of temperature and time (Rawson et al., 2011). The established processing conditions depend on the kind of food. Several studies have reported that some thermal processing methods including sterilization, microwave heating, boiling, and steam cooking showed potential applications in reducing food allergenicity (Kasera et al., 2012). For example, whey protein present in milk when treated by heat at 90 to 95 °C resulted in a reduction in its IgE-binding capacity as evaluated by ELISA (Taheri Kafrani et al., 2009). Moreover, several studies reported that

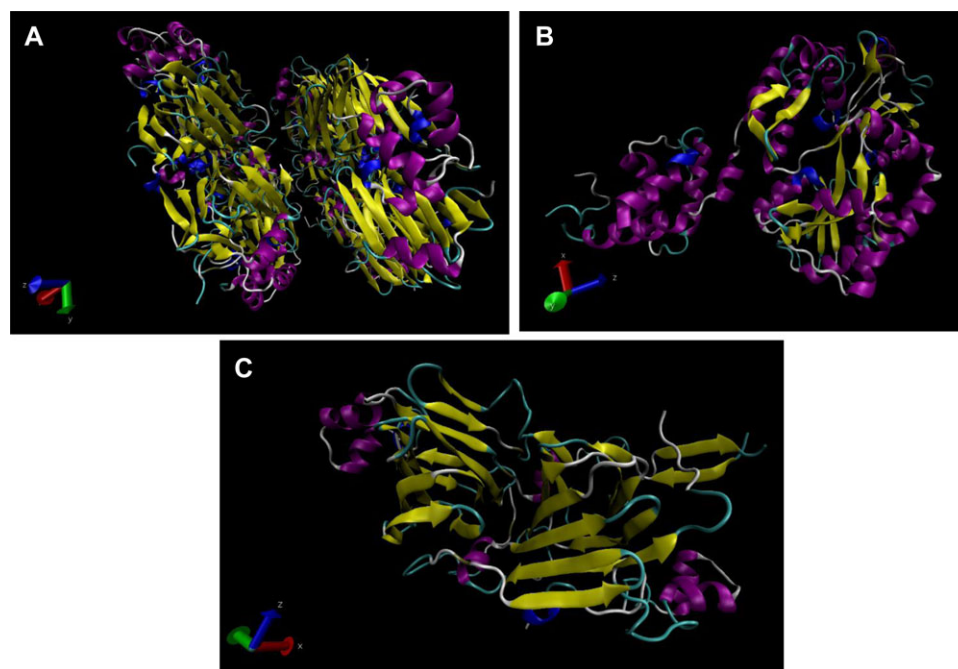


Figure 3—Secondary structure of Ara h 1 (A), Ara h 2 (B), and Ara h 3 (C) allergens present in peanut. (Source: protein data bank, α -helix: Purple, 3/10 helix: Blue, η -helix: Red, β -sheets: Yellow, Turns: Cyan, coils: White).

boiling peanuts at 100 °C for 20 to 30 min in water effectively reduced the allergen content of Ara h 1, Ara h 2, and Ara h 3 (Mondoulet et al., 2005; Turner et al., 2014; Figure 3). These changes in IgE-binding capacity and concentrations of allergens mentioned may be due to the denaturation of allergenic proteins under the high-temperature condition for a longer duration (Verhoeckx et al., 2015).

Among kiwifruit allergens, Act d 2 is from the family of TLPs. The structural integrity of these proteins is prone to change under stressful conditions (for example, higher temperature). For example, in one study, F2/4JRU, a TLP in grape wine was shown to be temperature sensitive to temperature such that the protein structure was unfolded when is exposed to high temperatures (56 °C; Marangon, Van Sluyter, Waters, & Menz, 2014). Denaturation of TLPs may be related to the unstable properties of some bonds (for example, hydrogen bonds; Falconer et al., 2009). There are three domains in the secondary structure of most TLPs. Domain I is located in the center of protein and consists of several β -strands; domain II consists of several α -helices, whereas domain III is comprising of β -strands and small loops. S-S bonds present in each domain can stabilize the protein (Min et al., 2004). The S-S bonds present in soy milk proteins (Ren, Tang, Zhang, & Guo, 2009) and whey proteins (Wijayanti, Bansal, & Deeth, 2014) can be cleaved under specific stressful conditions such as high temperatures. The cleavage of S-S bonds results in the loss of secondary structure which may lead to the reduction in the IgE binding capacity of protein allergens (Tong et al., 2012; Zhu, Vanga, Wang, & Raghavan, 2018). In kiwifruit, two major allergens, Act d 1 and 2 when treated with steam cooking at 100 °C for 10 min were lighter, when running on an SDS-Page gel compared to untreated controls (Fiocchi et al., 2004). These heated proteins also had reduced the IgE-binding capacity as demonstrated by immunoblotting. Together these data suggest that Act d 1 and 2 are thermally unstable proteins and are prone to progressive loss of

tertiary and secondary protein structures under specific temperature conditions. The effects of thermal processing on the structures of Act d 8 and Act d 11 have not been studied. In contrast, Act d 12 (50.2 kDa) is a novel relevant kiwifruit allergen from the globulin protein family. The secondary structure of Act d 12 shows slight reversible alterations when exposed to temperatures in the range of 20 to 80 °C. It suggests that this allergen is highly resistant to thermal denaturation (Sirvent et al., 2014b). Overall data suggest that thermal processing can reduce the allergenic potential of kiwifruit.

However, thermal processing may also lead to chemical and physical changes, which in turn may decrease the sensory quality and amounts of nutritional compounds in the fruit, especially some heat-sensitive compounds such as ascorbic acid and polyphenols (Pérez-Conesa et al., 2009; Rawson et al., 2011). In apple juice, thermal processing at 90 °C for only 30 s led to 20% to 100% reduction of volatile flavor-related compounds (Aguilar-Rosas, Ballinas-Casarrubias, Nevarez-Moorillon, Martín-Belloso, & Ortega-Rivas, 2007). The overall sensory properties of apple juice decreased significantly under thermal processing at 90 °C for one minute compared to untreated apple juice (Mosqueda-Melgar, Raybaudi-Massilia, & Martín-Belloso, 2012). Thermal treatment at 90 °C for 100 s resulted in improving turbidity of apple juice compared to untreated fresh apple juice (Krapfenbauer, Kinner, Gössinger, Schönlechner, & Berghofer, 2006). Tomato puree has also been shown to be affected by thermal processing. The total phenolic content, vitamin concentration, and antioxidant activity significantly decreased after pasteurization processing at 98 to 128 °C compared to untreated samples (Pérez-Conesa et al., 2009). Currently, minimally processed food products with high nutrients content, natural flavor, and taste are increasing in popularity over the processed products. Thus, there is a need for novel thermal or nonthermal processing technologies that will potentially reduce the food allergenicity and also maintain or improve the food quality.

Nonthermal processing: high-intensity ultrasound treatment

A novel nonthermal application, ultrasound treatment has garnered attention as higher nutrients amounts, freshness, flavor, and color attributes are maintained during ultrasound processing (Cheng, Zhang, & Adhikari, 2014). This technique is an alternative processing method that is inexpensive, reliable, and environmentally friendly (Soria & Villamiel, 2010). Several studies have shown that high-intensity ultrasound (20 to 100 kHz) treatment could reduce food allergenicity. In one study, the shrimp were treated with a sonicator at 30 kHz, 800 W for 30 to 180 min (Li, Lin, Cao, & Jameel, 2006). There was significantly decreased shrimp allergenicity (IgE-binding capacity) by 74.7% after 180-min ultrasonic processing compared to untreated samples. A study of soybean protein demonstrated that high-intensity ultrasound treatment at 37 kHz for 10 min effectively disrupted the secondary structure of soy proteins resulting in a decrease of 24% in soy protein allergenicity (Nayak, Li, Ahmed, & Lin, 2017). In peanuts, the IgE-binding activity of peanut protein extracts was decreased by 10% after a high-intensity ultrasound processing at 50 Hz for 1 hr compared to untreated peanut samples (Li, Yu, Ahmedna, & Goktepe, 2013).

These reductions in the IgE-binding activity of related food proteins may represent secondary structural changes of the proteins following ultrasound processing. Generally, cavitation effects are formed by bubble collapse during high-intensity ultrasound processing leading to a significant increase in pressure up to 70 to 100 MPa and temperature up to 5000 K (Bermudez-Aguirre, 2017; Kentish & Ashokkumar, 2011). This provides enough energy to cause physical and chemical modifications of the proteins resulting in the changes of allergens conformation and their IgE binding activity. Further, high shear stress generated by ultrasound processing can produce microstreams resulting in the formation of a molten globule state of the protein (Kentish & Ashokkumar, 2011; Soria & Villamiel, 2010). These data suggest that ultrasound treatment may be a potential processing technology in the reduction of kiwifruit allergen, although this remains to be rigorously investigated.

Chemical processing: enzyme and ethylene treatment

Enzyme treatment. In addition to thermal processing, chemical treatments may also reduce food allergenicity. Several studies have observed that specific allergy-related proteins are hydrolyzed by related enzymes. For example, when gliadin, a major wheat flour allergen, was treated with 0.01% alcalase combined with papain. The gliadin content significantly decreased, and lower IgE-binding was demonstrated compared to untreated samples (Li, Yu, Goktepe, & Ahmedna, 2016). In another study, there was degradation of major soybean allergen (proglycinin; Figure 4A) up to 100%, 100%, and 95.9% after alcalase, pepsin, and papain treatments, respectively (Meinlschmidt, Sussmann, Schweiggert-Weisz, & Eisner, 2016). In avocado, *Pers a 1*, a major avocado allergen was fully inactivated after pepsin treatment (0.32% [w/v]) measured by an immunoblot inhibition analysis (Díaz-Perales et al., 2003). These reductions of food allergens by enzymatic hydrolysis may result from the changes in their structure, solubility, and foaming characteristics.

In kiwifruit, studies have reported that allergen properties are impacted by enzymes such as pepsin (Yagami, Haishima, Nakamura, Osuna, & Ikezawa, 2000). Specifically, when Act d 1 and Act d 2 were treated with pepsin in the ratio of 1:20 by weight (Bublin et al., 2008). There was a slight reduction

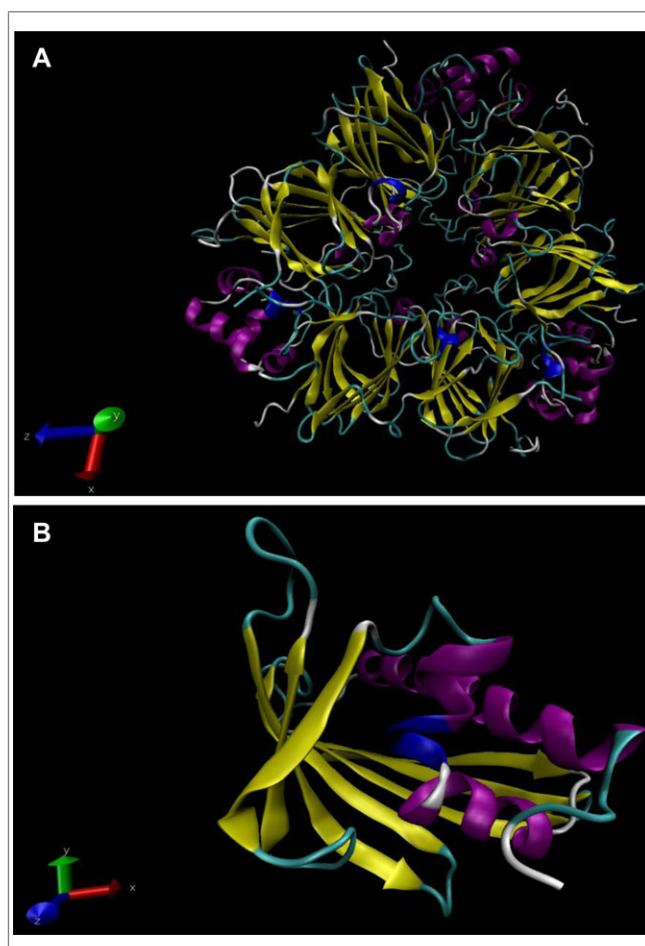


Figure 4—Secondary structure of glycinin (A) allergen present in soybean and Mal d 1 (B) allergens present in apple. (Source: protein data bank, α -helix: Purple, 3/10 helix: Blue, η -helix: Red, β -sheets: Yellow, Turns: Cyan, coils: White).

in IgE-binding ability of Act d 1 after 120 min. Importantly, a 75% reduction in IgE binding capacity of Act d 2 was noted in these pepsin-treated samples. Act d 1 and Act d 2 differ in protein structures and molecular weight which may explain the differences in the effectiveness of pepsin treatment. The fragments of Act d 1 and Act d 2 remaining after pepsinolysis were then treated with trypsin and chymotrypsin in the ratio of 1:400:100 by weight. The remaining fragments were rapidly broken down by this additional treatment (Bublin et al., 2008). During these two enzymatic treatment stages, the allergenicity of these allergens was reduced drastically due to the disruption of disulphide bonds present in these allergens. The S-S bonds play a role in resisting digestion with proteases. Similar studies had reported that *Pers a 1*, an avocado allergen was highly sensitive to related enzymes (for example, pepsin A) resulting in the elimination of allergic reactions when its structure was disrupted by fracture of disulphide bonds (Bublin et al., 2008; Díaz-Perales et al., 2003).

However, several studies have reported that enzymatic hydrolysis treatment shows a negative effect on food quality and taste. For example, soy protein isolates were treated with alcalase, pepsin, or papain, respectively. Alcalase treatment increased the intensity of bitterness (8.2/10) when compared to all other treatment groups (Meinlschmidt et al., 2016). Pepsin treated samples were significantly more “sour” and “astringent” taste compared to other

treatments and untreated samples. Similar results have been shown with pea protein hydrolysates, alcalase treated samples had the most bitter taste compared with that of papain and α -chymotrypsin treatment and untreated samples (Humiski & Aluko, 2007). This extra “bitter” or “astringent” flavor is strongly related to the production of hydrophobic bitter peptides during proteolytic reactions resulting from enzymatic hydrolysates (Meinlschmidt et al., 2016; Sun, 2011). These negative attributes limit the application of enzymatic hydrolysis processing in food systems. Therefore, it is necessary to evaluate the advantages and disadvantages before using this processing technology in the reduction of food allergens.

Ethylene treatment. During the growth, development, and senescence of kiwifruit, ethylene plays a primary role in the synthesis and metabolism of nutrients (for example, sugars, vitamins, or proteins), and physiological changes (for example, color, flavor, texture), especially during ripening stages (Tucker et al., 2017; Villarreal, Bustamante, Civello, & Martínez, 2010). Ethylene is considered as a multifunctional phytohormone that regulates the growth and senescence of plants depending on its concentration and mode of application. For example, strawberries when treated with ethylene accumulated higher amounts of sugar and titratable acidity compared to untreated controls (Villarreal et al., 2010). Although, fresh green in-husk walnut fruit treated with 500 mg/L ethephon had reductions in the decay index of fruit, increases of total phenol content and maintenance of a better kernel quality when compared to untreated walnuts (Wang, Liang, Ma, Zhang, & Shi, 2016). Treatment of kiwifruit with 1000 μ L/L ethephon significantly increased the soluble solid concentrations and total phenols content leading to maintenance of a better kiwifruit quality (Zhang, Li, Liu, Song, & Liu, 2012).

Ethylene has also been shown to influence the *de novo* synthesis of proteins in fruit. The total protein content of apples significantly increased by 13.5% following ethylene treatment, and gene expression of a major apple allergen (Mal d 1; Figure 4B) was found to be upregulated (Zheng et al., 2013). In kiwifruit, ethylene treatment slightly increased the total protein content. Interestingly, two kiwifruit allergens, pectin methylesterase (Act d 7) and pectin methylesterase inhibitor (Act d 8) are undetectable after ethylene treatment (Ciardiello et al., 2009). It is possible that, in kiwifruit, the process of ripening following ethylene treatment leads to degradation of these allergic proteins with a small molecular weight. Ethylene treatment for purposes of allergen reduction requires further study.

Management and Treatment of Food Allergy

Dietary management

Kiwifruit allergic individuals must maintain complete abstinence from ingestion of the fruit and must learn to manage unexpected allergic reactions that may occur following accidental exposure to the kiwifruit or related products. Kiwifruit is a versatile ingredient, which is found in various food products worldwide including cakes, juice, jam, ice cream, fruit wine, or fruit salads. Avoidance is challenging especially for children. The Intl. Life Sciences Inst. (ILSI) has provided official guidelines and recommended that dietetic support should be sought to provide accurate dietary limitation information, and a comprehensive list of allergens that are known to be implicated in cross-reactivity should be provided (Turnbull, Adams, & Gorard, 2015). However, as there are multiple allergenic proteins in kiwifruit, the list of potential cross-reactive foods is significant, and many patients are not sensitized to all the potential allergens found in the fruit. Thus,

although one patient should avoid all foods with cross-reactivity, another may only need to avoid kiwifruit in the fresh form. For kiwifruit, the potential allergen sources include pollens from birch tree, grass or ragweed, other kind of fruit (for example, banana) or vegetables (for example, avocado), peanut or tree nuts, and latex or related products (Merima Bublin et al., 2010; Lee et al., 2013; Ozkaya, Coskun, Turkmenoglu, & Samanci, 2010; Sirvent et al., 2014b). Generally, apples, oranges, and pears or their combination can be used as the substitutes for kiwifruit in the diet due to similar amounts of vitamin C and dietary fiber.

Unlike the canonical “Big Eight” major food allergens, kiwifruit is an allergenic species for which labeling is only recommended in Japanese legislation, but not in the revised EU Labelling Directive (Gendel, 2012; Shoji, Adachi, & Akiyama, 2018). It is essential that the consumers allergic to kiwifruit read the detailed ingredients information of each product carefully. Furthermore, in some cases contacting the manufacturer to make sure there is no kiwifruit in a particular food product is required. Kiwifruit may be found as a “hidden ingredient” in various food products such as yogurt, juice, jams, and confections. Therefore, it is necessary to access the detailed ingredients lists of these food products before purchasing.

Emergency treatment

Kiwifruit can cause a wide range of symptoms from OAS to severe, life-threatening anaphylactic reactions which may include hypotension, tachycardia, or loss of consciousness (Ciardiello et al., 2009). These reactions may lead to coma or even death if emergency treatments are not used in a timely manner. Antihistamines are prescribed to treat mild local symptoms including urticaria (hives), pruritus (itch), itchy eyes, and runny nose. Antihistamines act by blocking the histamine receptor and preventing histamine released from activated mast cells (Sicherer & Sampson, 2014). When the allergic reaction extends to involve two organ systems, epinephrine injection is considered as the first treatment required (Sicherer & Simons, 2007). Epinephrine also known as adrenaline is available as a self-injectable medication and was approved by the U.S. Food and Drug Administration (FDA) in 1987 as its highly effective and safe for management of anaphylaxis. Epinephrine primarily acts on α and β -adrenergic receptors of the sympathetic nervous system. The insulin secretion is inhibited by regulating glycogenolysis when it combines with the α -adrenergic receptors. The combination of epinephrine with β -adrenergic receptors increases the secretion of glucagon and adrenocorticotrophic hormone, and also enhance lipolysis in the organs (Tsfaye & Seaquist, 2010). Together, these effects improve blood pressure and relax the smooth bronchial muscles improving airflow and respiration. Additional doses of epinephrine and intravenous fluids are also used to expand the blood volume in hypotensive patients.

Future immunotherapy

Currently, there are no immunotherapy options that consistently cure food allergies. However, several immunotherapy strategies are under investigation. The final goal of oral immunotherapy, or allergen-specific desensitization is to increase the level of tolerance to specific allergens by gradually increasing the amounts of the offending allergens ingested by allergic patients. In one study of 62 peanut allergic children aged one to ten years, there was a decrease in the wheal size of the peanut-specific skin prick test following 18 months of oral peanut immunotherapy (Tang et al., 2015). Many patients were able to tolerate ingestion of small amounts of peanut without clinical symptoms. However, there were significant side effects, and some patients experienced anaphylactic episodes

during the process. Although oral immunotherapy is under development for other food allergens, this approach is time-consuming and carries significant risks of anaphylaxis during desensitization. Sublingual immunotherapy is also used for pollen allergies. In Canada there are now four sublingual pollen allergen immunotherapy products: Grastek, Oralair, Acarizax, and Ragwitek which are approved by Health Canada, for patients aged 10 to 65 years with grass or ragweed pollen and dust mite allergy (Li et al., 2016). Interestingly, although sublingual therapy does reduce the symptoms associated with inhalation of pollens during allergy seasons, there as yet appears to be no significant improvement in OAS in these patients. Taken together, these approaches may reduce the clinical symptoms in some patients but not for most. Thus, much work remains to be done in reducing the risks of allergic reactions to foods in individuals living with food allergies.

Conclusion

Kiwifruit can trigger a range of allergic symptoms from mild OAS to the severe, life-threatening anaphylaxis. Kiwifruit allergy affects a significant number of individuals and the frequency of the allergy appears to be increasing possibly due to an increased sensitization to other related allergens including pollen (for example, birch pollen), other fruits (for example, avocado or banana), or legumes (for example, peanuts). Further studies regarding the pathogenesis, clinical features, and diagnosis of kiwifruit allergy will progress our understanding of the specific mechanisms of kiwifruit allergy. Complicating management of kiwifruit allergy is the variability of allergenic proteins during ripening stages. The four allergenic proteins Act d 1, Act d 2, Act d 5, and Act d 11 present in kiwifruit are ripening-related allergens. These findings provide a deep understanding of the relationship between the kiwifruit allergens concentrations and the ripening stages of kiwifruit. In food industries, many studies focus on the food processing impact on the reduction of kiwifruit allergens concentrations through changing of the secondary and tertiary protein structures. Although several processing methods such as steam cooking, enzyme, and ethylene treatment can be beneficial to reduce the allergenicity of kiwifruit, the efficacy of these processing methods need to be improved and well-studied. Novel processing techniques also need to be developed. Recognition of kiwifruit allergy, education regarding appropriate management and development of strategies for desensitization would improve outcomes and quality of life parameters for patients living with this food allergy.

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Conflicts of Interest

The authors report no conflict of interest.

Authors' Contributions

Jin Wang and Sai Kranthi Vanga designed the manuscript, performed preliminary data analysis, composed the manuscript, and conducted the initial review. Dr. Christine McCusker (MD) contributed critical feedback to the concept, design, and language of the manuscript based on her medical research background. Dr. Vijaya Raghavan supervised the project and edited the final version of the manuscript.

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