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Effect of pre-harvest and post-harvest conditions on the fruit allergenicity：A review

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Abstract

Fruits are an important source of vitamins and antioxidants that can effectively delay aging and contribute to health and well-being of the human kind. However, they are growing to be one of the primary elicitors of food allergies around the world. Fruit allergens can induce an IgE-mediated (Immunoglobulin E) reaction, presenting with a symptom like localized oral allergy syndrome (OAS). Numerous studies showed that varying environmental and cultivation conditions can influence the fruit allergen content during flowering and ripening stages. Further, the variety, harvesting maturity, and storage conditions can also significantly influence the allergenicity potential. For example, unripe apples and tomatoes have lower levels of allergens compared to ripened fruits. Researchers have also reported that modified atmosphere packaging (MAP) can help reduce Mal d 3 content present in apples during storage. Post-harvest processing like peeling is also considered a good method to help reduce the overall allergenicity in few fruits whose peel might contain majority of the allergens. This review will discuss the overall influence of both pre-harvest and post-harvest factors on the fruit allergens. We will also

discuss the progress regarding the cause, symptoms and diagnostic methods of fruit based allergies.

Keywords

Fruit allergy; cross-reactivity; storage; pollen allergy; harvesting maturity; modified atmosphere package

Abbreviation

IgE Immunoglobulin E

OAS Oral Allergy Syndrome

nsLTPs non-specific Lipid Transfer Proteins

LTPs Lipid Transfer Proteins

MAP Modified Atmosphere Packaging

Bp Base Pair

PPO Polyphenol Oxidase

SPT Skin Prick Test

DCs Dendritic Cells

IP Integrated Production

OC Organic Cultivation/Organic Production

DM Dry matter

WHO/IUIS World Health Organization and International Union of Immunological Societies

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1 Introduction

Food allergy is a widespread phenomenon: An estimated 2-5% of the adult population and up to 8% of the children and infants suffer from some types of food allergy(Chafen et al., 2010; Sicherer and Sampson, 2014). Fruits are considered to be among the primary elicitors of food allergy in humans (Laimer and Maghuly, 2010). Recent data suggested that pollen allergies affect approximately 40% of the population all over the world (Asam et al., 2015). Due to the similarity between the allergens present in various pollens and fruits, the individuals sensitive to pollen can have cross-reactivity to various fruits and latex allergens. It has been reported that up to 70% of birch pollen allergic people had allergenic reactions after consuming raw fruits (Hofmann and Burks, 2008). Fruit allergy is an IgE-mediated (Immunoglobulin E) reaction and is the result of a sensitization process occurring in the gastrointestinal tracts (Krebitz et al., 2003). Many reports show that fruit allergies cause a wide range of symptoms, mostly limited to localized oral allergy syndrome (OAS) (Kerzl et al., 2007; Mancuso and Berdondini, 2001). Fruit allergy is becoming more and more common. Many of the consumed fruits from around the world, are known to trigger allergic reactions in sensitive individuals (Vanga et al., 2016). A survey was conducted in France, containing a total of 182 children varying in the ages from 2-14 years, who are reported to be allergic to one or more fruits. Of these children, 12% were reported

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to be hypersensitive to kiwis, 5.5% to tomatoes, 4.4% to strawberries, 3.8% to pineapples, 2.7% to oranges and about 1.2% to apples (Rance et al., 2005).

However, fruits are a vital part of our daily life due to the presence of rich essential nutrients and health-promoting bioactive compounds. For example, strawberry fruit is a source of vitamins, phenolic compounds (i.e. flavonols, flavones, and anthocyanins) and various biofactors which in turn can delay aging, resist cancer and prevent infections(Battino et al., 2009; Tumbas et al., 2010). Also, strawberry is appreciated worldwide for its unique flavor (Bianco et al., 2009; Laimer and Maghuly, 2010). However, various studies reported that allergenic protein, Fra a 1 present in strawberries could cause discomfort and allergic symptoms (Franz-Oberdorf et al., 2016; Tulipani et al., 2011).

Many studies have shown that a wide range of factors such as storage conditions, variety, and harvest maturity of fruit could have an impact on the final allergenicity level at the time of consumption. Research found that one of major apple allergens, Mal d 1 had a significant increase during modified atmosphere packaging (MAP) use for storage (Sancho et al., 2006a). While the content of other major allergen like Mal d 3 present in apples was lower when stored under the controlled atmosphere conditions (0.5% O_2, 1.5% CO_2 at 3.8℃) compared to those were kept under room temperature (Sancho et al., 2006b). Moreover, López-Matas et al. (2011) reported that the protein profile and allergen quantification of six varieties of tomatoes (Rama, Rambo, Canario, Kumato, Pera and Raf) were totally different. The highest allergen content

(Lyc e 3) was shown in the 'Rambo', followed by 'Pera', and 'Canario'. The 'Rama' showed the lowest value of allergen content. Also, Schmitz-Eiberger and Matthes (2011) reported that the Mal d 1 content was the highest in 'Topaz' apples, followed by 'Golden Delicious' and 'Braeburn'. Studies were also done to evaluate the impact of harvest maturity on fruit allergen content. A study found that apples showed a higher Mal d 1 content when they were ripe than that of unripe apples (Schmitz-Eiberger and Matthes, 2011). Similarly, Sancho et al., (2006b) reported that the apples that were picked at later stages of maturity showed a 3-4 times higher allergen content (Mal d 1). Further, research found that apple allergen content had a relationship with the antioxidant activity and enzyme activity. Higher polyphenol oxidase (PPO) activities and polyphenolic content resulted in less Mal d 1 whereas, higher antioxidant activity inhibited the interaction between oxidized phenols and Mal d 1, resulting in lower allergenicity (Mal d 1 content) (Schmitz-Eiberger and Matthes, 2011). Similarly, Tulipani et al., (2011) found that strawberry allergen Fra a 1 content decreased with an increase in the total antioxidant capacity, total phenolic content and total flavonoid content in 'Adria', 'Sveva', 'AN94.414.52' and 'AN00.239.55', varieties of strawberry.

This review will report the available information about the cause and symptoms of various fruit allergies and also detail the diagnostic methods and related proteins responsible for causing allergic reactions. Finally, this review will discuss the influence of various factors including cultivars, harvesting maturity, the difference in the peel and pulp of the fruit, storage conditions, and different environmental cultivation conditions i.e. nitrogen, water shortage and climatic factors on the fruit allergenicity. Hopefully, it can provide new ideas for the growers, breeding industry and consumers who are suffering from one or more types of fruit allergies.

2 Causes, symptoms and diagnosis of fruit allergies

2.1 Causes

Fruit allergies are often caused by profilins present in a wide range of fruits and can trigger hypersensitivity because of conflicting immune feedback to dietary antigens which are often difficult to avoid (Andersen et al., 2011; Sicherer, 2002). These allergens are kinds of specific antigens presenting with the capacity to induce IgE-mediated reactions. The allergenic proteins have certain site(s) which can combine with the specific antibodies; these sites are called epitopes with linear or conformational features (Kumar et al., 2012). After the first consumption of fruit, the specific allergens are recognized by certain antigens present in cells especially dendritic cells (DCs) of lamina propria in the intestine (Li et al., 2007). The allergens are incorporated by DCs because of receptor-mediated endocytosis process, macropinocytosis or phagocytosis (Morelli et al., 2004). When an allergy-prone person has a secondary exposure to the same allergen, a hypersensitive reaction is presented with a series of symptoms, and can even lead to anaphylactic shock due to allergen exposure (Kumar et al., 2012).

The profilins causing allergies are usually found in pollens of grass (ex: mugwort), trees (ex: birch) and weeds (ex: ragweed) other than in fruits and vegetables (Sicherer, 2001). These allergens from various sources mentioned above have a similar structure to the profilins found in various fruits. Hence, in the case of patients with tree-pollen allergies, their immune systems cannot recognize the difference between allergens present in birch pollen and apples because of their similar three-dimensional structures (Dreborg and Foucard, 1983). Ebner et al., (1991) reported that proteins present in birch pollen and apples share the common allergenic structures (i.e. Epitopes) by using western and northern blotting techniques. For example, apple allergen (Mal d 1), pear allergen (Pyr c 1) and cherry allergen (Pru av 1) can induce birch pollen-related fruit allergies i.e. their structural conformation is similar to that of allergens present in birch pollen and hence can have similar epitopes leading to cross-reactivity in hypersensitive patients (Patel and Volcheck, 2015).

In patients who suffer from hay fever, the immune system would recognize profilins present in pollens as harmful proteins which can trigger an allergic reaction. This condition is referred to as OAS which is considered a form of contact allergy that is confined almost solely to the oropharynx and hardly affects other target organs (Ortolani et al., 1988). In about 35% of people suffering from hay fever might be due to an allergy to profilins. They may find that they experience mild allergy symptoms after eating fruits to which they are sensitive or that contain allergens similar to their counterparts in pollen. Some people with OAS only react to one or two fruits, while others are allergic to a wide range of products. Several of the most common culprits

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include apples, strawberries, pears, tomatoes, cherries, peaches, plum, kiwifruit, and melon (Vanga et al., 2016).

2.2 Symptoms

Symptoms of allergy usually arise just several minutes after eating the fruit, although they can sometimes take up to two hours to manifest itself. These symptoms often can be settled down within one hour. Fortunately, profilins are easily inactivated during the cooking process and by digestion, meaning the immune system can no longer recognize them. Common fruits allergy symptoms can be divided into mild oral and systemic reaction. The former is referred to as OAS which is considered a form of contact allergy and its symptoms include mild itching and swelling (Mari et al., 2005; Ortolani et al., 1988; Sicherer and Sampson, 2010). The symptoms of systemic reaction can be observed in certain organs, such as skin (local or systemic urticaria, hereditary allergic eczema), gastrointestinal tract (abdominal cramps, diarrhea, vomiting), nose and lung (rhinitis and asthma), cardiovascular system (anaphylactic shock) (Capurro and Levi, 1975; Sicherer, 2000; Wilson et al., 2005).

Many studies have reported where these symptoms vary among different varieties of fruits. As shown in Table 1, the patients showed an allergic contact dermatitis and presented a two-day history of patchy pruritic erythema of the face, neck, and arms with periorbital edema after eating mango (Calvert et al., 1996; Weinstein et al., 2004), and the symptom of systemic shock occurs according to the level of severity. Kiwifruit can cause allergic asthma, urticaria, allergic purpura, allergic dermatitis, itching and difficulty in breathing (Lucas et al., 2004; Lucas et al., 2007). After eating raw or fresh apples, the main allergen (i.e. Mal d 1) present in apples causes OAS, which is generally restricted to the lips, tongue, and throat (Sancho et al., 2006a). In strawberry, a Bet v 1-homologous allergen, Fra a 1, was identified as a major allergen (Franz-Oberdorf et al., 2016; Tulipani et al., 2011) which causes allergic symptoms presenting with tightness of the throat, swelling, burning or prickling sensation in the lips or tongue and other parts of the oral cavity after consuming the fruit.

2.3 Diagnosis of allergy

Nowadays, there are several common methods for the diagnosis of fruit allergies such as skin prick test and blood test. The skin prick test (SPT) is one of the primary diagnostic methods and can be taken through using various solutions of suspected allergens during the first consultation. SPT produces reaction for an immediate type of allergies leads to the determination. Hence, determines allergy by the reaction of a patient’s skin to different substances based on the medical history and clinical symptoms. The principle of SPT is when certain allergens are contacted into the the skin, specific IgE combining with the surface receptors present in mast cells are cross-linked resulting in mast cells degranulation, and mediators (i.e., histamine) being released (Heinzerling et al., 2013), which leads to corcles looking like a wheal. The subjects of the skin prick test are mostly children compared to adults when the total numbers are considered. The processing time of a test is generally short and evaluated within 15-20 minutes.

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Also, it is very sensitive and low risk with no reported fatalities as reported in a study of five years in the USA (Novembre et al., 1995; Reid et al., 1993). However, during the skin prick test, it would cause a slight discomfort because of itching; and it is difficult to perform in patients with eczema or dermatographism. Blood test detects specific IgE antibodies by using radioimmunoassay test. A single needle is used to obtain blood samples, and the needle stick is often more gentle than other skin tests. Moreover, any age of individuals including adults and children can take this blood test. Compared to the SPT, blood test shows a higher specificity and sensitivity as it binds specific IgE to a certain antibody.

After the allergy testing, an elimination diet is usually designed by the medical professionals. It would remove one or more food from patient’s diet for several days. This eliminated food group is then gave back to determine if certain food allergic reactions develop again. Therefore, an elimination diet may also be used one of diagnostic methods to help identify if a person has food allergies or not. An allergist or dietician must be involved in designing the diet to prevent imbalances in the nutrient intake. It is necessary to read food labels carefully for people who are allergenic to a certain food. In some countries, they already enacted the related law to protect those people who are easily allergenic to some food. For examples, in the year of 2004, the Food Allergen Labeling and Consumer Protection Act (United States) mandated that nutritional labels on food packages should plainly identify the eight specified food allergen sources including milk, eggs, fish, crustacean shellfish, tree nuts, peanuts, wheat, and soybeans if present.

3 Fruit allergens

3.1 Common allergenic fruits and their allergens

A wide variety of fruits have been reported to cause allergic reactions which are listed in the database (www.allergen.org) of World Health Organization and International Union of Immunological Societies (WHO/IUIS). However, the most prevalent and widely studied are reactions to apple, peach, strawberry and kiwifruit. As shown in Table 2, several fruit allergens are present in each fruit and their size (molecular weights) are widely different.

3.2 Fruit allergen families

To date, many researchers have identified various plant-derived allergens which have been classified into specific groups, such as PR proteins due to their similar sequences and biological function (Hoffmann-Sommergruber, 2002). PR proteins are regulatory proteins which are produced in the plant in response to a pathogenic bacterial attack (van Loon, 1985). Some of these proteins are antimicrobial and can protect the plant through attacking the cell wall of a bacteria or fungi (Liu and Ekramoddoullah, 2006). As shown in Table 3, researchers found that five members of the 14 member PR protein family can trigger allergic reactions in humans (Breiteneder, 2004; Hoffmann-Sommergruber, 2002). These five members are:

β-1,3-glucanases (PR-2), class I chitinases (PR-3), thaumatin-like proteins (TLPS, PR-5), Bet v 1 homologous proteins (PR-10) and nonspecific lipid transfer proteins (nsLTPs, PR-14).

PR proteins play an major role in fruit allergy and can induce reactions in a wide variety of fruits, such as allergy to grapes (Vit v Glucanase), avocados (Pers a 1), apples (Mal d 1 and Mal d 2), cherries (Pru av 2), peach (Pru p 3), pear (Pyrc 3) and strawberries (Fra a 1) (Table 3). As the main function of these proteins is to protect the plant from external predators including pathogens, the development of disease and pathogen resistant varieties for enhancing the yield in modern farming could have increased the plant's ability to produce these PR proteins in higher quantities. With this increased rate in production, the higher residual levels of these proteins could be responsible for causing hypersensitive reactions in humans. As mentioned earlier, main fruit allergens are from four different protein families, pathogenesis-related protein (i.g. PR-10), thaumatin-like protein, non-specific lipid transfer protein, and profilins. They have different characters and cause various fruit allergies (Table 4).

3.2.1 Pathogenesis-related (PR-10) proteins

The PR-10 proteins are widely present in seed plants. Most genes of the PR-10 proteins have an 456-489 bp open reading frame which can encode a polypeptide with 151-162 amino acids (Liu and Ekramoddoullah, 2006). PR-10 proteins are identified as intracellular pathogenesis-related proteins with homology to ribonucleases, including allergens from tree pollen and food (Wen et al., 1997). Also, they are generally heat-labile proteins and hence are denatured when cooked or processed thermally for pasteurization and/or sterilization. They belong to the Bet v 1 homologues associated with local symptoms (e.g. OAS) and are usually found in strawberry (Fra a 1), peach (Pru p 1), apple (Mal d 1) and sweet cherry (Pru av 1) (Table 4).

3.2.2 Thaumatin-like proteins (TLPs)

The thaumatin-like proteins (TLPs) are polypeptides with 200 amino acid residues and are named based on the similar sequences to the sweet tasting protein in *Thaumatococcus daniellii* (Selitrennikoff, 2001). There are three types TLPs which are included those produced due to pathogen infection, and osmotins produced in response to osmotic stress, and antifungal proteins present in cereal seeds (Breiteneder, 2004). In some species, TLPs are expressed in flowers and fruits that are susceptible to pathogen infection and it is hypothesized that they play a primary function in the defense mechanism against infections (Clendennen and May, 1997; Salzman et al., 1998). Recently, TLPs are becoing as a rich source of allergens and are usually found in peach, apple, grape and kiwifruit (Ebner et al., 2001). For example, one of major apple allergens, Mal d 2 which is a kind of TLP with molecular mass of 23 kDa. It can cause IgE-mediated reactions in patients allergic to apples. Similarly, Pastorello et al. (2003) found that a 24 kDa TLP which is classified as a minor allergen in grapes (Pru av 2) have a highly similar amino acid sequence to the apple allergen (Mal d 2) (Table 4).

3.2.3 Non-specific lipid transfer proteins (ns-LTPs)

The non-specific lipid transfer proteins (ns-LTPs) are basic, 7-9 kDa proteins which are widely distributed throughout the plant kingdom, comprising over 100 potential sources from 50 different species of plants. They are also able to bind and transfer various lipids among membranes *in vitro* due to their three-dimensional structure and affinity towards lipids (Kader, 1996; Salcedo et al., 2007). Douliez et al., (2000) identified that there are two main types of plants nsLTPs; nsLTP1 of molecular mass of 9 kDa and nsLTP2 of 7 kDa. The disulfide bond linkages are located in between Cys_1-Cys_6 and Cys_5-Cys_8 of nsLTP1, wheal these disulfide bond linkages are at Cys_1-Cys_5 and Cys_6-Cys_8 present in nsLTP2. Another main structural difference is the size of the hydrophobic cavity which is usually larger in nsLTP1compared to nsLTP2 protein (Wang et al., 2012). Many researchers have stated that nsLTPs show an essential biological function which include mediating phospholipid transfer in plant defense system (Lindorff-Larsen and Winther, 2001). nsLTPs are also associated with maintenance of hydrophobic cell wall and their absence can disrupt the basic structure and functioning of the cell wall. They also facilitate the extension of cell wall when required depending on the surrounding environmental conditions (Nieuwland et al., 2005). However, nsLTPs are also involved in triggering food allergies especially in fruits and vegetables. These proteins are stable to heat and digestion, and hence can trigger allergenic reactions in cooked foods (Table 4). In addition to OAS, it maybe induces systemic reactions and more severe symptoms. They are usually found in strawberry, peach, apple and sweet cherry.

3.2.4 Profilin

The profilin is a 12-15 kDa protein which is generally found in all eukaryotic organisms (Sohn et al., 1995). It plays a major role in controlling the growth of actin microfilaments, which is a crucial step in cellular locomotion (Hussey et al., 2006). However, Ebner et al., (1995) reported that profilin is one of the major causes to induce the cross-reactive allergies between pollen and fruits (Table 4). It is considered as a clinically relevant fruit allergen as it induces profilin hypersensitivity. Various fruits that can trigger allergic reactions due to profilin include melon, watermelon, tomato, banana, pineapple and orange (Asero et al., 2008). For example, peach allergen (Pru p 4) is a 14 kDa allergenic profilin that induces IgE-mediated symptoms in allergic patients after consuming this fruit (Table 4).

3.3 IgE-binding epitopes of allergens in various fruits

Jerne (1960) was first in defining the term of epitope and in charactering the epitopes as “surface configurations, single determinants, structural themes, immunogenic elements, haptenic groups, antigenic patterns, specific areas” of an antigen. His definition of the epitope is focused on the contacting relationship between the antibody and the antigen (Aalberse and Crameri, 2011). The IgE recognition sites i.e. IgE-binding epitopes are classified into linear and conformational epitopes. Linear epitopes consist of continuous amino acid sequences, while the conformational ones are formed by spatially adjacent amino acids (that constitute the secondary and tertiary structures) but are distantly located in the amino acid primary sequence of the proteins (Hensen et al., 2014; Vanga et al., 2016). There are also many non-peptidic epitopes such as glycan epitopes and classical haptens. For example, IgE-binding glycan epitopes are the cross-reactive carbohydrate determinants (Aalberse and Van Ree, 1997) and galactose alpha-1, 3-galactose (Commins and Platts-Mills, 2010). Therefore, it is important to identify the epitope structure for the development of new strategies for accurate diagnosis and allergen-specific immunotherapy of fruit allergy as well as the production of hypoallergenic foods (Matsuo et al., 2015).

The definition of the epitope is focused on the actual contacts

between the atoms of the antigen and those of the antibody

As shown in Table 5, Fra a 1 is a 15 kDa fragment with accession no. of DQ385511 (Fra 1.0102) and it has already been identified as the major allergen present in strawberries. One of the epitope in Fra a 1, 47GDGGPGTIK55 has been mapped by Muñoz et al., (2010). Similarly, Mal d 3 (accession no: AY572500) is one of the main allergens present in apples with a 9 kDa molecular weight. The three main IgE-binding epitopes of Mal d 3, 16YVRSGGAVP24, 35INGLARTADRQ46 and 76NVPYKISTS84 have been mapped by Borges et al. (2008) using spot membranes. The physicochemical properties of allergens from other Rosaceae fruit are well characterized (Table 5). 10 kDa Pru p 3 is one of the main allergens of peach and belongs to nsLTP family. Its accession no. is P81402 (Pru p 3.0101). Garcia-Casado et al., (2003) reported three possible IgE binding peptides present in Pru p 3 which are 11APCIPYVRGGGAVPP25, 31IRNVNNLARTTPDRQ45 and 71GKCGVSTPYK80. Also, Borges et al., (2008) reported epitope sites from another two Rosaceae family members, plum, and apricot with 9 kDa molecular weights. Their possible IgE binding peptides are 16YVKGGGAVP24, 37LARTTADRRAACNCLHQL54 and 76NVPYKISASTNCATVK91 in plum and 16YVRGGGAVP24, 37LARTTPDRRTACNCL51 and 76NIPYKISASTNCATVK91 in apricot. The two fruits share similar epitope sites, which easily induce an an allergic reaction in patients with plum or apricot allergy. Therefore, patients with fruit allergies are vulnerable in showing allergic potential to different fruits at the same time.

3.4 Cross-reactive fruit allergy

The definition of cross-reactivity is when the antibodies exposure to a specific allergen are also shown to react against allergens from other sources even when the person is not allergic to that particular food (Valenta et al., 1999). Cross-reactions in the case of fruits, nuts, and vegetables are generally limited to OAS with pollen allergy (Breiteneder and Ebner, 2000). For example, some people are allergic to birch pollen may react to apples as well (Geroldinger-Simic et al., 2011; Mauro et al., 2011). This cross-reactivity is due to the homologues structure leading to similar epitopes in allergens from multiple sources. For example, antibodies released when exposed to birch pollen allergens can also be triggered when exposed to apples because of their homologous structure resulting in similar epitope configuration. The cross reactivity also can cause various reactions including swelling, redness, and itching restricted to the lips, tongue, and throat (Sancho et al., 2006b).

As mentioned earlier, various allergens similar to the ones from fruits are mainly found in pollens of grass (ex: mugwort), trees (ex: birch) and weeds (ex: ragweed). As shown in the Table 6, many studies have been reported where the major allergen, Bet v 1 from birch pollen has shown cross-reactivity to homologous protein allergens existing in a wide range of fruits, such as apple (Mal d 1), cherry (Pru av 1), pear (Pyr c 1), and kiwi (Act d 8) (Geroldinger-Simic et al., 2011; Mauro et al., 2011; Oberhuber et al., 2008). Pollen present in grass (e.g. ragweed) can also induce cross-reactivity to various fruit allergies sourcing from mango, tomato, melon and orange due to their similar protein (epitope) structure (Paschke et al., 2001; Patel and Volcheck, 2015; Takamatsu et al., 2016; Werfel et al., 2015). Similarly, allergens from peach, mango, kiwifruit and melon share their epitope structure with pollens from mugwort (Lauer et al., 2007; Paschke et al., 2001; Patel and Volcheck, 2015).

Some proteins present in natural rubber latex or related products made from latex rubber trees can trigger latex allergy with allergic symptoms i.e. skin irritation, or even a potentially life-threatening situation. Allergy to latex proteins has been known since 1980s and is currently a well-recognized health trouble among using products made of natural latex such as protective gloves or other goods (Palosuo et al., 2002). As shown in Table 6, many studies have reported the clinical and immunochemical cross-reactivity between latex and banana, tomato, pineapple and chestnut, avocado and other fruits (Poley and Slater, 2000; Werfel et al., 2015). People sensitive to pollen and latex can suffer from cross reactivity to various fruit allergens due to the similarity in the protein structures (Hofmann and Burks, 2008).

3.5 Fruit allergy in different countries

Fruits belonging to Rosaceae family are responsible for most of the fruit-related allergenic reactions around the world (Kanny et al., 2001). The first clinical report was from northern and central Europe, where apple allergy which is the primary fruit allergy, is associated with birch pollens due to the cross-reactivity (Fernández-Rivas et al., 2006). However, in Spain, the country which is free of birch trees, peach from the Rosaceae family was the primary fruit inducing allergic reactions, followed by apple. Up to 70% of peach-allergic patients also showed an allergic potential to pollen which is mainly from grasses, mugwort, olive and cypress (Cuesta-Herranz et al., 2010). The fruit allergens, Pru p 1, Pru p 2, Pru p 3 and Pru p 4 have been identified as the major allergens present in peaches (www.allergen.org).

It has been reported that about 2% of the North American population is allergic to apples (Kerkhof et al., 1996). Consumption of fresh apples can trigger allergic reactions because of the allergen, Mal d 1 present in apples (Schmitz-Eiberger and Matthes, 2011). In addition, the apple allergen Mal d 1 shares similar allergenic epitopes with the Bet v 1 which is a major birch pollen allergen, resulting in IgE cross-reactivity (Mauro et al., 2011). In Asian countries (such as Korea and Japan) kiwifruit is the main fruit that can easily induce allergic reactions, followed by peach and apple (Lee, 2013). In recent years, it has been widely reported that fruit allergy has a strong

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association with pollen and latex. Many studies found that kiwi allergy has a cross-reactivity with birch pollen, latex, avocado and banana (Möller et al., 1998; Oberhuber et al., 2008). To be exact, the patients suffering from aforementioned allergies are prone to experience allergic reaction upon consumption of Kiwi. This is because the protein contained in Kiwi is similar to those contained in the birch pollen as well as latex i.e. they share similar epitopes and hence can trigger cross-reactivity in spite of the patient not being allergic to all the proteins. Five major allergens including Act d 1, Act d 2, Act d 4, Act d 5 and Act d 11 responsible for kiwi allergy have been extracted and characterized (www.allergen.org).

3.6 Global statistics of publications on fruit allergies

As of February 2017, the data from Web of Science showed that a total of 1265 manuscripts are published all over the world that deal with fruit allergies. As shown in Fig. 1(A), most of publications come from Europe (70%) followed by Asia (14%), North America (10%) and others (6%). Most of these publications are research articles accounting to 76.9%, followed by reviews (10.2%) (Fig.1 (B)). Conference proceedings account for 4.5% of the total manuscripts, followed by meeting abstract (3.7%) and others (4.7%) (Fig.1 (B)). In terms of countries contributing to fruit allergy research, 247 papers were published by researchers from Spain, followed by Germany with 194 and Italy with 161 (Fig. 1(C)). Other European countries like France (110) and Austria (100) have a similar number of publications. From North America, there were a total of 129 publications from USA and 10 from Canada. South Korea (31) published the most articles between 1991-2017 in Asia followed by China (27) and India (25).

4 Influence of various factors on fruit allergenicity

4.1 Environmental cultivation conditions

During the plant growth, environmental cultivation conditions (e.g. nitrogen, water and climatic changes) have a significant influence not only on the plant growth and well-being, but also on the overall quality of the fruits which include various nutritional aspects such as sugar content, organic acids and health-related carotenoids (Domis et al., 2002; Dorais et al., 2008). Nitrogen is a necessary element for all plants in appropriate quantities for their growth and maintenance. Plants need nitrogen in combination with the carbon absorbed from the air to synthesize proteins for production of enzymes and structural components such as 'rubisco' which is a photosynthetic protein and lignin in cell walls. Further, nitrogen intake can significantly influence the fruit quality and yield. George and Nissen (1992) found that when peach trees were treated by 30 g nitrogen in the form of nitram before the flowering stage, increased peach yields by 48% and improved brix by about 14% when compared with untreated trees. On apples, researchers reported that nitrogen applied during summer period can increase the quantity of fertile apple blossoms for the next year (Williams, 1965), which indicates fruit trees might generally starve due to lack of nitrogen before the development of flowering stage. Nitrogen application during this growth period is beneficial and can increase the yield and overall quality of fruits.

Further studies reported that mature fruits of tomato plants after water stress have an excellent taste and flavor. For example, Veit−Köhle et al. (1999) found lower water treatment (50% water supply) could increase the sugars, titratable acids, aroma volatiles and vitamin C contents in tomatoes, compared to that of a higher water treatment (70% water supply). In peach, George and Nissen (1992) stated that water stress improved fruit size by 37% when compared with untreated trees. Climatic changes during the growth season is also one of the major factors that could influence the fruit quality. Studies have been reported temperatures, carbon dioxide and ozone levels could directly or indirectly affect the yield and quality of fresh fruits. For example, Moretti et al. (2010) found that temperature increase could directly affect photosynthesis, which results in alterations in sugars, organic acids, flavonoids contents, firmness and antioxidant activity.

Furthermore, studies have shown that environmental cultivation conditions have an impact on the fruit allergen content. Klockenbring et al. (2001) reported that patients showed a higher sensitivity to allergens that are organically cultivated ‘Boskoop’ fruits compared to those apples produced using IP techniques (using chemical fertilizers and pesticides) through skin prick test. As mentioned earlier, Mal d 1 is one of major apple allergens and belongs to the PR-10 protein family. The environmental stress factors such as fungi, viruses, and bacterial attack can induce

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PR-10 proteins which leads to the synthesis of various components including Mal d 1. Fruit trees under organic cultivation method are more susceptible to the stress factors that synthesize higher Mal d 1 compared to fruits that are under the IP method with pesticide treatments. Similarly, Matthes and Schmitz-Eiberger (2009) found that 'Jonagold' apple fruit organically cultivated at Bonn University, Germany showed significantly higher level of Mal d 1 when compared to those apples produced through IP technique using the test of Sandwich-ELISA which is similar to the results obtained few years earlier as reported by Klockenbring et al. (2001). However, the apples cultivated under IP method at Hohenheim University, Germany under the German IP guideline QS-Gap 9, showed higher apple allergen (Mal d 1) level in comparison to that of the fruits cultivated using OC in 'Jonagold' cultivar. The same cultivar (i.e. 'Jonagold') showed a different Mal d 1 trend at two locations, which might be due to various OC standards. The OC was performed differently according to EU directive 2092/91 at Bonn University and 'Bioland' guidelines at Hohenheim University, respectively. Further, the growing conditions of apple trees were different in these two places. The orchard in Bonn University provided a growing period of 170 days, 596 h sunshine and a rainfall of 1534 nm. In contrast, the apple trees at Hohenheim University had a 185-day growing period, 1678 h of sunshine and 861 nm rainfall. This can also be due to the influence of external triggers which could have led to the excess production of Mal d 1 in the apples cultivated in Hohenheim University, Germany. Pesticide treatment can be also responsible for inducing stronger responses than any biotic factors (such as fungi, viruses, and bacteria) for the accumulation of PR-10 (e.g. Mal d 1) in apples. The mechanism leading to synthesis of Mal d 1 and the metabolic pathways are not clear, and more research about the influence of environmental conditions on fruit allergen should be conducted in detail.

Tulipani et al. (2011) reported that in the year of 2007, strawberry allergen, Fra a 1 content present in all the cultivars was lower than that of the strawberries cultivated in 2008. In the experiment, the daily minimum and maximum temperatures were all higher in 2007 compared to 2008, especially during the development of fruits i.e. in the months of April and May. Further, the weather in the month of April 2007 was drier when compared to April 2008. It indicated a possible inverse correlation between stressful environmental factors (such as higher temperature and drier weather) and the strawberry allergen Fra a 1 content. It is a conflicting result when compared to the research on the apple cultivation, where water shortage (completely deprived of the irrigation from June) strongly up-regulated the transcription and expression of genes in Mal d 1.04 and 4.01 present in apples (Botton et al., 2008). Fra a 1 and Mal d 1 all belongs to PR-10 proteins, while the mechanism of synthesis is influenced differently by various stressful environmental conditions, such as water shortage or higher temperature. Also, maybe the mechanism involved in the synthesis and degradation of the above mentioned fruit allergens are different in apples and strawberries and hence the discrepancy.

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Further research is warranted to understand the mechanism involved in synthesis of various allergens in spite of them belonging to the same PR-10 protein family

4.2 Variety

Variety is one of the most important factors influencing the fruit allergenic potential. López-Matas et al. (2011) determined the allergenic profile of six commonly known varieties of tomatoes (Rama, Rambo, Canario, Kumato, Pera and Raf) and found that their protein profile and allergen quantification showed differences in the allergen composition. The highest allergen content (Lyc e 3) present in the tomato peel was shown in the 'Rambo', followed by 'Pera', 'Canario', 'Raf' and 'Kumato'. The 'Rama' showed the lowest value of allergen content. The 'Kumato' variety belongs to black tomatoes and is not generally consumed. It has an intense taste, higher sweetness and juiciness than others, which might have resulted in its high allergenic potential compared to 'Rama'. Other components (e.g. type of carbohydrates), present in the pulp of 'Kumato' tomatoes are also considered as possible reasons (López-Matas et al., 2011). Similarly, in another study, two different tomato varieties were used. The 'Reisetomate' induced significantly less positive skin reactions through skin prick test technique and caused fewer symptoms, compared to the cultivar 'Matina' (Dölle et al., 2011). 'Matina' is a variety selected for organic farming which can effectively resist environmental stress and diseases (Dölle et al., 2011). As mentioned early, plants growing in stressful environmental conditions could induce production of higher levels of certain PR proteins. The main tomato allergen (Lyc e 3) belongs to this protein group and hence the higher quantities of PR proteins leading to synthesis of higher allergen content.

In addition, four strawberry varieties were considered by Tulipani et al. (2011) for allergy analysis and they found that the highest strawberry allergen (Fra a 1) concentration was shown in the variety of ‘AN94.414.52’, followed by the ‘Adria’ and ‘AN00.239.55’, whereas the ‘Sveva’ variety showed the lowest Fra a 1 content. Further, this study showed that the lower level of Fra a 1 in the ‘Sveva’, ‘Adria’ and ‘AN00.239.55’ varieties had a strong negative correlation with higher content of total antioxidant capacity and total anthocyanin contents (Tulipani et al., 2011). These results showed a relationship between the antioxidant compounds and the expression of allergen (Fra a 1) in strawberries. The high level of antioxidants present in fruits possibly benefits in reducing the biosynthesis of fruit allergens. Similarly, Schmitz-Eiberger and Matthes (2011) reported that apple allergen content had a relationship with the antioxidant activities and related enzymes activities. The lower level of apple allergen (Mal d 1) might be due to the higher PPO activity and polyphenols contents, which in turn can inhibit the interaction between oxidised phenols and Mal d 1, resulting in lower allergenicity. Moreover, many researchers stated that allergenic differences between various apple varieties are mainly due to the variation in expression of Mal d 1 (Matthes and Schmitz-Eiberger, 2009; Son and Lee, 2001). In fruits cultivated at the farm in Germany, lowest amounts of Mal d 1 were found in ‘Jonagold’, ‘Kanzi’, ‘Greenstar’, ‘Pinova’, ‘Topaz’, and ‘Golden Delicious’ fruits. The highest amounts of Mal d 1 levels were found in cultivars ‘Rubens’ and ‘Gala’ (Matthes and Schmitz-Eiberger, 2009). In another research, among twenty-one cultivars selected for the assessment of allergenicity, ‘Golden Delicious’ apples showed the highest level of allergenicity, followed by Gala apples. The lowest level of allergenicity was observed in the ‘Santana’ apples (Bolhaar et al., 2005). Similar results were observed in mango, depending on different varieties, the main allergen, 5-alk(en)ylresorcinols content ranged from 79 to 1850 mg/kg of dry matter in samples of mango peels (Knödler et al., 2009).

As discussed above, the fruit allergen level is different in various fruit varieties due to many reasons. The relation between fruit allergen concentration and the variety is not clear and more research should be warranted. As far as practical implications are concerned, all available information should be used in breeding projects addressed in the selection of hypoallergenic fruit varieties.

4.3 Harvest maturity

Maturity at harvest is one of the essential factors that influence the shelf-life and fruit quality (Kader, 1997). During the maturity stage, the overall fruit quality including various sensory attributes (such as color, glossiness, size, shape, flavor, texture and taste) and nutrient content (acids, sugars, vitamins, polysaccharides, polyphenols and valuable minerals) change distinctly (Golding et al., 2005). For example, the ‘golden’ papaya were harvested at four different maturity stages, and the results showed a significant difference in fruit quality (Bron and

Jacomino, 2006). During the ripening period, the ascorbic acid content increased 20-30%, and fruit harvested at late maturity stages reported excellent scores for sensory evaluation including flavor and appearance, compared to that fruit harvested at early stage.

Ethylene is one of the primary plant hormones that regulates fruit ripening. Further, studies found that the level of allergens present in apples might be influenced by the maturity levels through the regulation of ethylene levels. Sancho et al. (2006b) found that apple allergen, Mal d 3 increased when fruits reached their physiological maturity, which coincided with the increase in ethylene. Similarly, in three apple cultivars, ‘Braeburn’, ‘Topaz’ and ‘Golden Delicious’, Schmitz-Eiberger and Matthes (2011) found that apples had a higher Mal d 1 content when they were ripe than that of unripe apple fruits. In the apples that were picked at a later stage, the allergen, Mal d 1 was 3-4 times higher, compared to those picked at an earlier stage (Sancho et al., 2006b). Other relevant physiological factors (e.g. anthocyanin content, related to the color change) and environmental conditions (e.g. illumination intensity) could also influence the allergen content present in fruits. Therefore, consuming ripe and dark color fruit can easily induce allergic reactions, compared to unripe fruit.

4.4 The difference in allergenicity between the peel and pulp of fruit

Most of the fruits have the peel, pulp, and seeds. For some fruit, such as orange and banana, the pulp is the primary part used for consumption, and in other fruits, the entire fruit is consumed (such as tomatoes and strawberries). Many researchers stated that allergic components were

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determined at present not only in the peel but also in the pulp of fruit (Bässler et al., 2009; Carnés et al., 2002; Pravettoni et al., 2009). Fruit allergen contents vary within the different sections of fruit. The peel contains the majority of allergens in mango. In the cultivar 'Tommy Atkins', Knödler et al. (2009) found that main mango allergen, alk(en)ylresorcinol content in the peel was 419.30 mg/kg which is 16 times higher than that in the pulp (26.33 mg/kg). In Rosaceae family fruits, Borges et al. (2006) reported that the lipid transfer protein (allergen) was mainly concentrated in the peel, with lower detectable amounts present in the pulp. In apples and peaches, the allergic reaction to peel was found to be higher than that of the pulp (Fernández-Rivas et al., 2006; Marzban et al., 2005). Similarly, among 113 patients with sensitivity to tomato, Larramentdi et al. (2008) found that 110 patients showed positive reaction to the tomato peel extract whereas 47 patients were allergic to the pulp extract. López-Matas et al. (2011) found that the tomato allergen (Lyc e 3 and PG2A) content in peel extract was higher than that of in the pulp extract when six commonly ingested varieties of tomato fruits were tested. Furthermore, the protein content in the peel extract was approximately double than that of the pulp extract. The difference in the allergen content between peel and pulp extracts is due to the lower protein concentration in the matrix/pulp composition leading to lower reactivity in fruits upon removal of the peel (Carnés et al., 2006). It is also possible that the pulp which is the outer layer of the fruit is exposed to various environmental stresses resulting in higher allergen levels compared to the pulp.

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Therefore, peeling might be a solution to reduce the overall allergenicity in few fruits whose peel contains the majority of allergens. For example, the peeled-off apples significantly reduced their fruit allergenicity, compared to those apples with peel (Fernandez-Rivas and Cuevas, 1999). Similarly, in the peaches and tomatoes, peeled-off fruit had a lower allergen content than that of fruit with peel (Ahrazem et al., 2007; Pravettoni et al., 2009). Therefore, peeling the fruits can be a potential treatment in the processing industries to drastically reduce their allergenicity (Brenna et al., 2004).

4.5 Storage conditions

Storage conditions are major factors for maintaining fresh and good quality of post-harvest attributes of fruits. The application of several storage technologies including cold storage, modified atmosphere packaging and ozonation are beneficial to inhibit decay, extend shelf life, and maintain the nutritional quality of fresh fruits (Connor et al., 2002; Nielsen and Leufvén, 2008; Rodoni et al., 2009; Wang et al., 2016).

During the storage of fruits, many studies found that a considerable change in the level of allergens depending on environmental stress and/or storage conditions (Sánchez-Monge et al., 1999). Bolhaar et al. (2005) reported that five apple cultivars under controlled atmosphere storage at 3℃ (i.e. 2.5% O_2 and 1% CO_2) showed a significant reduction amounting to 15% in allergic reactivity （P<0.001）compared to that of fruits under cold storage at 2℃. Similarly, Sancho et al. (2006b) indicated that under room temperature, cold storage (2℃) and controlled atmosphere conditions (0.5% O_2, 1.5% CO_2 at 3.8℃), the levels of Mal d 3 decreased in three apple varieties (i.e. Cox, Jonagored and Gala). The rate of overall reduction was greatest when fruits were stored at controlled atmosphere conditions (Bolhaar et al., 2005). In contrast, Hsieh et al. (1995) reported that another major apple allergen, Mal d 1 present in the three apple varieties (i.e. McIntosh, Red Delicious and Granny Smith) increased during cold storage at 4℃. Similar results were reported by Sancho et al. (2006a) that apple allergen, Mal d 1 gene expression showed a significant increase under modified atmosphere packaging during storage. It suggests a difference in the regulation of gene expression between the two major apple allergens (Mal d 1 and Mal d 3). Mal d 1 is a pathogenesis related protein belonging to PR-10 family which can be concluded by stress factors (ex, cold temperature). Apples stored under modified atmosphere packaging at cold temperature could induce more Mal d 1 synthesis because of cold stress or CO_2 and O_2 concentration changes present in packages. Whereas, the Mal d 3 belongs to the PR-14 family which responds to various external stimulus when compared to the PR-10 family (Sancho et al., 2006b; Van Loon and Van Strien, 1999). The reduction in Mal d 3 under controlled atmosphere conditions or cold storage was due to better fruit quality (firmness, moisture content and antioxidant compounds content). The synthesis and degradation mechanism of Mal d 1 and Mal d 3 are not clear, and hence requires further research.

4.6 Difference in structural stability of fruit allergens

Most of the fruits are not only consumed fresh, but are also applicated as the ingredient in various related products such as drink, dry powder, jam, yogurt, and cereals. Many reports stated that the allergenicity of fruits has a strong relationship to the form in which the fruits are consumed. It is well known that cooking substantially can help reduce the allergenicity of fresh fruit because heating destroys the pollen related fruit allergens through changing their protein structures (secondary or tertiary structure) or conformational epitopes (Fermín et al., 2011; Moore and Stewart, 2017; Vanga et al., 2016). Therefore, consuming cooked fruits can be beneficial to help patients with birch pollen allergy to avoid cross-reactivity allergy (Lahti and Hannuksela, 1978). Fruits share a similar allergen structure with birth pollen allergen which belongs to the PR-10 family of pathogenesis related proteins and are easily destroyed by cooking process due to its relatively unstable secondary structure (Fig. 2). Relevant examples are Pru av 1 allergen from cherries (Scheurer et al., 1997), Mal d 1 allergen in apples (Fig. 3A) (Son et al., 1999), Pru a 1 allergen present in peaches, Fra a 1 allergen in strawberries (Fig. 4A) and Act d 11 allergen in kiwifruit (Fig. 5C). Similarly, studies also reported that a commercial processing method, steam cooking at 100℃or heating at 80-90℃for several minutes can effectively eliminate the allergenic potential of patients to kiwifruit (Fiocchi et al., 2004; Gall et al., 1994).

However, few allergens have a stable structure in some fruits. For example, the peach allergen (Pru p 3) is heat stable and therefore can also be found in juice and other thermally processed products. In an experiment, fresh peaches were heat-treated at 121℃ for 30min. This treatment was not beneficial to decrease the allergenicity of the main allergen, Pru p 3 due to its stable secondary structure (Fig. 6) (Brenna et al., 2000). Similarly, Cit s 1 and Cit s 2 were still found in orange juice after thermal processing (Crespo et al., 2006). Many studies reported that the allergens Mal d 2 (Fig. 3B) and Mal d 3 in apples, the strawberry allergen, Fra a 3 (Fig. 4C) from the non-specific lipid transfer protein family, the kiwifruit allergen, Act d 2 (Fig. 5B) and cherry allergen, Pru av 2 (Fig. 7) all have the heat stable secondary structures (Asero et al., 2003).

5 Future trends of fruit allergies

As mentioned earlier, many factors including environmental conditions, variety, maturity, parts of a fruit i.e. peel, pulp and seeds, storage conditions, different forms of processing can affect the allergenicity in various fruits. As suggested in Fig. 8, a gradual increase in publications was observed between the years 2001 and 2016 (the related data is from Web of Scinece). It is understandable that various researchers may have different views pertaining to fruit allergy resulting in varied sub fields of research that are being developed around the world. The future trends and challenges in the field of fruit allergies are outlined below:

5.1 Breeding

As discussed earlier, environmental conditions such as nitrogen, water and climatic changes have a significant influence on the fruit quality and fruit allergen content during the growth of fruit trees. Researchers found that organic fruits have a lower level of allergenicity in apples and tomatoes compared to the fruits cultivated by using chemical fertilizers (Matthes and Schmitz-Eiberger, 2009). Hence, proper application of specific cultivation techniques and conditions (organic cultivation) can be beneficial in reducing the allergic potential of few fruits during their growth. Many studies have reported that the allergenicity level was different in various fruit varieties. Fox example, apple varieties ‘Jonagold’, ‘Kanzi’, ‘Greenstar’, ‘Pinova’, ‘Topaz’, and ‘Golden Delicious’ had lower quantities of Mal d 1 than in varieties ‘Rubens’ and ‘Gala’ (Matthes and Schmitz-Eiberger, 2009). Therefore, breeding techniques can be used in development of new varieties of apple presenting with a lower level of allergens (Buchanan, 2001; Shewry et al., 2001). Many bio-technological techniques have been applied to the field of plant breeding, such as molecular plant breeding, which is a widely accepted technique. Transgenic technique is a common application in molecular plant breeding where transgenic events can be designed to facilitate the molecular stacking of transgenes that control a trait or suite of traits into a single locus haplotype (Moose and Mumm, 2008). For example, recently released ‘Yield-Guard VT’ triple transgenic maize hybrids where herbicide tolerant and multiple insect resistance traits were integrated as one genomic locus (position of chromosome) that simultaneously increases the synthesis and decreases the catabolism of Lysine in maize seeds (Frizzi et al., 2008). Therefore, molecular plant breeding can provide a possible solution to reduce the level of allergen present in fruits by transgenic technique to regulate the expression of target genes (allergen synthesis related genes). Specific cultivation standards and varieties developed through breeding can lead to development of innovative fruit cultivation techniques for hypoallergenic fruits and fruit-based products.

5.2 Food processing industry

Fruit allergens are not only present in the peel but also in the pulp of fruit. Many studies found that the lipid transfer protein (allergen) was mainly contained in the peel, with lower but detectable concentrations in the pulp of fruits from Rosaceae family (Borges et al., 2006). For example, in apples and peaches, researchers reported that the reactivity of patient to the peel was higher than to the pulp when tested using skin-prick test (Fernández-Rivas et al., 2006). In addition, some fruit allergens belong to the PR-10 family of pathogenesis related proteins which are easily destroyed by thermal processing, such as Pru av 1 present in cherries (Scheurer et al., 1997) and Mal d 1 present in apples (Son et al., 1999). Therefore, peeling or heating is an effective method to reduce the overall allergenicity in few fruits whose peel contains the majority of allergens for the food processing industry. More novel processing methods like high pressure processing (Huang et al., 2014), high voltage electric fields (Vanga et al., 2015), EHD processing (Singh et al., 2015), microwave (Vanga et al., 2016), pulsed ultraviolet light (Yang et al., 2012) and ultrasonication (Li et al., 2013) should be explored to help reduce the allergen level present in fruit or vegetables.

6 Conclusion

At present, a considerable amount of the population around the world is allergic to various fruits and their only option is complete avoidance of such fruits. This can dramatically reduce their intake of natural vitamins, antioxidant compounds and others bio-factors which can effectively resist diseases. Further research with regard the cause, symptoms and diagnostic methods for fruit allergies are needed to understand its manifestation in fruit and vegetable allergies. Many researchers found that a wide range of factors including pre-harvest and post-harvest methods can influence the allergen potential to fruits. For example, water stress can reduce the allergenicity level in pre-harvested fruits whereas, during the post-harvest storage, MAP can help reduce allergen (Mal d 3) content in apples. Therefore, research should be carried out to explore the relationship between allergen content in fruits to their pre-harvest and post-harvest conditions.

Conflict of interest

The authors report no conflict of interest.

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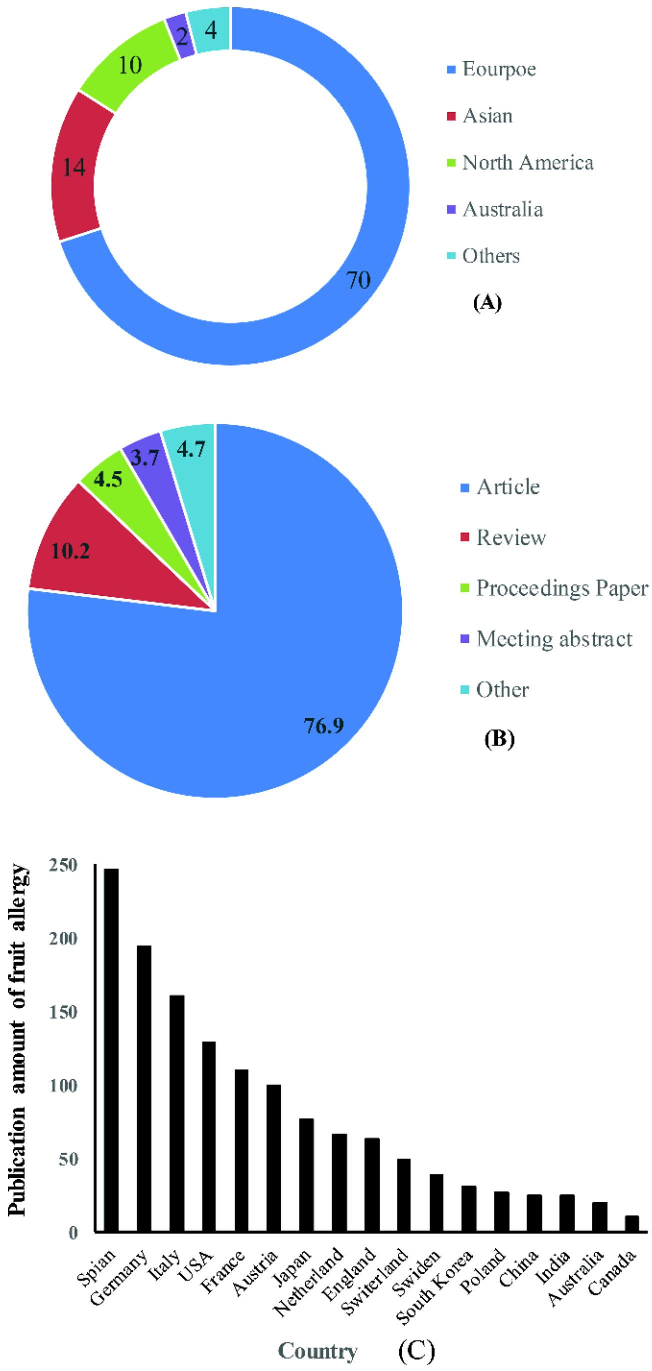

Figure 1. Percentage of published articles about fruit allergy in different country (A), percentage of different article types (B) and number of publications in different counties (C) since February, 2017 (the data is collected from the Web of Science).

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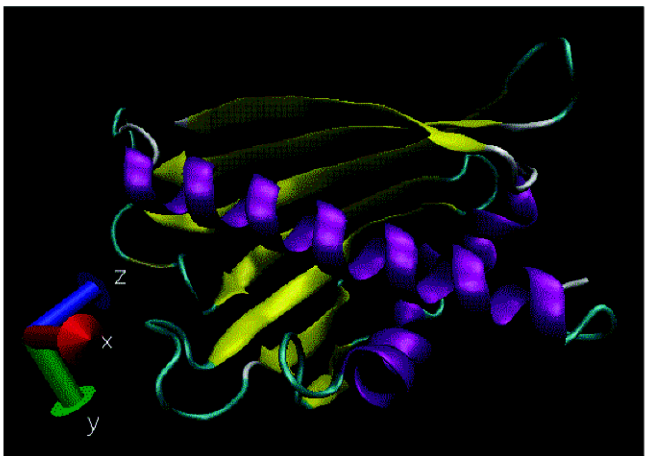

Figure 2. Secondary structure of birch pollen allergen Bet v 1 (Source: protein data bank; PDB code: 4MNS) [?-helix: Purple, 3/10 helix: Blue, ?-helix: Red, ?-sheets: Yellow, Turns: Cyan, coils: White]

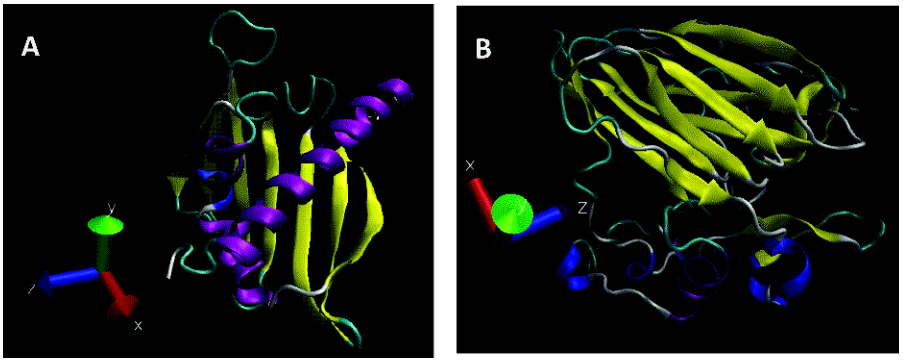

Figure 3. Secondary structures of Mal d 1 (A) and Mel d 2 (B) allergens in apples (Source: protein data bank; PDB code: 5MMU and 3ZS3, respectively). [?-helix: Purple, 3/10 helix: Blue, ?-helix: Red, ?-sheets: Yellow, Turns: Cyan, coils: White]

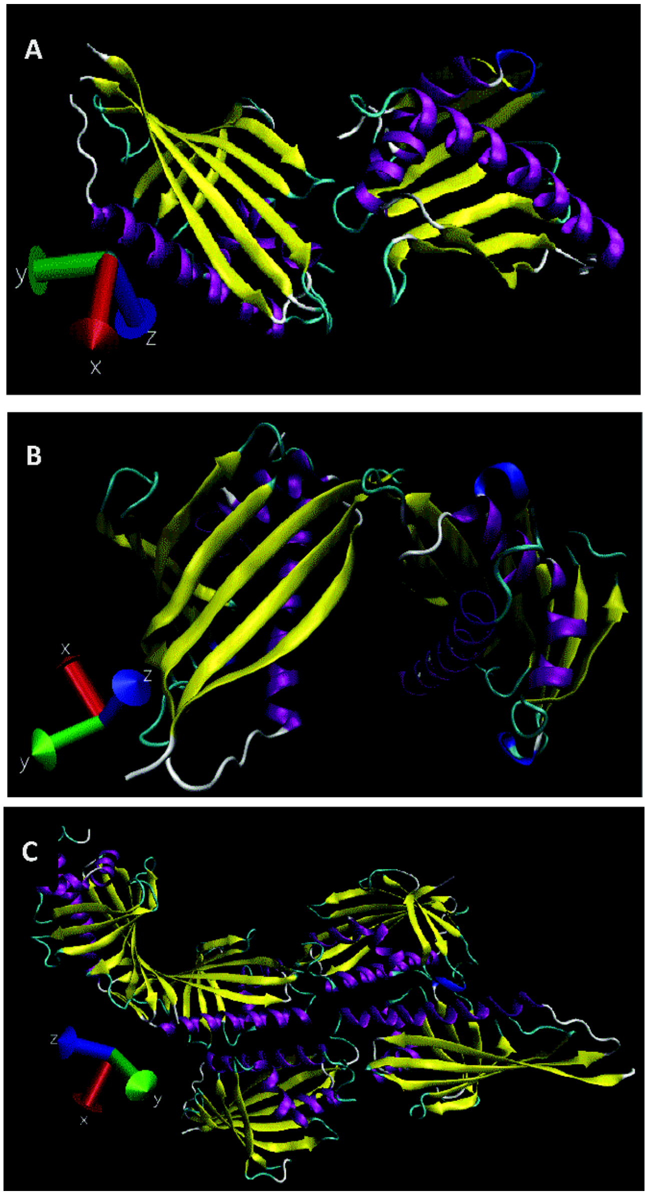

Figure 4. Secondary structures of Fra a 1 (A), Fra a 2 (B), Fra a 3(C) allergen (Source: protein data bank; PDB code: 4C9C, 5AMW and 4C94, respectively). [?-helix: Purple, 3/10 helix: Blue, ?-helix: Red, ?-sheets: Yellow, Turns: Cyan, coils: White]

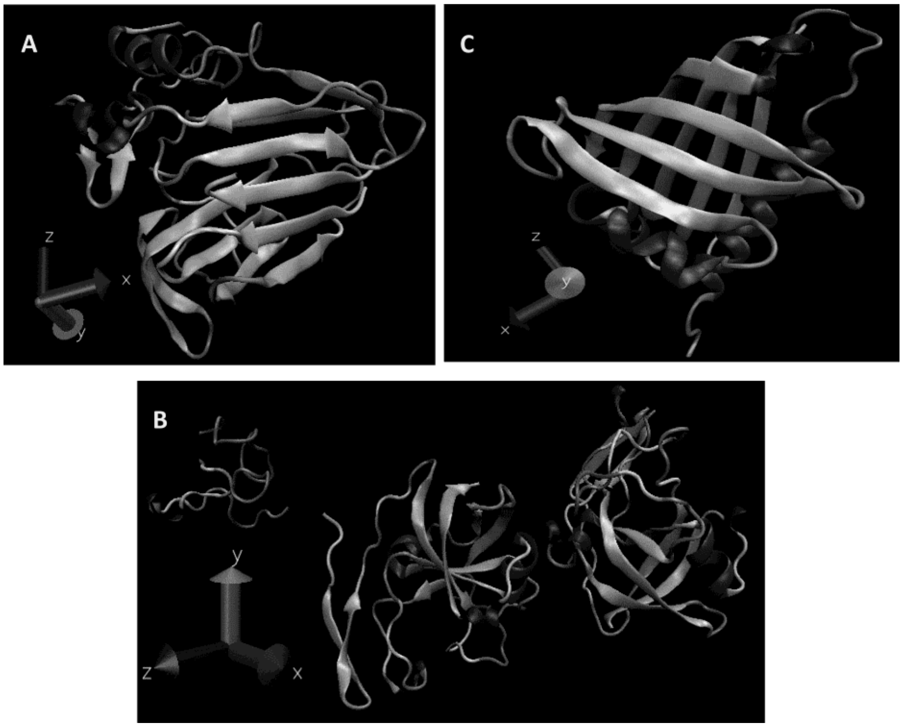

Figure 5. Secondary structures of Act d 2 (A), Act d 5 (B) and Act d 11 (C) allergen in kiwifruits (Source: protein data bank; PDB code: 4BCT, 4V9U and 4IGV, respectively). [?-helix: Purple, 3/10 helix: Blue, ?-helix: Red, ?-sheets: Yellow, Turns: Cyan, coils: White]

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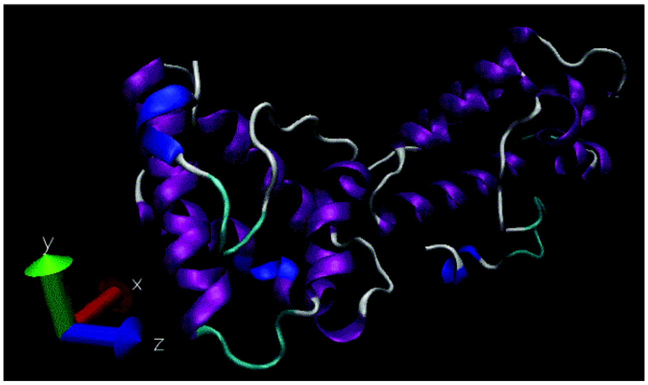

Figure 6. Secondary structure of Pru p 3 allergen in peaches (Source: protein data bank; PDB code: 2ALG) [?-helix: Purple, 3/10 helix: Blue, ?-helix: Red, ?-sheets: Yellow, Turns: Cyan, coils: White]

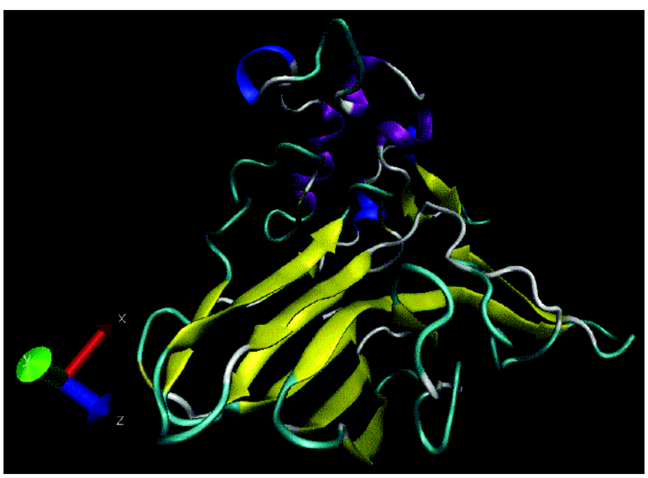

Figure 7. Secondary structure of Pru av 2 allergen in cherries (Source: protein data bank; PDB code: 2AHN) [?-helix: Purple, 3/10 helix: Blue, ?-helix: Red, ?-sheets: Yellow, Turns: Cyan, coils: White]

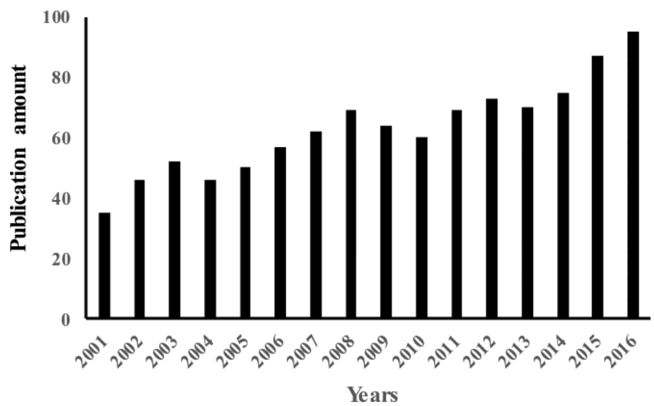

Figure 8. Number of published journal articles on fruit allergy from 2001 to 2016 (The data is collected from Web of Science).

Table 1. Allergic symptoms on consumption of different fruits

Allergen sources	Symptoms	References
Mango	a two-day history of patchy pruritic erythema of the face, neck, and arms with periorbital edema, systemic shock occurs according to the level of severity.	Calvert et al., 1996 Weinstein et al., 2004
Kiwifruit (Act d 1, Act d 2)	causes allergic asthma, urticaria, allergic purpura, allergic dermatitis, itching and difficulty in breathing.	Lucas et al., 2004 Lucas et al., 2007
Apple (Mal d 1, Mal d 3)	causes OAS, which is generally restricted to the lips, tongue, and throat.	Sancho et al., 2006a Sancho et al., 2006b

Strawberry (Fra a 1)	allergic symptoms presenting with tightness of the throat, swelling, burning or prickling sensation in the lips or tongue and other parts of the oral cavity.	(Franz-Oberdorf et al., 2016 Tulipani et al., 2011

Table 2. Common allergenic fruits and their main allergens (www.allergen.org; Vanga et al., 2016)

Species	Major allergen	MW(SDS-PAGE)	Year	Biochemical name
Malus domestica (Apple)	Mal d 1	17 kDa	2003	Pathogenesis-related protein (PR-10)
	Mal d 2	23 kDa	2003	Thaumatin-like protein
	Mal d 3	9 kDa	2003	Non-specific lipid transfer protein
Prunus persica (Peach)	Pru p 1	18 kDa	2007	Pathogenesis-related protein (PR-10)
	Pru p 2	25 kDa	2010	Thaumatin-like protein
	Pru p 3	10 kDa	2003	Non-specific lipid transfer protein
	Pru p 4	14 kDa	2003	Profilin
Fragaria ananassa	Fra a 1	18 kDa	2006	Pathogenesis-related protein (PR-10)

(Strawberry)	Fra a 3	9 kDa	2006	Non-specific lipid transfer protein
	Fra a 4	13 kDa	2006	Profilin
Prunus avium (Sweet Cherry)	Pru av 1	9 kDa	2003	Pathogenesis-related protein (PR-10)
	Pru av 2	30 kDa	2003	Thaumatin-like protein
	Pru av 3	10 kDa	2003	Non-specific lipid transfer protein
	Pru av 4	15 kDa	2003	Profilin
Actinidia deliciosa (Kiwi-fruit)	Act d 1	30 kDa	2007	Cysteine protease (actinidin)
	Act d 2	24 kDa	2007	Thaumatin-like protein
	Act d 4	11 kDa	2007	Phytocystatin
	Act d 5	26 kDa	2007	Kiwellin
	Act d 11	17 kDa	2009	Bet v 1 family member

Table 3. Allergens of pathogenesis-related proteins (Breiteneder, 2004; Hoffmann-Sommergruber, 2002; www.allergen.org)

Pathogenesis-related protein	Protein families	Examples
PR-2	β-1，3-glucanases	Grape (Vit v Glucanase)
PR-3	class I chitinases	Avocados (Pers a 1)

PR-5	TLPs	Apple (Mal d 2), Cherry (Pru av2)
PR-10	Bet v 1 homologous proteins	Apple (Mal d 1), Strawberry (Fra a 1)
PR-14	ns-LTPs	Peach (Pru p 3), Pear (Pyr c 3)

Table 4. Main allergen protein family in fruits (www. allergen.org)

Protein family	**Characteristics**	**Examples**
Pathogenesis-related protein (PR-10)	Heat-labile proteins and cooked foods are therefore often tolerated. They are Bet v 1 homologues and often associated with local symptoms such as OAS.	Strawberry (Fra a 1) Peach (Pru p 1) Apple (Mal d 1) Sweest cherry (Pru av1)
Thaumatin-like proteins (TLPS)	Polypeptides of about 200 amino acid residues, defence-related PR proteins. It's unstable to heat and are easily destroyed by cooking.	Kiwifruit (Act d 2) Apple (Mal d 2) Peach (Pru p 2)
Non-specific lipid transfer proteins	Stable to heat and digestion, causing reactions also to cooked fruit. Often	Strawberry (Fra a 3) Peach (Pru p 3)

(ns-LTPs)	associated with systemic and more severereactions in addition to OAS.	Apple (Mal d 3) Sweest cherry (Pru av3)
Profilin	Actin-binding proteins showing great homology and cross-reactivity even between distantrelated species. Recognized as a minor allergen in plants and plant-related foods. Profilinsare seldom associated withclinical symptoms.	Kiwifruit (Act d 9) Mango (Man i 3) Apple (Mal d 4) Strawberry (Fra a 4) Sweest cherry (Pru av4)

Table 5. Property of allergens in different fruit

Fruit	Allergen	MW(kDa)	Accession no.	Ig-E banding Epitopes	References
Strawberry	Fra a 1	18	DQ385511 (Fra 1.0102)	47GDGGPGTIK55#	Muñoz et al., 2010
Cherry	Pru a 2	30	U32440 (Pru av 2.0101)	157ANVNAVCPSELQ168	Schein et al., 2007
Tomato	Lyc e 2	50	AF65612 (Lyc e 2.0101)	148ANINGECPRALK159	Schein et al., 2007
Kiwifruit	Act c 2	24	AJ871175 (Act c 2.0101)	56CNFDGAGRGKCQTG69 127TADINGQCPNELRAPGGCN146	Sharma et al., 2013

Apple	Mal d 3	9	AY572500 (Mal d 3.0101w)	16YVRSGGAVP24 35INGLARTADRQ46 76NVPYKISTS84	Borges et al., 2008
Peach	Pru p 3	10	P81402 (Pru p 3.0101)	11APCIPYVRGGGAVPP25 31IRNVNNLARTTPDRQ45 71GKCGVSTPYK80	García-Casado et al., 2003; Zuidmeer et al.,2006
Plum	Pru d 3	9	P82534 (Pru d 3.0101)	16YVKGGGAVP24 37LARTTADRRAACNCLHQL54 76NVPYKISASTNCATVK91	Borges et al., 2008
Apricot	Pru ar 3	9	P81651 (Pru ar 3.0101)	16YVRGGGAVP24 37LARTTPDRRTACNCL51 76NIPYKISASTNCATVK91	Borges et al., 2008

A, F, G, I, L, M, P, V and W are categorised as hydrophobic amino acids, C, N, Q, S, T and Y are categorised as polar amino acids and D, E, H, K and R are categorised as charged amino acids. A: Alanine; C: Cysteine; D: Aspartic acid; E: Glutamic acid; F: Phenylalanine; G: Glycine; H: Histidine; I: Isoleucine; K: Lysine; L: Leucine; M: Methionine; N: Asparagine; P: Proline; Q: Glutamine; R: Arginine; S: Serine; T: Threonine; V: Valine; W: Tryptophan; Y: Tyrosine.

Table 6. Lists of common fruits cross-reacting with pollen allergy

Species	Pollen allergy			Latex allergy	References
	Tree (e.g. birch)	Grass (e.g.ragweed)	Mugwort		
Apple	Yes				Mauro et al., 2011
Kiwi	Yes		Yes		Gall et al., 1994
Peach	Yes		Yes		Lauer et al., 2007
Cherry	Yes				Neudecker et al., 2003
Pear	Yes				Karamloo et al., 2001
Mango	Yes	Yes	Yes		Paschke et al., 2001
Tomato	Yes	Yes		Yes	Werfel et al., 2015
Melon		Yes	Yes		Patel et al., 2015
Orange	Yes	Yes			Takamatsu et al., 2016
Banana				Yes	Werfel et al., 2015
Pineapple				Yes	Werfel et al., 2015

Avocado	Yes	Poley and Slater, 2000

