3 Definition of Allergens: Inhalants, Food, and Insects Allergens

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Contents

3.1 Introduction ... 54

3.2 Nomenclature System for Allergens ... 55

3.3 Types of Allergens ... 55
3.3.1 Allergenic Epitopes ... 55
3.3.2 Component-Resolved Diagnostics ... 58
3.3.3 Cross-Reactive Carbohydrate Determinants (CCDs) ... 58

3.4 Environmental Allergens ... 58
3.4.1 Outdoor Allergens ... 58
3.4.2 Indoor Allergens ... 70

3.5 Food Allergens ... 74
3.5.1 Grains ... 74
3.5.2 Milk ... 76
3.5.3 Eggs ... 77
3.5.4 Fruits ... 77
3.5.5 Berries ... 78
3.5.6 Melons ... 79
3.5.7 Tree Nuts ... 79
3.5.8 Vegetables ... 81

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3.5.9 Leafy Green Vegetables ... 81
3.5.10 Inflorescent Vegetables ... 83
3.5.11 Bulb Vegetables ... 83
3.5.12 Stalk Vegetables ... 84
3.5.13 Root Vegetables ... 84
3.5.14 Nightshade Vegetables ... 85
3.5.15 Other Plants ... 86
3.5.16 Meats ... 86
3.5.17 Seafood ... 86

3.6 Special Categories ... 89
3.6.1 Stinging Insect Allergens ... 89
3.6.2 Latex ... 89
3.6.3 Oral Allergy Syndrome (OAS) ... 89

3.7 Summary and Conclusions ... 89

References ... 93

Abstract

The environment we live in and the food we consume on a daily basis contain numerous foreign antigens. During embryonic development and throughout our entire lives, the human body develops tolerance to many of these allergens in order that we do not suffer from the various maladies that result from an aberrant response to otherwise non-dangerous non-self-antigens. However, it is not always clear to the human immune system which antigens should be granted "immunity." For some pathogenic organisms, it is appropriate to protect ourselves against these invaders, as they may be harmful and cause disease or death. For other non-self-antigens, the immune system must develop tolerance to these proteins because they may be essential for our survival. On the other hand, the inability to develop tolerance to food, or to pollen, or to animal dander can lead to undesired biological consequences, which in many cases manifest in the form of an allergy. The molecules that cause symptoms are most often proteins or glycoproteins and lipoproteins. For many of them, their native function is known, but this is not always the case. There are also many allergenic substances which have not been well defined from either from a structural or functional perspective. The common mechanism for the development of IgE-mediated hypersensitivity involves the cross-linking of IgE antibodies on the surface of mast cells and the subsequent degranulation of preformed and newly synthesized mediators by the latter. Allergenic proteins can contain linear or conformational epitopes or be heat stable or heat labile. Food allergens can be modified by food processing or are affected by specific methods of cooking, which can denature the protein or, conversely, render a protein more allergic through various known chemical pathways such as the Mallard reaction. The end result is either a protein that is less or more allergic than the native protein. Pollens can be carried through biotic or abiotic means, but not all pollen allergens have been characterized. The peak season for pollens varies by the species, geography, and climate. This complex network of exposure is what the human immune system needs to navigate through to reach the balance where it knows exactly what to defend against and what to ignore. This is not always successful.

Keywords

Pollen · Allergenic determinants · Component-resolved diagnosis · Food allergy · Allergic rhinitis · Asthma · Eczema · Atopic dermatitis · Dust mite · Dander · Heat labile

3.1 Introduction

Allergic diseases, or the predisposition to develop allergic diseases known as atopy, have been on the increase both in the developed world and in less affluent parts of the world (Bhattacharya et al. 2018; Gonzales-González et al. 2018; Leung et al. 2014a; Ojeda et al. 2018; Simonsen et al. 2018; Vrbova et al. 2018). Potential reasons for this increase include the "hygiene hypothesis" and the increased ability for people to travel and be exposed to a higher number of allergens, air pollution, climate change, the exposure to adjuvants such as those in air pollution, and many others. However, the common environmental allergens, for the most part, have remained the same. Indoor allergens mostly include dust mite and epidermals, with cockroach and mouse being increasingly blamed for inner-city allergies and asthma. Outdoor allergens include grass, tree, and weed pollens, and while the specific species may vary geographically and temporally, the primary culprits are somewhat consistent. Mold allergies can arise from the exposure in areas of high humidity or failures of water maintenance, but mold spores generally originate from outdoor environments. Since the proposal of the hygiene hypothesis in 1989, the scope of the "hygiene hypothesis" in allergic diseases has become a theory with diverse influence and of course includes the interaction of microbiome with the immune system (Alexandre-Silva et al. 2018; Von Mutius 2007).

The development of allergies arises not only via the respiratory tract. Sensitization can occur through any biological interface including the skin and the mucous membranes of the gut. For this reason, foods are a frequent trigger of both IgE- and non-IgE-mediated immune reactions. With respect to common foods that may cause anaphylaxis, the chief culprits worldwide still tend to be cow's milk, egg, soy, wheat, peanut, tree nuts, fish, and shellfish, though the primary offenders may vary from country to country, within countries, between cultures, and even within cultures (Loh and Tang 2018; Prescott et al. 2013). Some regions of the world may have specific food allergies related to their respective diet, such as buckwheat in Japan, sesame in the Middle East, and various legumes in India (Koike et al. 2018; Irani et al. 2011; Boye 2012; Verma et al. 2013a) (Fig. 1).

3.2 Nomenclature System for Allergens

Allergens are named using a standardized methodology that is maintained by the World Health Organization, International Union of Immunological Societies (WHO/IUIS) Allergen nomenclature subcommittee, which was established in 1984 for the purpose of classifying and defining allergens according to the genus and species from which they are derived (Pomés et al. 2018). But the idea apparently had been tossed around as early as 1980 (de Weck 1996). Other considerations in naming allergens include structure, function, order of discovery, and relationship with other allergens from similar species.

The name of an allergen contains the first three letters of the genus, a space, followed by the first letter of the species, a space, and finally a number. For example, the scientific name for the common household cat is *Felis domesticus*. The major allergenic protein in cat is known as *Fel d 1*. There may be other allergenic proteins, and they would normally be numbered in the order of their discovery, but the numbering may later be revised based on common functions in related species. Thus, all of the "Group 1" allergens of dust mite species have the same function. In some cases, the first three letters of two or more genus are the same, in which case a fourth letter may be added. An example of this would be *Can* for dog and *Cand* for candida. If two or more species of the same genus have the same first letter, then an additional letter can be added. An example would be *Ves v 1* and *Ves vi 1* for the allergens from *Vespula vulgaris* and *Vespula vidua*.

3.3 Types of Allergens

3.3.1 Allergenic Epitopes

Allergens can come in many forms. Most are proteins, although glycoproteins and lipoproteins can also trigger production of IgE (Xu et al. 2018; Jappe et al. 2018; Shahali et al. 2017). Other allergens are not proteins at all but may be

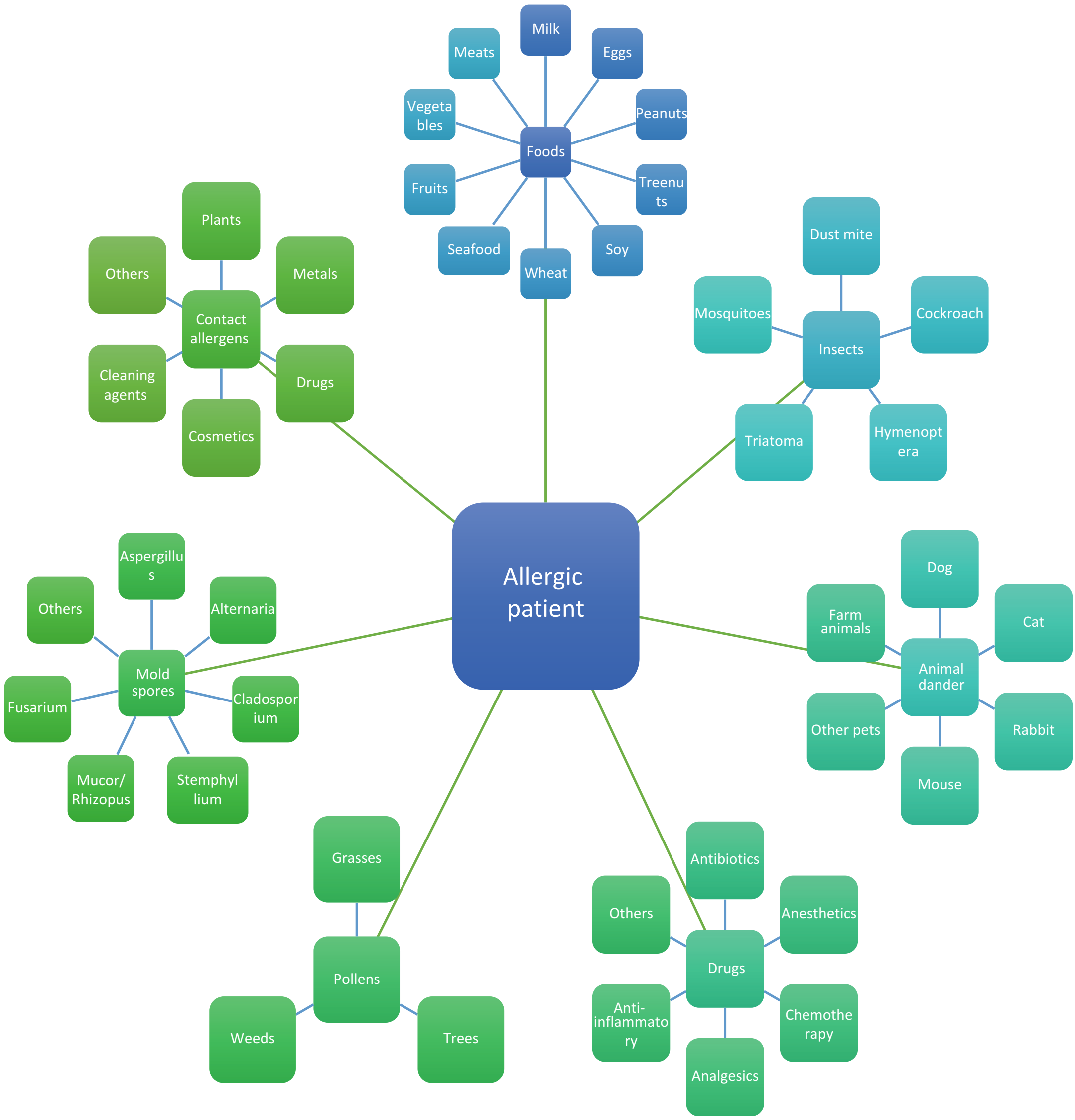

Fig. 1 Sources of allergens. Allergens can originate from many diverse environmental sources. Outdoor allergens include pollens from grasses, trees, or weeds, as well as mold spores. Failure to control indoor humidity means that mold spores can also originate indoors. Other indoor allergens include dust mites, cockroach, and pet dander. Any food can be a potential allergen, although the more common ones include cow's milk, egg, soy, wheat, peanut, tree nuts, fish, and shellfish, which account for 90% of all food allergies. Venom stings can produce allergic symptoms, as can latex and medications, which are not discussed in this paper. Contact allergy can result from a wide range of plants, metals, medications, and foods. Oral allergy syndrome can result from sensitization to a cross-reacting pollen allergen

polysaccharides, lipids, polysaccharides, or other molecules (Del Moral and Martinez-Naves 2017; Russano et al. 2008; Wieck et al. 2018). Proteins, however, are generally considered to be the most immunogenic or allergenic.

The human immunoglobulin repertoire is capable of generating antibodies with 10^{16}–10^{18} specificities, by undergoing somatic hypermutation and immunoglobulin VDJ gene rearrangements. An allergen can have many IgE antigenic determinants.

In general, a molecule must be of a certain size before it can illicit an immunological response. This size can vary but has been estimated to be in the range of 5–10 kD. If one assumes the average molecular weight of an amino acid is 110 daltons, then one would need a peptide or protein of at least 45 amino acids to generate an allergic response through binding of IgE. In fact, the process is not quite so simple, and smaller proteins do bind IgE either in their native or denatured forms.

Proteins are conventionally listed as primary sequences, starting from amino-terminal to the carboxyl-terminal. Biologically, protein structures are constrained by hydrogen bonds as specific secondary structures. Local interactions between secondary structures within a protein further generate tertiary structures which are defined biochemically by its atomic coordinates. Thus, proteins can fold into complex structures and possess multiple structural antigenic sites that can be targeted by antibodies. Most epitopes bind to IgE via a lock and key mechanism in which the antibody recognizes a secondary or tertiary structure of the protein, a so-called conformational shape. Conformational epitopes are formed from amino acids residues that are brought together by folding of the protein (Barlow et al. 1986). Conformational epitopes may be composed of either continuous or discontinuous amino acid sequences. Continuous amino sequences in a linear form can also elicit allergic responses through a variety of assistive mechanisms.

The allergens of many species have been studied extensively, while at the same time, we have very little information on the allergens of other species of animals or plants. Many allergens have been characterized and their function(s) defined. Some have even been characterized in terms of allergenic potential. Many allergenic proteins have been cloned, and the recombinant protein utilized in research to identify epitopes and developed vaccines for immunotherapy.

3.3.1.1 Conformational Epitopes Versus Linear Epitopes

Conformational epitopes can be envisioned as a lock and key model, in which the shape of the molecule, also known as secondary and tertiary structure, fits into the specific structure formed by the hypervariable region of the antibody molecule. The cross-linking of two or more IgE antibodies bound to antigen on the surface of mast cells leads to degranulation of mast cells, releasing preformed and newly synthesized mediators which can lead to allergic symptoms. Conformational epitopes generally require the antigen to be of a minimum size. This size has been thought to be at least 5 kD.

Linear epitopes are based upon the primary amino acid sequence of a portion of the protein. Accurate prediction of linear epitopes is a challenging task. Multiple algorithms are available for B-cell epitope prediction, with most of them based on limited epitope data sets (Larsen et al. 2006; Chen et al. 2007; Wang et al. 2011a; Söllner and Mayer 2006), and/or multi-algorithm parameters based on hydrophobicity, flexibility, accessibility, and biochemical properties of the amino acid side chains. However, their accuracy is unreliable (Sanchez-Trincado et al. 2017). Recently, new frameworks for linear B-cell epitope prediction, which are based on extensive immune epitope databases, have been reported (Lian et al. 2014; Manavalan et al. 2018).

Although most epitopes are conformational, progress in the prediction and mapping of conformational IgE epitopes are much impeded because such studies are technologically tedious (Breiteneder 2018) and often require detailed understanding of the three-dimensional structure of the molecule of interest, which is available for only a few allergens. To date, computational methods on predicting conformational epitopes have been largely based on spatial features of the protein with regard to solvent accessibility, physiochemical properties, and structural geometry. In addition, methods are also available for antibody-antigen-specific epitope prediction, which is largely based on a docking-like approach by analyzing interfaces of antigen-antibody 3-D structure to identify antibody-antigen recognition regions (Soga et al. 2010; Krawczyk et al. 2014; Sela-Culang et al. 2014). Despite many IgE epitopes prediction methods available, cross-validation with clinical samples will ensure such knowledge can be translated into clinical applications such as component-resolved diagnosis and vaccine design.

3.3.2 Component-Resolved Diagnostics

Component-resolved diagnosis is the analysis of individual allergenic proteins present in a particular environmental or food allergen. Previously, specific IgE testing quantified all antibodies directed against an allergen, and did not break it down based on individual proteins, let alone epitopes. Recently, however, antibody characterization has taken on a more precise mandate, and antibodies against individual allergenic proteins can be quantified in the evaluation of allergic patients. This is especially important with foods, where the differentiation of antibodies against various components in the food can affect treatment decisions. The most widely used example of this is with peanut allergen, where it has been found that the presence of IgE antibodies against the component Ara h 2 is more commonly associated with anaphylaxis, whereas the predominance of IgE antibodies directed against Ara h 9 is more commonly found in patients with oral allergy syndrome. Although not as widely used, component-resolved diagnosis can be helpful in the evaluation of pollen allergies as well.

3.3.3 Cross-Reactive Carbohydrate Determinants (CCDs)

Cross-reactive carbohydrate determinants are protein-linked carbohydrates that are being used to explain the high degree of cross-reactivity between allergens from foods, plants, and insects. It is believed that CCDs do not elicit clinical allergy symptoms; however, it has been suggested that these cross-reactive allergens may be the reason for oral allergy syndrome (Aalberse 1998; Ebo et al. 2004; van Ree 2002).

3.4 Environmental Allergens

3.4.1 Outdoor Allergens

There are numerous tree species in all regions of the world. Susceptibility to allergies in sensitized individuals depends on the pollinating seasons, which can vary from region to region. The predominance of tree species can also vary. Pollinating seasons vary for the same tree species depending on the region and climate. The majority of tree pollinating seasons begin in the springtime, although there are exceptions to this, such as a winter pollinating season for mountain cedar in the Southern United States. Some trees pollinate later in the year, and so there is a possibility that even a seasonal allergic rhinitis patient can suffer from symptoms throughout the year.

Grasses tend to pollinate in the springtime, but again the timing and duration of grass pollen season vary depending on climate. Rainfall and temperatures can affect grass pollen seasons. In some areas, grass is considered a perennial allergen. The grasses that are used in most lawns throughout the world tend to be a mixture of fairly common species, including fescue, Kentucky, perennial rye, and others. Other grasses can be found on the side of roads and can grow wild, such as Timothy grass or Johnson grass. Timothy grass can be found throughout the continental United States. It is native to Europe but not the Mediterranean region. Johnson grass is native to the Mediterranean region. It was and is considered an invasive weed and is used as a perennial forage crop in many states. Bahia grass is often found in lawns in the Southeastern United States.

Weeds tend to pollinate later in the year, and there are several species well known to be fall pollinators, including ragweed, which has a short but very intense season. Ragweed is native to North America. The family to which ragweed belongs is known as Compositae and also includes sage, marsh elder, mugworts, rabbitbrush, goldenrod, sunflower, marigolds, and zinnias.

The clinical impact of pollen also depends on the type of pollen itself, as some pollens tend to be more allergenic than others. It should also be noted that pollen exposure is a dynamic process. Changes in climate, especially due to global warming which can directly and indirectly affect pollinating seasons, and human introduction of new species can affect regional exposures. The presence of other extraneous material, such as diesel exhaust particles, can act as an adjuvant and increase Th2 response to accentuate the effects of pollens. So where one lives or works or the road they travel to work can make a difference.

3.4.1.1 Tree Pollen

Acacia

The genus *Acacia* contains over 1000 species. Acacia trees are considered small and fast growing. Acacia is abundant in California and pollinates early in the season, even as early as February. It is a yellow pollen and covers the road surfaces and cars during heavy pollination. However, it has been deemed not to be an allergen, and thus some allergists do not test for it at all. Acacia has been cited as having a role in occupational disease of floriculturists (Ariano et al. 1991). In addition, gum arabic, a natural gum derived from hardened sap of various acacia tree species, such as *Acacia senegal*, has also been described as a cause of occupational allergy (Viinanen et al. 2011). The allergens of Acacia have not been characterized.

Alder

Grey alder can be commonly found in North America as well as in Europe. Adler allergens have been characterized, based on the study of European alder (*Alnus glutinosa*) (Hemmens et al. 1988). There are over 30 allergens that have been identified. But only three of these allergens have been characterized from *A. glutinosa*, although not from *A. incana* (Grey alder). These include *Aln g 1,* which is a 17 kd protein (Breiteneder et al. 1992) and which is homologous to Bet v 1 from the birch tree. Aln g 2 has been categorized as a profilin (Niederberger et al. 1998), while the Aln g 4 allergen has been characterized as being a two EF-hand calcium-binding protein of 9.4 kD molecular weight. Recombinant Aln g 4 has been shown to trigger basophil histamine release and in vivo skin reactions in alder-sensitized patients (Hayek et al. 1998).

Ash

Ash (genus *Fraxinus*) is closely related to olive trees. *Fraxinus* is widely distributed throughout the Northern Hemisphere, including Asia, Europe, and North America (Vara et al. 2016). The European species of ash is *Fraxinus excelsior*, of which multiple allergens have been characterized. In Europe, ash is a major allergen causing allergic rhinitis symptoms in the springtime (Imhof et al. 2014). The major allergen from *Fraxinus excelsior* cross-reacts with the same group allergen of other related trees, such as olive. Fra e 1 is a glycosylated protein of unknown function comprising 15 isoforms (Poncet et al. 2010). Fra e 2 is a profilin of about 14 kD molecular weight (Poncet et al. 2010), and Fra e 3 is a 9 kD protein thought to be a calcium-binding protein (Poncet et al. 2010). Fra e 9, which is homologous to the corresponding allergen from the related olive tree, Ole e 9, is a 1,3-beta-glucanase (Palomares et al. 2005), and finally, Fra e 12 is an isoflavone reductase (Castro et al. 2007).

White ash (*Fraxinus americana*) is native to North America but also present in Europe. Ash trees are medium to large trees. Ash pollen has a distinctive shape in that it is usually four-sided, making its identification by pollen counters fairly easy.

Birch

Birch trees are commonly found in the Northern Hemisphere, in temperate climates. The scientific name for the genus is *Betula*, and it is member of taxonomic order Fagales. Birch trees like cool and moist areas and are often found along the shores of rivers and lakes. Most birch trees are small to medium in size, but some species do grow to be quite large (e.g., yellow birch, *Betula alleghaniensis*). There are currently over 100 known taxa of birch. Birch is often used to make furniture or as firewood or kindling.

Birch pollen allergy is believed to affect some 100 million people globally (Ipsen and Løwenstein 1983; Wiedermann et al. 2001). Birch pollen is a particularly potent allergen, and data suggests that up to 50% of the population in some endemic areas may be allergic. People sensitized to birch pollens are often also sensitized to nuts (Uotila et al. 2016). The white birch tree (*Betula verrucosa*) is one of the more common species and is the basis for the common allergens for birch. There are four common birch allergens. Bet v 1 is a 17 kd protein of unknown function, although it has been purported to act as a pathogenesis-related protein in plants, specifically PR-10, that is expressed during stress and illness in plants. There are multiple isoforms of Bet v 1, labeled from Bet v 1a to Bet v 1n. The protein possesses ribonuclease activity and shows homology and cross-reactivity with other tree species, including alder, hazel, and hornbeam. Bet v 1 also shows homology with various fruit, seed, and vegetable allergens, including apple, celery, cherry, and peanut, which is believed to be the root cause of oral allergy syndrome, whereby patients present with itchiness around the mouth and throat after eating such fruits, after having been sensitized to Bet v1. The PR-10 pathogenesis-related proteins are believed to have RNase enzymatic activity as well as the ability to bind cytokines (Swoboda et al. 1996; Bufe et al. 1996; Bantignies et al. 2000).

Among the other birch allergens, Bet v 2 is a profilin, Bet v 4 is a polcalcin, and Bet v 6 is an isoflavone reductase. These minor allergens are rarely sole sensitizers but may contribute to cross-reactivity between birch and foods in oral allergy syndrome.

Cedar

The genus known as Cedar includes a variety of small to large evergreen, coniferous trees. Cedars are related to firs and produce a very pleasant scented wood. Most cedars can withstand cold and have been transplanted from their Mediterranean and Western Himalayan origin to other regions with more temperate climates, such as Western Europe, North America, Australia and New Zealand. Cedars are quite hardy as they are able to withstand cold temperatures down to −25 °C, with some species such as the Turkish cedar able to survive even at lower temperatures.

A common species of cedar, white cedar or *Libocedrus decurrens*, is actually a member of the family Cupressaceae. On the other hand, Japanese cedar (*Cryptomeria japonica*) is a member of the Taxodiaceae family. *Libocedrus* is also related to the genus *Thuja*. *Thuja* includes Western red (*Thuja plicata*) and Eastern white (*Thuja occidentalis*) cedars.

In the Southern United States, such as Texas, mountain cedar (*Juniperus ashei*) is well known as a species that pollinates in the wintertime (December–January). Many allergens have been defined in Japanese cedar. But Cry j 1 and Cry j 2 are the most common. Cry j 1 is a glycoprotein similar to pectate lyase. Cry j 2 is a polygalacturonase. Both have molecular weights about 45 kD. Another major allergen of Japanese cedar, Cry j 3, is a smaller protein of 19–27 kD and is a thaumatin-like protein. Other allergens found in Japanese cedar include chitinases, isoflavone reductase-like proteins, and lipid transfer proteins (Fujimura and Kawamoto 2015). Studies on desensitization to Japanese cedar using oral immunotherapy are ongoing (Wakasa et al. 2013).

Cypress

Arizona cypress (*Cupressus arizonica*) is native to the southwest United States and Mexico, but it has also been exported to Europe. It thrives in dry soil, requiring only 10–12 inches of water annually. Arizona cypress is a medium-sized tree that grows to up to 60 feet high. Allergens of cypress include Cup a 1, considered a major allergen of 43 kD molecular weight (Di Felice et al. 1994; Di Felice et al. 2001). Other allergens are mostly glycoproteins and include Cup a 2 (Di Felice et al. 2001); Cup a 3, a 21 kDa protein (Palacín et al. 2012); and a calcium-binding protein, Cup a 4 (de Coaña et al. 2010). The Italian cypress (*Cupressus sempervirens*) allergen Cup s 1 is a pectate lyase (Arilla et al. 2004), and Cup s 3 is homologous to other pathogenesis-related group 5 (PR-5) proteins (Togawa et al. 2006).

Elm

There are six genera of the elm family (Ulmaceae), with *Ulmus*, *Zelkova*, and *Planera* (Weber 2004) being more common. *Ulmus* is the most common elm genus in the United States. Elm is native to the United States and Europe (Torri et al. 1997; Kosisky and Carpenter 1997), although there are also transplanted species, such as Chinese elm, which is native to China, Korea, and Japan. Elm trees grow by streams and in damp places of regions of temperate climate. Flowers develop in winter and early spring, and the season may vary from region to region. There is a report on the association of increase hospitalizations for asthma with daily increase in elm pollen counts in urban Canada (Dales et al. 2008). The individual allergenic proteins in elm are currently not commercially analyzed by component-resolved diagnostics.

Eucalyptus

Eucalyptus are large trees that grow quickly; a common species is *Eucalyptus globulus*. Eucalyptus is known to be able to cause asthma exacerbations (Galdi et al. 2003). The commonly used Eucalyptus oil is extracted from the fresh leaves of this species and can cause toxicity (Darben et al. 1998; Schaller and Korting 1995). Symptoms can include slurred speech, muscle weakness, and ataxia which may progress to loss of consciousness. It can also cause contact dermatitis (Gyldenlove et al. 2014). No allergens from this plant have yet been characterized.

Mango

Allergens from the mango tree, *Mangifera indica*, include Man i 1, a major allergen 40 kD in size which functions as a glyceraldehyde 3-phosphate dehydrogenase (GAPDH). It shares 86.2% homology in amino acid sequence with the wheat GAPDH. This particular allergen has been cloned. Other allergens include a 30 kD protein named Man i 2 (Dube et al. 2004) and a minor allergen, Man i 3, which is a profilin (Song et al. 2008). An additional 27 kD protein has been associated with anaphylactic reactions to mango (Renner et al. 2008). Low-abundance mango allergens have been shown to be cross-reactive with banana species (Cardona et al. 2018). Mango is an evergreen tree with a long history. It is in the same family as cashew, pistachio, and sumac.

Maple/Box Elder

Box elder is related to the maple family and belongs to the genus *Acer*. The scientific name for box elder is *Acer negundo*. Maples in general are abundant in northern, temperate climates. There are over 125 species of Acer. Box elder is a medium-sized tree and is fast growing. It is a known trigger for exacerbations of asthma and allergic rhinitis (Sousa et al. 2012). To date no allergens have been characterized (Ribeiro et al. 2009). Maple is considered to be a major allergenic tree in many locales.

Mulberry

There are about ten species of mulberries. Mulberries can be either a tree or a shrub and can be either monoecious or dioecious. Mulberries originated from Asia but can be found all over the world now. There are two species found native to North America. Mulberry trees are medium trees, with a light bark and a wide, round canopy. Flowers are small, as are the pollen grains. While leaves from white mulberries (*Morus alba*) can be used as food for silkworms, the red mulberry (*Morus rubra*) is cultivated for its fruits. Mulberry is an important allergen that causes significant symptoms of allergic rhinitis, allergic conjunctivitis, and asthma (Navarro et al. 1997; Targow 1971). Like sumac, the leaves of the mulberry tree have been reported to cause a form of contact urticaria (Muñoz et al. 1995). No allergens from this plant have yet been characterized.

Oak

Oak belongs to the order Fagales, the family Fagaceae, and the genus *Quercus*. *Quercus* is a very large genus with over 500 species. Some of the more common species for which allergenic extracts have been developed include Virginia live oak, California black oak, Oregon white oak, and Valley oak.

Oak can be either trees or shrubs. The widespread sensitization to oak observed throughout many regions of the world reflects the near ubiquitous presence of various oak species, whether they be native to a particular region or transplanted. For example, Virginia live oak is native to the Southeastern United States but can also be found in Cuba and Mexico. White oak is even more common than live oak. Oak sensitization has been found to occur in Europe, Asia, and South Africa. *Quercus alba* is a common species found in many locales. Oak pollen allergies may cross-react with birch allergens Bet v 1, 2, and 4 (Egger et al. 2008). Recently, a major allergen from Mongolian oak, which is found in Korea, was characterized. The allergen, Que. m 1 (from the species *Quercus mongolica*), has been reported to be homologous to pathogenesis-related 10 (PR-10) like protein (Lee et al. 2017).

Olive

Olive is a very important allergen that is widely cultivated in many parts of the world. It belongs to the family Oleaceae. This family includes olive (*Olea*), ash (*Fraxinus*), privet (*Ligustrum*), and lilac (*Syringa*). Olive is native to the Mediterranean area, but it is grown widely in other parts of the world, including Northern California, and in the dry climates of the Western States. It is a well-characterized allergen, and over 20 specific allergens have been identified. The pollination season varies depending on the region, but the further north one goes, the later the season seems to last. *Olea europaea* is the main species of olive tree of which Ole e 1, Ole e 4, and Ole e 7 are considered major allergens. Ole e 1 is a trypsin inhibitor, and Ole e 7 is a lipid transfer protein (Villalba et al. 1990). Ole e 9, a 1,3 beta-glucanase, is also a major allergen of olive (Castrillo et al. 2006; Duffort et al. 2006; Palomares et al. 2006a; b). Ole e 1 is homologous to Fra e 1, and patients exhibit cross-reactivity between the two (Palomares et al. 2006c).

Pine

Pinus radiate is a common species of the pine tree, from the family Pinaceae. Other pine species include *Pseudotsuga taxifolia* and *Picea excelsa* and *Pinus strobus*, corresponding to the well-known trees Douglas fir, spruce, and white pine. All of these are commonly harvested for Christmas trees so they make their way into homes and other indoor environments. Certain species of pine, including white pine, are native to North America, but there are over 100 species distributed throughout both hemispheres. Five allergenic proteins of 82 kD, 67 kD, 54 kD, 44 kD, and 38 kD have been identified from pine trees (Fountain and Cornford 1991). As an allergen, pine is not considered to be one of the more prevalent or more potent allergens (Freeman 1993; Bousquet et al. 1984).

Sycamore

Maple leaf sycamore (London plane tree or hybrid plane) is *Platanus acerifolia*, a hybrid of Oriental plane tree (*P. orientalis*) and American sycamore (*P. occidentalis*) (Weber 2004). They are planted along the streets in London and in Philadelphia. The tree can reach 30 meters in height. Several allergens that have been characterized from *Platanus acerifolia*, including Pla a 1, an invertase inhibitor of molecular weight 18 kD (Asturias et al. 2006). Other allergens include Pla a 2, a polygalacturonase of 43 kD (Asturias et al. 2002), a 10 kD lipid transfer protein Pla a 3 (Asturias et al. 2002), and a profilin with the designation Pla a profilin (Enrique et al. 2004). Sycamore maple belongs to the maple family, and its scientific name is *Acer pseudoplatanus*.

Walnut

Walnut trees belong to the genus *Juglans*, a member of the family Juglandaceae. They are found throughout the United States and other regions including Asia, the Middle East, and Western and Eastern Europe. Walnut trees generally pollinate between April and June, but the season can begin earlier in the year in the Southeastern United States. The spores can be circular or triangular and are generally between 30 and 40 microns in diameter. Two walnut species, *Juglans regia* and *Juglans nigra*, are common in the human diet and can be food allergens as well. Five allergens have been identified in *J. regia*. Jug r 1 is a 2S albumin, Jug r 2 is a vicilin, Jug r 3 is a non-specific lipid transfer protein, Jug r 4 is a legumin, and Jug r 5 is a profilin. Two allergens have been identified in *J. nigra*. Jug n 1 is a 2S albumin, and Jug n 2 is vicilin. All except Jug r 5 have been shown to cause severe and systemic allergic reactions (Costa et al. 2014). Two allergens, Jug r 1 (a storage protein) and Jug r 3 (a lipid transfer protein), have been identified to cause food allergy reactions including anaphylaxis (Sato et al. 2017).

Willow

Willow is a member of the family of trees known as Salicaceae. Salicaceae actually includes poplars, cottonwood, aspen, and willow trees. Willow belongs to the genus *Salix*, which also includes 400 species of shrubs and trees including willows, osiers, and sallows. Willows like to grow in the Northern Hemisphere in colder regions. From a seasonal standpoint, willow trees are early bloomers, sometimes heralding the arrival of early spring. While willow is an important allergenic tree, the specific allergens have not been characterized. Willow pollen is anemophilous, or wind borne, and is small, between 18 and 21 microns in diameter, depending on the species. Wind-borne pollens, as opposed to insect borne or entomophilous pollens, tend to be more relevant as triggers of allergies because they travel for longer distances.

3.4.1.2 Grass Pollen

Grass allergy is one of the more common types of seasonal allergy. Symptoms include rhinorrhea, nasal congestion, sneezing, itching of the eyes and nose, and eye inflammation and drainage. There are thousands of grass pollen species throughout the world. Grass pollen seasons tend to be short, lasting 2–3 months, but this can vary significantly with climate, and longer seasons can be present in areas where there is a lot of rainfall. A study in the Netherlands showed that patients tend to have more severe symptoms early in the grass pollen season (de Weger et al. 2011). This can have an impact on the timing of studies done to assess effectiveness of treatment. There are three major families of grass pollen with a high degree of cross reactivity within each family.

The Poaceae Family

Pooideae is the largest subfamily with the Poaceae family, comprising 3850 species. Members of this family include Timothy grass, sweet vernal grass, meadow fescue, perennial rye, June grass, Kentucky bluegrass, orchard grass, redtop grass, velvet grass, canary grass, and the cereal grains including wheat, rye, and barley. The second family is Chloridoideae, which includes Bermuda grass, lovegrass, and the prairie grasses, including salt grass, grama grass, and buffalo grass. The third family is called Panicoideae. This is the second largest family of *Poaceae* and comprises over 3250 species. Members of this family include Johnson grass, Bahia grass, sugarcane, and corn. There is less cross-reactivity within members of this group compared to members of the other two groups. Other subfamilies of Poaceae can also be important from a geographical perspective. For example, pampas grass, a member of the Danthonioideae subfamily, is endemic to South America and is a very attractive grass but is invasive as well and often takes over flower beds. It can also be found in Florida.

Bahia

Bahia grass, or *Paspalum notatum*, is a perennial grass considered to be a Southern subtropical grass. A major allergen of Bahia grass is Pas n 1 (Davies et al. 2011a; Drew et al. 2011). It has been cloned and sequenced. Recombinant Pas n 1 shows 85% homology to the maize pollen group 1 allergen. rPas n 1 can activate basophils and competitively inhibit serum IgE activity with a 29 kD band of the grass pollen extract. It can also react with IgE from Bahia allergic patients (Davies et al. 2008). Another study reported a 55 kD protein allergen, designated Pan n 13, that cross-reacts with the group 13 allergens of maize pollen and Timothy grass (Davies et al. 2011b).

Bermuda

Bermuda grass, or *Cynodon dactylon*, is an evergreen perennial grass that is found in many regions around the world, especially in regions with warm climate. Three allergens have been characterized to date. Its major allergen is Cyn d 1 (Han et al. 1993) which is a group 1 glycoprotein allergen belonging to the β-expansin family (Drew et al. 2011). Another major allergen is a 12 kD allergen, designated as Cyn d 7 (Suphioglu et al. 1997) that shares sequence similarity with other pollen allergens such as Bet v 4 from birch. A profilin, Cyn d 12, is the third identified allergen that also shares some epitopes with sunflower profilin (Asturias et al. 1997a). Bermuda grass is often used on greens of golf courses, the other grass being Bentgrass. Bentgrass is preferred in cooler climates, but Bermuda is more heat tolerant and is often found in warmer regions.

Johnson

Johnson grass, or *Sorghum halepense*, is a perennial grass that generally grows as a weed along with multiple crops and is considered to be one of the more invasive weeds in the world (Holm et al. 1977). Johnson grass was originally cultivated in South Asia, Southern Europe, and North Africa. Among those characterized, major allergens include a group 1 grass allergen known as Sor h 1 (Smith et al. 1994), a calcium-binding protein known as Sor h 7 (Vallier et al. 1992a; Wopfner et al. 2007), and a profilin identified as Sor h 12 (Yman 1981). Johnson grass allergens have also been shown to have cross-reactivity with some Bermuda grass allergens (Smith et al. 1994).

Meadow Fescue

Meadow fescue, or *Festuca pratensis*, is primarily used as a pasture grass, but it can also be a turf grass. It is native to Western Asia and Northern Europe and grows alongside roads and in meadows, hence its name. It is a relatively short grass and is used in lawns worldwide. Fes p 1 is a Group 1 grass allergen (Hiller et al. 1997) and is identified as the major allergen for meadow fescue. Other identified allergens include a group 4 and 60 kD grass allergen, Fes p 4 (Gavrović-Jankulović et al. 2000), Fes p 5 which is a ribonuclease and a Group 5 grass allergen (Matthiesen and Løwenstein 1991), and finally, Fes p 13 which is a polygalacturonase and a Group 13 grass allergen (Petersen et al. 2001). Meadow fescue usually enjoys temperate climates.

Orchard

Dactylis glomerata, commonly known as cocksfoot or orchard grass, is a perennial grass found in temperate regions of Africa, Australia, North America, and South America. It is also used as a forage grass. Dac g 4 is a major 59 kD allergen (Leduc-Brodard et al. 1996). Other characterized allergens include Dac g 1 (Mourad et al. 1988), Dac g 2 (Roberts et al. 1992), Dac g 3 (Guérin-Marchand et al. 1996), and Dac g 5 (van Oort et al. 2001). Orchard grass also shares epitopes with group I (Mourad et al. 1988) and group II grass allergens (Roberts et al. 1992) of perennial rye.

Perennial Rye

Lolium perenne, commonly known as perennial rye or just ryegrass, is native to Europe and is highly valued for its erosion control properties and as a forage grass. Perennial ryegrass is one of the predominant grass pollens causing allergic rhinitis, allergic conjunctivitis, and asthma. Ryegrass is the pollen that is mainly attributed to "thunderstorm asthma," a condition whereby thunderstorm downdrafts drive ruptured ryegrass pollen particles of approximately 3 microns in diameter to ground, breathing zone level, mimicking conditions during an allergen challenge study, and leading to rapid progression of allergic and asthma flares (Thien et al. 2018). Lol p 1 (Perez et al. 1990) and Lol p 2 (Tamborini et al. 1995) have been characterized as major allergens of perennial ryegrass. Other allergens include Lol p 3 (Ansari et al. 1989), Lol p 4 (Jaggi et al. 1989), Lol p 5, Lol p 9 (Blaher et al. 1996), Lol p 10 (Ansari et al. 1987), and Lol p 11, which is a soybean trypsin inhibitor (van Ree et al. 1995). Studies show that Lol p 5 has two isoforms, identified as Lol p 5A and Lol p 5C, respectively (Suphioglu et al. 1999; Klysner et al. 1992).

Timothy

Timothy grass, or *Phleum pratense*, is one of the most common grasses and is often considered the representative grass of the Pooideae subfamily, especially when conducting investigations for immunotherapy (including sublingual immunotherapy). It is native to Europe, with the exception of the Mediterranean region, as well as Northern Asia and North Africa (Gavrović et al. 1997). It is considered a pasture grass, having been introduced to the New World regions in America and Australia, and is a very highly used fodder for animals, including small pets such as bunnies. It is therefore most commonly found in meadows or fields but is also commonly seen on roadsides. The proteins in Timothy grass pollen have been characterized in detail. Allergens characterized to date include Phl p 1, a major group 1 allergen

(Suck et al. 1999); Phl p 4 (Fischer et al. 1996); Phl p 5, which is a major group 5 allergen (Flicker et al. 2000); a 11–12 kD protein identified as Phl p 6 (Vrtala et al. 1999); a calcium-binding protein known as Phl p7 (Niederberger et al. 1999); a profilin identified as Phl p 12 (Asturias et al. 1997b); and finally, Phl p 13 (Suck et al. 2000). The group 13 grass pollen allergens are polygalacturonases. The group 11 allergen Phl p 11 is a 20 kD protein that has been characterized and shown to have allergenic activity (Marknell DeWitt et al. 2002). Many of the grass allergens, including Timothy, have been standardized for skin testing and have also been developed as sublingual immunotherapy that is commercially available and FDA approved, such as Grastek® and Oralair®.

Redtop

Redtop is one of the common names of *Agrostis stolonifera*. As with Bermuda grass, red top is actually a type of Bentgrass (see above) and therefore is used on golf course greens and lawns and as turfs. It is a very hearty grass and can grow in a variety of soil conditions and climates. No allergens from this plant have been characterized yet, although a group 5 allergen (Agr s 5) has been identified.

The list of grasses described above is by no means comprehensive. Other common grasses include Kentucky bluegrass, June grass, and salt grass. In most cases, these grasses will cross-react within the same group, so not all grasses needed to be tested for or included in an immunotherapy mix.

3.4.1.3 Weeds

Cocklebur

Cocklebur, or *Xanthium commune*, is an annual weed that grows to about 1.5 meters tall. It is native to the Northern Hemisphere, having been found in Asia, Europe, and the North and Central Americas. Cocklebur flowers are monoecious, and the plant is self-fertilizing. Pollinating seasons usually begin in April and continue through October. Cocklebur belongs to the family Asteraceae and therefore is related to ragweed. However, there doesn't appear to be much allergenic cross-reactivity with ragweed. Allergens have not been characterized, although two, designated as Xan lb. and Xan Vla, have been identified.

English Plantain

English plantain, ribwort or *Plantago lanceolata*, is an erect perennial with a base of leaves. The plants are found mostly in temperate regions but can actually grow anywhere. Pollen season for English plantain ranges from April to about August. Plantains are commonly found on roadsides as flat leaves at the base of a stalk that will grow to be 0.3–0.5 m tall. The major allergen for English plantain is Pla l 1, a 17–20 kD protein, which acts as a trypsin inhibitor. Trypsin inhibitors are considered to be pathogenesis-related proteins (PR) (Calabozo et al. 2001). Other allergens include Pla l cytochrome C (Matthews et al. 1988a) and Pla l CBP, which are a calcium-binding protein (Grote et al. 2008). English plantain is a significant allergen in many parts of the world, causing seasonal allergic rhinitis and conjunctivitis as well as asthma exacerbations (Garcia-Gonzalez et al. 1998; Matthews et al. 1988b; Spieksma et al. 1980; Wuthrich and Annen 1979).

Mugwort

Mugwort is a common weed which originated from Europe and Asia. It often grows on roadsides and by old buildings and invades nurseries and lawns. Mugwort belongs to the family Asteraceae (Compositae). The Latin name for mugwort is *Artemisia vulgaris*. Mugwort is related to sagebrush (*A. tridentate*), wormwood (*A. absinthium* or *A. annua*), and tarragon (*A. dracunculus*) (Yman 1981; Katial et al. 1997; Hirschwehr et al. 1998; Leng and Ye 1987). Allergens from mugwort that have been characterized include Art v 1, which is a defensin of size 28 kD (Oberhuber et al. 2008a), Art v 2 (Arilla et al. 2007), Art v 3 (Gadermaier et al. 2007), Art v 4 (Oberhuber et al. 2008a), Art v 5 (Wopfner et al. 2005), Art v 6 (Wopfner et al. 2005), Art v 60 kD (Lombardero et al. 2004), and Art v 47 kD (Nilsen and Paulsen 1990). Interestingly, artemisinin, the active ingredient in sweet wormwood (*Artemisia annua*), has been used successfully in the treatment of malaria. This treatment has been credited with saving over five million lives worldwide and won its discoverer the Nobel Prize in Physiology or Medicine in 2015 (Andersson et al. 2015).

Nettle

Nettle can be found worldwide and likes to grow in nitrate-rich soils. Like mugwort, it is often used in herbal remedies. It is fast growing and is dioecious and wind pollinated. The nettle pollen season is between April and October. The scientific name of Nettle is *Urtica dioica*, and it belongs to the family Urticaceae. It is a frequent cause of allergic rhinoconjunctivitis and asthma (Wuthrich and Annen 1979). Allergens from nettle have not yet been characterized.

Pigweed

Common pigweed or *Amaranthus retroflexus* is a member of a large family of weedy herbs consisting of 40 genera and up to 475 species (Wurtzen et al. 1995). It is widely distributed worldwide and is a significant trigger of asthma and allergic rhinoconjunctivitis (Calabria et al. 2007; Calabria and Dice 2007). Allergens of pigweed have not been characterized although two allergens of 14 kD and 35 kD have been reported. Pigweed cross-reacts with lamb's-quarter, or *Chenopodium album (*Lombardero et al. 1985*)*.

Ragweed

Ragweed is a group of weeds that are commonly found throughout the world. Common ragweed, also known as short ragweed or annual ragweed, scientific name *Ambrosia elatior* or *Ambrosia artemisiifolia*, is native to North America. It is one of the more common causes of allergic rhinitis and asthma in Europe, Asia, and the United States. Ragweed is one of only a handful of allergens with a commercially available, FDA-approved sublingual immunotherapy agent, while the others being grass mixture, Timothy grass, and dust mite (Creticos and Pfaar 2018; Nelson 2018; Pfaar and Creticos 2018). *Ambrosia* is nearly ubiquitous, mostly seen by roadsides, woodlands, dry fields, and pastures. The ragweed season in the Eastern United States is generally from August to October, but there is a very short peak from mid-August to September. The highest pollen counts for ragweed are in the middle of the day. Ragweed pollen constitutes an abundant, potent allergen which is one of the most important allergens among atopic individuals with allergic rhinitis or asthma (Pollart et al. 1989).

The allergens of ragweed have been extensively studied and characterized. These include Amb a 1, which is a pectate lyase of 38 kD in size (Wopfner et al. 2008; Oberhuber et al. 2008b); Amb a 2, also 38 kD, and another pectate lyase (Kuo et al. 1993); Amb a 3 (Kurisaki et al. 1986; Atassi and Atassi 1986); and Amb a 5 (Pilyavskaya et al. 1995; Mole et al. 1975; Zhu et al. 1995; Huang and Marsh 1991; Huang et al. 1991; Ghosh et al. 1991; Marsh et al. 1991; Zwollo et al. 1991), small proteins of 9 kD and 5 kD in size, respectively. Amb a 6 is also a small protein of 10 kD and is a lipid transfer protein (Marsh et al. 1987). The other proteins are also small proteins and function as profilin, calcium-binding proteins, and a cystatin protein inhibitor (Vallier et al. 1992b; Liebers et al. 1996; Rogers et al. 1993). Allergens from ragweed have been found to cross-react with each other and with pollens from mugwort or *Artemisia vulgaris*. Plant profilin is considered a panallergen, and on this basis, ragweed does cross-react with other pollens that have allergens functioning as profilins. Ragweed pollen also cross-reacts with yellow dock or sheep sorrel (Shen et al. 1985a).

Ragweed pollen is a common sensitizer in oral allergy syndrome, leading to mouth itching and tingling associated with ingestion celery, mango, carrot, watermelon, and other fruits (Paschke et al. 2001; Dechamp and Deviller 1987; Enberg et al. 1987; Caballero and Martin-Esteban 1998). Ragweed can also act as a skin sensitizer, causing a type of contact dermatitis (Fisher 1996).

Russian Thistle

Russian Thistle (or Saltwort), is *Salsola kali*, Russian Thistle has a widespread distribution, favors semiarid to arid climates and places such as sandy shores or beaches. It can even grow in the desert and is prevalent in dry climates such as the Middle

East. Several allergens have been identified from Russian thistle. Sal k 1 is a major allergen, of 43 kD in size, and functions as a methylesterase (Carnés et al. 2003). While reactivity to Sal k 1 is observed in most people allergic to Russian thistle, this is not the case for some of the lesser allergens, including Sal k 2 (Civantos et al. 2002), Sal k 3 (Assarehzadegan et al. 2011), Sal k 4 (Assarehzadegan et al. 2010), and Sal k 5 (Castro et al. 2008). Sal k 2 has been characterized as a protein kinase, while Sal k 3 is a methionine synthase. Sal k 4 is a profiling of 14 kD in size, while Sal k 5 is related to Ole e 1. Russian thistle, like many other trees, weeds, or grasses, has been implicated in oral allergy syndrome. The dried tumbleweed that one may see rolling around in the wind is derived from Russian thistle, among other weeds.

Sage

Sage is an herbal plant with the scientific name *Salvia officinalis*. Sage is the basis for the common spice which is used to flavor food. Sage has also been used in soaps and perfumes. *Salvia officinalis* is a small herbaceous shrub which originated from the Mediterranean (Yman 1981; Daniela 1993). But *Salvia divinorum* or sacred sage is native to Central America. Allergens from sage have not been characterized, but sage has been implicated in oral allergy syndrome or latex-fruit syndrome.

Scotch Broom

Scotch broom belongs to the family Fabaceae. The scientific name for Scotch broom is *Cytisus scoparius*. It is native to Europe and introduced into other countries such as the United States, South Africa, and the Southern Pacific. It is a small shrub and considered an invasive plant. The allergens from sage have not yet been characterized.

Sheep Sorrel

A common perennial herbal plant that originated in Asia and Europe, sheep sorrel or *Rumex acetosella*, is an invasive weed that has been transplanted to the United States. The plant is wind pollinated in the fall. It is commonly found in lawns and pastures and even on roadsides. It is known as a significant trigger for allergic rhinoconjunctivitis and asthma (Gniazdowska et al. 1993; Solomon 1969; Larenas et al. 2009; Dursun et al. 2008; Liang et al. 2010). Allergens from sheep sorrel have not been characterized, but sheep sorrel is an important allergen in the Northern Hemisphere.

Yellow Dock

Yellow dock (*Rumex crispus*) belongs to the family Polygonaceae. Therefore it is related to sheep sorrel. Pollination season is from June to October. Although several allergenic proteins have been identified, with molecular weights of 40, 38, 24, and 21 kD, none of these allergens have been fully characterized (Shen et al. 1985b).

3.4.1.4 Molds

Fungi, with the exception of mushrooms, are collectively called molds. Molds are saprophytes in nature, living on the decomposition of organic materials and are also occasional human pathogens. Molds can be found indoors and outdoors under moist environment. Molds that are known to cause allergies include the phylum Ascomycota such as *Aspergillus* and *Penicillium*, the phylum Zygomycota such as *Mucor* and *Rhizopus*, and the phylum Basidiomycota such as *Rhodotorula* and *Ustilago* (Levetin et al. 2016).

Phylum Ascomycota

The phylum *Ascomycota* is highly diverse and includes unicellular organisms to well-defined fruiting bodies that produce ascospores. Although aerial ascospore count is higher after the rain or during the season of high humidity, no ascospore allergens have been characterized.

Alternaria

Alternaria is a genus of ascomycete fungi. It is generally considered a saprophyte and plant pathogen. Although it is mainly an outdoor fungus and is considered a dry air spora, *Alternaria* allergens have been detected indoor (Peters et al. 2008). *Alternaria alternata* is known to be associated with severe asthma (Bush and Prochnau 2004). To date, 17 IgE-reactive *Alternaria alternata* proteins of diverse biochemical and functional properties have been identified, of which Alt a 1 is considered a major airborne fungal allergen and a marker of primary sensitization to *Alternaria alternata (*Postigo et al. 2011*)*. The other *Alternaria* allergens include heat shock protein 70 (Alt a 3), disulfide isomerase (Alt a 4), ribosomal protein P2 (Alt a 5), enolase (Alt a 6), flavodoxin YCP4 protein (Alt a 7), mannitol dehydrogenase (Alt a 8), aldehyde dehydrogenase (Alt a 10), acid ribosomal protein P1 (Alt a 12), glutathione transferase (Alt a 13), manganese superoxide (Alt a 14), and vacuolar serine protease (Alta 15) (Gabriel et al. 2016). Alt a NTF2 is identified as nuclear transport factors, and Alta TCTP is identified as translationally controlled tumor proteins. The functions of the other *Alternaria* allergens (Alt a 2, Alt a 9, Alt a 70 KD) are unknown.

Aspergillus

Aspergillus belongs to the phylum of Ascomycota and is ubiquitous in nature. Several species of *Aspergillus* have been shown to be allergenic; they include *Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus niger*, and *Aspergillus oryzae*.

Aspergillus fumigatus, also known as the common mold, is a major cause of allergic bronchopulmonary aspergillosis (ABPA). Currently, over 20 allergens of *A. fumigatus* have been reported. Five recombinant aspergillus allergens (rAsp f1-f4 and f6) are commercially used for diagnosis of allergic aspergillosis. *Aspergillus* is also a common culprit in allergic fungal sinusitis (AFS). These patients have peanut butter like mucous in their sinuses which is difficult to clear.

Aspergillus flavus, also known as cereal mold, is a saprophyte that grows on cereal grains, tree nuts, and legumes. It can also be found in soil. *Aspergillus flavus* is notorious for its production of a toxin called aflatoxin which causes acute hepatitis and liver cancer. Asp fl 13, a 34 KD alkaline serine protease, has been identified as a major allergen (Chou et al. 1999).

Aspergillus niger, also known as black mold, is ubiquitous in nature. It can be found in many different habitats such as soil, rotting fruits, and decaying substances. To date, three *Aspergillus niger* allergens have been identified. Asp n 14 is a beta-xylosidases of about 105 KD (Sander et al. 1998), Asp n 18 is a vacuolar serine protease of 34 KD, and Asp n 25 is 3-phytase B of 66–100 KD.

Aspergillus oryzae, also known as rice mold, has been widely used in the fermentation of soybeans in making soya sauce and rice to make sake. Two *Aspergillus oryzae* proteins, the 34 KD alkaline serine protease (Asp o 13) and the 53 KD TAKA-amylase A (Asp o 21), have been reported as allergens (Baur et al. 1994; Shen et al. 1998).

Phylum Basidiomycota

Basidiomycota is the second largest phylum of fungi and are best characterized by their fruiting bodies that produce sexual spores called basidiospores which are released to the air during high humidity. The mushrooms described below under food allergens are part of this group of plants. *Basidiospores* have strong asthma-environmental association, with spikes in emergency department visits. Two basidiospore allergens have been described in *Rhodotorula mucilaginosa*, one is an n enolase, and the other is a serine protease (Chang et al. 2002; Chou et al. 2005). In addition, *Ustilago* is a smut fungus that produces airborne smut spores. Allergic reactions to grain smuts and corn smut (*Ustilago maydis*) extract have been reported (Santilli Jr. et al. 1985).

Cladosporium

Cladosporium is commonly found in areas with moisture, humidity, and water damage, producing spores that are easily spread in the air. The scientific name is *Cladosporium herbarum*. The old name of *Cladosporium* was *Hormodendrum*. Two proteins Cla c 9 of 36 KD and Cla c 14 of 36.5 KD molecular weight have been identified as *Cladosporium cladosporioides* allergens. Cla c 9 is a vacuolar serine protease, and Cla c 14 is a transaldolase. Ten allergens have been identified in *Cladosporium herbarum*: Cla h 5 is an acid ribosomal protein P2, Cla h 6 is an enolase, Cla h 7 is a YCP4 protein, Cla h 8 is a mannitol dehydrogenase, and Cla h 9 is a vacuolar serine protease (Achatz et al. 1995; Pöll et al. 2009; Simon-Nobbe et al. 2006). The molecular identities of Cla h1, Cla h 2, Cla h 3, Cla h 10, and Cla h 12 remain unknown (Bowyer and Denning 2007; Kurup and Vijay 2008).

Epicoccum

Epicoccum purpurascens is a fungus which is a frequent sensitizer for allergies and asthma. It is an important outdoor mold and is considered a dry air spora. It is often found on dying substrates, including spoiled vegetables and fruits, compost, and even human skin or sputum. The allergens in *Epicoccum* have not been characterized (Lehrer 1983; Chapman and Williams 1984; Karlsson-Borgå et al. 1989; Guill 1984).

Fusarium

No allergens have been functionally characterized, but a few allergens of molecular weight 14, 19, 35, 45, 50, and 70 kD occur commonly among three *Fusarium* species: *F. solani*, *F. equiseti*, and *F. proliferatum* or *F. moniliforme* (Horner et al. 1995). *Fusarium* is a large genus with over 100 species (Verma and Gangal 1994; Pumhirun et al. 1997). It is a soil fungus that can be found on decaying plants and grains worldwide. Fusarium is a significant allergen and a trigger for asthma and allergic rhinitis (Mohovic et al. 1988; Enríquez et al. 1997). In addition, it is a known culprit for onychomycoses (Ninet et al. 2005).

Helminthosporium

A common mold found on cereals, grains, sugarcane, and soil is *Helminthosporium*. These spores are found worldwide and are considered a dry air spora, which release on dry days. In a study of 110 pediatric asthmatic and/or allergic rhinitis subjects in the Mid-Atlantic United States, 38% had positive skin testing to *Helminthosporium* (Hendrick et al. 1982; Al-Doory and Domson 1984). A common species is *H. halodes*. The allergens of *Helminthosporium* have not been characterized.

Mucor

Mucor is a large genus. *Mucor racemosus* was identified in soil samples nearly 140 years ago. It is found worldwide, growing on animal waste, decaying vegetables, and grains. It can be found at high elevations. *Mucor* are also found indoors and has been isolated from dust samples. It is a significant trigger of allergy symptoms (Mohovic et al. 1988; Dezfoulian and De la Brassinne 2006). The allergens of *Mucor* species have not yet been characterized.

Penicillium

Penicillium is of industrial importance in food and drug production. Penicillium represents the genus, and there are multiple varieties on the food staple, such as *P. herbarum*, *P notatum*, etc. The most well-known species is *P. chrysogenum* which produces penicillin, a molecule that is used as an antibiotic. Penicillia are ubiquitous soil fungi that prefer cool and moderate climates. *Penicillium* species can also be found in the air and dust of homes and public buildings. The following allergens have been identified from *P. chrysogenum*: Pen ch 13, a 32 kD protein is an alkaline serine protease (Lai et al. 2004); Pen ch 18, a 34 kD protein is a vacuolar serine protease (Shen et al. 2003); and Pen ch 20, a 68 kD protein is a N-acetylglucosaminidase (Shen et al. 1992).

Rhizopus

Rhizopus nigricans also known as bread mold is one of the more common *Rhizopus* species found worldwide. Its spores are released in hot, dry weather. It feeds on old food, decaying fruits and vegetables, and is also found in soil. Interestingly, it is also found in storage facilities and libraries (Zielińska-Jankiewicz et al. 2008). The spores contain allergenic proteins with 31 distinct allergens (Bush et al. 2006). However, no allergens have been characterized. In addition, a heat shock protein, Hsp70, has been isolated (Černila et al. 2003). *Rhizopus* is often blamed for occupational asthma in sawmills and food handlers of strawberries, peaches, corn, and peanuts (Zhang et al. 2005; O'Connell et al. 1995; Wimander and Belin 1980; Belin 1987; Belin 1980; Hedenstierna et al. 1986; Rydjord et al. 2007).

Stachybotrys

Stachybotrys chartarum and *S. alternans* is the black mold found in homes on substrates with a high cellulose content, such as Sheetrock, wood, and ceiling tiles. It is usually found in areas of high humidity. Contrary to folklore, there is no such thing as toxic black mold or any human disease that has been blamed on mycotoxins. Mycotoxins have to be ingested in large quantities to be harmful to humans. There is no good scientific evidence that demonstrates that airborne *Stachybotrys* causes any of the vague symptomatology associated with the so-called toxic mold syndrome or sick building syndrome (Rudert and Portnoy 2017). *Stachybotrys* species have not been shown to be a significant allergen.

Stemphylium

Stemphylium herbarum is a mold which is common in subtropical and temperate regions of the world. Other members of the genus *Stemphylium* include *S. solari* and *S. botryosum.* They grow on vegetables and plants and are thus a plant pathogen. They can be commonly found on tomatoes and decaying vegetations in forested areas. The allergens of *Stemphylium* have not been characterized, but it is known that they share cross-reactivity with *Alternaria*, *Curvularia*, and *Aspergillus* species (Agarwal et al. 1982; Schmechel et al. 2008; Schumacher et al. 1975; Wijnands et al. 2000; Bonilla-Soto et al. 1961). *Stemphylium* are known to be a significant inducer of asthma and allergy symptoms in sensitized individuals (Karlsson-Borgå et al. 1989; Prince et al. 1971). Angioedema has been reported from exposure to *Stemphylium* (Gaudibert 1971).

Ulocladium

Ulocladium chartarum is a mold that is related to *Alternaria* and is found in soil and on decaying vegetation. It is ubiquitous and can function as food spoilers or plant pathogens. It has been demonstrated to be a significant allergen in inner-city, low socioeconomic areas with high population density. Allergens of *Ulocladium* have not been characterized. Like *Fusarium*, *Ulocladium* has also been blamed for skin fungal infections (Hilmioğlu-Polat et al. 2005; Altmeyer and Schon 1981; Teresa Duran et al. 2003; Badenoch et al. 2006).

Phylum Zygomycota

There are approximately 1000 species within this phylum. The subphylum *Mucoromycota* is known for producing airborne sporangiospores.

3.4.2 Indoor Allergens

3.4.2.1 Dust Mites

Dust mites of the family Pyroglyphidae are microscopic bugs that feed on dead skin shed from animals, including humans. They are members of class Arachnida, which include spiders, and can be found in beddings, carpets, and upholstered furniture. They are also more abundant in humid climates, and certain species in particular thrive on high humidity. Dust mites require moisture in the air to propagate.

The major allergenic dust mites include *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Euroglyphus maynei*, and *Blomia tropicalis*. House dust mite allergy can trigger rhinitis, asthma, and even eczema (Miller 2018).

Dermatophagoides

In *Dermatophagoides pteronyssinus*, three allergens with protease activity have been identified. They are Der p 1, Der p 3, and Der p 6. Other *Dermatophagoides pteronyssinus* allergens with identified functions include Der p 4 (amylase), Der p 7 (a bactericidal permeability increasing like protein), Der p 8 (glutathione S-transferase), Der p 9 (collagenolytic serine protease), Der p 10 (tropomyosin), Der p 11 (paramyosin), Der p 14 (apolipophorin), and Der p 20 (arginine kinase). Der p 2 is a protein of the NPC2 family, and Der p 23 is identified as a peritrophin-like protein domain (Asturias et al. 1998; Caraballo et al. 1998; Lin et al. 1994; Lynch et al. 1997; Mills et al. 1999; Pittner et al. 2004; SHEN et al. 1996; Tsai et al. 2005).

Similar to *Dermatophagoides pteronyssinus,* there are three protease allergens in *Dermatophagoides farinae*. They are Der f 1, Der f 3, and Der f 6. Der f 2 is a protein of the NPC2 family. Der f 7, Der f 10, Der f 11, and Der f 14 are proteins with bactericidal permeability, tropomyosin, paramyosin, and apolipophorin, respectively. In addition, Der f 13 is a fatty acid-binding protein, Der f 15 is a chitinase, Der f 17 is a calcium-binding protein, and Der f 18 is a chitin-binding protein (Thomas 2015). Recently, a cofilin-related molecule has been identified as a novel *Dermatophagoides farinae* allergen Der f 31 (Lin et al. 2018). *Dermatophagoides farinae* seems to favor drier climates compared with *D. pteronyssinus*.

Dust mites may also play a role in sensitization in patients with atopic dermatitis or even eosinophilic esophagitis. The allergens of dust mite are found in the feces of dust mites. There are several important allergens, and they have been regrouped so that each group share common attributes between dust mite species.

Euroglyphus Maynei and Blomia Tropicalis

Euroglyphus maynei is found in areas of high moisture. These dust mites contain many individual allergens, but only a few have been fully characterized, including Eur m 1, which is a thiol cysteine protease; Eur m 3, a Group 3 allergen; and Eur m 4 or vitellogenin.

Blomia tropicalis is a storage mite that is found both in indoor environments and occupational setting in agricultural facilities. It is a mite that flourishes in tropical and subtropical climates, because of its requirement for moisture. *Blomia tropicalis* belongs to the family Glycyphagidae. Multiple allergens from *B. tropicalis* have been characterized. Blo t 1 is a homologue of the group 1 *Dermatophagoides* allergens, as is the case for Blo t 2 (Cheong et al. 2003a; Mora et al. 2003; Fonseca-Fonseca and Díaz 2003; Tsai et al. 2003). Blo t 3 is a trypsin-like protease (Flores et al. 2003; Cheong et al. 2003b; Yang et al. 2003), and Blo t 4 is an alpha-amylase. In total, there are over 30 allergens from *Blomia tropicalis*. Sensitization to *Blomia tropicalis* has been reported in North America, South America, and Asia, and it can be a significant trigger for asthma (Croce et al. 2000; Simpson et al. 2003; Fernandez-Caldas et al. 1993; Chew et al. 1999; Mariana et al. 2000; Fernández-Caldas et al., n.d.; Müsken et al. 2000; Arruda and Chapman 1992; Aranda et al. 2000; Montealegre et al. 1997; Rizzo et al. 1997).

3.4.2.2 Cockroach

Cockroach is one of the most common household pests worldwide. Cockroaches' allergen is an important cause of asthma. Two cockroach species, *Blattella germanica* and *Periplaneta americana*, are the focus of cockroach allergy research. *Blattella germanica* predominates in the temperate regions where the climate is cool and dry; *Periplaneta americana* predominates in the tropical areas where the climate is hot and humid.

Blattella germanica, also known as the German cockroach, usually infests unsanitary environment in restaurants and homes. German cockroaches are resistant to a broad range of pesticides. Currently, there are ten *Blattella germanica* allergens (Bla g 1, 2, 3, 4, 5, 6, 7, 8, 9, and 11) listed by the World Health Organization's International Union of Immunological Society as *Blattella germanica* allergens. Bla g 1 and Bla g 2 are used as markers to measure cockroach allergen exposure. Multiple *Blattella germanica* allergens have been defined at the molecular level. While Bla g 1 is a 46 kD protein of unidentified function, Bla g 2 is identified as a 36 kD inactive aspartic protease (Gustchina et al. 2005; Wunschmann et al. 2005), Bla g 3 is a 79 KD hemocyanin, Bla g 4 is a 21 kD lipocalin (Tan et al. 2009), Bla g 5 is a 23 kD glutathione S-transferase (Arruda et al. 1997; Jeong et al. 2008), Bla g 6 is a 17 kD troponin C (Hindley et al. 2006), Bla g 7 is a 33 kD protein tropomyosin (Jeong et al. 2003), Bla g 8 is myosin light chain (Hindley et al. 2006), Bla g 9 is a 40 kD arginine kinase, and Bla g 11 is a 57 kD alpha-amylase. (www.allergen.org).

Periplaneta americana, also known as the American cockroach, is not native to North America but is present worldwide. *Periplaneta americana* are most commonly found near food-processing and storage areas and sewers, particularly around pipes and drains. They spend most of their time in crevices for safety and feed on almost anything. To date, the *Periplaneta americana* allergens characterized include Per a 1, a 13–45 kD transmembrane protein (Schou et al. 1990); Per a 2, a 36 kD aspartic protease (Lee et al. 2012); Per a 3, a 72 or 78 kD a species-specific arylphorin (Wu et al. 2003); Per a 4, a

21 kD calycin (Tan et al. 2009); Per a 5, a glutathione-S-transferase homologue (Pan et al. 2006); Per a 6, a 18 kD calcium-binding protein (troponin) (Khantisitthiporn et al. 2007); Per a 7, a 33–37 kD tropomyosin (Yang et al. 2012); Per a 8, a myosin; Per a 9, a 43 kD arginine kinase (Tungtrongchitr 2009); Per a 10, a 28 kD serine protease (Sudha et al. 2008); Per a 11, a 55 kD alpha-amylase; and Per a 12, a 45 kD chitinase (Fang et al. 2015). Other *P. americana* allergens are Per a FABP, a fatty acid-binding protein; Per a trypsin, a trypsin; and Per a cathepsin.

3.4.2.3 Epithelial

Dog

The common species of dog is *Canis familiaris* and thus the allergen nomenclature of Can f 1. Dogs were the earliest domesticated animals and have been found in human households as early as 12,000 years ago. Can f 1 is a 25 kD lipocalin that is found in dog serum, dander, saliva, hair, and pelt. Dog dander is defined as the material shed into the environment from dog hair and dandruff. The dander itself consists of very small particles of less than or equal to 2.5 microns MAD. Therefore, dog dander, like cat dander, can be carried on clothing and spread very easily.

Contrary to popular belief, there is no such thing as a hypoallergenic dog. A study of Can f 1 levels in homes comparing those with hypoallergenic and non-hypoallergenic dogs showed no difference in levels. Similarly, characteristics of the breed such as those with “hair” versus “fur” also show no significant difference. The concept of the hypoallergenic pet is one that was introduced and perpetuated by dog breeders with limited to no knowledge of allergens.

Cat

The scientific name for cat is *Felis domesticus*. The major cat allergen is Fel d 1, and this accounts for allergic responses to cat in about 80% of cat allergic individuals (Leitermann and Ohman Jr 1984; Ohman et al. 1977). Cat allergen is very “sticky” and is carried on clothes, thus facilitating transfer into cat-free environments, including classrooms and homes without cats (Enberg et al. 1993). Clothing is a carrier of cat allergens (D’amato et al. 1997). Cat (Fel d 1), dog (Can f 1), and horse allergen can easily disperse in public environments over time (Egmar et al. 1998). Studies on cat allergen (Fel d 1) levels on school children’s clothing and in primary school classrooms in Wellington, New Zealand (Patchett et al. 1997), and others suggest that school can be a risky environment for children allergic to cats and a site for transfer of cat allergen to homes (Almqvist et al. 1999).

Fel d 1 is present in sebaceous glands, anal glands, and salivary and lacrimal glands of cats. It is a tetrameric glycoprotein of molecular weight 36 kD, consisting of two heterodimers of chain 1 and 2, which are encoded by the genes *CH1* and *CH2*. The function of Fel d 1 is unknown, although it shares homology with uteroglobin, which is a member of the secretoglobin super family (Kaiser et al. 2003).

Rabbit

The scientific name for rabbit is *Oryctolagus cuniculus*. Rabbit belongs to the family Leporidae. The two major allergens of rabbit are Ory c 1 and Ory c 2. These proteins are between 18 and 38 kD in molecular weight and belong to the lipocalin family of proteins. They are found in hair, saliva, urine, and dander. Serum albumin is another minor allergen (Bush et al. 1998; Wood 2001; Warner and Longbottom 1991; Price and Longbottom 1986; Price and PLongbottom 1988). Rabbit may be an important contributor to allergic symptoms in the homes where they are kept as pets or in an occupational setting such as in laboratories or pet stores. Rabbit allergy may cross-react with deer allergy, and allergy to rabbit meat has been reported, with some cross-reactivity to bovine.

Mouse

Native to Asia, house mice are now ubiquitous. They exist in all climates and are routinely found both indoors and out. They are also prevalent in fields and often can be detected in homes in new developments. Major allergens were found in mouse skin, serum, and urine. Mouse has been found to be a major allergen in inner city or urban environments with high population density. Sensitization to mouse allergens has been shown to be strongly associated with asthma outcomes (Ahluwalia et al. 2013). Two mouse allergens have been characterized. The major mouse allergen is Mus m 1, a prealbumin of 19 kD in molecular weight found in hair, dander, and urine (Lorusso et al. 1986). The other mouse allergen (Mus m 2) is a 16 kD glycoprotein found in hair and dander.

Rat

Rattus norvegicus is also known as the house rat, Norway rat, or brown rat. *Rattus norvegicus* has many relatives, and the major allergens, like other animals, tend to belong to the lipocalin class of molecules (Mäntyjärvi et al. 2000). Allergy to rat is a common cause of occupational allergies or asthma (Gordon et al. 1992; Thulin et al. 2002; Baur et al. 1998).

Guinea Pig

Guinea pigs (*Cavia porcellus*) are popular household pets and are also raised for meat in some countries. They belong to the family Caviidae. Guinea pig allergens are derived from their hair, dander, urine, saliva, and pelts. Five guinea pig allergens have been characterized to date, Cav p 1, Cav p 2, Cav p 3, and Cav p 6, and are identified as members of the lipocalin family, and Cav p 4 is serum albumin (Bush et al. 1998; Swanson et al. 1984; Fahlbusch et al. 2002).

Other Household Pets

None of the allergens from other household pets, such as gerbils or hampsters (*Cricetus cricetus*), have been characterized, but there have been reports of allergy to small animals (Berto et al. 2002; Horiguchi et al. 2000; McGivern et al. 1985; Muljono and Voorhorst 1978; Osuna et al. 1997).

Horse

Horses (*Equus caballus*) are domesticated animals. They are found in almost all regions of the world. Previously serving as a means of transportation, they are now more widely used for entertainment, recreation, and/or sport. Allergens are found in horse dander and horse serum protein. The allergens of horses are primarily glycoproteins. Equ c 1, Equ c 2, and Equ c 4 are lipocalin proteins of 25 kD, 17 kD, and 18.7 kD, respectively (Mäntyjärvi et al. 2000; Botros et al. 2001), and Equ c 3 is a 67 kD serum albumin (Botros et al. 1998).

Cattle

Domestic cattle (*Bos domesticus*, *Bos taurus*) is composed of many breeds and is the source of domestic beef and dairy cattle worldwide. Cattle allergy is mostly reported in cattle farmers or veterinarians due to occupational exposure. Early studies determined cow hair and dander as the source of allergens. Lipocalins (Bos d 1 and Bos d 2) are considered the major allergens (Mäntyjärvi et al. 1996). Other allergens present in cow hair and dander extracts include the Ca-binding s-100 homologue Bos d 2 (11 kD), alpha-lactalbumin (14 kD), Bos d 5 beta-lactoglobulin (18 kD), serum albumin Bos d 6 (67 kD), and IgG Bos d 7 (160 kD). Bods d 8, Bos d 9, Bos d 10, Bos d 11 and Bos d 12 are caseins (20–30 kD) (Bernard et al. 1998; Zahradnik et al. 2015). Cow allergens may cross-react with deer allergens (Spitzauer et al. 1997). There is about a 20% chance of cross-reactivity between cow dander allergens and cows' milk allergens (Valero Santiago et al. 1997).

Sheep

Sheep are used for their fur in the production of wool clothing. Cheese can be produced from sheep's milk. There are no characterized allergens from sheep.

3.4.2.4 Feathers

Chickens

The scientific name for chicken is *Gallus domesticus*. However, the allergens that are named for this species, namely, Gal D x, are generally representative of hen's egg allergy. Chickens are bred almost worldwide for food. The allergens of chicken (not hen's egg) have not been characterized, but proteins between 20–30 kD in size and 67 kD have been identified through IgE immunoblots (Tauer-Reich et al. 1994). There does appear to be some cross-reactivity between chicken and other fowl and bird species including duck, goose, parrot, and others. There also seems to be some cross-reactivity between allergens in chicken feathers and hen's egg. It is the levitins that provide this cross-reactivity (de Blay et al. 1994; Mandallaz et al. 1988; Nevot Falco and Casas Ramisa 2003).

Duck and Goose

While no allergens have been characterized, there is likely some allergenic cross-reactivity among bird species. The Latin name for duck is *Anas platyrhyncha* and that for goose is *Anser anser*.

Canary

The scientific name of canary is *Serinus canarius*. Canaries, parrots, and budgerigars may contain similar proteins that cross-react with other bird species including chicken, duck, and goose (Tauer-Reich et al. 1994).

3.5 Food Allergens

The allergens in grains, egg, milk, and coffee are summarized in Table 1.

3.5.1 Grains

3.5.1.1 Rice

The genus *Oryza* contains about 20 rice species that grow in shallow water, swamps, and marshes. *O. sativa*, also known as the Asian rice, is one of the most important food crops cultivated worldwide, which constitutes a major dietary portion of half of the world population. Asthma, rhinitis, conjunctivitis, atopic dermatitis, and anaphylaxis due to the ingestion of rice or inhaling boiling rice vapors have been reported (Orhan and Sekerel 2003). The rice allergens that have been identified are Ory s LTP, a 14 kD lipid transfer protein (Poznanski et al. 1999; Enrique et al. 2005; Asero et al. 2007; Asero et al. 2002; Asero et al. 2001a); Ory s aA/TI, a 16 kD alpha-amylase/trypsin inhibitor (Izumi et al. 1999; Adachi et al. 1993; Alvarez et al. 1995a; b; Izumi et al. 1992; Nakase et al. 1996; Nakase et al. 1998; Tada et al. 1996; Yamada et al. 2006); Ory s Glyoxalase I, a glyoxalase (Enrique et al. 2005; Usui et al. 2001; Kato et al. 2000; Urisu et al. 1991); and Ory s 12, a profilin (van Ree et al. 1992). In addition, Ory s 1 (beta-expansin), Ory s 2, Ory s 3, Ory s 7, Ory s 11, Ory s 12, and Ory s 13 have been characterized in rice pollen and contribute to asthma, allergic rhinitis, and allergic conjunctivitis as a result from exposure to rice pollen. Ory s 12, a profilin, has been detected in both rice seed and rice pollen. There is some evidence that buckwheat may cross-react with rice.

3.5.1.2 Rye

Rye (*Secale cereale*) is a cereal grain grown primarily in Central, Eastern, and Northern Europe. It is also grown in North and South America, Australia, New Zealand, and Northern China. Like wheat and barley, rye contains gluten; thus people who have gluten related disorders should avoid rye consumption. The allergens isolated include Sec c 12, a profilin (van Ree et al. 1992); Sec c 20, a secalin (Rocher et al. 1996); and Sec c a A TI (renamed as Sec c 38), a 13.5 kD alpha-amylases/trypsin inhibitor (García-Casado et al. 1995; García-Casado et al. 1994). Sec c 1, Sec c 2, Sec c 4, Sec c 5, Sec c 12, and Sec c 13 are additional allergens that have been characterized. Some of these pollens are present in both rye pollen and rye seed. The panallergen profilin is heat labile, and Sec c 12 has been identified to be a profilin.

3.5.1.3 Oat

Although the allergens of oats have not been characterized, the allergic symptoms of oats, including atopic dermatitis, result from exposure to the seed storage protein (Varjonen et al. 1995). Oat contains gluten-like allergens, but these allergens including alpha 2, gamma 3, and gamma 4 avenins generally do not cause significant symptoms in patients with celiac disease (Hallert et al. 1999). Oat cross-reacts with grass pollen allergens, as well as other grains such as maize, rice,

Table 1 Allergens in grains, milk, eggs, and coffee

Identified function/ family	Allergen name
Lipid transfer protein	Ory s LTP (rice) Tri a 14 (wheat) Hor v LTP (barley)
Alpha-amylase/trypsin inhibitor	Ory s aA/TI (rice) Sec c a A TI (renamed as sec c 38) (rye) Tri a aA/TI (wheat)
Glyoxalase	Ory s Glyoxalase I (rice)
Profilin	Ory s 12 (rice) Sec c 12 (rye) Tri a 12 (wheat) Hor v 12 (barley)
Beta-expansin	Ory s 1 (rice) Sec c 1 (rye)
Secalin	Sec c 20 (rye)
Group 5 grass pollen allergen	Sec c 5 (rye)
Avenins	Alpha 2 (oat) Alpha 3 (oat) Alpha 4 (oat)
Hevein-like protein	Tri a 18 (wheat)
Chitinase	Tri a chitinase (wheat)
Thioredoxin	Tri a 25 (wheat)
Gluten	Tri a gluten (wheat) Tri a 26 (wheat) Tri a LMW Glu (wheat)
Peroxidase	Tri a Bd3 6 K (wheat) Tri a peroxidase (wheat)
Germin	Tri a germin (wheat)
Triosephosphate isomerase	Tri a TPIS (wheat)
Alpha-amylase	Hor v 15 (barley) Hor v 16 (barley)
Beta-amylase	Hor v 17 (barley)
Hordein	Hor v 20 (barley) Hor v 21 (barley)
Expansin	Hor v 1 (barley)
Alpha-lactalbumin	Bos d 4 (cow's milk)
Beta-lactoglobulin	Bos d 5 (cow's milk)
Bovine serum albumin	Bos d 6 (cow's milk)
Immunoglobulin	Bos d 7 (cow's milk)
Casein	Bos d 8 (cow's milk)
Ovomucoid	Gal d 1 (eggs)
Ovalbumin	Gal d 2 (eggs)
Ovotransferrin	Gal d 3 (eggs)
Lysozyme	Gal d 4 (eggs)
Serum albumin	Gal d 5 (eggs)
YGP42 protein	Gal d 6 (eggs)
Chitinase	Cof a 1 (coffee)

(*continued*)

Table 1 (continued)

Identified function/ family	Allergen name
Cysteine-rich metallothionein	Cof a 2 (coffee) Cof a 3 (coffee)
Gliadin	Tri a alpha-beta-gliadin (wheat) Tri a alpha-gliadin (wheat) Tri a beta-gliadin (wheat) Tri a gamma-gliadin (wheat) Tri a omega-2 gliadin (wheat)
Lactoferrin	Bos d Lactoferrin (cow's milk)
Lactoperoxidase	Bos d lactoperoxidase (cow's milk)
Undefined function	Ory s 2 (rice) Ory s 3 (rice) Ory s 7 (rice) Ory s 11 (rice) Ory s 13 (rice) Sec c 2 (rye) Sec c 4 (rye) Sec c 13 (rye) Tri a Bd 17 K (wheat) Hor v Z4 (barley) Hor v 2 (barley) Hor v 4 (barley) Hor v 5 (barley) Hor v 13 (barley)

and barley. Oat allergens have also been reported to be a common solid food cause of food protein-induced enterocolitis syndrome (FPIES) (Nowak-Wegrzyn et al. 2003; Sicherer 2005).

3.5.1.4 Wheat

Wheat is a staple food crop for many populations worldwide. *Triticum aestivum* is the most commonly cultivated wheat variety for human consumption. Wheat is an important source of carbohydrates, essential amino acids, and dietary fiber. However, because wheat is rich in gluten, it can also trigger celiac disease in susceptible individuals. To this date, there are 19 wheat allergens which have been identified and characterized. Among these, Tri a 12 is a profilin (Thulin et al. 2002), Tri a 14 is a lipid transfer protein and (Horiguchi et al. 2000), and Tri a 18 is a hevein-like protein (Weichel et al. 2006). Other common wheat allergens include Tri a Gluten (Morita et al. 2003), Tri a Chitinase, a chitinase (Diaz-Perales et al. 1999), Tri a Bd

17 K (Kimoto 1998), Tri a 25, a thioredoxin (Brant 2007), Tri a 26, a glutenin, Tri a aA/TI, an alpha-amylase/trypsin inhibitor (Buonocore et al. 1985), Tri a Bd3 6 K is a peroxidase (Yamashita et al. 2002), Tri a LMW Glu, a glutenin (Morita et al. 2003), Tri a Germin, a germin (Jensen-Jarolim et al. 2002), Tri a Peroxidase, a peroxidase (Watanabe et al. 2001), and Tri a TPIS, a triosephosphate isom-erase (Rozynek et al. 2002). Other allergens include Tri a alpha-beta-gliadin (Bittner et al. 2008), Tri a alpha-gliadin (Sandiford et al. 1997), Tri a beta-gliadin (Sandiford et al. 1997), Tri a gamma-gliadin (Sandiford et al. 1997), and Tri a omega-2 gliadin (Sandiford et al. 1997). Wheat is a common cause of food-dependent exercise-induced anaphylaxis (Fiedler et al. 2002). Occupationally, wheat allergens are a cause of Baker's asthma (Sander et al. 1998; De Zotti et al. 1994; Prichard et al. 1984; Valero Santiago et al. 1988).

3.5.1.5 Barley

Barley (*Hordeum vulgare*) is a major cereal grain grown in temperate climates. Like wheat and rye, barley contains gluten which makes it an unsuitable grain for consumption by people with gluten sensitivity. Multiple allergens for barley have been characterized: Hor v 15, a 16 kD protein (Armentia et al. 1993); Hor v 16 is an alpha-amylase (Perrocheau et al. 2005); Hor v 17 is a beta-amylase; Hor v 20 and Hor v 21 function as hordein, a form of storage protein (Palosuo et al. 2001); Hor v LTP, a 10 kD protein, a lipid transfer protein (Palosuo et al. 2001); and Hor v Z4, a 45 kDa protein (Palosuo et al. 2001). A few other allergens have been reported from Barley pollen as well. These include Hor v 1, which is an expansin, Hor v 2, Hor v 4, Hor v 5, Hor v 12, and Hor v 13. Group 2, 4, and 5 allergens show cross-reactivity to grasses (Nandy et al. 2005).

3.5.2 Milk

3.5.2.1 Cow's Milk

Cow's milk is the most consumed form of milk in the Western world. Cow's milk is one of the more common allergens worldwide. Aside from cattle, the other livestock also provides milk for human consumption, with goat and sheep milk being the second and third most commonly consumed. Cow's milk allergy usually presents early on in life, but many with cow's milk allergy will outgrow their allergy by adolescence. Cow's milk is one of those allergens that has been associated with food protein-induced enterocolitis syndrome. There is a slight (10%) chance of cross-reactivity to beef.

Cow's milk contains 30–35 grams of protein per liter, with 80% bound in the form of casein micelles. Besides casein, milk contains other proteins, which are more soluble than casein and are collectively known as whey proteins. However, whey proteins are not so easily digested in the intestine. Cow's milk has a higher casein/whey ratio than human milk. Lactoglobulin and lactalbumin are the most common whey proteins. Milk also contains several carbohydrates. Lactose intolerance can also cause symptoms that mimic cow's milk allergy.

Seven allergens have been characterized to date. Bos d 4 is an alpha-lactalbumin (Wal 2002), and Bos d 5 is a beta-lactoglobulin (Wal 2002). Bos d 6, a 67 kD protein, is a bovine serum albumin, also present in dander, muscle, and serum (Wal 2002). Bos d 7 is an immunoglobulin (Ayuso et al. 2000), Bos d 8 is a casein (Wal 2002), and two other allergens, Bos d lactoferrin (Wal 2002) and Bos d lactoperoxidase (Indyk et al. 2006), have been identified.

3.5.2.2 Sheep's Milk

The milk of sheep and other animals can cross-react with cow's milk. Clinically, respiratory symptoms have been reported in patients sensitized to sheep's milk (Vargiu et al. 1994).

3.5.2.3 Goat's Milk

There appears to be cross-reactivity between cow's and goat's milk. However, data on this is limited (Bernard et al. 1992). In one study, about 88% of cow's milk allergic patients also had IgE to goat milk (Dean et al. 1993). The cross-reactivity between the milk of these two species appears to be due to homology in the serum albumin and casein sequences of the two species (Spuergin et al. 1997).

3.5.3 Eggs

After cow's milk, hen's egg allergy is the second most common food allergy in infants and young children in many countries, though regional difference may exist (Caubet and Wang 2011). Eggs from chickens or hens weigh anywhere from 30 to 90 grams. About 10% of the weight is in the shell. Much of the weight of the egg white is from protein. Egg allergy can develop in response to proteins in egg whites or yolks. People with allergic reactions to chicken eggs may also be allergic to other types of eggs, such as goose, duck, turkey, or quail. Egg allergy may be defined as an adverse reaction of immunological nature induced by egg proteins and includes IgE antibody-mediated allergy as well as other allergic syndromes such as atopic dermatitis and eosinophilic esophagitis. Six allergenic proteins from the egg of the domestic chicken (*Gallus domesticus*) have been identified (Heine et al. 2006). Ovomucoid (Gal d 1, 11%), ovalbumin (Gal d 2, 54%), ovotransferrin (Gal d 3, 12%), and lysozyme (Gal d 4, 3.4%) (Bernhisel-Broadbent et al. 1994) are from the egg white. Serum albumin (Gal d 5) (Quirce et al. 2001) and YGP42 protein (Gal d 6) (Amo et al. 2010), a fragment of the vitellogenin-1 precursor, are from the egg yolk.

Although ovalbumin (OVA) is the most abundant protein comprising hen's egg white, ovomucoid (OVM) has been shown to be the dominant allergen in egg (Caubet and Wang 2011; Miller and Campbell 1950; Bleumink and Young 1971; Cooke and Sampson 1997). Ovomucoid is heat stable and therefore is not denatured by baking. Thus, patients who can tolerate baked egg products, but not baked milk products, are more likely to be allergic to ovalbumin rather than ovomucoid.

3.5.4 Fruits

The allergens in fruits are summarized in Table 2.

3.5.4.1 Citrus

Citrus allergy was thought to be much more common in the past. It is possible that in the past, its acidic nature led to more of an irritant dermatitis rather than a true allergy. However, there are still some people who develop allergy to citrus. Cross-reactivity among fruits is based on similarities in amino acid sequence and secondary and tertiary structures. Molecules that serve common functions across the different fruits are likely to be cross-reactive (Table 1).

3.5.4.2 Orange

The scientific name for orange is *Citrus sinensis*. Three orange allergens have been identified at the biochemical level. Cit s 2 is a natural profilin. An unexpectedly high reactivity to Cit s 2 was found in vivo (78% of positive SPT responses) and in vitro (87% of sera from orange-allergic patients had specific IgE to Cit s 2). The purified allergen inhibited around 50% of the IgE binding to an orange pulp extract (Lopez-Torrejon et al. 2005). Cit s 1 is a germin-like glycoprotein. Specific IgE to Cit s 1 was detected in 62% of 29 individual sera from orange-allergic patients, whereas positive SPT responses to the purified allergen were obtained in only 10% of such patients. Deglycosylation of Cit s 1 resulted in a loss of its IgE-binding capacity indicating carbohydrate is involved in its IgE epitope (Ahrazem et al. 2006). Cit s 3 is identified as a non-specific lipid transfer protein (Ahrazem et al. 2005), and recently the gibberellin-regulated protein has been reported as a novel orange allergen. Twelve of 14 subjects with orange allergy were positive by either ELISA, basophil activation tests, or skin prick tests (Inomata et al. 2018).

3.5.4.3 Lemon

Lemon (*Citrus limon*) is commonly grown for culinary and non-culinary purposes in households and also commercially. Cit l 1 is a germin-like protein (Pignataro et al. 2010). The N-terminal sequence of the lemon allergen (nCit l 3) is identical to the orange allergen Cit s 3 in 18 out of 20 amino acids, with lipid transfer protein characteristics and approximately 9.6 kD in molecular weight (Ahrazem et al. 2005).

Table 2 Allergens in fruits

Identified function/family	Allergen name
Lipid transfer protein	Cit s 3 (orange) nCit l 3 (lemon) Fra a 3 (strawberry) Pru av. 3 (cherries) Rub i 3 (raspberry)
Profilin	Cit s 2 (orange) Fra a 4 (strawberry) Pru av. 4 (cherries) Cit la 2 (watermelon) Cuc m 2 (melon)
Triosephosphate isomerase	Cit la TPI (watermelon)
Germin-like glycoprotein	Cit s 1 (orange)
Germin-like protein	Cit l 1 (lemon)
Bet v 1 homologue	Fra a 1 (strawberry) Pru av. 1 (cherries) Rub i 1 (raspberry)
Thaumatin-like protein	Pru av. 2 (cherries)
Malate dehydrogenase	Cit la MDH (watermelon)
Plant serine protease	Cuc m 1 (melon)
PR1 protein	Cuc m 3 (melon)

3.5.4.4 Grapefruit

The scientific name of grapefruit is *Citrus paradisi*, and it belongs to the family Rutaceae. Specific IgE reactivity to grapefruit has been detected in patients with atopic dermatitis, allergic rhinitis, bronchial asthma, and even food-dependent exercise-induced anaphylaxis (Matsumoto et al. 2009). However, the molecular identities of grapefruit allergens are unknown.

3.5.5 Berries

Berries include a variety of popular fruits such as strawberries, cherries, raspberries, blackberries, and blueberries. They are commonly used in cakes, shakes, and juices.

3.5.5.1 Strawberry

Strawberry (*Fragaria ananassa*) is a perennial herbaceous plant of the family Rosaceae, characterized by the distinct shape of its leaves, white flowers, and also by its fruits. "Strawberry" is not a true berry but a fleshy receptacle with multiple one-seeded fruits that do not split open when ripen. Strawberry is a common allergen in children (Eriksson et al. 2004; Zuidmeer et al. 2008). Three allergenic proteins have been identified. Fra a 1 is a Bet v 1 homologue with molecular weight 18 kD (Karlsson et al. 2004), Fra a 3 is a lipid transfer protein of 9 kD (Yubero-Serrano et al. 2003), and Fra a 4 is a profilin of 13 kD (Zuidmeer et al. 2006).

3.5.5.2 Cherry

The scientific name of cherry is *Prunus avium*. Cherry is a fast-growing deciduous tree of the family Rosaceae. The cherry plant is not self-fertilizing. Oral allergy syndrome and urticaria are common allergic reactions to cherries (Asero 1999; Pastorello et al. 1994). Four cherry allergens have been characterized. Pru av. 1 is a 18 kD Bet v 1-homologue, Pru av. 2 is a thaumatin-like protein of 23.3–29 kD (Inschlag et al. 1998), Pru av. 3 is a 15 kD lipid transfer protein, and Pru av. 4 is a profilin of 15 kD molecular weight (Wiche et al. 2005).

3.5.5.3 Raspberry

The scientific name of raspberry is *Rubus idaeus*. It is a member of the Rosaceae family. Allergens from raspberry include Rub i 1, a Bet v 1 homologue, and Rub i 3, a lipid transfer protein (Marzban et al. 2008), both isolated from the red raspberry, *Rubus idaeus*. In addition, two other IgE-reactive raspberry proteins, a chitinase and a cyclophilin, have also been identified (Marzban et al. 2008). Besides the allergens isolated and/or characterized, raspberry also appears to contain high-molecular-weight proteins which appear to be allergenic (Marzban et al. 2005). Occupational asthma due to raspberry has also been reported (Sherson et al. 2003). Raspberry cross-reacts with other berries in the genus *Rubus*.

3.5.5.4 Blackberry

The scientific name of Blackberry is *Rubus fruticosus*. It is in the family Rosaceae. Blackberries grow in the wild and are invasive, and they are protected by their thorny branches. To date, there is no blackberry allergens identified at the biochemical level, but a Mal d 1 homologue has been reported from blackberry (Marzban et al. 2005). As mentioned above, there is extensive cross-reactivity within the *Rubus* genus.

3.5.5.5 Blueberry

The scientific name of blueberry is *Vaccinium myrtillus*, and it belongs to the family Ericaceae.

Blueberry has been shown to contain a lipid transfer protein, but no blueberry allergens have been characterized. Blueberry cross-reacts with other plants as its lipid transfer protein shows homology with many of the stone fruits. Another member of the *Vaccinium* genus is cranberry (*Vaccinium oxycoccos*).

3.5.6 Melons

3.5.6.1 Watermelon

The scientific name of watermelon is *Citrullus lanatus*. Watermelon belongs to the family Cucurbitaceae. Allergic reactions to watermelon are commonly presented as oral allergy syndrome. Three allergenic proteins have been defined: they are Cit la 2, a 13 kD protein which is a profilin; Cit la MDH, a malate dehydrogenase; and Cit la TPI, a triosephosphate isomerase (Pastor et al. 2009). Although watermelon is largely composed of water and the protein content is rather low, individuals sensitized to profilins can be allergic to watermelons.

Other melons (honeydew, cantaloupe, winter melon) are a diverse group of fruits with varying sizes, colors, and flavors. They belong to the family Cucurbitaceae and genus *Cucumis*. A number of allergens have been characterized from *Cucumis melo*, including Cuc m 1, a plant serine protease (Cuesta-Herranz et al. 2003); Cuc m 2 (López-Torrejón et al. 2005), a profilin of molecular weight 13 kD; and the 16 kD molecular weight Cuc m 3, which is a PR1 protein (Asensio et al. 2004). In addition, Cuc m LTP is a lipid transfer protein. Melons are often considered a culprit in oral allergy syndrome, with cross-reactivity to Bet v 2, the birch tree profilin (Asero et al. 2003).

3.5.7 Tree Nuts

Among foods causing allergic reactions in children, tree nuts (i.e., walnut, hazelnut, Brazil nut, pecan) have attracted considerable attention for several reasons. Allergies to these foods are common and account for severe and potentially fatal allergic reactions (Sicherer and Sampson 2000). The many allergens in tree nuts can be categorized based on their function (Table 3).

3.5.7.1 Almond

Almonds are fruits of the almond tree (*Prunus amygdalus)* with two major varieties: the sweet (*Prunus amygdalus* var. *dulcis*) and the bitter (*Prunus amygdalus* var. *amara*) almonds. Bitter almond is not approved for sale in the United States because it contains amygdalin, which is toxic.

Almonds are widely consumed as a food item and are also processed for their oil content. The almond fruit measures about 4 cm in length and is an important ingredient in many cuisines around the world. Allergens characterized to date include Pru du 3, Pru du 4 which is a profilin (Sathe et al. 2002), Pru du 5 which is an acidic ribosomal protein (van Ree et al. 1992), and Pru du 6. The 2S albumin Pru du 2S albumin cross-reacts with many other nuts, including Ara h 2 from peanut.

3.5.7.2 Brazil Nut

The Brazil nut is the seed of the *Bertholletia excelsa* tree that primarily grows in South America's Amazon forest, along the banks of Amazon River. Allergic reactions including anaphylaxis to Brazil nuts have been reported (Arshad et al. 1991; Senna et al. 2005). Characterized allergenic proteins of Brazil nut include Ber e 1 which is a 9 kD 2S storage albumin and is resistant to digestion by pepsin (Alcocer et al. 2002) and Ber e 2 which is a 11S globulin seed storage protein (Guo et al. 2007).

3.5.7.3 Cashew

The cashew nut is harvested from the cashew nut tree (*Anacardium occidentale*). Cashew tree belongs to the Anacardiaceae family. Cashew nuts are consumed popularly as roasted snacks and are also an important ingredient in baked goods. Allergens include Ana o 1 which is a 7S vicilin-like protein (Teuber et al. 2002); Ana o 2 which is a legumin-like protein of molecular

Table 3 Allergens in tree nuts

Identified function/family	Allergen name
Profilin	Pru du 4 (almond) Cor a 2 (hazelnut) Jug r 7 (walnut) Ana o (cashew)
Bet v 1 homologue	Cor a 1 (hazelnut)
Acidic ribosomal protein	Pru du 5 (almond)
Storage albumin	Ber e 1 (Brazil nut)
Globulin seed storage protein	Ber a 2 (Brazil nut) Cor a 9 (hazelnut)
Vicilin-like protein	Ana o 1 (cashew) Car i 2 (pecan) Pis v 3 (pistachio) Cor a 11 (hazelnut) Jug r 2 (walnut) Jug r 6 (walnut)
Legumin-like protein	Ana o 2 (cashew)
2S albumin	Pru du 2S albumin (almond) Ana o 3 (cashew) Cor a 14 (hazelnut) Pis v 1 (pistachio) Car i 1 (pecan) Jug r 1 (walnut)
Isoflavone reductase homologue	Cor a 6 (hazelnut)
Luminal binding protein	Cor a 10 (hazelnut)
Oleosin	Cor a 12 (hazelnut) Cor a 13 (hazelnut)
Legumin seed storage protein	Car i 3 (pecan)
11S globulin subunit	Pis v 2 (pistachio) Pis v 5 (pistachio) Jug r 4 (walnut) Pru du 6 (almond)
Magnesium superoxide dismutase	Pis v 4 (pistachio)
Non-specific lipid transfer protein	Cor a 8 (hazelnut) Jug r 3 (walnut) Jug r 8 (walnut) Pru du 3 (almond)
PR-10	Jug r 5 (walnut)

weight 33 kD (Garcia et al. 2000); Ana o 3, a 12.6 kD 2S albumin (Robotham et al. 2005); and Ana o profilin. Cashew shows cross-reactivity primarily with pistachio, but the IgE epitopes of the vicilin allergen of many nuts are structurally similar.

3.5.7.4 Hazelnut

Hazelnuts belong to the Betulaceae or Corylaceae family. The scientific name of hazelnut is *Corylus avellana*. They grow in clusters on hazel trees which are found primarily in temperate zones of the world, such as in much of Europe. Hazelnuts are an important ingredient in a variety of dessert preparations around the world. Characterized allergens include Cor a 1 which is a 17 kD protein and a Bet v 1 homologue (Hirschwehr et al. 1992), Cor a 2 which is a profiling of molecular weight 14 kD (Hirschwehr et al. 1992), Cor a 6 which is a isoflavone reductase homologue, Cor a 8 which is a non-specific lipid transfer protein of molecular weight 9.4 kD (Pastorello et al. 2002), Cor a 9 which is a 40 kD 11S storage globulin (Beyer et al. 2002), Cor a 10 which is a 70 kD luminal binding protein, and Cor a 11 which is a 48 kD 7S vicilin-like seed storage globulin (Hansen et al. 2009). Cor a 12 and Cor a 13 are oleosins (Akkerdaas et al. 2006), and Cor a 14 is a 2S albumin (Masthoff et al. 2013). The latter three all range from 13 to 17 kD in size.

3.5.7.5 Pecan

The pecan tree (*Carya illinoinensis*) is an important source of timber and also known for its edible nuts. They are native to southern and southeastern North America. Pecan allergens characterized to date include Car i 1 which is a 16 kD 2S seed storage albumin (Barre et al. 2005; Jacquenet and Moneret-Vautrin 2007), Car i 2 which is a 55 kD vicilin-like protein, and Car i 3 which is a legumin seed storage protein. Pecan is closely related to walnut and hickory.

3.5.7.6 Pistachio

Pistachios nuts are green, edible seeds from pistachio trees *(Pistacia vera*). Pistachio nuts are widely used in ice creams and cakes or eaten as a roasted snack. Pistachio is in the cashew family of nuts. Although pistachio allergy is not so common, hypersensitive reactions to pistachio are similar to other nut allergies, and cases of food-dependent exercise-induced anaphylaxis to pistachio have been reported (Porcel et al. 2006). Allergens characterized to date include Pis v 1 which is a 2S albumin (Jacquenet and Moneret-Vautrin 2007; DÍaz-Perales et al. 2000), Pis v 2 which is a

11S globulin subunit, Pis v 3 which is a vicilin-like protein, Pis v 4 which is a magnesium superoxide dismutase, and Pis v 5 which is also a 11S globulin subunit.

3.5.7.7 Walnut

Walnuts are in the family Juglandaceae. Walnut is cultivated for its rich oil content that is used in pastas or salads. It is also consumed as a roasted snack. Allergens characterized for English walnut (*Juglans regia*) to date include Jug r 1 which is a 15–16 kD 2S albumin seed storage protein (Roux et al. 2003); Jug r 2 which is a 44–48 kD vicilin seed storage protein (Barre et al. 2005); Jug r 3 which is a 9 kD non-specific lipid transfer protein (Roux et al. 2003); Jug r 4 which is a 11S globulin seed storage protein (Wallowitz et al. 2006); Jug r 5, Jug r 6, and Jug r 7 which are a profilin (Wallowitz et al. 2006), and Jug r 8 which is also a 9 kD non-specific lipid transfer protein.

3.5.8 Vegetables

3.5.8.1 Legumes

IgE-binding proteins have been identified in the majority of legumes. Overall, allergenicity due to consumption of legumes in decreasing order may be peanut, soybean, lentil, chickpea, pea, mung bean, and red gram (Verma et al. 2013b).

3.5.8.2 Peanut

Peanut (*Arachis hypogaea*) is a member of the Fabaceae family. They grow close to the ground, and their fruits are produced underground. In the United States, peanuts are mainly consumed after being processed as peanut butter. However, they are also widely consumed as a snack or used as an ingredient in baked goods. There are 17 peanut allergens that have been characterized. These include Ara h 1, a 64 kD protein vicilin seed storage protein (Burks et al. 1991); Ara h 2, a 17 kD protein conglutin seed storage protein and a trypsin inhibitor (Burks et al. 1998); Ara h 3, a 60 kD protein and a 11S globulin seed storage protein (Burks et al. 1998); Ara h 4 (Boldt et al. 2005); and Ara h 5, a 15 kD protein and a profilin (Kleber-Janke et al. 1999). Ara h 6 and Ara h 7 are both 2S albumin and heat- and digestion-stable proteins (Kleber-Janke et al. 1999). Ara h 8 is a 17 kD protein that found to be a Bet v 1-homologous allergen (Mittag et al. 2004). Other characterized peanut allergens include non-specific lipid transfer proteins (Ara h 9 (Asero et al. 2000), Ara h 16, and Ara h 17), oleosins (Pons et al. 2002) (Ara h 10, Ara h 11, Ara h 14, and Ara h 15), and defensins (Ara h 12 and Ara h 13).

3.5.8.3 Soybean

Soybean is one of the world's most important legumes because of its wide use as a source of animal and human nutrition. It can be used fresh and processed into soybean flour, into oil, or into soy milk. The scientific name of soybean is *Glycine max*. A number of soybean allergens have been characterized. Major allergens of soybean include Gly m 1, a lipid transfer protein; Gly m 2 (Helm et al. 1998); Gly m 3, a profilin (Ogawa et al. 1991); Gly m 4, a bet v 1 homologue (Ogawa et al. 1991); Gly m 5, a 7S globulin or vicilin; Gly m 6, an 11S globulin called legumin (Natarajan et al. 2006); Gly m 7; and Gly m 8, a 2S albumin (Inomata et al. 2007).

3.5.8.4 Sesame

The scientific name of sesame is *Sesamum indicum*. Technically not a legume, sesame contains several allergens, including Ses i 1, Ses i 2, Ses i 3, Ses i 4, Ses i 5, Ses i 6, and Ses i 7. Ses i 1 is a 2S albumin and is heat stable and digestion. Ses i 3 is a vicilin-type globulin which is also a seed storage protein and is a major allergen. Another seed storage protein is Ses i 2, which is also a 2S albumin.

3.5.9 Leafy Green Vegetables

The allergens in vegetables are summarized in Table 4.

3.5.9.1 Spinach

Spinach is *Spinacia oleracea*, a member of the Chenopodiaceae family. Native to the Middle

Table 4 Allergens in vegetables

Identified function/family	Allergen name
Lipid transfer protein	Ara h 9 (peanut) Ara h 16 (peanut) Ara h 17 (peanut) Gly m 1 (soybean) Bro o 3 (cabbage) Lac s 1 (lettuce) Dau c 3 (carrot) Lyc e 3 (tomato) Broccoli (no allergens specified)
Profilin	Ara h 5 (peanut) Gly m 3 (soybean) Spi o 2 (spinach) Dau c 4 (carrot) Sol t 8 (potatoes) Lyc e 1 (tomato) Cap a 2 (chili pepper)
Chitinase	Lyc e chitinase (tomato)
Peroxidase	Lyc e peroxidase (tomato)
Bet v 1 homologue	Ara h 8 (peanut) Gly m 4 (soybean) Dau c 1 (carrot)
Thaumatin-like protein	Cap a 1 (chili pepper)
2S albumin	Ara h 6 (peanut) Ara h 7 (peanut) Gly m 8 (soybean) Ses i 1 (sesame) Ses i 2 (sesame)
Vicilin-like seed storage globulin	Ses i 3 (sesame) Ara h 1 (peanut)
11S globulin subunit	Ara h 3 (peanut) Gly m 6 (soybean) Ses i 6 (sesame) Ses i 7 (sesame)
Protein conglutin seed storage protein	Ara h 2 (peanut)
Trypsin inhibitor	Ara h 2 (peanut)
Heat- and digestion-stable protein	Ara h 6 (peanut) Ara h 7 (peanut)
Oleosin	Ara h 10 (peanut) Ara h 11 (peanut) Ara h 14 (peanut) Ara h 15 (peanut) Ses i 4 (sesame) Ses i 5 (sesame)
Defensins	Ara h 12 (peanut) Ara h 13 (peanut) Gly m 2 (soybean)
7 s globulin or vicilin	Gly m 5 (soybean)
PRP-like protein	Dau c 1.02 (carrot)
Glycosylated beta-fructofuranosidase	Lyc e 2 (tomato)

(*continued*)

Table 4 (continued)

Identified function/family	Allergen name
Glucanase	Lyc 3 (tomato)
Seed biotinylated protein	Gly m 7 (soybean)
Patatin	Sol t 1 (potato)
Cathepsin D inhibitor (PDI)	Sol t 2 (potato)
Cysteine protease inhibitor	Sol t 3 (potato)
Serine protease inhibitor	Sol t 4 (potato)
LTP	Aspa o 1.01 (asparagus) Aspa o 1.02 (asparagus)

East, it is now grown all over the world. Spi o 2 is a profilin. Among the protein bands that show up in spinach extract are 20 kD and 25 kD and several minor 14–18 kD proteins. Spinach cross-reacts with other leafy green vegetables. It is a rare allergen, with cases described mostly in the context of occupational asthma (Schuller et al. 2005).

3.5.9.2 Cabbage

Cabbage (*Brassica oleracea*) is vegetable crop characterized by its dense multilayer leafy head of either green, purple, or white in color. It is a member of the Brassicaceae family. It is valued for its vitamin C, vitamin K, and dietary fiber. Allergy to cabbage is uncommon (Dolle et al. 2013). Bra o 3, a 9 kD cabbage IgE-binding protein, was identified as a lipid transfer protein, and IgE from patients allergic to cabbage can also cross-react with mugwood pollen and peach (Palacin et al. 2006).

3.5.9.3 Lettuce

Lettuce is a common food, and there are many varieties. The scientific name for fresh lettuce is *Lactuca sativa*. There are many varieties of *Lactuca sativa*, as in *L. sativa* var. *capitate* (head lettuce). Only one allergen from lettuce has been characterized, Lac s 1, which is a lipid transfer protein of molecular weight 9 kD. Lettuce cross-reacts within its own family, the *Asteraceae* family, including chicory, endive, and romaine. It is an uncommon food allergen, although it has been reported in the occupational setting (Alonso et al. 1993; Fregert and Sjoborg 1982; Paulsen and Andersen 2016; Veien et al.

1983) or in the context of food-dependent exercise-induced anaphylaxis (Romano et al. 1995).

3.5.10 Inflorescent Vegetables

3.5.10.1 Broccoli

The scientific name of broccoli is *Brassica oleracea* var. *italica* and is a member of the family *Brassicaceae*. IgE-mediated reactions to broccoli are uncommon with occasional occupational contact dermatitis and other forms of allergies (Sanchez-Guerrero and Escudero 1998). Non-specific lipid transfer protein has been implicated as an potential allergen in broccoli (Pyee et al. 1994). Broccoli cross-reacts with other members within its family.

3.5.10.2 Mushrooms

Mushrooms are a large group of edible fungi. They are characterized by an exposed fruiting body. The mushroom is the reproductive part of the plant. They have been cultivated in multiple regions and used extensively as a food substance. Some common varieties that are commonly eaten are the oyster mushroom (*Pleurotus*), the shiitake mushroom (*Lentinus*), the white wood ear (Chinese translation, *Auricularia*), the champignon (*Agaricus bisporus*), and the maitake (*Grifola*). Certain varieties of mushrooms may also contain poisons or toxins or may have psychogenic properties when eaten (Chang 1996; Holsen and Aarebrot 1997). The actual allergens in mushrooms as well as their cross-reactivity have not been well studied, although enolases are considered a panallergen of mushroom (Breiteneder et al. 1992; Herrera-Mozo et al. 2006). There may be cross-reactivity to some of the environmental molds and edible mushrooms on skin testing. Mushroom can also be responsible for oral allergy syndrome (Dauby et al. 2002). Mushrooms can also be an occupational allergen and a cause of hypersensitivity pneumonitis in people who work on mushroom farms (Hoy et al. 2007; Kamm et al. 1991; Miyazaki et al. 2003; Takaku et al. 2009; Tanaka et al. 2000, 2002; Tsushima et al. 2000, 2005).

3.5.10.3 Artichoke

The scientific name of artichoke plant is *Cynara scolymus*. It is a member of the Compositae family. The lobed scale-like leaves of the immature flower heads is edible. Although mostly cultivated in the Mediterranean Basin, it is also grown in Northern California. Food allergic reactions to artichoke are rare among consumers. However, there are several case reports of occupational urticaria, rhinitis, and asthma in vegetable workers (Miralles et al. 2003; Quirce et al. 1996; Romano et al. 2000).

3.5.10.4 Cauliflower

Cauliflower is a member of the family *Brassicaceae*, and together with a number of other vegetables such as broccoli, kale, cabbage, and Brussels sprouts, they are all within the species *Brassica oleracea*. The scientific name of cauliflower is *Brassica oleracea* var. *botrytis.* Cauliflower can come in different colors, such as purple, green, orange, and white depending on the pigments each contains. No allergens from cauliflower has been identified. However, individuals allergic to other plant lipid transfer proteins may cross-react with cauliflower LTPs, and there was a case report of anaphylaxis to cauliflower (Hernandez et al. 2005).

3.5.11 Bulb Vegetables

3.5.11.1 Onion

Onion (*Allium cepa*) is a member of the family Amaryllidaceae, which also include leek, garlic, and chive commonly used in the human diet. Onion plants are cultivated for their underground bulbs, which are actually underground stems surrounded by fleshy leaves. Yellow, red, and white onions are the most common varieties available in the market. Young onion plants whose bulbs are not yet formed are also harvested and sold as scallions. Eye irritations caused by fresh cut onions are not allergic reactions to onion. Food allergy to onions is not common. A case report of systemic urticaria/angioedema after eating raw onions indicated that lipid transfer protein and another onion protein of 43 kD were IgE reactive (Asero et al. 2001b). On the other hand, the onion lipid transfer protein is implicated as a contact allergen (Arochena et al. 2012; Enrique et al. 2007).

3.5.11.2 Garlic

The scientific name of garlic is *Allium sativum*. It belongs to the family Alliaceae or Liliaceae. Garlic has been around for some time now and is used as a spice in many cultures of the world. It is also a natural antibiotic and was called the Russian penicillin during the Second World War. Besides its antibiotic properties, garlic also has been demonstrated to have antiplatelet activity and anticancer activity. There are multiple protein bands in garlic extract, and these are thought to include activities such as a mannose-binding lectin (Smeets et al. 1997) and an alliin lyase (Kao et al. 2004). Garlic cross-reacts with other members of the Alliaceae family, including leek and chives. As a food allergen, it is considered relatively uncommon, though reports of asthma contact dermatitis and anaphylaxis have been reported (Perez-Pimiento et al. 1999; Asero et al. 1998; Ma and Yin 2012; Pires et al. 2002; Yagami et al. 2015).

3.5.12 Stalk Vegetables

3.5.12.1 Celery

Celery is a plant belonging to the family Apiaceae. The Latin name for celery is *Apium graveolens*. The edible form of celery resulted from breading the bitterness out of wild celery or smallage. Celery is an important allergen because it is responsible for oral allergy syndrome. At least one of its allergenic proteins contains cross-reactive carbohydrate determinants (Bublin et al. 2003; Fotisch et al. 1999).

3.5.12.2 Asparagus

Asparagus (*Asparagus officinalis*) is a flowering perennial plant of the Liliaceae family. They are commonly available in the market as asparagus shoots. Asparagus can cause contact dermatitis (Rieker et al. 2004; Yanagi et al. 2010), urticaria, as well as occupational rhinitis and asthma (Eng et al. 1996; Escribano et al. 1998; Lopez-Rubio et al. 1998; Sanchez et al. 1997).

Two LTPs designated as Aspa o 1.01 and Aspa o 1.02 were identified as asparagus allergens (Tabar et al. 2004). Profilin and some glycoproteins in asparagus are also likely relevant allergens (Diaz-Perales et al. 2002).

3.5.12.3 Fennel

Fennel is often used as a spice. It can be found in Southern Europe, the Middle East, Asia, and other tropical or Mediterranean climates. The scientific name is *Foeniculum vulgare*, and it belongs to the family Apiaceae, which also contains carrot (see below), caraway, parsley, and anise. Possible allergens include a lipid transfer protein and other molecules that are cross-reactive to Bet v 1. Fennel has been reported to cause oral allergy syndrome and may cross-react with pollens from birch and hazelnut (Asero 2000). An allergy to the spices of the Apiaceae family is relatively rare (Moneret-Vautrin et al. 2002).

3.5.13 Root Vegetables

3.5.13.1 Carrot

Carrot is a common root vegetable of the Umbelliferae plant family (Apiaceae). The scientific name of carrot is *Daucus carota*. Wild carrot is native in Eurasia. Domesticated carrot (*Daucus carota* subspecies *sativus*) is cultivated, and the taproots are harvested for food. Carrots are valued for carotene and are widely used in the human diet. Although most carrots in the market are orange, they can be of a variety of colors such as purple, yellow, and red. Although carrot itself is rarely involved in food allergies, systemic allergic reactions including occupational asthma and anaphylaxis due to carrots have been reported (Moreno-Ancillo et al. 2005; Fernandez-Rivas et al. 2004; Kawai et al. 2014). Dau c 1, a 16 kD Bet v1 homologue, has been identified as a carrot allergen (Hoffmann-Sommergruber et al. 1999), Dau c 3 is a lipid transfer protein, and Dau c 4 is a profilin (Asero et al. 2000; Ballmer-Weber et al.

2005). The carrot cyclophilin and Dau c 1.02, a Dau c PRP-like protein, have also been identified as IgE-reactive carrot proteins (Fujita et al. 2001; Wangorsch et al. 2012).

3.5.13.2 Turnips

The scientific name for turnip is *Brassica rapa*. It is a root vegetable widely cultivated in temperate climate and its white taproot harvested for human diet. A 2S albumin from turnip was reported be an IgE reactive to sera from subjects with positive skin prick test to turnip rape (Puumalainen et al. 2006).

3.5.13.3 Beets

Beets or beetroot is indeed a bulbous root that is usually bright red (there are other colors) and commonly used in salads. The scientific name for beetroot is *Beta vulgaris craca*, in the family Chenopodiaceae. It is extremely rare to have a food allergy to beetroot. But it can cause urine to turn red due to the pigment betalain.

3.5.14 Nightshade Vegetables

The nightshade family consists of a variety of vegetables including eggplant, tomatoes, green peppers, and potatoes. These plants belong to the family Solanaceae.

3.5.14.1 Potatoes

Potatoes are a staple food in the Western world. It has a long history and interestingly was introduced back to Europe by the Invas (circa 1500s AD). The scientific name is *Solanum tuberosum*. Characterized allergens include Sol t 1, with molecular weight of 43 kD, Sol t 2–4, and Sol t 8, which is a profilin. Although potato consists mostly of starch and other complex carbohydrates, the allergens are proteins, and potato allergy has been reported (Eke Gungor et al. 2016; Nater and Zwartz 1967; Nater and Zwartz 1968; Pearson 1966).

3.5.14.2 Tomato

Tomato is *Lycopersicon esculentum* in Latin. There are many varieties of tomato. It is used in the cuisine of almost every culture. It is a great source of vitamin C. Like other plants, tomato has a profilin (Lyc e 1, 14–16 kD) and a lipid transfer protein (Lyc e 3, 8–10 kD) (Westphal et al. 2004; Le et al. 2006). Lyc e 2 is a glycosylated beta-fructofuranosidase (Westphal et al. 2003). Some of the other allergenic proteins characterized function as enzymes, e.g., Lyc e chitinase, Lyc e peroxidase, and Lyc 3 glucanase. Tomato possesses cross-reactive carbohydrate determinants (CCDs). Like many other fruits and vegetables, tomato is not an unusually powerful antigen but can precipitate oral allergy syndrome or auriculotemporal syndrome (Sicherer and Sampson 1996).

3.5.14.3 Chili Pepper

The chili pepper we are discussing here is *Capsicum frutescens*, of the family Solanaceae. This is not white or black pepper of the family Piperaceae. Chili peppers may contain several allergens, including Cap a 1 and Cap a 2. Cap a 2 is the profilin, while Cap a 1 is a thaumatin-like protein. A Bet v 1 homologue has been isolated from some peppers. Other allergens may include a chitinase, an ascorbic acid oxidase, a 1,3-beta-glucanase, and a beta-1,4,-glucanase (Ebner et al. 1998; Jensen-Jarolim et al. 1998; Wagner et al. 2004). None of these allergens have been characterized, but there is cross-reactivity to panallergen profilins and Bet v 1. Sweet pepper has been reported to cause rhinitis and contact dermatitis (Anliker et al. 2002; Meding 1993; Niinimaki et al. 1995). Chili peppers can be involved in an oral allergy syndrome (Wagner et al. 2004).

3.5.14.4 Eggplant

Eggplant originated in India and Africa and spread to the rest of Asia and Europe and then to the Americas. The scientific name for eggplant is *Solanum melongena*. This species is the East Indian aubergine. Another name for eggplant is aubergine. Eggplant is in the family Solanaceae. There are many varieties of eggplant. Eggplant seems to cross-react with latex (Lee et al. 2004). However, like other plants, eggplants possess proteins that are known to cause allergies, such as profilin and lipid transfer proteins (Pramod and

Venkatesh 2004; Pramod and Venkatesh 2008). Recently, two proteins of 64 kD and 71 kD with polyphenoloxidase activities were demonstrated to react with IgE from eggplant allergic subjects (Harish Babu et al. 2017).

3.5.15 Other Plants

3.5.15.1 Cacao

The scientific name of cacao is *Theobroma cacao*. It belongs to the family Sterculiaceae. Cacao is used for the production of cocoa and chocolate. A 2S seed albumin storage protein of molecular weight 9 kD has been identified as coming from the cacao plant and characterized (Kochhar et al. 2001). It shows homology with other plant 2S albumin allergens. Theobromine is found in young plants, while caffeine is in higher concentrations in the mature plant. It is not known if cacao is a significant allergen, as many of the reported reactions were case reports (Perfetti et al. 1997).

3.5.15.2 Coffee

Coffee, scientific name *Coffee arabica*, is derived from a small tree that produces dried seeds. These coffee beans are then roasted, ground up, and then brewed to form one of the most consumed drinks throughout the world. Allergic reactions to coffee are rare and mostly described as case reports (Francuz et al. 2010; Jelen 2009). Cof a 1, a chitinase and two cysteine-rich metallothioneins, Cof a 2, and Cof a 3 have been identified as coffee allergens (Peters et al. 2015).

3.5.16 Meats

Allergy to meats, such as chicken, beef, pork, and lamb, is relatively uncommon. However, two conditions have brought attention to meat allergy. The first is an allergy to galactose-alpha-1,3-galactose or alpha-gal as it is commonly called (Mabelane et al. 2018). Alpha-gal is a carbohydrate present in mammalian cell membranes. The second condition is cat-pork syndrome, or pork-cat syndrome, describing an allergen cross-reactivity between two animals based on the similarities of their albumin protein structure (Wilson and Platts-Mills 2018).

Table 5 Allergens in seafood

Identified function/family	Allergen name
Parvalbumin	Gad m 1 (cod) Sal s 1 (salmon) Gad c 1 (cod)
Beta-enolase	Sal s 2 (salmon)
Aldolase	Sal s 3 (salmon)
Tropomyosin	Met e 1 (shrimp) Pen a 1 (shrimp) Pen i 1 (shrimp) Pen m 1 (shrimp) Lit v 2 (shrimp) Cha f 1 (crab) Pan s 1 (lobster) Hom a 1 (lobster) Clams (no allergens specified) Cra g 1.03 (0yster) Per v 1 (mussel) Chl n 1 (scallop) Hal m 1 (abalone)
Arginine kinase	Pen m 2 (shrimp)
Myosin light chain	Cra c 5 (shrimp)
Troponin C	Cra c 6 (shrimp)
Triosephosphate isomerase	Cra c 8 (shrimp)
Sarcoplasmic calcium-binding protein	Cra c 4 (shrimp)
Hemocyanin	Shrimp
Actin	Clams
Undefined function	Gad m 45 kD (cod)

3.5.17 Seafood

There are allergens common within the fish group and within the shellfish group. Crustaceans usually cross-react with other crustaceans and mollusks with other mollusks. This is not always the case however. The allergens found in seafood are summarized in Table 5.

3.5.17.1 Fish

In human diet, fish is a valuable source of essential amino acids, polyunsaturated fatty acids, and lipid-soluble vitamins. In addition to the parvalbumins, several other fish proteins such as enolases, aldolases, and fish gelatin seem to be important allergens (Kuehn et al. 2014).

3.5.17.2 Tilapia

Tilapia is a freshwater fish known for high protein and vitamins but low on fat content. The Nile or Black tilapia (*Oreochromis niloticus*), Blue tilapia (*O. aureus*), and Mozambique or red tilapia (*O. mossambicus*) are the three most common tilapia in the fish market. Fish allergens have been identified in many species, but there is more to be known about freshwater fish. Some of the allergens identified include parvalbumin, collagen, fructose-biphosphate aldolase, enolase, and tropomyosin. The tilapia tropomyosin has been identified as an allergen (Liu et al. 2013).

3.5.17.3 Cod

Cod is a common fish used for food. Cod is known for its protein, phosphorus, niacin, and vitamin B-12 content. Two cod species are commonly harvested for human consumption. The Atlantic cod is of the family Gadidae. Two allergens have been identified from the Atlantic cod (*Gadus morhua*) (Kuehn et al. 2014). The first is Gad m 1, a parvalbumin that is similar to Gad c1 from the Baltic cod (*Gadus callarias*), as well as a calcium-binding protein that has a molecular weight of 12.3 kD (Aas and Elsayed 1969; Aas 1966). The second allergen of the Atlantic cod, Gad m 45 kD, has an unknown function (Ebo et al. 2010). The allergens of the Baltic cod are similar, as mentioned above (Elsayed et al. 1971; Untersmayr et al. 2006; Elsayed and Bennich 1975). Gad c 1 is a 41 kD protein (Galland et al. 1998).

3.5.17.4 Salmon

Salmon is a popular human food because it is high in protein content and rich in vitamin D and omega-3 fatty acids. Atlantic, Chinook, Chum, Coho, Pink, and Sockeye salmon are popular in the US diet. About one third of the salmon consumed in the United States are wild caught. In addition to wild caught and farmed salmon, the FDA has approved genetic engineered salmon for human consumption in 2015. Genetic engineered salmon is the first genetic engineered animal in the food market. Salmon allergens for *Salmo salar* (Atlantic salmon) (Kuehn et al. 2014) include Sal s 1 (beta-parvalbumin 1, 12 kD), Sal s 2 (beta-enolase, 47.3 kD), and Sal s 3 (aldolase A, 40 kD).

3.5.17.5 Tuna

The Latin name for tuna is *Thunnus albacares*. The allergens in tuna are less cross-reactive than those of cod, salmon, and pollock (Van Do et al. 2005). There also has been data showing that the parvalbumin content in tuna is lower than other fish. It has been shown that canned tuna is less reactive than fresh tuna, illustrating the lability of antigens in the context of food processing (Sletten et al. 2010; Kelso et al. 2003).

Not all fish are discussed in this paper. The panallergen for fish is parvalbumin, which shows cross-reactivity between fish species.

3.5.17.6 Shellfish

Crustaceans

Seafood allergens belong to a group of muscle proteins, namely, the parvalbumins in codfish and tropomyosin in crustaceans (Leung et al. 1999). In shellfish, crustaceans, and mollusks, the protein tropomyosin (TM) seems to be the major allergen responsible for allergic reactions (Leung et al. 2014b). Tropomyosin belongs to the family of actin filament-binding proteins with different isoforms (Rahman et al. 2012).

Shrimp

Shrimp is one of the most common allergenic food. IgE reactivity to tropomyosin from many shrimp species have been demonstrated and designated as Met e 1 (*Metapenaeus ensis*) (Shanti et al. 1993), Pen a 1 (*Penaeus aztecus*) (Daul et al. 1994), Pen I 1 (*Penaeus indicus*) (Shanti et al. 1993), Pen m 1 (*Penaeus monodon*) (Leung et al. 1994), and Lit v 2 (*Litopenaeus vannamei*) (Samson et al. 2004). Arginine kinase (40 kD) and an unidentified component of 16.5 kD have also been reported and might be additional cross-reacting allergens playing a role in allergy to crustaceans (Shanti et al. 1993; Daul et al. 1994; Leung et al. 1994; Leung and Chu 1998). Pen m

2 from *Penaeus monodon* is identified as arginine kinase (Yu et al. 2003). Other shrimp allergens reported are sarcoplasmic calcium-binding protein (Cra c 4), myosin light chain (Cra c 5), troponin C (Cra c 6) and triosephosphate isomerase (Cra c 8) from *Crangon crangon (*Bauermeister et al. 2011*)*, and hemocyanin from *Macrobrachium rosenbergii* (Yadzir et al. 2012). Interestingly, food-dependent exercise-induced anaphylaxis associated with consumption of shrimp has been reported (Matsumoto et al. 2009).

Crab

There are multiple genera of crab. Crab is of the order Brachyura, and there are nearly 7000 species in nearly 100 families of crab. Some are extinct. Some common species of crab consumed as food are the *Charybdis feriatus*, the brown crab (*Cancer pagurus*), the blue or red swimming crabs (*Portunus pelagicus* and *haanii*, respectively), Shanghai hairy crab or Chinese mitten crab, and the European crab (*Pilumnus hirtellus*). The Dungeness crab is *Metacarcinus magister* or *Cancer magister*. The hermit crab can but is not commonly eaten. Crab is a potent allergen, sometimes causing dramatic manifestations. It may also be considered an occupational allergen for workers in the food industry. Cross-reactivity between crab, crayfish, shrimp, and lobster have been identified (Daul et al. 1992; MALO et al. 1997). The crab tropomyosin from *Charybdis feriatus* has been identified an allergen and designated as Cha f 1 (Leung et al. 1998a).

Lobster

Patients who are allergic to lobster often are also allergic to other crustaceans such as crab and shrimp (Halmepuro et al. 1987). The lobster allergens that have been identified as tropomyosin include Pan s I in the spiny lobster (*Panulirus stimpsoni*) (Leung et al. 1998b) and Hom a I in the American lobster (*Homarus americanus*) (Leung et al. 1998b).

Mollusks

Tropomyosin has been identified as the major allergen among various common edible mollusks (Leung and Chu 1998; Leung et al. 1996) such as clam, oyster, abalone, mussel, and scallop.

Clam

The mollusks tend to be cross-reactive with each other but also with crustacean tropomyosin. There are more than 150 species of clams consumed in the human diet worldwide. From a nutritional standpoint, clams are low in fat and rich in protein and minerals. In the case of clam, cross-reactivity can occur between krill and oyster (Eriksson et al. 1989). Recently, Mohamad et al. reported that tropomyosin and actin as allergens in the carpet clam (Mohamad Yadzir et al. 2015).

Oysters

Although there are more than 200 species of oysters, the two common oysters consumed in the US diet are the Eastern oyster (*Crassostrea virginica*) and the Pacific oyster (*Crassostrea gigas*).

Exercise-induced anaphylaxis may occur after ingestion of smoked oysters (Maulitz et al. 1979). The oyster tropomyosin (Cra g 1.03) has been identified as an allergen (Leung and Chu 2001).

Abalone

The scientific name of Abalone is *Haliotis midae*, and it belongs to the class Gastropoda. Lopata et al. reported five patients with RAST responses to abalone whose serum bound to two major allergens of 38 and 49 kD molecular weight. The designation Hal m 1 was assigned to the 49 kD protein, while the 39 kD protein is a tropomyosin identified from *Haliotis diversicolor.*

(Lopata et al. 2002; Lopata et al. 1997; Chu et al. 2000). The heat shock protein from *H. discus* was also reported as an allergen (Lu et al. 2004; Wang et al. 2011b).

Mussels and Scallop

The blue mussel, *Mytilus edulis*, shows cross-reactivity to oyster. The mussel tropomyosin of *Perna viridis* (Per v 1) and scallop tropomyosin of *Chlamys nobilis* (Chl n 1) have been identified as shellfish allergens (Chu et al. 2000).

Squid and Octopus

Octopus is *Octopus vulgaris* of the family Octopodidae, and squid is *Loligo edulis* or *Loligo vulgaris* of the Loliginidae family. Squid are more aggressive than octopods.

Contrary to what might be expected, squid shows more cross-reactivity to crustaceans rather than octopus or other mollusks, with the exception of oyster (Leung et al. 1996; Carrillo et al. 1992).

3.6 Special Categories

3.6.1 Stinging Insect Allergens

In the context of allergy testing and treatment, there are five important species of stinging insects, including honey bee, yellow jacket, yellow hornet, white-faced hornet, and paper wasp. In addition, reactions to the fire ant have been described, and while this is technically not a sting, it is often discussed in conjunction with the five stinging insects. Mosquito allergy has been reported but is much rare. The most common reaction from a mosquito bite is a local, usually small wheal around the bite site.

The Latin names and allergens present in stinging insects are illustrated in Table 6. In general, it is believed that bumble bees (*Bombus terrestris*) are not aggressive and also differ from honey bees in that their stinging action is not suicidal, because it possesses a retractable stinging apparatus.

3.6.2 Latex

Latex from *H. brasiliensis* contains proteins, lipids, amino acids, nucleotides, cofactors, and abundant *cis*-1,4-polyisoprene. It is the last product that is purified and cross-linked (vulcanized) with use of heat and sulfur to make rubber (Palosuo et al. 1998). The finished product contains about 2–3 percent protein (Slater 1989; Slater 1991; Sussman et al. 1991).

3.6.3 Oral Allergy Syndrome (OAS)

OAS occurs in patients with a prior cross-reactive aeroallergen sensitization and clinically presents with initial oral-pharyngeal symptoms after ingestion of a triggering fruit or vegetable. Although controversial, these symptoms may progress to systemic symptoms outside the gastrointestinal tract in 8.7% of patients and anaphylactic shock in 1.7% (Webber and England 2010).

3.7 Summary and Conclusions

This chapter describes a number of common and environmental allergens that people with allergies may be exposed to. This is in no way meant to be a complete list, but it does cover most of the common allergens. It is clear that all forms of allergic diseases have been increasing in incidence over the past 50 years, but the causes for this increase is unknown, despite the proposed "hygiene hypothesis." The identification and evaluation of food allergies have become more precise with the development of component-resolved diagnostics, and patients with a true food allergy versus oral allergy syndrome can sometimes be distinguished by measuring the levels of the distinct protein allergens in certain foods such as peanut. However, obtaining a detailed and accurate allergy history and physical remains a critical part of the management of an allergic patient. The assimilation and consideration of all types of information, including history, physical examination, and improved laboratory strategies and analysis allow us to offer directed management advice to patients, ranging from avoidance of the suspect allergen, treatment with medications, and immunotherapy (Table 7). Well-informed communication between patients, family members, and care providers is critical to optimize patient care (Scurlock and Jones 2018).

Immunotherapy has been around for over a hundred years. Our understanding of the immunologic changes that accompany immunotherapy has improved, but we still do not know why some people respond better than others (Arasi et al. 2018; Virkud et al. 2018; Scurlock 2018). The twenty-first century brings

Table 6 Stinging insect allergens

Common name	Latin name	Primary allergen (s)	Type of molecule	Size (kD)	Comments
Honey bee	*Apis mellifera*	Api m 1	Phospholipase A2	16	Differs from vespid phospholipase
		Api m 2	Hyaluronidase	39	Cross-reacts between honey bees and *Vespula* but not *Polistes*
		Api m 3	Acid phosphatase	43	
		Api m 4	Melittin	3	
Yellow jacket	*Vespula* spp.	Ves v 1	Phospholipase A1	35	
		Ves v 2	Hyaluronidase	42	
		Ves v 3	Dipeptidyl peptidase	100	
		Ves v 5	Antigen 5	25	
		Ves v 6	Vitellogenin	200	
Paper wasp	*Polistes* spp.	Pol d 1	Phospholipase A1	34	
		Pol d 4	Serine protease	33	
		Pol d 5	Antigen 5	23	
White-faced hornet	*Dolichovespula maculata*	Dol m 1	Phospholipase A2	37	
		Dol m 2	Hyaluronidase	43	
		Dol m 5	Antigen 5	23	Significantly cross-reactive among *Dolichovespula* spp., *Vespula* spp., and *Polistes* spp.
Yellow hornet	*Dolichovespula arenaria*	Similar to white-faced hornet			
Bumble bee	*Bombus terrestris*	Bom t 1	Phospholipase A2		
		Bom t 4	Serine protease		
European hornet	*Vespa crabro*		Phospholipase A		Not a particular aggressive vespid
			Hyaluronidase		
			Antigen 5		
Fire ant	*Solenopsis invicta*	Sol i 1	Phospholipase	37	
		Sol i 2		26	
		Sol i 3	Antigen 5	24	

a number of new advances in immunotherapy, ranging from oral immunotherapy to foods and to the development of antigens that will be safer and more effective (Wai et al. 2017). The antigens may be recombinant peptides derived from the amino acid sequence of the allergenic epitope or may be accompanied with immune response modifiers. Other strategies include alternate routes of administration and the design of allergen polymers. All of these are being studied now, with the promise of safer and more effective ways to minimize the impact that allergens may have on patient's quality of life.

Table 7 Clinical trials of immunotherapy

Food allergy	How	Dose	Results
Egg allergy (Tan et al. 2017)	This experiment was conducted in infants from 4 to 6 months that had a risk of developing the allergy. Risk of allergy was determined upon whether the infants had at least one relative that had the allergy to egg. A skin prick allergy test was conducted on these infants in response to egg white. Those who reacted with a reaction less than 2 mm were given either whole-egg powder (experimental) or rice powder (control) until they were 8 months old. No other eggs were provided in the diet	The dose was either an incorporation of whole-egg powder or rice power (control) in the infants' diet	If an infant who is high risk for allergy development is introducing whole-egg powder into their diet, their sensitization will be reduced
Maize and rice pollen (Ramavovololona et al. 2014)	Pollen extracts from maize and rice were detected for their IgE and IgG reactivity		Sensitization resulting from high levels of maize and rice pollen is related
Food and inhalant allergens in Turkey (Parlak et al. 2016)	The sera of undiagnosed patients were tested with an IgE test kit. Once tested, specific IgE was found among allergens on cats, dogs, grass, *Dermatophagoides pteronyssinus*, and *Aspergillus fumigatus*	Sera for IgE test classification	The most frequent allergen was related to the high consumption of milk
Dust mites and mugworts (Kim et al. 2018)	Patients who had allergy symptoms received subcutaneous immunotherapy for the allergens HDM or mugwort. BAT (basophil activation test) was done to see the response of the stimulation from the allergen before the immunotherapy was started and 3,6,12, and 24 months after beginning immunotherapy. Personal allergy symptoms were later evaluated using a survey given to the patients	Subcutaneous (specifics not mentioned)	Significant drop in BAT to mugwort after 2 years of immunotherapy. The survey showed no association to actual relief of clinical symptoms. The change in BAT for HDM correlated to the change in non-specific basophil activation
Subcutaneous pollen allergoid (Bozek et al. 2017)	Patients underwent allergen-specific immunotherapy (SIT) for pollen. The rhinitis symptom score and asthma symptom score were measured after SIT was		25% of patients showed complete relief of allergies and did not need allergy relief medication during pollen season. SIT's long-term effect did not

(*continued*)

Table 7 (continued)

Food allergy	How	Dose	Results
	finished. Patients' outcomes were grouped into three groups: (A) no symptoms or intake of medication during the treatment period, (B) no symptoms during the analysis period but there could have been medication intake, and (C) at most one mild symptom during the analysis period		significantly depend on the duration of immunotherapy against pollen
Long-term follow-up of SLIT peanut allergy trial (Burks et al. 2015)	40 patients ranging from 12- to 40-year-olds were collected were collected to test an oral dose of 10 g peanut powder after doing SLIT for 2–3 years. After 3 years of being on SLIT, those patients were also given peanut butter to test their reaction toward it	10 g peanut powder oral dose for 2–3 SLIT patients; open feeding of peanut butter for 3-year SLIT patients	98% of study members tolerated the administered doses without adverse reactions; 4/37 patients had complete and continuous desensitization and unresponsiveness to the peanut powder
Oral immunotherapy of children with anaphylactic peanut allergy (Nagakura et al. 2018)	22 peanut allergy patients underwent oral immunotherapy. Overtime, the patients increased their ingestion of peanut protein until reaching 795 mg of peanut protein per day. Once they reached 795 mg, they would maintain that dose daily. Once 3 months had passed with no symptoms displayed, they would stop their daily ingestion of the 795 mg of peanut protein for 2 weeks and retest their tolerance afterward. A second food tolerance test was given after 2 years	Increasing daily dosage of peanut protein until 795 mg is reached; food dose test was also 795 mg of protein powder	All patients had reached desensitization after 8 months of trying oral immunotherapy. For the 2-year food tolerance test, 15/22 patients had no outstanding reaction to the peanut powder
Oral immunotherapy with AR101 for peanut allergies (Bird et al. 2017)	A double-blind experiment was conducted with subjects ranging from 4 to 26 years old who were sensitive to 143 mg of peanut proteins. Subjects were assigned either daily dosages of AR101 or the placebo whose dosages went up from 0.5 to 300 mg per day. Once they reached the maximum dosage, patients were tested to see how they handled over 443 mg of peanut protein (goal was to have mild to no symptoms)	Raising dose of 0.5–300 mg of protein powder for immunotherapy; for final test, they tested for reactions toward 443 mg	For the final test, 23/29 were able to tolerate the 443 mg of peanut protein, while 18/23 were able to tolerate over 1043 mg. In the placebo group, only 5/26 were able to tolerate above 443 mg, while 0 were able to tolerate 1043 mg

(*continued*)

Table 7 (continued)

Food allergy	How	Dose	Results
Epicutaneous immunotherapy for peanut allergies (Sampson et al. 2017)	They randomly assigned patients to receive different concentrations of peanut proteins in a patch or to receive a placebo patch. After 12 months of daily patch use, the patients took a food challenge to test their tolerance toward peanuts	Concentrations of patches included 50ug, 100ug, and 250 ug	93.7% of patients were able to do the challenge. The 250ug patch and the placebo had largest difference of response rate. 100ug patch and placebo patch had a negligible difference (therefore, 50ug has negligible results too)
SLIT therapy for peaches and peanuts (Gomez et al. 2017)	48 patients who were allergic to peaches were classified into subcategories based on their peanut sensitivity (A, allergic; B, sensitized; C, tolerant). SLIT's effects were tested with skin prick tests and food challenges		After 1 year of being on SLIT, the reaction of the skin prick test decreased outstandingly, and patients had a higher tolerance to peaches. Those in group A had a significant decrease in skin prick reaction and increase in peanut tolerance. Group B and C were not mentioned in results

Comments: With oral immunotherapy and epicutaneous immunotherapy clinical trials for peanuts, there has been a higher threshold noticed for children. Oral immunotherapy has been seen to provide a larger change in threshold than epicutaneous immunotherapy, but oral immunotherapy has had more adverse reactions that occur in patients. Oral immunotherapy, epicutaneous immunotherapy, and SLIT have been noted to change the immune response toward foods (Parrish et al. 2018)

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