

Fruits & Vegetables

Allergy – Which allergens?



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Fruit and vegetable allergens

The botanical term “vegetable” means either all plant material or all the edible parts of plants, compared to “fruit”, which denotes the ripened ovaries of flowering plants and surrounding tissues (1). True fruits, therefore, are developed from the ovary in the base of the flower and contain the seeds of the plant (though cultivated forms may be seedless). Thus, many botanical fruits are not edible at all, and some are actually extremely poisonous (2).

But in practice the definitions of the both words are traditional rather than scientific, and somewhat arbitrary and subjective, being determined by local customs of food selection and preparation. In general, vegetables have traditionally been regarded as those plant parts suitable for savoury or salted dishes, rather than sweet dishes. However there are many exceptions, such as the Pumpkin, which is eaten in both savoury and sweetened dishes. In contrast to this, some edible botanical fruits, including the Tomato, the Eggplant, the Bell pepper, and the Bean pod, are classed as culinary “vegetables”. The term “fruit” can refer to a part of a plant which is not technically a fruit but which is used in sweet cooking: Rhubarb, for example. Mushrooms belong to the biological kingdom Fungi, not the plant kingdom, and yet they are also generally considered to be vegetables. Some vegetables, such as Carrot, Celery, and Bell pepper are eaten either raw or cooked, while others, like the Potato, are eaten only when cooked. Most fruits are eaten both raw and cooked.

Fruits are a staple of the human diet predating agriculture by millions of years, if the evidence of primate diets is relevant. Preference for fruit-like sweetness in food is generally considered by anthropologists to be programmed into homo sapiens through natural selection and to serve as a signal that a new food is edible and not harmful. The human “sweet tooth” is probably heavily indebted to the prominence of fruit in the environment and nutrition of early hominids.

Fruit is experiencing a renewed importance in the human diet, as an indirect result of this very “sweet tooth”. With a very abundant food supply and wide choice among foods in the present-day developed world, the preference for sweetness has run amok, one result being widespread overindulgence in candy, pastries and other processed sweet foods. This has contributed to the obesity epidemic and unprecedented rates of diabetes and other obesity-related illnesses. But with health awareness growing, there is, at least in industrialised countries, a partial return to human dietary roots, with more and more “natural”, less-processed foods being eaten, and this trend includes the replacement of fattening sweets with non-fattening fruits.

Fruits and vegetables form a large part of the average middle-class diet. Fixed numbers of portions per day are recommended by dieticians, and the recommendations are widely heeded, especially by parents and schools. In the modern era, fruits can be cheap, abundant “convenience foods”. Apples, Oranges, Bananas, Lemons and Limes have for most of living memory been easy to transport and store and so very readily accessible. Commercial fruit juices, often available in single-portion servings, have expanded in variety from Apple and Orange juices and lemonade to a bewildering array, including exotic mixes. Some fruits such as Mangoes, which because of their tropical or semi-tropical origins and difficulty of transport and storage were seldom if ever tasted in temperate zones by previous generations, are now growing familiar because of advanced storage and transport technology. South African and Israeli fruits, for example, are transported by plane to Europe within a few hours, and boxed juices (many with shelf-lives of from six months to a year) are a growing industry in a number of tropical and semi-tropical countries. Additionally, fruit is often used as a flavourant or other additive in processed foods. Finally, there is broader fruit exposure through greatly increased travel opportunities. The increasing availability of vegetables is less dramatic but is still notable. Some of the same factors in transport and retail have been influential, and under consumer pressure, prepared salads have become common convenience foods.

Allergen exposure

It is not surprising that fruit and vegetable allergy is increasing: two very clear causes are the increasing availability of fruit and vegetables in general and the movement of some fruits and vegetables into regions where they were almost never eaten before. This movement complicates the increase in allergy, however, as some methods of processing and storage can activate or de-activate certain fruit allergens. Heat-lability and heat-stability, for instance, are important in fruit allergen metamorphosis.

Fruit and vegetable allergy symptoms span a wide range, from atopic dermatitis to urticaria to oral allergy syndrome (itching lips, tongue and throat, and sometimes swollen lips, tongue, throat or palate) to anaphylaxis (A claim put forth is that anaphylaxis-prone allergy does not exist in conjunction with oral allergy syndrome, but this is debatable). Some authors have suggested that “pollen-food syndrome” is a more apt description of reactions involving cross-reactive pollen and food allergens and encompassing symptoms of oral allergy syndrome.

Considered in isolation, fruit and vegetable allergy might seem to create relatively little danger or trouble. Fruits and vegetables, when compared to Peanut or fish, were initially not known for commonly causing anaphylactic reactions in very tiny amounts; and it was relatively easy to avoid one or several fruits or vegetables in a diet. However, severe reactions have been recorded to both (3-4). It also must be kept in mind that fruit and vegetables, like Soya, Wheat, and Cow’s milk, may now commonly be added to processed food, and that, like these allergens, fruits and vegetables are not always properly labelled. A fruit or vegetable extract called a “flavourant”, for example, can act as a hidden allergen (5).

More importantly still, the role of fruits and vegetables in cross-reactivity (see below) sets them in the middle of some of the major dramas of allergy. Fruit-fruit cross-reactivity in itself creates the danger of incomplete diagnosis and allergens unexpectedly encountered later on. Also, hay fever is on the increase, giving great importance to the role that fruits play in pollen-fruit cross-reactivity. Latex-fruit syndrome

(or Latex-food syndrome) links fruit and vegetables to one of the most vicious allergies, which has, among other depredations, forced some surgeons and dentists out of practice. The Mango component in an allergy complex may be trivial; but the Latex component could be devastating.

Occupational fruit and/or vegetable allergy are also important and increasing. Those employed in fruit and vegetable growing, handling and processing – not an inconsiderable group of people – are at risk from topical exposure to produce. Topical allergy occurs, and non-allergy topical reactions are factors as well, as fruits contain a variety of volatile chemicals and other substances that can be irritating to the skin. Even mechanical irritation is a problem in some fruit workers. Finally, sulphite as a preservative of fruits and vegetables would logically affect producers and handlers much more than it affects consumers.

A thorough interview and specific testing are necessary to determine the exact aetiology of occupational reactions to fruit, as well as of reactions to ingestion, in which such factors as histamine and the toxicity of pits and seeds may need to be taken into account.

Cross-reactivity

The analysis of cross-reactivity was initially fruit to fruit and vegetable to vegetable. It then moved from the botanical family level to the level of panallergens, which allow cross-reactivity among much more distantly related entities. It was panallergens that explained pollen-fruit cross-reactivity, pollen-vegetable allergy, and fruit-vegetable allergy. A greater number of culprit pollens can now be recognised, and a substance as unexpected as Natural rubber latex can be included in allergy equations.

Therefore, though fruits remain central to considerations of cross-reactivity, this phenomenon appears increasingly complex. To begin with, all fruits and vegetables contain a number of allergens, some of which are panallergens. It is possible simply to be allergic to Apple, because of one or more unique Apple allergens. It is more likely, however, that a patient will have a cluster of allergies, and it is

conceivable, because of multiple panallergens, to be vulnerable to overlapping patterns of cross-reactivity. (What actually manifests itself clinically depends, of course, not only on the array of allergens but also on the particular vulnerabilities and experiences of subjects. A heat-labile allergen in Apple, for example, would never affect someone who ate Apples only in pies. A heat-stable allergen in Apple, which occurs, would).

Certain genera such as *Citrus* (Grapefruit, Lemon, Lime, Mandarin, Orange) display cross-reactivity that is demonstrable at more or less the expected degree, but other genera simply do not show the expected cross-reactivity. The *Rosaceae* fruits (Apple, Apricot, Blackberry, Blueberry, Cherry, Peach, Pear, Plum, Raspberry, Rose hip, Strawberry) show cross-reactivity at a family level. These are the most important botanical relationships as far as demonstrated cross-reactivity is concerned, but the necessarily very incomplete nature of such an account should be kept in mind. The large number of fruit species, and the exotic history of many fruits, has meant that many species have not yet been adequately examined for their allergenic characteristics (6).

On the other hand, because of panallergens, there are strong patterns of cross-reactivity spanning distant, non-fruit relationships. These can be summarised under the headings of Latex-fruit cross-reactivity and pollen-fruit cross-reactivity.

Regarding the former, approximately 30-50% of individuals who are allergic to Natural rubber latex (NRL) show an associated hypersensitivity to some plant-derived foods, especially fresh fruits (7-9). An increasing number of plant sources, such as Avocado, Banana, Chestnut, Kiwi, Tomato, Potato and Bell pepper, have been associated with this syndrome (10-13). Chitinase appears to be the main panallergenic culprit in Latex-fruit cross-reactivity, but other panallergens play a role (8,14).

Regarding pollen-fruit syndrome, studies have reported cross-reactivity between Birch pollen and a number of foods, *e.g.*, Apple, Pear, Melon, Hazelnut, Peach, Cherry, Plum, Celery, Carrot and Potato, with oral allergy syndrome and allergic rhinitis being the pre-

dominant features, and profilin being the panallergen most frequently implicated (15-21). Subsequently, a number of allergens or panallergens have been identified, and this has shed light on causes and patterns. Profilin was originally considered to be unquestionably the most important factor, but LTP is now receiving significant attention (22-23).

Cross-reactivity may occur between fruits and pollens other than Birch. In a laboratory study, cross-allergenicity between Apple pulp and 5 pollen species, investigated by RAST inhibition, demonstrated that Apple pulp extract effectively inhibited RASTs to all the pollens except one, Japanese Cedar pollen (24). Similarly, a study reported on an association between grass pollen allergy and sensitisation to Tomato, Potato, Green pea, Peanut, Watermelon, Melon, Apple, Orange and Kiwi (25).

Pollen-fruit cross-reactivity is strongly (though not exclusively) characterised by oral allergy syndrome, which creates a fairly clear diagnostic guide. The particular symptoms of oral allergy syndrome (see above) should suggest to the clinician that he consider the involvement of a number of other fruits, and the probability of a co-existing allergic rhinitis to specific pollens. This is particularly relevant in the Northern Hemisphere, with its abundance of Birch, Mugwort and other implicated pollens.

Some panallergens, such as profilin, may result mostly in mild symptoms. However, others, and in particular lipid transfer proteins, are heat-stable and may result in severe reactions, including anaphylaxis; and importantly, they may be more prevalent in certain population groups than others (26). For example, Peach allergy has two different patterns: that of central Europe, with oral allergy syndrome (OAS), related to a primary sensitisation to Birch pollen Bet v 1 and profilins; and that of southern Europe, with mostly systemic symptoms, in many cases due to sensitisation to lipid transfer proteins (27-28).

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Allergen components – Recombinant/ purified native

f430	rAct d 8 PR-10, Kiwi
f417	rApi g 1.01 PR-10, Celery
f419	rPru p 1 PR-10, Peach
f420	rPru p 3 LTP, Peach
f421	rPru p 4 Profilin, Peach

Information regarding available allergen components can be found in “Allergy – Which allergens?, Native & recombinant allergen components”.

f49 Apple



Allergen Exposure

Geographical distribution

Apples are among the most widely grown fruits in the Western Hemisphere.

The Apple is the pomaceous fruit of the Apple tree, species *Malus domestica* in the *Rosaceae* (Rose) family. It is among the most widely cultivated tree fruits. The tree is small and deciduous, reaching 5 to 12 metres tall, with a broad, often densely twiggy crown. The leaves are alternately arranged simple ovals 5 to 12 cm long and 3 to 6 cm broad on a 2 to 5 cm petiole with an acute tip, serrated margin and a slightly downy underside. Flowers are produced in spring simultaneously with the budding of the leaves. The flowers are white with a pink tinge that gradually fades, 5-petaled, and 2.5 to 3.5 cm in diameter. The fruit matures in autumn and is typically 5 to 9 cm in diameter. The centre of the fruit contains 5 carpels arranged in a 5-point star, each carpel containing 1 to 3 seeds (1).

The tree originated from Central Asia, where its wild ancestor is still found today. Early cultivation probably predates written history, and over 7,500 known cultivars

Malus x domestica

Family: *Rosaceae*

Common names: Apple, Cultivated apple, Crabapple

Source material: Peel from green Apple

Synonymes: *M. domestica*, *M. communis*, *M. pumila*, *M. sylvestris*

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exist. Different cultivars are available for temperate and subtropical climates. Most of these cultivars are bred for eating fresh (dessert Apples), though some are cultivated specifically for cooking (cooking Apples) or producing cider. Cider Apples are typically too tart and astringent to eat fresh, but they give the beverage a rich flavour that dessert Apples cannot. Old cultivars are often oddly shaped and russeted, and have a variety of textures and colours (1).

Apples can be classified into 4 main groups: dessert, culinary, cider and ornamental. Varieties are also often grouped into summer and late-fall, according to the time of maturity. Apples are grown in temperate zones throughout the world. They are relatively easy to transport and store, and so are readily available throughout the year. Commercially, Apples can be stored for some months in controlled-atmosphere chambers to delay the ethylene-induced onset of ripening. Ripening begins when the fruit is removed.

Environment

Readily edible varieties are all cultivated. Apples are most valued as a fresh dessert fruit, but also may be made into jams, jellies, vinegars, fresh juice, a purée called applesauce, a preserve called Apple butter, wines, ciders, brandies and pastries. They may also be baked, fried, stewed, dried, spiced, candied, or used in mincemeat or chutney. The fruit is a source

of pectin. Pectin is a thickener in jams, etc., and a culture medium in laboratories. Apple can also be dried, in which case it may contain the preservative sulphur dioxide or another preservative, sulphite, which also prevents browning. An edible oil (that is also used for illumination) can be obtained from the seed.

Apple is also regarded as bactericide, astringent, carminative, cyanogenetic, depurative, diuretic, emollient, hypnotic, refrigerant, sedative, and tonic. Apple is used as a folk remedy for a number of medical conditions. The root and bark are considered anthelmintic, hypnotic, and refrigerant. Apple leaves contain an antibacterial substance called phloretin, which is active in doses as low as 30 ppm.

Apple contains over 266 volatile components that include alcohol, esters, aldehydes, ketones, ethers, acids, bases, acetals, and hydrocarbons (2).

Unexpected exposure

The hard wood is used for turnery, canes, tool handles, pipes and fuel.

Allergens

Early studies reported the presence of a number of allergenic proteins in Apple extracts: they were of 18, 31, 50, 38, 16, 14, and 13 kDa (3). An allergen of approximately 60 kDa, cross-reacting with the major Mugwort pollen allergen Art v 1, along with Birch pollen, Timothy grass pollen, Peanuts, and Celery, has been isolated. The allergen appeared to be distinct from Bet v 1 and profilin and was thought to represent a novel cross-reactive allergen involved in oral allergy syndrome (4).

An allergen present in Apple was reported as being similar in size to a 35 kDa protein isolated from Birch pollen, a minor allergen that 10 to 15% of Birch-pollen-allergic individuals are sensitised to. Cross-reactivity was demonstrated with proteins of comparable size from Litchi, Mango, Banana, Orange, Pear and Carrot. The 35 kDa protein was immunologically independent of the major Birch pollen allergen Bet v 1 (5).

The following allergens have been characterised:

Mal d 1, a 18 kDa heat-labile protein, a major allergen, a Bet v 1 homologue (PR 10) protein family member (6-30).

Mal d 2, a 31 kDa thaumatin-like protein (6,15,18-19,22,25,31-34).

Mal d 3, a 9 kDa lipid transfer protein, a minor allergen (6,15,19,22,24-25,35-50).

Mal d 4, a 14 kDa protein, a profilin and a major allergen (6,15,19,22,24,33,51-54).

A Bet v 6-related food allergen, a PCBER (Phenylcoumaran benzylic ether reductase) (55-56).

An isoflavone reductase (IFR) allergen has been described (57).

A novel putative allergen, a glyceraldehyde-3-phosphate dehydrogenase, has been detected; of 7 Apple-allergic patients, 71% reacted to this protein (58).

As in the case of other allergens, sensitisation to Apple allergens follows a heterogenous pattern: for example, in a study to determine the pattern of recognition of individual major and minor allergens among subjects with a positive *in vitro* diagnosis for Apple allergy, the following frequencies were found: nMal d1 (87%), rMal d2 (57%), nMal d3 (31%), nMal d4 (29%) (59).

The peel of Apple and other *Rosaceae* fruits has been reported to have a clinically relevant higher allergenicity than the pulp (60). The 18 and 31 kDa allergens, which are heat-labile and unstable in solution, experience almost complete elimination of allergenic potency with short heating (61). Mal d 1 and Mal d 2 are distributed throughout the Apple pulp and peel, while Mal d 3 is restricted to the peel. Different Apple cultivars show markedly different expression of major allergens (25). Interestingly, Mal d 1 and Mal d 3 and their homologues have been detected in *Rosaceae* pollen. Although the pollen load of *Rosaceae* is rather low as a rule, there is confirmed evidence for temporary peaks, indicating that allergen exposure for sensitised individuals is likely (62).

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Anecdotal reports from Apple-allergic patients hold that some Apple strains tend to be highly allergenic (Granny Smith, Golden delicious), whereas others (Jamba, Gloster, Boskop) are tolerated without any symptoms or with moderate symptoms (63). This may be true: the level of allergenic protein varies with the species of Apple and its ripeness; the IgE-binding potency depends on the 18 kDa allergen (63). The Mal d 1 content of Golden delicious apples was shown to rise considerably during maturation and storage (64). Golden delicious apples had the most 18 kDa allergen (compared with Macintosh, Red delicious, and Granny Smith). The 18 kDa allergen was found at levels in this order: Golden delicious > Boskoop > Jamba. This would explain the different results of skin prick test to allergens from different Apple extracts (65). Mal d 1 content ranged from 0.84 to 33.2 µg/g fresh weight in 39 selected cultivars (25). Other factors may influence the protein content or allergenicity of Apple. Apples in stores have been shown to have higher levels of allergens than freshly picked fruit. The amount of the 18 kDa allergen (Mal d 1) increased significantly when Apples were stored at 4 °C, but not under controlled exposure to oxygen and carbon dioxide (3).

Whether Apple cultivars containing low amounts of Mal d 1 are better tolerated by Apple-allergic patients was assessed: 3 different Apple cultivars induced wheals of similar size in most patients, but 2 cultivars induced significantly more-severe symptoms in 2/7 cases each, suggesting that allergy to Mal d 1 is characterised by significant inter-patient variability as well as marked inter-Apple and intra-Apple variability (20).

Further, different Mal d 1 isoforms can be present within a single cultivar (6). The divergent allergenicity of Apple strains appears to depend on different expression levels of the major allergen. The introduction of a proline residue in position 111 of Mal d 1 and in position 112 of Bet v 1 of Birch tree pollen resulted in a drastic reduction of allergenicity of both the pollen and the food allergen, obviously having removed the cross-reactive epitope (6). Also, it was demonstrated that, although Mal d 1 did not induce basophil activation after gastrointestinal digestion,

digested Mal d 1 (and Hazelnut Cor a 1.04) still activated Bet v 1-specific T cells, suggesting that gastrointestinal degradation of Bet v 1-related food allergens destroys their histamine-releasing, but not T cell-activating, property. This data emphasises that Birch pollen-related foods are relevant activators of pollen-specific T cells (66).

On the basis of band intensity in SDS-PAGE studies, the mean amount of Mal d 1 present in mature Golden delicious apples has been estimated to be 1 to 5 mg per 100 g fresh weight. A bite of Apple of approximately 10 g, which is able to elicit symptoms in Apple-allergic patients, represents 0.1-0.5 mg of the ingested major allergen (63).

Mal d 2, a thaumatin-like protein, shows high stability to proteolysis and heat treatment and remains intact after 2 hours each of gastric and subsequent duodenal digestion, retaining its full IgE-binding capacity. Mal d 2, although detected by an anti-TLP antibody in cloudy Apple juice, did not bind IgE of a serum pool of Apple-allergic patients. These findings suggest that Mal d 2 maintains its structure in the gastrointestinal tract, a feature essential for sensitising the mucosal immune system and provoking allergic reactions (32).

Mal d 3, a lipid transfer protein, was assessed in 53 Apple cultivars grown in Italy and 35 grown in The Netherlands, in order to determine whether levels of LTP varied among cultivars. Differences of around 100-fold in LTP levels existed between certain Apple cultivars. The authors suggested that whether the lowest observed levels of LTP warrant designation as hypo-allergenic required more extensive confirmation by oral challenges (44,67). Furthermore, LTP levels are greatly dependent on the position of the fruit growing on the tree, maturity, storage conditions, and cultivar. The highest LTP levels are found in mature, freshly picked fruits, whereas LTP levels decrease during storage (with the greatest decrease happening under controlled atmosphere conditions) (46,67). Most LTP concentrates in the pericarp (skin) of the fruit, whereas the pulp contains lower amounts of the allergen (45).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the *Rosaceae* family could be expected and in fact does occur frequently (68). For example, in a DBPCFC study, reactions to Peach occurred in 22 patients, to Apple in 6 and to Apricot in 5. The authors conclude that a positive skin prick test and IgE antibody test should not be taken as the only guide for multi-species dietary restrictions but that, nevertheless, the potential for clinical allergy to other *Rosaceae* should not be neglected (69).

Early studies reported cross-reactivity between Birch pollen and a number of foods, *e.g.*, Apple, Pear, Celery, Carrot and Potato (70). Subsequently, a number of allergens or panallergens have been identified, and this has shed light on the causes and patterns (71).

Birch pollen is a significant cause of allergy in temperate climates, affecting 5-54% of the population in Western Europe. Patients allergic to Birch pollen are more often allergic to fresh fruits and vegetables than are patients allergic to other pollens (72). About 40-70% of Birch pollen-allergic patients show allergic symptoms after ingesting or handling raw fruits, especially Apple, due to cross-reactivity between an allergen present in the food and Bet v 1, the major Birch pollen allergen (73-79).

Type I allergic symptoms in the oropharyngeal mucosa, upon contact with plant-derived food in patients with pollen allergies, have been termed oral allergy syndrome (OAS). IgE cross-reactivity between pollen, in particular Birch pollen, and food allergens is the molecular basis for this phenomenon. No single allergen in a single source can of course be responsible, but rather one or a number of cross-reacting allergens in multiple sources. For example, in a study of patients with a history of oral allergy syndrome after eating Apple, 16/28 (57%) reacted to Bet v 1; among 20 polysensitised subjects presenting oral allergy syndrome after consumption of Apple, 4 reacted to Bet v 2 (20%). Among patients with IgE against both recombinant allergens, 6 (35%) presented symptoms of allergy after eating Apples (80).

In a Japanese study of oral allergy syndrome and pollen allergy, in 101 patients the most common allergen was Birch tree pollen. In 61% of Birch-allergic patients, a concomitant allergy to fruit or vegetable was reported. Apple was the most prevalent allergen (97%), followed by Peach (67%), Cherry (58%), Pear (40%), Plum (40%) and Melon (33%) (81). Similar results were reported from a study in Hokkaido. In patients with Birch pollen allergy, the higher the serum IgE antibody level to Birch pollen were, the higher was the incidence of hypersensitivity to Apple pulp (82).

Laboratory evidence has demonstrated that the major cause of cross-reactivity between Birch pollen and Apple is biochemical and immunological similarity between the major allergens, Bet v 1 and Mal d 1, as shown by serological and cellular immunoassays (6,11,83-84). Mal d 1, the major Apple allergen, has been shown through sequence comparison to Bet v 1, the major Birch pollen allergen, to have a 64.5% identity on the amino acid level and a 55.6% identity on the nucleic acid level (12).

Clinical and laboratory evidence is supported by research demonstrating that patients who are Birch pollen- and Apple-allergic improve if desensitised to Birch pollen (85); and by research showing a marked reduction or a total disappearance of Apple-induced oral allergy syndrome after injection immunotherapy with Birch pollen extracts (86). These recent studies contradict an earlier study that reported a poorer response (85).

Allergy to Apple is commonly associated with Birch pollinosis because the 2 share homologous allergens. However, some patients have Apple allergy but no allergy to Birch pollen, suggesting that there are allergens in Apple that do not cross-react with Birch (39). Serum IgE antibodies to Apple allergens were detected in 90% of patients with clinical Apple allergy, with similar allergens being demonstrated in 44% of patients with clinical Birch pollen allergy and in 5-10% of patients with other atopic allergies. RAST inhibition studies confirmed that Apple and Birch pollen allergens cross-react (87). In other words, Bet v 1 has all the allergenic epitopes of Mal d 1, but Mal d 1 is only a weak inhibitor

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of IgE reactivity with the major Birch pollen allergen, probably due to the absence of some Bet v 1 epitopes on the fruit allergen. Other reasons for the latter observation have been proposed: there may be a lower association constant of Bet v 1-specific IgE to Mal d 1 epitopes; or Mal d 1 may represent most of the allergenicity of Apple fruit; or the high lability of allergens during extraction or processing of Apple is probably not due to destruction of discontinuous epitopes, but to interactions with compounds from the fruit tissue, and most of these reactions are catalysed by enzymes (9). Cross-inhibition assays have also demonstrated the existence of common B-cell epitopes present on Dau c 1 in Carrot and Api g 1 in Celery, as well as on Bet v 1 (88).

In Mediterranean areas, oral allergy syndrome occurs without Birch pollen allergy, and on occasion may present with no other associated pollen allergy. In a study to assess the possible association of OAS with London plane tree (*Platanus acerifolia*) pollen allergy, 720 patients were selected on the basis of seasonal or perennial rhinitis, or asthma, or both; 61 (8.48%) were found to be sensitised to *P. acerifolia* pollen, and a food allergy was observed in 32 (52.45%). Food allergens most frequently implicated included Hazelnut, Peach, and Apple (89).

Allergy to *Rosaceae* fruits in patients without a related pollen allergy has been reported to result in a severe clinical entity; it was also reported that profilin- and Bet v 1-related structures are not involved in *Rosaceae* fruit allergy without pollinosis (90).

Other allergens or panallergens may also contribute to cross-reactivity between Birch pollen and Apple allergy.

A minor allergen present in Birch pollen and a similar protein present in Timothy pollen were shown to have common epitopes with antigens in Apple, Carrot and Celery tuber (91). This may have been the minor Birch pollen allergen Bet v 6 (phenylcoumaran benzylic ether reductase [PCBER]), which occurs in many foods, including Apple, Peach, Orange, Litchi, Strawberry, Persimmon, Zucchini, and Carrot (57,76). This allergen may also have been the 35 kDa protein isolated from Birch pollen, a minor allergen

immunologically independent of the major Birch pollen allergen Bet v 1, to which 10-15% of Birch pollen-allergic individuals are sensitised, and for which cross-reactivity was demonstrated with proteins of comparable size from Apple, Litchi, Mango, Banana, Orange, Pear and Carrot (5).

Lipid transfer proteins (LTPs) have been reported to be important, clinically relevant panallergens. One has been characterised in Apple and named Mal d 3. LTP from *Artemisia* pollen and Chestnut has been demonstrated to cross-react with allergens of *Rosaceae* fruits, but significant differences in specific IgE binding capacities were observed among members of the plant LTP family (36, 38,41). Similarly, the LTP present in Peach and beer may cross-react with LTP from several other plant-derived foods (36,92).

Although cross-reactivity has been clearly established between Apple and Birch tree pollen, cross-reactivity may occur between Apple and other pollens as well. In a study of cross-allergenicity between Apple pulp and 5 pollen species (Birch, Japanese cedar, Orchard grass, Mugwort and Ragweed), investigated by RAST inhibition, it was demonstrated that Apple pulp extract effectively inhibited RASTs to all the pollens except Japanese Cedar pollen (93). Similarly, a study reported an association between grass pollen allergy and sensitisation to Tomato, Potato, Green pea, Peanut, Watermelon, Melon, Apple, Orange and Kiwi (94). This may be a result of a Group 4 grass pollen allergen, a 60 kDa glycoprotein, which is recognised by 70% of patients sensitive to these pollens and is found in Timothy grass, Mugwort and Birch pollen, and in Peanut, Apple, Celery root, and Carrot. Group 4-related allergens thus occur in pollens of unrelated plants and plant foods and may therefore contribute to cross-reactivity in patients allergic to various pollens and plant food (95).

Some patients with grass allergy show polysensitisation against other pollens and plant-derived foods. In these patients, oral allergic syndrome (OAS) is frequently found. This is a result of cross-reactive Bet v 1- and Bet v 2-like allergens. The most common foods implicated are Hazelnut, Peanut, Kiwi, Apple and Walnut. IgE antibodies for Bet v 1 is

associated more with nuts and legumes, while Bet v 2 is more often related to fresh fruit and vegetables (96).

Allergy to Apple has been associated with Kiwi-allergic individuals (97). Individuals with allergy to Grape or related products are often co-sensitised to Apple (98-99).

Sensitisation to profilin and/or bromelain-type cross-reacting carbohydrate determinants (CCD), caused by pollen (Timothy grass, Mugwort) or *Hymenoptera* venom allergens, can elicit positive IgE antibody tests against Natural rubber latex and Apple (100). These antibodies are most often of less clinical relevance.

Minor allergenic determinants cross-reactive with Apple and Birch pollen epitopes have also been isolated in the pollen of the Apple tree (101). Apple seed allergens have been reported to cross-react with Birch pollen allergen(s) (102).

Clinical Experience

IgE-mediated reactions

Allergy to Apple has been documented for over 3 decades, and may frequently induce symptoms of food allergy in sensitised individuals, in particular oral allergy syndrome (51,87,103-111). Itching, tingling and other mild reactions on the oropharyngeal mucosa are the most common complaints after eating raw Apples, and angioedema, urticaria and shock are less common. Other symptoms may include rhinoconjunctivitis, asthma, laryngeal oedema, abdominal effects, pruritis and hand dermatitis (112). Individuals may be highly allergic to Apple, with symptoms being elicited even from kissing, resulting in local or regional, mild, moderate or severe symptoms, including angioedema, bronchospasm, acute respiratory distress and anaphylaxis (113-114).

In a Japanese study of sera of 4,797,158 patients collected in laboratories during 1994-1998, evaluation of IgE antibody values of greater than 0.70 kU_A/l showed that among food allergens, Apple had the highest response (115). Similarly, in a food hypersensitivity study of Finnish university students, among 172 subjects, Apple was a frequent (29.1%)

cause of symptoms (116). Approximately 2% of the Northern and Central European population is allergic to Apple (117). A study was conducted at 17 clinics in 15 European cities to describe the differences among some Northern countries regarding what foods, according to the patients, elicit hypersensitivity symptoms, and it was found that Apple was responsible in 45% of 1139 participants (111).

However, symptoms of Apple allergy may show a geographically skewed distribution. In Northern and Central Europe, where Birch trees predominate, symptoms tend to be mild, whereas in Southern Europe and the Mediterranean, symptoms are more likely to be severe. This is illustrated by a study that sought to investigate the primary sensitisers in Apple allergy across Europe, the individual allergens involved, and whether these differences determine the clinical presentation. Results from 389 patients with Apple allergy (case histories and positive skin prick test) showed that in the Netherlands, Austria, and Italy, Apple allergy was mild (>90% isolated oral symptoms) and related to Birch pollen allergy and sensitisation to Bet v 1 and its Apple homologue, Mal d 1. In Spain, Apple allergy was severe (>35% systemic reactions) and related to Peach allergy and sensitisation to Mal d 3 (lipid transfer protein) (22). A study of an unselected Danish population of children and adults reported that 17% of pollen-sensitised adults were allergic to Apple (118). In an Indian study of 24 children aged 3 to 15 years with documented deterioration in control of their perennial asthma, the presence of IgE antibodies to Apple was found in 21 (88%) (119).

“Apple contact urticaria syndrome” and rhinitis are relevant phenomena. However, itching and tingling and other mild reactions on the oropharyngeal mucosa were reported in early studies to be the most common complaints after eating raw Apple (120). These became known as oral allergy syndrome, and Apple is the most frequently reported offending food in Birch pollen-sensitive patients with OAS (65,82,121-130). Up to 70% of patients with Birch pollen allergy exhibit this syndrome. The most frequent and therefore best characterised pollen-fruit syndrome combines Apple allergy and tree pollen-induced allergy. Some studies

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have reported an extremely close association: for example, in 196 Birch pollen-hypersensitive patients with oral allergy syndrome caused by various vegetable foods, 195 patients had Apple and/or Hazelnut allergy (131).

Oral allergy syndrome may occur following low-dose exposure to Apple, as demonstrated in a report of a 24-year-old woman who experienced acute oedema of the lips with itching in the mouth after a kiss from her boyfriend who had just eaten a green Apple (132). Because of symptoms of oral allergy syndrome, many individuals avoid eating fresh Apples. A study demonstrated that the allergens responsible vary between cultivars: out of 15 Apple-allergic individuals who underwent an open oral challenge with 3 different Apple cultivars – Santana, Golden Delicious, and Topaz – during the Birch pollen season, 8 of the participants (53%) developed no symptoms following challenge with Santana apple, than after challenge with the Topaz apple (1 participant) and Golden Delicious apple (1 participant) (117). Apple allergy confined to the gingival tissues was reported in a 48-year-old woman. Skin reactivity and IgE antibodies detection with commercial extract of Apple were negative, whereas the oral challenge test resulted in blister and ulcer formation (133).

Among 1,129 adult patients with bronchial asthma and/or allergic rhinitis responding to a questionnaire regarding food sensitivity, 276 (24%) reported allergic symptoms on eating or handling various foods, of which Hazelnut, Apple and shellfish were the most often named (134).

The prevalence of atopy caused by Apple, Peach, and Hazelnut in patients with tree pollen allergy was evaluated. Skin prick tests for Apple, Peach, and Hazelnut were positive in 51 (64.6%), 61 (77.2%), and 71 (89.9%) patients, respectively. Granny Smith showed more positive skin reactions and a better agreement with clinical history than did Golden delicious. RAST for Apple, Peach, and Hazelnut was positive in 53 (68.8%), 13 (16.9%), and 31 (40.3%) patients, respectively (65).

Although not as common as allergy to Apple associated with pollen allergy, allergy

to *Rosaceae* fruits in patients without a related pollen allergy is reported to be a severe clinical entity. Profilin- and Bet v 1-related structures are not involved (51,135).

Anaphylaxis to Apple has been reported, including that of a 23-year-old woman and a 14-year-old girl with 3-year and 7-year histories, respectively, of anaphylactic reactions to Apple pulp. In the first patient, eating raw Apples immediately elicited itching and tingling of the lips and mouth with severe oedema of the lips and tongue, irritation of the throat and slight colic in the upper abdomen. In the second, nausea and vomiting occurred after ingestion of Apples (93). Anaphylaxis may occur in association with other allergic manifestations such as contact urticaria (136). Anaphylaxis may be precipitated by Apple in association with exercise: this is food-dependant exercise-induced anaphylaxis (FDEIA) (137-143). Food-dependent exercise-induced anaphylaxis as a result of Apple has been described in a 14-year-old Japanese male who experienced repeated episodes of generalised urticaria and dyspnoea after ingesting Apple followed by exercise (143).

In a study of 99 children with atopic dermatitis, Hen's egg was the most common food allergen in children under 1 year of age. After that age, Apple, Carrot, Pea, and Soybean elicited positive reactions as often as Hen's egg (144).

Contact urticaria, although uncommon, can occur following contact with Apple (145).

Apple may present as a “hidden allergen” (146).

The authors of one study reported that oral challenge tests indicated an increase in clinical reactivity to Apples during the Birch pollen season in Birch-pollen allergic individuals (147).

Other reactions

All members of this genus contain the toxin hydrogen cyanide in their seeds and possibly also in their leaves, but almost never in their fruits. Hydrogen cyanide is the substance that gives Almonds their characteristic taste, but it should be consumed only in very small quantities. Apple seeds do not

normally contain very high quantities of hydrogen cyanide, but even so they should not be consumed in large quantities. In small quantities, hydrogen cyanide has been shown to stimulate respiration and improve digestion; it is also claimed (probably not accurately) to be of benefit in the treatment of cancer. In excess, however, it can cause respiratory failure and even death.

An anaphylactic reaction has been recorded to Apple juice containing acerola, the allergy reaction being to the acerola (148).

The acidity of Apple juice may result in bronchoconstriction in some individuals (149).

Auriculotemporal syndrome (Frey's syndrome, gustatory flushing) has occurred within minutes of eating Apple (150).

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Prunus armeniaca

Family: *Rosaceae*

Common name: Apricot

Source material: Peel from fresh fruit

Synonymes: *P. armeniaca* var. *vulgaris*, *Armeniaca vulgaris*, *Amygdalus armeniaca*

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is enclosed in a hard stony shell, often called a "stone", with a grainy, smooth texture except for 3 ridges running down the same side; the stone falls out easily when the fruit is halved. There are many varieties of Apricot (1).

Environment

Apricot is sold fresh, canned or dried. Dried Apricots are usually treated with sulphur dioxide to preserve their colour and to prevent spoilage.

Allergen Exposure

Geographical distribution

Apricot is a species of *Prunus*, classified with the Plum in the subgenus *Prunus*. Apricot most likely originated in northern and western China and Central Asia. It now thrives in most temperate climates. It ranks fifth in worldwide deciduous fruit production.

The Apricot tree grows 8 to 12 m in height. The leaves are ovate, 5 - 9 cm long and 4 - 8 cm wide, with a rounded base, a pointed tip and a finely serrated margin. The flowers are 2 - 4.5 cm in diameter, with 5 white to pinkish petals; they are produced singly or in pairs in early spring, before the leaves (1).

The Apricot fruit is a drupe similar to its relative Peach, but smaller, 1.5 - 2.5 cm in diameter (larger in some modern cultivars). Apricot ranges in colour from pale yellow to brilliant orange, often tinged red on the side most exposed to the sun; its surface is usually pubescent. The oval single seed (pit)

Unexpected exposure

A green dye can be obtained from the leaves or the fruit. The durable and handsome wood is used for tools. The kernels are poisonous until roasted, since they have high concentrations of cyanogenic glycosides, which are found in most stone fruit seeds, bark, and leaves. But the roasted pits are used in confections and to flavour liqueurs. An edible gum is obtained from the Apricot tree trunk. The oil may be used in perfumery, cosmetics and pharmaceuticals.

Allergens

The following allergens have been characterised:

Pru ar 1, a Bet v 1 homologue (2-3).

Pru ar 3, a lipid transfer protein (2,4-8).

Lipid transfer proteins concentrate in the pericarp (skin) of the fruit, whereas the pulp contains lower amounts of this allergen (5).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the *Rosaceae* family (Almond, Apple, Apricot, Peach, etc.), and more specifically of the genus *Rubus* (Cloudberry, Dewberry, Raspberry), could be expected, but this has not been documented as yet (9). Although extensive cross-reactivity among the family members may occur, it will be dependent on the specific allergens present and the individuals sensitisation to those allergens. This is illustrated by a study of 34 adult patients complaining of adverse reactions to *Rosaceae*, of whom 26 and 24 were shown to have skin reactivity and IgE antibodies, respectively, directed at *Rosaceae*. No evidence of clinical reactivity was found in 66% percent of positive SPT or 63% of positive IgE antibody determinations to fruits. A total of 226 food challenges was performed; most reactions were caused by Peach (22 patients), Apple (n=6), and Apricot (n=5). Ten patients (46%) were clinically allergic to Peach and other *Rosaceae*. The authors concluded that positive SPT and IgE antibody tests should not be taken as the only guide for multi-species dietary restrictions, yet potential clinical allergy to other *Rosaceae* should not be neglected (3).

Panallergens present in Apricot may result in variable degrees of cross-reactivity with other foods and plants containing these panallergens.

The major allergen Pru ar 1 from Apricot, along with the major allergens in Apple (Mal d 1), Pear (Pyr c 1) and Sweet cherry (Pru av 1), is a structural homologues of the Birch pollen major allergen Bet v 1, and may result in cross-reactivity with these and other plants and foods containing this panallergen (3).

Apricot lipid transfer protein (LTP), Pru ar 3, has a sequence amino acid identity of 91% and 94% with Peach and Almond LTPs, respectively, and is therefore highly cross-reactive. Apricot and Peach LTPs have a very similar structure to Maize LTP (6,8). Cherry LTP has a high amino acid sequence identity with the LTP from Apricot, Pru ar 3 (86%), as well as with that of Peach (Pru p 3, 88%), and Maize (Zea m 14, 59%) (7,10). Other foods that contain LTP include Blueberry,

Peanut, Walnut, Pistachio, Broccoli, Carrot, Celery, Tomato, Melon, Kiwi and Lettuce; this LTPs may contribute to severe systemic reactions (11-16). The LTPs of *Rosaceae* fruits, in particular Peach, are major allergens for Mediterranean and southern European populations, where LTP allergens play a large contributory role in adverse effects, mostly systemic, compared to Northern or Central Europe, where Bet v 1 homologues and profilin play a greater role, resulting mainly in oral allergy syndrome (17-18). However, the IgE-binding cross-reactivity due to fruit lipid transfer protein has varying degrees of clinical relevance, and this cross-reactivity is not necessarily accompanied by cross-allergenicity to the corresponding fruits (4,16).

Cross-reactivity with Latex has been suspected (19). In 137 patients with Latex allergy and food allergy diagnosed by a convincing history of possible IgE-mediated symptoms occurring within 60 minutes of ingestion, 49 potential allergic reactions to foods were identified in 29 patients. Foods responsible for these reactions included Banana in 9 patients (18.3%), Avocado in 8 (16.3%), shellfish in 6 (12.2%), fish in 4 (8.1%), Kiwi in 6 (12.2%), Tomato in 3 (6.1%), Watermelon, Peach, and Carrot in 2 (4.1%) each, and Apple, Chestnut, Cherry, Coconut, Apricot, Strawberry, and loquat in 1 (2.0%) each (20). Importantly, as suggested in a study of 2 children with Latex hypersensitivity, skin prick tests with fruit, including Apricot, may be positive, but no symptoms might result after ingestion (21).

Therefore, elimination diets requiring avoidance of all foods containing a panallergen, or relying only on the results of allergy testing, might result in unnecessary restriction of food (22).

Clinical Experience

IgE-mediated reactions

Apricot may result in allergic reactions, ranging from mild symptoms such as oral allergy syndrome to severe systemic reactions such as anaphylaxis (14-15,22-25).

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Allergy to Apricot and other *Rosaceae* fruit, in patients without a related pollen allergy, is often a severe clinical entity and occurs more commonly in Mediterranean and other southern European patients. A lipid transfer protein allergen is often implicated. Profilin and Bet v 1-related structures are not involved. *Rosaceae* fruit allergy is frequently associated with Birch pollinosis in Central and Northern Europe, and with grass pollen allergy in central Spain. The main cross-reactive structures involved for Birch pollen allergy are Bet v 1 and profilin, and for grass pollinosis they are profilin and carbohydrate determinants (26). In a study of 11 patients from central Spain allergic to *Rosaceae* fruit (Apple, Peach, and/or Pears) but not to pollen, who were compared with 22 control subjects with combined grass pollen and fruit allergy, symptoms were reported to be severe in the former group, with 82% of patients reporting systemic symptoms, mainly anaphylaxis (73%), whereas oral symptoms were less frequent (64%). Anaphylactic shock was observed in 36% of patients. The fruit allergens involved showed cross-reactivity among *Rosaceae* species but were not related to profilin or Bet v 1. Ninety-one percent of patients with combined grass pollinosis and fruit allergy reported oral allergy, 45% reported systemic symptoms, 18% reported anaphylaxis, and 9% reported anaphylactic shock (24).

Similarly, 30 Italian patients, all with oral allergy syndrome (2 with systemic reactions) to Apricot, were investigated with food challenges, SPT and IgE antibody tests to Apricot. All sera recognised a LTP, whereas other detected allergens were minor allergens (8).

A study was conducted at 17 clinics in 15 European cities to evaluate the differences among some Northern countries regarding what foods, according to patients, elicit hypersensitivity symptoms. It was reported, on the basis of questionnaires completed by food-allergic individuals concerning 86 different foods, that the foods believed to be most often eliciting symptoms in Russia, Estonia, and Lithuania were citrus fruits, chocolate, honey, Apple, Hazelnut, Strawberry, Fish, Tomato, Egg, and Milk, a profile that differed from Sweden and Denmark, where Birch

pollen-related foods, such as nuts, Apple, Pear, Kiwi, stone fruits, and Carrot, were the most common perceived causes. The most common symptoms reported were oral allergy syndrome and urticaria. Birch pollen-related food allergens seemed to dominate in Scandinavia, whereas some Mugwort-related foods were apparently of more importance in Russia and the Baltic States. Among 1,139 individuals, Apricot as the 27th most reported allergenic food, resulting in adverse effects in 18% (25).

A number of case studies illustrate the clinical effects of allergy to Apricot.

A 39-year-old female described the onset of acute urticaria, angioedema, shortness of breath, wheezing and dry cough after eating Mulberry for the first time. She described reactions which had previously occurred after eating White grape and, on another occasion, White grape and Apricot. Reactions were life-threatening, requiring emergency room visits. The IgE antibody level was 0.59 kU_A/l for Apricot and 1.15 kU_A/l for Grape (27).

In a study aimed at characterising Raspberry allergens, a 44-year old patient was described who had experienced oral allergy syndrome to Apple, facial angioedema from Peach, and anaphylaxis to Apricot. Prick-to-prick tests were positive to Apple, Peach, Cherry, and Apricot (24).

A study described a 21-year-old woman who developed primarily airborne sensitisation to LTP of Peach, with symptoms of severe perennial rhinitis, 6 months after starting work in a wholesale fruit storehouse in southern Italy, where large amounts of fruits, including Peach, were handled. Symptoms subsided when she left the workplace for more than 5 days and relapsed as soon as she was back at work. She subsequently developed severe food allergies to Peach, Hazelnut, Peanut, Apricot, Plum and Tomato (28).

Authors have suggested that in Birch pollen-allergic patients with allergy to *Rosaceae* fruit, skin prick tests with fresh food remain the most reliable method of diagnosing food hypersensitivity. In contrast, in patients not allergic to Birch pollen but with allergy to *Rosaceae* fruit, the most reliable strategy for detection of LTP sensitivity is skin prick testing

with properly prepared fruit peel extracts (29). However, with the advent of representative recombinant LTP allergens, IgE antibody evaluation may contribute to the diagnosis of allergy to Apricot (7).

Other reactions

Contact urticaria to Apricot stone has been described (30).

Intestinal obstruction in a 16-month-old boy as a result of the ingestion of whole dried Apricot has been reported. The fruit had been eaten several hours earlier and had swelled in the intestinal lumen (31).

Sulphur dioxide and other sulphite preservatives, used to preserve dried Apricot, may result in respiratory and other adverse reactions (32-33).

Cyanogenic glycosides are present in Apricot seed (kernel) (34). A 41-year-old woman became weak and dyspneic within 20 minutes of ingestion of Apricot kernels purchased at a health food store. The patient was comatose and hypothermic on presentation but responded promptly to antidotal therapy for cyanide poisoning (35).

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Asparagus officinalis

Family: *Alliaceae* (*Liliaceae*)

Common name: Asparagus

Source material: Frozen stem

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Allergen Exposure

Geographical distribution

Asparagus is a widely grown vegetable. Together with Garlic, the Onion and the Leek, it belongs to the *Alliaceae* (previously known as *Liliaceae*) or Lily family, which contains ferns and vegetables and flowers such as tulips. The genus *Asparagus* is made up of some 300 species.

The well-known table delicacy *Asparagus* has been cultivated for more than 2,000 years and has been much esteemed from the time of the Greeks and Romans. It is an important commercial and garden crop in many parts of the world. Its relatively high price tends to make it a luxury.

Asparagus is native to the marshes of southwest Europe and may be found wild on the seacoast in southwest England. In the southern parts of Russia and Poland the waste steppes are covered with this plant. It is also common as a wild plant in Greece. Otherwise, it is found in cultivated beds.

Asparagus plants are perennials with edible aerial stems (spears). There are 2 main varieties of *Asparagus*, the tougher green one, and the more tender white one, which is preferred in Europe and grown in shade or underground to keep it from producing chlorophyll.

Environment

Asparagus is available fresh, canned or frozen and is often served as a side dish after being steamed or briefly boiled. The tough base of the stem is usually removed before cooking, and sometimes the plant is peeled as well.

The smell in one's urine after eating *Asparagus* is caused by the substance methyl mercaptan. *Asparagus* is well known as a diuretic and laxative and has been used to treat gravel and dropsy. It has been a folk remedy for eye ailments, toothache, cramps, convulsions, and sciatica.

Allergens

At least 6 IgE-binding components, ranging from 22 to 73 kDa, have been detected in raw *Asparagus* and shown to be very labile and quite sensitive to heat denaturation (1). However, the presence of a heat-stable allergen was suggested due to the fact that IgE-mediated allergy has been reported to canned *Asparagus* (2). Subsequently, a heat-stable lipid transfer protein was characterised (3-4). In addition, profilin and glycoproteins harbouring complex asparagine-linked glycans may also be involved in *Asparagus* allergy (4). In a study of 10 *Asparagus*-allergic individuals, IgE-binding components of 15 and 45-70 kDa were detected (5).

The following allergens have been characterised:

Aspa o 1, a lipid transfer protein (3-4,6).

Aspa o 4, a profilin (4).

A Bet v 1 homologue is present (7-8).

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Two LTP (lipid transfer protein) isoforms (Aspa o 1.01, Aspa o 1.02) have been isolated from Asparagus, and demonstrated to have an amino acid sequence similar to that of Pru p 3 from Peach. Each elicited positive SPT responses in 9 of 18 patients with Asparagus allergy (4).

An allergen has been detected that may be a plant growth inhibitor, 1,2,3-Trithiane-5-carboxylic acid, which is present in young shoots (9). This substance, identified as a sulfur-containing growth inhibitor in one study, was shown to be a first contact allergen from Asparagus (10).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected, as well as to a certain degree among other members of the family *Alliaceae*, such as Onion, Leek, Garlic, and Chives (2,11-12).

Cross-reactivity can be expected with other foods or plants containing profilin or a Bet v 1 homologue allergen (4,6-7).

Asparagus contains a lipid transfer protein (Aspa o 1), which will result in variable degrees of cross-reactivity with other foods containing lipid transfer proteins (3).

Clinical Experience

IgE-mediated reactions

In sensitised individuals, Asparagus can induce symptoms of food allergy through ingestion, respiratory symptoms through inhalation, or cutaneous allergy through skin contact (1). Occupational contact dermatitis, contact urticaria, rhinoconjunctivitis and asthma have been reported (13-15).

Both delayed cell-mediated reactions and IgE-mediated reactions secondary to Asparagus have been described. IgE-mediated reactions can occur as food allergy or can be due to cutaneous or respiratory exposure, which is often occupational. Most reports of allergic reactions to Asparagus are from occupational settings. Anaphylaxis is the most common clinical picture of food allergy, while contact urticaria, rhinitis and asthma,

appearing either isolated or associated, are typical clinical pictures of occupational allergy. Sensitisation to different allergens is the likely cause of the different reactions to Asparagus (4,16).

Significantly, there appears to be no single typical clinical pattern for the expression of Asparagus allergy. In a Spanish study of 27 patients who had been diagnosed in the previous 5 years with hypersensitivity to Asparagus, 10 were diagnosed with urticaria or allergic contact dermatitis. All of these 27 cases seemed to result from occupational exposure (80% packing employees and 20% housewives). IgE antibodies for Asparagus were detected in 19 patients. Five had associated symptoms of respiratory allergy. Ten patients were diagnosed with rhinoconjunctivitis, of whom 8 had coexisting occupational asthma, confirmed by means of bronchial provocation. With the exception of 1 patient with asthma who had experienced an episode of severe anaphylaxis, all the others consumed Asparagus without symptoms. The authors attribute this to the fact that the LTPs are located preferentially in the external layers of the plant, which were removed before its consumption. In a group of 3 subjects who were diagnosed with allergy from ingestion of Asparagus, in 2 the symptoms were those of anaphylaxis, and 1 experienced only oral allergy syndrome. None of these were occupationally exposed to Asparagus. The authors concluded that the Asparagus LTPs appeared to be associated with more severe symptoms, e.g., anaphylaxis (12).

These findings were further elaborated upon in a second report evaluating these 27 subjects: 8 had allergic contact dermatitis alone, 17 had IgE-mediated allergy, and 2 had both allergic contact dermatitis and IgE-mediated allergy. Positive patch tests with crude Asparagus extract but not with lipid transfer protein were observed in subjects with allergic contact dermatitis (n=10). Of 19 patients with IgE-mediated disease, 10 had contact urticaria after Asparagus handling. Of these, 5 subjects and 5 others without skin allergy showed respiratory symptoms. Eight were diagnosed with occupational asthma, and this was confirmed by positive Asparagus inhalation challenge, whereas the remaining 2 had isolated rhinitis. Four patients

experienced immediate food-allergic reactions following ingestion of Asparagus; 3 reported anaphylaxis, and 1 experienced oral allergic syndrome. IgE antibody-binding proteins of 15 and 45-70 kDa were detected in 10 subjects. Of 10 subjects with skin reactivity to lipid transfer proteins, 6 showed bands at 15 kDa. The presence of IgE antibodies or skin reactivity for lipid transfer proteins was demonstrated in those with asthma (62%) and anaphylaxis (67%). The study concluded that Asparagus may result in occupational allergy, inducing allergic contact dermatitis as well as IgE-mediated reactions, that severe disease (anaphylaxis or asthma) is common, and that lipid transfer proteins appeared to play a major role (5).

In a study assessing the role of lipid transfer proteins in asparagus allergy, 18 patients with allergy to asparagus were enrolled. Asparagus allergy resulted in symptoms of asthma in 7, anaphylaxis in 1, rhinoconjunctivitis in 1, oral allergy syndrome in 1, contact urticaria in 6, and contact dermatitis in 2. Three patients had a combination of two symptoms. IgE antibody testing was positive in all, varying from 0.43 to 12.7 kU_A/l. The majority were exposed to Asparagus in an occupational setting (4).

Conjunctivitis, rhinitis, tightness of the throat and coughing during preparation of fresh Asparagus have been reported in 2 individuals. No symptoms occurred while the individuals were eating the cooked food. The authors suggest that the allergen was inhaled. Skin-prick tests with native green and white Asparagus were strongly positive, but negative with cooked Asparagus. Both patients had measurable levels of IgE antibodies against Asparagus (3.0 and 6.2 kU/l respectively). The Asparagus-specific IgE antibodies of the 2 patients were inhibited only by Asparagus, indicating that the patients were specifically sensitised by Asparagus and were not affected by cross-reactivity. No immunological cross-reactions could be detected (17).

Allergy to Asparagus may not always be obvious. In a 4-year-old child with multi-food allergy, significant skin reactivity was found to be directed at a number of foods, including Asparagus. However, IgE antibody testing was not able to detect Asparagus IgE above 0.35 kU_A/l (18).

Acute urticaria after ingestion of Asparagus has been reported (19). Two patients were reported with IgE-mediated contact urticaria to canned Asparagus (2).

Occupational asthma and rhinoconjunctivitis within 10 minutes were reported to occur in a 28-year-old man due to inhalation of Asparagus allergens during cutting of the spears while harvesting Asparagus (1).

Other reactions

Allergic contact dermatitis and contact urticaria have been caused by Asparagus (9,20). A 53-year-old farm worker presented with a 3-year history of occupational allergic contact dermatitis to Asparagus (8).

Fixed food eruptions caused by Asparagus in a 50-year-old white woman were reported. She presented with 2 sharply marginated, round, slightly elevated erythemas on her right forearm and left chest wall that appeared a few hours after ingestion of tinned Asparagus and persisted for more than 4 weeks, then faded slowly without treatment, leaving circumscribed areas of hyperpigmentation. She later experienced another 2 episodes at exactly the same locations after eating either fresh or tinned Asparagus. These areas of erythema never developed independently of Asparagus intake (21).

A 55-year-old cook presented with seasonal (always in May) recurrent eczema on both hands, which prevented him from working. He also reported several episodes of dysphagia and dyspnoea after ingestion of asparagus. IgE antibody level to Asparagus was 15.1 kU_A/l whereas IgE antibodies directed against other *Liliaceae* vegetables including Garlic and Onion could not be detected. Skin reactivity detected using prick-to-prick tests with native material of fresh, raw Asparagus and Asparagus cooked at 100 °C were positive, whereas Onion, Garlic, and Leek were negative. Epicutaneous patch testing with Asparagus resulted in a strong delayed-type skin reaction with a peak response on day 2 (22).

Asparagus is associated with the production of malodorous urine. This occurs in approximately 43% of people, and the propensity has been shown to remain with

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individuals for virtually a lifetime. Genetic studies suggest an autosomal dominant trait. Those who produce this odour assume that everyone does, and those who do not produce it have no idea of its potential olfactory consequences (23-24).

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Solanum melongena

Family: *Solanaceae*

Common names: Aubergine, Eggplant, Brinjal, Garden egg, Jew's apple, Mad apple, Pea apple, Egg apple, Guinea squash

Source

material: Fresh fruit

Major Varieties:

S. melongena – East Indian Aubergine

S. melongena esculentum – Common Aubergine

S. melongena depressum – Dwarf Aubergine

S. melongena serpentium – Snake Aubergine

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Allergen Exposure

Geographical distribution

Aubergine is a member of the nightshade (*Solanaceae*) family, which includes Tomato, Potato, and Bell pepper.

The cultivated Eggplant, *Solanum melongena*, is a species of considerable economic importance in many tropical and subtropical parts of the world (1). Eggplant is native to India or Africa. It spread eastward clear to Japan, and was introduced to Europe as early as the 13th century AD. From there it spread early to North and South America. The most important countries of production are China, Turkey, Japan, Egypt and Syria. It is often called “the poor man’s meat”, as it is rich in nutrients.

Eggplant is a perennial plant, but is cultivated as an annual. It is spiny and grows as high as 2 m, and has star-shaped, blue-violet leaves. Though commonly thought of as a vegetable, Eggplant is actually a fruit, specifically a berry. The fruit varies in shape from round to oblong, in size from a few centimetres to 30 cm, and in colour from dark violet to white. In the United States, the most common Eggplant is the large cylindrical or

pear-shaped variety with a smooth, glossy, dark-purple skin. It is available year-round, the peak season being August and September.

Environment

Eggplants are unknown in any wild variety, and their cultivation requires abundant water and warmth. They can be prepared in many ways: in stews, roasted or grilled, sautéed, stir-fried, breaded and fried, baked, pickled or stuffed.

Aubergines may contain large quantities of histamine. They cannot be eaten raw due to the potentially dangerous amounts of solanine they contain in that state.

In Suriname’s traditional medicine, the roots of the Eggplant are used against internal haemorrhage and asthma, the leaves and bark against dysentery.

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Allergens

No allergens from this plant have yet been characterised, although several IgE-binding Eggplant proteins have been reported (2). Recently, protein bands of 71, 64 and 60 kDa were detected in sera of 3 Indian Eggplant-allergic individuals. The 71 kDa protein appears to be heat-stable (3). The same authors subsequently reported on a 31-year old-individual with allergy caused by ingestion of Eggplant, in whom skin prick testing was positive with 4 varieties of Eggplant but with negative Aubergine IgE antibody levels. Laboratory analysis revealed that the causative allergen was a low-molecular-weight non-protein secondary metabolite of less than 1 kDa (4). The authors point out that possible non-protein but reaction-causing compounds in Eggplant include pigments (cyanidin, delphinidin, lycopanthin, and nasunin), alkaloids (solamargine, solanidine, solanine, solasodine, solasonine, and trigonelline), and phytosterols (5). The alkaloid properties of Aubergine have been suggested as the cause of occasional sensitivities to Aubergine (6), though direct evidence is still lacking (4).

In a Korean individual who experienced anaphylaxis to Aubergine with cross-reactivity to Latex, 3 IgE-binding proteins were identified from fresh and cooked Aubergine: 1 band between 22 and 36 kDa, 1 band near 36 kDa, and 1 band between 36 and 50 kDa (7).

A lipid transfer protein has been detected in Aubergine (8). In an allergenicity assessment of the related Ethiopian eggplant (*Solanum aethiopicum*), profilin and lipid transfer proteins have been detected (9).

Potential cross-reactivity

Eggplant is a member of the Nightshade family; it is closely related to the Potato and the Tomato. An extensive cross-reactivity among the different individual species of the genus could be expected, as well as to a certain degree among members of the family *Solanaceae* (2,10). This is supported by research reporting that antigenically cross-reactive material from Tobacco leaf could be found in Eggplants, Green peppers, Potatoes, and Tomatoes, which are all members of the family *Solanaceae* (11).

Allergic reactions to Eggplant in subjects with *Parietaria* pollen sensitisation have been reported (12).

A lipid transfer protein has been detected in Aubergine, which may result in cross-reactivity with other lipid transfer protein-containing foods (8).

Anaphylaxis to Eggplant was described in a patient with Latex allergy. Further investigation demonstrated that a protein in boiled Eggplant (and to a lesser degree, raw Eggplant) significantly inhibited Latex antigen. One IgE-binding component with the same molecular weight (between 22 and 36 kDa), from Eggplant and Latex, was detected as a candidate for the cross-reactivity; the protein did not display cross-reactivity with Potato (7). The clinical significance of this cross-sensitisation was illustrated in a 31-year-old Spanish woman with Latex allergy who was also allergic to Banana and Eggplant, as shown by case history and a skin prick test (13).

Clinical Experience

IgE-mediated reactions

Aubergine can induce symptoms of food allergy in sensitised individuals (4,8,12-13). But food allergy to ingesting the fruit of this plant is uncommon; reactions have been attributed to cross-reactivity with Tomato and grass pollen allergens in 1 individual (2), and with *Parietaria* pollen allergen in 5 cases (12).

Eggplant allergy following ingestion of the fruit has been described in 5 individuals, who were also sensitised to Wall pellitory (*Parietaria*) pollen: 3 women and 2 men aged between 24 and 50 years. In 3 cases, symptoms of OAS were reported (only oropharyngeal symptoms in 1; another also had symptoms of cough and dysphonia, and 1 had vomiting). Two had systemic symptoms as well (1 urticaria, 1 anaphylaxis) (12).

In a random survey of 500 individuals in India, 66 (11%) were reported as having Eggplant allergy, based on case history and skin tests. The authors suggest that this high incidence is probably due to the presence of histamine and serotonin in the plant. In this

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report, 3 cases of allergy following ingestion of Aubergine were described:

1) A 23-year-old woman with itchiness and an unpleasant feeling while eating food prepared with Eggplant. There was immediate rash, and facial oedema in about 20 minutes.

2) A 25-year-old man who developed itching within 15 minutes after eating any food prepared using Eggplant. Within an hour, the rash became prominent, with itching of the throat and hoarseness.

3) An 18-year-old-girl developed itching in the throat and of the skin within 30 minutes of the ingestion of Eggplant. Generalised uricaria with severe pruritis developed within 1 to 2 hours. SPT and prick-to-prick tests were positive in all 3. IgE antibodies to raw and cooked Eggplant were detected (3).

An Indian study reports on allergy caused by ingestion of Eggplant in a 31-year-old man. His allergy to Aubergine had clearly manifested at the age of 10 years, although symptoms had been first noticed by his mother at the age of 6. He experienced itching or discomfort while eating curry or other foods containing Aubergine. Within 1 to 2 hours of consuming foods containing Aubergine, itchy skin rashes appeared all over the body, along with itching of the throat and hoarseness. Skin prick tests were positive with 4 varieties of Eggplant; however, serum Aubergine-specific IgE antibodies were not detected. It was suggested that the causative allergen was a low-molecular-weight non-protein secondary metabolite of less than 1 kDa (4).

A 31-year-old Spanish woman developed anaphylaxis after eating Banana. She had had a previous diagnosis of Latex-fruit syndrome after presenting with rhinitis and skin and pharyngeal pruritus after eating Chestnut. She also experienced angioedema of the face and hands, conjunctivitis, generalised pruritus, glottic oedema and difficulty in breathing immediately after ingesting Aubergine (13).

Eggplant fruit has induced IgE-mediated immediate-type hypersensitivity reactions, such as rhinorrhoea, urticaria, food allergy and asthma (2).

An Indian study evaluated the possible effect of a specific elimination diet on symptoms of 24 children aged 3 to 15 years with documented deterioration in control of their perennial asthma. IgE antibody analysis for a range of food items found that 22 (92%) had IgE antibodies directed at Aubergine (14).

Anaphylaxis to Aubergine in a Latex-allergic 27-year-old female doctor was reported. She experienced generalised itching, dyspnoea, dizziness, vomiting, nausea, abdominal pain, diarrhoea, and rash over the whole body immediately after eating boiled Eggplant. Skin reactivity to raw and cooked Aubergine was detected. IgE antibodies to raw and cooked Aubergine were found, and 1 protein demonstrated a degree of cross-reactivity with a Latex protein (7).

Allergy to Aubergine pollen has been described. Immediate IgE-mediated hypersensitivity reactions (rhinorrhoea and asthma) were described in a 43-year-old man. He presented with rhinoconjunctivitis and a dry cough when working in a greenhouse where Eggplants were cultivated. SPT to Eggplant fruit was negative, but SPT and conjunctival challenge with extract from the flower petals and pollen was positive (16). Similarly, occupational allergy to the plant pollen in 2 commercial gardeners was reported (17).

Other reactions

Contact dermatitis due to Eggplant has been reported (15).

Contact dermatitis was reported in a 28-year-old woman. She had a 3-month history of bilateral hand eczema following home cultivation of Eggplants, Roses and Tomatoes. A patch test to chopped Eggplant leaves was positive. A delayed-type hypersensitivity reaction was suggested (18).

Aubergine is high in histamine, which may result in histamine reactions in susceptible individuals (19).

Aubergine contains the alkaloid alpha-solanine, which is a human plasma cholinesterase inhibitor (20).

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Persea americana

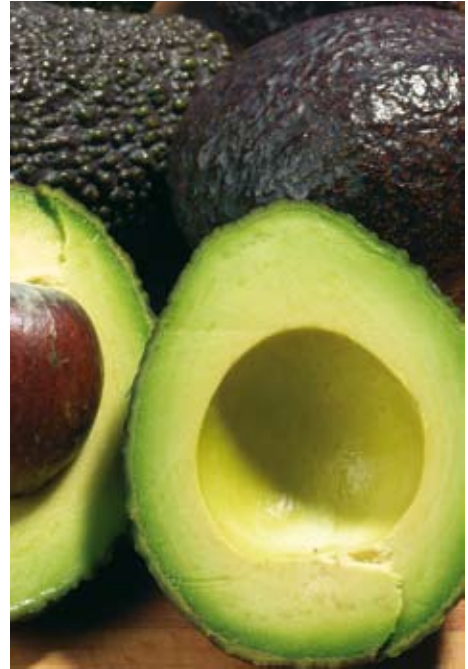
Family: Lauraceae

Common names: Avocado, Alligator pear, Midshipman's butter, Vegetable butter, Butter pear

Source material: Pulp from fresh fruit

Varieties:
 Guatemalan: *Persea nubigena* var. *guatemalensis* L. Wms.
 Mexican: *P. americana* var. *drymifolia* Blake
 West Indian: *P. americana* Mill. var. *americana* (*P. gratissima* Gaertn.)

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Allergen Exposure

Geographical distribution

The Avocado originated in Central and South America and spread to nearly all parts of the tropical and subtropical world with suitable environmental conditions. Among leading producers are the larger islands of the Caribbean, California, New Zealand, the Philippines, Australia, South Africa and several Mediterranean countries. It belongs to the *Lauraceae* family, together with Cinnamon and Laurel. There are many varieties of Avocado. Two of the most common are Hass avocado (dark-coloured, wrinkled skin) and Strong avocado (green, smooth skin).

The Avocado tree may be 18 m tall or more. It is almost evergreen, with dark-green, glossy leaves. The fruit is pear-shaped, oval, or nearly round, and up to 33 cm long and 15 cm wide. The skin varies from yellow-green to almost black according to which variety the fruit belongs to. Generally, the flesh is pale to rich yellow, buttery, and bland or nutlike in flavour.

Environment

Avocados can be diced into salads, added to soups, stews, chili or omelettes, stuffed or garnished (with other vegetables, seafood, or mayonnaise or other dressings), or mashed to make guacamole (a blend of the pureed flesh with Lemon or Lime juice, Onion juice or powder, minced Garlic, Chili powder or Tabasco sauce, and salt and pepper) or sandwich spreads or dressings. In some cultures Avocados are treated more as a fruits and used in desserts. But they are less versatile than many fruits and vegetables, as they cannot be frozen or cooked, and their rapid discoloration when exposed to air necessitates that they be added to dishes at the last minute or kept fresh with Lemon juice or other preservatives. The oil is sometimes extracted for food uses and the pulp saved for stock feed.

The fruit are a good source of vitamins and minerals, having twice the potassium content of Bananas. Avocados are high in monosaturates. The oil content is second only to that of Olives among fruits, and sometimes greater. Clinical studies in humans have shown that Avocado oil can reduce blood cholesterol.

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The oil is used as hair-dressing and as an ingredient in facial creams, hand lotions and fine soap. It is said to filter out the tanning rays of the sun, and is similar to lanolin in its penetrating and skin-softening action.

The seed and the roots contain an antibiotic that prevents bacterial spoilage of food and is the subject of 2 United States patents.

The skin and leaf juice are antibiotic. Among other uses, they are a treatment for worms, dysentery, pyorrhoea, wounds, diarrhoea, sore throat, toothache, skin eruptions and haemorrhage. Other functions include the stimulation and regulation of menstruation and the induction of abortion.

After 6 weeks, Avocado/Soybean unsaponifiables reduced the need for NSAID in patients with lower limb osteoarthritis (1).

Unexpected exposure

Avocado oil may be added to cosmetics.

Allergens

Several antigenic constituents between 10 and 120 kDa have been revealed by immunoblotting studies (2-3). Sera of 11 patients were used to characterise allergens in Kiwi fruit, Latex, Avocado, and Banana and to identify cross-reactions among these allergen extracts. In Avocado extract, IgE-binding components of 27, 43, 52, 58, 65, 75, and 88 kDa were seen. Immunoblot inhibition demonstrated that almost all IgE-reactive bands in Latex, Avocado, and Banana extracts and 2 components of 43 and 67 kDa in Kiwi fruit shared common IgE epitopes (4).

The following allergens have been characterised:

Pers a 1, a class 1 chitinase, also known as a hevein-like protein (5-12).

Pers a 4, a profilin (13).

Pers a hevein (11).

Pers a 1, the major Avocado allergen, is a class I chitinase. It is a 32 kDa heat-labile protein. In a study, Pers a 1 induced positive skin reactivity responses in 7 of 8 patients with Latex-fruit allergy (5,7-8); and in another study, it was recognised by 15 out of 20 Avocado- and/or Latex-allergic patients (9).

Pers a 1, a class I chitinase, is the panallergen involved in Latex-fruit syndrome. This substance was shown to be extensively degraded when subjected to simulated gastric fluid digestion, but the resulting peptides, particularly those corresponding to the hevein-like domain, were clearly reactive both *in vitro* and *in vivo* (10).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected but has not been documented yet (14).

Natural rubber latex IgE-mediated hypersensitivity is probably among the greatest challenges in the treatment of allergies during recent years. Some Latex allergens cross-react with plant-derived food allergens, and this has been termed the "Latex-fruit syndrome" (15). Almost 50% of the Latex-sensitised children have food allergies, mostly to Banana, Kiwi and Avocado (16).

Avocado contains a class I chitinase, a defense-related plant protein, and this panallergen results in extensive cross-reactivity with foods from different food families, including Green bean (6,17-18). The class I chitinase cross-reacts with a major Latex allergen, hevein, and is responsible for the syndrome (19-21). Hevein (Hev b 6.02 and Hev b 6.01) has elsewhere been reported to be the major cross-reacting allergen with Avocado in subjects with Latex allergy (8, 22-23). Sequence comparison has shown that Pers a 1 and prohevein had 70% similarity in their chitin-binding domains (9). This was confirmed by a study of Banana, Avocado, and Chestnut, which demonstrated a 65-70% sequence identity with the Latex hevein (24). Highly related 25 kDa class II chitinases lack the hevein-like domain, and in Avocado no IgE-binding capacity was shown by these class II enzymes (25). Skin prick test reactivities against purified proteins were examined in 15 patients with Natural rubber latex allergy. Eleven (73%) patients had skin prick test reactions to isolated hevein-like domains of Avocado and Banana, but only 1 (7%) patient reacted to their corresponding 31 kDa endochitinases. A hevein-like domain from Avocado and one from Banana inhibited

binding of IgE to prohevein (Hev b 6.01) in 59% and 38% of patients, respectively, whereas corresponding percentages for 31 kDa endochitinases were 17% and 20%, respectively. The study concluded that the isolated hevein-like domain molecules alone, but not when linked to endochitinases, seem to be responsible for IgE-mediated clinical reactions in Latex-fruit syndrome. Isolated hevein-like domains, but not 31 kDa endochitinases, are responsible for IgE-mediated *in vitro* and *in vivo* reactions in Latex-fruit syndrome (11).

Hevein has also been implicated in the cross-reactivity seen between Avocado, Custard apple and Aubergine. Purified Hev b 6.02 and Pers a 1 induced positive responses in skin prick tests (12).

The *Hevea brasiliensis* Latex chitinase, designated Hev b 11, displays 70% identity to the endochitinase from Avocado, and its hevein domain displays 58% identity to hevein (Hev b 6.02). A study concluded that Hev b 11, a class I chitinase, is another allergen from *Hevea* Latex with a chitin binding domain, but that it displays a different IgE binding capacity, compared with hevein (26). A recombinant Hev b 11.0102 class I chitinase from Natural rubber latex plant leaves was reported to represent an allergen of intermediate prevalence in NRL, and cross-reactivity with certain fruits was suggested (27).

Considerable immunologic cross-reactivity between Natural rubber latex and Avocado has been reported. In a study, sera from 18 patients with previously verified Latex allergy were used as the source of IgE antibodies, and 11 of the patients underwent SPT with fresh Avocado. Fourteen of the 18 sera (78%) had IgE antibodies that bound to a total of 17 Avocado proteins with apparent molecular weights ranging from 16 to 91 kDa. The 10 most strongly reacting sera were used for immunoblot inhibition studies. Binding of IgE antibodies to solid-phase Avocado proteins was inhibited in a dose-dependent manner: 100 micrograms of NRL proteins inhibited IgE binding to 15 of the 17 Avocado proteins, and 10 micrograms caused inhibition to 13 protein bands. Skin reactivity to fresh Avocado was detected in 7 of the 11 patients with Latex allergy. The study reported that

the large number of inhibitable proteins in immunoblot experiments, and clinical observations from skin prick tests suggest considerable immunologic cross-reactivity between NRL and Avocado. The study concluded that the observed cross-reacting protein components may be responsible for the recently reported type I hypersensitivity reactions to NRL and Avocado in patients with a pre-existing allergy to either allergen (3).

In a French study of 243 children attending an allergy out-patient unit during 1 year, the prevalence of Latex allergy was 1.3%. Avocado allergy was the food allergy most commonly associated with clinical symptoms (28).

A number of studies have reported cross-reactivity between Latex and a variety of foods, including Chestnut, Banana, Avocado, Passion fruit, Celery, Potato, Tomato, Kiwi and Peach (29-34).

An increasing number of plant sources, such as Avocado, Banana, Chestnut, Kiwi, Peach, Tomato, Potato and Bell pepper, have been associated with the Latex-fruit syndrome (35). Although in Latex-allergic patients multiple sensitisation to fruits may be observed, Banana and Avocado are the substances most frequently involved, followed by Chestnut and Melon (59). In 3 patients who developed anaphylactic reactions to both Latex and food, the food items that led to anaphylactic reactions were, for each patient, Banana and Avocado; Banana, Avocado and Buckwheat; and Banana, Avocado and Tomato (36).

Cross-reactivity with fruit in Latex-allergic patients has to be taken into account in evaluating and counseling, as it will be relevant for 60 to 70% of these individuals (37). Cross-reactivity may not be equal among the foods implicated. For example, in a study of 47 Latex-allergic patients, immunological reactivity to foods was found in 33. Seventeen patients manifested a clinical allergy to at least 1 food, including 11 cases of anaphylaxis, and 14 cases of local sensitivity reactions. Positive food skin reactivity was detected most frequently with Avocado (53%), Potato (40%), Banana (38%), Tomato (28%), Chestnut (28%), and Kiwi (17%). Cross-reactivity to Potato in

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Latex-allergic patients may result from a broad class of plant proteins known as patatins (38). Hev b 7 is a *Hevea brasiliensis* Latex allergen with sequence identities of 39% to 42% to patatins. However, Hev b 7, patatins, and their homologues do not contribute to cross-reactivity in Latex-fruit syndrome (39).

Other studies have reported similar findings. In a study of cross-reactivity among 13 Latex-allergic individuals also allergic to food, the most frequent food hypersensitivities were to Avocado (n=9), Chestnut (n=9), Banana (n=7), Kiwi (n=5) and Papaya (n=3) (40). Similarly, in a study investigating the prevalence of Natural rubber latex sensitisation and allergy in children with atopic dermatitis, 12 of the 74 atopic children studied had circulating IgE antibodies to Latex. Of the specific food IgE evaluations, 18.4% (93 out of 505) were positive, and 69.9% were observed in the group of children with Latex-specific IgE antibodies; the evaluations were most frequently positive to Potato, Tomato, Sweet pepper, and Avocado. Twenty children without proven Latex sensitisation showed increased food-specific IgE antibodies, most frequently to Potato, Banana, and Chestnut (41).

Similarly, in 82 patients (43 men and 39 women, aged between 18 and 45 years) with Latex allergy, 39 (47.5%) were found to have positive SPT to fruit. SPT with fruit extracts was positive in 28 patients (Kiwi [n=21], Banana [n=17], Avocado [n=8], Papaya [n=3]); the prick-by-prick test showed a lower number of positive results (Kiwi [n=7], Banana [n=4], and Avocado [n=3]) (42).

In 137 patients with Latex allergy (with food allergy having been diagnosed by a convincing history of possible IgE-mediated symptoms occurring within 60 minutes of ingestion), 49 potential allergic reactions to foods were identified in 29 (21.1%) patients. Foods responsible for these reactions included Banana (n=9; 18.3%), Avocado (n=8; 16.3%), shellfish (n=6; 12.2%), fish (n=4; 8.1%), Kiwi (n=6; 12.2%), Tomato (n=3; 6.1%), Watermelon, Peach, Carrot (n=2; 4.1% each), and Apple, Chestnut, Cherry, Coconut, Apricot, Strawberry, and loquat, (n=1; 2.0% each). Reactions to foods included local mouth irritation, angioedema, urticaria, asthma, nausea, vomiting, diarrhoea, rhinitis, and anaphylaxis (43).

In a Latex allergy study, positive food-specific IgE antibody tests occurred most frequently with Avocado (53%), Potato (40%), Banana (38%), Tomato (28%), Chestnut (28%), and Kiwi (17%) (38).

The majority of studies document cross-reactivity between Latex allergy and Avocado, 1 among a number of cross-reactive foods, but not often between Avocado and other food. Nonetheless, these studies indicate that an Avocado-allergic individual is at risk of being allergic to a number of these foods because of the presence of the class I chitinase. Illustrating this, in a study of 17 serum samples from patients with well-documented Latex allergy, 10 demonstrated an allergy to Avocado, sometimes associated with Banana (2). In a study examining Banana allergy in 4 patients who were Banana-allergic, 1 patient also had a sensitisation to Avocado, but not to Latex or pollen (44).

However, Latex-allergic individuals may demonstrate IgE antibodies to these cross-reactive foods without clinical significance. For example, in a report of 2 children with Latex allergy, skin reactivity was detected for Banana, Kiwi, Pineapple, Apricot, Avocado, and Grape, but these children presented no symptoms after ingestion of these fruits (45). This finding is supported by a number of other studies. In a study of 136 patients with well-documented, clinically relevant, immediate-type hypersensitivity against Latex proteins, serum samples were analysed for IgE antibodies against a panel of different fruits. Cross-reacting IgE antibodies recognising Latex and fruit allergens (Papaya, Avocado, Banana, Chestnut, Passion fruit, Fig, Melon, Mango, Kiwi, Pineapple, Peach, and Tomato) were demonstrated by RAST-inhibition tests. Of the patients, 42.5% reported allergic symptoms after ingestion of these fruits, and a total of 112 intolerance reactions were recorded. However, fruit-specific IgE antibodies were detected in serum samples from only 32.1% of the patients who perceived symptoms due to these fruits. Therefore, serologic tests seem to be of low efficacy for prediction of food allergy in Latex-allergic patients (46). In 2 atopic Latex allergy patients with skin reactivity and IgE antibodies to Avocado and other fruit, no clinical symptoms occurred (47).

Chao 2, a major allergen of Japanese cypress (*Chamaecyparis obtuse*) pollen, displays a high homology (a 74.3% identity) with Cry j 2, a major allergen of Japanese cedar (*Cryptomeria japonica*) pollen. This allergen is a polygalacturonase and showed a significant identity with a similar protein isolated in Avocado, Tomato, and Maize, as well as Cry j 2 (48). The deduced amino acid sequence of cloned Cry j II showed significant identities to those of the polygalacturonases associated with fruit ripening in Tomato (40%) and Avocado (43%) and also found in pollen of Maize (34%) (49). The allergenic potential of the Avocado-equivalent protein was not examined.

Allergy to other foods has been associated with Kiwi allergy: among Kiwi-allergic patients, there were strong reactions to Apple and Hazelnut; and moderate reactions to Carrot, Potato, and Avocado. A proposed mechanism was not suggested (50). Similarly, cross-reactivity among Apricot, Avocado, Banana, Cherry, Chestnut, Grape, Kiwi, Papaya, Passion fruit, Peach and Pineapple was reported (51).

In a study of 5 patients with oral allergy syndrome or anaphylaxis after the ingestion of Fig, and 1 patient with symptoms from exposure to *Ficus benjamina* trees (Weeping Fig), skin reactivity was demonstrated most often to Kiwi fruit, Papaya, and Avocado. Sensitisation to Rubber latex could not be demonstrated in any of the patients. The study concluded that allergic reactions to fresh or dried Fig can present as a consequence of primary sensitisation to airborne *Ficus benjamina* allergens independent of sensitization to Rubber Latex allergens. Kiwi fruit, Papaya, and Avocado as well as Pineapple and Banana may be other fruits associated with sensitisation to *Ficus* allergens (52).

Among 4 patients with an allergy to *Ficus benjamina*, the 2 plant growers showed a cross-allergy to other *Ficus* species. Two patients had a cross-allergy to Latex and the associated cluster of tropical fruit (Banana, Kiwi, Avocado, and Chestnut) (53).

In a study that reported a sensitisation prevalence of 2.5% to *Ficus benjamina* Latex that occurred mostly independently of Latex

allergy, sensitisation to *F. benjamina* was specifically associated with positive skin tests to fresh Fig (83%), dried Fig (37%), Kiwi fruit (28%), Papaya (22%), Avocado (19%), Banana (15%), and Pineapple (10%) (n = 54). The authors suggested that the cross-reactivity was mediated at least in part by the thiolproteases ficin and Papain (54).

In a study investigating the prevalence of Avocado allergy, 8 of 21 Avocado SPT positive patients reported that symptoms repeatedly followed the ingestion of Avocado; 7 also reported oral symptoms following Cantaloupe ingestion (55).

Clinical Experience

IgE-mediated reactions

Avocado may commonly induce symptoms of food allergy in sensitised individuals (9,56-58), although the majority of reports describing allergy to Avocado do so in the context of cross-reactivity to Latex allergy ("Latex-fruit syndrome") (11,42). The prevalence of Avocado allergy in the general population has been estimated to be around 1%, but this is increasing as consumption of Avocado dishes is increasing (9). Approximately 20% of atopic patients may have positive SPT to Avocado (55). Symptoms include local mouth irritation, angioedema, urticaria, abdominal pain, asthma, nausea, vomiting, diarrhoea, rhinoconjunctivitis, and anaphylaxis (31,43,55,59). Individuals experiencing itching in the mouth, diarrhoea, and/or swelling of the lips have been described (4). Oral allergy syndrome has also been reported (3,60).

In a study examining the prevalence of Avocado-induced symptoms, these were reported to occur in 8% of 100 consecutive atopic allergic rhinitis patients unselected for Avocado reactivity (55).

A study was conducted at 17 clinics in 15 European cities to evaluate the differences among some northern countries regarding what foods, according to food-allergic patients, elicit hypersensitivity symptoms. It was reported, after evaluation of questionnaires concerning 86 different foods, that the foods apparently most often eliciting symptoms in

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Russia, Estonia, and Lithuania were citrus fruits, chocolate, honey, Apple, Hazelnut, Strawberry, fish, Tomato, Hen's egg, and Milk; these results differed from those of Sweden and Denmark, where Birch pollen-related foods, such as nuts, Apple, Pear, Kiwi, stone fruits, and Carrot, were the most common reported causes. The most common symptoms reported were oral allergy syndrome and urticaria. Birch pollen-related foods apparently dominated as allergens in Scandinavia, whereas some Mugwort-related foods seemed to be of more importance in Russia and the Baltic States. Among 1,139 individuals, Avocado was the 50th most reported food allergen, resulting in adverse effects in 9.0% (61).

In a study investigating the prevalence of Avocado allergy, 100 consecutive atopic patients with allergic rhinitis who underwent skin testing were also skin prick-tested to Avocado and/or tested for IgE antibodies to Avocado. Of the 100 atopic patients not selected for Avocado sensitivity, 21 had positive prick skin tests to Avocado. Eight of the 21 Avocado SPT-positive patients reported that symptoms repeatedly followed the ingestion of Avocado; 2 reported systemic reactions, but 6 noted oral symptoms only. Serum IgE antibodies to Avocado were elevated in 7 of the 8 patients reporting symptoms after eating Avocado (55).

In a study of 17 patients with immediate hypersensitivity to Avocado, systemic anaphylaxis occurred in 7, angioedema/urticaria in 6, vomiting in 2, asthma in 1, and rhinoconjunctivitis in 1. Skin prick tests with fresh Avocado were positive in all patients with the Strong avocado variety (SAv) and in 14 patients with the Hass avocado variety (HAv). Patient-associated sensitisations were as follows: 10 to Latex, 8 to Chestnut, 8 to Banana, 4 to Kiwi, and 4 to Walnut. Avocado-sensitised patients with Latex allergy were typically middle-aged women, professionally exposed to Latex, who also exhibited frequent associated sensitisations to Chestnut, Banana, and other fruits. IgE antibodies against Avocado were demonstrated in 11 of the patients. The study reported that despite its lower protein content, SAv seems to be more allergenic than HAv, both *in vivo* and *in vitro* (40).

Food hypersensitivity is less frequent among adult patients than in childhood. In a study of 7,698 patients visiting an outpatient clinic, 120 reported consistent clinical symptoms after consumption of 1 or more foods: Shrimp (n=48), Squid (n=33), Kiwi (n=14), Papaya (n=14), Avocado (n=13) and Banana (n=12) were the most frequent causes of food hypersensitivity (62).

A 6-year-old boy was reported who presented with cutaneous and respiratory reactions to Banana and Avocado and from whom a history of adverse reactions to common Latex products was also elicited. IgE antibody test to Latex was strongly positive, equivocal to Avocado and Chestnut, and negative to Banana and Kiwi fruit, but the skin prick test was positive for Banana, Avocado and Chestnut (63). Other case reports indicate the variability of Avocado allergy; for example, a report was made of a Banana-allergic infant with IgE reactivity to Avocado but not to Latex (64).

Anaphylactic reaction to Avocado has been reported in a patient with pre-existing allergy to Natural rubber latex (65), and *vice versa* (66). In 2002, 107 cases were reported to the French Allergy Vigilance Network, of which 59.8 % were cases of anaphylactic shock, 18.7% systemic reactions, 15.9% laryngeal angioedema, and 5.6% serious acute asthma (including a fatality). Adults represented 69% of cases (74 cases). The most frequent causal allergens were Peanut, nuts, shellfish, and Latex group fruit (with 9 cases). The most frequent culprit foods for patients allergic to Latex were Avocado (n=4), Kiwi (n=2), Fig (n=2), and Banana (n=1) (67).

Contact urticaria from Latex in a patient with immediate hypersensitivity to Banana, Avocado and Peach was reported (68).

Reaction to Avocado oil in sunscreen has been documented (69-70).

Other reactions

Ingesting large amounts of Avocado may interfere with warfarin's anti-clotting effects (71-72).

Vasoactive amines may result in allergy-like reactions.

Lactating livestock eating Avocado leaves may develop non-infectious mastitis and agalactia. The effects were attributed to an isolate, termed “persin,” found in Avocado leaves, which has been shown to have antifungal properties and to be toxic to silkworms (73). Other animals affected adversely are goats, horses and ostriches that have died of cardiomyopathy, heart failure and respiratory distress after eating Avocado leaves of Hass and Fuerte cultivars (74-75). Adverse effects have occurred in dogs that eat Avocado fruit (76). Dopamine has been found in the leaves. The leaf oil contains methyl chavicol. The seeds, ground and mixed with cheese or cornmeal, have been used to poison rodents.

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f51 Bamboo shoot



Allergen Exposure

Geographical distribution

The Bamboo is cultivated in China and Japan for its edible young shoots and for other uses. There are 91 genera and about 1,000 species (1), but only a small number of species produce ingredients common in Asian cookery. Although Bamboo plants are tree-like and can be very tall, they are grasses and are closely related to Maize and Wheat.

Moso is the name common in the East for the evergreen type of Bamboo tree that produces edible shoots. The tree has blue-green culms covered with white powder when new, and pale, dense, bending foliage. Growth can be over 6 m high, and flowering may be at intervals of many years. The shoots are harvested in the spring when they are about 8 cm above the ground. They are cut about 5 cm below soil level.

The season for Bamboo shoots in Japan is the early part of the spring, when 3 kinds are common: Moso, Madake and Hachiku. Several species of the closely related genera *Phyllostachys*, *Bambusa* and *Dendrocalamus* are eaten fresh in season or canned.

Phyllostachys pubescens

Family: *Poaceae*

Common names: Bamboo shoot, Pubescent bamboo, Moso, Madake, Hachiku

Source material: Fresh shoot

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Environment

Bamboo grows in woodland and cultivated groves, but requires special damp, steadily warm, sheltered and rich-soiled conditions that make it rare in the West.

The tender-crisp, ivory-coloured shoots (new culms that come out of the ground) of Bamboo are edible. They are used in numerous Asian broths and other dishes, and are available in supermarkets in various sliced forms, both canned and (rarely in the West) fresh. Fermented Bamboo shoots, called khorisa, are an important ingredient in certain cuisines. The shoots of some species must be cooked before eating, as they contain hydrocyanic acid that can cause cyanide poisoning (1).

Like other grasses, Bamboo has stems containing sugar, and syrup is made from them. The traditional Taiwanese manner of preparing this food involves fermenting the stems. They are most often used as an ingredient in traditional Asian dishes, but may be a garnish on other foods as well.

Bamboo is used in Chinese medicine for treating infections. The leaves are used in the treatment of arthritic inflammations. The sheaths of the stem are a treatment for nausea and sour stomach.

The canes make good water pipes. They are also used for household utensils, various types of woven handicrafts, papermaking, and even heavy construction. The rhizomes are used as walking sticks and umbrella handles.

Unexpected exposure

See under Environment.

Allergens

No allergens from this plant have yet been characterised.

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected, as well as to a certain degree among members of the family *Poaceae* (2).

Clinical Experience

IgE-mediated reactions

Anecdotal evidence suggests that Bamboo can occasionally induce symptoms of food allergy in sensitised individuals; however, few studies have been reported to date.

IgE antibodies to Bamboo have been reported in patients with atopic dermatitis, rhinitis and asthma (3). The efficacy of Pharmacia CAP System ImmunoCAP® for Bamboo f51, compared to SPT, was reported to be high (4).

Bamboo shoots were suspected of contributing to allergic symptoms in agricultural workers in Japan (5).

Other reactions

Contact allergy and delayed hypersensitivity has also been reported (6).

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f92 Banana



Musa acuminata / sapientum / paradisiaca

Family: *Musaceae*

Common names: Banana, Plantain

Source material: Ripe fresh fruit

Commercial dessert (or common) Banana cultivars most frequently eaten in temperate countries are of the species *M. acuminata* or the hybrid *M. x paradisiaca*, a cultigen). However, *M. x paradisiaca* is also the generic name for the common plantain, a coarser and starchier variant not to be confused with *M. acuminata*, or the Cavendish variety. Common banana is most often eaten raw, whereas plantain is eaten cooked.

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Allergen Exposure

Geographical distribution

Banana is the common name for a fruit and also for the herbaceous plants of the genus *Musa* that produce this popular fruit. Banana plants are of the family *Musaceae*. They are cultivated primarily for their fruit, and to a lesser extent for the production of fibre and as ornamental plants (1).

Banana originated in Southeast Asia. Bananas are now grown in a variety of tropical regions throughout the world, and the ease of harvesting, shipping and storing makes them the cheapest and most readily available fruits. “Ripening rooms” allow distributors to control the state of Bananas for optimum convenience. Ripening rooms are special rooms made air-tight and filled with ethylene gas to induce ripening.

Bananas are often mistaken for trees, when in fact the main or upright stem is a pseudostem. This grows from a corm, which for some species can obtain a height of 2-8 m, with leaves of up to 3.5 m in length. Each pseudostem can produce a bunch of yellow, green, or even red Bananas before dying and being replaced by another pseudostem (1).

The Banana fruit grows in hanging clusters, with up to 20 fruit to a tier (called a hand), and 3-20 tiers to a bunch. The total of the hanging clusters is known as a bunch, or commercially as a “Banana stem”, and can weigh from 30–50 kg. Banana has a protective outer layer (a peel or skin) with a fleshy edible inner portion. Western cultures generally eat the inside raw and throw away the skin while some Asian cultures generally eat both the skin and inside cooked (1).

There are two main species. Common banana is sweet and rather mealy and is most often eaten raw, whereas Plantain is hard and starchy and is eaten cooked. The colour, size and shape of the fruits, however, are similar.

Environment

Bananas eaten raw are an important natural convenience food in industrialised countries, not requiring (and in fact being spoiled by) refrigeration, and being very easy to peel and eat out of hand. Bananas are also found in fruit salads and many other deserts. Plantains are not a familiar food in the West, but in a number of other regions they form an important part of staple diets. Bananas are extremely nutritious, containing an especially high level of potassium, and several other

important substances. Banana's consistency makes it an ideal food to introduce into the diet of young infants.

Bananas have a very wide range of medicinal uses, including in the treatment of high blood pressure and constipation. Natural Banana essence is added to some processed foods and to some medicines as a flavourant. The peels have household uses such as cleaning and shining. Banana is a common ingredient of cosmetics and toiletries, but as in the case of edible products, the "Banana" may be artificial.

Unexpected exposure

See under Environment.

Allergens

The following allergens have been characterised:

Mus xp 1, a profilin (2-7).

Mus a Glucanase, (from *M. acuminata*), a member of the beta-1,3-glucanase family (8-11).

Mus xp Chitinase, a 32-33 kDa protein, a class 1 chitinase, a hevein-like protein (6,12-14).

Mus xp Hevein, a hevein-like protein (12).

Mus xp TLP, a thaumatin-like protein (15).

IgE binding to the recombinant Banana profilin was demonstrated in 7 of 16 Banana-allergic subjects (5).

Although no other allergens have been characterised to date, there have been a number of antigenic proteins identified. In a Latex-allergic patient study, 16 allergenic components were identified in Banana, with molecular weights ranging from 17 to 128 kDa. Two were considered to be major allergens: a 33 kDa protein was detected in 15 of 19 sera (88%), and a 37 kDa in 13 of 19 sera (76%) (6). The 33 kDa allergen may be a chitinase similar to that reported in a study describing the isolation of 32 kDa and 34 kDa allergens, class I chitinases with a hevein-like domain, shown to be major allergens in Banana fruit. The 2 purified allergens detected Banana skin reactivity in more than 50% of 15 Banana-

allergic patients (13,16). Proteins of 40, 52, 58, 88 and 94 kDa have also been detected (2). Other studies have isolated from Banana extract a 40 kDa protein showing strong IgE binding, and allergens of 52, 58, 88 and 94 kDa were detected (17). In a patient sensitised to Avocado, but not to Latex or pollen, a single allergen of 70 kDa was detected (2).

Among sera from 22 Latex-allergic patients, 10 (45%) recognised 14 allergens in Banana. The most frequently identified Banana allergens were 23, 32, 36, 39 and 47 kDa proteins. Skin reactivity to Banana was found in 14 of 18 Latex-allergic patients studied, and Banana RAST in 12 of 14 patient sera tested (18).

The pulp of ripe Bananas contains an abundant thaumatin-like protein (TLP) (19). Thaumatin allergens have allergenic potential, but in Banana, TLP may be different and was not evaluated. Although the Banana thaumatin-like protein adopts an overall fold similar to that of thaumatin and thaumatin-like PR-5 proteins, and TLPs have antifungal properties, the Banana TLP was apparently devoid of antifungal activity. Pulp of Plantains also contains a very similar TLP, which is even more abundant than its Banana homologue (20).

One of the predominant proteins in the pulp of ripe Bananas and Plantains has been identified as a lectin. The clinical relevance of this Banana lectin to food safety is at present unknown (21).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus, basically Banana and Plantain, could be expected (22).

Allergy to Latex is a increasing occupational and public health problem. Through the analysis of IgE antibodies against Latex, the prevalence of Latex sensitisation in the general population has been estimated to be approximately 4-7% (23). Certain groups are at higher risk. Approximately 24-60% of patients with spina bifida may be sensitised to Latex. Between 3 and 25% of healthcare workers may be sensitised (24-25). Other high-risk groups include greenhouse and rubber workers. Approximately 42%-50% of patients

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with Latex allergy have hypersensitivity to some foods; Avocado, Banana, Chestnut and Kiwi are those most frequently detected (26-38). In a study examining food items that led to anaphylactic reactions in Latex-allergic individuals, several patterns of cross-reactivity have been demonstrated: Banana and Avocado; Banana, Avocado and Buckwheat; and Banana, Avocado and Tomato (39). Furthermore, cross-reactivity may occur between Banana and Avocado without concomitant sensitisation to Latex (40).

A number of panallergens may be involved in Latex-fruit cross-reactivity. Banana, Avocado, Chestnut and Kiwi are the most frequently implicated foods, but associations with several other fruits and vegetables have been reported. The allergen responsible for most cases of this syndrome is an isolated hevein (Hev b 6.02), the amino-terminal fragment of prohevein, but not the 31 kDa endochitinase. The homologous protein in Banana is Mus xp Hevein (12,41). This panallergen has recently been shown to occur in Custard apple, with affected individuals also experiencing anaphylaxis to Banana (42). Endo-beta-1,3-glucanase, the Banana glucanase, may account for some of the IgE-binding cross-reactivity frequently reported in patients with Latex-fruit syndrome (9). This allergen has also been shown to occur in Olive (Ole e 9), Ash and Birch pollens, and in Tomato, Potato, Bell pepper and Latex (10).

Approximately 45% of Latex-allergic individuals are also allergic to Banana, Kiwi and Avocado (35,43-44). In a study of 47 Latex-allergic patients, immunological reactivity to foods was found in 33. Positive Banana SPT was demonstrated most frequently with Avocado (53%) and Banana (38%) (35). In another study, 8 of 16 Latex-allergic patients (50%) reported symptoms after eating Bananas, and skin reactivity was found to Banana in 5 of 14 patients (36%). Banana RAST results were positive in 12 of the 19 patients (63%). Seventeen of the 19 patients (89%) exhibited specific Banana IgE antibodies (6).

Other studies have had similar findings. Among 82 adult patients with Latex allergy, Banana skin reactivity was found in 17 (45).

Not all Latex-allergic individuals are also allergic to Banana. In a study examining the sera of 47 Latex-allergic individuals by RAST, 66% were shown to be positive to Latex and 55% to Banana. Of the 31 Latex-positive sera, 25 were also Banana-positive. Skin reactivity to Banana was found in 11 of the 31 patients tested, and symptoms after eating Bananas were reported by 16 (52%) of the 31 patients. Cross-reactivity between Banana and Latex was demonstrated in inhibition studies and other studies (46). Similarly, in 2 children with Latex hypersensitivity, Banana SPT and SPT to a number of other fruits were positive, but the children presented no symptoms after ingestion of these fruits (47).

The association between Latex and Banana allergy has been shown to be due to a class I chitinase panallergen (13,16,48). In a study of patients allergic to Latex, 9 of 15 sera with IgE to hevein showed IgE binding to 32 and 33 kDa Banana proteins. The 33 kDa protein showed over 90% identity to endochitinases of several plants (14). The role of chitinase has been demonstrated in other studies (49). The Banana, Avocado, and Chestnut chitinases share 65-70% sequence identity with the Latex hevein chitinase (50). Therefore, although Banana contains a number of allergens, individuals allergic to the class I chitinase allergen in Banana will likely be cross-reactive with other class I chitinase-containing foods, *e.g.*, Avocado, Chestnut, Cherimoya, Passion fruit, Kiwi, Papaya, Mango, Tomato and Wheat (these allergens are heat-inactivated and appear to be activated by "stress" to the plant) (51). Chitinases have been shown to play a major role in the cross-reactivity between Banana, Chestnut and Kiwi (52).

The corollary holds, that in Banana-allergic children (or children with allergies to other fruits), co-existing Latex allergy should be considered, in particular in cases of urticaria or anaphylaxis for which the cause is unknown (32,53). Among 57 fruit-allergic patients, immunologic Latex sensitisation occurred in 49 (85.9%). Six out of 57 (10.5%) suffered from clinically relevant Latex allergy. In all patients, clinical symptoms to fruits preceded a history of Latex allergy. The fruits most often associated were Melon, Peach, and Banana (54).

Banana contains a profilin panallergen. Banana profilin has been demonstrated to have a 71-84% sequence identity to other pollen and ingested profilins. Cross-reactivity between pollen and exotic foods containing profilin is possible (5). Ten percent to 15% of Birch pollen-allergic individuals have IgE antibodies to the 35 kDa minor Birch pollen allergen, and there is cross-reactivity with proteins of comparable size from Litchi, Mango, Banana, Orange, Apple, Pear and Carrot (55). In a study of Birch pollen allergy, hypersensitivity to Bet v 2 was strongly associated with clinical allergy to citrus fruits, Melon and Watermelon, Banana, and Tomato. The efficacy of a history of allergy to gourd fruits, citrus fruits, Tomato, Banana, or a combination thereof as a means of detecting profilin-hypersensitive patients was 85% (41/48). The study concluded that in clinical settings in which laboratory investigations are not easy to carry out, allergy to Melon, Watermelon, citrus fruits, Tomato, and Banana can be used as a marker of profilin hypersensitivity once a sensitisation to Natural rubber latex and lipid transfer protein is ruled out (7,56).

In some instances, cross-reactivity has been described for which a panallergen had not been determined. In individuals sensitised to Ficus allergens, sensitisation to Kiwi fruit, Papaya, and Avocado, as well as to Pineapple and Banana, may occur (57). Sensitisation to *Ficus benjamina* Latex has been shown to be specifically associated with positive skin tests to fresh Fig (83%), dried Fig (37%), Kiwi fruit (28%), Papaya (22%), Avocado (19%), Banana (15%), and Pineapple (10%). This cross-reactivity is mediated at least in part by the thiol proteases ficin and Papain (58).

Similarly, sensitisation to the Latex of *F. benjamina*, *H. brasiliensis*, breadfruit and Banana was demonstrated in a patient allergic to Banana, *F. benjamina* and breadfruit. RAST inhibition studies showed that IgE antibodies to breadfruit Latex cross-reacted more strongly with Latex of *H. brasiliensis* and Banana than it did with Latex of *F. benjamina* (59). Two of 4 patients with an allergy to *Ficus benjamina* had a cross-allergy to Latex and the associated cluster of tropical fruit (Banana, Kiwi, Avocado) and Chestnut, implying that

the panallergen chitinase is responsible for these items cross-reacting (60).

A positive allergenic correlation between *Platanus* (London plane tree) pollen and Hazelnut, Peanut, Banana and Celery has been described. RAST inhibition experiments indicated an important cross-reactivity among the pollen of *Platanus acerifolia* and Hazelnut and Banana fruit, and an intermediate cross-reactivity with Celery and Peanut as foods (61). Whether this cross-reactivity occurs as a result of the panallergen profilin was not determined.

In a study of 53 patients (19 positive on a DBPCFC) with Melon allergy, the most common foods associated with this allergy were Avocado (n=7), Banana (n=7), Kiwi (n=6), Watermelon (n=6), and Peach (n=5) (62).

Similarly, in a study investigating the prevalence of Avocado allergy, in 100 consecutive atopic patients with allergic rhinitis, 4 reported similar symptoms upon eating Banana (63).

In 11 Greek patients studied for allergy to Grape, wine, or other Grape products, other foods that induced anaphylaxis were Apples (54.5%), Cherries (18.6%), Peaches (18.6%), and Bananas (9.3%). Potential allergens were not investigated (64).

Associations between weed pollen allergy and hypersensitivity to certain kinds of food have also been observed, such as the Ragweed-Melon-Banana association (65). The panallergen was not identified. Goosefoot profilin has been shown to be inhibited by Banana by 68% (66).

Clinical Experience

IgE-mediated reactions

Banana may commonly induce symptoms of food allergy in Latex-sensitised individuals, but may also induce symptoms of food allergy in non-Latex sensitised individuals (2,67-69). Allergenicity of Banana increases with ripeness. Case reports describe a wide heterogeneity of responses to Banana (4). For example, in a study of 4 patients who were Banana-allergic, 1 reported itching of the mouth and throat, followed 30 minutes later

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by urticaria, angioedema, and hypotension, a second reported oral itching (OAS) only, and a third experienced urticaria, conjunctivitis and OAS. One patient was co-sensitised to Avocado, but not to Latex or pollen. One patient worked with Bananas (4).

In one of the earliest reports of adverse reactions to Banana, 2,067 allergic patients studied in 1968-1969 included 36 patients who complained of various symptoms after eating Banana. Among these symptoms were itching throat, "gassiness" and indigestion, cramps, diarrhoea, vomiting, sore mouth or tongue, "canker sores", swollen lips, wheezing, hoarseness, urticaria and other rashes, and angioedema (67). Another report indicates that adverse reactions may include oral allergy syndrome, urticaria and, in severe instances, anaphylaxis (5).

In 142 adults among 7,698 patients visiting an outpatient clinic and reporting sensitisation to foods, 120 experienced clinical symptoms after consumption of 1 or more foods. The most frequently recorded symptoms were urticaria/angioedema (70%), oral allergy syndrome (54%), asthma (37%) and anaphylaxis (27.5%). Banana sensitisation occurred in 12 patients (70). In a cross-sectional, descriptive, questionnaire-based survey conducted in Toulouse schools in France to determine the prevalence of food allergies among schoolchildren, it was reported that, out of 2,716 respondents, 192 self-reported a food allergy, but that there was only a single reported case of allergy to Banana (71). A study was conducted at 17 clinics in 15 European cities to evaluate the differences among some Northern countries regarding what foods, according to the patients, elicit hypersensitivity symptoms. It was reported, based on a questionnaire concerning 86 different foods, that among 1,139 individuals, Banana was the 38th most reported food allergen, resulting in adverse effects in 14% (72). In a Japanese survey of 1,383 patients concerning self-reported severe food allergies, 319 patients reported food allergy, of whom 9 (2.8%) reported allergy to Banana (73). Of 3,025 children with asthma followed up at a clinic in Ankara, Turkey, only 2 were skin prick test positive for Bananas (74). In Delhi, India, of 216 asthmatics with food

sensitisation, skin prick tests were positive to Banana in 11 (75). In an Indian study of 24 children, aged 3 to 15 years with documented deterioration in control of their perennial asthma, IgE antibodies to Banana were found in 20 (83%) (76).

Banana allergy may occur early in life, as reported in 2 infants. A 6-month-old girl developed vomiting, generalised urticaria with erythema, and wheezing an hour after ingesting fresh Banana with yogurt. IgE antibody level was 1.97 kU_A/l. This was the third time she had ingested Banana. The second patient was a 6-month-old boy who developed urticarial rash on his whole body and erythema around the lips 1 hour after eating fresh Banana (with yogurt) for the first time. His mother had frequently eaten Banana since the baby's birth, and she had been breastfeeding him. IgE antibody level was 1.25 kU_A/l. The authors speculated that sensitisation may have occurred through the mother's breast milk (77). Similarly, a 6-month-old boy with mild eczema developed 30 minutes after ingestion of a spoonful of mashed fresh Banana pulp, urticarial rash with erythema on the face and neck, extending over the whole body. He had been breastfed only, and this was the first time he ate Banana. He was shown to have IgE antibodies against Avocado and Banana, but not to Latex or pollen (40). A 5-month-old boy suffered 3 episodes of generalised urticaria 20 minutes after the ingestion of a fruit purée containing Apple, Banana and Orange. Skin testing was positive for Banana and Chestnut. IgE antibody levels to Banana was 58 kU_A/l, to Orange 9.7 kU_A/l, to Chestnut 5.6 kU_A/l, and to Latex 1.6 kU_A/l. However, Orange, Apple and Latex products were well tolerated. He had never eaten Chestnut. The authors of reports of Banana-allergic infants suggest that the route of sensitisation may have been via placenta, breast-milk, inadvertent oral intake of food, or even via inhalation (40,78).

Anaphylaxis may occur to Banana (42,46, 68,79-80). A 15-year-old girl developed anaphylactic shock, asthma, angioedema, and urticaria after eating a Banana. She had eaten Banana 2 weeks earlier without adverse effects (81). Anaphylaxis was reported in a 32-year-old woman. She experienced swelling

of her lips, developed severe oro-pharyngeal symptoms and generalised urticarial rash, and had difficulty breathing. Skin reactivity to Banana and Kiwi was demonstrated. Serum Banana RAST was 0.68 kU_A/l. She had no Latex-associated symptoms (82). A 33-year-old woman with multiple episodes of anaphylaxis after ingestion of Apple, Banana and Lychee was described. Skin prick tests for Apple and Banana were positive. She was allergic to fruit without concomitant allergy to other common airborne/contact allergens (68). Significantly, individuals who have developed anaphylaxis to Banana may be negative to commercial skin tests (79). A 6-year-old boy presented with a history of cutaneous and respiratory reactions to Banana and Avocado and was Latex-allergic; he was shown to have high IgE antibody level to Latex, equivocal IgE to Avocado and Chestnut, and no IgE to Banana or Kiwi fruit. However, skin sensitisation was demonstrated to Banana, Avocado and Chestnut (83).

Anaphylaxis has been described in a 3-year-old boy with associated Latex allergy. He had undergone 5 successive surgical operations during the first months of life and had had eaten Banana previously without any untoward effects. He developed generalised urticarial rash, difficulty in breathing, and oro-pharyngeal symptoms, including itching and swelling of the lips, after eating a Banana. On interrogation, it was found that swelling of the lips had occurred after blowing up rubber balloons; and a week later, periorbital oedema occurred after he touched a balloon. Banana SPT was positive, and IgE antibody level was 6.10 kU_A/l. For Latex, it was 5.2 kU_A/l (84).

Among 107 cases reported in 2002 to the French Allergy Vigilance Network, 59.8% involved anaphylaxis, 18.7% systemic reactions, 15.9% laryngeal angioedema, and 5.6% serious acute asthma. Latex-fruit was the fourth-most-common cause (9 patients), following Peanut (n=14), nuts (n=16), and shellfish (n=9). In the Latex-fruit group, the following were involved: Avocado (n=4), Kiwi (n=2), Fig (n=2), and Banana (n=1) (85).

In Latex-fruit cross-reactivity, the expression of adverse reactions to the implicated allergens may not occur concomitantly. For example,

a 48-year-old female nurse with asthma and rhinitis developed contact urticaria to Latex gloves, but only two years later developed glottic oedema after the ingestion of Chestnuts, and only subsequently experienced adverse effects to Banana and Kiwi (generalised urticaria). Level of IgE antibodies to Latex was 49 kU_A/l, Chestnut 3.5 kU_A/l, Kiwi 1.5 kU_A/l and Banana 0.86 kU_A/l. Skin prick tests were positive (52).

Banana may be a “hidden” allergen. An IgE-mediated reaction to a Banana-flavoured drug additive was described in an 8-year-old girl, who developed oral itching with wheals over her face and trunk and angioedema on both eyelids within 1 hour of her first oral dose of penicillin containing a Banana essence as a flavouring additive. Tests for penicillin allergy were negative, but IgE antibody level to Banana was positive (1.25 kU_A/l). The presence of Banana proteins in the Banana essence was demonstrated (86). Similarly, a 42-year-old woman, with a history of 8 episodes of angioedema over 2 years from Latex gloves or from eating Banana, developed similar symptoms while working on a production line of a company manufacturing a natural Banana hair conditioner. Skin prick was positive to Latex, Banana, Cucumber, Avocado, Kiwi, and Banana hair conditioner (87).

Adverse effects to Banana may manifest only in the skin. Symptoms include contact urticaria (88), urticaria-angioedema (89), and worsening of eczema (46). In a study investigating the prevalence of Natural rubber latex sensitisation and allergy in 74 children with atopic dermatitis, 12 had circulating IgE antibodies to Latex. Twenty children without proven Latex sensitisation showed increased food-specific IgE, most frequently to Potato, Banana, and Chestnut (90).

Other reactions

Banana has been reported to precipitate migraine in susceptible individuals (91-92). This may result from the normal presence of vasoactive substances such as serotonin and tyramine.

f92 Banana

A forty-seven-year-old female was described who had experienced 3 attacks of acute pancreatitis after eating Banana. Elevated serum and urine amylase levels returned to normal in parallel with the clinical symptoms. Total serum IgE was 644 kU/l, and Banana-specific IgE antibody level was 2.18 kU_A/l. Endoscopic examination of the upper digestive tract showed the ampulla of Vater swollen and edematous. Biopsy specimens showed mast cells accumulating in mucosa and submucosa (93).

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f92 Banana

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f319 Beetroot



Beta vulgaris

Family: *Chenopodiaceae*

Common names: Beetroot, Beets, Garden beets, Table beets

Source material: Fresh root

There is confusion among Beetroot, Sugar beet and Spinach beet in many instances in the literature. We have taken note and distinguished these as Beetroot (f319), Sugar beet (w210) and Spinach beet

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Allergen Exposure

Geographical distribution

The ancestor of cultivated Beetroot grows wild on the seashores of southern Britain, through Europe and Asia, as far as the East Indies. Beets and their relatives are grown throughout the world for human and stock food. Sugar beets and Chard are among the more familiar types.

Beets are grown primarily for the enlarged bulbous root, which forms near or just above the soil surface. The plant is naturally a biennial, producing a rosette of leaves and a bulbous root one year, and a seed stalk the following year. Except for seed production, however, the plant is grown from seed as an annual. It is usually harvested when the near-globular or oblate enlarged root is not more than 6 cm in diameter. Colours range from the familiar bright red ("beetroot") to white to striped. The Beet develops best under cool conditions, and so may be grown in winter in the far south, or in summer in the north.

Environment

Beets grow only in cultivated beds. Beetroot is available fresh or canned, and can be eaten raw or cooked. It is traditionally boiled until tender, then pickled in vinegar and used in salads, but it can also be baked, steamed, or microwaved. The leaves can be eaten raw or cooked like Spinach. Wine has been made from Beetroot. Beetroot has one of highest sugar contents among vegetables. It is an excellent source of vitamins and minerals.

Beetroot contains betacyanin pigment (betaine), which is commercially extracted to make the colourant Beetroot red. The root of this and other red-rooted forms contains betanin, an anthocyanin similar to those found in red wine, which is partly responsible for red Beets' immune-enhancing effect. This is one reason for use of the root as an herbal remedy.

Allergens

No allergens from this plant have yet been characterised.

A gene has been isolated from a *Beta vulgaris*, which encodes for a protein that resembles members of the Latex allergen Hev b 5 family (1). A gene encoding for a chitinase with a hevein-like domain was isolated from the leaves of the close family member Sugar beet. The gene is activated by fungal infection. Whether these proteins are clinically significant, or also present in the close family relative Beetroot, has not yet been determined (2).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected, as well as to a certain degree among members of the family *Chenopodiaceae* (3).

Clinical Experience

IgE-mediated reactions

Anecdotal evidence suggests that Beetroot can occasionally induce symptoms of food allergy in sensitised individuals; however, no studies have been reported to date.

Other reactions

Beetroot is known to produce red urine in some people following its ingestion, whereas others appear to be able to eat the vegetable with impunity (4-5). Beeturia is the excretion of red Beetroot pigment (betalaine) in urine and faeces. It occurs in about 14% of humans. Betalaine is a redox indicator whose colour is protected by reducing agents. Thus, beeturia results from colonic absorption of betalaine: oxalic acid preserves the red colour through to the colon; otherwise, in non-beeturic individuals, betalaine is decolourised by non-enzymatic processes in the stomach and colon (6).

Beetroot has one of the highest nitrate contents found in vegetables (7).

Beetroot is also high in oxalate (8).

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f211 Blackberry



Allergen Exposure

Geographical distribution

Blackberry is native to Britain. It was always popular as a wild fruit and only developed as a garden fruit about 1850. The Blackberry is an evergreen or semi-evergreen plant with woody, scrambling stems. The ripe fruit is an aggregate of small, purplish-black droplets attached to a cone-shaped receptacle, which readily separates from the plant when the berries are ripe. Some 250 species of Blackberry are known. Blackberry is not a real berry but a conglomerate fruit much more closely related to Apple and Peach than to such true berries as Gooseberry, Blueberry and Tomato.

Environment

Blackberries can grow wild, mostly in hedgerows or meadows or on the edges of forests, but most commercially available Blackberries are cultivated. The fruit is eaten raw and in pastries, and is used in making

Rubus fruticosus

Family: *Rosaceae*

Common names: Blackberry, Common blackberry, Allegheny blackberry, European blackberry, Bramble, Bramble-kite, Brambleberry, Brameberry

“Blackberry” is a common name for several fruits, including Raspberry, Loganberry and Cloudberry. See also Raspberry f343

Source material: Frozen fruit

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syrups, jams and liqueurs. The root can be cooked, and a tea is made from the dried leaves. The young shoots are peeled and eaten in salads. Blackberries are a good source of vitamin C, fibre and folate.

The root bark and the leaves are strongly astringent, depurative, diuretic, tonic and vulnerary. They are used as a remedy for dysentery, diarrhoea, haemorrhoids, cystitis, etc. Externally, they are used as a gargle to treat sore throats, mouth ulcers, thrush and gum inflammations. Blackberry contains salicylates (natural aspirin) – but these may cause reactions in anyone intolerant to aspirin. Some people find that if they eat the fruit before it is very ripe and quite soft, it gives them stomach upsets.

Unexpected exposure

A fibre is obtained from the stem and used to make twine. A purple to dull blue dye is obtained from the fruit.

Allergens

No allergens from this plant have yet been characterised.

Investigation of the serum of a 45-year-old man who developed systemic anaphylaxis after ingestion of Blackberry revealed IgE bands to Blackberry proteins of between 25

and 100 kDa, indicating that they were neither lipid transfer proteins nor proteins from the Bet v 1 family (both are low-molecular-weight proteins) (1).

However, a study reported that Blackberry may have a Mal d 1 homologues allergen (homologous to Bet v 1) (2).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the *Rosaceae* family (Almond, Apple, Apricot, etc.), and more specifically the genus *Rubus* (Cloudberry, Dewberry, Raspberry), could be expected, but this has not been documented as yet (3).

Clinical Experience

IgE-mediated reactions

Although hypersensitivity to the pollen and fruit of the Mulberry tree (*Morus alba*) has been reported, allergy to Blackberry has rarely been reported (2). This may be related to the general low allergenicity of this berry, the small amounts consumed or the restricted time frame of consumption. Low exposure to certain allergens might be the reason for the limited complaints recorded so far, but with the ongoing promotion for the consumption of small fruits, this situation might change (3).

Although anecdotal reports of allergy to Blackberry have been received, only 1 report has been published in the medical literature. Nonetheless, Blackberry may induce symptoms of food allergy in sensitised individuals (1,4), and suspicion of adverse symptoms to Blackberry should be entertained, in particular because of its frequent consumption and its allergenic potential. This fruit should be taken into consideration in the case of patients with a history of allergy to other fruits of the *Rosaceae* family, and in the case of pollen-sensitised patients with oral allergy syndrome (1).

A 45-year-old man is reported to have developed systemic anaphylaxis after the ingestion of Blackberries. He had experienced dyspnoea and pharyngeal and labial pruritus over the previous 25 years and clearly related these symptoms to the ingestion of

Blackberries, Raspberries, Peanuts, certain brands of margarine, and fruity wines. However, symptoms of oral allergy syndrome were the most intense with Blackberry. In an episode 2 months prior to consultation, he had developed oral allergy syndrome accompanied by generalised urticaria, oedema of the glottis, dyspnoea, vomiting, diarrhoea and loss of consciousness after the ingestion of 2 Blackberries. SPT confirmed sensitisation to Blackberry. Skin reactivity was also found for Goosefoot/Lamb's quarter (*Chenopodium*), Peanut, Wheat, Barley and Rye. An oral challenge test was not performed (1).

The same patient was included in a study of 4 patients with thrombosis associated with antiphospholipid syndrome, each of whom had experienced anaphylaxis attributable to ingestion of vegetables or fruit. The presence of IgE antibodies for a 45 kDa protein band in an Almond extract was detected in all 4 of these patients. No IgE antibodies specific for food panallergen lipid transfer proteins were detected (4).

Other reactions

See under Environment.

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f288 Blueberry



Allergen Exposure

Geographical distribution

The name Blueberry is given to several related shrubs, and at least 50 species belong to the same genus as Blueberry. Other similar berries are Cranberry, lingonberry, bilberry and huckleberry (this last name is sometimes applied to Blueberry, mistakenly). The round, smooth-skinned, blue-black berries are juicy and sweet and only about 10 mm in diameter. The Highbush variety of bush can grow up to 5 m in height; the hardier Lowbush blueberry plants can reach 1 m high. Blueberries are found wild and are cultivated in temperate to cold climates, especially in Canada, New England, Great Britain and New Zealand, but they are relatively uncommon and expensive, and so are a rarity in most diets.

Environment

Blueberries often grow wild on heaths, the sunny edges of woods and other brushy environments, but most commercially available Blueberries are cultivated. They are usually eaten as a raw snack or in baked goods, jams, pancakes, or salads. They can be dried and used like currants. A tea is made from the leaves.

Vaccinium myrtillus

Family: *Ericaceae*

Common names: Blueberry, European blueberry, Lowbush blueberry, Highbush blueberry, Whinberry, Whortleberry, Bilberry

Source material: Frozen fruit

Synonym: *V. myrtillus*

Two important varieties:

V. angustifolium – Lowbush Blueberry

V. corymbosum – Highbush Blueberry

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While the fresh fruit has a slightly laxative effect upon the body, when dried it is astringent and is commonly used in the treatment of diarrhoea, cystitis, etc. The dried fruit is also antibacterial. The skin of the fruits contains anthocyanin and is specific in the treatment of hemeralopia (day-blindness). The fruit is a rich source of anthocyanosides, which have been shown experimentally to dilate the blood vessels: this makes it a potentially valuable treatment for varicose veins, haemorrhoids and capillary fragility.

A tea made from the dried leaves is strongly astringent, diuretic, tonic, and an antiseptic for the urinary tract. The tea (containing glucoquinones, which reduce the levels of sugar in the blood) is also said to be a remedy for diabetes if taken for a prolonged period. Another report says that the tea can be helpful in pre-diabetic states.

A decoction of the leaves or bark is applied locally in the treatment of ulcerations. A distilled water made from the leaves is used for soothing inflamed or sore eyes.

The closely related lingonberry (*V. vitis-idaea* L.), Small cranberry (*V. microcarpum*) and Bigger cranberry (*V. oxycoccos* L.,) are popular in Nordic countries and Russia, and are used in gravies, and a salad dressing. Cranberry and lingonberry have been increasingly marketed as a natural remedy for recurrent urinary infections (1).

Unexpected exposure

A green dye is obtained from the leaves and the fruit and is used to colour fabrics. A blue or black dye is obtained from the fruit. This can be used as an ink. Blueberry juice can also be used as an oral contrast agent in upper abdominal magnetic resonance imaging (MRI).

Allergens

No allergens from this plant have yet been characterised.

Blueberry has been shown to contain a lipid transfer protein (2).

Very strong reactivity has also been detected to high-molecular-weight proteins (2).

Potential cross-reactivity

Although none has been documented to date, there may be cross-reactivity with other fruits in the genus *Vaccinium*, which are erroneously called Cranberries (3). *V. vitis-idaea* (cowberry, foxberry, mountain cranberry, rock cranberry, lingonberry) is not cultivated but gathered, and is used in Europe, especially in Scandinavia, in food products such as preserves and beverages.

Blueberry has been shown to contain a lipid transfer protein that is cross-reactive with LTPs of a number of foods, in particular stone fruits, e.g., Pru p 3 (Peach), Pru a 3 (Apricot), and Pru av 3 (Cherry) (2). Raspberry also contains an LTP-homologous protein, and LTPs have been identified in, among others, Grape, Chestnut, Hazelnut, Maize, Barley, Asparagus, Carrot and Lettuce (2).

Clinical Experience

IgE-mediated reactions

Anecdotal evidence suggests that Blueberry can occasionally induce symptoms of food allergy in sensitised individuals; however, no studies have been reported to date. This may be related to the generally low allergenicity of this berry, the small amounts consumed, or the restricted time frame of consumption. Low exposure to certain allergens might be the reason for the limited complaints recorded

so far, but with the ongoing promotion of the consumption of small fruits, this situation might change (2).

Nonetheless, based on adverse effects reported to other berries, and particularly to members of the same family, it can be said that Blueberry may induce symptoms of food allergy in sensitised individuals (4).

For example, a 25-year-old woman reported adverse reactions to the close family member lingonberry (*V. vitis-idaea*). While eating lingonberry jam, she developed itching wheals around her mouth. Symptoms resolved spontaneously. During a second episode, when she again ingested a very small amount of lingonberry jam several days later, she immediately noticed more-intense symptoms, including severe itching on the mouth, tongue and throat, and wheals over the mouth. Symptoms resolved spontaneously within an hour. Skin reactivity testing using a prick-prick method with fresh lingonberry was positive (1).

In a study aimed at characterising allergens from Raspberry, sera from 8 female patients were assessed. A 25-year-old with periorbital oedema and rhinitis from Lemon and other citrus fruits was described, who was prick-to-prick positive to Peach, Lemon, Sweet Lime, Orange, Banana, Blueberry, Tomato, Grape and Bell pepper (5).

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f260 Broccoli



Allergen Exposure

Geographical distribution

Broccoli, a cultivar of wild cabbage, is a plant of the Cabbage family, *Brassicaceae* (formerly *Cruciferae*). Wild cabbage/wild mustard originated along the northern and western coasts of the Mediterranean. This plant was domesticated and eventually bred into widely varying forms, including Broccoli, Cauliflower, Cabbage, kale, kohlrabi, and Brussels sprouts, all of which remain the same species (1).

Broccoli is considered to be a further development of Cauliflower. It has been known only since the 18th century. It prefers areas with mild winters such as Italy, France, England, California, the southern American States, and sub-tropical Africa.

In contrast to Cauliflower, the flower head develops to a certain extent before harvesting. The edible parts of the Broccoli plant are the stout, tender stem and unopened flower buds. Broccoli must be cut as soon as it reaches full bud development, before buds swell and open into flowers. Varieties exist with white, yellow, purple and deep emerald-green heads. There are 3 main types of Broccoli. The typical green

Brassica oleracea var. italica

Family: *Brassicaceae*

Common names: Broccoli, Spear Cauliflower, Winter Cauliflower, Purple Cauliflower, Calabrese, Romanesco

Source material: Frozen florets

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or purple Broccoli with a large, central head is a “Calabrese”. “Romanesco” Broccolis have flower buds grouped in numerous small cone-shaped heads, arranged in spirals; the “Sprouting Broccolis” produce a succession of small flowering heads over an extended season.

Environment

Broccoli is found in cultivated beds. The stems and florets can be steamed or boiled and served as a side dish, or served raw on a crudité platter, or stir-fried.

Broccoli is an excellent source of vitamins A and C, as well as riboflavin, calcium and iron, and is a rich source of vitamin K. However, Broccoli reduces iodine absorption. Broccoli and other members of the genus *Brassica* (Cabbage-like vegetables) contain very high levels of antioxidant and anticancer compounds. Vitamins and nutrients typically are more concentrated in the flower buds than in the leaves, and that makes Broccoli a better source of vitamins and nutrients than Brassica crops in which only the leaves are eaten. Some research has suggested that the compounds in Broccoli and other Brassicas can protect the eyes against macular degeneration, the leading cause of blindness in older people.

Allergens

No allergens have been characterised to date.

A 9 kDa protein, a lipid transfer protein (LTP), has been detected or inferred (2-5). LTP's are heat-stable allergens.

A 9 kDa lipid transfer protein has been isolated from the surface wax of Broccoli leaves. The amino acid sequence showed 40 to 50% identity with nonspecific lipid transfer proteins isolated from various other plants. Antigenicity was not determined in this study (6).

A study has demonstrated that Oilseed rape and Turnip rape, closely related family members, contain 2S albumins (7). Broccoli was not evaluated for this potential allergen.

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected, as well as to a certain degree among members of the family *Brassicaceae*, such as Broccoli, Cauliflower, Brussels sprouts, and Cabbage (8). This has been borne out by a study that reported cross-reactivity among Cabbage, Broccoli, Cauliflower, Mustard, Rape and Turnip (9). Some authors disagree and state that cross-reactivity among the *Brassicaceae* species is rare (10).

A lipid transfer protein (LTP) was isolated from Broccoli and found to be similar to the LTP purified from Peach peel and Carrot (1,3). Cross-reactivity among plants containing LTP is possible.

Clinical Experience

IgE-mediated reactions

Anecdotal evidence suggests that Broccoli can occasionally induce symptoms of food allergy in sensitised individuals; however, few studies have been reported to date.

A positive reaction to Broccoli in a skin test of a female patient has been reported (8). She experienced pain and swelling in the mouth and throat, plus breathing difficulties, after intake of coleslaw. The researchers concluded: "IgE sensitivity can occur to foods in the *Brassica* family not normally thought to cause allergic reactions in man. It is vital for the physician to consider these foods when evaluating patients for food allergy".

Other reactions

Allergic and occupational contact dermatitis to Broccoli has been reported (11-12). A 56-year-old female nurse presented with a 3-year history of severe eczema and recurrent blisters of her palms, with the left being more severely affected than the right. She was patch tested with, among other substances, parts of fresh vegetables that she commonly used (Carrot, Parsnip, Potato, Broccoli, Onion, Tomato and Bean (unspecified)). There was a positive reaction to cobalt, *Compositae* mix and Broccoli at 48 and 96 hours. A usage test with Latex gloves, a skin prick test to commercial Latex solution, and a skin prick test to Broccoli were negative. The patient's hand eczema improved remarkably on avoiding direct contact with Broccoli and other vegetables (11).

Maternal intake of Cabbage, Cauliflower, Broccoli, Cow's milk, Onion, and Chocolate were significantly related to colic symptoms in exclusively breast-fed infants (13).

f260 Broccoli

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f217 Brussel sprouts

Brassica oleracea var. gemmifera

Family: *Brassicaceae*

Source

material: Frozen sprouts

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Allergen Exposure

Geographical distribution

Brussels sprouts, a cultivar of wild cabbage, belong to the Cabbage family, *Brassicaceae* (formerly *Cruciferae*). Brussels sprouts originated in the Mediterranean region from a loose-leafed wild plant, from a leafy wild cabbage/wild mustard plant. This was domesticated and eventually bred into widely varying forms, including Brussels sprouts, Cabbage, Broccoli, Cauliflower, kale, and kohlrabi, all of which remain the same species (1).

Said to have been cultivated in 16th-century Belgium, Brussels sprouts, indeed, resemble tiny Cabbage heads. Important growing areas are Western and Central Europe, Japan, and North America.

The Brussels sprouts plant is a cool-season biennial, ranging in colour from light green to deep grayish-green, and with round to heart-shaped leaves. The sprouts are modified leaves forming “heads.” Many rows of sprouts grow on a single long stalk. They range from 1 to 4 cm in diameter.

Environment

Brussels sprouts are restricted to cultivated beds. They are available canned, frozen or fresh, and are most often boiled or steamed and served as a side dish. They are high in vitamins A and C, and are a fairly good source of iron.

Brussels sprouts are useful in providing suitable replacement foods for many patients with multiple food allergy.

Allergens

No allergens from this plant have yet been characterised.

A lipid transfer protein (LTP) has been isolated from a close family member, Broccoli, suggesting that Brussels sprouts may contain a LTP. This has not been demonstrated to date (1-3).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected, as well as to a certain degree among members of the family *Brassicaceae*, including Broccoli, Cauliflower, Brussels sprouts, and Cabbage (4). This has been supported by a study that reported cross-reactivity among Cabbage, Broccoli, Cauliflower, Mustard, Rape and Turnip (5). Some authors disagree and state that cross-reactivity among the *Brassicaceae* species is rare (6).

Cross-reactivity between Brussel sprouts and other plants containing LTP is possible.

Clinical Experience

IgE-mediated reactions

Anecdotal evidence suggests that Brussels sprouts can occasionally induce symptoms of food allergy in sensitised individuals; however, no studies have been reported to date.

f217 Brussel sprouts

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f216 Cabbage

Brassica oleracea var. capitata

Family: *Brassicaceae*
Common names: Cabbage, Head cabbage, Heading cabbage
Source material: Whole head of cabbage
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Allergen Exposure

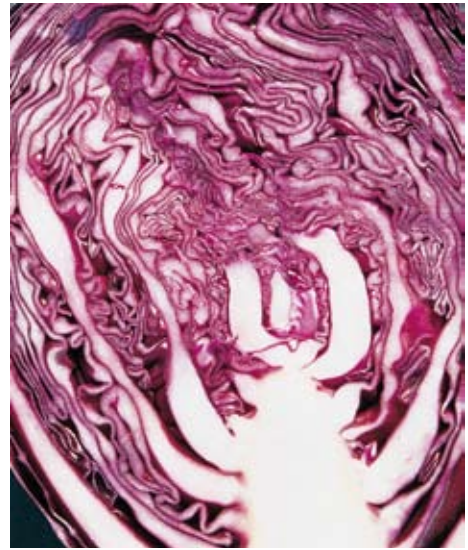
Geographical distribution

Cabbage, a cultivar of wild cabbage, is a plant of the Cabbage family, *Brassicaceae* (formerly *Cruciferae*). Cabbage originated in the Mediterranean and Adriatic regions as a loose-leaved wild plant, from a leafy wild cabbage/wild mustard plant. It was domesticated and eventually bred into widely varying forms, including Cabbage, Broccoli, Cauliflower, kale, kohlrabi, and Brussels sprouts, all of which remain the same species (1-2).

“Cabbage” is the common term for those members of the Cabbage family of which the leaves and not the flower heads are normally eaten. These Cabbages are biennials growing up to 0.75 m. Among these plants, the shapes can be flat, conical or round, the heads compact or loose, and the leaves curly or plain. But most varieties of Cabbage have a short, broad stem and leaves or flowers that form a compact head. These hard-headed Cabbages were developed in 16th century. The main growing areas are Western Europe and the Baltic countries, the ex-USSR, China, Japan and the US. By careful selection of cultivars, it is possible to harvest Cabbages all year round.

Environment

Cabbage is not known in the wild, and grows only in cultivated beds. Its leaves are generally used as a cooked vegetable (often appearing in soups and stews), though the shredded leaves can also be eaten in salads, especially with mayonnaise and other ingredients as coleslaw. The sprouts can also be added to salads. The leaves can be fermented and made into sauerkraut, used as a health food and said to be good for the digestive system. Cabbage



contains a fair amount of vitamin C and fibre, and some vitamin A.

Raw Cabbage juice has been used as a peptic ulcer treatment, due to its S-methylmethionine content. But the juice, if consumed in excess, begins to inhibit iron absorption. Cabbage has also been used to help prevent cancer of the colon.

Unexpected exposure

A blue dye can be obtained from the leaves of purple cultivars.

Allergens

In the case of an atopic 21-year-old woman who had anaphylaxis to Cabbage, allergenic activity was demonstrated by RAST-inhibition in 2 fractions of the Cabbage extract: a fraction of intermediate molecular weight (between 45 and 67 kDa) and a fraction of low molecular weight (< 45 kDa) (3).

The following allergen have been characterised:

Bra o 3, a 9 kDa lipid transfer protein, a heat stable allergen (4-5).

Among 17 patients allergic to Cabbage, skin prick testing with the lipid transfer protein Bra o 3 was positive in 12 of 14 cases (86%) (4).

f216 Cabbage

Chitinase has been purified from an extract of Cabbage and Cabbage stems with roots (6-7). The clinical significance of this allergen in Cabbage has not been determined to date, but there may be antigenic properties similar to those of the panallergen chitinase in other foods.

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected, as well as to a certain degree among members of the family *Brassicaceae*, such as Broccoli, Cauliflower, Brussels sprouts, and Cabbage (8). This has been supported by a study that reported cross-reactivity among Cabbage, Broccoli, Cauliflower, Mustard, Rape and Turnip (3). Ortolani *et al.* differ and state that cross-reactivity among the *Brassicaceae* species is rare (9).

Among 17 patients allergic to Cabbage, most showed associated sensitisation to Mugwort pollen, Mustard, and Peach. A lipid transfer protein (Bra o 3) with 50% identity to Peach lipid transfer protein, Pru p 3, was demonstrated. Bra o 3 inhibited significantly the IgE binding to Cabbage, Mugwort pollen, and Peach (4). A lipid transfer protein has been isolated from a close family member, Broccoli (10). Cross-reactivity among plants containing LTP is possible (11).

A chitinase has been isolated from Cabbage. The potency of this allergen in Cabbage has not yet been determined, but there may be cross-reactivity with other plants containing the panallergen chitinase (6-7).

Clinical Experience

IgE-mediated reactions

Cabbage can occasionally induce symptoms of food allergy in sensitised individuals (3-4,12-13).

Proteins of these vegetables may cause immediate-type allergy, the pollens may be involved in hay fever (14), and skin contact with the isothiocyanates released may cause contact dermatitis (15).

In all of 17 patients allergic to Cabbage, SPT and IgE antibody tests were positive to Cabbage. Five experienced anaphylactic reactions when eating Cabbage, and in another 5, Cabbage allergy was further confirmed by double-blind placebo-controlled food challenges. Skin prick tests with the isolated lipid transfer protein Bra o 3 were positive in 12 of 14 cases (86%) (4).

Anaphylaxis was reported in a woman, who experienced facial and throat swelling after the ingestion of coleslaw on 2 separate occasions. IgE antibody level to Cabbage was raised. She also demonstrated skin reactivity to other members of the *Brassicaceae* family: Mustard plant, Cauliflower, and Broccoli. The authors suggest that allergy to this vegetable is more common than believed (3).

An Indian study evaluated the possible effect of a specific elimination diet on symptoms of 24 children aged 3 to 15 years with documented deterioration in control of their perennial asthma. IgE antibody analysis for a range of food items found that 8 (33%) of the subjects had IgE antibodies directed at Cabbage (16).

Occupational asthma due to the inhalation of Cauliflower and Cabbage vapours was reported in a 41-year-old woman. She experienced recurrent episodes of ocular and nasal itching, sneezing, watery nose, tearing, dry cough, chest tightness, and dyspnoea within a few minutes after inhaling cooking vapours of Cauliflower and Cabbage in a hotel kitchen. She had previously also reported an acute episode of generalised urticaria and facial and oropharyngeal angioedema 6 hours after eating Cabbage. SPT was positive for raw and stewed Cauliflower, Cabbage and Radish, and negative for Turnip, Brussels sprouts, Mustard, cress, and Broccoli. IgE antibody tests were positive for Cabbage, Brussels sprouts, Broccoli, Cauliflower and Oilseed rape, and negative for Mustard. An inhalation challenge to boiling Cauliflower was positive (12).

A report was made of anaphylaxis in a 20-year-old girl following ingestion of String bean; the report also described her developing urticaria from fresh Fennel, boiled Cabbage, Mustard, commercial Hazelnut, and commercial Pear juice (17).

Contact urticaria from Cabbage has been reported (18). IgE antibodies and positive skin tests to Cabbage were also found in cases of contact urticaria (19), and in adult patients with immediate symptoms after intake of vegetables (20).

Other reactions

Maternal intake of Cabbage, Cauliflower, Broccoli, Cow's milk, Onion, and chocolate were significantly related to colic symptoms in exclusively breast-fed infants (21).

Pickled Cabbage (sauerkraut) contains high levels of histamine, which may result in histamine reactions (22).

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f295 Carambola



Allergen Exposure

Geographical distribution

The fruit comes from a tree growing up to 12 metres. This tree has been cultivated in Southeast Asia and Malaysia for hundreds of years, and now is also found in many places in the New World with appropriate climates. The fruit, ovate to ellipsoid and 6 to 13 cm in length, has a yellowish or greenish, waxy, translucent skin. Slices cut in cross-section are star-shaped, with five corners. The flesh is yellow, translucent, crisp and very juicy. There may be up to 12 flat, thin, brown seeds. There are 2 distinct classes of Carambola: the smaller, very sour type, richly flavored, with more oxalic acid; and the larger, “sweet” type, mild-flavored, with less oxalic acid.

Environment

Ripe Carambolas are eaten out of hand, sliced and served in salads, or used as garnish. Their juice is very popular in the East. They are also cooked in puddings, tarts, stews and curries. The sweeter type may be cooked

Averrhoa carambola

Family: *Oxalidaceae*

Common names: Carambola, Star fruit, Starfruit

Source material: Fresh fruit

Related species: Bilimbi (*Averrhoa bilimbi* L.)

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green as a vegetable. They can serve as the main ingredient of sherbet, seasoning, jelly, or relish. The fruits may be stewed, dried, canned, pickled or candied.

Medicinally, the fruit is used against haemorrhages, fevers, diarrhoea, eye afflictions, eczema, and kidney, liver and bladder complaints. There are, however, health risks from the oxalic acid in fully ripe Carambolas: see under Other reactions.

The acidic types of Carambola are used to clean and polish metal, especially brass, as they dissolve tarnish and rust. The juice is also used as a stain remover. Unripe fruits serve as a mordant in dyeing.

Unexpected exposure

See under Environment.

Allergens

No allergens from this food have yet been characterised.

Potential cross-reactivity

No cross-reactivity has been reported to date.

Clinical Experience

IgE-mediated reactions

Carambola may rarely induce symptoms of food allergy in sensitised individuals.

Other reactions

Six patients in a dialysis programme were apparently intoxicated by ingestion of 2-3 fruits or 150-200 ml of the juice and developed a variety of symptoms ranging from insomnia and hiccups to agitation, mental confusion and (in one case) death. The effects were believed to come from an excitatory neurotoxin in the fruit (1). A recent study concluded that oxalate is a main contributor to Carambola neurotoxicity, rather than an excitatory neurotoxin. Carambola contains a large quantity of oxalate, which can induce depression of cerebral function and cause seizures (2).

There have been other reports of hiccup, confusion, and occasional fatal outcomes in uraemic patients after ingestion of Star fruit. A group of 7 patients is described who developed symptoms including hiccup, confusion, vomiting, impaired consciousness, muscle twitching and hyperkalaemia shortly after ingestion of Star fruit. Symptoms of most patients resolved after intensified dialysis or spontaneously, and no mortality was observed (3).

Further support for oxalate as the cause of the adverse effects seen is reported in 2 other cases, where patients developed nausea, vomiting, abdominal pain, and backache within hours of ingesting large quantities of sour Carambola juice; then acute renal failure followed. Both patients needed hemodialysis for oliguric acute renal failure, and pathologic examinations showed typical changes of acute oxalate nephropathy. Renal function recovered 4 weeks later without specific treatment. Sour Carambola juice is a popular beverage in Taiwan, but commercial juice usually is prepared by pickling and dilution processes that reduce oxalate content markedly, whereas pure fresh or semi-fresh juice for traditional remedies, as had been used in the above cases, contains high quantities of oxalate. An empty stomach and a dehydrated state may pose additional risks for development of renal injury (4).

In patients on dialysis, consumption of Carambola can lead to alterations of consciousness, as described in a patient with underlying chronic kidney disease who developed a rapid increase in serum

creatinine and oxalate nephropathy after chronic ingestion of Carambola juice; there was no overt neurotoxicity. The decline in renal function was not fully reversible after stoppage (5). However, toxicity may occur after a very short duration of ingestion, and may also result in epilepsy: an 84-year-old Asian woman with hypertension and chronic renal failure developed incoherent speech, followed by intermittent interruptions of consciousness, and then status epilepticus after ingesting a single Carambola fruit each day for 3 days (6). Non-convulsive status epilepticus has also been reported in chronic renal failure patients on maintenance dialysis therapy after they eat Star fruit (7).

Carambola contain agents that inhibit cytochrome P450 3A4 (CYP3A4), which is the most important enzyme in drug metabolism. Interactions with drugs result (8).

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f31 Carrot



Daucus carota

Family: *Apiaceae*

Common name: Carrot

Source material: Fresh frozen juice

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The following allergens have been characterised:

Dau c 1, a 16 kDa (or 18 kDa (3)) protein, a Bet v 1-homologue, a major allergen (4-13).

Dau c 3, a lipid transfer protein, which is heat-stable (11,14-16).

Dau c 4, a 12 kDa protein, a profilin (4,11,16-21).

Dau c Cyclophilin, a 20 kDa protein (22).

A 35 kDa protein related to Bet v 5, an isoflavone reductase-related protein, has been detected (23-24). Its clinical relevance was not determined.

A Bet v 6-related food allergen of approximately 30-35 kDa, which is a phenylcoumaran benzylic ether reductase (PCBER) – a plant defence protein – has been detected (4,16,25).

The presence of cross-reactive carbohydrate determinants (CCDs) has been reported (4,11,16).

Among 26 subjects with allergy to Carrot, Dau c 1 was recognised by IgE from 85%; 45% were sensitised to cross-reactive carbohydrate determinants, and 20% to Carrot profilin. In 1 subject, a Bet v 6-related Carrot allergen was recognised. In 4 patients, IgE binding to Dau c 1 was not inhibited or was only weakly inhibited by rBet v 1 or Birch pollen extract. The authors suggest that the lack of inhibition of IgE binding to Dau c 1 by Birch pollen allergens in a subgroup of patients might indicate an secondary immune response to new epitopes on the food allergen that are not cross-reactive with Bet v 1 (5).

In a study of sera from 40 Carrot-allergic patients, 98% were positive to at least 1 recombinant Carrot allergen: 98% reacted to rDau c 1.0104, 65% to rDau c 1.0201,

Allergen Exposure

Geographical distribution

Carrot is a biennial, indigenous to Europe. This member of the Parsley family has lacy green foliage and long, slender, fleshy, orange storage roots, which are eaten raw or cooked. Wild Carrots have small, woody taproots, but cultivated varieties have been improved by selection and breeding. The best Carrots are young and slender.

Environment

Carrot is used in a wide range of foods, including soups and stews. It is rich in sugar and has been renowned for over 2000 years for health-giving properties, and recently for high vitamin A content.

Allergens

Various allergens have been detected, including 23, 31 and 42 kDa protein bands, and 2 weaker bands between 66 and 87 kDa (1). A number of these cross-react with pollen allergens due to the presence of panallergens (2).

38% to rDau c 4 and 20% had IgE against CCD (11).

Carrot lipid transfer protein (Dau c 3), thought to be relevant in Carrot allergy, is not present at detectable levels in the edible parts of Carrot. The absence of this protein may explain why Carrot allergy is very rare in Mediterranean, countries, where LTP sensitisation is common (26).

Dau c Cyclophilin has been shown to react with about 14% of Carrot-allergic patients' sera. No cross-reactivity between this allergen and Bet v 7, a Birch pollen cyclophilin, was observed (22).

Carrot allergens are reported to be more stable to heat and processing influences than are Apple allergens (27).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the *Apiaceae* family could be expected. Members include Carrot, Celery, Fennel, Anise, Caraway, Dill, Lovage and Parsley (10,28-29). Hypersensitivity to Carrot is also frequently associated with sensitisation to Birch and Mugwort pollen (10).

In European countries, vegetables belonging to the *Apiaceae* family are frequent causes of pollen-related food allergy (30-32). As up to 25% of food-allergic subjects in this region are allergic to Carrot (33), it is important to evaluate Carrot-allergic patients for allergic rhinitis and/or asthma. The most frequent instances of cross-reactivity with Carrot have been reported as being to Birch pollen, Celery, a number of other vegetables, and spices (34-36).

Cross-reactivity between members of the *Apiaceae* family and Birch pollen is due to panallergens, in this case proteins that share common epitopes with allergens from Birch tree, *i.e.*, Bet v 1-like proteins and profilin (4,19). Carrot contains more than 1 allergen that is cross-reactive with Birch tree pollen allergens. Approximately 70% of Europeans who are allergic to Birch pollen may experience symptoms after consumption of cross-reactive foods. The most important cross-reactive

allergen is Dau c 1, cross-reactive with Bet v 1, the major Birch pollen allergen, which occurs in pollens of several tree species, and in fruits and vegetables: Apple, stone fruits, Celery, Carrot, nuts, and Soybean (37).

Cross-reactivity between Mango, Mugwort pollen, Birch pollen, Celery, and Carrot has been reported and is based on allergens related to Bet v 1 and Art v 1, the major allergens of Birch and Mugwort pollen, respectively (38).

However, sensitisation to Bet v 1 does not mean certain cross-reactivity, as indicated by a study assessing IgE binding to different food allergens in 50 Bet v 1-positive patients. It was found that 99% reacted with Mal d 1 from Apple, 93% with Cor a 1 from Hazelnut, 59% with Api g 1 from Celery and 38% with Dau c 1 from Carrot. Conversely, patients with Birch pollen-related food allergy were predominantly sensitised to Bet v 1 homologues and less frequently recognised other allergens contained in both sources, such as profilins (39).

Some individuals may have allergy to Carrot without it being associated with Birch pollen allergy (36). This observation is supported by a study of 4 patients who demonstrated strong immediate systemic reactions after contact with or ingestion of raw Carrot, all of whom had significant levels of IgE antibodies to Carrot Dau c 1; but no IgE antibodies to Birch pollen were detected in any of them. Although the Carrot IgE-binding protein's N-terminal sequence was homologous to that of Bet v 1 and to allergens previously described in Celery and other foods, the 4 patients studied were not sensitised to Birch pollen, and 3 of them tolerated fruit ingestion. The study concluded that sensitisation to Dau c 1 induces IgE antibodies that do not cross-react with Birch pollen allergens (3). This finding is supported by a study reporting that, although cross-reactivity of the major allergens of Cherry (Pru a 1), Apple (Mal d 1), Pear (Pyr c 1), Celery (Api g 1) and Carrot (Dau c 1) was due to structural similarities reflected by high amino acid sequence identities with Bet v 1, IgE inhibition experiments with Mal d 1, Pru a 1 and Api g 1 demonstrated the presence of both common and different epitopes among the tested food allergens (40).

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Minor Birch pollen allergens may also contribute to cross-reactivity: approximately 10-15% of Birch pollen-allergic individuals have IgE antibodies to a 35 kDa minor Birch pollen allergen, and cross-reactivity with proteins of comparable size from Carrot (along with Litchi, Mango, Banana, Orange, Apple, and Pear). This 35 kDa protein is immunologically independent of the major Birch pollen allergen Bet v 1 (41).

Profilin, a ubiquitous cross-reacting plant allergen related to Birch pollen Bet v 2, is also present in Carrot and may result in cross-reactivity (17-18). In an earlier study, ELISA inhibition assays demonstrated allergenic similarity among Celery, Cucumber, Carrot, and Watermelon. A 15 kDa protein band common to all 4 foods was demonstrated, and attributed to a protein now thought to be a profilin (42).

Cross-reactive patterns may vary among Birch pollen-allergic individuals and may be complex. Of 196 Birch pollen-hypersensitive patients with oral allergy syndrome (OAS), 195 had Apple and/or Hazelnut allergy, and 103 had *Apiaceae* sensitivity; only 1 patient had *Apiaceae* (Carrot, Celery, and Fennel) allergy alone. This study suggests that most *Apiaceae* determinants cross-react with Apple or Hazelnut determinants, whereas only some Apple or Hazelnut determinants cross-react with *Apiaceae* allergy determinants (43).

Carrot contains a lipid transfer protein, which may cross-react with LTP from several other plant-derived foods including Peach peel, Broccoli, Apple, Walnut, Hazelnut, Peanut, Corn, Rice and beer (14-15).

Carrot also contains a PCBER (phenylcoumaran benzylic ether reductase), a plant defense protein related to the Birch pollen minor allergen Bet v 6. Cross-reactivity with other plant substances containing this allergen is possible, and these include Birch pollen, Pear, Apple, Peach, Orange, Litchi, Strawberry, Persimmon, and Zucchini (25,37).

Although the cyclophilin allergen detected in about 14% of Carrot-allergic patients' sera was found to be homologous with other plant cyclophilins, no cross-reactivity between this Carrot allergen and Bet v 7, a Birch pollen cyclophilin, was observed (22).

Some individuals may also experience cross-reactivity to Mugwort. Carrot allergy associated with a sensitisation to Celery, spices, Mugwort, and Birch pollen is often referred to as the "Celery-Mugwort-spice-syndrome" or "Celery-Carrot-Birch-Mugwort-spice syndrome" (44-48). For instance, in a study of 26 patients with histories of allergy to Carrot, 22 reported pollinosis symptoms during the Birch flowering season, and 7 reported pollinosis symptoms during the Mugwort flowering season (4).

A number of studies have reported other relationships between Carrot and other foods or pollens but have not determined the molecular reasons for these. A relationship between Birch pollen allergy and sensitisation to Carrot, Hazelnut, Apple, Potato and Kiwi has been reported (49); also reported are cross-reactions among Celery, Carrot, Parsley, and Ragweed (50); allergy to Apple, Carrot and Potato in children with Birch pollen allergy (30); cross-reactions among Kiwi, Apple, and Hazelnut; and moderate reactions to Carrot and Potato (51).

RAST inhibition experiments demonstrated that Carrot does share allergens with Lettuce, although Carrot allergens are more potent than those of Lettuce (52).

Group 4 grass pollen allergens are 60 kDa glycoproteins recognised by 70% of patients sensitive to these pollens. In Timothy grass, Mugwort, and Birch pollens, these allergens are located in the cell wall, and in Timothy grass and Birch pollens additionally in the cytoplasm. In Peanut, Apple, and Celery and Carrot root, these occurred only in the cytoplasmic areas. Group 4-related allergens thus occur in pollens of unrelated plants and plant foods and may contribute to cross-reactivity in patients allergic to various pollens and plant foods (53).

Clinical Experience

IgE-mediated reactions

Carrot commonly induces symptoms of food allergy, oral allergy syndrome, and asthma in sensitised individuals (1,35,42-43,54-61). Allergy to Carrot is often associated with allergy to Birch pollen (30-32). Carrot allergy may occur in the elderly (62).

Carrot allergy has been reported to affect up to 25% of food-allergic subjects (33). In a Swiss study, Carrot was found to be the third-most-common food allergen, affecting 13% of food-allergic patients, and was more common than allergy to Hen's egg or fish (63). In a similar study in Switzerland, in 173 patients with food allergy (predominantly adults), the most frequent food allergens were found to be Celery in 40.5%, Carrots (20%), Green beans (6%), eggs (21%), Milk and dairy products (20%), and fish (12%) (54). Similarly, in a German study, the most prevalent allergy was to Celery, in 44.5%, followed by Carrot (14.4%) (57). Other studies have demonstrated the high prevalence of Carrot allergy (64-65). In an Indian study of 24 children aged 3 to 15 years with documented deterioration in control of their perennial asthma, IgE antibodies to Carrot were documented in 21 (88%) (66).

The most frequently reported symptoms are oral allergy syndrome (35), but other symptoms include angioedema, urticaria, dyspnoea, vertigo, tightness of the throat or chest, dysphagia, hoarseness, conjunctivitis and rhinitis (4).

Allergy to Carrot may follow complex patterns. This is illustrated by a study that assessed the role of the Carrot allergen Dau c 1 in 3 patients with Carrot-induced asthma: Patient 1 had asthma when handling raw Carrot but was not sensitised to any pollens; Patient 2 experienced rhinoconjunctivitis due to grass, Olive pollen allergy, and asthma when handling raw Carrot; Patient 3 experienced rhinoconjunctivitis and asthma due to allergy to House dust mite, several pollens, and Cat, and asthma due to raw Carrot ingestion and inhalation. Patients 1 and 2 were shown to be sensitised to Dau c 1 from Carrot extract as well as to the recombinant rDau c 1. Bet v 1 from a Birch pollen extract was not recognised by either. Patient 3 were not sensitised to any of these allergens. Inhibition studies with Carrot showed 30% inhibition between Carrot and rDau c 1 in patient 1, nearly 100% inhibition between Carrot and rDau c 1 in patient 2, and no inhibition in patient 3. The study concluded that airborne Carrot allergens are able to sensitise without previous sensitisation to pollen. Dau c 1 was the main

allergen in patient 2. In patient 1, there was a 30 kDa protein band that appeared to be the predominant allergen. Patients 1 and 2 were sensitised directly from Carrot allergens. In patient 3, Carrot allergy was not caused by Dau c 1 but seemed to be related to allergy to pollens other than Birch pollen (9).

A number of case reports further demonstrate how adverse reactions may vary among individual patients.

In a report on 2 patients with allergy to Carrot, 1 presented with sneezing, rhinorrhoea, contact urticaria on her hands and face, and coughing and wheezing after handling raw Carrots. She experienced no symptoms after eating cooked Carrots, but oropharyngeal itching, hoarseness, cough and wheezy dyspnoea occurred after eating raw Carrots. The second experienced oropharyngeal itching, a swollen throat, hoarseness and asthma after eating raw Carrots, and had similar but milder symptoms after eating cooked Carrots. She experienced itching of her hands, palpebral angioedema, ocular and nasal itching, and rhinorrhoea when handling raw Carrots. Bronchial provocation with Carrot extract elicited a FEV₁ fall of 30% within 10 minutes (1).

A 34-year-old female cook experienced allergic rhinoconjunctivitis and contact urticaria with severe itching on both hands when she handled raw Carrot. The patient had had anaphylactic episodes after accidental ingestion of raw Carrots, but tolerated cooked Carrots. In this instance, monosensitisation to an 18 kDa protein in Carrot was reported (67).

Other studies have reported allergy to Carrot in adults. Two adult patients with respiratory and/or ocular symptoms from handling or eating Carrot and/or Lettuce were shown to have, on challenge, prolonged nasal obstruction and ocular symptoms (68).

A study of a 50-year-old non-pollen-allergic woman who presented with vomiting, diarrhoea, dyspnoea, and generalised urticaria to Carrot juice suggests that the allergen involved was a thermolabile, low-molecular-weight allergen, probably not related to any of the Carrot allergens identified so far (16).

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A 38-year-old woman developed rhinoconjunctivitis, dyspnoea and general malaise after inhaling steam of cooking Green bean, Potato and Carrot. She reported contact dermatitis when preparing these vegetables. A bronchial provocation test with Carrot resulted in a FEV₁ decrease, and in an intense cough and general malaise that lasted for more than 24 hours (12).

Although Carrot is frequently involved in food allergy and oral allergy syndrome, usually in association with other foods, it alone is rarely responsible for severe systemic reactions (69). Nevertheless, anaphylaxis has been described (70-71). As with other foods, anaphylaxis may occur to minute quantities of allergen, as described in an individual who developed anaphylactic shock due to the inadvertent ingestion of Carrot as a hidden allergen contained in ice cream (69).

Allergic manifestations in the skin have been reported. Contact urticaria to fresh Carrot has been described. A 16-year-old boy and a 45-year-old woman were reported on, the former with dermatitis and urticaria affecting the perioral area, hands and nape of the neck, and the latter with symptoms involving the face and hands. Individuals transfer the allergen to these areas through scratching or merely touching (72).

Allergic contact dermatitis from Carrot has been described. Exposure is usually occupational rather than domestic. Carrot is among the commonest causes of contact dermatitis of the hands (73-79).

A 38-year-old man experienced a single episode of facial allergic contact dermatitis, which developed after peeling and grating raw Carrots in the kitchen at home (74). In a study of 57 children under 1 year of age, 43 children aged 12 to 35 months, and 42 children aged 3 to 15 years with atopic dermatitis, they were skin-tested with foods suspected to have caused their dermatitis and other possible allergic symptoms. Hen's egg was the most common food allergen in children under 1 year of age. After that age, Apple, Carrot, Pea, and Soybean elicited positive reactions as often as egg (73).

In a report, ingestion of 60 ml of freshly squeezed Carrot juice 2 hours after intake of 100 mg of aspirin induced striking angioedema and shortness of breath in an individual after 3 further hours, whereas a challenge with either on separate occasions did not result in any reaction (80).

Carrot has also been reported to result in eosinophilic cystitis (81).

Carrot may result in occupational allergy and is a cause of allergic dermatitis in the food industry (82). A 40-year-old female cook described sneezing, rhinorrhoea, contact urticaria and wheezing within few minutes of handling or cutting raw Carrot. Skin tests were positive to Carrot, Celery, Aniseed and Fennel. A rubbing test with fresh Carrot was positive. The level of IgE antibodies to Carrot was 4.44 kU_A/l. A bronchial provocation test was positive, but instead of introducing the Carrot extract in the usual methodology, the patient was asked to peel and handle Carrot. She was shown to be sensitised to Dau c 1 and a 30 kDa Carrot protein thought possibly to correspond to a phenylcoumaran benzylic ether reductase (PCBER) (10).

In a study of the value of IgE antibody testing as compared to SPT for Carrot allergy, 20 of 26 patients were positive to Carrot in a DBPCFC study. IgE antibodies for Carrot (≥ 0.7 kU_A/l) were demonstrated in 90%. The presence of skin reactivity tested through commercial extracts was shown in 26%, and through prick-to-prick tests with raw Carrot, in 100% (4).

Other reactions

Phytophotodermatitis is a phototoxic dermatitis resulting from contact with psoralen-containing plants such as Celery, Limes, Parsley, Figs, and Carrots (83-84).

Consuming large quantities of Carrots may result in inadvertent increased vitamin A intake, which may cause papilloedema, as described in a patient with documented idiopathic intracranial hypertension; she had consumed large quantities of raw Carrots as part of a fad diet (85). Another adverse effect of ingesting

large quantities of Carrots, usually in the form of Carrot juice, is carotenaemia, also known as xanthoderma, in which the individual's skin develops an orange colour (86). This has also been reported from the excessive consumption of Carrot products from nursing bottles in children ages 1 to 5 (87).

Carrot soup can be the cause of methemoglobinemia in infants (88-91). This appears to be due to the soup being rich in nitrate and nitrite (92). Fresh and canned Carrots have been reported to contain between 40 and 850 mg NO₃/kg Carrot. Processed infant foods made of Carrots was found to contain between 55 and 215 mg NO₃/kg (93).

Carrot has been reported to have monoamine oxidase inhibiting activity (94).

Carrot, though a common vegetable, has been involved in unusual clinical phenomena, including Carrot addiction (95). Air embolism occurred in a 40-year-old woman subsequent to vaginal insertion of a Carrot for an autoerotic purpose. The Carrot acted like a piston, displacing a sufficient amount of air to create an air embolism (96). This condition needs to be differentiated from anaphylaxis resulting from allergy to Carrot.

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f291 Cauliflower

Brassica oleracea var. botrytis

Family: *Brassicaceae*

Common names: Cauliflower, Broccoflower, Calabrese, Romanesco

Source material: Fresh cauliflower

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Allergen Exposure

Geographical distribution

Cauliflower, a cultivar of wild cabbage, is a plant of the Cabbage family, *Brassicaceae* (formerly *Cruciferae*). Wild cabbage/wild mustard originated along the northern and western coasts of the Mediterranean. This plant was domesticated and eventually bred into widely varying forms, including Cauliflower, Broccoli, Cabbage, kale, kohlrabi, and Brussels sprouts, all of which remain the same species (1).

Cauliflower is a cool-season annual, coming in white (the most popular and readily available), lime-green and purple varieties. On clusters of stalks are thousands of aborted, malformed flower buds. The entire floret portion (called the “curd”) is edible. The green leaves at the base are also edible.

Environment

Cauliflower plants are limited to cultivated beds. The florets can be eaten raw or cooked in a number of ways, including boiling, baking and sautéing. They often appear in soups, or as a side dish smothered with a cheese sauce, or served raw on a crudité platter. Cauliflower is high in vitamin C and is a fairly good source of iron.

Cauliflower (and other members of the genus *Brassica*) contain very high levels of antioxidant and anticancer compounds. Vitamins and nutrients typically are more concentrated in flower buds than in leaves, and that makes Cauliflower a better source of vitamins and nutrients than *Brassica* crops in which only the leaves are eaten. Other

research has suggested that the compounds in Cauliflower and other *Brassicaceae* can protect the eyes against macular degeneration, the leading cause of blindness in older people.

Sulphurous compounds can emit unpleasant smells during cooking, and can result in tainted flavour. Cauliflower is also said to cause flatulence.

Allergens

No allergens from this plant have yet been characterised.

In the evaluation of a 70 year-old man who had experienced an IgE-mediated anaphylactic reaction to Cauliflower, immunoblotting with Cauliflower extract showed several IgE-binding components with molecular masses ranging between 30 and 45 kDa (2).

A lipid transfer protein (LTP) has been isolated from a close family member, Broccoli, suggesting that Cauliflower may contain an LTP. This has not been demonstrated to date (3-4).

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Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected, as well as to a certain degree among members of the family *Brassicaceae*, such as Broccoli, Cauliflower, Brussels sprouts and Cabbage (5). This has been supported by a study that reported cross-reactivity among Cabbage, Broccoli, Cauliflower, Mustard, Rape and Turnip (6). Ortolani *et al.* disagree and state that cross-reactivity among *Brassicaceae* species is rare (7).

Cross-reactivity between Cauliflower and other plants containing LTP is possible.

Clinical Experience

IgE-mediated reactions

Anecdotal evidence suggests that Cauliflower can uncommonly induce symptoms of food allergy in sensitised individuals; however, few studies have been reported to date (2).

A 70-year-old man suffered acute oropharyngeal itching, facial and hand swelling, dyspnoea and severe bronchospasm within a few minutes after eating vegetable paella containing Cauliflower. A strong SPT response was obtained with Cauliflower and Peach LTPs. IgE antibody determinations were positive for Cabbage ($0.79 \text{ kU}_A/\text{l}$), Cauliflower ($0.49 \text{ kU}_A/\text{l}$) and Apple ($1.54 \text{ kU}_A/\text{l}$), and negative for Mustard. Laboratory analysis of the patient's serum with Cauliflower extract showed several IgE-binding components. The authors concluded that the patient experienced an IgE-mediated anaphylactic reaction to Cauliflower (2).

An Indian study evaluated the effect of a specific elimination diet on symptoms of 24 children aged 3 to 15 years with documented deterioration in control of their perennial asthma. IgE antibody analysis for a range of food items found that 19 children (79%) had IgE antibodies directed at Cauliflower (8).

Other reactions

Maternal intake of Cabbage, Cauliflower, Broccoli, Cow's milk, Onion, and chocolate were significantly related to colic symptoms in exclusively breast-fed infants (9).

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Apium graveolens

Family: *Apiaceae*

Common names: Celery, Stick celery, Celeriac, Celery root, Root celery, Celery tuber, Knob celery

Source material: Freeze-dried stem and root

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Allergen Exposure

Geographical distribution

Celery is a herbaceous edible biennial plant in the family *Apiaceae*. It is native to the coasts of western and northern Europe, and of the Middle East. It was used by the ancient Greeks and Romans as a flavouring. The ancient Chinese used it as a medicine.

The wild form of Celery is known as smallage. The stalks are furrowed and more stringy, the leaves are wedge-shaped, and the taste is rank and bitter. Around the 17th and 18th centuries, modern Celery was developed by breeding the bitterness out of smallage. The most common commercial variety now sold is the Pascal variety, although gardeners can grow a range of cultivars under two classes, white and red. The white cultivars are generally the most crisp and tender and the best flavoured.

Celery grows to 1 m tall, with pinnate to bipinnate leaves, and rhombic leaflets 3-6 cm long and 2-4 cm broad. The edible Celery stalk is not a plant stem but a petiole, which is part of a leaf. The flowers are creamy-white, 2-3 mm in diameter, produced in dense compound umbels. The seeds are broad ovoid to globose, 1.5-2 mm long and wide.

Environment

The pale-green, succulent Celery stalks are consumed not only raw as fresh salad but also, both blanched and green, as a cooked vegetable and as a constituent of sauces and soups.

Celery is claimed to be effective against a number of ailments; for example, it is a treatment for hypertension in traditional oriental medicine. It is said to help maintain healthy blood pressure and also to help kidneys function efficiently. This is evidently due to 3 n-butyl phthalide, which also acts as a sedative. Celery has been employed as a herbal infusion to induce abortions (1).

Celery seed is dried and used as a spice. It is combined with salt for a seasoning called Celery salt. It is notably used to enhance the flavour of Bloody Mary cocktails. The seeds are also the basis for a homeopathic extract that is a diuretic and a remedy for gout, among other uses. The furano-coumarin bergaptene, found in the seeds, is a potent photosensitiser and may cause photo-dermatitis, particularly in gardeners and field workers. Similarly, an essential oil made from the seed should not be applied externally by those about to go into bright sunshine.

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Dried and powdered Celery root is a common ingredient of spice mixtures. The root also has medical uses, *e.g.*, as a diuretic and as a digestive remedy.

Chinese celery (also known as Oriental celery) has thinner stalks and a stronger flavour. It is rarely consumed raw but is often added to soups and stir-fries.

Celeriac (*Apium graveolens rapaceum*) is a closely related plant that forms a greatly enlarged, solid, globular body just below the soil surface. It is not used raw but is especially well suited for soups and stews.

Unexpected exposure

See under Environment.

Allergens

Early allergen studies indicated the presence of IgE antibodies binding to Celery proteins with molecular weights of around 14, 15, 16, and 17 kDa (2-3). Celery was also shown to contain at least 3 distinct cross-reacting allergens: a homologue of Bet v 1, a homologue of Birch profilin (Bet v 2), and a group of proteins with a molecular-weight range of 46 to 60 kDa (4). These allergens cross-reacted not only with Birch and Mugwort pollen, but also with a number of other fruits and vegetables (5). The allergens were not classed as either heat-labile or heat-stable (6). Early studies did not necessarily differentiate between Root celery (Celeriac) or Stick celery, possibly presuming the allergens to be similar.

The following allergens have been characterised:

Api g 1, the major allergen, a 16 kDa protein and a Bet v 1 homologue (7-18).

Api g 1.0101 and Api g 1.0201, the isoforms of Api g 1 (19-20).

Api g 3, a chlorophyll Ab-binding protein (7,21).

Api g 4, a 14.3 kDa protein, a profilin and a minor allergen (7,11-12,16,22-29,34).

Api g 5, a 60 kDa protein, isolated from the tuber, with homology to FAD-containing oxidases (7,16,30-31).

A lipid transfer protein has been determined (32-33).

Api g 1 was shown to be a heat-labile protein, but was stable upon exposure to high voltage, high pressure, gamma rays, drying and powdering, and therefore has allergenicity potential as a spice (34).

A number of isoforms have been isolated, including Api g 1.0201. This allergen displays 72% sequence similarity to a previously identified Api g 1.0101 isoform. In general, Api g 1.0201 displays a weaker IgE-binding capacity than does Api g 1.0101, as concluded from immunoblotting experiments (19).

Recombinant rApi g 1 has been cloned by a number of researchers (35-38).

Celery profilin, Api g 4, has been cloned and expressed in *Escherichia coli* (39). Profilin has also been isolated from the Celery tuber (40).

Api g 5 may be a protein with cross-reactive carbohydrate determinants (CCD); and importantly, there is convincing evidence that IgE directed to CCD is capable of eliciting allergic reactions *in vivo* (30-31). This allergen may be similar or identical to a 60 kDa allergen isolated in an earlier study (41).

The presence of CCDs (cross-reactive carbohydrate determinants) has been reported in other studies (12). Celery-allergic individuals have been shown to be monosensitised to CCDs, with exclusively CCD-specific IgE (22). A report stated that IgE antibodies for CCDs are common in Celery-allergic patients and can represent the major proportion of IgE against this food. Alpha 1,3-fucose was shown to be an essential part of the IgE epitope, and immunoblotting inhibition indicated the presence of this carbohydrate determinant on multiple glycoproteins in Celery extract (42). Similarly, other studies have concluded that ubiquitous CCDs are important in allergy to Celery (and Zucchini) (7); and that, depending on the structure of the CCD-containing glycoproteins, CCDs can indeed be important epitopes for IgE; they may be clinically relevant allergens in certain patients and irrelevant in others (22).

In studies examining the prevalence of IgE against Api g 1, the percentage of positive reactions varied from 59% of 22 patients who

had positive DBPCFC to Celery (22), to 80% of 30 patients with pollen allergy who reported immediate allergic reactions after ingestion of raw Celery (43), to 74% of a group of 23 patients who had type 1 Celery allergy (4). The sensitisation rate to profilin was similar: 23%, 23% and 30% respectively. This is in contrast with other research reporting that 42% of Celery-allergic individuals were sensitised to Celery profilin (23), and with a study reporting that 20% of all patients with pollen allergy were sensitised to the profilin in Celery (28). IgE to CCDs has been found to be present in sera of 27% of Celery-allergic individuals (43).

A major allergen of Celery, possibly a lipid transfer protein, has been shown to be heat-stable. Heating Celery tuber for 30 minutes at 100 °C did not deplete the immunoreactivity of the major allergens (44). Other studies have concurred: Celery remained allergenic even after extended thermal treatment (76.07 min/100 °C), indicating that Celery spice is allergenic for patients with an allergy to raw Celery (45). The *in vitro* immunochemical stability of 3 known allergenic structures of Celery was investigated for stability when processed by microwaving, drying, gamma irradiation, ultra-high pressure treatment and high-voltage impulse treatment; it was reported that the heat stability of the known Celery allergens decreased in the following order: carbohydrate epitopes > profilin > Api g 1 (46). In a study of *in vivo* stability, EAST inhibition showed that heat resistance of Celery allergens decreases in the following order: CCDs > Api g 4 > Api g 1. Five of 6 patients with a positive DBPCFC to cooked Celery were sensitised to profilin and/or CCDs. The study concluded that in a subset of patients with a positive DBPCFC to cooked Celery, the CCD allergens remain allergenic even after extended thermal treatment (76.07 min/100 °C) and that Celery spice is allergenic for patients with an allergy to raw Celery. All patients undergoing DBPCFC with Celery spice (dried and powdered Celery) reported reactions comparable to symptoms observed with raw Celery challenges (45).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the family could be expected and in fact does occur frequently (47).

In an early study of Celery allergy, in 20 patients, among whom the ingestion of Celery resulted in generalised urticaria and angioedema in 18, respiratory symptoms in 7, and anaphylaxis in 4, the main cross-reactivity was to pollen allergens in 16/20. Food allergy to other vegetables, mainly other family members and Apples, coexisted in 12 cases. Fourteen were allergic to Mugwort pollen and 9 to Birch pollen. The study suggested the presence of common antigenic epitopes (48). Similar results were reported in other studies (49-51).

Subsequently, Celery allergy was shown in a number of studies to be strongly associated with Birch and Mugwort pollen allergy, a phenomenon often referred to as “Birch-Mugwort-Celery syndrome” (6,52) or “Celery-Carrot-Birch-Mugwort-spice syndrome” when Carrot and Spices are included (6,53-56). Cross-reactivity with other members of the *Apiaceae* family was reported to be more prevalent, the members including Anise, Fennel, Coriander, Cumin, Caraway, Carrot, Dill, Lovage and Parsley (57-61). The syndrome is reported to occur more frequently in females (81.4%) than in males and may be severe, resulting in anaphylactic reactions (62).

Up to 70% of patients with tree pollen allergy display allergic symptoms when eating certain fruits and vegetables. Allergy to Celery brought about through sensitisation to Birch tree pollen occurs only in areas where Birch trees are common. In areas where no Birch trees grow, primary sensitisation takes place through other pollen allergens (*e.g.*, Mugwort pollen). Birch pollen allergy and Celery allergy are closely related in Central Europe, whereas in Southern Europe the Mugwort-Celery type is predominant (37).

Therefore, even if there are no overt symptoms of pollen allergy in a Celery-allergic patient, IgE antibodies may be found, usually to the pollen most common to that region; for example, in Sweden it is Birch, whereas

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in the area of Lyons in France, Ragweed, Mugwort and Compositae tend to be the culprits. An early study stated that the allergic sensitisation is strictly one-way, Celery → pollen: a patient allergic to Celery is likely to be sensitised to pollen, but not the other way around. But the reverse can occur: the presence of IgE antibodies to Celery is often found when the allergy is caused by Ragweed or Mugwort (63).

Allergy to other pollen may result in a variable degree of cross-reactivity with Celery allergy. Utilising SPT and RAST inhibition experiments, an important cross-reactivity was found between the pollen of *Platanus acerifolia* (London Plane tree) and Hazelnut and Banana fruit, and an intermediate cross-reactivity with Celery and Peanut (64). *Hop Japanese* pollen may have links with Celery, Hop, and Sunflower pollens on skin-prick testing (65).

Recent studies have demonstrated that cross-reactivity among Birch pollen, Mugwort pollen and Celery was due to at least 4 distinct cross-reacting allergens, of which a Bet v 1 homologue (Api g 1) and a profilin (Api g 4) have been clearly elucidated.

Api g 1, the major Celery allergen, is a homologue of the major Birch pollen allergen Bet v 1 (15). Bet v 1 cross-reacts with homologous proteins in Celery, Apples, stone fruits, Carrot, nuts, Soybean, Hazelnuts and pollens of several tree species (4,66). Approximately 70% of patients who are allergic to Birch pollen may experience symptoms after consumption of foods from these groups (67). Two minor allergenic structures – profilin and cross-reactive carbohydrate determinants (CCDs) – were shown to have sensitised approximately 10-20% of all pollen-allergic patients and to be present in Celery and in grass pollen and weed pollen (4,67) (See below).

The patterns may appear complex. For example, among sera of 61 patients with IgE antibodies to Mugwort pollen, 36 were positive for Celery and 23 had IgE antibodies to Birch pollen (2). Similarly, of 196 Birch pollen-hypersensitive patients with oral allergy syndrome (OAS), 195 had Apple and/or Hazelnut allergy, and 103 had *Apiaceae*

sensitivity; only 1 patient had *Apiaceae* (Carrot, Celery, and Fennel) allergy alone. The study suggested that most *Apiaceae* determinants cross-react with Apple or Hazelnut determinants, whereas only some Apple or Hazelnut determinants cross-react with *Apiaceae*-allergenic determinants (68). Similarly, cross-reactivity has been reported between Celery and Zucchini, and it is stated that a specific association with Birch pollen allergy exists in allergy to Celery (mediated by Api g 1), but not in Zucchini allergy (7).

Given that Mugwort and Birch pollen allergy are frequently associated with IgE-mediated hypersensitivity to Celery and spices, a study of sera from 22 patients with Mugwort-Birch-Celery-spice syndrome proved interesting. In an immunoblotting test for IgE binding to the spices Pepper and Paprika, it was found that in the Mugwort-Birch-Celery-spice syndrome, IgE cross-reactivity to Pepper and Paprika was not caused by homologues of Bet v 1 and profilin (69).

Bet v 1 plays a significant role in the cross-reactivity described. Celery Api g 1 has a 40% identity (60% similarity) to this major allergen of Birch pollen (35), and Birch pollen-allergic individuals frequently develop type I hypersensitivity reactions to Celery (70-71). Api g 1 has in fact been identified as the Celery homologue of Bet v 1 (19). A number of studies have demonstrated that cross-reactions among Birch pollen, Celery, Carrot, and various fruits and other vegetables are based on allergens related to Bet v 1 and Art v 1, the latter of which is the major allergen of Mugwort pollen (5,38,71-72).

Nevertheless, epitope differences between Bet v 1-related food allergens exist, indicating different degrees of cross-reactivity among these allergens (73). Similar results with other allergens have been reported: concurrent sensitisation to Mugwort or Birch pollen and Camomile may occur, and binding was inhibited to varying degrees by extracts from Celery and Anise, and pollen from Mugwort, Birch and Timothy grass. Profilins (Bet v 2) were not detected in the Camomile extracts (74).

A protein related to Bet v 1 was isolated from cells of the Madagascar periwinkle, and shown to also be present in Celery, but it had no allergenic characteristics (75).

Individuals may be allergic to Celery without allergy or sensitisation to Birch tree pollen; 8% of Swiss patients allergic to Celery were not sensitised to rBet v 1 or rBet v 2 (76). Similarly, in a study of sera from 4 patients showing strong immediate systemic reactions after contact or ingestion of raw Carrot, all the patients had significant levels of IgE antibodies to Carrot allergen, Dau c 1, a Bet v 1 homologue, but no IgE antibodies to Birch pollen was detected in any. The sera contained a single band of around 18 kDa with raw Carrot and with Celery (with a weaker reaction), but no reactive band was found with Birch pollen. The Carrot IgE-binding protein's N-terminal sequence was homologous to that of Bet v 1 and to allergens previously described in Celery and other foods. The 4 patients studied were not sensitised to Birch pollen, and 3 of them tolerated fruit ingestion. The study indicated that a sensitisation to Dau c 1 induces IgE antibodies that do not cross-react with Birch pollen allergens (77).

Research has focused on the T cell response and epitope involvement influencing cross-reactivity between Birch pollen and Celery. In a study evaluating the T cell response to the major allergen Api g 1 in Celery, and the cellular cross-reactivity with its homologous major allergen in Birch pollen, Bet v 1, the latter allergen was identified as the most important T cell epitope for cross-reactivity with Api g 1. The study concluded that the activation of Bet v 1-specific Th2 cells by Api g 1, in particular outside the pollen season, may have consequences for Birch pollen-allergic individuals (78). A study investigating the IgE-binding capacity of 2 cross-reactive allergens, Apg1.0101 from Celery and Pru av 1 from Cherry, showed that the IgE-binding epitopes are highly patient-specific (79-80).

The panallergen profilin, an allergen homologous to Bet v 2, is particularly important in patients allergic to Celery who have a Birch-Mugwort-Celery sensitisation (4,43,81). Celery profilin has a high degree of identity with other plant profilin (71-82%) (39). Profilin is recognised by IgE from about 20% of Birch pollen- and plant food-allergic patients. In a study of the immunological properties of a number of profilins, including profilin from Celery (Api g 4) and Birch

pollen (Bet v 2), 43 of 49 patients (88%) were pre-selected for an IgE-reactivity with Bet v 2; among these, IgE antibodies to the equivalent Celery protein were demonstrated in 80% of the sera. However, IgE binding profiles also indicated the presence of epitope differences among related profilins. Nevertheless, profilin from a number of plants (Pyr c 4, Pru av 4, Api g 4 and Bet v 2) presented almost identical allergenic properties in cellular mediator release tests (24). Profilin has also been detected in both Hazel pollen and Hazelnut extracts (25). A study suggested that Celery profilin is more important in patients with an additional sensitisation to Mugwort pollen (12). Other studies have demonstrated the importance of profilin in cross-reactivity between Celery, Mugwort, Birch and other plants, including numerous other species such as *Cynodon dactylon*, *Sorghum halopense*, *Poa pratensis*, *Ambrosia elatior*, and Apple and Carrot (11,26). *Lolium perenne* grass pollen was shown to contain profilin. In a grass pollen-sensitive population, patients with IgE to vegetables have been reported to have a high incidence of antibodies against profilin (82). However, cross-reactivity as a result of profilin may be variable.

Other studies have also reported on the presence of an approximately 60 kDa allergen in fruit and vegetables, resulting in cross-reactivity with the major Mugwort pollen allergen Art v 1. Pre-adsorption of Mugwort-allergic patients' sera with the 60 kDa Mugwort allergen led to a reduction of IgE binding to components of similar molecular weight present in Birch pollen, Timothy grass, Apple, Peanuts, and Celery extracts. The allergen was distinct from Bet v 1 and profilin and was reported to possibly represent a novel cross-reactive allergen in oral allergy syndrome (41,83). A 60 kDa Group 4 grass pollen allergen, recognised by 70% of patients sensitive to grass pollen, may be similar to or the same as that reported in previous studies. In Timothy grass, Mugwort and Birch pollens, these allergens were located in the cell wall, and in Timothy grass and Birch pollen in the cytoplasm as well. In Peanut, Apple, Celery, and Carrot, the allergen was detected only in cytoplasmic areas (84).

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An association of Celery-Mugwort allergy with allergy to Mango fruit was also reported (61).

Celery contains a lipid transfer protein, which may result in cross-reactivity among a number of vegetables and fruits, including members of the *Rosaceae* family (such as Peach), cereals from the *Poaceae* family, Pistachio, Broccoli, Carrot, Tomato, Melon, and Kiwi. Many of these cross-reactivities may be accompanied by clinical food allergy, frequently including systemic reactions (32-33). It has been stated that in view of the high prevalence and severity of the allergic reactions induced, Hazelnut, Walnut, and Peanut should be regarded as potentially hazardous for patients allergic to lipid transfer proteins (85-86). In a study aimed at examining the relationship between Peach LTP-specific IgE levels and cross-reactivity to several non-*Rosaceae* plant-derived foods, results suggested that all allergenic determinants in LTP from vegetable foods other than Peach cross-react with Peach LTP determinants, whereas only some Peach LTP epitopes cross-react with allergenic determinants on botanically unrelated plant-derived foods (32).

A number of reports indicate cross-reactivity between Celery and Ragweed (63,71,87).

Frequently, the occurrence of cross-reactive IgE antibodies is not correlated with the development of clinical food allergy. In particular, the clinical relevance of sensitisation to cross-reactive carbohydrate determinants (CCD) was reported to not be important (67). However, recently inhibition experiments with a purified carbohydrate moiety clearly showed that the IgE epitope mannose-xylose-fucose-glycan or a closely related structure is present in Celery and is important in patients with clinical allergy to Celery (22).

A study investigated the relationship between pollen sensitivity and sensitivity to food in Latex-allergic patients. Forty-four Latex-allergic patients, 24 of whom were also allergic to tree and/or grass pollen, and 25 pollen-allergic patients who were not allergic to Latex, were studied. Latex-allergic patients were most likely to have a positive skin test and a history of a reaction to Avocado or

Banana, whereas patients with pollinosis only were most likely to have positive SPT and a history of a reaction to Apple, Peach or Celery (88). Notably, healthcare providers who have coexisting risk factors, such as atopy and food allergies (Chestnuts, Bananas, Avocados, Passion fruit, Celery, Potatoes, and Peaches) have been reported to be at an even greater risk for severe allergic reactions following repeated Latex exposure (89).

Recently, homology was reported between the Celery allergen Api g 5 and the pollen allergen rPhl p 4 from Timothy grass, a berberine bridge enzyme-like protein (90). Whether this was clinically relevant was not determined.

Clinical Experience

IgE-mediated reactions

The first case of allergic reaction to Celery root was reported in 1926 (91). Since then, many studies from across the world, and in particular from European countries, have documented the high prevalence of allergy to Celery, especially in association with cross-allergy to pollen (3-4,7,42,48,54,56,62-63,86,92-102). IgE antibodies to Celery may be present in an individual's sera but without clinical sensitisation (4).

In Switzerland, about 40% of patients with food allergy are sensitised to Celery, some of them having severe anaphylactic reactions (98-99). Other studies have reported a higher prevalence of allergy to Celery; one reported 42% (103); among the 69% of a group of 32 patients who had a history of Celery allergy, DBPCFC resulted in systemic reactions in 50% (11/22) (7). In a study from 1978 to 1982, 173 cases of food allergy were diagnosed in patients (predominantly adults) attending the University of Zurich. The most frequent food allergens were found to be Celery in 40.5%, Carrots (20%), Green beans (6%), Hen's egg (21%), Cow's milk and other dairy products (20%) and fish (12%) (104).

In France, 30% of 580 patients with food allergy were sensitised to Celery, as determined by IgE antibody analysis. Sixty presented with severe, near-fatal reactions; the most common food implicated was Celery: 30% of severe

anaphylactic reactions to food were thought to be due to Celery, according to patient histories (100).

In Germany, of 167 patients with a pollen-related food allergy, 70% were sensitised to Celery, as shown by IgE antibody analysis or SPT, and 14% reported allergy to Celery (34).

In a Swiss and German study, 22 of 32 patients claiming to be allergic to Celery were positive on DBPCFC with Celery. Celery IgE antibodies ($\geq 0.7 \text{ kU}_A/\text{l}$) was detected in 73% of patients with a positive DBPCFC result; skin reactivity ($\geq 3 \text{ mm}$) was detected in 48% to 86%, with the use of various commercial extracts; and 96% were positive in prick-to-prick tests with raw Celery. The positive predictive value of the SPT and IgE antibody tests was between 87% and 96%, whereas the specificity and negative predictive values were poor. The study concluded that the skin reactivity and IgE antibodies test methods proved to be reliable for the diagnosis of a relevant allergy to Celery in regard to sensitivity and positive predictive value, but not in regard to specificity and negative predictive value (52).

In a German study, 20.8% of 1,537 subjects reported symptoms to food. One quarter of the subjects (25.1%) were sensitised to at least 1 food allergen, as shown by SPT, with Hazelnut (17.8%), Celery (14.6%), and Peanut (11.1%) being the most prevalent (94). A second German study, of 229 patients experiencing immediate-type allergy to 1 or more specific foodstuffs and diagnosed from 1983 to 1987, reported that Celery was responsible in 44.5% of cases, followed by Carrots (14.4%) and spices (16.6%). In 24 cases, Celery-spice sensitisation was responsible for severe anaphylactic reactions (62).

In a multi-centre Polish study, the greatest number of positive skin prick tests with food allergens were to nuts, Celery, Rye flour, Carrot, Strawberry, Pork and Beans (102). Twenty to 40 percent of Polish children sensitised to Birch pollen were shown to have skin reactivity to Celery, Carrot, Potato, Tomato, Apple, Peach and Grape (95).

In an American study of 132 children aged 3-19 years, 58% reported food-allergic

reactions in the past 2 years. The offending food was identified in 34 of 41 reactions, Cow's milk being the causative food in 11 (32%); Peanut in 10 (29%); Egg in 6 (18%); tree nuts in 2 (6%); and Soy, Wheat, Celery, Mango, and Garlic in 1 (3%) each (105).

Celery can cause oral symptoms (aphthae, stomatitis, swelling of the lips or tongue, pharyngitis, hoarseness and laryngeal oedema) and can often also induce acute generalised symptoms, such as severe laryngeal oedema, bronchial asthma, urticaria or allergic shock (106). Oral allergy syndrome has been documented (35,107), and the symptoms have been reported to be more marked in severity compared to reactions to other vegetables (108).

The prevalence of OAS was significantly higher in patients having IgE antibodies to Birch pollen or Mugwort pollen than those negative to either pollen. The main causative foods were fruits of the Rose family in patients with only Birch pollen-specific IgE antibody; foods outside the Rose family, such as Kiwi, Melon, Orange, Celery and Onion, were causative in those with only Mugwort pollen-specific IgE antibody. A close relationship was suggested between Mugwort pollen sensitisation and OAS (109).

The major Birch pollen allergen Bet v 1 cross-reacts with homologous food allergens, resulting in IgE-mediated oral allergy syndrome (OAS). To avoid this type of food allergy, allergologists and guidebooks advise patients to consume Birch pollen-related foods only after heating. A study evaluated whether cooked Bet v 1-related food allergens induce IgE- and T cell-mediated reactions *in vitro* and *in vivo*, and found that *in vitro*, cooked food allergens lost the capacity to bind IgE and to induce mediator release, but had the same potency in activating Bet v 1-specific T cells as native proteins had. *In vivo*, ingestion of cooked Birch pollen-related foods did not induce OAS but caused atopic eczema to worsen. Therefore, T-cell cross-reactivity between Bet v 1 and related food allergens occurs independently of IgE cross-reactivity *in vitro* and *in vivo*. In patients with atopic dermatitis, the resulting immune reaction can even manifest as late eczematous skin symptoms. In consequence, the view that

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cooked pollen-related foods can be consumed without allergologic consequences should be reconsidered (110).

Even oral allergy syndrome may occur with cooked Celery. In a DBPCFC with cooked Celery, 5 of 11 patients reacted with oral allergy symptoms. During DBPCFC with Celery powder, 4 patients developed symptoms of oral allergy syndrome. One patient also had rhinoconjunctivitis and angioedema, and another patient responded with a flush and angioedema (45). Similarly, in 12 patients with a history of allergic reactions to raw or raw and cooked Celery, DBPCFC with raw Celery (n=10), cooked Celery (110 °C /15 min; n=11), and Celery spice (n=5) was performed. Nine patients who underwent an open mucosal challenge with 4 samples of canned Celery retorted at Co-values (cooking effect) of 7.45-76.07 (corresponding to the time periods in minutes at a thermal influence of 100 °C). Six out of 11 patients showed a positive DBPCFC to cooked Celery, and 5 out of 5 patients to Celery spice. The allergenicity of Celery was preserved for 4 patients with a positive DBPCFC to cooked Celery, even if Celery was treated at a Co-value of 76.07 (45).

In a study of 20 patients, the ingestion of Celery was responsible for generalised urticaria and angioedema in 18 and respiratory symptoms in 7. Four cases of systemic anaphylaxis were reported. Sixteen had concomitant pollen allergy. Food allergy to other vegetable products, mainly other *Umbelliferae* and Apples, coexisted with Celery allergy in 12 cases. Cosensitisation with Mugwort pollen (14 cases) and Birch pollen (9 cases) was found. The study reported that Celery allergens responsible for clinical sensitisation originate chiefly in the tuber and are at least partly thermally labile, and a higher incidence of allergic reactions to the root than to the leaves was reported (48). In a similar study, the same author reported on 20 patients with Celery allergy and concomitant hypersensitivity to Mugwort and Birch pollen. He found that symptoms induced by eating Celery were attacks of urticaria and angioedema in 17 of the 20, respiratory complaints in 8, and systemic anaphylaxis with vascular collapse in 3 (55).

Laryngeal oedema and bronchospasm have been reported (3). A 54-year-old woman was described as experiencing increasing difficulty breathing, due to laryngeal oedema, with onset 3 hours after eating raw Celery (111).

Celery and Parsley were shown to be aetiological agents in 14 patients with severe attacks of angioedema and urticaria (112). These foods may have severe effects, including urticaria, oedema and anaphylaxis (86).

A number of studies have reported anaphylaxis following the ingestion of Celery (113-116). A French study reported that the food products most frequently incriminated in anaphylactic reactions were not of a primary nutritional importance: Celery (30%), crustaceans (17%), fish (13%), Peanuts (12%), Mango (6%), and Mustard (3%); but they are often hidden allergens in commercial foods. In a group of 580 patients, sensitisation to food products was demonstrated, in decreasing order of frequency, as follows: Wheat (39%), Peanuts (37%), Crab (34%), Celery (30%), and Soy (30%). The authors reported that the frequency of sensitisation to various foods had changed and that sensitisation to a number of foods, including Celery, was definitely increasing (100).

In 102 patients with an initial diagnosis of idiopathic anaphylaxis, who were skin tested with a battery of 79 food-antigen, 32 (31%) had positive tests to 1 or more food antigens, and in 5, subsequently eating a food that had elicited a positive test provoked an anaphylactic reaction. Celery was one of the foods implicated (117).

Celery has been associated with food-dependant exercise-induced anaphylaxis (FDEIA) (118-119). Four patients with Celery FDEIA were described in a study: 2 developed symptoms when Celery ingestion preceded exercise, and 1 when exercise preceded Celery ingestion. A fourth, a woman 23 years of age, abruptly developed a diffuse erythematous rash, oedema, syncope, and sustained hypotension while exercising. Within 20 minutes, a sensation of throat tightness occurred, along with warmth, dizziness, blurred vision, and swelling of the extremities. She vomited once, then had a several-second syncopal episode. She experienced abdominal pain (120).

Celery has also been reported to be responsible for dermatitis (121), and particularly for occupational dermatitis in gardeners (122).

Other reactions

Celery has been reported to adversely affect individuals with irritable bowel syndrome (IBS) (123).

Phytophotodermatitis is a phototoxic dermatitis resulting from contact with psoralen-containing plants such as Celery, Lime, Parsley, Fig, and Carrot (124-125). A number of studies have reported that Celery may result in pyodermitis (121-122). Skin reactions have been reported in grocery workers (126-127). An epidemic of dermatitis was reported, featuring a vesicular, peeling rash due to occupational exposure to blanched Celery. A phytophototoxic dermatitis due to exposure to blanched Celery was diagnosed (128). An outbreak of phytophotodermatitis among 11 workers during a Celery harvest in southern Israel was reported. It was found that the Celery harvested in the south of the country contained 84 micrograms/g fresh weight (fwt.) total psoralens, as compared to 35 micrograms/g fwt. in Celery harvested in the north of the country the same year. A late harvest in the south of the country was incriminated in the unusually high levels of psoralens in that Celery (129).

Berloque dermatitis is a variant of phytophotodermatitis and is caused by high concentrations of psoralen-containing fragrances, most commonly oil of bergamot. Berloque dermatitis is rarely seen today because of the removal of these fragrances from most cosmetic products in the United States. There is a report, however, of a group of patients still at risk for berloque dermatitis. These patients use the colognes "Florida Water" and "Kananga Water," which are popular in Hispanic, African-American, and Caribbean populations. These fragrant waters are used for spiritual blessing, treating headaches, and personal hygiene (130).

Reactions may occur following Celery ingestion and exposure to sunlight, as described in a 65-year-old woman who developed a severe, generalised phototoxic

reaction following a visit to a tanning parlour. Further interrogation showed that she had consumed a large quantity of Celery root 1 hour earlier (131-132). Similarly, ingestion of Celery soup can result in severe phototoxicity during PUVA therapy, even if the soup is cooled (133).

A new Celery cultivar (a result of plant breeding to produce a more pest-resistant variety) was responsible for significant incidences of phytophotodermatitis in grocery employees (134). Adverse reactions may not be due to Celery per se: 11 men developed a severe phototoxic dermatitis of the hands and forearms after harvesting Celery infected with *Sclerotinia sclerotiorum* (135).

Celery in a herbal product was reported to increase the risk of bleeding and to potentiate the effects of warfarin therapy (136).

A phototoxic side-effect following Celery ingestion during PUVA therapy has been reported (137).

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Prunus aviumFamily: *Rosaceae*

Common names: Cherry, Sweet cherry, Wild cherry

Source material: Fresh fruit

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www.immunocapinvitrosight.com**Allergen Exposure****Geographical distribution**

The Wild cherry or Sweet cherry (*Prunus avium*) is a species of Cherry native to Europe, northwest Africa, and western Asia

Botanically, Cherries are more closely related to Plums than to Peaches or Apricots. Europe leads the world in production. The cultivated varieties have large, red, purple or yellow berries.

The deciduous tree grows 15-32 m tall, with a trunk up to 1.5 m in diameter. The bark is smooth and purplish-brown with prominent horizontal grey-brown lenticels showing on young trees and becoming thick dark blackish-brown and fissured on old trees. The leaves are alternate, simple ovoid-acute, 7-14 cm long and 4-7 cm broad, glabrous matt or sub-shiny green above, variably finely downy beneath, and with a serrated margin and an acuminate tip; the green or reddish petiole is 2-3.5 cm long and bears 2 to 5 small red glands. The tip of each serrated edge of the leaves also bears small red glands (1).

In autumn, the leaves turn orange, pink or red before falling. The flowers are produced in early spring at the same time as the new leaves, borne in corymbs of 2 to 6 together, each flower pendent on a 2–5 cm peduncle, 2.5-3.5 cm diameter, and with 5 pure white petals, yellowish stamens, and a superior ovary; they are hermaphroditic and pollinated by bees. The fruit is a drupe 1-2 cm in diameter (larger in some cultivated selections), bright red to dark purple when mature in midsummer, edible, variably sweet to somewhat astringent and bitter when eaten fresh; it contains a single hard-shelled stone 8-12 mm long, 7-10 mm



wide and 6-8 mm thick, grooved along the flattest edge; the seed (kernel) inside the stone is 6-8 mm long (1).

Environment

Sweet cherry and its ancestor the Wild cherry supply most of the world's commercial cultivars of edible Cherry (the other source being the Sour cherry, *Prunus cerasus*, of which the varieties are used mainly for cooking). A great many various Cherry cultivars are now grown worldwide wherever the climate is suitable. The species has also escaped from cultivation and become naturalised in some temperate regions (1).

Allergens

The following allergens have been characterised:

Pru av 1, an 18 kDa protein, a Bet v 1-homologue, a major allergen (2-18).

Pru av 2, a 23.3 – 29 kDa thaumatin-like protein (2,19-23).

Pru av 3, a 15 kDa lipid transfer protein (2,4,6-7,11,13,24-28).

Pru av 4, a 15 kDa profilin (2,4,6-7,11,13,29-31).

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A beta-glucosidase (68 kDa) was isolated from ripe fruits of Sweet cherry (32) (Its allergenicity was not assessed, but beta-glucosidase is an allergen in other fruit).

Pru av 1 was previously known as Pru a 1.

A heterogeneous sensitisation to Cherry allergens occurs, and is influenced by geographic location. For example, Pru av 3, a LTP, has been identified as a major allergen in Mediterranean patients allergic to Cherry, but was shown to be of minor clinical relevance in Central and Northern Europe, where Birch trees are abundant. Patients with Birch pollen-related Cherry allergy are predominantly sensitised to the Bet v 1-homologous allergen Pru av 1 (7,13,17). Nonspecific LTPs are predominant *Rosaceae* fruit allergens in the Mediterranean population, and sensitisation to these allergens occurs independently from allergy to Birch pollen. Whereas symptoms to pollen-related food allergens in fruits typically causes only oral allergy syndrome (OAS), symptoms, in addition to OAS, of LTP-sensitised subjects are frequently systemic, including anaphylactic reactions. IgE reactivity to pollen-related food allergens is a consequence of primary sensitisation to inhalant allergens, commonly Birch pollen, and of IgE cross-reactivity with homologous food allergens. In contrast, LTPs are probably capable of sensitising by the ingestion route (7).

In a study of 101 Cherry-allergic German and Italian patients, IgE prevalence was as follows: LTP (Pru av 3), 3 of 101 (3%); rPru av 1, 97 of 101 (96.0%); rPru av 4, 16 of 101 (16.2%); and Cherry extract, 98 of 101 (97%). All 7 Italian patients had IgE against the Cherry LTP (13). In a study evaluating a panel of recombinant allergens for use in component-resolved *in vivo* diagnosis, with Cherry as a model food, 79 subjects were included in the study: 24 Swiss patients (group 1) with a positive double-blind placebo-controlled food challenge result to Cherry; 23 Swiss patients with Birch pollen allergy but without Cherry allergy (group 2); 23 nonatopic Swiss subjects (group 3), and 9 Spanish patients with a history of a Cherry allergy (group 4). SPT responses with rPru av 1, rPru av 4, and rPru av 3 were positive in 92%, 17%, and 4%, respectively, of the patients in group 1; in 74%, 30%, and 0% of

the patients in group 2; in 0%, 22%, and 89% of the patients in group 4; and negative for all nonatopic subjects (group 3) (11).

In a study of 186 Cherry-allergic subjects from central Europe and Spain, serum IgE were analysed with IgE antibody tests against rPru av 1, 3 and 4, combined and separately, and Cherry extract. Consistent with previous reports, major geographic differences in sensitisation patterns and prevalence of systemic reactions were found. A significantly higher rate of systemic reactions was found in Spanish patients sensitised to Pru av 3, whereas German patients sensitised to LTP had only oral allergy syndrome (4).

Cherry Pru av 2, a thaumatin-like protein, is the most abundant soluble protein in ripe Cherry; accumulation of this protein begins at the onset of ripening as the fruit turns from yellow to red (23). Pru av 2 was recognised by the majority of Cherry-allergic patients in a study, binding IgE of 50% of Cherry-allergic patients (19).

Cherry LTP, Pru av 3, has been shown to have a high degree of resistance to digestion, and immunologically active Pru av 3 was detectable after 2 hours of digestion by pepsin, whereas IgE reactivity of Pru av 1 and Pru av 4 was abolished within less than 60 minutes. Pru av 3 is also heat-stable (7). There are no marked differences among the LTP of 6 Cherry cultivars. LTP is found mainly in the peel, and chemical peeling has been shown to successfully remove Pru av 3 (24).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the family could be expected (27,33).

Like other *Prunus* fruits, Cherry contains a variety of allergenic proteins, including 2 Birch tree pollen-homologous allergens, Bet v 1 and Bet v 2 (a profilin). Both Bet v 1 homologues and profilin may result in mild symptoms such as oral allergy syndrome, although sensitisation to profilin is commonly associated with more-generalised symptoms, in particular urticaria and angioedema (34). Lipid transfer protein may also be responsible for OAS in patients without pollen allergy

(24,27), though adverse reactions are typically more severe. This is exemplified by a study of 14 subjects with Pru av 3 (LTP) sensitisation experiencing OAS, which was associated in some of the patients with gastrointestinal, respiratory or cardio-vascular symptoms (7).

The relationship between pollen allergy and OAS to fruits and vegetables was evaluated in Sapporo, Japan, and it was found that, out of 843 patients with Birch pollen allergy, 378 (37%) had episodes of OAS. The most frequent foods causing OAS were Apple, Peach and Cherry, followed by Kiwi, Pear, Plum and Melon (35). In an earlier study of 87 patients, in 61% of patients with Birch allergy, Apple (97%) was the most prevalent allergen resulting in OAS, followed by Peach (67%), Cherry (58%), Pear (40%), Plum (40%) and Melon (33%) (36). In a European study, Hazelnut (53%) was shown to be the most common food allergen associated with OAS in 380 Birch pollen-allergic patients. Approximately 33% of these patients were also hypersensitive to Almond and Cherry, as reported on questionnaires (37).

Pru av 1, a Bet v 1-homologous panallergen, has a 67% homology to Bet v 1 (16-17). Cloned Cherry allergen has a 59.1% identity to Bet v 1 (17). Some authors have described Pru av 1 as nearly identical with Bet v 1 (9,18). This cross-reactive panallergen is found in, among other substances, Cherry (Pru a 1), Apple (Mal d 1), Pear (Pyr c 1), Celery (Api g 1), Peach (Pru p 1) and Carrot (Dau c 1) (16,34,38). Bet v 1 homologues mainly cause mild symptoms such as oral allergy syndrome (OAS) (34). Other Bet v 1 homologues are found in Soybean (Gly m 4) and Peanut (Ara h 8) (39).

Pru av 2, a thaumatin-like protein (TLP), is a panallergen found in Cherry and other foods. The amino acid sequence of Cherry TLP has been shown to be highly homologous to Grape and Apple thaumatins (40).

Pru av 3, a lipid transfer protein (LTP), is found in Cherry. Pru av 3 shows high amino acid sequence identity with LTPs from Peach (Pru p 3, 88%), Apricot (Pru ar 3, 86%), and Maize (*Zea m 14*, 59%), and no IgE cross-reactivity with Birch pollen (13). LTPs have

also been shown to be present in Walnut and Peanut (41), Mugwort and Chestnut (42-43), Vit v 1 from Grape (44), Cor a 8 from Hazelnut (45), Mal d 3 from Apple (46-47), and Lac s 1 from Lettuce (48). Vit v 1, the LTP from Grape, was shown to completely inhibit Cherry LTP Pru av 3 (26). Hazelnut LTP has an amino acid identity of 59% with Cherry LTP (25). LTPs are also found in Blueberry, Raspberry, Hazelnut, Barley, Asparagus, and Carrot (49). However, there is no firm correlation between sequence identity and clinical cross-reactivity, and therefore the degree of cross-reactivity resulting from LTPs varies among foods containing this panallergen (48,50). Lipid transfer proteins of *Rosaceae* fruits, including Cherry, represent major allergens for atopic Mediterranean populations (51).

Pru av 4, a profilin and panallergen, is recognised in about 20% of pollen-allergic patients from Central Europe. However, sensitisation depends on the geographic area: in Swedish and Finnish patients, approximately 5-7% are sensitised to Birch profilin, compared to 20-38% in Central and Southern Europe (52). Approximately 20% of Spanish patients allergic to Bermuda grass were found to be sensitised to profilin, and about 42% of Celery-allergic individuals to Celery-profilin (52). Sensitisation to profilin may result in cross-reactivity between Cherry and other profilin-containing foods, although the cross-reactivity is quite variable, especially as profilin is heat-labile. Other foods containing profilin include Tomato (*Lyc e 1*), Celery (*Api g 4*), Pineapple (*Ana c 1*), Banana (*Mus xp 1*), Carrot (*Dau c 4*) and Pear (*Pyr c 4*) (29-30,53).

Pear (*Pyr c 4*) and Pru av 4 from Cherry showed high amino acid sequence identity with Birch pollen profilin, Bet v 2 (76-83%). Forty-three of 49 patients (88%) preselected for an IgE reactivity with Bet v 2 showed IgE antibodies to recombinant Pear profilin, 92% to recombinant Cherry profilin, and 80% to Celery profilin. Profilins of Peanut, Cherry, Pear, Celery and Birch have been shown to have marked differences in their IgE binding capacity (31). IgE binding profiles indicate the presence of epitope differences among the related profilins, suggesting that cross-

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reactivity among related profilins may explain pollen-related allergy to food in a minority of patients (29).

In a study of 61 patients with a documented history of IgE-mediated reactions to Grapes or their products (wine, juice, and wine vinegar), 81.9% were co-sensitised to Apple, 70.5% to Peach, 47.5% to Cherry, 32.8% to Strawberry, 49.2% to Peanut, 42.6% to Walnut, 31.1% to Hazelnut, 26.2% to Almond, and 29.5% to Pistachio. The high prevalence of concomitant reactivity to other fruits elicits an interest in the clinical relevance of these findings for the Grape-allergic population (54). In 11 Greek patients studied for IgE-mediated reactions to Grapes, wine, or other Grape products, other foods that induced anaphylaxis were Apple (54.5%), Cherry (18.6%), Peach (18.6%), and Banana (9.3%). Panallergens were not tested for (55).

Clinical Experience

IgE-mediated reactions

Cherry may commonly induce symptoms of food allergy in sensitised individuals. Adverse reactions may range from mild oral allergy syndrome (OAS), to nausea, vomiting, diarrhoea, cough, dysphagia, rhinitis, conjunctivitis, angioedema, urticaria, laryngeal oedema, and severe anaphylaxis following ingestion of Cherry (4,7,27,56-64).

As mentioned above, symptoms of Cherry allergy are dependent on geographic location and predominant sensitization, whether to Pru av 1 or Pru av 3. Severe reactions, including anaphylaxis, are often associated with sensitisation to Pru av 3, a lipid transfer protein, but sensitisation to this allergen may manifest as OAS alone, or OAS associated with gastrointestinal, respiratory or cardiovascular symptoms (7). This is exemplified by a study of 186 Cherry-allergic subjects from central Europe and Spain, where the most frequently reported symptoms to Cherry were OAS and dyspnoea. OAS was found in 68% and dyspnoea in 13% of the entire Cherry-allergic group. None of the other recorded symptoms (angioedema, urticaria, rhinitis, flush, conjunctivitis, larynx oedema, cough, dysphagia, nausea, emesis, diarrhoea

and cardiovascular reactions) were reported in more than 5% of the subjects. However, the subjects from central Europe and Spain showed marked differences in the frequency of specific symptoms. Ninety-three per cent (113/121) of the central European study population reported OAS and other mild symptoms, with 1.7% (2/121) having urticaria and 0.8% (1/121) having angioedema, after ingestion of Cherry. The same symptoms were reported by 64%, 27% and 27% of the Spanish subjects, respectively. Further, episodes of anaphylactic reactions upon consumption of Cherry were reported by 3 of the Spanish but none of the central European subjects. An unusual observation was that 1 Swiss subject, who displayed symptoms upon Cherry ingestion that were unusually severe (urticaria, severe angioedema, cough, dyspnoea and gastrointestinal symptoms) compared with other central European subjects, in fact originated from the Mediterranean area, and allergy to Cherry first occurred when the subject had already been living in Switzerland for a couple of years (4).

Allergy to *Rosaceae* fruits in patients without a related pollen allergy is also a severe clinical entity. Profilin- and Bet v 1-related structures are not involved (65).

A cross-sectional, descriptive, questionnaire-based survey was conducted in Toulouse schools to determine the prevalence of food allergies among schoolchildren. Of 2,716 questionnaires returned, 192 questionnaires reported a food allergy. One reported allergy to Cherry (66).

A study was conducted at 17 clinics in 15 European cities to evaluate the differences among some Northern countries regarding what foods, according to the patients, elicit hypersensitivity symptoms. It was reported, the informants being food-allergic individuals responding to questionnaires concerning 86 different foods, that the foods eliciting symptoms in Russia, Estonia, and Lithuania were citrus fruits, chocolate, honey, Apple, Hazelnut, Strawberry, Fish, Tomato, Egg, and Milk, which differed from the situation in Sweden and Denmark, where Birch pollen-related foods, such as nuts, Apple, Pear, Kiwi, stone fruits, and Carrot, were the most common reported causes. The most

common symptoms reported were oral allergy syndrome and urticaria. Birch pollen-related foods dominate in Scandinavia, whereas some Mugwort-related foods were of more importance in Russia and the Baltic States. Among 1,139 individuals, Cherry was the 23rd most reported culprit food, resulting in adverse effects in 19% (67).

A 24-year-old with allergy to Grape also reported experiencing oropharyngeal pruritus after eating Cherry. Skin prick tests with commercial food extracts were positive for Cherry and Plum (58).

Anaphylaxis (vomiting, dyspnoea, itching, and generalised oedema) following ingestion of Cherry has been described. This patient had previously tolerated other fruit from the same family (Apple, Plum and Peach) (68).

A 4-year-old child was described with allergy to multiple foods. Symptoms of urticaria and asthma were clearly associated with ingestion of Hen's egg at the age of 2. He subsequently developed rhinitis, angioedema, headache, and gastroenteritis, symptoms variously associated and started between a few minutes and 2 hours after the ingestion of numerous foods. Skin prick tests with fresh food were positive for Fig, Asparagus, Cherry, Walnut, medlar, Orange, Chicory, Strawberry, fish, Peanut, Peach and Egg. IgE antibodies were detected for Hen's egg, fish, Peanuts, Walnut, Fig, Orange, Strawberry, Peach and Cherry. DBPCFC was positive to various degrees for all the skin prick test-positive foods (69-70).

Other reactions

Respiratory allergy to pollen from Cherry tree has been reported (71).

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Vaccinium oxycoccus

Family: *Ericaceae*
Common names: Bog cranberry, Small cranberry, Bigger cranberry, Wild cranberry, Swamp cranberry, Marshwort, Fenne berry, Marsh whortleberry, Bounceberry, Craneberry

Source material: Fresh fruit

Synonymes: *V. microcarpos*,
V. palustre,
V. hagerupii,
Oxycoccus quadripetala,
O. palustris,
O. hagerupii,
O. intermedius,
O. microcarpus,
O. microcarpos,
O. ovalifolius,
O. oxycoccus,
O. quadripetalus

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Allergen Exposure

Geographical distribution

Cranberry is a very small, prostrate, evergreen shrub, growing wild in northern Europe and in the northern regions of North America, but now also extensively cultivated in Russia and North America. This helps to compensate for the extensive loss of the berry's natural habitat of large sandy bogs.

The stem is very slender, vinelike and creeping, and the leaves are small (less than 1.2 cm), leathery and lance-shaped. The small flowers are pink to red and appear in June. The bright red, round berries are about the size of currants (about 6 mm) and have an acid taste. They ripen in September and often persist through the winter.

The varieties may be confused, especially as Small cranberry (*Vaccinium microcarpum*) and Bigger cranberry (*Vaccinium oxycoccus* L.) are popular berries in Nordic countries

and Russia. The American cranberry (*V. macrocarpon*) is very similar to *V. oxycoccus* and is sometimes regarded as the same species. Other fruits in the genus *Vaccinium* are erroneously called Cranberries; *V. vitis-idaea* (cowberry, foxberry, mountain cranberry, rock cranberry, lingonberry) is not cultivated but gathered and is used in Europe, and especially in Scandinavia, in food products such as preserves and beverages. The highbush cranberry, *Viburnum opulus*, belongs to the family *Caprifoliaceae*.

Environment

Cranberry is commonly too bitter to be eaten fresh but may be sweetened and preserved as sauce, chutney, jelly or pastry filling, or bottled as juice. Cranberry juice "cocktail", with other juices used for sweetening, is a popular commercial product in the US. In the United States and Canada, Cranberries are traditionally associated with Thanksgiving and Christmas meals. The fruit is even used to make gravy. Canned whole Cranberries and Cranberry sauce and jelly are commercially available, as are frozen Cranberries. Dried

Rf341 Cranberry

Cranberries can be used like raisins in baked goods or as snacks. A tea is made from the leaves.

Native Americans used the berries, twigs, and bark for medicinal purposes. An infusion of the plant has been used to treat cases of slight nausea.

In recent years, Cranberry products have been increasingly marketed as a natural remedy for recurrent urinary infections. Cranberry appears to inhibit the attachment of pathogens to uroepithelium and may decrease the number of symptomatic urinary tract infections (1-2).

The juice of the fruit is used to clean silver.

Unexpected exposure

A red dye is obtained from the fruit.

Allergens

No allergens from this plant have yet been characterised.

In Southern blot analyses DNA fragments homologues to Mal d 1 and Mal d 3 could be detected in genomic DNA from cranberry and the respective genes were yet to be cloned (3). However, the potential allergenicity of the recombinant gene products had not been defined.

A report was made about the closely related family member cowberry (lingonberry; *V. vitis-idaea*). A patient experienced intense itching on her mouth, tongue and throat, and wheals over her mouth after eating lingonberry jam. IgE antibodies were detected to medium- and high-molecular-weight proteins, indicating that they were probably neither lipid transfer proteins nor proteins from the Bet v 1 family, which are both low-molecular-weight proteins (2).

Potential cross-reactivity

There is potential cross-reactivity with other fruits in the genus *Vaccinium* that are erroneously called Cranberries (4), such as *V. vitis-idaea* (cowberry, foxberry, mountain cranberry, rock cranberry, lingonberry), about which see above under Geographical distribution.

Clinical Experience

IgE-mediated reactions

No clinical allergy to Cranberry has been documented to date. This may be related to the general low allergenicity of this berry, the small amounts consumed or the restricted time frame of consumption. Low exposure to certain allergens might be the reason for the limited complaints recorded so far, but with the ongoing promotion for the consumption of small fruits, this situation might change (3).

Nonetheless, to judge from reports of adverse effects from other berries, and especially other family members, Cranberry may induce symptoms of food allergy in sensitised individuals.

For example, a 25-year-old woman reported adverse reactions to the close family member lingonberry (*V. vitis-idaea*). While eating lingonberry jam, she developed itching wheals around her mouth. Symptoms resolved spontaneously. During a second episode, when she again ingested a very small amount of lingonberry jam several days later, she immediately noticed more-intense symptoms, including intense itching on her mouth, tongue and throat, and wheals over her mouth. Symptoms resolved spontaneously within an hour. SPT using a prick-prick method with fresh lingonberry was positive (1).

Therefore, as Cranberry is frequently and increasingly being consumed, suspicion of adverse symptoms to Cranberry should be entertained.

Other reactions

High intake of Cranberry juice may result in interaction with the drug warfarin, which can potentiate bleeding (5). A previous study demonstrated that ingestion of 250 ml of Cranberry juice 3 times a day for 2 weeks was associated with a marked increase of salicylic and salicylic acids in urine within 1 week of the start of the intervention. After 2 weeks, there was also a small but significant increase in salicylic acid in plasma (6). The presence of salicylic acid in Cranberry was proposed as responsible for fatal bleeding in a patient on warfarin who ingested Cranberry juice (7).

See also Blueberry f288 (*Vaccinium myrtillus*).

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f244 Cucumber



Allergen Exposure

Geographical distribution

First recorded in the Himalayan foothills of India, Cucumber has been cultivated for over 4,000 years. This long, cylindrical, green-skinned fruit of the gourd family has edible seeds surrounded by a mild, crisp flesh. Leading countries in the cultivation of Cucumbers include Britain, China, India, Iraq, Java, Kurdistan, Turkey, and Venezuela.

Cucumber is among the most widely grown vegetables, common in home gardens, on truck farms and as a greenhouse crop. It consists of around 96% water. The plant is trailing, usually on the ground in the open, but on trellises in greenhouses. The Cucumber is called a Gherkin when small and used in preserves and pickles, often with dill-flavoured vinegar. Cucumbers are available year-round, with the peak crop from late spring to late summer.

Cucumis sativis

Family: *Cucurbitaceae*

Common names: Cucumber, Cuke, Gherkin, Cowcumber

Source material: Fresh fruit

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Environment

Cucumbers grow only under cultivation. They are used for fresh consumption, or for preservation, marinated with vinegar, salt, or spices. The thin skin, unless waxed, does not require peeling.

Cucumbers contain 5 calories per ounce and only very small amounts of nutrients. But some cultivars have significantly higher levels of vitamins A and C. Many people find the fruit to be indigestible: this is due to the high cellulose content. Oil from the seed is used in salad dressings and French cooking.

The leaf juice is emetic and used to treat dyspepsia in children. The fruit may be used as a natural remedy.

The fruit is applied to the skin as a cleansing cosmetic to soften and whiten it. The juice is used in many beauty products.

Cucumber skins have been shown to repel cockroaches in laboratory experiments. The roots of Cucumber plants secrete a substance that inhibits the growth of most weeds.

Allergens

The following allergen has been characterised:

Cuc s 2, a profilin (1-2).

The activity of a chitinase has been detected in xylem sap from Cucumber stems. Cucumber roots produce a chitinase and secrete it into xylem sap for delivery to aboveground organs (3). Whether this chitinase is found in the Cucumber fruit, and whether it has panallergen activity, are questions that have not been investigated yet. Cucumber leaves may contain a chitinase protein following a plant infection (4).

A beta-1,3-glucanase protein, a PR panallergen, was shown to be activated by plant stress in Cucumbers. Whether this panallergen has any clinical significance, or whether it occurs in the Cucumber fruit, has not been determined yet (5).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected, as well as to a certain degree among members of the family *Cucurbitaceae*, such as Watermelon, Melon, and Cucumber (6).

An association between Ragweed pollinosis and hypersensitivity to *Cucurbitaceae* vegetables and Banana has been reported (7). Six of 26 patients who had Watermelon IgE antibodies reported developing oropharyngeal symptoms (itching and/or swelling of the lips, tongue, or throat) after ingesting at least 1 of the study foods of the gourd family (Watermelon, Cantaloupe, Honeydew melon, Zucchini, and Cucumber), or Banana (8).

There is cross-allergenicity among Celery, Cucumber, Carrot, and Watermelon. Immunoblots of individual sera showed a 15 kDa protein band common to all 4 foods (9).

Cross-reactivity was demonstrated among Pumpkin, Pumpkin seed, Muskmelon, Watermelon, Cucumber and Zucchini (10). Cuc m 3 from Melon shares a sequence identity of 60% or more with PR-1 proteins from Grape and Cucumber (11).

Hevamine, an enzyme with lysozyme/chitinase activity from *Hevea brasiliensis* Latex, has a sequence identity of about 60% with a chitinase from Cucumber, and 95% with the N-terminal sequence of the lysozyme/chitinase of *Parthenocissus quinquefolia*. The differences in cellular location, charge properties and sequence between hevamine and Cucumber chitinase are similar to those between class I and class II chitinases from Tobacco and other plant species (12).

Clinical Experience

IgE-mediated reactions

Cucumber can induce symptoms of food allergy in sensitised individuals (5-6,13-14). A French cross-sectional, descriptive, questionnaire-based survey was conducted in Toulouse schools to determine the prevalence of food allergies among schoolchildren. Out of the questionnaires, 2,716 were returned. Of the 192 questionnaires reporting a food allergy, 1 reported allergy to Cucumber (15).

Oral allergy syndrome and pruritis of the lips, tongue and throat have been reported (6,10). Contact with Cucumber may result in atopic dermatitis or contact urticaria (16-17).

Anaphylaxis due to Cucumber is rare but has been reported (7).

An Indian study evaluated the effect of a specific elimination diet on symptoms of 24 children aged 3 to 15 years with documented deterioration in control of their perennial asthma. IgE antibody analysis for a range of food items found that 21 children (88%) had IgE antibodies directed at Cucumber (18).

Cultivation of Cucumber in greenhouses may lead to occupational allergy caused by the vegetable or tetranychus mites living on the plants among other mites (19-21).

Other reactions

Contact dermatitis to Cucumber has been reported (22-23). Cucumber plants produce elevated levels of phytoalexins in their leaves in response to treatment of powdery mildew with a fungicide. Phytoalexins are important causes of contact dermatitis (24).

Red spider mite found on carnation, Cucumber and vegetable marrow growing in greenhouses may result in occupational asthma and rhinitis (25).

High levels of nitrate are found in Cucumbers and may be a risk, especially to young children (26).

f244 Cucumber

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f289 Date

Phoenix dactylifera

Family: *Areaceae*

Common names: Date, Date fruit, Soft date, Bread date, Dry date

Source material: Fresh fruit from palmtree

See also: Canary Island date palm tree (*Phoenix canariensis*) t214

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Allergen Exposure

Geographical distribution

Although there are many Palms that we call “Date palms”, *Phoenix dactylifera* is the true Date palm, with a 5,000-year history of human use. Dates require a hot, dry climate and flourish in Africa, the Middle East, California, and Arizona. Although there are at least 150 varieties, there are 2 main types: Dry and Bread dates are self-curing on the tree; Soft dates require harvest at the appropriate time, and sun-drying to increase sugar content and prevent spoilage. The latter are traditionally packaged in Palm leaves and widely traded. The Date is often the only available staple food for the inhabitants of desert and other arid lands, and as such it is vital to millions throughout North Africa and the Middle East.

The fruit of the Date is a drupe and can vary in size, shape, colour, and quality of flesh. Dates are usually reddish-brown when fully ripe. The maximum length of the fruit is about 6 cm. All Dates have a single, long, narrow seed. The skin is thin and papery, the flesh cloyingly sweet. Wild Dates are morphologically and ecologically similar to domesticated Dates but have smaller, inedible fruits.

Environment

Edible Dates are produced only by cultivation. When fresh, Dates contain about 55% sugar, a percentage that increases dramatically as the Date dries and the sugar becomes concentrated. Dates can be eaten fresh, but are usually marketed dried, and sometimes as a syrup. They yield food products such as vinegar, wine, “honey,” chutney or sweet pickle, paste for bakery products, and flavourings, in particular additional flavouring for Oranges, Bananas and Almonds. Date syrup is a sugar substitute. Date sap is made into a fermented beverage, and a flour is made from the pith of the tree. The seeds yield an edible oil. Even the tree’s terminal buds (heart of palm) make tasty additions to vegetable salads. Dates are a good source of protein, iron, fibre, potassium, and vitamin C.

Regarded as aphrodisiac, contraceptive, demulcent, diuretic, emollient, expectorant, laxative, pectoral, purgative, and refrigerant, the Date is used in many folk remedies, especially for respiratory complaints and diseases of the gentio-urinary system. A plaster of the nuts or of the bark is also a folk remedy.

f289 Date

Unexpected exposure

See under Environment for the potential of Date to be a hidden allergen. The leaves are used for making ropes, mats, baskets, crates, furniture, fencing and roofing. Bases of the leaves and the fruit stalks are used as fuel. The wood is used for construction and the seed oil for soap manufacture.

Allergens

No allergens from this plant have yet been characterised.

A panallergen, a profilin, has been isolated from Date fruit (1).

The presence of another panallergen, a lipid transfer protein (LTP), has been inferred from a study assessing foods that may be regarded as safe for LTP-allergic patients (2).

Date fruit extracts from 8 cultivars were evaluated with SPT in an atopic population. About 13% of patients were shown to have skin reactivity to at least 2 Date fruit extracts. Between 15 and 18 proteins of 6.5 to > 100 kDa were detected. All sera from Date fruit-allergic and pollen-allergic individuals bound strongly to 2 anti-IgE reactive bands of 6.5 to 12-14 kDa and 28-33 kDa, respectively; and about 50% of sera bound to a 54-58 kDa band. The authors state that these results strongly indicate that 1) Date fruit is a potent allergen; that 2) sera from fruit-allergic as well as pollen-allergic patients recognise common fruit-specific epitopes; and that 3) there is heterogeneity in patient responses to the different extracts (3).

In a subsequent study, 18 of the most commonly sold varieties of Dates were investigated for allergenicity utilising a study group of 32 Date fruit-sensitive patients. Six of the cultivars demonstrated highly positive SPT in some patients, and 5 were associated with high IgE antibody levels. However, individual cultivars varied in the number of IgE bands seen. Cultivar-specific IgE-binding patterns showed that only certain cultivars bound IgE at molecular weights of $< \text{or} = 14.3$ and 27-33 kDa, while all cultivars bound to a 54-58 kDa doublet. Cultivars that bound to the ≤ 14.3 and 27-33 kDa bands appeared to form the majority of the cultivars resulting in

high skin reactivity. When individual sera of 24 of the 32 SPT positive patients were used in IgE immunoblots with the pooled cultivar extract, all sera bound IgE at ≤ 14.3 and 27-33 kDa, and about 60% of sera bound to the 54-58 kDa doublet. Sixty to 100% of sera from Date fruit-allergic patients bound IgE to 3 major allergens of around 14.3, 27-33 and 54-58 kDa. The authors concluded that the allergenicity of Date fruits is a cultivar-specific phenomenon (4).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected (5).

Date fruit and pollen antigens share a number of cross-reactive epitopes. Date pollen has been shown to cross-react with antigens from *Artemisia* species, Cultivated rye (*Secale cereale*), Timothy grass (*Phleum pratense*), Sydney golden wattle (*Acacia longifolia*), and Bermuda grass (*Cynodon dactylon*) pollen. A study was carried out to examine cross-reactivity between Date palm protein and some common foods that have been implicated in oral allergy syndrome (OAS). Several antigens were shown to be cross-reactive among Birch, Date and Timothy grass profilin. Sixty-six percent of sera from Date-hypersensitive individuals bound IgE to Date fruit profilin, and pooled sera bound IgE to Birch pollen profilin. The authors suggest that these results indicate that Date palm protein shares cross-reactive IgG and IgE epitopes with a number of foods implicated in OAS; binds to Birch and Timothy grass profilins; and binds IgE through glycosyl residues. They state that the clinical relevance of these cross-reactivities needs to be further elucidated (1).

Cross-reactivity between Date fruit and other foods containing LTPs is possible (2).

Clinical Experience

IgE-mediated reactions

Date fruit may commonly induce symptoms of food allergy in sensitised individuals, in particular in communities where this fruit is commonly ingested (2-3,6). In a population where Date fruit is commonly eaten, SPT

positivity to at least 2 Date fruit extracts was shown in approximately 13% of the study group of atopic patients. Eight cultivars were evaluated (2). Allergic reactions may include symptoms of immediate hypersensitivity: pharyngeal pruritis, oedema of the lips, dyspnoea, wheezing, dysphagia, dysphonia, oral allergy syndrome, and other symptoms of food allergy (2-3,7).

A study was conducted at 17 clinics in 15 European cities to evaluate the differences among some Northern countries regarding what foods, according to the patients, elicit hypersensitivity symptoms. According to questionnaires administered to food-allergic individuals concerning 86 different foods, the foods that were most often elicited symptoms in Russia, Estonia, and Lithuania were citrus fruits, chocolate, honey, Apple, Hazelnut, Strawberry, Fish, Tomato, Hen's egg, and Cow's milk, a situation that differed from that of Sweden and Denmark, where Birch pollen-related foods such as nuts, Apple, Pear, Kiwi, stone fruits, and Carrot were the most common reported causes. The most common symptoms reported were oral allergy syndrome and urticaria. Birch pollen-related foods dominated as reported culprits in Scandinavia, whereas some Mugwort-related foods were of more importance in Russia and the Baltic States. Among 1,139 individuals, Date was the 76th most reported food, resulting in adverse effects in 5.3% (6).

Other reactions

Dates contain tyramine, which may cause migraine in susceptible people. Since Dates are high in sugar, they may cause tooth decay and gum disease.

Edible Dates have been reported to contain the moulds *Cladosporium cladosporioides* and *Sporobolomyces roseus*. Both organisms have been previously reported in opportunistic infections involving skin in immunocompromised patients (8).

In a study, 25 varieties of Dates (*Phoenix dactylifera*) were examined at different maturation stages for total microbial counts, aflatoxins and aflatoxigenic *Aspergillus* species, and lactic acid bacteria. Microbial counts were high at the first stage of maturation and

increased sharply at the second stage, then decreased significantly at the final dried stage. Aflatoxins were detected in 12% of the samples, while aflatoxigenic *Aspergillus* was detected in 40% of the varieties examined; all at the first stage of maturation only. No aflatoxins or aflatoxigenic *Aspergillus* were detected at the final edible stage of maturation (9).

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f276 Fennel



Foeniculum vulgare

Family: *Apiaceae*

Common names: Fennel, Florence fennel, Finocchio, Sweet fennel, Wild fennel, Common fennel, "Sweet Anise"

Source material: Swollen leave-base from fresh fennel

Synonyms: *F. officinale*,
F. capillaceum,
F. foeniculum

This plant is not to be confused with Dog fennel (*Anthemis cotula*). In the USA, *Foeniculum vulgare* is often mistakenly called Anise.

See also: Fennel seed f219 (another description of *Foeniculum vulgare*).

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Allergen Exposure

Geographical distribution

Fennel is native to southern Europe (where it has been popular since Mycenaean times), and is common there and in Britain, Ethiopia, the Middle East, the Far East, the Caribbean, and parts of South America.

Fennel is an evergreen perennial herb growing to 1.5 m by 1 m. There are 2 main types of this aromatic plant, both with pale green, Celery-like stems and bright green, feathery foliage. Florence fennel, also called Finocchio, is cultivated throughout the Mediterranean and in the United States. It has a broad, bulbous base that is treated like a vegetable. Common fennel is the variety from which the oval, greenish-brown Fennel seeds come.

Environment

Fennel grows in meadows and cultivated beds. Both the base and stems of Florence fennel can be eaten raw in salads or cooked by a variety of methods such as braising, sautéing or boiling in soups. The fragrant, graceful greenery can

be used as a garnish or snipped into small pieces like dill. This type of Fennel is often mislabelled "Sweet anise", but the flavour of Fennel is sweeter and more delicate than Anise. The leaves or the seeds can be used to make a pleasant-tasting herbal tea.

The plant is used as a herbal remedy, including as a gargle and an eyewash.

Unexpected exposure

Yellow and brown dyes are obtained from the flowers and leaves combined. The oil may be used as a flavourant or fragrance in toothpastes, soaps, perfumery, air fresheners, etc.

Allergens

No allergens from this plant have yet been characterised.

A profilin-related allergen to Bet v 1, and cross-reacting allergenic molecules in the molecular weight range of 60 kDa, have been detected in Fennel (1).

A lipid transfer protein has been detected (2).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected and in fact is frequently manifested (3). Cross-reactivity among the *Apiaceae* is the cause of the pattern of positive results obtained with Carrot, Parsely, Anise, Fennel and Caraway (4-6).

As Fennel contains a profilin-related allergen, cross-reactivity between Fennel and other profilin-containing plants is possible (1,7).

Caraway, Fennel, cumin, and Coriander extracts showed similar IgE-binding patterns. Enzyme immunoassay inhibition studies with a serum from a patient allergic to Aniseed revealed cross-reactivity among the IgE components from Aniseed, Caraway, Coriander, Fennel, and Dill extracts (8).

Clinical observations have also been the source of reports that in Mugwort and Birch pollen allergy, hypersensitivity to spices is frequently seen in association (1).

A study suggested that most *Apiaceae* determinants cross-react with Apple or Hazelnut determinants, whereas only some Apple or Hazelnut determinants cross-react with *Apiaceae*-allergenic determinants (9).

Clinical Experience

IgE-mediated reactions

Fennel may commonly induce symptoms of food allergy in sensitised individuals. Allergic symptoms may occur in children (10-12). Fennel allergy in children may result in symptoms of food allergy and/or atopic dermatitis (10).

Typical features of oral allergy syndrome (OAS) may occur with the ingestion of Fennel (13-14). Among 196 Birch pollen-hypersensitive patients with OAS caused by various vegetables who were examined in a cross-sectional part of a study, 195 had Apple and/or Hazelnut allergy, and 103 had *Apiaceae* sensitivity; only a single patient had *Apiaceae* allergy alone. *Apiaceae*-positive patients showed significantly higher Birch pollen IgE antibody levels than did negative ones (8).

Food-dependent exercise-induced anaphylaxis following ingestion of Fennel has been reported (15).

The presence of IgE antibodies to Fennel may be detected in serum of sensitised individuals (16). Tests for skin reactivity to native spices have been carried out in patients suspected of food allergies to spices. Frequent sensitisation to *Apiaceae* (Coriander, Caraway, Fennel, and Celery) was observed in 32% of children and 23% of adults, demonstrating the presence of IgE antibodies to these spices (4,17).

Other reactions

A survey of the literature shows essential oils of 11 plants (Eucalyptus, Fennel, hyssop, pennyroyal, Rosemary, Sage, savin, tansy, Tthuja, turpentine, and wormwood) to be powerful convulsants due to their highly reactive monoterpene ketones (18).

Vegetables containing psoralens are responsible for contact phytophotodermatitis, but they probably do not produce photodermatitis when taken orally. In a study, healthy volunteers ingested Celery in large amounts (500 grams and more): plasma concentrations of psoralens were found to be non-existent in all subjects and at all sampling times, and no phototoxic reaction was detected by MPD. The authors report that Celery roots do not appear to be photosensitising, even after ingestion in large amounts, but that they might increase the risk of phototoxicity in PUVA-therapy. The same applies to Fennel and parsnip (19).

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Ficus carica**Family:** *Moraceae***Common names:** Fig, Common fig, Edible fig**Source material:** Fresh fruit**For continuous updates:**
www.immunocapinvitrosight.com**Allergen Exposure****Geographical distribution**

The Fig tree is believed to be indigenous to western Asia and to have been distributed by man throughout the Mediterranean area. It has been cultivated for thousands of years, remnants of Figs having been found in excavations of Neolithic sites dating back to at least 5000 BC. European types were eventually taken to China, Japan, India, South Africa, Australia, and North and South America. Some members of the Fig family are ornamental plants (*e.g.*, Weeping fig, or *Ficus benjamina*), and some produce rubber. Over 700 varieties of Fig are in existence.

The fruit (usually pear-shaped and up to 5 cm in diameter) is actually a swollen flower stalk; female flowers are borne on the inside of a fleshy structure called a receptacle, which expands greatly as the fruit matures. In some varieties, a female Fig wasp crawls through the ostiole (a small hole at the end of the Fig) to pollinate the flowers. Some varieties can bear fruit without pollination. Fermentation of the fruit can occur if there is too much rain during maturation, since rain can seep inside fruit.

Environment

The tree grows among rocks and in woods and scrub, or in cultivated groves. In warm, humid climates, Figs are generally eaten fresh and raw without peeling. Peeled or unpeeled, fresh, canned or dried, the fruits may be stewed or cooked in various ways, as in pies, puddings, cakes, bread or other bakery products, or can be added to ice cream mix. The fruits are sometimes preserved in sugar syrup or prepared as jam, marmalade, or paste. In



Europe, western Asia, northern Africa and California, commercial canning and drying of Figs are industries of great importance. Figs have been roasted and ground up as a coffee substitute. In Mediterranean countries, low-grade Figs are converted into alcohol, which is sometimes used as a flavouring for liqueurs and tobacco. The seed yields an edible oil that can also be a lubricant. The leaves can be an animal fodder. The latex is dried and powdered for coagulating plant and animal milk. From it can be isolated the protein-digesting enzyme ficin, which is used for tenderising meat, rendering fat, and clarifying beverages.

The latex is widely applied on warts, corns, skin ulcers, insect bites, and piles, and taken as a purgative and vermifuge, but with considerable risk (see under Other reactions). In Latin America, Figs are often employed as folk remedies. A decoction of the fruits is gargled to relieve sore throat and diseases of the chest; Figs boiled in milk are packed against swollen gums; the fruits are often used as poultices on tumours and other abnormal growths. The unripe green fruits are cooked with other foods as a galactagogue and tonic. A leaf decoction is taken as a remedy for stomach complaints,

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diabetes and calcifications in the kidneys and liver, and is used as a steam bath for swollen piles. The young branches are also a pectoral remedy. Fresh and dried Figs have long been appreciated for their laxative action.

Unexpected exposure

See under Environment. Also, some members of this tree family produce rubber. Fig wood, though of low quality, may be used for hoops, garlands, emery boards, etc.

In southern France, there is some use of Fig leaves as a source of a perfume material called “Fig-leaf absolute” – a dark-green to brownish-green, semi-solid mass or thick liquid of herbaceous-woody-mossy odor, employed in creating woodland scents.

Allergens

In an investigation of the serum of 2 individuals who experienced oral allergy syndrome (OAS) to Fig, a major band of about 20 kDa and a minor band with a lower molecular weight were recognised in the serum of 1, while 3 proteins of about 10, 22 and 24 kDa were detected using the serum of the second patient. However, immunoblotting experiments confirmed the presence of IgE binding proteins in the phosphate-buffered saline (PBS)-soluble fractions of the skin of the Fig, whereas the PBS extract of the pulp did not show any potential allergens. Though the 2 patients examined had similar clinical features, they did not show IgE binding to the same protein bands, which suggested that OAS symptoms can be induced by different allergens present in the PBS-soluble fraction of the Fig skin. The authors pointed out that in 1 patient, IgE recognised 2 protein bands of the pulp that were insoluble in PBS, and that these proteins are, therefore, unlikely to act in the aqueous environment of the mouth, but may be involved in allergic responses (e.g., anaphylaxis) at the gastrointestinal level (1).

Indeed, in the assessment of the serum of a 35-year-old woman who experienced anaphylaxis to dried Fig and symptoms to Weeping fig (*Ficus benjamina*), IgE antibodies directed at a protein of 35 kDa, found in dry Fig and fresh Fig, were demonstrated in her serum. The *F. benjamina* extract contained 2

allergens of 35 and 19 kDa that were totally and partially inhibited by fresh and dried Fig, respectively (2).

The following allergens have been characterised:

Fic c Ficin, a protease (3).

Fig c LTP, a lipid transfer protein (4).

In Jelly fig (*Ficus awkeotsang*), a related family member, 2 thaumatin-like protein isoforms were isolated, as well as a pectin methylesterase and a chitinase in the Jelly fig curd (5). Whether similar allergens are present in Fig has not been determined to date.

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected, but this has not been fully investigated to date (6).

In a Fig-allergic individual, detection of IgE antibodies to Weeping fig tree pollen (*F. benjamina*) indicated sensitisation. Further investigation revealed that these 2 species of *Ficus* share some allergens (2,7). Where cross-reactivity between *F. benjamina* and Fig occurs, authors have suggested that it is likely that allergy to Fig is a consequence of initial sensitisation to *F. benjamina* pollen (2). Therefore, in a patient with asthma and conjunctivitis caused by an immediate-type allergy to Weeping fig pollen, who was shown to have IgE antibodies to Fig, the patient tolerated Fig in an oral provocation test. Sensitisation to Latex protein, a possible cross-reaction allergen (see below) was not found (8).

The Fig has also been included among those plant foods responsible for “Latex-fruit syndrome”, an allergic disease resulting from cross-sensitisation to Latex (*Hevea brasiliensis*) and several types of fruits (9-10). Studies have reported and confirmed cross-sensitisation among Fig, Weeping fig, and Natural rubber latex (11), and among Latex, Papaya, Avocado, Banana, Chestnut, Passion fruit, Fig, Melon, Mango, Kiwi, Pineapple, Peach, and Tomato. Fruit-specific IgE antibodies were detected only in 32.1% of the 136 patients investigated (10).

Hypersensitivity to Weeping fig latex may cause IgE-mediated respiratory allergy. In a report, the authors conclude that an allergic association between Fig and Papain is likely, due to the existence of cross-reactive allergen structures (12).

Recently, it was reported that sensitisation to *Ficus benjamina* latex usually occurs independently of Latex (*H. brasiliensis*) allergy, but that the *Ficus* sensitisation is commonly associated with allergic reactions to Fig and other tropical fruits (“*Ficus*-fruit syndrome”). In a study of 54 *F. benjamina*-allergic individuals, sensitisation to *F. benjamina* was specifically associated with positive SPT to fresh Fig (83%), dried Fig (37%), Kiwi fruit (28%), Papaya (22%), Avocado (19%), Banana (15%), and Pineapple (10%). Fig-specific IgE antibodies were inhibited 87% by *F. benjamina*, 89% by fresh Fig, 80% by dried Fig, 38% by Kiwi, and 59 and 44% by the thiolproteases ficin and Papain, respectively. The authors concluded that this cross-reactivity was mediated at least in part by the thiolproteases ficin and Papain (3,13).

Serum from 4 patients with known allergy to *F. benjamina* leaves, Fig and Kiwi, and from 1 patient allergic to *F. benjamina* leaves and Kiwi, were studied for cross-reactivity patterns. Inhibition studies showed a high degree of cross-reactivity between *F. benjamina* leaves and Fig extracts, and a lower level between these and Kiwi extract (14).

A study reported on 3 individuals with associated Fig and Mulberry (*Morus nigra* and *Morus alba*) allergy. They also were sensitised to multiple other food allergens (mostly fruits) and airborne allergens. The authors speculated that, as *Ficus* and *Morus* are closely related genera of the *Moraceae* family, concomitant hypersensitivity to Fig and Mulberry might be a result of allergen cross-reactivity rather than a mere coincidence (15).

In an evaluation of the clinical characteristics of Melon allergy in 66 Melon-allergic patients, 48% self-reported allergy to Fig. Skin reactivity was most frequently demonstrated, after pollen, to Peach, Fig, and Kiwi. About 82% of the patients were shown to have positive SPT to Fig (16).

Clinical Experience

IgE-mediated reactions

Fig may uncommonly induce symptoms of food allergy in sensitised individuals (17). Symptoms include pruritis, generalised urticaria, facial angioedema, asthma, gastrointestinal symptoms, oral allergy syndrome, and anaphylaxis (1-2,7,14,18-19).

A study was conducted at 17 clinics in 15 European cities to evaluate the differences among some Northern countries regarding what foods, according to the patients, elicit hypersensitivity symptoms. Questionnaires concerning 86 different foods were administered to food-allergic individuals. The foods most often reported as eliciting symptoms in Russia, Estonia, and Lithuania were citrus fruits, chocolate, honey, Apple, Hazelnut, Strawberry, Fish, Tomato, Egg, and Milk, which differed from the situation in Sweden and Denmark, where Birch pollen-related foods, such as nuts, Apple, Pear, Kiwi, stone fruits, and Carrot were the most common reported culprits. The most common symptoms reported were oral allergy syndrome and urticaria. Birch pollen-related foods dominated as reorted allergens in Scandinavia, whereas some Mugwort-related foods were apparently of more importance in Russia and the Baltic States. Among 1,139 individuals, Fig was the 68th most reported food resulting in adverse effects in 6.7% (17).

A number of case reports have recorded the diverse range of adverse clinical effects reported with Fig allergy.

A report was made on 3 individuals with associated Fig and Mulberry allergy, who were sensitised to multiple other food allergens (mostly fruits), along with airborne allergens. A 12-year-old girl developed lip and oropharyngeal angioedema and pruritis a few minutes after eating White mulberry; she also experienced shortness of breath, a sense of suffocation, and lip, tongue and oropharyngeal swelling and pruritis after eating a Fig. The second patient, a 43-year-old female, developed acute generalised urticaria with pruritis, flushing, a sensation of heat, conjunctival injection, colic and drowsiness 2 hours after eating Fig. The third patient, a 47-year-old male, reported several episodes

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of generalised pruritis, acute urticaria, and attacks of severe abdominal pain after eating fresh Fig. Similar reactions had occurred after eating White and Black mulberries. The authors suggested that cross-reactivity occurred between Mulberry and Fig as a result of the family relationship of *Ficus* and *Morus* (15).

The unusual characteristics of Fig allergy were further elucidated in a report of 2 cases of oral allergy syndrome (OAS) to Fig. Patient 1 was a 27-year-old woman with seasonal allergic rhinitis and asthma resulting from grass and Birch pollens, and OAS to Apple, Peach and Kiwi. She reported oral symptoms after the ingestion of Fig, which she had previously tolerated. Her most recent episode had resulted in OAS, followed by rhinoconjunctivitis, mild oedema of the eyelids and lips, and burning of the throat. Patient 2 was a 34-year-old woman with seasonal rhinitis and asthma from grass and Birch pollens. She experienced OAS after eating Apple, Pear, Peach and Hazelnut. Similarly, she had tolerated Fig until a recent episode, in which, while chewing a Fig, she experienced marked itching of the mouth, followed by severe conjunctivitis and rhinitis, sore throat, wheezing, dyspnoea and oedema of the lips and face. Skin reactivity evaluation with a skin fraction of green Fig was markedly positive in both patients, while only a minimal reaction occurred to Fig pulp. Phosphate-buffered saline (PBS) extracts of both Fig skin and pulp resulted in similar responses. No skin reactivity was detected for, among others, Latex (*Hevea Brasiliensis*) and Weeping fig pollen, and IgE antibody tests to Weeping fig and Fig were negative. The oral challenge tests with Fig were positive in both patients. Symptoms appeared approximately 10 minutes after the challenge. For patient 1, the oral mucosal symptoms were followed by conjunctivitis, eyelid and lip oedema, and slight rhinitis with nasal obstruction. For patient 2, the oral symptoms were followed by rhinoconjunctivitis and asthma with significant nasal obstruction and bronchospasm (1). The authors state that, although the 2 patients had similar clinical features, they did not show IgE binding to the same protein bands in immunoblotting, which indicates that OAS symptoms can be induced by different allergens (1).

Further, the authors point out that Fig is an unusual multiple fruit, consisting of a hollow receptacle with hundreds of small fleshy flowers facing each other on the inside (a syconium); and that in these patients the allergic symptoms appeared to be due to components present in the skin (receptacle), whereas the flowers (the internal red part of the Fig) do not appear to be allergenic. This is relevant, as Figs are sometimes eaten with the skin. If not, the skin is only partly removed by peeling. In any case, eating a peeled Fig may result in different symptoms of hypersensitivity than eating an unpeeled one (1).

Five patients with oral allergy syndrome (OAS) or anaphylaxis after the ingestion of Fig were described. The authors concluded that allergic reactions to fresh or dried Fig can present as a consequence of primary sensitisation to airborne *F. benjamina* allergens, independent of sensitisation to Natural rubber latex allergens (20).

Anaphylaxis has also been reported in a 35-year-old woman following contact with Fig. Immediately after eating a dried Fig, she experienced pruritus of the palate, sneezing, nasal obstruction, hydrorrhoea, sore throat, dyspnoea, cough, and bilateral palpebral angioedema that required urgent treatment. She had previously had no adverse effects to Fig. She had previously reacted to *F. benjamina*: after touching its leaves, she experienced severe bilateral palpebral angioedema, watery eyes, ocular pruritus, and dry cough. She also described a blocked nose, hydrorrhoea, watery eyes, and dry cough in her domestic environment, the symptoms disappearing when she left the house. Skin reactivity was demonstrated to dried Fig, to the skin and pulp of green Fig, and to the leaf and latex of *F. benjamina*, as well as to commercial extract of Fig. IgE antibody level for Fig was $4.2 \text{ kU}_A/\text{l}$, and $0.35 \text{ kU}_A/\text{l}$ for Latex (*H. brasiliensis*). No skin reactivity was demonstrated for Kiwi, Banana, Hops, Chestnut, or *Hevea brasiliensis* Latex: *i.e.*, there was no evidence for "Latex-fruit syndrome" (2).

In 2002, 107 cases were reported to the French Allergy Vigilance Network, of which 59.8% were cases of anaphylactic shock (1 being fatal). The most frequent causal allergens were Peanut (n=14), Nuts (16), Shellfish (9),

and fruits of the Latex group (9); occurring most often in patients allergic to Latex were allergies to the following: Avocado (n=4), Kiwi (n=2), Fig (n=2), and Banana (n=1) (21).

A multifoed allergy was described in a 4-year-old child, who had a positive SPT wheal of 4 mm, and IgE antibodies to Fig (18).

Other reactions

The latex of the unripe fruits and of any part of the tree may be severely irritating to the skin and eyes if not removed promptly. It is an occupational hazard not only to Fig harvesters and packers but also to workers in food industries, and to those who employ the latex to treat skin diseases. In tropical America, the latex was an ingredient in some of the early commercial detergents for household use but was abandoned after many reports of irritated or inflamed hands in housewives.

Contact with sap from Fig leaves and stems can result in contact dermatitis, phototoxicity or phytophotodermatitis (22). Phytophotodermatitis is an acute skin reaction that may be easily confused with other causes of contact dermatitis. It is characterised by sunburn, blisters, and/or hyperpigmentation. The reaction takes place when certain plant substances known as psoralens, after being activated by ultraviolet light from the sun, come into contact with the skin (23-24). Psoralen and bergapten appear to be the only significant photoactive compounds in Fig; they are present in appreciable quantities in the leaf and shoot sap but are not detected in the fruit or its sap. Lower concentrations of both compounds are present in autumn, compared to spring and summer. The higher content of both photoactive compounds in spring and summer is partly responsible for the increased incidence of Fig dermatitis during these seasons (25).

Cutaneous reactions may be severe. Two arborists presented with acute blistering eruptions on their forearms, hands, and fingers a day after both men had pruned branches from a large Fig tree that had sustained damage during a storm. The initial symptom was burning discomfort, which rapidly evolved into erythema and bullae on the skin that had been in direct contact with the tree

branches. Symptoms gradually resolved over 4 to 6 weeks (26-27).

Cutaneous reactions may mimic a burn injury (28).

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Allium sativum**Family:** *Alliaceae (Liliaceae)***Common names:** Garlic, Cultivated garlic, Poor Man's treacle**Source material:** Garlic powder**For continuous updates:**
www.immunocapinvitrosight.com**Allergen Exposure****Geographical distribution**

Garlic is a small, very pungent Onion-like plant. It has been used for millennia (it was mentioned in 1550 BC) as a flavouring and a medicine, and is now important in many cuisines worldwide. In some parts of the world, Garlic's use also has religious connotations.

Only a few members of this family are important as food plants, notably Onion, Garlic, Chive, Leek, and Rakkyo. Garlic's edible bulb or "head" grows beneath the ground. This bulb is made up of sections called cloves, each encased in its own parchment-like membrane. Today's major Garlic suppliers include the United States (mainly California, Texas and Louisiana), France, Spain, Italy and Mexico. There are several major types of Garlic available, with cloves up to 6 cm in diameter. The flavours, in addition to being characteristic, are complex, as they are derived enzymatically from a number of involatile precursors. Fresh Garlic is available year-round.

Environment

Garlic grows in cultivated beds, with occasional escapes. Garlic bulbs are eaten, either raw or cooked, as flavouring. They are usually peeled before use in recipes. Crushing, chopping, pressing or pureeing Garlic releases more of its essential oils and provides a sharper, more assertive flavour than slicing or leaving it whole. Garlic is readily available in forms other than fresh, such as dehydrated flakes or

powder. Garlic salt is Garlic powder blended with salt and a moisture-absorbing agent. Garlic extract and Garlic juice are derived from pressed Garlic cloves. One unfortunate side-effect of Garlic is that, because its essential oils permeate the lung tissue, it remains with the body long after it has been consumed, affecting breath and even skin odour. The stems, leaves, flowers and seed can be eaten raw or cooked, and are rather milder than the bulbs.

Garlic can reduce nasal congestion and lower blood pressure and blood cholesterol (for example, demographic studies suggest that Garlic is responsible for the low incidence of arteriosclerosis in areas of Italy and Spain where consumption of the bulb is heavy). It has been employed as an antiviral, antibacterial, fungicidal, vermifuge, vasodilator, expectorant, diuretic, antiasthmatic, antispasmodic, febrifuge, stomachic, skin-soothing, tonic, and immunostimulant agent. It may, however, induce migraines. Garlic extract inhibits chromosomal breaks due to sodium arsenite (arsenic), a contaminant in ground water. It has been shown that Garlic aids detoxification of chronic lead poisoning. It is also said to

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have anticancer activity. Recent research has indicated that Garlic reduces glucose metabolism in diabetics.

The growing plant is said to repel insects, rabbits and moles. An extract of the plant can be used as an insect repellent.

Unexpected exposure

Cloves of Garlic are sometimes spread among stored fruit to delay rotting. The juice is also used as glue for mending glass and china.

Allergens

No allergens from this plant have yet been characterised.

Using serum from a Garlic-allergic individual, a 12 kDa protein band to young Garlic, mature Garlic, Onion, and Leek extracts was detected. Similar bands could also be detected with Mugwort pollen and Hazelnut extract (1).

Protein bands of 10, 20 and 40 kDa were detected in a patient with urticaria who was affected by cooked and raw Onions. Garlic appears to have heat-stable and heat-labile allergens (2).

A 12 kDa and a 40-50 kDa protein have been detected (3), probably corresponding to a mannose-binding lectin (4) and alliinase (5) respectively, both previously reported and probably heat-labile.

In a patient with nasal symptoms following exposure to Garlic dust, significant protein bands at 14 and 40 kDa to Garlic extract were demonstrated (6).

In a study of 15 patients with Garlic allergy, with symptoms of rhinitis, urticaria, dermatitis, and asthma, IgE-binding components ranging from 31 to 60 kDa were isolated. A component with a molecular weight of approximately 56 kDa was detected by all 15 sera and identified as alliin lyase. Other IgE-binding components of various molecular weights were detected at frequencies of less than 30%; for example, 4 serum samples gave a positive reaction to a 42 kDa component. Periodate oxidation showed that carbohydrate groups were involved in the substance's antigenicity, allergenicity, and cross-reactivity (7).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected, as well as to a certain degree among members of the family *Alliaceae* (previously categorised as *Liliaceae*), such as Onion, Leek, Garlic, Asparagus and Chives (8-9).

The major Garlic allergen, alliin lyase, showed strong cross-reactivity with alliin lyases from other *Allium* species, namely Leek, shallot, and Onion (7).

Cross-allergenicity between Garlic and other members of the *Liliaceae* family was documented through the RAST inhibition technique (10).

The presence of structurally similar allergens in Garlic, Onion, and certain pollens of *Phleum* and *Chenopodium* has been described. There was partial abolishment of the IgE binding to several of these allergens (11). The clinical significance of this is not yet known.

Clinical Experience

IgE-mediated reactions

Garlic can induce symptoms of food allergy in sensitised individuals (12-13). Garlic is well-known cause of contact dermatitis and asthma. However, it is thought to be an uncommon cause of food or other allergy in children (1-2,14-16). In a European study of 589 individuals with food allergy, SPT positivity to *Liliaceae* (Garlic, Onion, Chive) was documented in 4.6% of children and 7.7% of adults (17).

In an evaluation of 163 asthmatic French children with food allergy who were assessed for food-induced asthma using DBPCFC, the most frequent offending foods were, sometimes in association, Peanut (30.6%), Hen's egg (23.1%), Cow's milk (9.3%), Mustard (6.9%), Codfish (6%), Shrimp (4.5%), Kiwi fruit (3.6%), Hazelnut (2.7%), Cashew nut (2.1%), Almond (1.5%), and Garlic (1.2%) (18). A subsequent study was done by the same main author of a cross-sectional, descriptive, questionnaire-based survey conducted in Toulouse schools in France to determine the prevalence of

food allergies among schoolchildren; it was reported that, out of 2,716 respondents, 192 self-reported a food allergy, but that there was only a single reported case of allergy to Garlic (19).

A study was conducted at 17 clinics in 15 European cities to evaluate the differences among some northern countries regarding what foods, according to food-allergic patients, elicit hypersensitivity symptoms. It was reported, after evaluation of questionnaires concerning 86 different foods, that the foods apparently most often eliciting symptoms in Russia, Estonia, and Lithuania were citrus fruits, chocolate, honey, Apple, Hazelnut, Strawberry, fish, Tomato, Hen's egg, and Milk; these results differed from those of Sweden and Denmark, where Birch pollen-related foods, such as nuts, Apple, Pear, Kiwi, stone fruits, and Carrot, were the most common reported causes. The most common symptoms reported were oral allergy syndrome and urticaria. Birch pollen-related foods apparently dominated as allergens in Scandinavia, whereas some Mugwort-related foods seemed to be of more importance in Russia and the Baltic States. Among 1,139 individuals, Garlic was the 57th most reported food allergen, resulting in adverse effects in 8.2% (20).

In an Indian study of 24 children aged 3 to 15 who had documented deterioration in control of their perennial asthma, IgE antibodies to Garlic were documented in 14 (58%) (21).

A large population-based study of adverse reactions to food in adults in Istanbul found Garlic to be an uncommon self-reported cause of adverse reactions (22).

A study described a small population of patients in the mid-southern region of Taiwan who were allergic to Garlic. Symptoms included rhinitis, urticaria, dermatitis, and asthma. All the patients had lived near Garlic fields, worked or played near a Garlic store, and eaten Garlic over a long period of time. Serum samples were obtained from all 15 patients, and the allergen alliin lyase was identified in all. All 12 patients were positive on intradermal testing with purified Garlic alliin lyase, whereas 58% were positive with a lower concentration (7).

A 16-month-old boy with a history of Cow's milk and Hen's egg white allergy has been reported as developing urticaria on the face and neck immediately after contact with fresh Garlic. He tolerated cooked Garlic (3).

Garlic may result in anaphylactic reactions, as described in a 23-year-old woman who had eaten young Garlic (1).

Occupational asthma and rhinitis have been reported, which may have an onset long after work with the substance (11,23-24). Occupational allergy to Garlic dust has also been reported (25-26). In an atopic patient, repeated exposure to Garlic dust induced severe asthma. The patient subsequently also developed marked adverse responses after ingesting Garlic. A skin prick test and a bronchial challenge test with Garlic dust and extract were both positive, as was an oral challenge test with Garlic dust. Serum Garlic-specific IgE was unusually high (10).

A study reported on a patient who presented with nasal symptoms when working with spices that included Garlic and Onion dust. Skin prick tests were positive for Onion, Garlic powder and fresh *Liliacea* (not specified). IgE antibody levels were found to Garlic and Onion, and significant protein bands at 14 and 40 kDa with Garlic extract were demonstrated. Nasal challenge showed an increase in inspiratory nasal resistance that was higher than 100% of the basal value for both Onion extract and Garlic (6).

Allergic contact dermatitis to Garlic has a typical clinical presentation, but this is often masked if the reaction presents concurrently with another form of hand dermatitis or other conditions (27-29). Reactions may be immediate or delayed (30). Occupational airborne allergic contact dermatitis from Garlic has been reported (31).

Allergic contact cheilitis to Garlic has been described (32).

Other reactions

The spectrum of Garlic-related skin adverse reactions comprises irritant contact dermatitis (with the rare variant of zosteriform dermatitis), pemphigus, contact urticaria, protein contact dermatitis, and allergic contact dermatitis, as well as combinations of these (33-34).

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Garlic is a common cause of contact dermatitis, in particular in an occupational environment (35-39). Contact dermatitis from Garlic is usually due to handling of Garlic for cooking, especially in the cases of greengrocers, housewives and cooks (40-43). In India, Garlic was reported to be the offending agent in 6.7% of patients seen with contact dermatitis (44). Occupational contact dermatitis from a Garlic and herb mixture has been described (45). Garlic-induced systemic contact dermatitis has also been reported (46). Garlic-sensitive patients showed positive tests to diallyldisulfide, allylpropyldisulfide, allylmercaptan and allicin, all present in Garlic (47).

Patients have experienced second-degree burns of the forehead, breast, and other parts of the body, induced by topical application of crushed Garlic (48-50). These burns may mimic herpes zoster (51). Children have also been adversely affected by poultices containing Garlic (52).

A case of superficial pemphigus has been reported as appearing spontaneously in a 49-year-old man and running a course that proved to be affected by dietary factors, in particular by the consumption of Garlic (53).

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Allergen Exposure

Geographical distribution

Vitis vinifera is one of the oldest cultivated plants. It grows in temperate and subtropical climates, especially around the Mediterranean, and its fruit, the Grape, is consumed either directly or as juice or wine. Western Europe is the world's biggest producer of Grapes. France, Italy, and Spain are the major producers of wine that is sold and drunk throughout the world (1), though Grapes are grown on nearly all continents.

Grapes belong to the *Vitis vinifera* species, subfamily *Ampelideae*, of the *Vitaceae* family. The only species grown around the Mediterranean is *Vitis vinifera*, and the composition of the pulp of the ripe fruit varies widely, depending on the variety of vine, the climate, the physicochemical characteristics of the soil, and the agricultural methods employed (fertilisation, irrigation, etc.) (2).

Environment

Grapes are widely consumed in as fresh fruit, juice, and wine, and the boiled vine leaves are used for the preparation of stuffed vine leaves, so-called "dolmades."

Vitis vinifera

Family:	<i>Vitaceae</i>
Common name:	Grape
Source material:	Fresh fruit
Synonyms:	<i>V. vinifera</i> subsp. <i>sylvestris</i> <i>Vitis sylvestris</i> <i>V. vinifera</i> subsp. <i>vinifera</i>

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Allergens

Assessing Grape allergens is hampered by the low protein and high tannin and pectin concentrations of Grape (3). A number of allergenic proteins have been isolated, but few have been characterised. In a Spanish study of sera of 5 of 14 children who had suffered allergic reactions involving fresh Grapes or Grape juice, an IgE-binding Grape protein of 94 kDa was recognised in a patient, proteins of 100, 60, 34, 28, 24 and 17 kDa in a second, a 31 and 24 kDa protein a third patient, a 34 kDa protein in a fourth, and a 17 kDa band in a fifth, indicating heterogenous sensitisation to a variety of allergenic proteins (4). Other studies have reported similar- or different-sized allergenic proteins. A 5-year-old child with oral allergy syndrome and lip angioedema after eating Grape was shown to be sensitised to a 94 kDa antigenic protein (5). An 18-year-old woman experienced anaphylaxis to Grape only when concomitantly ingesting champagne, and 2 patients with allergic reactions to Grape tolerated alcoholic drinks. Grape IgE antibodies were detected only in the latter 2, although SPT was positive in all 3. IgE binding was reported to proteins of 28 kDa, 30.6 kDa, 43 kDa and 56 kDa in case 1, to proteins of 28 kDa, 30.6 kDa, 43 kDa, 56 kDa, and 75 kDa in case 2, and to none in case 3 (6).

In a 33-year-old woman with exercise-induced anaphylaxis to Grape and allergic symptoms after drinking white or red wine, no Grape-specific IgE antibodies could be

demonstrated in the serum by RAST, but serum IgE reactivity was shown to a protein band at about 67 kDa and to another between 25 and 35 kDa (7). In a study of 3 patients with anaphylaxis to Grape, a protein of approximately 30 kDa bound IgE antibodies from all 3 (8). In a patient with food-dependent exercise-induced anaphylaxis to wine, IgE directed against a 13 kDa protein was demonstrated (9). Further evidence of the allergens involved in Grape allergy derives from a study of 11 patients with severe allergic reactions to Grape and 3 with anaphylactic reactions to wine. IgE binding of proteins of 30 kDa in 79%, 9 kDa in 71%, and 24 kDa in 21% was demonstrated. The major allergens were identified as an endochitinase and a lipid-transfer protein (LTP). The 24 kDa protein, a thaumatin-like allergen, was a minor allergen (1).

Significantly, Grape allergy may be specific to a certain Grape variety, while there is tolerance to others, as demonstrated in a patient who had experienced several anaphylactic reactions to Grape and who was selectively sensitised to the Americana grape (*Vitis labrusca*) (10). Some patients may be allergic to Grape but not wine, whereas others might not tolerate Grape, wine or raisins (2).

The following allergens have been characterised:

Vit v 1, a 15 kDa lipid transfer protein (1,3,11-15).

Vit v 4, a profilin (12,16).

Vit v Thaumatin, a 24 kDa thaumatin-like protein (1,12).

Vit v Endochitinase, a 30 kDa chitinase-like protein (1,12).

Vit v Glucanase, a 39 kDa beta-1,3-glucanase protein (12).

Grape chitinases account for 50% of the soluble proteins of Grape and persists through the process of vinification (17). The lipid transfer protein Vit v 1 is a major allergen and may sensitise between 70% and 100% of Grape-allergic individuals (1,12). The beta-1,3-glucanase and thaumatin-like protein are minor allergens (12). Some authors regard the

endochitinases as minor allergens and other authors the opposite (1,12). Severe Grape allergy has been linked to lipid transfer protein (LTP) sensitisation. Grape LTP is resistant to gastric digestion (13). Grape LTP is highly homologous to Peach LTP (80%) (18).

Potential cross-reactivity

Cross-reactivity between Grapes and *Rosaceae* fruits may be suspected (19).

A Bet v 1 homologue from Melon, Cuc m 3, shares more than 60% sequence identity with PR-1 proteins from Grape and Cucumber (20).

Grape contains a thaumatin, analogous to the Cherry thaumatin-like allergen, which may result in cross-reactivity with other foods containing this panallergen. However, the protein is a minor allergen in Grape.

Grape contains a lipid transfer protein, which may result in cross-reactivity with other lipid transfer protein-containing foods such as Peach and Cherry (1,14,17-18,21). Lipid transfer protein is a widely cross-reacting plant panallergen found in *Rosaceae*, tree nuts, Peanut, beer, Maize, Mustard, Asparagus, Grape, Mulberry, Cabbage, Date, Orange, Fig, Kiwi, Lupine, Fennel, Celery, Tomato, Eggplant, Lettuce, Chestnut and Pineapple. However, the degree of homology and other factors may result in tolerance of certain LTP-containing foods, as demonstrated in an Italian study that concluded that Carrot, Potato, Banana and Melon seemed safe for LTP-allergic patients (22).

However, as Grape contains a number of allergens, of which some act as panallergens, cross-reactivity expression may be more complex. This is illustrated in a study of 11 patients with severe allergic reactions to Grape and 3 with anaphylactic reactions to wine, among whom IgE binding to an endochitinase occurred in 79%, to a LTP in 71%, and to a thaumatin in 21%. The endochitinase was the likely allergen in vino novello and in vino Fragolino; *V. labrusca*, which is used to make Fragolino wine, has 4 times the chitinase activity of *V. vinifera* (23), which may explain why certain patients reacted more strongly to this kind of wine than to others. The authors

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suggested that, given LTP as a factor, the primary sensitisation is to Peach LTP, which would influence the sensitisation to Grape LTP, but that only a few IgE epitopes of Peach LTP are present on Grape LTP. They also reported that the complete inhibition of IgE binding to a 20 kDa band of Latex, probably representing prohevein, demonstrated the existence of the hypothesised cross-reactivity between Latex and Grape, but that the cross-reactivity may not be clinically expressed (1). This is illustrated by a report that identified cross-reactivity between Latex and Grape (24); however, in a study of 2 children with Latex hypersensitivity, skin prick tests with Banana, Kiwi, Pineapple, Apricot, Avocado, and Grape were positive, but children presented no symptoms after ingestion of these fruits (25).

Cross-reactivity has been reported to occur among Apricot, Avocado, Banana, Cherry, Chestnut, Grape, Kiwi, Papaya, Passion fruit, Peach and Pineapple (26). Cross-reactivity has been reported between Grape and Peach (27), and between Grape and Cherry (2).

Cross-reactivity has also been reported to occur between allergens in vine pollen and Grape fruit, and also among botanically unrelated pollens. An 18-year-old female with seasonal rhinoconjunctivitis who was sensitised to pollens from vine, and also sensitised to grass, Olive tree, and *Chenopodiaceae* plants, described episodes of itching, maculopapular rash, and facial angioedema after eating Grape (28).

In a Japanese study of 272 patients and reciprocal relationships among foods causing OAS in patients with Birch pollen allergy, it was reported that Kiwi, Melon, Persimmon, Tomato, Grape, Watermelon, Mango, and Bananas made a large cluster and were partly associated with each other (29).

In a study of 61 Greek patients with IgE-mediated reactions to Grape or its products (wine, juice, and wine vinegar), 81.9% were co-sensitised to Apple, 70.5% to Peach, 47.5% to Cherry, 32.8% to Strawberry, 49.2% to Peanut, 42.6% to Walnut, 31.1% to Hazelnut, 26.2% to Almond, and 29.5% to Pistachio (30).

Clinical Experience

IgE-mediated reactions

Grape has been reported to cause oral allergy syndrome, generalised urticaria, asthma, atopic dermatitis, angioedema, gastro-intestinal symptoms, hypotension, rhinitis, and exercised-induced asthma and anaphylaxis. The aetiology has been confirmed with SPT, IgE antibody and challenge tests (1-2,4,12,19,27,31-37). Oral allergy to Grape is a common adverse effect. Importantly, patients may subsequently experience anaphylactic shock or exercise-induced anaphylaxis (19). Patients might not tolerate any Grape species, wine or raisins (2). Adverse reactions to wine may be caused by allergic reactions to Grape, but may result the presence of other components such as sulphites (sulphur dioxide), histamine or alcohol. Patients who complain of symptoms suggesting anaphylaxis should be tested for allergy to Grape (19).

Initially few reports of adverse reactions to Grape were reported in the literature, but recently a number of reports have highlighted the relevance of Grape allergy, and its characteristics. Grape allergy is not common, but the prevalence of allergy to Grape has been highlighted by studies such as the following.

In a study of food allergy in 674 allergic Spanish patients, food allergy was found in 106, but allergy to Grape in only 1 (38). In a cross-sectional, descriptive, questionnaire-based survey conducted in Toulouse schools to determine the prevalence of food allergies among schoolchildren, 2,716 questionnaires were returned, and 192 reported a food allergy. In 2 cases, Grape was reported to be the responsible allergen (39). In an Indian study of 24 children aged 3 to 15 years with documented deterioration in control of their perennial asthma, the purpose of which study was to evaluate any effect of a specific elimination diet on symptoms, 21 (88%) were sensitised to Grape (40). Allergy to Grape was not confirmed. In a Turkish study of 4,331 students, none reported allergy to Grape (41).

A number of studies and case reports have illustrated the complexity of allergy to Grape.

Thirty seven patients with reported severe allergic reactions to Grapes were described. Symptoms included generalised urticaria, asthma, atopic dermatitis, angioedema, gastro-intestinal symptoms, hypotension, rhinitis, and oral allergy symptoms. All subjects were poly-allergic, both sensitised and reactive to several additional foods and pollen. All the patients were sensitised to Grape LTP, although other minor Grape allergens, including a 28 kDa expansin, a polygalacturonase-inhibiting protein, a beta-1,3-glucanase, and an unidentified 60 kDa protein, were identified (12).

A study was conducted at 17 clinics in 15 European cities to evaluate the differences among some Northern countries regarding what foods, according to the patients, elicit hypersensitivity symptoms. It was reported, based on a questionnaire concerning 86 different foods, that among 1,139 individuals, Grape was the 28th most reported food allergen, resulting in adverse effects in 18% (42).

Sixty-one Greek patients, aged 14-52 years and with documented histories of IgE-mediated reactions to Grape or its products (wine, juice, and wine vinegar), were evaluated. The patients each reported 1-15 allergic episodes after consumption of Grapes or Grape products. Seventy-seven percent of the patients presented with OAS after eating Grape before the first reported reaction. The time for the onset of symptoms was between 4 and 160 minutes. Seventy-two percent of patients reported more than 1 reaction. Skin was involved in 93.4% of patients; the respiratory system in 75.4%; the cardiovascular system in 44.3%; and the gastrointestinal tract in 39.3%. Co-sensitisations identified by skin prick tests were mainly to Apple (81.9%), Peach (70.5%), Cherry (47.5%), Strawberry (32.8%), Peanut (49.2%), Walnuts (42.6%), Hazelnut (31.1%), Almond (26.2%), and Pistachio (29.5%) (30).

In a study of 11 Greek patients, aged 16-44 years and with documented histories of IgE-mediated reactions to Grape, wine, or other Grape products, 35 Grape-induced anaphylaxis episodes ranging from moderate to severe were reported. Causative agents were identified: wine 10/35 (28.6%); Red

grapes 9/35 (25.7%); stuffed vine leaves 8/35 (22.9%); raisins 3/35 (8.6%); White grapes 2/35 (5.7%); wine vinegar 2/35 (5.7%); and Grape juice 1/35 (2.9%). Other foods that induced anaphylaxis were Apple (54.5%), Cherry (18.6%), Peach (18.6%), and Banana (9.3%) (37).

In a Spanish study of 14 children aged 4-16 who had suffered allergic reactions involving fresh Grape or Grape juice, OAS was reported in 6, angioedema in 2, urticaria in 1, angioedema-urticaria in 1, and anaphylaxis in 3. A wide range of allergic proteins was isolated, with little commonality between individual patients (4).

In an Italian study of 14 patients aged 23-47 years with documented histories of severe allergic reactions to Grape (11 patients) or wine (3 patients), some patients reacted after drinking 2 particular kinds of red wine, namely Fragolino and young wine, or vino novello. The severity of the reactions precluded food challenges in all cases. Three patients with wine allergy experienced repeated reactions because they initially did not identify the relationship between symptoms and drinking young, new wine or Fragolino wine; they had not shown intolerance to other kinds of wine. A patient with OAS to fresh Grape, Peach, and Cherry had experienced anaphylaxis 3 times after drinking young wine, and another, twice after drinking a glass of Fragolino. One patient experienced OAS to Grape and young wine for 1 year and then suddenly experienced severe laryngeal oedema after drinking a single glass of Fragolino. Skin prick tests with fresh Grape was positive to both varieties in all 3 patients, although the patients reacted more strongly to the *V. labrusca* grape. One patient had 3 episodes of exercise-induced anaphylaxis after eating large amounts of Grape before going dancing or swimming. He could tolerate traditionally prepared red wines, and the reactions started after a generalised reaction to acetylsalicylic acid. Another patient developed severe asthma after eating Grape. Six other patients reported many years of OAS to Grape that had abruptly changed, causing laryngeal oedema. Many of these patients reported previous allergic reactions to Peach, Cherry, or tree nuts. Only a single patient, a nurse, reported severe cutaneous and respiratory reactions to Latex gloves (1).

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A 24-year-old man with seasonal spring oculorhinitis described how, 6 years earlier, 15 minutes after drinking white wine, he had experienced flushing of the face and neck, followed by local itchy skin rash, itching and oedema of the oral and perioral mucosa, and moderate dyspnoea. Subsequently, similar reactions occurred every time he drank red or white wine. Similarly, flushing of the face and neck with itchy skin rash, oedema of the oral and perioral mucosa, and dyspnoea occurred 10 min after ingesting fresh Grape. He had experienced similar reactions 30 minutes after eating a confection containing sultanas. He also reported oropharyngeal pruritus after eating Cherry. The prick by prick test was positive for Grape, Cherry and Plum. IgE antibody level was 2.88 kU_A/l for Grape. However, the RAST result was positive only when the polyphenols were chemically removed from the Grapes (43), since these substances can affect diagnostic results (19).

Oral allergy syndrome to Grape was described in a 4-year-old boy. The diagnosis was confirmed by a positive labial test to a fresh Grape, in addition to a positive SPT and IgE antibodies. He was also allergic to House dust mites, grass pollen, Egg, fish, Coconut, Kiwi, Almond and Latex (32).

A thirty-one year old Catholic priest presented with sneezing, nasal obstruction, and perennial rhinitis. Attacks occurred at any time. Skin tests were negative for the common inhalants and foods except for Timothy grass. A very restricted diet was instituted for a period of three weeks. During this period, he could continue saying Mass which also involved taking small quantities of Wheat and Grape wine. Although symptoms were not exacerbated nor ameliorated, the pattern of reaction changed. Symptoms all occurred simultaneously and were worse each morning about ten minutes after Mass. Grape wine fell under suspicion. Skin testing for Grape and raisin resulted in very positive reactions. Two weeks later, within ten minutes after drinking two ounces of wine, he experienced a violent reaction, with injected conjunctivae, sneezing, rhinitis, cough, wheeze, and generalised angio-oedema and urticaria. A grain alcohol challenge two weeks later was negative. Beer and whiskey caused no symptoms. Following

cessation of saying Mass, all symptoms cleared within fifty-six hours (31). On one occasion, the ingestion of wine resulted in the onset of symptoms within fifteen minutes and lasting three days. Limiting the wine to 5 drops, to which was added one drop of water, once daily, resulted in milder symptoms, but were otherwise continuously present.

A number of reports have described anaphylaxis to Grape (8,10,18,44-46). A total of 107 allergy cases was reported to the French Allergy Vigilance Network in 2002, of which 59.8% involved anaphylactic shock, 18.7% systemic reactions, 15.9% laryngeal angioedema, and 5.6% serious acute asthma, but only a single adverse reaction to Grape was reported (45). In an Italian study of 11 patients presenting with anaphylactic reactions following Grape ingestion, anaphylactic shock was reported in 4 cases, of which 2 followed Grape ingestion and 2 followed young wine consumption; there was severe asthma in 1 case, glottic oedema and angioedema in 4 cases, glottic oedema and urticaria in 2 cases, and gastrointestinal symptoms and hypotension in 1 case. In 2 cases symptoms followed exercise (18).

Anaphylaxis was described in 3 patients following ingestion of fresh Grape. Grape-specific IgE antibodies were detected by skin and serum tests. An unidentified protein of approximately 30 kDa bound serum IgE from all 3 (8).

A 28-year-old woman experienced generalised urticaria, facial/oropharyngeal angioedema, and dizziness after eating a bunch of White grapes. She became dyspnoeic and hypotensive. Skin prick tests were strongly positive. Grape-specific serum IgE was weakly positive according to a modified RAST and negative according to a commercial assay (44).

Importantly, Grape-allergic patients with symptoms of OAS may in future develop anaphylaxis and/or exercise-induced anaphylaxis to Grape (47). Furthermore, anaphylactic reactions may occur in patients selectively sensitised to a specific Grape cultivar, as described in an individual who experienced anaphylaxis to Americana grape (*Vitis labrusca*) specifically (10).

Food-dependent exercise-induced anaphylaxis to Grape has been reported (31,48-49). This is well illustrated by a report of a 33-year-old woman, with allergic rhinoconjunctivitis due to *Parietaria* and Mugwort, who reported facial flushing, oedema of the lips, and dyspnoea after drinking white or red wine. She could eat fresh Grapes. One month before, after she ate White grapes and exercised, urticaria, facial, pharyngeal oedema, abdominal pain, and dyspnoea appeared and rapidly worsened, followed by profound hypotension. Prick-to-prick tests with White and Red grape juice were positive. No Grape-specific IgE antibodies could be demonstrated in the patient's serum by commercial assays, but IgE reactivity of serum against Grape extract was positive (7).

A number of individual case reports also illustrate the varieties of Grape allergy.

A 5-year-old child experienced oral allergy syndrome and lip angioedema after eating Grape. A prick test with commercial Grape extract and a prick-by-prick test with pulp and peel of fresh White grape (Muscatel variety) and with pulp and peel of Blue grape were all positive. Lip open challenge was positive (50).

A 38-year-old Latex-allergic individual developed an itchy nose and palate while eating a bowl of Raisin Bran cereal. He developed repeated bouts of sneezing, facial flushing, and periorbital angioedema. A skin test to commercial Grape extract was positive (51).

A 39-year-old female described the onset of acute urticaria, angioedema, shortness of breath, wheezing and dry cough after eating Mulberry for the first time. Previously, reactions had occurred after eating White grape, and on another occasion, White Grape and Apricot. The reaction appeared immediately after eating Mulberry, and within 2 hours after the other foods. The reactions were life-threatening, requiring emergency room visits. IgE antibody level was 1.15 kU_A/l for Grape (35).

A 66-year-old man developed anaphylaxis with swelling of the tongue and respiratory distress 2 hours after consuming red wine. He had previously tolerated red wine and

Grape. Prick-to-prick was positive for red wine, white wine and Grape. IgE antibody reactivity to 3 allergens in Grape and red wine was demonstrated, and endochitinase, a thaumatin-like protein and a lipid transfer protein were identified (17).

An 18-year-old woman was described who had anaphylaxis to Grape only when concomitantly ingesting champagne; and a further 2 patients with allergic reactions to Grape who tolerated Grape-based alcoholic drinks. Grape IgE antibodies was detected only in the latter 2, although SPT were positive in all 3 (6).

Anaphylaxis to wine was reported in a 27-year-old German woman. She described several episodes of palmoplantar pruritus, angioedema of the lips, eyelids and tongue, dyspnoea, dysphagia and tachycardia 20–60 minutes after drinking red wine and champagne and eating fresh White grapes and raisins. Prick-to-prick tests were positive to fresh and cooked White and Blue grapes, to raisins, to white and red wine, and to Grape extract. Grape-specific IgE antibody level was 2.43 kU_A/l. A lipid transfer protein was identified as the responsible allergen. The authors pointed out that the study shows that sensitisation to lipid transfer protein can occur outside the Mediterranean area, resulting in severe fruit allergy without association with pollen allergy (14).

A 28-year-old woman had 2 episodes of systemic allergic reactions after eating White grapes. The anaphylactic symptoms included generalised pruritus, acute generalised urticaria, facial swelling, lip and oropharyngeal angioedema, and dysphagia. Skin prick tests with a commercial extract of Grape were negative, while prick by prick testing with White grapes and White grape juice was positive. Grape-specific serum IgE was confirmed. The authors highlight that, in the diagnosis of Grape allergy, commercial extracts might not be completely reliable, so that the prick-by-prick procedure with fresh Grape should be performed (52).

An 18-year-old female student suffered from seasonal rhinoconjunctivitis, with sensitisation to pollens from vine and also from grass, Olive, and *Chenopodiaceae*

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plants. She had recently developed episodes of itching, maculopapular rash, and facial angioedema after eating Grapes. Testing revealed positive reactions to vine pollen and Grapes, and IgE antibodies were found for both allergens. Immunoblotting and inhibition assays revealed cross-reactivity between the allergenic structures of vine pollen and Grape fruit, and also among botanically unrelated pollens (28).

Grape workers have been reported to have developed occupational contact dermatitis and lichenified hand dermatitis (53-54). Authors have suggested that, as asymptomatic sensitisation to Grape was detected only in workers handling the Grape, sensitisation may be more likely to occur through cutaneous exposure and/or minor wounding than through the gastrointestinal tract (55).

Allergy to Grape in individuals with adverse reactions to wine may be influenced by a number of factors, some reported above. The composition of red wines is affected by both the active wine-making process and aging (56). Vini novelli (vins nouveaux or young red wines) have become popular in recent years; in these wines, the Grapes are processed by means of carbonic maceration (57). The wines are intended to be drunk within a short time, so that polymerisation of the polyphenols present in red wines cannot occur; the result is that any proteins remain in solution. Polymerisation of polyphenols causes the tiny residual proteinaceous material in red wines to coalesce, so that it can be filtered off once the wine has aged, thus theoretically explaining why patients tolerated older wine. Fragolino wine, obtained from a blue *V. labrusca* grape, is also drunk young (1). Furthermore, authors have reported that RAST results were positive only when the polyphenols were chemically removed from the Grape, since they can affect diagnostic results (43). Plant cells contain the enzyme polyphenoloxidase, which accelerates the oxidation of phenols to quinones; these react in various ways with proteins, leading to the formation of polymers that interfere with allergenic reactivity. Therefore, for a reliable extract, compounds such as polyvinylpyrrolidone (PVPP) are employed to eliminate the polyphenols (2).

Other reactions

Some patients complain of abdominal distension and excessive flatus after ingesting Grape. This has been attributed to the presence of fructose in Grape (58).

After wine consumption, symptoms such as flush, rhinitis, asthma, and migraine are not rare. Such symptoms could be caused by an immediate-type reaction to Grape or moulds, as well as by intolerance reactions to histamine and sulphite (14). Sulphite preservatives (sulphite, metabisulphite and sulphur dioxide) are not only found in wine but are also used to prevent spoilage of fresh Grape. Sulphite preservatives may precipitate asthma. The likelihood of a reaction is dependent on the nature of the food, the level of residual sulphite, the sensitivity of the patient, and perhaps on the form of residual sulphite and the mechanism of the sulphite-induced reaction (59).

Vine pollen could be the cause of rhinoconjunctivitis and asthma in allergic individuals living in areas with a high density of vineyards (60-61). Grape farmers have been shown to have a high prevalence of allergic rhinitis and work-related respiratory symptoms as a result of Grape pollen exposure, compared to control subjects (62). However, other factors, such as pesticides and the Two-spotted spider mite (*Tetranychus urticae*), may be causal or contributory factors (63-65). Wall rocket is a common *Crucifera* plant that grows in European and American vineyards and Olive groves. A study reports on 2 farmers working in vine plantations who experienced asthma and rhinitis after exposure to this plant (66).

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Citrus paradisi

Family:	<i>Rutaceae</i>
Common names:	Grapefruit, Shaddock
Source material:	Freeze-dried fruit
For continuous updates:	www.immunocapinvisight.com

In a patient with anaphylaxis from Mandarin (*Citrus reticulata*), a lipid transfer protein was isolated from Mandarin fruit. Analysis of the patient's serum demonstrated sensitisation also to the lipid transfer protein Cit s 3, from Orange, as well as to Cit s 1, a germin-like allergen (1). Whether similar allergens occur in Grapefruit, a closely related family member, was not assessed.

Potential cross-reactivity

Cross-reactivity within the *Rutaceae* family (Lemon, Lime, Orange, Tangelo) can be expected, but has not been documented to date.

Latex allergy has been reported to be associated with allergy to a number of other foods, including Avocado, Banana, Kiwi, Papaya, Chestnut, Peach and Grapefruit (2). A 34-year-old female with asthma and atopic dermatitis who developed severe anaphylaxis to Latex was described. She was shown to have IgE antibodies directed against Latex, Banana, Kiwi, Grapefruit, and Avocado. Skin reactivity was also detected to Banana, Grapefruit, Avocado, and Latex extract (3).

Clinical Experience

IgE-mediated reactions

Citrus fruits such as Grapefruit are among the most common causes of atopic dermatitis (4-7). IgE antibodies to Grapefruit were detected in patients with atopic dermatitis, allergic rhinitis, and bronchial asthma (8). In a study of children with atopic dermatitis, many were shown to have IgE antibodies directed against Grapefruit (9). Many patients were also found positive in a similar study of adults (10).

A study was conducted at 17 clinics in 15 European cities to evaluate the differences

Allergen Exposure

Geographical distribution

Grapefruit, Orange, and Lemon are the principle members of the citrus family. Grapefruit is a subtropical citrus tree grown for its fruit. Its origin is not clear, but it may originally have been a hybrid of the pomelo and the Sweet orange tree. Tangelo is a hybrid of Grapefruit and Orange and has a less bitter taste than Grapefruit.

Grapefruit is pinkish- to yellow-skinned and oblate to round, ranging in diameter from 10 to 15 cm. The most popular varieties cultivated are referred to by the colour of the segmented pulp, which can be red, white, or pink. Grapefruit flavour ranges from highly acidic and somewhat bitter to sweet and tart. Unlike other citrus fruits, Grapefruit contains mercaptan, a terpene partly composed of sulphur; mercaptan has a strong influence on the taste and odour of the fruit.

Allergens

No allergens from this plant have yet been characterised.

among some Northern countries regarding what foods, according to the patients, elicit hypersensitivity symptoms. Questionnaires concerning 86 different foods were administered to food-allergic individuals. The foods most often reported as eliciting symptoms in Russia, Estonia, and Lithuania were citrus fruits, chocolate, honey, Apple, Hazelnut, Strawberry, Fish, Tomato, Egg, and Milk, which differed from the situation in Sweden and Denmark, where Birch pollen-related foods, such as nuts, Apple, Pear, Kiwi, stone fruits, and Carrot were the most common reported culprits. The most common symptoms reported were oral allergy syndrome and urticaria. Birch pollen-related foods dominated as reported allergens in Scandinavia, whereas some Mugwort-related foods were apparently of more importance in Russia and the Baltic States. Among 1,139 individuals, Grapefruit was the 18th most often reported food allergen, purportedly resulting in adverse effects in 21% (7).

A 3 1/2-year-old boy is reported to have developed anaphylaxis after eating Cashew nut, and later after eating a pectin-containing fruit "smoothie". He was also reported to have a history of generalised pruritus after eating Grapefruit. The child had positive SPT for pectin, high levels of IgE antibodies for Cashew nut and Pistachio, and low levels for Grapefruit. The pectin in the smoothie was confirmed to be of citrus origin. The authors concluded that ingestion and inhalation of pectin can cause hypersensitivity reactions, and that allergy to Cashew nut, and possibly Pistachio, may be associated with pectin allergy (11).

Other reactions

Grapefruit contains naringin, bergamottin and dihydroxybergamottin, which inhibit the protein isoform CYP3A4 in the intestine. It is via inhibition of this enzyme that Grapefruit increases the effects of a variety of drugs. Therefore, the coadministration of certain drugs with Grapefruit juice can markedly elevate drug bioavailability, and can alter pharmacokinetic and pharmacodynamic parameters of the drugs. A single glass of the juice is usually sufficient to produce this interaction (12-14).

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f292 Guava



Photo by Forest & Kim Starr

Allergen Exposure

Geographical distribution

Guavas are native to Central or South America but now grow in many countries. Guava was said to be a favourite food of the Incas and Aztecs. The trees are among the most gregarious of fruit trees.

A small tree with spreading branches, the Guava is easy to recognise because of its smooth, thin, copper-coloured bark that flakes off, showing the greenish layer beneath. The fruit, exuding a strong, sweet, musky odour (attributed to carbonyl compounds), may when ripe be round, ovoid, or pear-shaped. It has a thin, light-yellow skin, frequently blushed with pink. Next to the skin is a layer of somewhat granular flesh of varying colour and flavour. The central pulp is juicy and normally filled with very hard, yellowish seeds.

Environment

The Guava can be a home fruit tree or planted in small groves. In many parts of the world, the Guava runs wild and forms extensive thickets, overrunning pastures, fields and

Psidium guajava

Family: *Myrtaceae*

Common names: Guava, Brazilian guava, Common guava, Guinea guava, Lemon guava, Mountain guava, Purple guava

Source material: Fresh fruit

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roadsides so vigorously that it can be classed as a noxious weed subject to eradication. Nevertheless, wild Guavas in some countries (though underutilised) constitute the bulk of supply for major industries.

Raw Guavas can be eaten out of hand but are preferred seeded and served sliced as dessert or in salads. The sweet yellow fruit is eaten fresh; the pulp of the red, sour varieties is used for jelly, juices, etc. More commonly, the fruit is cooked, as cooking eliminates the strong odour. There are innumerable recipes for utilising Guavas in pies, cakes, puddings, sauces, ice cream, tapioca, juice, syrup, jam, butter, marmalade, chutney, relish, catsup, breakfast cereal, baby food and other products. Guavas may be canned or frozen, and extracts provide flavourants, pectin for food processing, and vitamin C for enrichment of other foods. Besides vitamin C, Guavas are a good source of potassium and fibre.

Guava is an important medicinal plant in tropical and subtropical countries is widely used in folk medicine around of the world (1). The roots, bark, leaves, shoots, and immature fruits are astringent. They are also thought to be analgesic, emmenagogue, febrifuge, and vermifuge, and are used to treat a variety of ailments both internal and external.

Unexpected exposure

The wood is used in carpentry, turnery, engravings and other ornaments, but is not durable when wet. It is good firewood and also a source of charcoal.

The leaves, bark and young fruit are rich in tannins and other volatile compounds. The bark is used in Central America for tanning hides. The leaves, used with other plant materials, make a black dye for silk, cotton, and matting.

Allergens

No allergens from this plant have yet been characterised.

A 30 kDa allergenic protein, possibly a panallergen, has been detected (2).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected; also frequent cross-reactivity to the different species of the genus *Melaleuca*, and occasional cross-reactivity to Eucalyptus and other genera of the family *Myrtaceae* (3). Rose-apple and Clove are the most closely related members of this family, which includes the Bottlebrush tree (*Callistemon citrinis*), feijoas (*Feijoas sellowiana*), the Eucalyptus tree (*Eucalyptus* species), the Melaleuca tree (*Melaleuca leucadendron*), and the Melaleuca tea tree (*Melaleuca alternifolia*).

IgE antibodies were found to Peach, Guava, Banana, Mandarin and Strawberry in a patient experiencing anaphylaxis after eating Peach. The cross-reactive protein was identified as a 30 kDa protein occurring in all the fruits (2).

Clinical Experience

IgE-mediated reactions

Anecdotal evidence suggests that Guava can occasionally induce symptoms of food allergy in sensitised individuals; however, no studies have been reported to date.

In an Indian study to evaluate the effect of a specific elimination diet on symptoms, among 24 children aged 3 to 15 years with documented deterioration in control of their perennial asthma, 79% were shown to have IgE antibodies directed at Guava (4).

Allergic contact dermatitis due to Guava tea has been reported (5).

Other reactions

According to Chinese medicinal folklore, Guava has been useful in the treatment of diabetes mellitus. A study shows that Guava produced a marked hypoglycemic action in mice (6).

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f318 Jack fruit



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Artocarpus heterophyllus

Family: *Moraceae*

Common names: Jack fruit, Jackfruit, Jak-fruit, Jak, Jaca, Nangka

Source material: Whole fresh fruit

Synonyme: *Artocarpus heterophyllus*

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Allergen Exposure

Geographical distribution

The genus *Artocarpus* contains *A. altilis* (Breadfruit) and *A. heterophyllus* (Jack fruit). The Jack fruit is a tropical fruit which belongs to the *Moraceae* family (Mulberry) and is cultivated at low elevations throughout Southeast Asia. It is grown to a limited extent in Queensland, Mauritius, the Pacific Islands, Brazil and Surinam. In Africa, it is often planted in Kenya, Uganda and Tanzania.

This huge relative of the Breadfruit can weigh up to 50 kg. It is spiny and oval or oblong-shaped.

Environment

The tree is cultivated in some places and wild in others. The fruit is an excellent example of a food prized in some areas of the world and allowed to go to waste in others. Jack fruit is little used in the West (and tends to be available only in canned form) because of the copious latex and the foul odor of the raw fruit. The fruit is eaten raw, boiled or fried; its seeds are roasted like Chestnuts. It may be made into ice cream, chutney, jam, liqueur, pulp, custard, jelly, nectar, powder or

concentrate, paste, “leather” or “papad,” or even a Potato-like chip. It may also be pickled, canned or frozen. It is often included in curried dishes. The roasted, dried seeds are ground to make flour, which is blended with Wheat flour for baking. Tender Jack fruit leaves and young male flower clusters may be cooked and served as vegetables. In India, the leaves are used as food wrappers in cooking, and they are also fastened together for use as plates.

The Chinese consider Jack fruit pulp and seeds to be tonic and cooling, and recommend them as a hangover cure. The seeds and leaves may be used as a herbal remedy. The dried latex yields artostenone, convertible to artosterone, a compound with marked androgenic action. Mixed with vinegar, the latex is said to promote healing of abscesses, snakebite and glandular swellings. The root and wood may also be used as a herbal remedy. The pith is said to induce abortion.

The seeds of Jack fruit contain 2 lectins, jacalin and artocarpin. Jacalin, a 66 kDa protein, is among the very few proteins which are known to bind T-antigen and thus has great potential diagnostic value. T-antigen is expressed in more than 85% of human carcinomas.

Jack fruit extract significantly lowered the fasting blood glucose level and markedly improved glucose tolerance in Sprague-Dawley rats. The maximum effect was not observed even at +5 hrs. The hypoglycaemic activity was better than that of tolbutamide (1). The significance of this finding for humans has not been evaluated yet.

Unexpected exposure

The inedible portions of the fruit yield jelly, pectin and a syrup used for tobacco curing. In some areas, the fruit and the leaves are fed to cattle. The latex serves as birdlime, and as household cement and caulk. The mahogany-like wood has a variety of uses. The sawdust yields a rich yellow dye commonly used for dyeing silk and cotton. The bark is occasionally made into cordage or cloth.

Allergens

No allergens from this plant have yet been characterised.

A 17 kDa protein with characteristics of Bet v 1, *i.e.*, a Bet v 1 homologue, has been isolated (2).

Both species of *Artocarpus* (*Artocarpus altilis* [Breadfruit] and *Artocarpus heterophyllus* [Jack fruit]) contain lectins, which are very similar to each other (3).

Potential cross-reactivity

Cross-reactivity among the different individual species of the genus could be expected (4).

To assess whether Jack fruit allergy might be common in patients with Birch pollen and fruit allergy, 5 Birch pollen and concomitant fruit allergy patients were orally challenged with Jack fruit. All 5 developed symptoms of oral allergy. The study concludes that Jack fruit contains at least 1 panallergen, which may result in Birch pollen-related food allergy (2).

Clinical Experience

IgE-mediated reactions

Anecdotal evidence suggests that Jack fruit can occasionally induce symptoms of food allergy in sensitised individuals; however, few studies have been reported to date (2,5). Increased consumption of this fruit will result in a rise in allergic reactions (2).

A 30-year-old Filipino man with pollen allergy developed symptoms of oral allergy syndrome (OAS) after eating raw Apple, raw Peach, raw Celery, and Jack fruit. Despite

evidence of multiple sensitisation in skin prick tests and serum IgE tests for Birch, Grass and Mugwort pollen, related fruits and vegetables, and Jack fruit, in RAST inhibition studies neither rBet v 1 nor rBet v 2 (profilin), the well-known cross-reacting allergenic components in OAS, could inhibit the IgE antibody response to Jack fruit. Whether the reaction to Jack fruit is specific or whether other pollen-related cross-reacting allergenic components exist could not be elucidated, and the authors suggested that this should be further investigated (4).

Two Jack fruit-allergic patients are described. Both patients claimed they had never eaten Jack fruit before. A 31-year-old man with a history of hay fever in the Birch pollen season increasingly reported episodes of OA symptoms after eating Apple, Hazelnut or Peanut. He developed oral allergy symptoms within 5 minutes of eating a very small piece of fresh Jack fruit. Within 10 minutes, that had progressed to hoarseness, swelling of the throat and dyspnoea. A 27-year-old female with hay fever in the Birch and grass pollen season reported increased oral allergy-like symptoms after eating Apple, Hazelnut and Peanut. She experienced oral allergy symptoms and abdominal cramps within 5 minutes of eating a small piece of fresh Jack fruit. Double-blind placebo-controlled challenges confirmed the diagnosis in both patients. SPT were positive, and the IgE antibody level to Jack fruit were 5.9 and 0.8 kU_A/l for the 2 patients. Sensitisation was demonstrated to a Bet v 1-related allergen. Five patients with concomitant Birch pollen and fruit allergy who underwent an oral challenge with Jack fruit developed oral allergy, confirming the presence of a panallergen and suggesting that individuals with both Birch pollen and fruit allergy should avoid this fruit (2).

Other reactions

Adverse reactions to lectins present in the fruit are possible, including the agglutination of red cells in humans and animals.

f318 Jack fruit

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Ziziphus jujuba

Family: *Rhamnaceae*
(Buckthorn)

Common names: Jujube fruit, Azufaifa fruit, Chinese date, Chinese jujube, Chinese red date, Common jujube, Cottony jujube, Indian jujube

Source material: Whole fresh fruit
Terminological confusion exists between the related species *Ziziphus zizyphus* and *Ziziphus mauritiana*. Some sources give the common name Jujube, Red date, or Chinese date for *Ziziphus zizyphus* (the species used primarily for its fruit); and Indian jujube, Chinese apple or Cottony jujube for *Ziziphus mauritiana*

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Allergen Exposure

Geographical distribution

Jujubes originated in China, where they have been cultivated for more than 4,000 years, and where there are over 400 cultivars. The spiny trees travelled beyond Asia centuries ago and today are grown to some extent in Russia, northern Africa, southern Europe, the Middle East and the southwestern United States.

The fruit is a drupe, varying from round to elongated and from cherry-size to plum-size, depending on the cultivar. It has a thin, edible dark-red skin surrounding whitish flesh of a sweet, agreeable flavour. The single hard stone contains 2 seeds. Confusingly, Jujube is also the name of a tiny fruit-flavoured candy with a hard, gelatinous texture, but the name is the only connection between the 2 foods.

Environment

The naturally drooping tree is graceful and ornamental, and it is grown in gardens as well as in orchards. The fruit can be eaten out of hand or in a variety of desserts, but is not readily available in the West. Oil is extracted from the seeds. Some tests indicate very high vitamin C content.

The fruit has been used medicinally for millennia by many cultures. One of its most popular uses is as a tea for sore throat. The aqueous extract from the leaves of the related *Zizyphus mauritiana* has been used in traditional medicine. It has been shown to have anti-diabetic activity, resulting in a decrease in blood glucose (1).

Allergens

No allergens from this plant have yet been characterised.

Proteins of 15 to 60 kDa were detected, but on immunoblotting studies with a patient's serum, only a single band of around 30 kDa was found. The authors postulated that this protein may represent a chitinase panallergen, but this could not be confirmed (2).

1336 Jujube

A more recent report describes the isolation of a 42 kDa Latex protein and a 42 kDa Indian jujube protein from 2 Jujube and Latex-allergic subjects. In addition, IgE from 1 subject bound to a 30 kDa Indian jujube protein (3). The study reported Indian jujube as *Zizyphus mauritiana*, whereas other sources regard Indian jujube as *Zizyphus jujuba*.

Ziz m 1, a Class 3 chitinase has been characterised in the close relative *Zizyphus mauritiana* (4-5).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected (6).

In a study of 2 subjects, both allergic to Jujube and Latex, cross-reactivity between Latex and Jujube was demonstrated. The authors suggest that Jujube is therefore part of "Latex-fruit syndrome" (3).

Clinical Experience

IgE-mediated reactions

Anecdotal evidence suggests that Jujube may induce symptoms of food allergy such as urticaria, angioedema, rhinoconjunctivitis, dyspnoea, and wheezing in sensitised individuals; however, few studies have been reported to date (2-3,7).

Two patients described were Jujube- and Latex-allergic. Both patients had positive SPT responses and positive IgE antibody assays to Indian jujube and Latex extracts. Jujube was shown to be cross-reactive with Latex (3).

Urticaria, angioedema, rhinoconjunctivitis, dyspnoea, wheezing, abdominal pain, and diarrhoea were reported in a 38-year-old Latex- and food-allergic nurse after she ate Jujube fruit. Her prior food allergy was to Banana, Chestnut, Kiwi and Avocado (2). This co-sensitisation is typical of "Latex-fruit syndrome".

Other reactions

The seeds and leaves of *Zizyphus spinosa* exert an inhibiting effect on central nervous system function, while the fruits have a synergism with pentobarbitol sodium and thiopental sodium on prolongation of sleep and sedation, and also decrease coordinated action. Jujuboside A exerts no inhibiting effect, but has a synergistic effect with phenylalanine on central nervous system function (8). Whether a similar effect may occur with *Zizyphus jujuba* was not assessed.

Perforation of the small bowel due to the pointed pit of Jujube fruit has been described (9).

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Actinidia deliciosa

Family: Actinidiaceae
(Dilleniaceae)

Common names: Kiwi, Chinese gooseberry, Kiwifruit, Monkey peach, Sheep peach

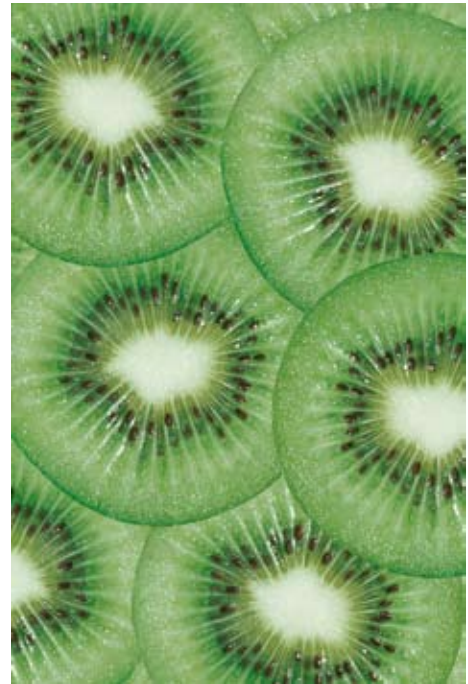
Source material: Peeled fresh fruit

Synonymes: *A. latifolia* var. *deliciosa*,
A. chinensis deliciosa

There are 2 common species of Kiwi commercially available:

A. chinensis – Gold kiwi
A. deliciosa – Green kiwi

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Allergen Exposure

Geographical distribution

The Kiwi fruit (or Kiwi) is the edible berry of a cultivar group of the woody vine *A. deliciosa* and hybrids between this and other species in the genus *Actinidia* (1). This interesting species is native to the Yangtze Valley, China. It was cultivated on a small scale at least 300 years ago, but still today most of the crop is derived from wild vines. The Chinese have never shown much interest in exploiting the fruit. Kiwi was developed commercially in New Zealand and named after the national bird. Commercial crops are grown mainly in New Zealand, the United States and France. Kiwi fruit is, however, a latecomer to Western cuisines, and the extent of its use varies radically according to fashion.

The Kiwi plant is a tough, woody, deciduous twining vine or climbing shrub. The oblong fruit, up to 8 cm long, has russet-brown skin densely covered with short, stiff brown hairs. The flesh is usually bright green and pleasantly acidic in flavour. The minute, dark-purple or nearly black seeds are unnoticeable in eating (1).

Gold kiwis have a smooth, bronze skin, a pointed cap at one end, and distinctive golden-yellow flesh with a less tart and more tropical flavour than that of Green kiwi. Gold kiwi is less hairy than the green cultivars and can be eaten whole after rubbing off the thin, fluffy coat. Green kiwi skin is thick and unpalatable.

Environment

Kiwis are available year-round due to storage. The fruits are eaten fresh or may be added to meat dishes, pies, puddings or cakes. As Kiwi contains enzymes similar to Papain, the raw fruit can act as a meat tenderiser. After peeling (usually with lye), fruits are canned, frozen, or freeze-dried. Kiwi is used in sauces, jams, ice creams, breads and various beverages, including wine. Blending with Apple juice or malic acid tends to be important in Kiwi processing, for reduction of Kiwis' acidity. Slightly underripe fruits, which are high in pectin, are chosen for making jelly, jam and chutney (1).

The Chinese regard the Kiwi as a tonic for growing children and for women after childbirth (1).

f84 Kiwi

Unexpected exposure

Because of shortages of the bees needed for pollination, pollen may be sprayed onto the plants in a suspension.

Allergens

At least 12 allergenic proteins have been detected in Kiwi fruit, ranging from 12 to 64 kDa in size. The allergens of 12, 24, 28 and 30 kDa appeared to be the most important. Only the 30 kDa protein was recognised by sera of 100% of patients, and was later characterised as the major protein Act c 1, a protein which also exists in the closely related family member *A. deliciosa* (2-4). A 43 kDa protein, only partially characterised, has been isolated and shown to account for only 0.1% of total Kiwi protein content (5). In a study of 76 patients with a history of Kiwi allergy, of whom 23 had had a positive DBPCFC, serum IgE bound to 12 protein bands in Kiwi protein extract. A protein band with a molecular weight of 38 kDa was the major allergen, recognised by 59% of the patients. Unlike in other studies, which had reported actinidin (Act d 1) as a major allergen, IgE did not bind to actinidin in this extract, or to purified native or recombinant forms of actinidin. The study concluded that major allergens in a patient group may not necessarily be recognised in another (6).

The protein content of Kiwi increases during the ripening process. Importantly, a different protein pattern has been demonstrated in Green and Gold kiwi. In Green kiwi, actinidin and kiwellin were the major components. Thaumatin-like protein was found in high amounts in both Green and Gold kiwi. Variations in the relative amounts of the proteins, as well as new protein bands, were seen during the ripening process of Green kiwi and, to a minor extent, of Gold kiwi. Similarly, after ethylene exposure, with or without previous cold storage, the relative amount of some protein bands varied, especially in Green kiwi (7). Other studies have demonstrated similar results (8-9). Despite having different protein profiles and IgE-binding patterns, the 2 species have proteins that extensively cross-inhibit the binding to IgE (8). However, the relevance of these differences may be complex.

In 90 Kiwi-allergic individuals, IgE studies showed marked differences in the allergen compositions of Green and Gold kiwi extracts. Phycocystatin (Act d 4) and a thaumatin-like protein (Act d 2) were identified as allergens common for both cultivars. Two allergens with homologies to chitinases were found in Gold kiwi, whereas actinidin (Act d 1) was detected exclusively in green Kiwi. Patients from Central Europe and central Italy showed distinct sensitisation profiles toward Green and Gold kiwi, as well as actinidin, and whereas sera from Austrian and Dutch patients mainly recognised Green kiwi and actinidin, almost all Italian sera showed IgE binding to both Kiwi species, but only half of them contained actinidin-specific IgE. Green and Gold kiwi extracts were shown to be highly cross-reactive in inhibition studies. This implies that Gold kiwi may be tolerated by patients exclusively sensitised to Act c 1 (7).

The following allergens have been characterised:

Act d 1, a 30 kDa protein, also known as actinidin, belonging to the cysteine protease protein family (3,5,7,10-19).

Act d 2, a 24 kDa thaumatin-like protein (7,9-14,17-18,20-21).

Act d 3, a 40 kDa protein (9,12).

Act d 4, a 11 kDa protein, a phycocystatin, a cysteine protease inhibitor (7,9,22-23).

Act d 5, also known as kiwellin, a 26-28 kDa protein (3,9,21,24-25).

Act d 6, a pectin methylesterase inhibitor (9,26-29).

Act d 7, a 50 kDa protein, a pectin methylesterase (9,25,27).

Act d 8, a Bet v 1 homologue (9).

Act d 9, a profilin (4,9,30).

Act d 10, a lipid transfer protein (9,31).

A class 1 chitinase (32) and a glycosyl hydrolase have been isolated (33).

Actinidin has physical and chemical properties similar to those of Papain, which can perhaps explain some hypersensitivity reactions (34).

Act c 2, from *A. chinensis*, the thaumatin-like defence protein, was shown to be a rapidly digestible protein, eliciting positive SPT in 4 (80 %) of 5 patients with oral allergy syndrome (10).

Act c 5, from *A. chinensis*, accounts for approximately a third of Gold Kiwi total protein content (35).

Studies have reported that patients with systemic reactions showed IgE binding to digestion-resistant allergens, but that patients with oral symptoms reacted only to digestion-labile allergens. Furthermore, an increase in pH from 1.5 to 2.5 significantly reduced pepsin breakdown of Kiwi allergens, and the study suggested that patients with hypoacidic gastric conditions are at increased risk of systemic absorption of allergens (36). Moreover, Act d 1 and Act d 2 appear to display nearly unchanged IgE binding abilities following simulated gastric digestion (11). Although heat may deactivate many Kiwi allergens, heat-stable allergens may still result in adverse reactions being elicited (18).

A heterogenous response to the various Kiwi allergens can be expected. This is illustrated by a number of studies. For example, in a study examining purified Act d 28 kDa (Act d 5), Act d 1 and Act d 2 with 30 sera of 30 Kiwi-allergic patients, 10 (33%) patients showed IgE reactivity to Act d 28kD, 14 (47%) to Act d 1, and 9 (30%) to Act d 2. Different profiles of IgE binding were observed. Combined reactivity to the 3 Kiwi allergens was shown in 2 subjects (6.6%). Four subjects (13.3%) recognised Act d 1 and Act d 2, whereas 4 and 3 subjects (13.3% and 10%) showed reactivity to Act d 1 plus Act d 28kD, and Act d 2 plus Act d 28kD, respectively. Sera of 5 (Act d 1, 16.6%), 4 (Act d 28kD, 13.3%), and 2 (Act d 2, 6.6%) subjects recognised a single allergen. Importantly, 8 (26.6%) subjects were negative to all 3 Kiwi proteins (14).

Similarly, in a study of 43 patients with allergy symptoms who were sensitised to Kiwi, of whom 33 were evaluated with DBPCFCs (and of whom 23 were positive), the most frequent clinical manifestation was oral allergy syndrome. Twenty-one percent of the patients were not allergic to pollen. Forty-six percent of the patients experienced systemic symptoms, which occurred with higher frequency in

patients not allergic to pollen (100%). Twenty-eight percent of the patients were sensitised to Latex. The IgE-binding bands in Kiwi extract more frequently recognised by patient sera were those of 30, 24, 66, and 12 kDa. No allergens could be associated with any particular pattern of Kiwi-induced allergic reactions, confirming that Kiwi allergy is not a homogeneous disorder but consists of several clinical subgroups (17).

Ninety patients with Kiwi allergy from Austria, central Italy, and the Netherlands, most of them having OAS and associated systemic symptoms, were tested for IgE binding to Green and Gold kiwi protein extracts and to purified actinidin. Differences between allergens recognised by sera from northern European countries and sera from Italian patients were demonstrated. Actinidin (Act c 1) was recognised by IgE from almost all the Northern European patients, but by less than 50% from Italian patients (7).

In a study that aimed to isolate major Kiwi allergens utilising sera of 92 Kiwi-sensitised Spanish patients with different clinical symptoms, 3 major IgE-binding proteins were isolated and identified as actinidin Act d 1, the thaumatin-like Act d 2 and Act d 3.02. IgE antibodies to each of the 3 allergens were found in over 60% of sera from Kiwi-sensitised patients, and Act d 1 and Act d 2 induced positive SPT responses in over 50% of the tested patients. A significant link between IgE antibody levels to Act d 1 and Act d 3 and anaphylaxis was uncovered: severe symptoms after Kiwi ingestion were associated with high IgE antibody levels to Act d 1 and Act d 3 (12).

A German study of 25 subjects with Birch pollen and Kiwi allergy reported that 23 had localised oral symptoms and 2 had urticaria. Sensitisation was demonstrated to a 67 kDa allergen in 55%, a 43 kDa in 68%, a 30 kDa in 19%, a 22 kDa in 31%, and a 13 kDa in 9% (37).

Of 12 Latex-allergic patients with Kiwi allergy, 9 were sensitised to kiwellin (Act d 5), and 4 to cystatin (Act d 4). Of 38 sera from patients with multiple pollen and Kiwi allergy, 25 (68%) were shown to have IgE specific for kiwellin and 23 (54%) for cystatin (21).

f84 Kiwi

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected, but manifestations are variable, depending on allergen composition as described above (38).

The association of Kiwi allergy with allergies to pollen and Latex has been described, and cross-reactivity has been confirmed by inhibition studies with Birch pollen (2,35,39,47,51), Timothy pollen (2), Avocado (31,40), Banana (38,41), Latex (31,38), Rye (42), and Hazelnut (40). Kiwi allergy has also been associated with grass allergy, as in a Northern Italian study that reported grass pollen to be the most common pollen allergy, and to be frequently associated with oral allergic syndrome (OAS). In 56 children with respiratory allergy due to grass pollen, 5 of the 14 cases (36%) sensitised to Bet v 1 showed food allergy, and 8 (57%) food sensitisation; 6 (46%) of the 13 children sensitised to Bet v 2 showed food allergy, and 7 (54%) food sensitisation. Among the 16 patients with food allergy, Hazelnut was the major triggering food (50%), followed by Peanut (38%), Kiwi (31%), Apple and Walnut (19%) (43). Oral allergy syndrome to Kiwi associated with Japanese cedar pollen allergy has been reported (44).

Specific Kiwi allergens may play a role in cross-reactivity among Kiwi, other foods, and pollens.

The Kiwi allergen Act c 1 appears to cross-react with thiol proteinases, *e.g.*, bromelain and Papain, from Papaya and Pineapple (33,45). In a study of 20 patients with occupational asthma (baker's asthma) caused by Wheat flour inhalation, ingestion of Kiwi elicited oral allergy syndrome in 7 (35%). Skin reactivity and IgE antibodies for Kiwi were found in all of these Kiwi-allergic patients, and IgE to Act d 1 and Act d 2 was detected in 57% and 43%, respectively. The authors suggested that cross-reactive carbohydrate determinants and thiol-proteases (bromelain) homologous to Act d 1 were responsible for Wheat-Kiwi cross-reactivity in some patients (13).

Cross-reactivity between the thaumatin-like protein Act c 2 and other fruits or vegetables containing this protein could be expected (46).

Cross-reactivity between Kiwi and plants containing profilin (4,29,47) or lipid transfer protein (30,48) can also be expected. Timothy, Rye, Mugwort (*Artemisia vulgaris*) and Birch pollen have been reported to show strong cross-reactivity with some Kiwi allergens, suggesting complete identity between certain food and pollen allergens (49-51). Cross-reactivity demonstrated between Birch pollen and Kiwi allergens was due to a 10-12 kDa protein, which would appear to be a profilin (2,4,47). Studies have reported a high prevalence of Kiwi allergenicity in Birch-allergic individuals, but other studies have not concurred. In a Japanese study of 171 Birch pollen-sensitised individuals (ImmunoCAP positive, score ≥ 2), 6 (3.5%) were shown to be hypersensitive to Kiwi fruit. In a study of 253 patients with Birch pollen sensitisation, as measured by IgE antibody test, 3 (1%) were shown to be hypersensitive to Kiwi fruit (52). Some authors have suggested that cross-reactivity between Kiwi and Birch pollen is due mainly to carbohydrate moieties that are said to have a much weaker cross-reactivity (53). Interestingly, patients with Birch pollen allergy and without clinical signs of Kiwi allergy may show positive SPT to Kiwi, and patients with Kiwi allergy have higher IgE antibody levels to Birch pollen, compared to patients with isolated Birch pollen allergy (54).

Approximately 30-50% of individuals who are allergic to Natural rubber latex (NRL) show an associated hypersensitivity to some plant-derived foods, especially fresh fruits. This association of Latex allergy and allergy to plant-derived foods is called Latex-fruit syndrome (31,55-61). An increasing number of plant sources, such as Avocado, Banana, Chestnut, Kiwi, Peach, Tomato, Potato, Bell pepper and Custard apple, have been associated with this syndrome (62-64). Kiwi and NRL cross-reactivity is common, with 17% of Latex-allergic individuals being sensitised to this food (65-66). Approximately 12.2% of NRL-allergic individuals appear to be Kiwi-allergic (67). Several types of proteins have been identified as being involved in Latex-fruit syndrome (38). A plant defence protein, a class I chitinase (which cross-reacts with hevein [Hev b 6.02]) and a major IgE-binding allergen for patients allergic to NRL, is probably the most important allergen responsible for cross-

reactions between Kiwi and Latex; (68) but other panallergen-like proteins, *e.g.*, patatin, may also play a role (63), including Hev b 5, a NRL protein probably responsible for anaphylaxis in NRL-allergic individuals; this allergen has significant homology with Kiwi and Potato (69-70). Other allergens may also play a role: Ole e 10, a glycosyl hydrolase and a major allergen in Olive pollen, has a 53% identity with Ole e 9, a 1,3-beta-glucanase. Ole e 10 shares IgE B cell epitopes with proteins from a number of pollens, including Latex, Tomato, Kiwi, Potato, and Peach, and may therefore be a candidate for involvement in pollen-Latex-fruit syndrome (32).

Cross-reactivity among the Latex from leaves of *Ficus benjamina* (Weeping fig), Fig and, to a lesser extent, Kiwi has been reported (71). In a study of 54 *Ficus benjamina*-sensitised individuals, sensitisation was specifically associated with positive skin tests to fresh Fig (83%), dried Fig (37%), Kiwi (28%), Papaya (22%), Avocado (19%), Banana (15%), and Pineapple (10%). This cross-reactivity is mediated at least in part by thiolproteases, ficin and Papain (72).

From a study reporting reduced IgE binding to Kiwi and Celery in RAST inhibition studies, the presence of a 60 kDa allergen distinct from Bet v 1 and profilin has been deduced. It was suggested that this was a novel cross-reactive allergen that may also contribute to symptoms of oral allergy syndrome (73).

Other cross-reactive associations between Kiwi and other plants have been reported. Of 134 patients with allergy to Olive pollen, 40 reported adverse reactions to plant-derived food. SPT and oral challenges confirmed allergy to a number of foods, including Kiwi. The cross-reactive allergen may be associated with the Olive pollen allergen Ole e 3 (74). Kiwi allergy has also been reported to be commonly associated with allergy to Melon (75). Allergy to Kiwi, Poppy seed, and/or Sesame seed has also been reported to occur often in patients with a simultaneous sensitisation to nuts and flour. These cross-reactions were verified by RAST inhibition studies. Further studies demonstrated that the degree of cross-reactivity among Kiwi, Sesame, Poppy seed, Hazelnut, and Rye grain was found to be very high in the patients studied.

The existence of both cross-reacting and unique components was observed; however, the cross-reacting and unique components could be different for different patients (40).

Cross-reactivity between an isolated 24 kDa Kiwi allergen and Fes p 4 (*Fescue* meadow pollen) was confirmed by anti-grass group 4 moab 2D8 (76).

Clinical Experience

IgE-mediated reactions

Acute allergy to Kiwi fruit was first described in 1981: a 53-year-old atopic woman developed urticaria, wheeze and laryngeal oedema on handling Kiwi (77). Since then, there have been reports of Kiwi allergy presenting with a wide range of symptoms, from localized oral allergy syndrome (OAS) to life-threatening anaphylaxis (33,49-50,78-86). As Kiwi is a new food in many countries and dietary habits vary from one locale to another, the prevalence of allergy to Kiwi may be much more common in some countries than in others.

A questionnaire-based survey conducted in Toulouse schools in France found that, out of 2,716 questionnaires returned, 192 reported a food allergy, and that Kiwi was the third-most-often-reported, purportedly causing allergic symptoms in 22 (9.0%) cases (87).

A study was conducted at 17 clinics in 15 European cities to evaluate the differences among some northern countries regarding what foods, according to food-allergic patients, elicit hypersensitivity symptoms. It was reported, after evaluation of questionnaires concerning 86 different foods, that the foods apparently most often eliciting symptoms in Russia, Estonia, and Lithuania were citrus fruits, chocolate, honey, Apple, Hazelnut, Strawberry, fish, Tomato, Hen's egg, and Milk; these results differed from those of Sweden and Denmark, where Birch pollen-related foods, such as nuts, Apple, Pear, Kiwi, stone fruits, and Carrot, were the most common reported causes. The most common symptoms reported were oral allergy syndrome and urticaria. Birch pollen-related foods apparently dominated as allergens in Scandinavia, whereas some Mugwort-related foods seemed to be of more importance in Russia and the Baltic States.

f84 Kiwi

Among 1,139 individuals, Kiwi was the fifth most commonly reported food allergen, resulting in adverse effects in 32% (88).

The most common symptoms attributed to Kiwi allergy are those associated with oral allergy syndrome, which include pruritis of the eyes, ears, tongue, pharynx and mouth, and swelling of the lips, tongue and pharynx (10,42,49,89). Symptoms of oral allergy syndrome from Kiwi fruit once resulted from a lover's kiss (90). Many other allergic symptoms are also possible: nausea, vomiting, diarrhoea, abdominal pain, asthma, angioedema, allergic contact dermatitis, atopic dermatitis and contact urticaria have also been reported (91-93). Sensitisation to Kiwi skin has been documented (94). Allergy to Kiwi is often associated with Latex allergy, as described in the Potential cross-reactivity section above.

Although OAS has been reported to occur with Kiwi, a Japanese study of sensitisation to Japanese cedar, Orchard grass, Short ragweed, and Alder tree pollen among 1,067 pediatric patients with allergic diseases, among whom 16 cases of childhood OAS were identified and further explored, the most frequent allergen resulting in OAS was Kiwi, followed by Tomato, Orange and Melon. The study found that childhood OAS was not associated with pollen allergy, as was seen with adults (95).

No specific allergens could be associated with any particular pattern of Kiwi-induced allergic reactions, confirming that Kiwi allergy is not a homogeneous disorder but consists of several clinical subgroups (17). Studies and case reports are illustrative.

In a British study of 273 subjects with a history suggestive of allergy to Kiwi, the most frequently reported symptoms were localised to the oral mucosa (65%), but severe symptoms (wheeze, cyanosis or collapse) were reported by 18% of subjects. Young children were significantly more likely than adults to react on their first known exposure, and to report severe symptoms. Twenty-four of 45 subjects (53%) evaluated by DBPCFC had allergy confirmed. A prick-to-prick skin test with fresh Kiwi was positive in 93% of subjects who had allergy confirmed by DBPCFC, and also in 55% of subjects with

a negative food challenge. The commercial extract was significantly less sensitive, but with fewer false-positive reactions. IgE antibody levels were positive in only 54% of subjects who had a positive challenge (81).

A 26-year-old patient with a localised pruritic reaction a few minutes after eating Kiwi fruit has been described; a similar incident happened a few months later, accompanied by dysphagia, vomiting and urticaria (96).

A German study of 25 subjects with Birch pollen and Kiwi allergy reported that 23 had localised oral symptoms and 2 had urticaria (35).

In a prospective trial of 20 children with a history of immediate allergic reactions to Kiwi who underwent double-blind placebo-controlled food challenges with fresh, steam-cooked and industrially homogenised Kiwi, fresh Kiwi induced positive skin-prick wheals in all the children. Sera from all children showed IgE antibodies to raw Kiwi, and 1 to the homogenised preparation. Act c 1 and Act c 2 were the major allergens identified. Clinical reactivity following challenge with heated Kiwi was negative, except for 1 child who developed symptoms (18).

Numerous instances of anaphylaxis to Kiwi fruit have been reported (97-102), including in a 12-year-old boy who initially experienced localised oral symptoms, vomiting, urticaria and dizziness (103). A 57-year-old man, who had experienced 2 anaphylactic reactions when eating Kiwi, had a severe systemic reaction on skin testing performed at home by his daughter (104). A 29-year-old woman described several episodes of severe anaphylaxis after consumption of Kiwi fruit, including 3 episodes of allergic shock with loss of consciousness and subsequent hospitalisation. During the first 2 episodes, the symptoms started shortly after ingestion of fresh Kiwi alone, and the third episode was elicited by minute amounts of Kiwi left on a knife that was subsequently used to prepare a Strawberry dessert served to the patient in a restaurant (97).

Food-dependant exercise-induced anaphylaxis to Kiwi has also been reported (105).

Of 22 patients allergic to Kiwi fruit, 10 with severe systemic reactions and 12 with localised symptoms confined to the oral and pharyngeal mucosa (oral allergy syndrome), SPT was positive to Kiwi fruit in all, whereas IgE antibodies to Kiwi were present only in those with generalised severe symptoms. Surprisingly, all 22 patients with clinical Kiwi allergy had positive SPT and elevated IgE antibody levels to Birch pollen. Clinically, all complained of rhinitis during Birch pollen season. Many patients showed sensitisation to Grass and Mugwort pollen. Allergy to other food was also found to be associated with Kiwi allergy: strongly to Apple and Hazelnut, moderately to Carrot, Potato, and Avocado, and weakly to Wheat and Rye flour, Pineapple and Papaya, and their enzymes bromelain and Papain (51).

An association between allergy to Kiwi and asthma has also been reported. Among 163 asthmatic children with food allergy and food-induced asthma, Kiwi fruit was reported to have resulted in asthma in 3.6% following DBPCFC oral challenges to Kiwi (106).

Considering that adverse reactions to Kiwi may be severe, the possibility that Kiwi is a “hidden” allergen needs to be considered in “idiopathic” anaphylaxis (107). Inadvertent contact with Kiwi via kissing may need to be considered (108).

Allergy to Kiwi is reported to have resulted in acute pancreatitis in a 48-year-old man (109).

Sensitivity of the measurements of IgE antibodies in Kiwi-allergic patients was reportedly between 13% and over 70%, a range that may reflect the different Kiwi-allergic populations being studied, and also the different techniques used to measure IgE antibodies (35,82).

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f208 Lemon



Allergen Exposure

Geographical distribution

Lemon is the fruit of the Lemon tree. The true home of the Lemon is unknown, though some have thought it to be northwestern India (1).

The Lemon tree grows 3 to 6 m in height. It usually has sharp thorns on the twigs. The alternate leaves, reddish when young, later become dark-green above and light-green below. They are oblong, elliptic or long-ovate, 6-11 cm long, finely toothed, and with slender wings on the petioles. The mildly fragrant flowers may be solitary, or there may be 2 or more clustered in the leaf axils. The buds are reddish; the opened flowers have 4 or 5 petals, 2 cm long, white on the upper surface and purplish beneath. They have 20 to 40 more or less united stamens with yellow anthers (1).

The fruit is oval and 7 to 12 cm long, with a nipple-like protuberance at the apex. The peel is usually light-yellow, though some Lemons are variegated with longitudinal stripes of green and yellow or green and white. The skin is 6 to 10 mm thick and aromatic, being dotted with oil glands. The pulp is pale-yellow,

Citrus limon

Family: *Rutaceae*

Common name: Lemon

Source material: Whole fresh fruit

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formed in 8 to 10 segments, juicy and acid. Some fruits are seedless, but most have a few seeds, elliptic or ovate, pointed, smooth, 9.5 mm long, and white. Lemons for export may be harvested early and naturally “cured” in transit (1).

Several Lemon cultivars or true Lemons and of Lemon-like fruits are accepted as Lemons in home or commercial usage.

Environment

The Lemon is used for culinary and non-culinary purposes throughout the world. The fruit is used primarily for its juice, though the pulp and rind (“zest”) are also used, primarily in cooking and baking. Lemon juice is about 5% citric acid, which gives Lemons a tart taste and a pH of 2 to 3 (1).

Unexpected exposure

Lemon is also a preservative of colour. Oils from the skin are used in perfume making and to flavour drinks and other foods.

Allergens

The following allergen has been characterised:

Cit l 3, a lipid transfer protein (2-3).

The major protein component of citrus seeds is the globulin seed storage protein citrin. Albumin seed storage proteins have also been described as components of citrus seeds (4). Citrus seed extracts display similar antigenic profiles, indicative of close phylogenetic relationships. Protein bands between 9 and 61 kDa have been demonstrated, with strong bands at 9, 14, 15, and 27 kDa. The bands between 9 and 15 kDa may represent the panallergens profilin and lipid transfer protein (5).

Potential cross-reactivity

Cross-reactivity within the *Rutaceae* family (Lemon, Lime, Orange, Tangelo, Grapefruit) can be expected, but has not been documented to date.

Both Orange and Lemon lipid transfer protein has been shown to display cross-reactivity with the major Peach allergen Pru p 3, a lipid transfer protein (6). In a patient with anaphylaxis from Mandarin (*Citrus reticulata*), a lipid transfer protein was isolated from Mandarin fruit. Analysis of the patient's serum also demonstrated sensitisation to the lipid transfer protein Cit s 3, from Orange, as well as to Cit s 1, a germin-like allergen (3). Whether similar allergens occur in Grapefruit, a closely related family member, was not assessed.

Latex allergy has been reported to be associated with allergy to a number of other foods, including Avocado, Banana, Kiwi, Papaya, Chestnut, Peach and Grapefruit (7). A 34-year-old female with asthma and atopic dermatitis was described who developed severe anaphylaxis to Latex; she was shown to have IgE antibodies directed against Latex, Banana, Kiwi, Grapefruit, and Avocado. SPT was also positive to Banana, Grapefruit, Avocado, and Latex extract (8).

Clinical Experience

IgE-mediated reactions

Ingestion of Lemon may result in allergic reactions, including food allergy, allergic rhinoconjunctivitis, atopic dermatitis and anaphylaxis (9-11). Citrus fruit such as Lemon is among the most common causes of atopic dermatitis (12-14). IgE antibodies to Lemon have been detected using Pharmacia CAP System in food-allergic children (15) and in children with atopic dermatitis and respiratory disease (16). Lemon-dependent, exercise-induced anaphylaxis has been reported (17).

A study was conducted at 17 clinics in 15 European cities to evaluate the differences among some northern countries regarding which foods, according to the patients, elicit hypersensitivity symptoms. A questionnaire concerning 86 different foods

was administered to food-allergic individuals. The foods most often reported as eliciting symptoms in Russia, Estonia, and Lithuania were citrus fruits, chocolate, honey, Apple, Hazelnut, Strawberry, fish, Tomato, Hen's egg, and Cow's milk, a profile that differed from Sweden and Denmark's, where Birch pollen-related foods, such as nuts, Apple, Pear, Kiwi, stone fruits, and Carrot, were the most common reported causes. The most common symptoms reported were oral allergy syndrome and urticaria. Birch pollen-related foods apparently dominate as culprits in Scandinavia, whereas some Mugwort-related foods were of more importance in Russia and the Baltic States. Among 1,139 individuals, Lemon was the 16th most often reported culprit food, resulting in adverse effects in 23% (18).

An Indian study evaluated the effect of a specific elimination diet on symptoms of 24 children aged 3 to 15 years who had documented deterioration in control of their perennial asthma. IgE antibody analysis for a range of food items revealed that 19 (79%) had IgE antibodies directed at Lemon (19).

A number of case reports describe a range of adverse effects to Lemon.

A 26-year-old Peanut-allergic man exhibited sensitivity to citrus seed and experienced anaphylaxis to Lemon soap (after showering and washing his torso and face with Lemon-impregnated soap). Ingestion of whole crushed oranges and citrus seeds, including Lemon, Orange, and Mandarin seeds, had previously resulted in anaphylaxis. Processed citrus fruit juice was tolerated. Symptoms included laryngeal oedema, generalised urticaria, and asthma, and occurred within minutes of ingestion. IgE antibody levels were raised to Peanut (4.0 kU_A/l), Orange (4.0 kU_A/l), Lemon (1.1 kU_A/l), Walnut (15.2 kU_A/l), and Hazelnut (6.77 kU_A/l) (5).

In a study aimed at characterising Raspberry allergens, a 25-year-old patient was described who had experienced periorbital oedema and rhinitis from Lemon and other citrus fruit. Prick-to-prick tests were positive for Peach, Lemon, Sweet lime, Orange, Banana, Blueberry, Tomato, Grape and Bell pepper (10).

f208 Lemon

Eosinophilic gastroenteritis and urticaria following ingestion of citrus fruit was described in a 46-year-old male, who presented with a 2-month history of non-bloody, frequent loose bowel movements with abdominal cramping and nausea without emesis. He had been diagnosed approximately 10 years previously with citrus fruit-dependent, exercise-induced anaphylaxis. Lemon or Grapefruit consumption followed by exercise caused urticaria and wheezing but not gastrointestinal symptoms. IgE antibody levels were $> 100 \text{ kU}_A/\text{l}$ to Lemon and $27.4 \text{ kU}_A/\text{l}$ to Grapefruit (17).

A cross-sectional, descriptive, questionnaire-based survey was conducted in Toulouse schools to determine the prevalence of food allergies among schoolchildren. Out of 2,716 questionnaires returned, 192 reported a food allergy. Three reported allergy to Lemon (11).

Importantly, individuals allergic to Mandarin or other citrus fruit may not necessarily be allergic to all citrus fruits. For example, in a study of 6 patients with Orange allergy (type 1 hypersensitivity after ingestion of Orange juice and a positive skin prick test on at least 2 occasions), 3 patients tolerated small quantities of Lemon juice, 1 patient tolerated Mandarin, but 2 patients experienced oral allergy syndrome to this fruit. Serum Orange-specific IgE antibody levels were raised in all patients, Mandarin-specific IgE antibodies in 5 patients (highest $6.04 \text{ kU}_A/\text{l}$), Lemon-specific IgE antibodies in 6 patients, and Grapefruit-specific IgE antibodies in 5 (20). Cross-reactivity was not evaluated.

Other reactions

Lemon contact with human skin may result in adverse skin reactions, e.g., phytophotodermatitis (21-22). A bartender with hand dermatitis was described who experienced allergic contact sensitivity to the skin of Lemon, Lime, and Orange but not to their juice. The authors pointed out that, although most reported cases of citrus peel allergy are due to d-limonene, in this patient patch tests for geraniol and citral, 2 minor components of citrus peel oil, were positive, whereas tests for d-limonene were negative (23).

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f215 Lettuce



Lactuca sativa

Family: *Asteraceae (Compositae)*

Common names: Lettuce, Garden lettuce

Source material: Fresh lettuce

Main types:

L. scariola – Prickly Lettuce

L. sativa var. *capitata* – Head Lettuce

L. sativa var. *asparagina* – Stem Lettuce

L. sativa var. *crispa* – Leaf Lettuce

L. sativa var. *longifolia* – Romaine.

There are more than 100 varieties of Lettuce and salad greens. This family contains many weeds of great importance in allergy, e.g., Mugwort and Ragweed.

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Allergen Exposure

Geographical distribution

Probably the world's most widely used salad vegetable, Lettuce is thought to have originated in the Mediterranean region in the form of Prickly lettuce. It is recorded as having been served in Persia in 400 BC.

Annual and biennial Lettuce is cultivated in many parts of the world for its edible leaves. Of the many varieties, basic forms have been classified as follows: heading or head varieties, cutting or leaf varieties, and Cos or Romaine. A fourth, very minor type, is the so-called Stem, Celery or Stalk Lettuce.

Environment

Lettuce grows in cultivated beds. Its most common use – as leaves, but sometimes also as spouted seeds – is in salads and sandwiches, but it may also appear in soups and stews. Edible oil is obtained from the tiny seeds, but extraction of the oil on any scale would not be feasible.

The sap of the plant contains lactucarium, which is used in medicine and folk medicine for its anodyne, antispasmodic, digestive, galactagogue, diuretic, hypnotic, narcotic, sedative, anaphrodisiac, carminative, emollient, febrifuge, hypoglycaemic, and parasiticide properties. Lactucarium has the effects of a feeble opium, but without tendency of opium to cause digestive upsets; nor is lactucarium addictive. It is taken internally in the treatment of insomnia, anxiety, neuroses, hyperactivity in children, dry coughs, whooping cough, rheumatic pain, etc. The sap has also been applied externally in the treatment of warts. Even normal doses can cause drowsiness, while excess doses cause restlessness, and overdoses can cause death through cardiac paralysis.

Allergens

Four protein bands with molecular weights of 50, 43, 39 and 16 kDa have been detected in Lettuce, and these exhibited IgE-binding properties (1). A second study reported detecting 14 allergens in Iceberg lettuce, with weights between 13 and >113 kDa (2). A 42-year-old female presented with widespread erythema and a subsequent episode of

anaphylaxis after ingesting “Tudela” lettuce hearts (*Lactuca sativa* var.); serum from this patient revealed several bands, predominantly in the range of 15–65 kDa (3). Researchers have reported predominant reactivity to a protein of 42-48 kDa (4-6).

The following allergen has been characterised:

Lac s 1, a 9 kDa lipid transfer protein (7-8).

Two Lac s 1 isoforms were identified, with an amino-acid identity of 62% to each other, up to 66% to Pru p 3 from Peach, and 72% to the N-terminal peptide of the London plane pollen LTP Pla a 3. The prevalence of IgE binding to nLac s 1 was 90%, as shown in immunoblotting experiments with Lettuce extract (8).

No differences in the protein profiles of several Lettuce varieties (Chicory, Butterhead, Iceberg, [mini]-Romaine, Frisée) were found, or between younger (inner) and older (outer) leaves, but the authors could not exclude slight differences in the level of LTP accumulation in the leaves (8).

IgE binding to a 24 kDa protein and HMW proteins (> 50 kDa) was due to cross-reactive carbohydrate determinants (CCDs) (8).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected, as well as to a certain degree among members of the family *Asteraceae* (9).

A patient allergic to Chicory reported reactions to botanically related Endive (*Cichorium endivia*) and Lettuce (*Lactuca sativa*). No cross-reactivity was found with pollen from Mugwort, a member of the same family (6). This is contradicted by a report on subjects allergic to *Artemisia*, who appeared to be at a higher risk of concomitant sensitisation to various foods, including Lettuce. A common allergen may be responsible (10). Four patients with occupational contact dermatitis to Lettuce were shown to be cross-reactive with endive (11).

Lettuce contains a lipid transfer protein (Lac s 1), which may result in cross-reactivity with other lipid transfer protein-containing

foods (12). Lac s 1 was shown to have a high amino acid sequence identity with other lipid transfer proteins, from Peach and Cherry, among others. A clear partial cross-reactivity was observed between Lettuce LTP and London plane tree- (*Platanus*) pollen extract (7). Although a partial IgE cross-reactivity between Lac s 1 and *Platanus* pollen exists, a more pronounced cross-reactivity occurs with the LTPs from the *Rosaceae* family, e.g., Pru av 3 from Cherry (13), and Pru p 3, the major allergen from Peach (14-15). Lac s 1 also showed broad IgE cross-reactive properties with Walnut and Peanut extract (16), LTPs from Mugwort and Chestnut (17-18). Vit v 1 from Grape (19), Zea m 14 from Maize (20), Cor a 8 from Hazelnut (21), and Mal d 3 from Apple (22). Although the highest degree of sequence identity of the N-terminus of Lac s 1 was found with Mal d 3, only a single subject in the Lettuce-allergic group reported Apple allergy (7). The authors therefore postulated a lack of correlation between sequence identity and clinical cross-reactivity (7-8).

RAST inhibition demonstrated that Carrot does share allergens with Lettuce, although Carrot allergens are more potent than those of Lettuce (2).

One study concludes that cross-reactivity was observed between *Platanus acerifolia* pollen and plant-derived foods. OAS in these patients may have been caused by primary respiratory sensitisation to Plane tree pollen, and the authors propose profilin as the cause. Approximately 22% of the Spanish patients with Plane tree pollen allergy and food allergy had allergy to vegetables, including Lettuce (23).

Clinical Experience

IgE-mediated reactions

Lettuce allergy is not frequently reported in the literature, but is found in clinical practice, predominantly in the southern part of Europe (8). Lettuce may induce symptoms of food allergy, in particular oral allergy syndrome, in sensitised individuals (1-5,7-8,12,23-24). Adverse reactions may be severe, resulting in anaphylaxis (7). Lettuce and Carrot can account for clinically significant IgE-mediated allergic reactions, including prolonged nasal

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obstruction (25). This finding is supported by a Mexican study, in which, among 1,419 allergic patients aged between 1 and 18 years, 442 (31%) had positive skin prick test (SPT) results to 1 or more among 33 tested foods. Fish, milk, seafood, beans, Orange, Onion, Tomato, Chicken, nuts, Lettuce and Strawberry were responsible for 58% of the total of allergic reactions. Of those, fish, milk, seafood, Soy and Orange (39%) had the highest frequency (26).

In a study of 29 Lettuce-allergic patients, with or without concomitant Peach allergy, and 19 Peach-allergic patients without Lettuce allergy, it was concluded that the data provided indirect evidence that Pru p 3, a lipid transfer protein, might act as the primary sensitising agent in patients allergic to both Lettuce and Peach. Of those with Lettuce allergy, anaphylaxis was reported in 15, gastrointestinal symptoms in 2, OAS in 8, urticaria in 3, and angioedema in 3. Skin prick testing was positive in 17, and prick to prick testing in 18, (a number of SPT-positive cases were prick to prick-negative, and *vice versa*); IgE antibody levels for Lettuce were negative in 7, and for nLac s 1 negative in 2 but positive in 27 of the 29 (8).

A study of 14 patients with allergy to Lettuce described how all were sensitised to *Platanus* pollen. Ten were allergic to a lipid transfer protein in Lettuce. Fifty percent of the subjects experienced anaphylaxis to Lettuce. Symptoms of oral allergy syndrome was followed by more severe symptoms in the majority of cases. Lac s 1, the lipid transfer protein, was the responsible allergen (7).

A 42-year-old female presented with widespread erythema with pruritus after ingesting "Tudela" lettuce hearts (*Lactuca sativa* var.). She experienced an anaphylactic shock episode a few days later after eating the Lettuce hearts dressed with Olive oil. She had concomitant seasonal rhinitis, which coincided with the pollination of *Platanus acerifolia*. Skin prick tests were positive to "Tudela" lettuce heart, Lettuce, endive, pollen from *P. acerifolia* and *Artemisia vulgaris*; but negative to Leek, Potato, Carrot and Latex. In spite of her tolerating the ingestion of Leeks, Potatoes and Carrots, presence of IgE antibodies to these foods was demonstrated (3).

However, IgE antibodies may be found in asymptomatic patients. Skin-sensitising allergens have been identified, but reactions do not appear to be IgE-mediated (27).

Food-dependent exercise-induced anaphylaxis has been reported (28-29).

Generalised, pruritic, papular and erythematous eruption, associated with facial and lingual oedema and a tight throat, due to Lettuce, has been documented in a patient (1).

Previously unsuspected Lettuce allergy in a patient with delayed metal allergy has been reported (30).

Other reactions

Occupational eczema or contact dermatitis, combining delayed and immediate-type reactions, has been reported (11,31-34), including contact hypersensitivity to Lettuce in a chef (35). A 35-year-old woman complained of an itchy rash on her fingers, which occurred for the first time 3 months after commencing work at a vegetable packing plant. The rash then spread to her arms and neck. Despite a negative standard battery, targeted patch testing revealed Lettuce as the offending agent (36).

Greenhouse workers and gardeners are at risk of *Compositae*-related allergy to Chrysanthemum (*Dendranthema*), Daisy (*Argyranthemum frutescens*) and Lettuce (*Lactuca sativa*) (37-38). Ingestion of Lettuce was reported to result in lip and facial swelling, and in aggravation of pre-existing *Compositae* dermatitis (39).

Other substances, including allergens, may be present that result in adverse effects. Powdered Latex glove use in salad preparation may result in measurable amounts of Latex protein on Lettuce, with an exposure-dependent increase in the Latex protein levels (40). Sulphite-treated Lettuce (sulphite is used as a preservative) is capable of provoking bronchospasm in sulphite-sensitive asthmatics and may be a cause of restaurant-provoked asthma in these individuals (41).

Lettuce contains high levels of naturally occurring nitrates (42-43).

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Citrus aurantifolia

Family:	<i>Rutaceae</i>
Common names:	Lime, Green lemon, Sour lemon
Source material:	Whole fresh fruit
Synonymes:	<i>C. acida</i> , <i>C. lima</i> , <i>C. medica</i> , <i>Limonia aurantifolia</i>

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Allergen Exposure**Geographical distribution**

The Lime is native to the Indo-Malayan region. It is now grown in tropical regions almost throughout the world, particularly in Florida. There are 2 main types of this small, lemon-shaped green citrus fruit: the acidic (the chief kinds being Persian limes and Mexican or Key limes), which is commercially grown, and the sweet, which is uncommon in North America. Limes have been crossed with other types of citrus.

Environment

Limes are available, if not common, throughout the industrialised world, and have many traditional uses in the developing world. Sweetened or unsweetened bottled Lime juice, frozen Lime juice, Lime syrup and limeade are some of the more popular Lime products and are available in most supermarkets. The Lime is used in mixed drinks (such as margaritas), as a marinade, garnish, and sauce, and in the famous Key lime pie. Limes are often made into jam, jelly and marmalade, and they are sometimes pickled. The juice and the skin oil are used for flavouring processed foods. The minced leaves are consumed in certain Javanese dishes. In the Philippines, the chopped peel is made into a sweet with milk and Coconut. In tropical Africa, Lime twigs are popular chewsticks. Limes are an excellent source of vitamin C.



The juice has been used in the process of dyeing leather, and as an ingredient in cosmetics. The dehydrated peel is fed to cattle. In India, the powdered dried peel and the sludge remaining after clarifying Lime juice are employed for cleaning metal. The hand-pressed peel oil is utilised in the perfume industry.

The juice, leaves and root bark are used in a variety of homeopathic applications. In addition, there are many purely superstitious uses of the Lime in Malaya.

Allergens

No allergens from this plant have yet been characterised.

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus *Citrus* could be expected (1).

f306 Lime

Clinical Experience

IgE-mediated reactions

Lime may uncommonly induce symptoms of food allergy in sensitised individuals. Allergic reactions are similar to those seen with other citrus fruit and consist mainly of contact dermatitis and contact urticaria (2).

In a study aimed at characterising allergens from Raspberry, sera from 8 female patients were assessed. A 25-year-old with periorbital oedema and rhinitis from Lemon and other citrus fruits was described, who was prick-to-prick positive to Peach, Lemon, Sweet lime, Orange, Banana, Blueberry, Tomato, Grape and Bell pepper (3).

An instance has been reported of a bartender with hand dermatitis who developed allergic contact sensitivity to the skin of Lemon, Lime, and Orange, but not to their juices. Although most reported cases of citrus peel allergy are due to d-limonene, in this instance reactions to patch tests for geraniol and citral, 2 minor components of citrus peel oil, were positive, whereas those for d-limonene were negative (4).

Similarly, a 52-year-old woman presented with an eczematous rash at the side of her mouth and lips. She had been sucking the Lime from her gin and tonic for up to 1 minute after finishing her drink. Patch tests were positive for geraniol 2%, geranium oil and Lime peel. Citrus oil is made up of 90% limonene, and the remaining 10% consists of citral, gerraniol and bergapten (5).

Other reactions

Non-allergic phytophotodermatitis, a phototoxic reaction occurring in skin exposed to sunlight after contact with plants containing furanocoumarins, has been reported (6-7). Ninety-seven (16%) of 622 children and 7 (7%) of 104 counsellors at a camp developed a phototoxic dermatitis. The eruptions were confined to the hands, wrists, and forearms, and appeared as discrete and confluent polymorphous patches and linear streaks. The cause was thought to be the making of pomander balls (sachets). The makers punctured the skin of Limes (the principal component) with scissors, releasing oils known to contain photoreactive furocoumarin (psoralen) compounds (8).

A 6-year-old boy presented with marked, symmetric, painful erythema and oedema of both hands that rapidly developed into dramatic bullae covering the entire dorsum of the hands. The history revealed that the hands had been bathed in Lime juice for a prolonged period during the preparation of limeade. This resulted in phytophotodermatitis. The rind contains 6- to 182-fold greater concentrations of all furanocoumarins measured, when compared with pulp. Bergapten was the most abundant substance in the rind (9).

In a group of Thai patients with contact dermatitis, patch test reactions to extracts of fragrance raw materials, traditionally used in Indonesian cosmetics, were evaluated. Positive reactions to extracts of *Citrus aurantifolia* Swingle were observed. Specimens taken directly from the citrus fruits (the unconcentrated sources of the fragrance raw materials) were less antigenic (10).

Sensitisation to pollen from the Lime tree may occur (11).

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f348 Litchi



Allergen Exposure

Geographical distribution

Litchi is a member of the family *Sapindaceae*, which also contains 2 related species: rambutan (*Nephelium lappaceum*) and longan (*Euphoira longana*). These fruits are similar in appearance and taste.

The Litchi tree is native to Southeast Asia, in particular to southern China, where it flourishes, especially along rivers and near the seacoast. It spread through other parts of Asia, and in the nineteenth century to the New World. China, however, still leads in Litchi fruit production.

The Litchi tree is a dense, round-topped, slow-growing tree with smooth gray bark, growing (rarely) up to 14 m high. The leathery leaves are reddish when young, becoming shiny and bright green later. The flowers are abundant, tiny petal-less, and yellowish-green. The fruit is covered by a leathery rind, which is pink to strawberry-red in colour and rough in texture. The fruit is oval, heart-shaped or nearly round, 2.5 to 5 cm in length and 7 to 12 cm in diameter. The rind separates from the flesh readily. The edible portion or aril is

Litchi chinensis

Family: *Sapindaceae*

Common names: Litchi, Litchi nut, Lychee, Leechee, Lichee

Source material: Pulp from fresh fruit

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white to translucent, firm and juicy. The flavor is sweet and fragrant. Inside the aril is a single seed that varies considerably in size.

Strictly speaking, these are nuts and not fruits. Their closest non-tropical relatives are the Walnut, Cashew nut and Pistachio nut of the *Anacardiaceae* family.

Environment

Litchis are increasingly well known and available in the West. They are usually eaten fresh, out of the hand. Peeled and pitted, they are often added to fruit cups and fruit salads. They can also serve as garnishes, hors d'oeuvres, and ingredients in a variety of desserts, including sherbet.

Litchis, being low in phenols and non-astringent in all stages of maturity, are canned with the addition of tartaric or citric acid to prevent browning.

Litchis are also occasionally spiced, pickled, or made into sauces, syrups, jams, jellies or wine. The flesh of dried Litchis is eaten like raisins. Litchis can also be frozen, but after thawing they spoil quickly. In China, honey from hives near Litchi groves is prized.

Litchis and their seeds, and decoctions of the peel, root, bark and flowers, are used in traditional medicine to treat coughing and other throat ailments, intestinal complaints, neuralgia, and tumours. The Chinese, however, believe that excessive consumption of raw Litchis causes fever and nosebleed.

Allergens

No significant differences in allergenicity among 7 Litchi varieties have been demonstrated. In

a study of 38 Litchi-allergic patients, 34 were shown to have IgE antibodies to a 55 kDa allergen. Proteins of 14, 20, 30, 40, 42, and ≥ 67 kDa were characterised. Significant differences in allergens were detected between the peel and flesh of the Litchi. The peel contained 16, 18, 22, 40, 50, 80 and 100 kDa proteins. The pericarp showed a higher allergenic activity. No profilin was found in the peel, but 4 profilins were detected in the aril of the Litchi. A sequence homology of 89% between a 40 kDa allergen from the aril and the glyceraldehyde-3-phosphate dehydrogenase from White mustard was demonstrated. The allergens were shown to be very heat-stable. Canned Litchi demonstrated stable proteins of 14, 40, 42, 55 and 94 kDa, which remained stable even after a storage time of 12 months. Freezing did not alter the allergens. Only the 14 and 55 kDa allergens were resistant to simulated gastric digestion. While no more bands were visible in the immunoblot, remaining allergic potential could be proven by EAST-inhibition (1).

In a study of 2 patients, both of them sensitised to Compositae pollen and Sunflower seed, who developed anaphylaxis after ingesting Litchi for the first time, allergens from Litchi, *Artemisia* pollen and Sunflower seed were characterised and protein bands in the 24-70 kDa range isolated in the 3 extracts. A protein band of approximately 70 kDa was recognised by serum IgE antibodies of both patients in Litchi, *Artemisia* pollen and Sunflower seed extracts, and was considered to be a possible candidate for cross-reactivity (2).

The following allergens have been characterised:

Lit c 1, a 16 kDa protein, a profilin (3-6) (previously known as Lit c 4).

Lit c IFR, a 35 kDa protein, an isoflavone reductase (7-9).

Lit c TPI, a triose-phosphate isomerase, a major allergen (10).

A Bet v 6-related food allergen, a phenylcoumaran benzylic ether reductase (PCBER) (11).

IgE reactivity of recombinant Lit c 1 was shown to bind to IgE antibodies in 5 out of 15 Litchi-allergic patients tested (6).

Unlike other profilin proteins, Litchi profilin appears to be quite thermostable; skin reactivity was detected to pasteurised (90 °C for 10-15 minutes) Litchi (3).

Lit c TPI bound to IgE antibodies in 67% of Litchi-allergic patients (10).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the family (Litchi, ackee fruit, longan and rambutan) could be expected but has not been documented (12).

Broad cross-reactivity between Litchi fruit and other plants has been reported, and profilin has been identified as the protein responsible (3). A high degree of cross-reactivity between Litchi profilin and Birch profilin was found in sera from Litchi-allergic patients (6).

The presence of an isoflavone reductase panallergen may result in cross-reactivity between this fruit and other plants containing this allergen, e.g., Birch pollen, Mango, Apple, Pear, Orange, Banana and Carrot (7,9).

A homologous allergen to the Birch pollen allergen Bet v 6, a phenylcoumaran benzylic ether reductase (PCBER), has been shown to be present in Litchi and may result in cross-reactivity with homologous allergens present in many foods such as Apple, Peach, Orange, Strawberry, Persimmon, Zucchini, and Carrot (11,13).

Cross-reactivity between Litchi, *Artemisia* pollen and Sunflower seed as result of the presence of a 70 kDa allergen has been suggested (2).

Cross-reactivity of Litchi with Latex has been demonstrated through inhibition experiments (14).

Among Birch pollen-allergic individuals, 10-15% have IgE antibodies to the 35 kDa minor Birch pollen allergen, and there is cross-reactivity with proteins of comparable size from Litchi, Mango, Banana, Orange, Apple, Pear and Carrot. The 35 kDa protein is immunologically independent of the major Birch pollen allergen Bet v 1; IgE binding to a 34 kDa structure, which appears to be a Bet v 1 dimer, has also been observed (15).

f348 Litchi

Clinical Experience

IgE-mediated reactions

Litchi may induce symptoms of food allergy, including anaphylaxis, in sensitised individuals (4,16-20). As exotic fruits enter new Western markets, the prevalence of allergy to this fruit is bound to increase, as demonstrated by a study of 38 Litchi-allergic patients (1).

A 12-year-old girl developed swelling of the lips, pruritus, generalised urticaria and dyspnoea 30 minutes after eating a raw Litchi. A second event occurred 10 minutes after eating a piece of cake covered with a fruit cocktail, resulting in generalised urticaria and pruritus, rhinoconjunctivitis and dyspnoea. Restlessness, flush, generalised urticaria and inspiratory stridor occurred 50 minutes after eating half a Litchi. Skin reactivity was detected to raw Litchi, and a cellular allergen stimulation test were positive, but IgE antibodies in serum was, surprisingly, negative to Litchi but positive to Latex. Cross-reactivity of Litchi to Latex was shown by inhibition studies (14).

Anaphylaxis to Litchi (2,4,18-19), has been described in a number of reports, including one of a 23-year-old woman with inhalant allergy to pollen from plants of the *Compositae* family, who experienced an acute episode of severe dyspnoea after eating 2 to 3 fresh Litchis. She felt an itching in her mouth and throat a few minutes after eating the fruit. Five minutes later her lips and throat swelled, and she experienced severe dyspnoea. Skin reactivity to fresh and tinned Litchi (pasteurised at 90 °C for 10 to 15 minutes) was found. IgE antibodies to Litchi were detected (4). Anaphylaxis was reported in a 21-year-old woman, who developed urticaria, angioedema, swelling of the oral mucosa, and dyspnoea within 10 minutes of eating Litchi on an empty stomach, although she had eaten this fruit many times previously without adverse effects. SPT with the fresh fruit and rind was positive. A double-blind oral challenge resulted in urticaria (18).

A 26-year-old man developed pruritus, generalised urticaria, and severe angioedema of his lips and tongue, followed by dyspnoea, within 15 minutes of ingesting a Litchi. Litchi-specific IgE antibodies were not detected, but a basophil activation test (BAT) and a cellular antigen stimulation test (CAST) to Litchi were both positive, as was a prick-to-prick test with fresh Litchi. The individual also experienced oral allergy syndrome to Parsley and was sensitised to Mugwort but not to Latex or profilin. The authors suggested that Mugwort was the allergen responsible for the cross-reactivity, as no sensitisation to Latex or profilin could be demonstrated (19).

A report described 2 patients who developed anaphylaxis after ingesting Litchi for the first time. Both had been previously diagnosed with respiratory allergy to *Compositae* pollen and food allergy to Sunflower seed. Both were prick-prick test-positive for Litchi fruit, *Artemisia* pollen, Sunflower seed, Pistachio nut and other pollens. Serum IgE was detected for Litchi in 1 individual (0.45 kU_A/l). Cellular stimulation tests for Litchi were positive in both, as well as for *Artemisia* pollen and Sunflower seed. Protein bands in the 24-70 kDa range were isolated in the 3 extracts, with a common 70 kDa recognised in both patients' serum (2).

A 33-year-old nonatopic woman with multiple episodes of anaphylaxis after ingestion of Apple, Banana and Litchi, fruits belonging to botanically disparate plant families, was described. Five years previously, minutes after eating an Apple, she had become breathless and developed widespread wheals, followed by respiratory arrest. Two years later, a similar but milder reaction occurred after she ate a Banana, which resulted in extensive whealing, dyspnoea and tongue oedema, but no respiratory arrest. She avoided all fruits for the next 3 years, during which she was symptom-free. A few months before being investigated, she ate Litchi, which resulted in severe urticaria, angioedema of the eyelids and mild wheezing. Prick testing was positive for Apple and Banana. No obvious cross-reactive mechanisms appeared to be playing a role (20).

Food-dependant exercise-induced anaphylaxis associated with Litchi has been reported (21).

Contact urticaria was described in a 34-year-old woman, who developed generalised urticaria and angioedema, associated with bronchospasm, shortly after eating Litchi. Skin reactivity was detected using a scratch test with Litchi extract (22).

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f302 Mandarin



Citrus reticulata

Family:	<i>Rutaceae</i>
Common names:	Mandarin, Mandarin orange, Tangerine, Clementine, Satsuma, Dancy
Source material:	Fresh fruit
Synonyms:	<i>C. deliciosa</i> , <i>C. nobilis</i>
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Environment

Since the Mandarin is easy to peel, it is a natural fruit for eating out of hand. The sections are also utilised in fruit salads, gelatins, puddings, and cakes. Very small types are canned in syrup. The dried rind is often used as a flavouring. The essential oil is expressed from the peel and, with terpenes and sesquiterpenes removed, is employed in flavouring hard candy, gelatins, ice cream, chewing gum, liqueurs and bakery goods. Mandarin essential oil paste is a standard flavouring for carbonated beverages. Petitgrain Mandarin oil, distilled from the leaves, twigs and unripe fruits, has the same food applications. Unlike the Orange, Mandarin is not widely used as a juice.

The fruit is said to be antiemetic, aphrodisiac, astringent, laxative and tonic. The flowers, pericarp, endocarp, exocarp and seed are said to have a number of medicinal properties and to have been used in the treatment of a number of ailments.

Mandarin essential oil and petitgrain oil, and their various tinctures and essences, are valued in perfume manufacturing. The substance bergapten, from this and other citrus fruits, is sometimes added to tanning preparations, since it promotes pigmentation in the skin, though it can cause dermatitis or allergic responses in some people. Some of the plant's more recent applications are as sources of anti-oxidants and chemical exfoliants in specialised cosmetics.

Allergen Exposure

Geographical distribution

Citrus fruits constitute several species of the genus *Citrus* of the subfamily *Aurantiodeae* of the plant family *Rutaceae*.

The Mandarin is a small, deep-orange-coloured Orange. The skin is loose and easily peeled. The Mandarin orange is considered a native of southeastern Asia and the Philippines. It is most abundantly grown in Japan, southern China, India, and the East Indies. These fruits have never been as popular in Western countries as they are in the Orient. For commercial exploitation, Mandarins have several disadvantages, including that, unlike the Orange, the fruit does not ship well. But increasing cultivation in non-Eastern tropical areas has led to increasing availability.

Unexpected exposure

See under Environment.

Allergens

The following allergen has been characterised:

Cit r 3, a lipid transfer protein (1).

Cit r 3 is present in both Mandarin peel and pulp (1).

The presence of a profilin has been inferred through a study reporting that hypersensitivity to Bet v 2 was strongly associated with clinical allergy to citrus fruit (Orange, Mandarin, or both): 39% of subjects were monosensitised to Bet v 2, compared to 4% monosensitised to Bet v 1 (2).

A cross-reactive 30 kDa protein has also been detected (3).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the *Rutaceae* or citrus family could be expected (4) but has not been reported specifically for Mandarin.

Mandarin contains a lipid transfer protein (LTP), Cit r 3, which is expected to result in cross-reactivity with other LTPs, in particular those in other citrus fruits. Two citrus fruit LTP allergens, Orange Cit s 3 and Lemon Cit l 3, have previously been characterised, and sensitisation to these allergens has been detected in a Spanish group of Orange-allergic patients: in around 50–45% by *in vitro* testing, and in 37–27% by skin prick testing (5).

Cross-reactivity between Mandarin and other profilin-containing foods and plants is possible (2).

A Peanut-allergic patient was described who exhibited co-sensitivity to citrus seed and had experienced anaphylaxis to Lemon soap. The major protein component of citrus seed is a globulin seed storage protein, citrin, which was shown to be completely cross-reactive among seeds from various citrus fruits (Orange, Lemon and Mandarin) and partially cross-reactive between Peanut and Orange seed extracts (6).

A patient who had experienced allergic responses to various fruits developed an acute anaphylactic reaction after the ingestion of Peach. The patient's serum contained IgE antibodies reactive to extracts from Peach, Guava, Banana, Mandarin, and Strawberry, but not Apple, Pear, or Nectarine. A common 30 kDa protein was demonstrated, which was not present in extracts from Pear or Apple (3).

Clinical Experience**IgE-mediated reactions**

Anecdotal evidence suggests that Mandarin may occasionally induce symptoms of food allergy in sensitised individuals; however, few studies have been reported to date (1). Clinical presentation of citrus fruit allergy, reported mostly for Orange, is heterogeneous, varying from mild oral allergy syndrome to severe anaphylaxis (1,7). Biphase anaphylactic reactions have been reported following ingestion of Mandarin (8).

Importantly, individuals allergic to Mandarin or another citrus fruit may not necessarily be allergic to all citrus fruits. For example, in a study of 6 patients with Orange allergy (type 1 hypersensitivity after ingestion of Orange juice and a positive skin prick test on at least 2 occasions), 3 patients tolerated small quantities of Lemon juice, 1 patient tolerated Mandarin, but 2 patients experienced oral allergy syndrome to this fruit. Serum Orange-specific IgE antibody levels were raised in all patients, Mandarin-specific IgE in 5 patients (highest 6.04 kU_A/l), Lemon-specific IgE in 6 patients, and Grapefruit-specific IgE in 5 (7). Cross-reactivity was not evaluated.

A 24-year-old-woman was described who experienced an anaphylactic reaction (pronounced oral allergy syndrome, throat swelling, angio-oedema of the face, and severe bronchospasm) beginning within half an hour after ingestion of a Mandarin. Mandarin-specific IgE antibody levels were 5.18 kU_A/l, and 5.26 kU_A/l for Lemon, 3.07 kU_A/l for Orange, and 2.21 kU_A/l for Grapefruit. IgE antibodies against House dust mite and Bromelain (which are indicators of sensitisation against cross-reactive carbohydrate determinants) were

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negative. She was shown to be sensitised to Orange (Cit s 3) and Mandarin (Cit r 3) LPT allergens, as well as to a germin-like allergen, Cit s 1. Her sensitisation was confirmed by skin prick testing and basophil activation testing (BAT) (1).

Allergic symptoms were observed in farmers engaged in Mandarin farming, but might have been due not to Mandarin but to pesticides, Mites, or some other cause (9).

Other reactions

See under Environment. Contact dermatitis from the essential oil of Mandarin in fragrance has been reported (10).

Occupational asthma in a Mandarin orchard worker, from inhaling arrowhead scale dust, has been reported (11).

Obstruction of the small intestine due to Orange and Mandarin has been reported (12-13). Reactions have also been noted to Mandarin seeds.

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Mangifera indicaFamily: *Anacardiaceae***Common**

name: Mango

Source

material: Dried fruit

For continuous updates:www.immunocapinvitrosight.com**Allergen Exposure****Geographical distribution**

This evergreen tree (in a family that includes Cashew, Pistachio and Poison ivy) has been cultivated for over 6,000 years. It is native to Southeast Asia and Indo-Malaysia. Some 35 *Mangifera* species grow in Southeast Asia, but many are now cultivated or have become naturalised in tropical and sub-tropical regions throughout the world (1).

The Mango tree grows 15-30 m high and bears green to yellow and red ovoid fruit, with pink-orange flesh and a large central seed.

Environment

Mangoes are delicious simply peeled and eaten plain. They are also good in fruit salads and have long been made into chutney, pickles and squash. The ground seed is a source of flour. Green or unripe Mango has many uses in the cuisines of India, Malaysia and Thailand. Mango is used in various vegetable and lentil dishes, and also as a meat tenderiser. It is a good source of beta carotene and vitamin C.

Allergens

More than 1,000 strains of Mango are cultivated. In a study, allergens from 4 Mango varieties were evaluated using sera from 7 Mango-sensitised patients: all 4 varieties shared at least 5 allergens, of approximately 14, 30, 40, 43 and 67 kDa. There were no significant differences in allergenic potency among the 4 Mango strains (2). Other studies have reported no significant differences in allergenicity among 8 Mango varieties. A 40 and a 30 kDa protein were characterised as



major allergens, and minor allergens between 24 and 94 kDa, as well as between 14 and 16 kDa (a profilin), were detected. Interestingly, the profilin was detected in the peel and pulp of Mango. Ripeness of Mango did not influence its allergenicity (3). Other studies have found similar-sized allergens: IgE binding to Mango proteins of 25-50 kDa in a patient's serum was demonstrated (4).

In a study utilising sera of 52 patients with IgE-mediated sensitisation to Mango to identify IgE-binding allergens, sera from 46 were shown to contain 2 allergens with molecular weights of approximately 40 and 30 kDa, designated Man i 1 and Man i 2, respectively. Other IgE-binding patterns were detected for fewer than 50% of the assigned sera. It was demonstrated that there was no significant difference in the allergenic potency during fruit ripening (5). Based on inhibition studies and observed cross-reactions among Mango fruit, Mugwort pollen, Birch pollen, Celery,

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and Carrot, a third allergen (now known as Man i 3), related to Bet v 1 and Art v 1, was isolated (6).

The following allergens have been characterised:

Man i 1, a major allergen, a 40 kDa protein with an unknown function (3,7-8).

Man i 2, a major allergen, a 30 kDa protein with an unknown function (3,7-8).

Man i 3, a minor allergen, a profilin (9-10).

Eight of 18 (44%) Mango-allergic patients tested were shown to have IgE antibodies directed at recombinant Mango profilin (9).

A 14 kDa protein, a Bet v 1 homologue/group 1 *Fagales*-related protein, has been isolated (6), as well as a chitinase allergen (11). The presence in Mango of an isoflavone reductase (IFR), a 35 kDa protein with homology to the Birch allergen Bet v 5, was inferred in studies (12-13).

Mango allergens were shown to be very stable during technological processing, irrespective of enzymatic matrix decomposition, mechanical tissue disintegration and heating during peeling, mash treatment, and pasteurisation. Significant loss of allergenicity could not be observed in the extracts of Mango purées and nectars (3,7). Unusually, Mango profilin appeared to show a very high stability against heat and processing (3).

The “allergens” causing contact dermatitis to Mango have long been suspected to be alk(en)yl catechols and/or alk(en)yl resorcinols; there have been observed cross-sensitivity reactions to Mango in patients known to be sensitive to poison ivy and poison oak. The 3 resorcinol derivatives are heptadecadienylresorcinol (I), heptadecenylresorcinol (II) and pentadecylresorcinol (III); they are collectively named “Mangol” and have been reported as Mango allergens. Heptadec(adi)enyl resorcinols known to be present in Mango have been shown to elicit positive patch test reactions in Mango-sensitive patient (14).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the family and genus, *e.g.*, Pistachio and Cashew nut, could be expected but in fact does not occur frequently (15).

Two isoforms of Mango fruit profilin have been characterised. Both have a high amino acid sequence identity with other allergenic profilins (73-90%). A high degree of cross-reactivity was found between Mango profilin with profilin from Birch pollen. Man I 3.02 was the isoform closer to profilin of other fruit such as Pear (80%), Peach (90%) and Apple (80%) (9).

A panallergen has been identified in Birch pollen, Ragweed pollen, Timothy grass pollen, Celery, Carrot, Apple, Peanut, Paprika, Anise, Fennel, Coriander and Cumin. EAST inhibition and immunoblot inhibition demonstrated that cross-reactions among Mango fruits, Mugwort pollen, Birch pollen, Celery, and Carrot are based on allergens related to Bet v 1 and Art v 1, the major allergens of Birch and Mugwort pollen, respectively (6).

In Latex-fruit syndrome, Banana, Avocado, Chestnut and Kiwi are the most frequently implicated foods, but associations with several other fruits and vegetables, including Pineapple, Fig, Passion fruit, Mango, Tomato, Bell pepper, Carrot, Oregano, Dill, Sage, Papaya, Wheat and Cherimoya, have been reported. The allergen responsible for most cases of this syndrome is hevein (Hev b 6.02; a class I chitinase-like protein), the amino-terminal fragment of prohevein; homologous proteins have been found in Avocado, Chestnut, Banana, Kiwi, Tomato, Passion fruit, Papaya, and Mango (11,16).

An association between allergies to Latex proteins and to various foods has been reported, and confirmed by RAST and immunoblotting inhibition. Serum samples of 136 patients with well-documented, clinically relevant, immediate-type hypersensitivity against Latex proteins were analysed for IgE antibodies against a panel of different fruits. Cross-reacting IgE antibodies recognising Latex and fruit and other allergens (Papaya, Avocado, Banana, Chestnut, Passion fruit, Fig, Melon, Mango, Kiwi, Pineapple, Peach,

and Tomato) were demonstrated by RAST inhibition tests (17). Similar patterns have been demonstrated in other studies (18).

Between 10% and 15% of Birch pollen-allergic individuals have IgE antibodies to the 35 kDa minor Birch pollen allergen, and there is cross-reactivity with proteins of comparable sizes from Litchi, Mango, Banana, Orange, Apple, Pear and Carrot. The 35 kDa protein is immunologically independent of the major Birch pollen allergen Bet v 1. A subsequent study determined this protein to be an isoflavone reductase (IFR) with homology to the Birch allergen Bet v 5 (9,12-13). Researchers also observed IgE binding to a 34 kDa structure, which appears to be a Bet v 1 dimer.

Cross-reactivity was found among Pistachio nut, Cashew nut, and Mango seed, but this cross-reactivity did not extend to Mango pulp (19).

Celery allergies have been commonly associated with Mugwort pollen allergy, and also commonly with an allergy to spices of the *Umbelliferae* family. An association of Celery-Mugwort allergy with allergy to Mango was described but could not be explained (20).

In Europe, as opposed to North America, Poison ivy rash is hardly known. A young German woman who became sensitised to Poison ivy or Poison Oak while in the USA showed a cross-reaction to other *Rhus* species as well as to Mango (21).

Clinical Experience

IgE-mediated reactions

Mango may result in hypersensitivity reactions in Mango-sensitised individuals (22). Adverse reactions may occur as a result of ingestion of Mango or contact with the skin of Mango. Allergy to Mango as a result of cross-reactivity to Latex has been frequently described (17). The frequency of reported adverse reactions to Mango resulting in symptoms of food allergy in sensitised individuals may be underestimated because of the infrequent consumption of this fruit in the Northern Hemisphere. With wider consumption of Mango, an increased frequency of reported adverse reactions is likely.

Oral Allergy Syndrome is a set of reactions to Mango ingestion (4). Among the symptoms reported in individual cases are urticaria, facial swelling, angioedema, pruritis of the eyes and/or mouth, more-generalised pruritis, abdominal cramping, erythema, and dermatitis (23-24). Respiratory complaints include wheezing, dyspnoea, and asthma (17,24).

A 42-year-old woman presented with systemic contact dermatitis (itchy palpable purpuric lesions over her arms, legs, neck and abdomen) 4 days after ingestion of a small amount of fresh Mango gelato. The lesions persisted for 5 weeks despite treatment with topical steroids and avoidance of Mango. The patient denied any prior contact with Mango skin but had experienced previous sensitising reactions to Mango flesh. Patch testing was strongly positive to Mango skin and Mango flesh. Skin-prick testing was negative (25).

Anaphylaxis after eating Mango has long since been described (26-28). A 32-year-old fruiterer presented with periorbital oedema, facial erythema, widespread urticaria, and dyspnoea 20 minutes after eating a fresh Mango. This was the first time he had eaten Mango; he had handled Mango only once before. SPT was positive, but no IgE antibodies were found (29).

A 43-year-old woman experienced oropharyngeal itching, swelling of the face and other parts of the body, and difficulty breathing within a few minutes of eating ripe Mango. The woman had no history of pollen or Latex allergy. However, she reported instances of milder food-allergic reactions to Indian dill and Cashew apple. Skin prick tests were positive to Mango fruit pulp, Indian dill, and Cashew apple extracts. A Mango-specific IgE antibody test was positive (28).

Nine patients with Mango allergy were reported (20). Mango allergy was reported in a Latex-sensitised 45-year-old nurse. She had been diagnosed with Latex allergy 3 years before and had occasionally eaten Mango for the 2 years before this episode. She suffered oral allergy syndrome, rhinoconjunctivitis, cough and dyspnoea immediately following ingestion of Mango. SPT and IgE antibody test were positive. Although cross-reactivity

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between Mango and Latex has been described, in this instance it could not be confirmed (4).

In a French study conducted over a period of 9 years (1984-1992), a group of 580 patients was analysed who had pathological reactions to foods, in 60 cases presenting with severe, near-fatal reactions. Researchers sought the causes of the food sensitisation and considered them in relation to the main tendencies of food consumption in France. The food products most frequently incriminated in anaphylactic reactions were found not to be of primary nutritional importance: Celery (30%), crustaceans (17%), fish (13%), Peanuts (12%), Mango (6%), and Mustard (3%); but these are often hidden allergens in commercial foods (30).

Of 132 children aged 3-19 years, 58% reported food-allergic reactions during the previous 2 years. The offending food was identified in 34 of 41 reactions, Cow's milk being the causative food in 11 (32%); Peanut in 10 (29%); Hen's egg in 6 (18%); tree nuts in 2 (6%); and Soy, Wheat, Celery, Mango or Garlic in 1 (3%) each (31).

Three patients were found to be allergic to Mango and Pistachio nut. Among them, a 28-year-old woman developed a burning sensation in her mouth, swelling of the lips, face and tongue, nausea and abdominal cramps immediately after eating a peeled Mango. A 28-year-old man experienced episodes of vomiting immediately after eating Mango. All 3 were skin prick test-positive to fresh Mango but not to Mango extracts (32).

A 36-year-old woman with allergic rhinitis, who had previously experienced urticaria and angioedema immediately after the ingestion of Sunflower seed, reported an immediate onset of urticaria and angioedema after the ingestion of Mango. She tolerated Pistachio and Cashew nut without any problem. Prick by prick to Mango, Pistachio nut, Cashew nut and Sunflower seeds were positive. The results of IgE antibody tests for Mango, Sunflower seed, Bet v1 and Bet v2 were ImmunoCAP class 0; ImmunoCAP class 2 for Pistachio nut and Cashew nut; and ImmunoCAP class 4 for *Artemisia* and Sunflower pollen. Inhibition studies demonstrated significant inhibition

of Pistachio and Cashew nut by *Artemisia* pollen. *Artemisia* pollen was inhibited only by *Helianthus* pollen (33).

A 22-year-old white female student presented with a 2-day history of patchy pruritic erythema of the face, neck, and arms, with periorbital oedema. The eruption began as an isolated patch of nasal erythema, with subsequent extension to involve the entire face. Within 2 days, fine pinpoint papules were noted on the face, anterior chest, neck, and upper extremities. Periorbital oedema was present without intraoral abnormalities or laryngeal changes. An erythematous, mildly lichenified plaque was noted on the ventral left wrist. She reported frequent ingestion of peeled Mango. Mango skin and Mango flesh were evaluated in patch tests and resulted in bullous reactions to both. Complete avoidance of Mango led to resolution of the initial eruption (35).

Other reactions

Contact dermatitis has been reported (34-35), as well as contact dermatitis of the face and lips (36). Mango dermatitis is sometimes limited to vesicles at the angles of the mouth, but it usually affects the entire periorbital region and may affect the buccal mucosa. The hands can carry the allergen to the eyes and neck. Eruptions may become generalised (1).

Sensitisation may occur to Mango pollen (37) and to Mango seed (19).

Some patients complain of abdominal distension and excessive flatus after ingesting certain fruits, such as Mango; this could be a result of fructose intolerance (38).

The leaves, stems and pericarp of the fruit of the Mango plant contain several substances thought to be sensitizers, such as cardol, uroshiol, beta-pinene and limonene. Beta-pinene and limonene are known to cause allergic contact dermatitis mediated by a type IV delayed hypersensitivity mechanism (29,39). Urushiol can also cause such dermatitis. Other species belonging to the family of *Anacardiaceae*, such as poison ivy, contain urushiols as well (see Cashew nut f202) and may cause allergic contact dermatitis (40). Acute allergic contact dermatitis can arise

on first exposure to Mango in patients who have been sensitised beforehand by contact with other urushiol-containing plants, e.g., poison oak or poison ivy. A study described 17 American patients employed in Mango picking at a summer camp in Israel, who developed a rash of varying severity. All the patients had been in contact with poison ivy/oak in the past or had lived in areas where these plants are endemic. None recalled previous contact with Mango. In contrast, none of their Israeli companions, who had never been exposed to poison ivy/oak, developed Mango dermatitis. The authors hypothesised that previous oral exposure to urushiol in the local Israeli population might have established immune tolerance to these plants (41).

Hawaiian locals were found to be able to tolerate the sap, whereas visitors were prone to developing contact dermatitis (42-43).

Asthma and allergic rhinitis from Mango tree pollen have been reported (44).

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Cucumis melo* spp.*Family:** *Cucurbitaceae***Common names:** Melon, Common melon, Muskmelon, Armenian cucumber (see also under Geographical distribution)**Source material:** Fresh fruit**For continuous updates:**
www.immunocapinvitrosight.com**Allergen Exposure****Geographical distribution**

Melons are probably native to Asia, though they have been in cultivation for so long that their original habitat is obscure.

Melons are warm-season vine plants belonging to the gourd family. Melon has been developed into many cultivars, including smooth skinned varieties, with fruit (gourd-like, but with sweet, very watery flesh) of many shapes, sizes and colours, *e.g.*, Honeydew melon, Muskmelon, Winter melon, and various “netted” cultivars known as Cantaloupe.

Among *Cucurbitaceae*, *C. melo* comprises very important cultivars. They are grown primarily for their fruit, which generally has a sweet, aromatic flavour; they have great diversity of size (50 g to 15 kg), of flesh colour (orange, green, white, and pink), of rind colour (green, yellow, white, orange, red, and gray), of form (round, flat, and elongated), and of dimension (4 to 200 cm). *C. melo* can be broken down into 7 distinct types based on these discussed variations in the species. The Melon fruits can be either climacteric or non-climacteric, so that the fruit can adhere to the stem or have an abscission layer and fall from the plant naturally at maturity (1).

Melon is an accessory fruit of a type that botanists call an epigynous berry. It is produced by an annual climbing or trailing herb with a fibrous root and grey-green, angular stems that have stiff, bristly spreading hairs, mainly on the ridges. The fruit is ellipsoid in shape and is attached by a stout 8-11 mm long stalk.

**Environment**

Melons are generally a dessert fruit, eaten raw in slices or cubes or serving as an ingredient in cold desserts like sorbet. Their delicate flavour and high water content make them poor candidates for cooking and preserving. Their availability tends to be seasonal, but more-sophisticated transport is changing this in many locales.

An edible oil is obtained from the seed, but since the oil is difficult to extract, it is in infrequent use.

The fruit can be used as a cooling light cleanser or moisturiser for the skin.

The fruit is used in a variety of homeopathic remedies, including as a first-aid treatment for burns and abrasions.

Allergens

Several IgE-binding proteins, ranging between 13 and 60 kDa, have been detected in Melon extract by means of pooled sera from patients with Melon allergy. A 13 kDa allergen was the main reactive protein band detected and was identified as a profilin (2).

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The following allergens have been characterised:

Cuc m 1, also known as cucumisin, a plant serine protease (3-5).

Cuc m 2, a 13 kDa protein, a profilin (1-2,6-9).

Cuc m 3, a 16 kDa protein, a PR 1 protein (2,10).

A lipid transfer protein has also been detected (11). It is highly resistant to pepsin digestion and is heat-stable, making it a potentially potent allergen.

In a study of Melon profilin, sera from 71% of 21 patients with oral allergy syndrome after Melon ingestion recognised Melon profilin. This profilin was shown to be highly digestible in gastric juice (1). In a study of 23 Melon-allergic patients, IgE antibodies to natural Melon profilin (nCuc m 2) and its recombinant counterpart (rCuc m 2) were found in 100% and 78% of the 23 individual sera analysed, respectively. In *in vivo* tests of 10 patients, nCuc m 2 resulted in a positive skin prick test in all (10/10) patients tested. Simulated gastric fluid readily inactivated rCuc m 2, but heat treatment did not affect the IgE-binding capacity of rCuc m 2 (7).

Cuc m 3 is a minor allergen. Cuc m 3 bound IgE from 12 of 17 sera from Melon-allergic patients and inhibited approximately 40% and 70% of the IgE binding to Melon pulp and juice extract, respectively. Positive skin prick test responses to purified Cuc m 3 were demonstrated in 2 of 14 allergic patients. The allergen accumulates mainly in the juice of the central part of Melon, where Cuc m 1 is also located (9).

Chitin oligosaccharides have been shown to elicit chitinase activity in Melon plants within 6 hours after treatment, with maximal levels at 12-24 hours. Chitinase induction was both local and systemic (12). Whether this chitinase has allergenic potential was not evaluated.

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the *Cucurbitaceae* (gourd) family could be expected. The family includes Melon, Watermelon, squashes and

Pumpkin (13). Cross-reactivity has been demonstrated *in vitro*: 13 kDa proteins of Zucchini, Cucumber, and Watermelon extracts were strongly recognised by the IgE antibodies of patients with Melon allergy. These proteins were identified as profilins (1).

Profilins are highly cross-reactive allergens, which bind IgE antibodies of almost 20% of plant-allergic patients. Cross-reactivity of Melon profilin with other plant profilins was evaluated utilising 17 patients with Melon allergy attested by clinical history and a positive skin prick test. Amino acid sequence analysis of Melon profilin alongside other profilins showed the most identity with Watermelon profilin, and substantial cross-reactivity with profilin from Tomato, Peach and Grape, and with profilin from the pollen of Bermuda grass. Serum IgE reacted only with Melon profilin. The study concluded that IgE reactivity to Melon profilin strongly depended on the highly conserved conformational structure, rather than on a high degree of amino acid sequence identity or even linear epitope identity (6).

Hypersensitivity to the Birch tree profilin Bet v 2 has been strongly associated with clinical allergy to Melon or Watermelon. A history of allergy to gourd fruits, citrus fruits, Tomato, Banana, or a combination of these is a sensitive means to detect profilin-hypersensitive patients, predictive in 85% (41/48). The authors suggested that in clinical settings in which laboratory investigations are not easily accessible, allergy to Melon, Watermelon, citrus fruits, Tomato, and Banana could be used as a marker of profilin hypersensitivity once a sensitisation to Natural rubber latex and lipid transfer protein is ruled out (14).

A study evaluated sensitisation to profilin in patients in central Portugal suffering from respiratory allergy who were sensitised to pollens. A total of 370 patients were evaluated; 65.9% showed positive skin prick tests, and 76.2% were positive to pollens. All the patients sensitised to pollens had rhinitis. Four profilin- and pollen-sensitised patients experienced oral allergy syndrome with Melon (15). Other studies have reported the relevance of profilin in Melon allergy and OAS (16).

Cuc m 3, a minor component of Melon juice, was shown to have a greater than 60% sequence identity with PR-1 proteins from Grape and Cucumber (9).

As a lipid transfer protein allergen is present in Melon, cross-reactivity with other fruits and vegetables containing this allergen is possible (10).

In an evaluation of the clinical characteristics of Melon allergy in 66 Melon-allergic patients, 48% self-reported allergy to Fig. Skin reactivity was most frequently demonstrated to, after pollen, Peach, Fig, and Kiwi. About 82% of patients were shown to have skin reactivity to Fig (17).

An association between grass pollinosis and sensitisation to Tomato, Potato, Pea, Peanut, Watermelon, Melon, Apple, Orange and Kiwi has also been reported (18), as well as among Watermelon, Melon and Ragweed (19-20). A number of patients with allergy to Birch, grass, and Mugwort pollen have been reported to be allergic to Melon (21); another study connected Birch-allergic patients with Melon allergy (22). The common allergen was not isolated. Furthermore, in 3 patients with confirmed allergy to Melon, analysis revealed that several distinct protein bands were shared by Melon with *Plantago* and *Dactylis* pollen. All allergens of Melon blotting were almost completely inhibited by grass and *Plantago* pollen extracts, giving evidence of the presence of structurally similar allergens in Melon (23-24).

Although allergy to plant-derived fresh food has usually been reported in geographical areas where Birch or Ragweed pollens are common and has been attributed to cross-reactivity to pollens, in a study that evaluated plant-derived fresh foods' effects on pollen-allergic patients from a Birch and Ragweed-free area, it was demonstrated that, among 95 pollen-allergic patients, 35 had positive SPT to some plant-derived fresh foods, the most frequent being to Peach and Pear (26.3%), followed by Melon (13.7%) (25).

An association between sensitisation to Olive tree (*Olea europaea*) pollen and plant-derived food allergy has also been demonstrated. In 134 patients with allergy to Olive pollen, 40 reported adverse reactions

to plant-derived food. Twenty-one (group A) reported symptoms of oral allergy syndrome, and 19 (group B) anaphylaxis. With SPT, reactivity to Ole e 7 was more frequent in patients from group B. Oral challenges confirmed the association with Melon allergy (26).

Among Japanese patients with allergic rhinitis to Japanese cedar tree, 45 patients (9.7%) out of 463 were diagnosed with oral allergy syndrome (OAS). The foods that most often provoked a reaction were, in order of frequency, Melon, Kiwi, Crab and Shrimp. The prevalence of OAS was higher in patients with Japanese cedar allergic rhinitis than without Japanese cedar allergic rhinitis. A higher prevalence of OAS was also found in House dust mite antibody-positive patients than in House dust mite antibody-negative patients (27).

An association of Latex-allergic individuals with fruit allergy has been reported by a number of studies. Fruits often associated include Melon, Peach, and Banana (28). Importantly, fruit-specific IgE antibodies may not always be detected, regardless of clinical allergy to the fruit (29).

Clinical Experience

IgE-mediated reactions

Melon may commonly induce symptoms of food allergy in sensitised individuals (9,19,22,30-31), in particular in Latex-allergic individuals (25).

Melon has been reported to be a frequent allergy-eliciting fruit in some areas in the United States (17), and the second-most-frequent allergy-eliciting fruit in Spain (22), where fruit allergy is the most important food allergy in adult patients (14,32-33).

The allergic reactions are usually immediate. Oral allergy syndrome is the most common manifestation of allergy to Melon, but urticaria, and gastrointestinal symptoms, including nausea, vomiting and diarrhoea, have been reported. Dermatitis, angioedema and anaphylaxis are possible. Melon allergy is commonly associated with oral allergy syndrome (OAS) and with hypersensitivity to

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pollens and other plant foods, as a result of the presence of profilin, a panallergen (7,15).

The most common clinical feature of Melon allergy is oral allergy syndrome (OAS) (1,7,10,34-37). OAS associated with the onset of immediate laryngeal oedema after the ingestion of Melon has been reported. In this instance, treatment with pollen-specific injection immunotherapy was successful (38). A Japanese study of 16 cases of childhood OAS concluded that childhood OAS does not always accompany pollen allergy, and that the most frequent allergen was Kiwi fruit, followed by Tomato, Orange and Melon (39). In a Japanese review of 63 patients with OAS aged 2 to 61 who were evaluated over 6 years, the most frequent causative foods were found to be Apple, Peach, Kiwi, and Melon, affecting 13, 12, 12, and 11 patients, respectively (40).

In a Spanish study of Melon allergy, 161 patients were included: 66 with Melon allergy and 95 in the pollen-allergic control group. Patients were aged between 5 and 61 years. Although all patients of the Melon allergy group had oral symptoms, 13 (19.7%) had extra-oral symptoms, but none experienced generalised urticaria or anaphylaxis. Five patients (7.6%) reported gastrointestinal symptoms, 3 patients (4.5%) reported conjunctivitis, 3 patients (4.5%) reported contact urticaria, 1 patient (1.5%) reported rhinitis, and 1 patient (1.5%) reported contact urticaria and conjunctivitis. Oral symptoms preceded extra-oral symptoms. A total of 22 patients (33%) had rhinoconjunctivitis, and 44 (67%) had rhinoconjunctivitis and asthma. Skin prick-prick tests with fresh Melon pulp were positive in all patients in the Melon allergy group. Skin testing with 3 commercially available Melon extracts resulted in positive skin tests in 12%, 17% and 90%, the outcome being dependant on the commercial extract. Up to 13.7% of pollen-allergic patients had a positive skin prick-prick test result to fresh Melon pulp; however, only 7.4% of the patients in the pollen allergy group had Melon allergy, a judgment based on positive results on the skin test and an oral challenge test. The fruits most frequently self-reported by the Melon-allergic patients to elicit symptoms were Peach (62% of patients), Fig

(48%) and Kiwi (42%). Forty-seven percent of patients reported symptoms caused by some nuts, with Walnut (35%) and Hazelnut (18%) most frequently implicated. Excluding other *Cucurbitaceae* fruits, Peach, Fig, and Kiwi most frequently elicited positive skin test results and symptoms. Up to 23% of Melon-allergic patients had a concomitant Latex sensitisation. Melon allergy was especially strongly linked to pollen allergy, since all the Melon-allergic patients were also allergic to pollen (14).

In many cases, Melon allergy cannot be detected by SPT or IgE antibodies. In 53 consecutive adult patients complaining of adverse reactions to Melon, actual clinical reactivity was confirmed in 19 (36%), using DBPCFC. The most frequent symptom was oral allergy syndrome (in 14), but 2 patients experienced life-threatening reactions, including respiratory symptoms and hypotension. The positive predictive value for SPT was 42%, and for IgE antibody measurement it was 44%. The authors reported that isolated Melon allergy is rare, with most patients having either allergic rhinitis, asthma, or both, or associated food allergies (41). The detection of IgE antibodies may also not be clinically relevant (42).

Anaphylaxis following ingestion of Melon has been reported (43-44).

Occupational protein contact dermatitis due to Melon has been described (45).

Other reactions

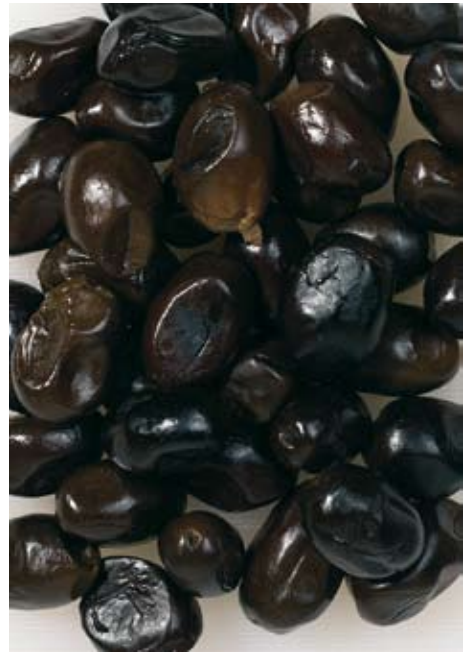
A study reports on a 24-year-old woman with ethanol-induced anaphylaxis who developed anaphylaxis following ingestion of overripe Rock melon (*Cucumis melo*). The accumulation of endogenous ethanol in overripe fruit may occur (46).

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Olea europaea**Family:** *Oleaceae***Common name:** Olive**Source material:** Fresh fruit (black)**See also:** Olive tree t9 for allergy to Olive tree pollen**For continuous updates:**www.immunocapinvitrosight.com**Allergen Exposure****Geographical distribution**

Olive is a small, large-pitted, firm fruit of the evergreen *Olea Europaea*, probably the first tree to be cultivated by man. Oil from the fruit had been produced by 3000 BC.

All Olives need to be processed, and this involves removing the bitterness, since fresh from the tree they are completely unpalatable. Methods abound, creating a large variety of Olive products. Processing also enhances the keeping qualities. If processed correctly, the brine should have a balance of salt and acid that preserves the fruit for years if the container is unopened and left at room temperature (a white film may develop on the surface of brine, but it is harmless).

There are plenty of Olive types, which include Manzanilla, Gordal Sevillana, Uova di Piccione, Ascolano Tenera, Mission, Kalamata and SA Leccinouse.

Environment

Olives are very versatile. They are eaten as snacks and in dishes, baked in bread, used in salads and on pizza, and so on. Olive oil has been a staple of the Mediterranean diet since ancient times, and is still a very common ingredient in several Mediterranean cuisines. It is used both as a cooking oil and a flavourant

Allergens

Although 9 allergens have been characterised in Olive tree pollen, no allergens from the fruit of this plant have yet been characterised.

A thaumatin-like protein has been detected (1).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected but in fact does not occur frequently (2).

Clinical Experience**IgE-mediated reactions**

Although Olive pollen may commonly induce symptoms of allergy (hayfever and asthma) in sensitised individuals (see Olive tree t9), the Olive fruit only uncommonly induces symptoms of food allergy in sensitised individuals (3-4).

IgE-mediated food allergy following ingestion of Olive was described in a 19-

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year-old woman who had a 4-year history of episodes of facial, neck, and hand angioedema, and intense itch of the palms. In one of the episodes, the angioedema affected the tongue too, and the itch was generalised. Symptoms abated in 24 hours. On each occasion, the patient had ingested Olive 15 to 30 minutes beforehand. The onset of symptoms was not related to exercise. She tolerated Olive oil and did not experience rhinitis or asthma during the pollen season. Prick-by-prick tests with 3 different types of Olive were positive. IgE antibody level of Olive was 1.7 kU_A/l, and 0.73 kU_A/l for Olive tree pollen (3).

Contact urticaria to Olive was described in a 22-year-old woman who presented with a 2.5-year history of hand dermatitis, which had started while she was working as a pizza chef. She gave a further history of perioral itching and lip swelling after consuming Olive, with the severity dependent on the type of Olive (which was, however, undetermined). Skin prick test with Olive resulted in a flare but no wheal reaction. The authors suggested that while a flare reaction is not normally considered positive, in view of the definite history and the weak positive control, the reaction was considered relevant. The patient declined repeat testing with a variety of other Olive types (5).

Olive oil, produced from Olive fruit, has been more frequently reported to result in adverse effects in sensitised individuals than has Olive fruit.

An early study reported that 13 cases of contact allergy to Olive oil were documented, but that known components of Olive oil could not be proven to be the cause of the allergy (6).

Other reports have contained similar findings: Olive oil can be a non-allergic skin irritant, but in 1 patient, the reaction could be classified as probably allergic. Among 77 female and 23 male eczema patients prospectively patch-tested with freshly prepared Olive oil, in only 1 patient could the reaction be classified as probably allergic (7).

Jung reports on a 43-year-old female who developed increasing eczematous reactions to Olive oil. She developed these reactions after treatment of her leg with a boric acid/zinc oxide preparation in an oil vehicle (8).

Twenty cases of contact allergy to Olive oil were described, and 3 of these involved occupational hand eczema as a result of exposure to Olive oil. Researchers describe a masseur who was allergic to Olive oil, resulting in occupational hand eczema. Patch tests were positive. The oral provocation test was negative (9).

Airway disease has been described in an Olive oil mill worker. A 41-year-old Spanish man working in an Olive oil mill reported a 2-year history of episodic rhinitis, shortness of breath, chest tightness, and wheezing. Symptoms occurred within 30 minutes after he arrived at the workplace and partially improved immediately after he left it. A skin prick test with Olive pulp extract was positive. The patient's serum demonstrated reactivity against a 23 kDa protein band in Olive fruit protein extract, and the band showed homology to allergenic thaumatin-like proteins (TLPs) from plant foods and pollen. A nasal challenge test with purified TLP was positive, with nasal obstruction, sneezing, and runny nose (1).

Other compounds present or forming in Olive oil may be responsible for the allergy-like reactions reported. Olive oil may contain lipid peroxidases, which can be inducers of irritant skin reactions. This is because unsaturated lipids in Olive oil are susceptible to oxidation by oxygen in the air. Furthermore, Olive oil may be contaminated with benzene or benzene derivatives such as toluene and C2 benzenes (10). Pesticides may be present, depending on the harvest time. Polychlorinated dibenzo-p-dioxins, as residues in Olive oil, can cause a variety of skin disorders (11).

Other reactions

See under IgE-mediated reactions.

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Allergen Exposure

Geographical distribution

Only a few members of this large family are important as food plants, notably Onion, Garlic, chive, leek, and rakkyo. Onion is known only in cultivation, although related wild species occur in Central Asia. References to Onions date back 3,000 years, and they were probably among the earliest cultivated vegetables. They are the most important of the bulb crops. They are in use worldwide, but are best grown in Mediterranean climates.

Most Onions are grown only for the mature edible bulbs, but there are some cultivars, the Spring or Green onions, or Scallions, that are eaten immature, along with the leaves. The Dry onions are mature Onions with a juicy flesh covered with dry, papery skin. There are 2 categories of Dry onions: Storage onions and Sweet onions. Storage onions are low in water and high in sulphur, so they store well and are available year-round. Sweet onions are usually available only in spring and summer. Storage onions are more pungent and flavourful than Sweet onions.

Environment

Edible Onions are not known in the wild, but are grown only in cultivated beds. The bulb can be eaten raw in salads, sandwich fillings, *etc.*, or cooked or preserved in a variety of

Allium cepa

Family: *Alliaceae (Liliaceae)*

Common names: Onion, Garden Onion, Shallot

Source material: Freeze-dried onion

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ways. Fresh, dried, pickled, canned or even frozen, it is the most common flavouring in many cuisines. The leaves, flowers and sprouted seeds are also eaten.

Onion is used as a homeopathic remedy for a variety of conditions. Onion juice rubbed into the skin is said to be a remedy for baldness. The growing plant is said to repel insects and moles and can therefore be rubbed onto the skin.

Unexpected exposure

The plant juice can be used as a rust preventative on metals and as a polish for copper and glass. A yellow-brown dye is obtained from the skins.

Allergens

A 12 kDa protein band to young Garlic, mature Garlic, Onion, and leek extracts has been detected in a Garlic-allergic individual. Similar bands could also be detected with Mugwort pollen and Hazelnut extract (1).

A heat-labile allergen has been detected (2).

The following allergens have been characterised:

All c 3, a 12 kDa lipid transfer protein (3).

All c 4, a profilin (4).

All c alliin lyase (5).

Diallyl disulphide is a major allergen in Garlic and Onion, causing contact dermatitis. Diallyl disulphide penetrates most commercially available glove types, and therefore patients with Onion contact dermatitis may not be protected by most commercially available gloves (6).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected, as well as to a certain degree among members of the family *Alliaceae* (previously categorised as *Liliaceae*), including Onion, Leek, Garlic, Asparagus, and Chives, but the level of cross-reactivity varies among individuals (7-8).

Onion contains a lipid transfer protein (LTP), All c 3, which may result in cross-reactivity with other lipid transfer protein-containing foods. The LTP has been detected to young Garlic, mature Garlic, Onion, and Leek extracts, and was similar to that detected in Mugwort pollen and Hazelnut extract (1). In a study examining the relationship between Peach LTP-specific IgE levels and cross-reactivity to several non-*Rosaceae* plant-derived foods, increasing levels of IgE to Peach LTP were associated with skin reactivity to nuts (72%), Peanut (67%), Maize (41%), Rice (36%), Onion (35%), Orange (28%), Celery (27%), and Tomato (20%) (9).

Onion contains a profilin, All c 4, which may result in cross-reactivity with other profilin-containing plants (4). However, the clinical significance of this has not been elucidated to date.

Garlic alliin lyase showed strong cross-reactivity with alliin lyases from other *Allium* species, namely Leek and Onion (5).

The presence of structurally similar allergens in Garlic, Onion, and certain pollens of *Phleum* and *Chenopodium* has been described. There was partial abolishment of the IgE binding to several of these allergens (10). The clinical significance of this is not yet known.

Clinical Experience

IgE-mediated reactions

Onion can induce symptoms of food allergy, asthma, rhinoconjunctivitis, and contact dermatitis in sensitised individuals (2-3,11-16). Onion is one of the commonest causes of contact dermatitis of the hands (17-18).

In a European study of 589 individuals with a history of food allergy, skin reactivity to *Alliaceae* (Garlic, Onion, Chive) was documented in 4.6% of children and 7.7% of adults (19). A study was conducted at 17 clinics in 15 European cities to describe the differences among some Northern countries regarding what foods, according to the patients, elicit hypersensitivity symptoms. It was found that Onion was the 56th most frequently reported food, and responsible for symptoms in 8.2% of 1,139 participants (20). In an Indian study of 24 children aged 3 to 15 years with documented deterioration in control of their perennial asthma, IgE antibodies for Onion were detected in 6 (25%) (21).

A number of case reports illustrate the range of clinical effects experienced with Onion.

A 19-year-old atopic woman who experienced urticaria after ingestion of raw Onions was described. She had suffered with rhinoconjunctivitis and contact urticaria to Mugwort for the previous 2 years, and she described the subsequent onset of oral pruritus after ingestion of raw Onion and Peach peel. Skin prick tests were positive for, among other allergens, Mugwort, Onion, and Peach. IgE antibody tests were positive to Onion (5.41 kU_A/l), Peach (18 kU_A/l), Mugwort (0.86 kU_A/l), and Pru p 3 (23.07 kU_A/l). IgE immunoblotting of Onion extract revealed only a 12-kDa IgE-binding protein band, identified as a lipid transfer protein. The authors pointed out that, while the clinical history suggested Mugwort LTP as the primary sensitising agent, laboratory results indicated that Mugwort pollen allergy was independent of Onion and Peach food allergy (3).

A 45-year-old man reported at least 5 episodes, over several years, of severe, systemic urticaria/angioedema some minutes after eating raw Onion. He tolerated cooked Onion as well as other fruits and vegetables, except for Peach, which he had avoided since childhood because of the oral allergy syndrome and gastric pain it induced. Skin prick tests were positive to, among other allergens, commercial extracts of Garlic and Onion, and Peach peel extract. The patient's serum strongly reacted against both Peach LTP and Onion extract. Analysis showed the patient's

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IgE was reactive to both a single band at approximately 15 kDa and to a double band at approximately 43 kDa in Onion extract. The former was shown to be an LTP. However, IgE reactivity to Onion proteins at other molecular weights was also demonstrated. As none of more than 50 patients hypersensitive to LTP reported Onion allergy, it was suggested that the 43 kDa band might have been the relevant allergen (13,22).

A study describes a number of patients with asthma, rhinoconjunctivitis, and/or contact dermatitis caused by Onion, illustrating the range of symptoms and clinical patterns of Onion allergy. Patient 1, a 45-year-old homemaker who for years had experienced episodes of rhinoconjunctivitis, dyspnoea, and coughing when chopping Onion went on to develop eczematous dermatitis, occurring mainly on the fingertips and exacerbated when she was chopping Onion. Patient 2, a 37-year-old female with rhinoconjunctivitis and asthma induced by pollen allergy, had for 15 years noticed intense rhinoconjunctival symptoms and slight dyspnoea when chopping Onion. Patients 3 and 4 were revealed when skin prick tests were performed on 106 randomly selected clinic patients, of whom 39 were atopic. Skin prick tests for Onion were positive in 8 (7.5%), of which all were sensitive to grass pollen. Patient 3, a 31-year-old man, and Patient 4, a 38-year-old female, had intense rhinoconjunctivitis, and 1 of the 2 also experienced chest tightness, wheezing, and dyspnoea after being exposed to the aerosols from Onion. All 4 patients were positive on skin prick testing with fresh Onion, Garlic, fried Onion, and leek. All were also positive to heated and non-heated Onion extract. Patients 2, 3, and 4 also had a positive skin test reaction to grass pollen. None of the 4 patients experienced a delayed skin reaction. Bronchial provocation tests with Onion extract in Patient 1 resulted in an immediate asthmatic response, and in Patient 3 at 10 minutes after challenge. Patients 2 and 4 were not challenged. A nasal provocation test resulted in an immediate nasal reaction in Patient 3. Double-blind oral provocation tests carried out in patients 1 and 3 were negative (with up to 2 gm of Onion powder). Patch tests done in patient 1 were positive. IgE antibody levels for Onion were positive in 3 patients (Patients 1 [1.4 PRU/ml],

3 [0.7 PRU/ml], and 4 [2.2 PRU/ml]). The authors concluded that the respiratory reactions occurring in Patients 1, 3, and 4 were IgE-mediated and that cell-mediated (type IV) mechanisms were involved in the contact dermatitis in Patient 1. The authors suggested that, since among 106 persons randomly selected for the study, 2 individuals had been found to have clinical Onion allergy, and 6 more were sensitised, Onion allergy was not as uncommon a condition as had been previously thought (11).

A 44-year-old woman experienced, over the last four years, immediate reactions (at least 5-6 episodes) occurring within minutes after eating raw or lightly cooked Onion. The reactions had become increasingly severe with intense itching in the mouth followed by a state of confusion, blurred vision, transient loss of consciousness, profuse sweating, tachycardia and subsequent transient prostration. The last episode had been the most serious, lasting several hours, and with the development of urticaria on the face and the neck. During the last few months she reported intolerance even simply to contact with raw Onion and to inhalation of the steam of Onion during cooking. She tolerated well-cooked Onion. She was shown to be monosensitised to Onion, unlike other cases in the literature. IgE antibody level for Onion was 3.7 kU_A/l. Her IgE antibodies recognised only thermolabile Onion fractions. She was not cross-reactive to other foods from the *Liliaceae* (*Alliaceae*) family (2).

Food-dependent exercise-induced anaphylaxis following the ingestion of Onion has been reported (23-24). A report describes a 26-year-old woman who, in a single year, experienced at least 10 episodes of generalised erythema with itching, urticaria, angioedema of the face, profuse sweating, malaise, chest tightness, wheezing and dyspnoea. Running precipitated the episodes (19).

Onion has also been shown to be a common cause of eosinophilic oesophagitis in adults. In a study of men and women aged 18-57 years, 17 of 21 were polysensitised to several different environmental allergens, and 19 of 23 (82%) had IgE antibodies specific for 1 or more food-associated allergens, with Wheat, Tomato, Carrot, and Onion identified most commonly (25).

The seeds of Onion have been reported as a new occupational allergen. A 27-year-old female developed episodes of rhinoconjunctivitis followed asthma attacks, which she attributed to contact with Red onion seeds (*A. cepa*, Brunswick variety). She had worked for 3 years in packaging of the seeds. Mild symptoms were experienced on contact with Onion seed other than Red onion seed. Handling of other seeds, including those of other members of the *Liliaceae* family (Asparagus, Leek) did not elicit symptoms. She was able to touch and eat raw and cooked Onion without experiencing symptoms. IgE antibody test to Onion was negative. Three different forms of Red onion extracts were created; skin prick tests with Red onion extract 3 and Italian and White Onion seed extracts were positive, and greater with the violet variety. Skin prick test with Red onion extract 1, Leek, Asparagus, and other non-*Liliaceae* seed extracts, and common aeroallergens, were negative. A bronchoprovocation test was positive (26).

Other reactions

When Onion tissue is damaged, an enzyme reaction releases sulphur-containing volatile compounds, which give Onion its characteristic flavour and lacrimatory properties. This special characteristic of the Onion, causing tearing and rhinorrhea in persons who slice it, is due to thiopropanal-s-oxide, a sulfur compound with irritative characteristics, which is released when the Onion is cut (27).

Onions are high in indigestible carbohydrates that may contribute to flatus. Onions are also rich in etheric oils and other irritants. There have been cases of poisoning caused by the consumption, in large quantities and by some mammals, of this plant. Dogs seem to be particularly susceptible. Onions can prevent blood clotting, but can trigger migraine in susceptible people.

Contact dermatitis and eczema have occurred in housewives, and in greengrocers, cooks and other food industry workers (28-31). A worker in the spice industry, exposed to Onion and Garlic dust, developed rhinitis. Skin-prick tests were positive for Onion, Garlic powder and other fresh *Liliaceae* (not specified). Presence of IgE antibodies for Garlic and Onion

was demonstrated. Nasal challenge resulted in an increase in inspiratory nasal resistance for both Onion extract and Garlic (32).

The triggering of asthma after eating pickled Onions due to the preservative sulphur dioxide has been reported (33). A female Onion and Potato sorter developed hypersensitivity pneumonitis as a result of exposure to *Penicillium* species and *Fusarium solani* found in the workplace (34).

Onions can be a potent and long-lasting refluxogenic agent in heartburn patients (35).

Maternal intake of Cabbage, Cauliflower, Broccoli, Cow's milk, Onion, and Chocolate were significantly related to colic symptoms in exclusively breast-fed infants (36).

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Citrus sinensis

Family: *Rutaceae*
Common names: Orange, Sweet orange
Source material: Frozen juice
Synonyms: *C. cinensis*,
C. macracantha

Other species:

Citrus aurantium – sour/bitter variety

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**Allergen Exposure****Geographical distribution**

Oranges, with orange-coloured peels and juicy fruit in separable quarter-moon-shaped sections, come from an evergreen tree growing to 9 m tall. Oranges are the most important commercial citrus fruit. They were cultivated over 3,000 years ago in China. They now thrive around the world in warm-climate areas including Portugal, Spain, North Africa and the southern United States (the world's largest producer). Spain and Israel are leaders in Orange exports. The many varieties (Mardarin, Tangerine, Blood orange, etc.) fall under the basic categories of loose-skinned and tight-skinned, and sweet and bitter (the latter not eaten raw and on its own but used as a flavouring in processed foods).

Environment

The fruit is often eaten fresh or raw. The juice is also extracted and sold fresh and as frozen concentrate, or employed as flavouring in jellies, ice cream, etc. The rind serves as flavouring in cakes, marmalade and other sweets. The flowers are cooked as a vegetable or made into a tea. Oranges are high in vitamin C and flavanoids. They contain thiamin, folate, and pectin, which may lower blood cholesterol levels. The fruit, juice and rind are folk remedies for many ailments.

An essential oil from the peel is used as a food flavouring and also in perfumery and

medicines. Some of the plant's more recent applications are as sources of antioxidants and chemical exfoliants in specialised cosmetics.

Allergens

A number of proteins of varying size have been isolated, and a number characterised. Furthermore, a 30-kDa protein, found in Orange tree pollen, Orange fruit and mandarin extract, but absent in Lemon extract, has been identified. This allergen is associated with primary sensitisation to Orange tree pollen as an occupational allergen (1).

The following allergens have been characterised:

Cit s 1, a 24-25 kDa protein, a germin-like glycoprotein, a major, heat-stable protein (2-6).

Cit s 2, a profilin (2-3,5-9).

Cit s 3, a heat-stable lipid transfer protein (2-3,5-6,10).

Cit s IFR, an isoflavone reductase (5,11-12).

Cit s 1 was previously known as Cit s 5;
 Cit s 2 as Cit s 4; and Cit s 3 as Cit s 6.

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Cit s 1 has been isolated from Orange peel and pulp. IgE antibodies to Cit s 1 were detected in 62% of 29 individual sera from Spanish orange-allergic patients, whereas positive skin prick test responses to the purified allergen were obtained in only 10% of such patients (3,6). A major IgE-binding protein band from Orange extract, later identified as Cit s 1 (6), was recognised by all 5 sera from children allergic to Oranges (8). A number of children were also sensitised to the lipid transfer protein now known as Cit s 3.

Cit s 2, a profilin, has been identified as a major Orange allergen. Among 23 Spanish orange-allergic patients, skin reactivity to Cit s 2 was found in 78% and 87% had detected IgE antibodies (7). Researchers have suggested that sensitisation to Orange profilin is associated with underlying pollen allergy (mainly to grass and Olive pollen), and an oral allergy syndrome is the principal clinical manifestation (3).

In a study of 56 subjects with self-reported reactions to Orange, 23 were Orange-allergic, expressing mainly oral allergy syndrome. Of the 23 subjects, 22 were sensitised to profilin, namely Cit s 2. Of the allergic patients 78% were also sensitised to Cit s 1. Both allergens retained IgE reactivity in heat-processed Orange juice. Interestingly, subjects with and without clinical allergy showed a comparable sensitisation profile. A predominant sensitisation to both allergens in subjects without symptoms also indicated a high frequency of clinically insignificant sensitisation (5).

Cit s 3, a lipid transfer protein, is associated with systemic and severe symptoms. The LTP allergen family is particularly relevant in the Mediterranean area, but shows a very limited effect in Central and Northern Europe (3). Citr 3, a lipid transfer protein in Mandarin and similar to Cit s 3, has been shown to be present in both Mandarin peel and pulp (3).

In a study of 27 Orange-allergic Spanish patients, mainly with oral allergy syndrome, IgE antibodies to purified Orange allergens were found in 54% for nCit l 3, 48% for nCit s 3, 46% for rCit s 3, and 37% for rPru p 3. Positive skin prick test responses were obtained in 7 out of 26 patients tested for nCit s 3,

3 out of 8 for nCit l 3, and 10 out of 26 for nPru p 3. ELISA inhibition assays showed an equivalent IgE-binding pattern for the natural and recombinant Orange LTPs, as well as IgE cross-reactivity among the purified Orange, Lemon and Peach LTP allergens. The study concluded that members of the LTP allergen family are involved in allergy to Oranges. Both Orange and Lemon allergens show cross-reactivity with the major Peach allergen Pru p 3 (10). A Bet v 6-related allergen, a phenylcoumaran benzylic ether reductase, has been detected in Orange (13).

An early study suggested that the major allergenic components of Orange reside in Orange seeds instead of Orange juice/pulp, and that Orange seed contains highly potent allergens, which may induce symptoms from careless chewing (14). More recently, citrus seed extracts were shown to have protein bands between 9 and 61 kDa, with strong bands at 9, 14, 15, and 27 kDa. The proteins present between 9 and 15 kDa were thought to represent profilin and lipid transfer protein. A 51 kDa protein was thought to represent citrin, with the 22 and 33 kDa proteins representing citrin subunits (15). It is therefore possible that individuals may react to allergens in Orange and/or Orange seed.

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected (16).

The presence of a profilin in Orange, Cit s 2 (a common cause of OAS), may result in cross-reactivity with other foods containing profilin. In a study of 200 consecutive patients with pollen allergy who were subjected to skin prick tests with purified natural Date palm profilin, 30% were positive. All were sensitised to grass pollen, and most of them reacted to Birch, Mugwort, Ragweed and Plantain pollen as well. Thirty-four of 60 (57%) of profilin reactors had food allergy; 21 of these were monosensitised to profilin, 11 were sensitised to both profilin and Bet v 1-homologous protein, 1 to both profilin and LTP, and 1 to all of the 3 allergens. The large majority of profilin-allergic patients reported oral allergy syndrome as the only food-induced symptom and were able to

tolerate the offending foods if they were cooked or otherwise processed. *Rosaceae* foods, tree nuts, Melon and Watermelon, Tomato, Pineapple, Citrus fruit and Banana were the more frequently offending foods. The authors suggested that allergy to Melon, Watermelon, Tomato, Banana, Pineapple and Orange may be considered markers of profilin hypersensitivity (17).

Orange contains a lipid transfer protein, Cit s 3, which may result in cross-reactivity with other lipid transfer protein-containing foods (18). Orange and Lemon lipid transfer proteins have been shown to be cross-reactive with the major Peach allergen Pru p 3 (10) and with other lipid transfer protein-containing foods (19).

A 35 kDa Birch pollen protein, which results in sensitisation in approximately 10-15% of Birch pollen-allergic individuals, has been demonstrated to have cross-reactivity with proteins of comparable size from Litchi, Mango, Banana, Orange, Apple, Pear and Carrot (20). This allergen may be the Birch pollen allergen Bet v 6, which in a later study was found to be a plant defence mechanism protein, named phenylcoumaran benzylic ether reductase (PCBER); it was also found to be present in many foods such as Apple, Peach, Orange, Litchi, Strawberry, Persimmon, Zucchini, and Carrot. The cross-reactivity of this allergen among foods was not thought to correlate with the development of clinical food allergy (21).

An association between grass pollinosis and sensitisation to Tomato, Potato, Green pea, Peanut, Watermelon, Melon, Apple, Orange and Kiwi has been reported (22).

When Peanut allergy coexists with citrus seed allergy, IgE cross-reactivity between Peanut and citrus seed proteins can be demonstrated, suggesting a basis for this cosensitivity (15).

Clinical Experience

IgE-mediated reactions

Orange may induce symptoms of food allergy in sensitised individuals (5,7-8,10,23-28). Earlier studies reported Orange to be

among the top 10 food allergens resulting in adverse effects in children (25). Symptoms reported included nausea, pruritis, abdominal cramping, abdominal pain, vomiting, diarrhoea, oral itching, angioedema, dyspnoea, bronchospasm, rhinitis, laryngeal oedema, urticaria, hypotension, and anaphylaxis. Oral allergy syndrome (OAS) is a common symptom (5,10,29-30); the last of these studies concluded that childhood OAS may have different mechanisms from adulthood OAS, which almost always accompanies with pollinosis or Latex allergy (29). Orange may also contribute to multifood allergy, such as reported in a 4-year-old child (31-32). Sensitisation to Orange has also been reported to occur in the elderly, as reported in a study examining the prevalence and risk factors for sensitisations in 109 people with a mean age of 77 living in a geriatric nursing home. IgE antibodies to Orange were detected in 5 of 109 (33).

A study was conducted at 17 clinics in 15 European cities to evaluate the differences among some Northern countries regarding what foods, according to the patients, elicit hypersensitivity symptoms. According to questionnaires administered to food-allergic individuals concerning 86 different foods, the foods that were most often elicited symptoms in Russia, Estonia, and Lithuania were citrus fruits, chocolate, honey, Apple, Hazelnut, Strawberry, Fish, Tomato, Hen's egg, and Cow's milk, a situation that differed from that of Sweden and Denmark, where Birch pollen-related foods such as nuts, Apple, Pear, Kiwi, stone fruits, and Carrot were the most common reported causes. The most common symptoms reported were oral allergy syndrome and urticaria. Birch pollen-related foods dominated as reported culprits in Scandinavia, whereas some Mugwort-related foods were of more importance in Russia and the Baltic States. Among 1,139 individuals, Orange was the 3rd most often reported food, resulting in adverse effects in 36% (34).

Approximately 3% of children aged 3 years were reported to be allergic to citrus fruit (35). In a study of 1,419 patients aged 1 year to 18, fish, Cow's milk, seafood, Soy, beans, Orange, Onion, Tomato, Chicken, nuts, Lettuce and Strawberry were responsible

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for 58% of the total allergic reactions. Fish, Cow's milk, seafood, Soy and Orange had the highest frequency (39%) (36). An early study also reported Orange to be a common allergenic fruit in China, inducing severe food allergy in sensitive individuals. Among 26 Orange-sensitive patients, intradermal testing with extracts of Orange juice and seeds was performed in 16. The authors suggested that the major allergenic components of Orange reside in Orange seed and not Orange juice. Systemic reactions developed in 5 patients after intradermal tests with Orange seed extracts. The authors conclude that Orange seed contains highly potent allergens which may induce Orange sensitivity due to careless chewing (14).

In an Indian study of 24 children with documented deterioration in control of their perennial asthma, IgE antibodies against Orange were determined in 17% of the group (37).

In a study of 27 Orange-allergic Spanish patients, mainly with oral allergy syndrome, approximately 50% were sensitised to a lipid transfer protein (10). In a European study of 56 subjects with self-reported reactions to Orange, 23 were classified as Orange-allergic, experiencing mainly oral allergy syndrome. Of 23 subjects classified as Orange-allergic, 22 were sensitised to profilin. The authors suggested that a high frequency of clinically insignificant sensitisation may occur in the population (5).

However, other symptoms have been reported, as illustrated by a study of 29 Orange-allergic patients, aged 6 months to 29 years, mainly with symptoms of OAS, but also with eyelid oedema, sneezing, epigastralgia, vomiting, generalised urticaria, throat swelling, atopic dermatitis and chest tightness. IgE antibodies to Cit s 1 were detected in 62% of 29 individual sera from these patients, whereas positive skin prick tests to the purified allergen were obtained in only 10% of the patients. The authors suggested that false positive diagnosis could occur if the diagnosis of allergy to Orange is based mainly on *in vitro* IgE antibody determination (6).

Other case reports have detailed the complexity of Orange allergy. Orange allergy was diagnosed in 6 patients following adverse reactions after ingestion of Orange juice and a positive skin prick test on at least 2 occasions. The dose eliciting symptoms was between 20 and 100 g. Three patients tolerated small quantities of Lemon juice. One patient tolerated Tangerine, but 2 patients had oral allergy syndrome to this fruit. Skin prick testing was positive to both pulp and peel. OAS was reported in all the patients. One reported OAS, atopic dermatitis, and general discomfort, and another reported OAS and generalised urticaria. IgE antibody levels were raised in all, ranging from 0.76 to 6.04 kU_A/l. IgE antibody levels was raised for Tangerine in 5 patients (highest 6.04 kU_A/l), for Lemon in 6 patients, ranging from 0.67 to 5.37 kU_A/l, and for Grapefruit in 5. Bet v 2 was raised in 4 patients (8.81 to 39.2 kU_A/l). These 4 patients experienced symptoms with pollen, but the 2 with values of < 0.35 kU_A/l for Bet v 2 did not. Cross-reactivity with other foods and pollens was not investigated (8).

Anaphylaxis to Orange may uncommonly occur (38-39). Food-dependant exercise-induced anaphylaxis has been described in a 12-year-old boy. Angioedema was the main symptom and was ascribed to the ingestion of an Orange prior to exercise (40). Food-dependent exercise-induced anaphylaxis due to ingestion of Orange has also been described in an 18-year-old Japanese woman. She was able to ingest citrus fruit without symptoms; however, after ingesting Orange and then exercising, she developed redness and swelling of her face, mild dyspnoea and abdominal distress: this was 30 minutes after the onset of exercise. IgE antibody level for Orange was 0.83 kU_A/l (41).

A Spanish study reports that the most common food allergens found to be associated with recurrent otitis media with effusion were Cow's milk, Hen's egg, bean, citrus, and Tomato, and that elimination of the culprit food from the diet led to a significant amelioration of the otitis in the majority of patients (42).

Orange has also been reported to result in contact dermatitis (24) and atopic dermatitis in children (43). Orange has been reported

to be a frequent cause of the exacerbation of atopic dermatitis (44). Occupational dermatitis in farmers and workers in the food industry who come into contact with Orange has been reported (45). Many cases of dermatitis seen in the industry are due to contact with the peel and oil of Orange, and not with the juice.

There have been some conflicting studies. A study reported that ingestion of fresh Orange juice per se did not heighten non-specific bronchial hyperreactivity (46). The number of patients was low (16), and they were stable asthmatics. The results may also indicate that processing influences the allergenicity of Orange. A second study evaluated the presence of IgE and IgG antibodies to the Oranges *C. aurantium sinensis* and *C. silension* in 41 atopic and 20 non-atopic children aged 8-12 years. The 41 atopic patients were selected as a result of an acute episode of hives and/or sneezing following a provocation test with 150 ml of Orange juice. Skin prick tests, IgE antibody and IgG RAST measurements were performed on both groups. Thirty-six of the 41 patients were skin prick test-positive to Orange. RAST was positive in 34 of the 41. A citrus fruit exclusion diet was maintained for 180 days. No significant changes in these tests occurred after the diet was established: even a slight increase was recorded. The authors speculate on the basis of these puzzling findings (47).

In a study aimed at characterising allergens from Raspberry, sera from 8 female patients were assessed. Three were described as having allergy to Orange. A 26-year-old experienced severe OAS from Orange, Asparagus, Banana, and Melon, with mild OAS from Apple, Peach, Carrot, and Kiwi. Prick-to-prick testing was positive to Peach, Banana, Melon, Cucumber, Orange, Asparagus, Tomato, and Potato. A 20-year-old reported erythema and pruritus to Peach, Kiwi, Orange, Dust mite, and Alternaria. Prick-to-prick testing was not done. The third, a 25-year-old with periorbital oedema and rhinitis from Lemon and other citrus fruits, was shown to be prick-to-prick positive to Peach, Lemon, Sweet lime, Orange, Banana, Blueberry, Tomato, Grape and Bell pepper (48).

Other reactions

An unusual report describes a 38-year-old woman who presented with a 10-year history of painful ulcerations on her tongue. She drank large quantities of diet cola and some Orange juice daily. Patch testing elicited positive reactions to Balsam of Peru; there was a resultant diagnosis of allergic contact dermatitis. She was put on a restricted diet and a fragrance-free regimen, and her condition resolved. The authors state that this substance is "a fragrance as well as a flavouring agent put in cola drinks that cross-reacts with Orange juice" (49).

Allergic reactions that appear to result from contact with Orange may be due to environmental exposure to Spider mites. This may occur in farmers and Orange orchard workers, as well as in children and adolescents living in environments leading to sensitisation and the clinical manifestation of asthma and rhinitis (50-51).

Non-allergic reactions may occur to other naturally occurring substances, e.g., aromatic substances and tyramine. Orange has been reported to be among the commonest foods causing migraine (52-53). Gustatory sweating due to Orange juice has been reported (54). Phytophotodermatitis may result from coumarins such as bergapten contained in the Orange skin (55). Bergapten is sometimes added to tanning preparations, since it promotes pigmentation in the skin.

d-Limonene, obtained as a by-product from the citrus juice industry, was introduced on the market as a more environmentally friendly defatting and cleaning agent than the organic solvents traditionally used. Autoxidation of d-limonene readily occurs, and yields a variety of oxygenated monocyclic terpenes that are strong contact allergens. Increased use of d-limonene in industry, where high concentrations are employed, as well as in domestic settings, might result in contact sensitisation and dermatitis (56).

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Allergen Exposure

Geographical distribution

Papaya trees, which originated in West India, Mexico or Central America, are widely cultivated in tropical and subtropical areas worldwide. There are 2 types of Papaya fruit, Hawaiian and Mexican. The Hawaiian varieties are the Papayas commonly found in supermarkets. These pear-shaped fruits generally weigh about half a kilo. Mexican Papayas are oblong and may weigh up to 5 kilos. Papaya skin is generally yellow to green. The flesh is bright orange, yellow or pinkish, depending on the variety, and small black seeds cluster in the centre. A properly ripened Papaya is juicy, sweetish and somewhat like a cantaloupe in flavour.

Environment

The fruit can be used to make drinks, salads, marmalade and candy. Papain, a protease enzyme weighing 23 kDa, is obtained from the latex of the full grown but unripe Papaya fruit; it is also present in the leaves and trunk. It has many industrial and consumer uses, including as a meat tenderiser, a clearing

Carica papaya

Family:	<i>Caricaceae</i>
Common names:	Papaya, Papaw, Paw paw, Tree melon
Source material:	Fresh fruit
See also:	Papain k201 and Chymopapain c209
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agent in the production of beer, a contact lens cleaner, and a reagent in the biochemical and pharmaceutical industries (see Papain k201). The edible seeds have a spicy flavour somewhat reminiscent of Black pepper.

Unusually for a fruit, Papaya contains butyric or butanoic acid (1.2 mg/kg) (1). This is a fatty acid also found in butter and used in the manufacture of plastics.

Unexpected exposure

See under Environment.

Allergens

The following allergens have been characterised:

Car p 1, a Papain (2-5).

Car p Chitinase, a 26.2 kDa protein, a chitinase (6-7).

Car p Chymopapain (2,8).

Car p Endoproteinase (9-10).

Car p 1 was previously known as Car p 3.

The latex is present in both the fruit and the plant, and is evident during various stages of ripening, after incision of the unripe fruit (11). The plant proteinases are present mainly in the unripe fruit of the Papaya tree (12).

A class II chitinase is said to be present in the latex of *Carica papaya*, but not in the fruit. It is completely free of any proteolytic and bacteriolytic activities (13). The allergenicity of this protein was not investigated. Although the

protein described in the study has properties similar to those of basic class I chitinases with lysozyme activity, it lacks an N-terminal hevein domain, and it has been suggested that it should be classified as a class II chitinase. Its allergenicity was not assessed (14).

The latex of the unripe fruit, from which Chymopapain is purified, contains another 3 immunologically distinct cysteine proteinases: 1) caricain, 2) glycyI endopeptidase, and 3) Papain. In a study, all 4 Papaya cysteine proteinases were demonstrated to be present in Chymodiactin, a pharmaceutical preparation of Chymopapain which is used in chemonucleolysis for the treatment of sciatica, and which may result in allergic reactions. The contribution that each of the 4 proteinases makes to the allergic response that occasionally occurs during injection of a damaged intervertebral disc with Chymopapain preparations was evaluated. IgE antibody levels to each of the 4 Papaya cysteine proteinases were assayed by an enzyme-linked immunoassay in 12 sera containing IgE antibodies to Chymodiactin. Chymodiactin contained 70% Chymopapain, 20% caricain, 4% glycyI endopeptidase, and 0.1% Papain. IgE antibodies to all 4 proteinases were found in most of the 12 sera, but in varying proportions. Antibodies to glycyI endopeptidase were predominant in 8 sera, and the mean amounts of IgE directed against each protein were the following: glycyI endopeptidase, 4.21 kU_A/l; caricain, 2.9 kU_A/l; Chymopapain, 1.97 kU_A/l; and Papain, 1.39 kU_A/l (15). See Chymopapain c209.

In another study of the cysteine proteinases, it was found that Papaya latex also contains other enzymes as minor constituents: a class-II and a class-III chitinase, an inhibitor of serine proteinases, and a glutaminyI cyclotransferase. The presence of a beta-1,3-glucanase and of a cystatin is also suspected, but they have not yet been isolated (3). Some of these substances are allergens in their own right, *e.g.*, Chymopapain c209 and Papain k201.

A profilin, probably with little clinical significance, has been demonstrated in Papaya (16).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected but in fact has not been reported (17).

Among patients with Kiwi allergy, a group of researchers found strong reactions to Apple and Hazelnut; moderate reactions to Carrot, Potato, and Avocado; and weak reactions to Wheat and Rye flour, Pineapple and Papaya, and their enzymes Bromelain and Papain (18).

It is clearly recognised that Natural rubber latex allergy can be associated with serological cross-reactivity to plant allergens, especially in tropical fruits and Ficus. In contrast, data on the frequency and clinical value of IgE antibodies against these allergens remain rare. The purpose of one study was to investigate the prevalence, the sensitivity, and the specificity of these different IgE antibodies in patients suffering from NRL allergy. Serum samples of 42 NRL-allergic adults were investigated. A plant food-specific IgE antibody was observed in 88% of the serum samples, most frequently to Papaya (71%) and least frequently to Kiwi (17%). According to the questionnaire and the threshold of 0.35 kU_A/l, sensitivity of the plant food IgE antibodies varied between 0% for Papaya and 73% for Avocado. Specificity varied between 28% for Papaya and 91% for Kiwi (19).

In 82 patients (43 men and 39 women, aged between 18 and 45 years) with Latex allergy, 39 (47.5%) were found to have positive skin tests to fruit. Prick tests with fruit extracts were positive in 28 patients (Kiwi, 21 patients; Banana, 17 patients; Avocado, 8 patients; and Papaya, 3 patients); and the prick-by-prick test had positive results in 11 patients (Kiwi, 7 patients; Banana, 4 patients; and Avocado, 3 patients) (20).

Among 25 patients with Latex allergy, including 9 greenhouse and 6 hospital workers, 42 food allergies were diagnosed in 13 patients (52%), and 23 of these allergies involved systemic anaphylaxis. The most frequent food hypersensitivities were to Avocado (n=9), Chestnut (n=9), Banana (n=7), Kiwi (n=5), and Papaya (n=3) (21).

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In a study of Latex allergy, cross-reacting IgE antibodies recognising Latex and fruit allergens (Papaya, Avocado, Banana, Chestnut, Passion fruit, Fig, Melon, Mango, Kiwi, Pineapple, Peach, and Tomato) were demonstrated by RAST-inhibition tests (22). Putative class I chitinases seem to be relevant cross-reactive components in foods associated with Latex-fruit syndrome, and to play a specific role in allergy to Latex but not to fruit (2).

A study concluded that allergic reactions to fresh or dried Figs can present as a consequence of primary sensitisation to airborne *Ficus benjamina* allergens, independent of sensitisation to Rubber latex allergens. Kiwi fruit, Papaya, and Avocado, as well as Pineapple and Banana, may be other fruits associated with sensitisation to *Ficus* allergens (23).

In RAST inhibition studies using *Carica papaya* pollen extract in solid phase, a significant cross-reactivity was found among Papaya pollen, Papaya fruit, and Papain (4).

Clinical Experience

IgE-mediated reactions

Anecdotal evidence suggests that Papaya may occasionally induce symptoms of food allergy in sensitised individuals; however, few studies have been reported to date (24-26). Reactions may occur to individual commercially extracted components of Papaya, *e.g.*, Papain or Chymopapain. Reactions include urticaria, colitis, and anaphylaxis (sometimes to Papain). Papaya allergy is thought to be mainly due to cross-reactivity to Latex, but may occur on its own.

A 23-year-old female presented with classical features of an immediate hypersensitivity reaction after contact with Papaya. SPT to Papaya extracts was positive (25).

A 28-year-old atopic patient was described who had experienced angioedema after ingestion of Papaya cake during a party. A year before, he had also experienced angioedema, urticaria, and acute dyspnoea after contact with rubber gloves. IgE antibody test was positive to Papain. Two other Latex-allergic patients tested with Papaya latex were positive to this substance (26).

In 142 adult patients sensitised to foods (from among 7,698 patients visiting an outpatient clinic), 120 experienced clinical symptoms after consumption of 1 or more foods. The most frequent recorded symptoms were the following: urticaria/angioedema, in 84 patients (70%), oral allergy syndrome in 65 (54%), asthma in 48 (37%), and anaphylaxis in 33 (27.5%). Shellfish sensitisation occurred in 50 patients, fresh fruit sensitisation in 33, and nut sensitisation in 29. The most frequent causes of food hypersensitivity were Shrimp (n=48 patients), Squid (n=33), Kiwi (n=14), Papaya (n=14), Avocado (n=13), and Banana (n=12) (16).

A 55-year-old woman without a history of atopic disease or drug allergy developed a maculopapular symmetric exanthematous rash about 2 days after taking throat lozenges containing Papaya juice (27).

Other reactions

Carotenemia has been associated with Papaya ingestion (28).

Atmospheric surveys carried out in different parts of India reveal that *Caraica papaya* is one of the allergenically important pollens of the country (29-30).

Asthma and hayfever to pollen from the tree have been recorded elsewhere. Among 6 patients with clinical histories of seasonal rhinoconjunctivitis or bronchial asthma in relation to *Carica papaya* tree exposure (suggestive of IgE-mediated respiratory allergy), commercial SPT and IgE antibody determinations to Papaya fruit and Papain were positive in 4. IgE-mediated hypersensitivity to a Papaya pollen extract was demonstrated in all patients by means of SPTs, IgE antibody determinations, and conjunctival challenge tests (15).

Five hundred allergy clinic patients were skin-prick tested with Papain. Five of 475 subjects with seasonal allergic disease had positive skin tests to both Papain and local pollens. The 5 subjects with positive skin tests to Papain underwent double-blind placebo-Papain challenges: all the challenges were positive. Papain-induced symptoms included palatal itching, watery, itchy eyes, sneezing, rhinorrhea, abdominal cramps, diarrhoea, and

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diaphoresis. Circulating Papain-specific IgE antibodies were detected in all of the Papain-sensitive individuals (31).

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f294 Passion fruit

Passiflora edulis

Family: *Passifloraceae*

Common names: Passion fruit, Granadilla, Grenadilla, Maypop, Apricot vine, Passion vine

Source

material: Whole fresh fruit

P. edulis – Purple/Black passion fruit

P. edulis flavicarpa – Golden/Yellow passion fruit

Not to be confused with other closely related members of the genus:

P. alata

P. caerulea

P. foetida

P. herba

P. incarnata

P. pulchella

P. quadrangularis

P. incarnata and *P. edulis* are 2 important plants of the family *Passifloraceae* that have been reported as synonymous in many literature references because of their identical morphological and microscopic characteristics (1). But *P. incarnata* is a popular sedative and anxiolytic, whereas *P. edulis* is rarely reported to possess significant central nervous system depressant activity. *P. edulis*, as the name of the species reflects, is grown mainly for eating

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The Passion fruit vine is a woody, climbing, evergreen perennial, growing up to 9 m tall. The nearly round or ovoid fruit, 4-7.5 cm wide, has a tough, smooth, waxy rind, ranging from dark-purple to light-yellow or orange (the main varieties are Purple and Golden passion fruit, but these can be crossed, and there are many hybrids). Under a thin layer of white pith is a cavity with an aromatic mass of membranous sacs filled with orange-coloured, pulpy juice and as many as 250 small, hard, pitted seeds. The flavour is musky and subacid to acid and can probably be compared most closely to Guava.

Allergen Exposure

Geographical distribution

Passion fruit is grown in much of the tropical and subtropical world, including Brazil, Australia, New Zealand, Israel, Jamaica, South Africa, Malaya, Fiji and Hawaii. The plant has, however, proved significantly disease-prone, retarding the development of plantations and commercial markets. The name derives from the flowers' resemblance to the implements of crucifixion.

Environment

The fruit is usually used for flavouring other foods, but it can be eaten on its own, raw or cooked. It is normally allowed to wrinkle and develop sweetness. It is juiced, made into syrup or used in sauces, cakes, etc. In some countries it is the source of specialty products such as Passion fruit ice cream and bottled cocktails. An edible oil is obtained from the seed.

The pulp of the fruit is stimulant and tonic.

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Unexpected exposure

See under Environment. Extracts from the aerial parts from the closely related *Passiflora incarnata* and *P. herba* are widely used as components of herbal sedatives (2). The extract of *P. incarnata* exhibited significant anxiolytic activity at an oral dose of 125 mg/kg, whereas *P. edulis* is devoid of any significant activity (3). *P. coerulea* may also possess anxiolytic properties (4).

Allergens

No allergens from this plant have yet been characterised.

A class I Chitinase has been reported to be present in pulp of Passion fruit (5-6).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected but has not been formally evaluated (7).

A class I Chitinase has been reported to be the relevant protein linked to cross-reactions in Latex-fruit allergy syndrome, which includes Passion fruit, Cherimoya, Kiwi, Papaya, Mango, Tomato and Wheat (5,8).

A class I chitinase from Avocado or Latex extract was used as an inhibitor in a study whose aim was to evaluate the role of chitinases and complex glycans as cross-reactive determinants linked to Latex-food allergy. Putative class I chitinases of 30 to 45 kDa were recognised by both specific polyclonal antibodies to chitinases and sera from patients with Latex-fruit allergy in Chestnut, Cherimoya, Passion fruit, Kiwi, Papaya, Mango, Tomato, and Wheat flour extracts. Pers a 1, the major allergen and class I chitinase from Avocado, along with the Latex extract, strongly or fully inhibited IgE binding by these components when tested in immunoblot inhibition assays. Additional bands of 16 to 20 kDa, 23 to 28 kDa, and 50 to 70 kDa were detected by the antichitinase serum but not by the patients' pooled sera. The putative 30- to 45-kDa chitinases present in different food extracts did not react with a pool of sera from subjects allergic to Latex but not to fruit. The study concluded that

putative class I chitinases seem to be relevant cross-reactive components in foods associated with Latex-fruit syndrome, but do not play a specific role in allergy to Latex without fruit reactivity. Cross-reactive carbohydrate determinants are not important structures in the context of Latex-fruit cross-sensitisation (6).

In children, cross-reactivity has been reported among Apricot, Avocado, Banana, Cherry, Chestnut, Grape, Kiwi, Papaya, Passion fruit, Peach and Pineapple (9).

Healthcare providers who have coexisting risk factors, such as atopy and food allergies (Chestnut, Banana, Avocado, Passion fruit, Celery, Potato, and Peach) are at an even greater risk of severe allergic reactions following repeated Latex exposure (10).

Clinical Experience

IgE-mediated reactions

Passion fruit may occasionally induce symptoms of food allergy in sensitised individuals, and more frequently in Latex-allergic individuals (5,8-10).

IgE-mediated occupational asthma and rhinitis to *P. alata* (related to *P. edulis*) and *Rhannus purshiana* were reported in a patient who worked in a pharmacy devoted to the manual preparation of herbal products (11).

Other reactions

A 34-year-old female developed severe nausea, vomiting, drowsiness, prolonged QTc interval on her ECG, and episodes of non-sustained ventricular tachycardia following self-administration of the herbal remedy *Passiflora incarnata* (related to *P. edulis*, but with bioactivity) at therapeutic doses. The association of symptoms with *Passiflora* was not recognised for several days. She required hospital admission for cardiac monitoring and intravenous fluid therapy (12).

Vasculitis associated with an herbal preparation containing *Passiflora* extract has been reported (13).

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f95 Peach



Allergen Exposure

Geographical distribution

Peach, *Prunus persica*, is the fruit of a deciduous tree growing as high as 10 m and belonging to the subfamily *Prunoideae* of the family *Rosaceae*. It is classified with the Almond in the subgenus *Amygdalus*, distinguished from the other subgenera by the corrugated seed shell. The Peach is a tree native to China. It was introduced to Persia and the Mediterranean region through the Silk Road in early historical times, probably by about 2000 BC. Important historical Peach-producing areas are China, Japan, Iran, and the countries in the Mediterranean region; and more recently, the US, Canada, and Australia.

The leaves are lanceolate, 7–15 cm long and 2–3 cm broad. The flowers are produced in early spring before the leaves; they are solitary or paired, 2.5–3 cm in diameter, pink, with 5 petals. Peaches, along with Cherries, Plums and Apricots, are stone fruits (drupes). The fruit of all of these is roundish, with a single large seed encased in hard wood (called the “stone” or “pit”). The Peach skin is velvety, downy, and can be red, pink, yellow, white or any combination of these. It is often flushed with red, and bruises easily. On one side of the fruit is a distinctive vertical indentation. The pulp is yellow or whitish, highly flavoured, and sweet. The seed or “pip” is red, oval-shaped and 1.5–2 cm thick.

Prunus persica

Family: *Rosaceae*

Common name: Peach

Source material: Peel from fresh fruit

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Peach comes third in the world production of deciduous tree fruits. Peaches are divided into “freestone” and “clingstone” cultivars, depending on whether the flesh sticks to the stone or not. These two types merge in some varieties, so that even the same trees may be freestone in one season and clingstone in another. Both kinds can have either white or yellow flesh. They are cultivated throughout warm-temperate and subtropical regions of the world. Nearly 300 varieties of Peaches are grown in America alone, each having its particular physical characteristics and ripening season.

The nectarine is a cultivar of Peach that looks very similar, except that it has a smooth, shiny skin without fuzz (hair). Nectarines can be white, yellow, clingstone, or freestone. Ordinary Peach trees occasionally produce a few nectarines, and vice versa.

Harvesting is done manually in summer, and storage is in cold rooms.

Environment

Peach is usually consumed fresh but may be canned, dried or pickled. Its classic uses are in pastries, but it also often features in chutneys and jams.

Allergens

Several Peach allergens of major importance have been detected, including a lipid transfer protein, a profilin, and many larger proteins (1-2).

The following allergens have been characterised:

Pru p 1, a 9 kDa protein, a Bet v 1 homologue, a Group 1 *Fagales*-related protein (3-6).

Pru p 3, a 9 kDa lipid transfer protein (1-24).

Pru p 4, a profilin (2-5,7,9,25-26).

Pru p glucanase, a 1,3-beta-glucanase (27-28).

The allergen that was known as Pru p 1 has been renamed Pru p 3, and Pru p 1 is now the name for a Group 1 *Fagales*-related Protein, a Bet v 1 homologue. Pru p 1 and Pru p 3 are major allergens in Peach fruit. Pru p 1 has low concentrations and is highly labile, whereas Pru p 3 is highly abundant in Peach peel and is heat- and gastric-acid stable (4). Mean Pru p 3 levels were approximately 132, 0.6, and 17 microg/g of fresh weight of peels, pulps, and whole Peach fruits, respectively, whereas mean Pru p 1 levels were 0.6, 0.3, and 0.1 microg/g of fresh weight. Most US Peach cultivars showed higher levels of both allergens than Spanish cultivars (5). LTP levels are also greatly dependent on maturity and storage conditions (29).

Allergy to lipid transfer protein (LTP) is quite common in the Mediterranean countries but virtually absent in Northern Europe (30). Lipid transfer protein is associated with systemic reactions more severe than the milder symptoms such as oral allergy syndrome. Peach LTP (Pru p 3) is a minor allergen in Northern European countries but a major allergen in the South, affecting over 60% of patients allergic to Peach in the Spanish population and over 72% in the Italian population (19). Of Peach-allergic patients who have experienced systemic reactions to Peach, up to 100% may be sensitised to LTP (14).

Lipid transfer proteins (LTPs) concentrate in the skin of *Rosaceae* fruits as cell surface-exposed allergens (1,16). LTP is found in Peach peel in concentrations approximately 7 times greater than in the pulp. LTP contents were as follows: Yellow peach peel, 15.48; Yellow peach pulp, 2.25; Red peach peel, 14.67; and Red peach pulp, 1.84 (13). The substance may be absent from chemically peeled fruit, and levels of LTP vary among cultivars and at different stages of the ripening process, showing a progressive increment during ripening (31). A hypothesis that Peach may lose its allergenicity and therefore its primary role as a sensitiser to LTP as a consequence of processing preceding marketing in Northern Europe was evaluated in a study. Peach surface fuzz reactivity in Peach-allergic individuals

was shown to be stronger than reactivity to peel. Pre-absorption of one serum with Peach LTP caused an 87% reduction of IgE reactivity to Peach fuzz extract (30).

Pru p 4 is a member of the profilin plant family, allergens that bind IgE antibodies of almost 20% of plant-allergic patients. Human IgE reactivity to profilin appears to strongly depend on the highly conserved conformational structure, rather than on a high degree of amino acid sequence identity or even on the linear epitopes that have been identified, as demonstrated in a study evaluating Melon profilin (32). Peach contains 2 profilin isoforms, Pru p 4.01 and Pru p 4.02, which show 80% amino acid sequence identity and are very similar (>70% identity) to allergenic profilins from plant foods and pollens. In a study of sera of 29 patients with Peach allergy (confirmed by DBPCFC in evaluating recombinant Peach profilin isoform reactivity), Pru p 4.01 was recognised by all sera (15 of 15) with IgE antibodies to Bet v 2, whereas no sera (0 of 14) without IgE to Birch allergen reacted with rPru p 4.01 (26). In the Spanish population, where Peach LTP is a major allergen, sensitisation to profilin is observed with an associated pollen allergy but does not appear to be related to clinical reactivity to Peach (19). This may obtain in other countries, in particular in Southern Europe, where Peach LPT is the dominant Peach allergen.

Potential cross-reactivity

A high level of cross-reactivity occurs among members of the *Rosaceae* family (33). Allergy to fruits and vegetables is often associated with pollen allergy, but the relationship between fruit and pollen allergens is not simple. Cross-reactivity patterns observed differ among geographical areas and climates, depending on the differences in exposure to inhaled and ingested allergens. For example, the association between Birch tree pollen allergy and Peach allergy in Northern Europe (58) may be explained by the detection of a Bet v 1-related protein in Peach (2), whereas in Southern Europe and other countries, cross-reactivity associated with Peach is more likely associated with other fruits and vegetables containing lipid transfer proteins (30.)

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Pru p 3, a lipid transfer protein allergen, possibly along with other larger Peach proteins, is involved in allergenic relations with other fruits from the family *Rosaceae*, particularly Apricot, Cherry, and Plum (1-2,34). A high level of cross-reactivity occurs among fruits and vegetables containing lipid transfer proteins, which include Sweet Chestnut (35), Cabbage (with 50% of identity to Peach LTP) (36), Walnut (37), Lettuce (38) and Hazelnut (39). Grape and wine may contain lipid transfer protein homologous to and cross-reactive with Peach LTP (40). A report was made on a 19-year-old boy with a history of oral allergy syndrome, who after eating Peach presented with several episodes of generalised urticaria and angioedema approximately 15-20 minutes after drinking beer. The responsible allergen was found to be a lipid transfer protein from the Barley that is present in beer (41). Lipid transfer cross-reactivity is often accompanied by clinical food allergy, frequently including systemic reactions (10).

In a study examining the relationship between Peach LTP-specific IgE antibody levels and cross-reactivity to several non-*Rosaceae* plant-derived foods, patients with negative SPT for non-*Rosaceae* foods showed significantly lower levels of IgE to Peach LTP than did patients showing skin reactivity to 1 or more non-*Rosaceae* foods. Increasing levels of IgE to Peach LTP were associated with skin reactivity to nuts (29/40 [72%]), Peanut (27/40 [67%]), Maize (16/39 [41%]), Rice (14/39 [36%]), Onion (13/37 [35%]), Orange (9/32 [28%]), Celery (11/40 [27%]), and Tomato (8/39 [20%]). The study suggested that all allergenic determinants in LTP from vegetable foods other than Peach cross-react with Peach LTP, whereas only some Peach LTP epitopes cross-react with allergenic determinants in botanically unrelated plant-derived foods. The high levels of IgE to Peach LTP seemed to reflect the presence of IgE that targeted common allergenic determinants of LTP, causing cross-reactivity to botanically unrelated plant foods. The authors concluded that in LTP-allergic patients, increasing levels of IgE to Peach LTP are paralleled by an increasing number of foods other than *Rosaceae* triggering positive SPT and causing clinical symptoms (42).

Allergenic LTPs from Peach fruit and Mugwort (*Artemisia vulgaris*) pollen are responsible for clinical symptoms in Mediterranean patients, as a result of cross-reactivity (35,43). A study was done to assess the pattern of sensitisation to an array of Mugwort allergens in a Mediterranean population, and the cross-reactivity of Art v 3 (Mugwort) with Pru p 3 and Par j 1, all of these being relevant lipid LTP allergens in the area. The 3 *Artemisia* allergens elicited a positive SPT response in 70-80% of the patients. Seven patients were clearly sensitised to Par j 1 and 11 to Pru p 3. There was no correlation between Par j 1 and Pru p 3 sensitisation, but a highly significant correlation was found between Peach and Art v 3 with regard to skin reactivity. No IgE cross-reactivity was observed between Art v 3 and Par j 1 or between Pru p 3 and Par j 1. In contrast, Art v 3 significantly inhibited the binding to Pru p 3 of IgE from 3 patients' sera out of 6 studied, but Pru p 3 was not able to inhibit IgE binding to Art v 3. The study concludes that Art v 3 is a major Mugwort allergen, and that in some patients with IgE to both Art v 3 and Pru p 3, Art v 3 behaves as the primary sensitising agent (44).

Therefore, hypersensitivity to Mugwort in patients with Peach allergy is due to a common lipid transfer protein allergen, but it is often without clinical expression (45). This is illustrated by a study of 47 patients allergic to Peach and 20 patients sensitised to Mugwort pollen but with no clinical food allergies: the rate of positive SPT for Peach, Apple, Chestnut and Mugwort LTPs were, respectively, 91, 77, 23, and 36% in the Peach group, and 30, 5, 15 and 40% in the Mugwort group. In Peach-allergic patients, the most frequent pattern of cross-reactivity to LTPs appears to be the combination Peach-Apple (45%), followed by Peach-Apple-Mugwort-Sweet Chestnut (21%). Significant correlation was found between Peach and Apple LTPs, and between Mugwort and Sweet Chestnut LTPs (46). Importantly, the IgE-binding cross-reactivity due to fruit lipid transfer protein has varying degrees of clinical relevance, and this cross-reactivity is not necessarily accompanied by cross-allergenicity to the corresponding fruits (21).

Cross-reactivity of lipid transfer proteins may therefore be complex. Mugwort Art v 3 and Plane tree Pla a 3 are implicated in plant food-pollen co-sensitisation, displaying partial cross-reactivity with Peach Pru p 3 and other food allergens. Art v 3 shares 40% of its sequence with Pru p 3 and has an approximately 70% prevalence of IgE antibodies in *Artemisia*-allergic patients. However, sensitisation to Pla a 3 is low in Plane tree pollen-allergic subjects without food allergy (27.3%), but high (> 60%) among those with associated Peach allergy (23). A second type of allergenic nonspecific LTP from pollens corresponds to Ragweed Amb a 6 and Olive Ole e 7, which are minor allergens. These present less than 35% sequence identity with Pru p 3, and have not been involved in pollen-plant food cross-reactivity. Par j 1 and Par j 2, the major allergens of *Parietaria*, represent a further type of nonspecific LTP member, with low levels of sequence identity (26–29%) with Peach Pru p 3 and no reported cross-reaction with any food or even pollen allergens (such as Art v 3) of the family (47).

It has been suggested that the primary sensitiser to LTP is the Peach, based on the following observations:

- Virtually no LTP-allergic patient not sensitised to Peach has been reported so far; the few who showed no skin reactivity for Peach had been tested with fresh fruit only, a method that in this particular type of food allergy is less sensitive than SPT with commercial food extract;
- Peach-allergic, LTP-hypersensitive patients frequently tolerate other *Rosaceae* as well as non-*Rosaceae* plant foods and are negative on skin- and serum-specific IgE evaluation with these foods;
- Cross-reactivity to non-*Rosaceae* plant foods is strongly dependent on the level of IgE to Peach LTP (30).

IgE antibodies to profilin seem to be responsible for at least part of the observed relationship between Peach food allergy and allergy to grass and Olive tree pollen in the Mediterranean area, where *Betulaceae* pollens in the air are rare or absent (25,48–49,61). Profilins are highly cross-reactive allergens,

which bind IgE antibodies of almost 20% of plant-allergic patients. Melon profilin has been shown to have substantial cross-reactivity with profilins from Peach, Tomato, Grape and Bermuda grass (*Cynodon dactylon*) pollen (32).

A 1,3-beta-glucanase, isolated from Olive tree pollen (Ole e 10) and shown to be a major allergen in Olive tree pollen-allergic patients, has been shown to be a panallergen with cross-reactivity to a number of pollens, and to fruits and vegetables such as Tomato, Kiwi, Potato, and Peach. This allergen was suggested as a strong candidate for involvement in pollen-Latex-fruit syndrome (27). Indeed, cross-reactivity with Latex has been suggested (50–51).

A number of other reports have been published documenting cross-reactive relationships between Peach on the one hand and pollens and foods on the other, but the specific allergens were not characterised.

Cross-reactivity has been described between Cypress pollen allergy and Peach food allergy: 7 patients with Cypress pollen allergy, with symptoms during winter, developed oral allergy, urticaria or oedema immediately following ingestion of Peach. Cypress pollens and Peach were shown to have common epitopes on allergens of 45 kDa molecular weight (52).

A study of patients in Sapporo, Japan, found that among the 61% of a group of 54 patients with Birch allergy, a high number were also allergic to fruits: Apple (97%), Peach (67%), Cherry (58%), Pear (40%), Plum (40%) and Melon (33%) (53). Similarly, in a Swiss study of serum of 274 patients allergic to 1 or more of 3 pollens (Birch, Grass, Mugwort), 111 patients (47%) were positive (≥ 0.71 kU_A/l) for a food allergen. Of these, 92 were sensitised to Apple, 68 to Potato, 64 to Carrot, 63 to Celery, 61 to Peach, and 44 to Melon (54).

Cross-reactivity between Raspberry and Peach has been reported (55).

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Clinical Experience

IgE-mediated reactions

Peach is a well-documented and common cause of allergy in children and adults, resulting in oral allergy and systemic reactions such as urticaria, asthma and anaphylactic shock following the ingestion of the fresh or processed fruit. This is particularly the case in the Mediterranean area, where Peach is regarded as a major allergen (19,26,33,46,54,56-65). Peach has also been described as the primary cause of food anaphylaxis in Israel (62). In Japan, Peach has been reported to be a frequent cause of oral allergy syndrome (OAS) (66-67).

Peach allergy has 2 basic patterns: that of Central and Northern Europe, with OAS related to a primary sensitisation to Birch pollen Bet v 1 and profilins; and that of Southern Europe, with mostly systemic symptoms, in many cases due to sensitisation to lipid transfer proteins (24).

Patients in the Mediterranean area are invariably not allergic to Birch tree pollen, and the main reactions are not directed to Bet v 1 homologues or profilin but to LTPs, as described above (30). Allergic symptoms involving LTPs are more likely to be systemic and severe, and occur in addition to oral allergy syndrome. However, sensitisation to the lipid transfer protein Pru p 3 is rare among the Central and Northern European population (14). There, allergy to Peach and other *Rosaceae* fruits in patients with a related pollen allergy is a milder clinical entity, and profilin- and Bet v 1-related structures are involved (68).

This is further illustrated by a study of 30 Spanish Peach-allergic patients with positive skin and food challenge tests. Pru p 3 was the major allergen in the patient group from northern Spain, with sensitisation to this allergen occurring in all of the patients who had systemic symptoms or contact urticaria. Of the patients with OAS, all were sensitised to profilin, and 60% to allergens of the Bet v 1 family, with only 60% being sensitised to Pru p 3. Thus, in the northern Spanish patients, there was a mixed central-south European pattern, with LTP-profilin-Bet v 1 sensitisation, and with the symptoms depending on individual profiles (24).

In a study of Lettuce allergy involving 29 Lettuce-allergic patients, with or without concomitant Peach allergy, and 19 Peach-allergic patients without Lettuce allergy, out of the total Peach-allergic patients (23 + 19), 2 had experienced anaphylaxis, 13 OAS, 13 urticaria, 9 angioedema, 1 contact urticaria, and 1 rhinoconjunctivitis (69).

Even young infants may experience allergic symptoms, as described in an infant of 4 months who developed urticaria and anaphylaxis following the ingestion of Peach (60). Peach is also among a number of foods causing multifoed allergy, as described in a 4-year-old child (70). Anaphylaxis may occur in a biphasic manner (71).

Contact urticaria from Peach skin has been described (72). In particular, LTP-allergic patients frequently report local urticaria or pruritus upon contact with fresh Peaches; in a Spanish study (notably in a geographic area where Birch trees are virtually absent and the prevalence of allergy to LTP is very high), 61% of 70 Peach-allergic subjects had contact urticaria from Peaches, and this was the most frequent symptom of Peach allergy after oral allergy syndrome. Oral allergy syndrome affected 86% of the study group, followed by contact urticaria (61%) and systemic symptoms (26%). Approximately 67% of the patients were allergic to Peach pulp, and 36% reported symptoms related to canned Peach. Canned Peach and pulp symptoms were statistically associated, and symptoms to canned Peach were significantly more frequently reported by patients with systemic symptoms (61).

Interestingly, an Italian report on patients with Peach-induced contact urticaria stated that these patients do not experience similar symptoms after handling botanically related fruit such as nectarines or other *Rosaceae* such as Apple, Pear, Cherry or Plum, suggesting possible differences in the surface layers of these fruits: freshly picked Peaches are characterised by abundant surface fuzz, which is higher in lipid transfer protein (30).

A study of the prevalence of allergy to various foods was conducted in the Netherlands. Individuals with tree pollen allergy were evaluated for skin reactivity, and the prevalence of sensitisation to Apple, Peach,

and Hazelnut was found to be 51 (64.6%), 61 (77.2%), and 71 (89.9%) patients, respectively. The concordance between Peach-specific IgE antibodies and a case history for Peach allergy was 71% in 79 consecutive patients with Birch pollinosis (59).

Oral allergy to Peach is often associated with pollen allergy. A study reports on 7 patients with Cypress pollen allergy, including symptoms during winter, who experienced oral allergy syndrome, urticaria or angioedema immediately following Peach ingestion: 3 reported lip pruritus and oedema, 3 reported generalised urticaria, and 1 experienced angioedema (52). In Spanish patients, every member of a group with pollinosis caused by grass or Olive pollen, and with oral allergy symptoms after eating Peach, had IgE antibodies to Peach, and 4 out of 5 also to Bet v 2 (profilin) (25).

The relationship between pollen allergy and oral allergy syndrome to fruits and vegetables was evaluated in Sapporo, Japan. Of 843 patients with Birch pollen (BP) allergy, 37% had episodes of oral allergy syndrome, and the rate of OAS combined with Birch pollen allergy was higher than the rate of OAS combined with other allergies. The most common foods to cause OAS were Apple, Peach and Cherry, followed by Kiwi, Pear, Plum and Melon. Birch pollen allergy patients demonstrated much more OAS with these foods than the patients without Birch pollen allergy (73).

In a Japanese study of 23 patients with Japanese cedar pollen allergy and OAS for fresh fruits and vegetables, the fruits that caused OAS included Melon, Apple, Peach, and Kiwi. Most patients with OAS exhibited hypersensitivity to more than 2 foods. Eleven of the 16 subjects with IgE antibodies for Birch pollen did not suffer symptoms during the Birch and Alder pollen season. In those with IgE antibodies for fruit, 13 of 20 showed IgE for Apple, and 17 had no IgE antibodies for Melon; only 2 patient had IgE for Kiwi fruit, and 1 for Peach (74).

A 32-year-old nurse with Latex allergy experienced anaphylaxis following the ingestion of several members of the stone fruit family (*i.e.*, Plum, Peach, and Nectarine). A year before a recent anaphylactic episode

following ingestion of Plum, she had developed generalised pruritus, a sensation of a “thick” tongue, and difficulty in swallowing and breathing following ingestion of a Peach. She has eaten canned Peach since that episode without difficulty. Following this episode and one month prior to the hospitalisation for anaphylaxis to Plum, she experienced anaphylaxis 30 minutes after eating a fresh Nectarine. Presenting complaints included acute shortness of breath, a swollen tongue, and generalised pruritus. She was treated for anaphylaxis but six hours later developed a recurrence of tightness in her chest and throat. The patient had strongly positive SPT to the freshly prepared fruit extracts but IgE antibody tests were equivocal or very low positive. *In vitro* latex-specific IgE antibody tests were strongly positive (75).

The allergenicity of Peach is retained in the dried fruit. In a study of 102 children and adults with hypersensitivity to dried fruits, hypersensitivity to Peach was detected in 47% of the cases (57).

Allergic reactions to Peach may occur to the hidden allergen in ice cream, or by indirect contact through kisses or utensils (76).

Other reactions

A 28-year-old woman factory worker experienced occupational asthma and occupational rhinitis as a result of inhalation while handling Peach. She also developed urticaria from ingesting Peach. Bronchial challenge resulted in a 60% FEV₁ fall within 10 minutes (77). A study described a 21-year-old woman who developed primarily airborne sensitisation to lipid transfer protein of Peach and symptoms of severe perennial rhinitis 6 months after starting work in a wholesale fruit storehouse in Southern Italy where large amounts of fruits, including Peaches, were handled. Symptoms subsided when she left the workplace for more than 5 days and relapsed as soon as she was back at work. She subsequently developed severe food allergies to Peach, Hazelnut, Peanut, Apricot, Plum and Tomato (78). Both instances may have resulted from the inhalation of lipid transfer protein, which is found in intact Peach fuzz and may in particular result in respiratory allergy in fruit store workers (78).

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The lipid transfer protein from Peach, Pru p 3, has also been isolated from Peach tree leaves and can act as a respiratory allergen and cause occupational rhinoconjunctivitis and asthma, as described in a fruit grower. In this case, SPT was positive for Peach leaf and fruit. A specific bronchial provocation test with Peach leaf was positive, with both an immediate and a delayed response. Peach leaf extract contained concentrations of Pru p 3 similar to those found in Peach skin. Specific IgE immunodetection showed that the patient's sera reacted with Pru p 3, and with a single major band from the Peach leaf extract that was fully inhibited by Pru p 3. The conclusion was that the lipid transfer protein Pru p 3 from Peach leaves can act as a respiratory allergen and cause occupational rhinoconjunctivitis and asthma (79).

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f94 Pear



Allergen Exposure

Geographical distribution

Pear is a pomaceous fruit produced by a tree of the genus *Pyrus*, classified within *Maloideae*, a subfamily of *Rosaceae*. Apple is also a member of this subfamily. Peach and Apricot are also members of the *Rosaceae* family. Pears are thought to have originated in China. The Pear tree grows wild in western Asia and eastern Europe, but many varieties are under cultivation. Pears are now found in coastal and mildly temperate regions, from Western Europe and North Africa and clear across Asia. There are about 30 primary species, major subspecies, and naturally occurring interspecific hybrids of Pear. Several thousand varieties are known (1).

The enormous number of varieties of the cultivated European pear (*Pyrus communis*), are probably derived from 1 or 2 wild species (*P. pyraster* and *P. caucasica*), widely distributed throughout Europe. These sometimes form part of the natural vegetation of forests in Europe. Asian species with medium to large edible fruit include *P. pyrifolia*, *P. ussuriensis*, *P. × bretschneideri*, *P. × sinkiangensis*, and *P. pashia*.

Pyrus communis

Family: *Rosaceae*

Common names: Pear, European Pear

Source material: Peel from fresh fruit

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Pear trees are medium-sized, reaching 10–17 m, often with a tall, narrow crown. A few species are shrubby. The leaves are alternately arranged, simple, 2 to 12 cm long, glossy green on some species, densely silver-haired in some others; leaf shape varies from broad oval to narrow lanceolate. Most Pear trees are deciduous, but 1 or 2 species in southeast Asia are evergreen.

Pear tree flowers are white, rarely tinted yellow or pink, 2 to 4 cm in diameter, and have 5 petals. Like Apple, Pear fruit is a pome. In most wild species it is 1 to 4 cm in diameter. In some cultivated forms it may be up to 18 cm long and 8 cm broad; the shape varies from oblate to globose to the classic pyriform “Pear shape” of the European Pear, with an elongated basal portion and a bulbous end.

The Pear is very similar to the Apple in cultivation, propagation and pollination.

The fruit is composed of the receptacle or upper end of the flower-stalk (the calyx tube) which is greatly dilated, and enclosing within its cellular flesh the 5 cartilaginous carpels which constitute the “core” and are really the true fruit. From the upper rim of the receptacle are the 5 sepals, the 5 petals, and the very numerous stamens. Quince and Apple are major relatives of the Pear.

Environment

Pears may be eaten raw or cooked, or may be used for the manufacture of alcoholic beverages such as Perry (a cider).

Allergens

The following allergens have been characterised:

Pyr c 1, a major allergen, a Bet v 1 homologue, a Group 1 *Fagales*-related protein (2-5).

Pyr c 3, a lipid transfer protein (2).

Pyr c 4, a 14 kDa protein, a major allergen, a profilin (2,5-7).

Pyr c 5, a 30-35 kDa protein, an isoflavone reductase (IFR) (2,8-10).

A study reported that peels of *Rosaceae* fruits such as Apple, Peach, and Pear have a higher allergenicity than the pulps. In 33 patients allergic to these fruits, adverse reactions were reported to appear more frequently and to be more severe when the whole fruit was eaten. More than 40% of patients allergic to Apple and Pear tolerated the ingestion of the pulp of these fruits, and reactions were elicited only by the intake of the whole fruit (11).

Potential cross-reactivity

Foods belonging to the order *Rosacea*, which include Apple, Pear, Peach and Almond, most commonly cause symptoms in Birch-allergic patients. Bet v 1, the major Birch tree pollen allergen, accounts for most of the pollen's cross-reactivity (12). In areas where Birch pollen is an important aeroallergen, there is an association between spring pollen allergy and allergy to Pear and Apple (5,13-15). However, studies have shown that, although the related major allergens Bet v 1 from Birch pollen and Mal d 1 from Apple inhibit to a high degree the binding of IgE to Pear Pyr c 1, Api g 1 from Celery, also belonging to this family, had little effect, indicating epitope differences among Bet v 1-related food allergens (3). A number of other factors also influence cross-reactivity among foods and plants containing a Bet v 1-homologous protein. For example, the prevalence of Birch-fruit syndrome varies depending on geographic location. The primary sensitisation in Birch-fruit syndrome is to Birch pollen, and the symptoms elicited by foods are a secondary phenomenon (16). The primary allergen responsible for these phenomena is a Bet v 1 homologue.

However, Pear allergens detectable by Birch pollen-sensitised patients were shown to be closely related to and to cross-react not only with Bet v 1 but also with Bet v 2 (5). For example, 18 of 20 pollen-allergic patients studied had IgE antibodies against Pear allergens; 14 of them reacted to a Bet v 1 homologue, and 4 to the Bet v 2 homologue (profilin). In addition, a 35 kDa Birch pollen allergen was shown to be related to a Pear allergen (14). The 35 kDa protein was subsequently identified as Bet v 5 (17).

In Mediterranean areas like central Spain (and probably other areas), where *Betulaceae* pollens are not important, allergy against *Rosaceae* fruits may be completely unrelated to pollen allergy. In such cases the disease is often severe, generally with systemic reactions and with a high frequency of anaphylaxis (18). The causative allergen is most likely a lipid transfer protein that not only results in severe allergy but also cross-reacts with other lipid transfer protein-containing foods (19). Patients with clinical reactivity to Pear had IgE antibodies to Pear and related *Rosaceae* fruits, but not to pollens, Bet v 1 or Bet v 2. Possible allergenic relations between Pear and Latex have been discussed but have not been confirmed by data (20).

The influence of lipid transfer proteins is similarly indicated in a Spanish study of 134 patients with allergy to Olive pollen and also allergy to foods. Twenty-one patients were classified as Group A based on symptoms of OAS, and 19 as Group B based on symptoms of anaphylaxis. Patients in Group B were more frequently sensitised to Ole e 7, a lipid transfer protein. Oral challenges confirmed approximately 50% of positive skin prick tests, with the following positive results: Peach (68.4%), Pear (50%), Melon (71.4%) and Kiwi (53.8%). In patients from Group B, there was a significant association between positive skin prick tests to *Rosaceae* fruits and to Ole e 3 and Ole e 7 (21).

Pear profilin, Pyr c 4, and Cherry profilin, Pru av 4, have a high amino acid sequence identity with Birch pollen profilin, Bet v 2 (76-83%), as well as with other allergenic plant profilins. Eighty-eight percent of 49 patients preselected for IgE-reactivity with Bet v 2 showed specific IgE-antibodies to

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recombinant Pear protein; 92% of the sera were positive with the recombinant Cherry allergen, and 80% of the sera were reactive with the Celery protein. Strong IgE cross-reactivity with profilins from plant foods and Birch pollen was shown. However, IgE binding profiles also indicated the presence of epitope differences among related profilins. The authors concluded that cross-reactivity among related profilins may explain pollen-related allergy to food in a minority of patients (6). A Mango profilin isoform, Man I 3.02, was shown to be closely related to the profilin of Pear (80%), Peach (90%) and Apple (80%) (22).

In a Japanese study that investigated spring pollen allergy and OAS, the most common allergen was found to be Birch, affecting 62% of 87 patients. Among the patients with Birch allergy, Apple was the most prevalent allergen (97%), followed by Peach (67%), Cherry (58%), Pear (40%), Plum (40%) and Melon (33%) (23). Similar results were reported in a recent Japanese study of 843 patients with Birch pollen allergy, of whom 37% reported OAS (24).

Pyr c 5, an isoflavone reductase (IFR), may result in cross-reactivity with other foods containing a similar IFR, *e.g.*, Pea, Orange, and Banana (9).

In a study of 59 subjects 2 to 40 years old with spina bifida, Latex sensitisation was present in 25%. Allergy to Pear and Kiwi were significantly associated with Latex sensitisation (25).

Clinical Experience

IgE-mediated reactions

Pear may result in symptoms of food allergy, anaphylaxis, and in particular oral allergy syndrome (OAS), in sensitised individuals (18,26-28). In an Italian study of OAS in patients suffering from pollen allergy and allergic reactions after eating fruits and/or vegetables, allergy to Pear was detected in 22% (18).

Allergy to *Rosaceae* fruits in patients with a related pollen allergy, usually to Birch pollen, is often expressed as OAS. However, allergy

to *Rosaceae* fruits in patients without a related pollen allergy tends to be a severe clinical entity. Profilin- and Bet v 1-related structures are not involved (18). In Mediterranean areas like central Spain, and probably in other areas where *Betulaceae* pollens are not important, allergy against *Rosaceae* fruits may be totally unrelated to pollen allergy. In such cases, the disease is often severe, generally with systemic reactions and a high frequency of anaphylaxis (18) (see "Potential cross-reactivity", above).

The aim of a study conducted at 17 clinics in 15 European cities was to describe the differences among some northern countries regarding self-reported food hypersensitivity symptoms. Patients with a history of food hypersensitivity were asked to fill in a questionnaire in which 86 different foodstuffs were listed. "Slight symptoms" were most commonly reported. This was the case with Pear, which was the 10th most often reported culprit in adverse effects, purportedly affecting 28% of 1,139 individuals. The foods that were most often reported as eliciting symptoms in Russia, Estonia, and Lithuania were citrus fruits, chocolate, honey, Apple, Hazelnut, Strawberry, fish, Tomato, Hen's egg, and Cow's milk; which differed from the situation in Sweden and Denmark, where Birch pollen-related foods, such as nuts, Apple, Pear, Kiwi, stone fruits, and Carrot were the most common causes (29).

Anaphylaxis and food-dependant exercise-induced anaphylaxis to Pear has been reported (26-27). In 2002, 107 cases of severe allergic reactions were reported to the French Allergy Vigilance Network, of which 59.8% were cases of anaphylactic shock (1 being fatal), 18.7% of systemic reaction, 15.9% of laryngeal angioedema, and 5.6% of serious acute asthma (1 fatal). Pear was implicated in only 1 instance (27).

A 20-year-old woman who experienced anaphylaxis to String bean also reported urticaria from ingesting fresh Fennel, boiled Cabbage, Mustard, Hazelnut cream and commercial Pear juice (30).

Occupational contact urticaria and contact dermatitis to Pear has been reported (31).

Other reactions

Ingestion of Pear fruit juice may result in chronic, non-specific diarrhoea in infancy and childhood (32).

Pear and Japanese pear (*P. pyrifolia*) pollen may result in asthma and rhinoconjunctivitis in sensitised individuals (33-34).

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Diospyros kaki

Family:	<i>Ebenaceae</i>
Common names:	Persimmon, Kaki fruit, Sharon fruit
Source material:	Whole fresh fruit
Synonym:	<i>D. virginiana</i> (Am. persimon)
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Allergen Exposure

Geographical distribution

The Persimmon tree is native to China and Japan, where it has been cultivated for centuries. It was introduced to Europe and California (where it has become *D. virginiana* or American persimmon) in the mid-19th century. It is commercially grown in Italy, Spain and the south of France, where it is known as Kaki, but it is still most common in the Far East.

The trees can be classified into 2 general categories: those bearing fruit that is astringent until it is extremely ripe, and those bearing non-astringent fruit (1). Astringent-fruit cultivars contain high levels of soluble tannins and cannot be eaten until very soft unless the astringency has been artificially removed. Non-astringent cultivars contain low levels of soluble tannins and can be eaten at various stages of firmness, from very hard to very soft. The fruit consists of a berry resembling a Tomato in shape and texture, and is the size of an Apple and orange in colour.

Environment

Diospyros is numerically and economically the most important genus of *Ebenaceae*. The fruits are eaten fresh, dried, cooked, and canned. They are high in glucose and protein, and also have various medicinal and chemical uses. Unique to the genus is its large number of pentacyclic triterpenes and juglone-based 1,4-naphthoquinone metabolites.



Allergens

The following allergen has been characterised:

Dio k 4, a profilin (2-3).

A 17 kDa protein, a Bet v 1 homologue, has been isolated (3).

A Bet v 6-related food allergen, an isoflavone reductases (IFR)/phenylcoumaran benzylic ether reductase (PCBER), has been detected (3-4). A pectin methylesterase inhibitor of unknown allergenic potential has been isolated (5).

Cross-reactive profilin was shown in 1 patient and IgE to cross-react with carbohydrate determinants in all patients (2).

f301 Persimmon

Potential cross-reactivity

Cross-reactivity with pollen allergens as a result of the presence of a profilin and Bet v 6-like and Bet v 1-like allergens has been reported. Two patients with hypersensitivity reactions upon first exposure to Persimmon, as well as 7 patients with Birch-pollen-related Apple allergy, were included in a study. Sera from both patients were reactive to Bet v 1 and Bet v 6, which were cross-reactive with Persimmon (3).

The Birch pollen allergen Bet v 6 appears to be related to proteins in some fruits. Bet v 6, a plant protein related to a defence mechanism protein, was named phenylcoumaran benzylic ether reductase (PCBER). A study suggested that homologous allergens may be present in many plant foods, such as Apple, Peach, Orange, Lychee, Strawberry, Persimmon, Zucchini, and Carrot. In extracts of Pear, Apple, Orange, and Persimmon, the presence of proteins of approximately 30-35 kDa containing Bet v 6 cross-reactive epitopes was demonstrated with 2 Bet v 6-specific monoclonal antibodies (3).

Pollen-allergic patients frequently present allergic symptoms after ingestion of several kinds of plant-derived foods. The majority of these reactions are caused by 4 distinct cross-reactive structures that are present in Birch pollen: Bet v 1, profilin, cross-reactive carbohydrate determinants (CCDs), and Bet v 6. Bet v 6-like allergens have actually been found in many plant foods such as Apple, Peach, Orange, Lychee, Strawberry, Persimmon, Zucchini, and Carrot (6).

Clinical Experience

IgE-mediated reactions

Anecdotal evidence suggests that Persimmon can occasionally induce symptoms of food allergy in sensitised individuals; however, few studies have been reported to date (1-2,7-8).

Oral allergy to Persimmon has been reported. One study reports on 3 patients: after the ingestion of Persimmon, the first reacted with pruritus, penis oedema, urticaria, and asthma; the second with nausea and vomiting; and the third with rhinoconjunctivitis, asthma, and stomachache (2).

In a study evaluating cross-reactivity with pollen allergens as a result of the presence of a profilin and Bet v 6-like and Bet v 1-like allergens, 2 patients with hypersensitivity reactions upon first exposure to Persimmon, as well as 7 patients with Birch-pollen-related Apple allergy, were assessed. Sera from both patients were reactive to Bet v 1 and Bet v 6, which were cross-reactive with Persimmon. The patient with the severest reactions was reactive to profilin. An open challenge with Persimmon in 7 patients allergic to Birch pollen and Apple, who had not eaten Persimmon previously, was positive in 6/7 cases. The study concluded that Birch-pollen-related allergy to Persimmon is mediated by known cross-reactive pollen allergens, including Bet v 1, and may become more of a problem should Persimmon consumption increase (3).

A case was reported of a 33-year-old man with an anaphylactic reaction immediately after ingestion of Persimmon fruit. SPT with Persimmon was positive and IgE antibodies were demonstrated as well (1).

In another case of anaphylaxis, a 20-year-old man reported itching, generalised urticaria, facial oedema, asthma, gastrointestinal symptoms and diarrhoea 10 minutes after eating a fresh Persimmon fruit. Prick to prick and SPT were positive. RAST was negative (9).

Other reactions

Some patients complain of abdominal distension and excessive flatus after ingesting Persimmon, and these reactions were attributed to fructose intolerance (10).

Persimmon phytobezoar, although in general an infrequent entity, is not rare in some countries (11). Because of their particular features, management of diospyrobezoars is difficult (12). Most patients with bezoars have ingested unpeeled fruits. While ingestion of Persimmon carries a 9.8-fold elevated risk of bezoar development, ingestion of the unpeeled fruit increases the risk of this complication 56 times over that of age- and sex-matched controls (13). Small bowel obstruction in children due to Persimmon phytobezoars may occur (14).

Lycopenaemia is a benign condition, secondary to an excessive dietary intake of lycopene-rich fruits. It was described in a 68-year-old Caucasian woman who presented with red-orange-tinged skin on her palms and soles. Her diet included about 1 kg of Persimmon daily. The discoloration of the palms and soles resulted from pigment deposits, due to the slow conversion of carotene to vitamin A. This condition resolved after changes in her dietary habits (15).

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f210 Pineapple



Ananas comosus

Family:	<i>Bromeliaceae</i>
Common name:	Pineapple, Ananas, Piña
Source material:	Fresh fruit
See also:	Bromelain nAna c 2 k202

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is expensive and not common in comparison to other fresh tropical fruits. But it is often canned and is available as a juice or in juice combinations. Canned Pineapple is often used in desserts, salads, meat dishes and “fruit cocktail”. Pineapple enzymes are useful in marinades and meat tenderizers, and have various industrial uses. Pineapple is a topical anti-inflammatory and proteolytic remedy.

Allergen Exposure

Geographical distribution

Pineapple is the tropical fruit of a perennial herb, the only bromeliad in widespread agricultural cultivation. Hundreds of varieties of Pineapple exist, but only a few are commercially important. Pineapple farming spread from the areas that are now southern Brazil and Paraguay to many tropical locales. At present, Hawaii is the world leader.

The name reflects the fruit’s similarity to very large pine cones; it is ovoid, with a tough, brownish, tessellated rind. Hard, long, spiky leaves form a tuft at the top. The Pineapple is a multiple fruit, with many spirally-arranged flowers along the axis, each producing a fleshy fruit that presses against the fruits of adjacent flowers and congeals with them to form a single fleshy fruit. This is yellow, very juicy, sweet to acidic and with a distinctly rich taste.

Environment

Because of difficulties in storage, transport, and control of ripening, and because of the awkwardness of cutting it, fresh Pineapple

Unexpected exposure

See under Environment and Other reactions.

Allergens

The following allergens have been characterised:

Ana c 1, a profilin (1-2).

Ana c 2, Bromelain, a protease (1,3-5).

A chitinase protein has been shown to be present in Pineapple stems, fruit and leaves. It is produced following ethylene induction (6-7). Its allergenic potential was not evaluated.

The presence of a lipid transfer protein has been reported, but the allergen has not been characterised (8).

Ana c 1, a profilin, and Banana profilin have been shown to have a 71-84% sequence identity to other known pollen and ingested profilins. Recombinant profilin was shown to bind to IgE antibodies in 8 of 19 Pineapple-allergic subjects. High cross-reactivity to the Birch pollen profilin Bet v 2 and the Latex profilin Hev b 8 was demonstrated (2).

Ana c 2, Bromelain, is a protease. The Pineapple plant has been shown to contain at least 4 distinct cysteine proteinases. The major

proteinase present in extracts of the plant stem is stem Bromelain, while fruit Bromelain was the major proteinase in the fruit. Two additional cysteine proteinases have been detected only in the stem: ananain and comosain. Stem Bromelain, fruit Bromelain, and ananain were shown to be immunologically distinct (4).

As Bromelain cross-reactive carbohydrate determinants have been shown to cross-react with several glycoallergens, Bromelain can be used to detect IgE antibodies to the carbohydrate side chain of glycoproteins.

Potential cross-reactivity

Cross-reactivity with Latex was demonstrated in a study with Latex-allergic patients, where 19% exhibited IgE antibodies to Pineapple, as demonstrated by the Phadia ImmunoCAP® System (11). Cross-reactivity has also been found with Perennial rye grass pollen, and with Papain (12-14).

As a result of the profilin present in Pineapple, cross-reactivity with Banana, Bell pepper, Celery and Pineapple may occur, as seen in Latex-fruit syndrome (2). In patients with Tomato allergy who are sensitised to other foods and Birch pollen, IgE directed against Tomato profilin (Lyc e 1) showed strong cross-reactivity with profilin from Birch (Bet v 2), Celery (Api g 4), Sweet cherry (Pru av 4), Pineapple (Ana c 1), Banana (Mus xp 1), and Carrot (Dau c 4) (9).

Banana and Pineapple profilin have a high amino acid sequence identity to known allergenic pollen and food profilins (71-84%). IgE binding to the recombinant profilin was demonstrated in 7/16 sera from subjects with suspected Banana allergy (44%), and in 8/19 sera from subjects with suspected Pineapple allergy (42%). High cross-reactivity to the Birch pollen profilin Bet v 2 and the Latex profilin Hev b 8 was demonstrated. The authors concluded that, since such a high IgE-binding prevalence was observed in both Banana and Pineapple allergy, profilin is an important mediator of IgE cross-reactivity between pollen and exotic fruits (2).

In a study of 200 consecutive patients with pollen allergy who underwent skin prick tests with purified natural Date palm profilin (Pho d 2),

60 patients (30%) showed skin reactivity to Pho d 2. All were sensitised to grass pollen, and most reacted to Birch, Mugwort, Ragweed and *Plantain* pollen as well. The large majority of profilin-allergic patients reported oral allergy syndrome as the only food-induced symptom and were able to tolerate the offending foods if they were cooked or otherwise processed. Twenty-eight of 34 reported reactivity to 2 or more plant-derived foods. *Rosaceae*, tree nuts, Melon and Watermelon, Tomato, Pineapple, citrus fruits and Banana were the more frequently offending foods. The authors suggest that profilin should therefore be considered a clinically relevant food allergen. Allergy to Melon, Watermelon, Tomato, Banana, Pineapple and Orange may be considered to be a marker of profilin hypersensitivity (10).

Cross-reactivity among Latex, Pineapple and other foods may occur due to cross-reactive allergens. This association has been termed "Latex-fruit syndrome" (11-13).

Cross-reactivity has been reported to occur among Apricot, Avocado, Banana, Cherry, Chestnut, Grape, Kiwi, Papaya, Passion fruit, Peach and Pineapple (14).

Kiwi fruit, Papaya, Avocado, Pineapple, Fig and Banana may be associated with sensitisation to *Ficus benjamina* allergens (15).

Clinical Experience

IgE-mediated reactions

Ingestion of Pineapple has been reported to cause asthma, rhinitis and gastrointestinal symptoms (2,16-19). Angioedema and shock have also been observed (11,13). One study reports that Pineapple is one of the most common self-reported triggers of atopic dermatitis (20).

A cross-sectional, descriptive, questionnaire-based survey was conducted in Toulouse schools to determine the prevalence of food allergies among schoolchildren. It was reported that, out of 2,716 questionnaires returned, 192 reported a food allergy. Of these, 7 reported adverse reactions to Pineapple (21).

f210 Pineapple

A study was conducted at 17 clinics in 15 European cities to evaluate the differences among some Northern countries regarding what foods, according to the patients, elicit hypersensitivity symptoms. According to questionnaires administered to food-allergic individuals concerning 86 different foods, the foods that were most often elicited symptoms in Russia, Estonia, and Lithuania were citrus fruits, chocolate, honey, Apple, Hazelnut, Strawberry, Fish, Tomato, Hen's egg, and Cow's milk, a situation that differed from that of Sweden and Denmark, where Birch pollen-related foods such as nuts, Apple, Pear, Kiwi, stone fruits, and Carrot were the most common reported causes. The most common symptoms reported were oral allergy syndrome and urticaria. Birch pollen-related foods dominated as reported culprits in Scandinavia, whereas some Mugwort-related foods were of more importance in Russia and the Baltic States. Among 1,139 individuals, Pineapple was the 26th most commonly reported food, resulting in adverse effects in 18% (22).

Of 32 patients who became symptomatic shortly after they had eaten Pineapple, most complained of intense itching and urticarial rashes, followed by abdominal pain, vomiting and diarrhoea; 68% became symptomatic within half an hour of eating the Pineapple; 20 presented with shock (13).

Other reactions

See Bromelain k202.

The protease Bromelain from Pineapple is used frequently in industry as an enzyme and results in occupational allergy. A study reviews the literature concerning occupational airway sensitisation due to Bromelain (23).

Bromelain is a natural mixture of proteolytic enzymes derived from the Pineapple stem and has been shown to have anti-inflammatory activity when administered orally. Although most proteins given orally without an adjuvant (which would usually be food) are tolerated, researchers previously reported that long-term oral exposure to Bromelain stimulated the development of serum anti-Bromelain antibody titers (24).

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f255 Plum



Prunus domestica

Family:	<i>Rosaceae</i>
Common names:	Plum, Gage, Prune
Source material:	Fresh fruit without stone
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Allergens

The following allergens have been characterised:

Pru d 3, a 9 kDa lipid transfer protein (1-5).

Pru d 4, a profilin (6).

The lipid transfer protein tends to concentrate in the skin of *Rosaceae* fruits; in Plum, it predominates as a cell-surface-exposed allergen (3).

Potential cross-reactivity

Extensive cross-reactivity among the fruit of the different individual members of the *Rosaceae* family occurs (7). However, as judged from reports on the prevalence of allergic reactions (8) and studies on the cross-reactivity, Plum, Cherry, Apricot, and Peach allergens show overlapping but far from identical specificity (9-11). This is illustrated by examples below.

Plum contains a non-specific lipid transfer protein (LTP), Pru d 3, which is highly homologous to the major allergen of Peach (4) and may result in cross-reactivity with other LTP-containing foods such as the LTPs of *Rosaceae* fruits (Peach, Apricot, Cherry, Plum and Apple), which are major allergens for Mediterranean atopic populations (12-13). LTPs may result in cross-reactivity between botanically unrelated foods, as demonstrated for LTPs of Maize and Peach (13). However, IgE-binding cross-reactivity due to fruit LTP has varying degrees of clinical relevance. This cross-reactivity is not necessarily accompanied by cross-allergenicity to the corresponding

Allergen Exposure

Geographical distribution

A Plum is a stone fruit tree in the genus *Prunus*, family *Rosaceae*.

There are more than 2,000 varieties of Plum cultivated throughout the world. The round, smooth-skinned fruits can be red, yellow, blue or green; *P. domestica* is usually a purple-black colour, and *P. salicina*, Japanese plum, tends to be yellow to crimson. In Canada and the US, Plums are widely cultivated and dried into Prunes. Botanically, all Prunes are Plums.

Environment

Plums are popular as a dessert fruit and are often eaten out of hand, as well as in pastries and preserves. The fruit is, however, most readily available dried, under the name Prunes, which are legendary as a laxative.

Unexpected exposure

See under Environment.

fruits (2); and elimination diets that rely on total avoidance of a group of foods, or only on the results of allergy testing, may result in unnecessary restriction of foods such as Plum (14). For example, Mal d 3, the Apple LTP, has been shown to have significant cross-reactivity to Peach, Cherry and Nectarine, and to a lesser extent to Hazelnut and Plum (15). Cowpea LTP has been shown to have high homology to plant LTPs of Mung bean (94%), Plum (82%) and Maize (72%) (5).

Birch pollen-allergic individuals have a high prevalence of oral allergy syndrome (OAS) to fruits and vegetables. In a Japanese study of 843 patients with Birch pollen allergy, 378 patients (37%) reported episodes of oral allergy syndrome. The most frequent foods causing OAS were Apple, Peach and Cherry, followed by Kiwi, Pear, Plum and Melon (16). A second study in the same region, investigating spring pollen allergy and OAS, found that the most common allergen was Birch tree pollen, affecting 54 of 87 patients (62%). Of this group, 61% reported adverse reactions to fruit and vegetable: Apple in 97%, Peach in 67%, Cherry in 58%, Pear in 40%, Plum in 40%, and Melon in 33% (17).

Allergy to Plum has occasionally been reported to be associated with Latex allergy (18-19) (see below).

Clinical Experience

IgE-mediated reactions

Plum may induce symptoms of food allergy in sensitised individuals (8-9,14,20-26). Oral allergy syndrome is the most often reported symptom to Plum. Oral allergy syndrome to fruits from the genus *Prunus* (Plum, Cherry, Apricot, and Peach) has been described as a cluster of hypersensitivities and occurs mostly as a result of the presence of a profilin (8-9,19-20,22). As a result of the presence of profilin and lipid transfer proteins, adverse reactions to Plum will vary according to geographical locality, for example, severe reactions from lipid transfer protein being more common in Southern Europe, and milder symptoms as a result of profilin being more common in Northern Europe.

In a study conducted at 17 clinics in 15 European cities to evaluate the differences among some northern countries regarding what foods elicit hypersensitivity symptoms, it was reported, according to food-allergic individuals surveyed concerning 86 different foods, that the foods most often eliciting symptoms in Russia, Estonia, and Lithuania were citrus fruits, chocolate, honey, Apple, Hazelnut, Strawberry, fish, Tomato, Hen's egg, and Cow's milk; this profile differed from that of Sweden and Denmark, where Birch pollen-related foods, such as nuts, Apple, Pear, Kiwi, stone fruits, and Carrot, were the most common causes. The most common symptoms reported were oral allergy syndrome and urticaria. Birch pollen-related foods dominate in Scandinavia, whereas some Mugwort-related foods were of more importance in Russia and the Baltic States. Among 1,139 individuals, Plum was the 20th most reported food, resulting in adverse effects in 21% (25).

The prevalence of Plum allergy varies widely. In a cross-sectional, descriptive, questionnaire-based survey conducted in Toulouse schools to determine the prevalence of food allergies among schoolchildren, with 192 questionnaires reporting a food allergy, allergy to Plum was self-reported in 1 individual (27). However, among patients (mainly adult) with Birch pollen allergy, the prevalence of oral allergy syndrome (OAS) to Plum varied from 21% in Northern Europe (28) to 37% and 62% in Japan (16-17). Authors have suggested that skin prick tests with commercial extracts of Plum and Walnut may be usefully employed to detect patients with OAS reacting against allergens (19).

Anaphylaxis to Plum has been reported (29). Severe adverse reactions to Plum may commonly occur as a result of the presence of a lipid transfer protein (LTP). LTPs are the major allergens in patients sensitive to *Rosaceae* who are not also allergic to Birch pollen (30).

A 32-year-old nurse with Latex allergy experienced anaphylactic reactions following the ingestion of several members of the stone fruit family (Plum, Peach, and Nectarine). Within 30 minutes of ingestion of fresh Plum, she began to experience vaginal pruritus, generalised erythema, facial swelling, shortness

f255 Plum

of breath, and the sensation of tightening in her throat. Skin tests were strongly positive to freshly prepared fruit extracts, but IgE antibody tests were equivocal or very weakly positive. *In vitro* Latex-specific IgE antibody tests were strongly positive (18).

Similarly, a 53-year-old man experienced severe dyspnoea and pruritus of both hands 30 minutes after drinking a milkshake containing Peach, Banana, and Grapefruit. A similar episode occurred after eating Plum. He subsequently noted itching and urticaria of his hands when wearing Natural rubber latex gloves. He was found to be Latex-allergic and shown to be sensitised to uncharacterised high-molecular-weight Latex proteins that cross-reacted with proteins in plant-derived foods (19).

A 21-year-old woman began having severe perennial rhinitis 6 months after starting to work in a wholesale fruit storehouse in Southern Italy where large amounts of fruits, including Peaches, were handled. Symptoms subsided when she left the workplace for more than 5 days, and relapsed as soon as she was back at work. She subsequently developed severe food allergy to Peach, Hazelnut, Peanut, Apricot, Plum and Tomato. Sensitisation to an LTP was demonstrated. The authors concluded that LTP may induce sensitisation via the respiratory tract due to inhalation of air-dispersed food particles, and that this may precede the onset of food allergy; they suggested that individuals are at risk where high levels of airborne LTP exposure may occur, e.g., from Peach fuzz (31).

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f35 Potato



Solanum tuberosum

Family: *Solanaceae*

Common names: Potato, Irish potato, Spud

Source material: Fresh raw potato

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Unexpected exposure

The Potato is a source of starch for sizing cotton and making industrial alcohol. It also has many other uses in industry. Ripe Potato juice is an excellent cleaner of silks, cottons and woolens. The water in which Potatoes have been boiled can be used to clean silver and to restore a shine to furniture.

Emollient and cleansing face masks are made from Potatoes; these are used to treat hard, greasy and wrinkled skins.

Allergen Exposure

Geographical distribution

First cultivated by the Incas, the Potato even at this period existed in thousands of edible varieties. It was brought to Europe in the 16th century by the Spaniards. It comes fourth after Wheat, Rice and Maize as a staple crop, as Potato tubers are high-yielding, store well and can be available all year round.

Environment

The Potato is not known in a truly wild situation. Potatoes are a very versatile food, having a mild flavour and readily accepting the flavour of other foods. Occasionally eaten raw, they are usually boiled, baked, fried, or added to soups, stews, etc. Cooked Potato can also be dried and made into a powder and then used as a thickener, or can be added to cereal flours for bread, biscuits, and so on. The Potato is a very rich source of starch but does not contain high quantities of other nutrients. When exposed to light, the skin turns green and develops the toxin solanine, an alkaloid (as do all other green parts of the plant).

While mainly used as a staple food, raw and cooked Potatoes also have medicinal virtues.

Allergens

Potato contains a number of allergens, ranging from 16 to 65 kDa in size, of which a few have been characterised (1-2). In a Korean study of GM Potato and wild-type Potato, IgE-immunoblot analysis demonstrated the presence of 14 IgE-binding components within the wild-type Potato and 9 within the GM Potato. A common 45-kDa binding component that yielded similar IgE-binding patterns was noted in more than 80% of the reactions in sera from patients sensitised to either wild-type or GM Potato (3).

Evaluation of extracts of 6 different Potato strains showed differences in the pattern of the IgE-binding proteins, but no distinctions could be observed in the allergenic potency as evidenced in inhibition experiments. IgE binding to 14, 18, 20 23 and 43 kDa molecules occurred to all strains. Three cultivars (Karlana, Quarta, Mentor) contained additional IgE-binding protein at approximately 45 and 25 kDa. Only a slight decrease of allergenic activity from raising the temperature occurred. A new protein band of approximately 50 kDa resulting from heated Potato was detected and showed IgE binding activity (4).

The following allergens have been characterised:

Sol t 1, 43 kDa storage protein, patatin (5-11).

Sol t 2, a cathepsin D inhibitor (5,12).

Sol t 3, a cysteine protease inhibitor (5,12-13).

Sol t 4, an aspartic protease inhibitor (5,12).

Sola t 8, a profilin (4,14-15).

Sola t Glucanase (16-17).

Potato flour and starch are reported not to be allergenic (18). Simulated digestion is reported to abolish IgE reactivity in them (3), although another report found Sol t 1 (patatin) to be partially stable to digestion *in vitro* (8).

Patatin (Sol t 1), a major Potato allergen, is present as 4 isoforms representing 62%, 26%, 5%, and 7% of the total amount of patatin. All isoforms of the patatin family contain proteins with 2 molecular masses of approximately 40.3 and 41.6 kDa (11).

Sol t 1 has been reported to be both a heat-stable and a heat-labile allergen; there are conflicting studies (4,10). Potato certainly contains at least 1 heat-stable protein; this may be Sol t 1, as evidenced by reported immediate and delayed reactions, *i.e.*, exacerbation of atopic dermatitis after oral challenge to cooked Potato (10). A recent study concluded that the heat-lability of patatin-IgE interaction is explained by aggregation of patatin with other Potato proteins rather than by denaturation of patatin itself. Aggregation of patatin resulted in a nonreversible unfolding and a concomitant important decrease in affinity for IgE (9). A report suggested that a new protein band of approximately 50 kDa forms in heated Potato and is capable of IgE binding (4).

Sol t 1 (patatin) in Potatoes is reported to be a significant IgE-binding protein for children with positive SPT to raw Potato. Twenty of 27 (74%) children with positive skin prick test responses to Potato showed specific binding of IgE antibodies to purified patatin. A positive wheal-and-flare reaction was seen in 8 of 14 children prick-tested with purified patatin (12). Similarly, a study reported that

75% of Potato-sensitised people reacted with patatin (8).

Sol t 2, Sol t 3 and Sol t 4 have molecular masses ranging from 16 to 20 kDa and have been identified as cathepsin D-, cysteine-, and aspartic protease-inhibitors belonging to the family of Soybean trypsin inhibitors (Kunitz type). In ELISA tests, 51% of the sera of 39 atopic children showed IgE antibodies to Sol t 2, 43% to Sol t 3.0101, 58% to Sol t 3.0102, and 67% to Sol t 4 (12).

Three protein inhibitors of proteolytic enzymes with molecular weights of 21, 22, and 23 kDa were isolated from Potato and showed a high degree of homology to the other Kunitz-type proteinase inhibitors from plants (19-20). The clinical significance of this protein was not determined.

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected, as well as to a certain degree among members of the family *Solanaceae* (21). Antigenically cross-reactive material found in Tobacco leaf has been demonstrated in Eggplant, Green Pepper, Potato, and Tomato, which are all members of the family *Solanaceae* (22).

Cross-reactivity has been shown among Birch, Apple, Pear, Celery, Carrot, Hazelnut and Potato (14,23-24), which may well be due to a profilin allergen. An association has also been reported between grass pollinosis and sensitisation to Tomato, Potato, Green pea, Peanut, Watermelon, Melon, Apple, Orange and Kiwi (25).

Patatin (Sol t 1) has been reported to be a major cross-reactive Potato allergen. A study reported that 75% of Potato-sensitised people reacted with patatin in immunoblots, and that 25% of the positive reactions to Hev b 7 could be blocked by preincubation of the patients' sera with purified Potato patatin. Examination of children with atopic dermatitis showed that most sera contained patatin-specific IgE, whereas no Hev b 7-IgE antibodies were detected (8). Hev b 7 has a sequence identities of 39% to 42% to patatins (26).

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Latex and Potato cross-reactivity has been reported by numerous studies. In one study, Tomato, Potato, and Latex were shown to have a common protein of 44-46 kDa. This protein could be implicated in the high degree of cross-reactivity among Tomato, Latex, and Potato observed in immunoblotting and CAP inhibition. The protein was reported to probably correspond to patatin (27). Other studies have reported that Latex proteins showed strong cross-reactivity with protein from several fruits and vegetables, such as Avocado, Potato, Banana, Tomato, Chestnut, and Kiwi (28-29). The implication is that individuals allergic to Potato may be at higher risk of reacting these other fruits and vegetables. In Latex allergy patients, positive food SPT occurred most frequently with Avocado (53%), Potato (40%), Banana (38%), Tomato (28%), Chestnut (28%), and Kiwi (17%) (30).

Cross-reactivity between Potato and Latex may depend on the age of the individual. In a study, 17 (49%) of 35 Natural rubber latex (NRL)-allergic adults had IgE antibodies to Hev b 7, in contrast to only 1 of 35 NRL-allergic children. Fifteen (43%) of the NRL-allergic adults and 29 (83%) of the NRL-allergic children had IgE antibodies to Sol t 1. Ten (29%) of the adult sera showed IgE binding to both Sol t 1 and Hev b 7, and crosswise inhibition tests with pooled sera revealed marked cross-reactivity. These results suggest that Hev b 7 is an important NRL allergen for adults, but not for children. The authors suggest that the clinical importance of the observed cross-reactivity between Hev b 7 and Sol t 1 requires further studies (7).

In a Finnish study of 177 children aged less than 4 years and suspected of food allergy who were prick tested with Soybean and fresh Potato, 10/177 (5%) had positive tests to Soybean, and 14 (7%) to Potato. Most Potato SPT-positive children (70%) showed IgE antibodies to a Kunitz-type Soybean trypsin inhibitor (KSTI) and 75% had IgE antibodies to Soybean. Significantly, 9 (75%) children suspected of Soy allergy had IgE antibodies to Sola t 2-4, and a marked crosswise inhibition was demonstrated between Sola t 2-4 and KSTI allergens. The study concluded that children with suspected food allergy are

frequently sensitised to Soybean and Potato, and that positive skin and serum IgE tests to Soybean may be due to cross-reactive IgE antibodies against structurally altered Potato allergens, and *vice versa*; and that this should be considered when evaluating children suspected of Soy or Potato allergy (31).

Sol t 8, a profilin, can be expected to cause a variable degree of cross-reactivity with other foods or pollens containing this panallergen (15,32). However, the clinical implications with specific reference to Potato have not been elucidated yet.

A recent study suggested that 1,3-beta-glucanase was a potential panallergen family involved in pollen-Latex-fruit syndrome. Ole e 10, a major allergen from Olive tree pollen, shows homology with Ole e 9, a 1,3-beta-glucanase (53% identity). Ole e 10 shares IgE B cell epitopes with proteins from a number of pollens, Latex, and vegetable foods such as Tomato, Kiwi, Potato, and Peach (17).

Clinical Experience

IgE-mediated reactions

Potato can induce symptoms of food allergy, sneezing, wheezing, asthma, rhinoconjunctivitis, atopic dermatitis contact urticaria, contact dermatitis and anaphylaxis in sensitised individuals (3,33-42).

In a Korean study of the allergenicity of wild-type and GM Potato, out of 1886 patients with various allergic diseases, skin prick tests for wild-type or GM Potato extracts were positive in 108 (5.7%). IgE antibodies were detected in 38 (58%) of 65 skin test-positive subjects evaluated (3).

In a Finnish study of 177 children aged less than 4 years and suspected of food allergy who were prick tested with Soybean and fresh Potato, 10/177 (5%) had positive SPT to Soybean, and 14 (7%) to Potato (31).

In an Indian study of 24 children aged 3 to 15 years with documented deterioration in control of their perennial asthma, IgE antibodies to Potato were documented in 83% (43). A French study reported that Hen's egg, Cow's milk, Wheat, fish, Potato, and Pork were the foods most frequently associated with childhood asthma (37).

In a Korean study whose aim was to evaluate the IgE sensitisation rate to and cross-reactivity among homemade agricultural products, 5,340 allergy patients complaining of various allergic diseases were evaluated. Sensitisation to Potato was documented in 5.7% (44).

In a European questionnaire-based study conducted at 17 clinics in 15 European cities, Potato was the 25th most prevalent cause of symptoms among 86 foods, affecting 18% of individuals (45).

An study of IgE-positive food-allergic patients in a hospital in Verona, Italy, during 2003 reported that IgE antibodies to Potato were found in 1 of 24 patients aged 0-2 years, 5 of 42 aged 3-12, 1 of 22 aged 3-5, 4 of 20 aged 6-12, and 20 of 191 over 12 years of age (46).

Studies and case reports demonstrate the range of symptoms that may occur in Potato allergy, and the variability of allergen sensitisation.

A study in Belgium evaluated 36 children, aged 4-36 months, with atopic symptoms and a positive SPT or IgE antibody test to Potato. Presenting symptoms in 17 children with proven Potato allergy were eczema (16/17), gastrointestinal complaints (8/17), urticaria and/or angioedema (5/17), wheezing/rhinitis (3/17), and anaphylaxis (2/17). Fifteen children were also Cow's milk-allergic and sensitised to Egg. The study reported that a serum Potato-specific IgE cut-off of $> 2 \text{ kU}_A/l$ provided 100% sensitivity and 62.5% specificity for diagnosis of Potato allergy, while a skin prick test score ≥ 3 had 100% sensitivity, and a score ≥ 4 had 100% specificity. Tolerance to cooked Potato was achieved in 80% of subjects at age 16-102 months. The authors concluded that most children with Potato allergy develop tolerance at a mean age of 4 years, and that allergy to cooked Potato was a risk factor for the development of pollen allergy (47).

Sera were assessed of 27 children, aged 4 months to 10 years, who were examined for food allergy and had atopic dermatitis, asthma, or allergic rhinitis and a positive skin prick test to raw Potato, and who were suspected of having allergy to Potato. The main clinical symptoms were asthma in 10,

atopic dermatitis in 25, and allergic rhinitis in 9. IgE antibodies for Potato were present in all 17 tested ($0.4 - 62.5 \text{ kU}_A/l$). Twenty of the 27 (74%) children were sensitised to purified patatin (6).

In a study evaluating allergens in 6 Potato strains, sera from 12 German patients suffering from adverse reactions to raw Potato were evaluated. All the patients also suffered from pollen allergy and had IgE to Birch and Mugwort pollen. Eight were males. Symptoms reported but not specifically attributed to Potato were diarrhoea ($n=1$), eczema ($n=5$), itching in the mouth ($n=5$), itching in the throat ($n=3$), rhinitis ($n=5$), swelling of the lips ($n=1$), and urticaria ($n=3$) (4).

An early study reported on a 24-year-old woman who experienced sneezing, rhinorrhoea, nasal obstruction, a tickling sensation and pain in the throat following inhalation of finely dispersed particles of raw Potato from the peeling and scraping of the Potato. Her atopic dermatitis was also aggravated. Cooked Potato was handled and eaten without any difficulty. Skin tests with raw Potato juice were positive. An intradermal test with cooked Potato was negative (34).

Two housewives have been reported in whom peeling raw Potatoes precipitated rhinoconjunctivitis and asthma attacks, and, in one of them, contact urticaria (48). Similarly, an atopic housewife is described with rhino-conjunctivitis, asthma, intense treatment-resistant dermatitis of the face, and contact urticaria from peeling raw Potatoes, all of which symptoms resolved on the removal of Potato (38). Other similar reports have been published (49).

Potato allergy has also been described as resulting in oral allergy syndrome (OAS) (40,50-51).

Contact urticaria due to raw Potato has been reported in children (52-53) and in adults (36,54) a 19-year-old man exhibited symptoms of immediate urticaria and angioedema related to contact with raw Potato (54). Pruritus, contact urticaria and generalised urticaria caused by the application of raw Potato to the face was described in a 25-year-old female. Surprisingly, skin tests were negative to raw Potato extract, but a provocation test, the

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application of raw Potato on the forearm, produced an immediate onset of pruritus and contact urticaria. High levels of IgE antibodies to raw Potato were demonstrated (41).

A 39-year-old woman with fingertip dermatitis complained that rubber gloves irritated her hands, but that handling uncooked Potato and Tomato aggravated her dermatitis; and that uncooked but not cooked Tomato, resulted in oral tingling and facial erythema. Cooked Potato did not affect her. IgE antibodies were detected for Latex, Tomato and Potato. The authors concluded that her allergy to Latex arose secondarily via primary sensitisation to Potato or Tomato (55).

The first report that cooked Potato could cause atopic dermatitis in infants under a year of age came in 1987 (whereas older children appeared to be asymptomatic) (56), and the symptom was subsequently reported in other age groups by other authors (10,57-58).

A study was conducted of 57 children under 1 year of age, 43 children aged 12 to 35 months, and 42 children aged 3 to 15 years, all with atopic dermatitis and all skin-tested with foods suspected to have caused this condition. Of the 24 patients aged 0-11 months who were skin prick-tested for Potato, 3 were positive, 2 of these cases being consistent with patient history. Of the 11 children aged 12-35 months who were skin prick-tested with fresh Potato, 1 was positive, and this was consistent with the patient's history. Four of 29 children aged 3-15 years tested positive, of which 3 cases were consistent with patient history. Allergen avoidance diets were beneficial; most symptoms disappeared within 2 weeks in 16 children, all of whom were under 5 years of age. Milk, cereals, cooked Potato, Banana, and Soy were the allergens responsible for hypersensitivity in these particular 16 cases (56).

Of 8 atopic children selected on the basis of suspicion of allergy to cooked Potato, all were found to have Potato-specific IgE antibodies; 2 of 8 had experienced immediate allergic reactions, and 6 of 8 had eczema that improved with a Potato-elimination diet. Seven patients were challenged with cooked Potato. The mean SCORAD index decreased from 43.3 before to 11.5 after elimination of

Potato from the diet. Potato ImmunoCAP® values ranged from 3.71 to greater than 100 kU_A/l. Potato challenge results were positive in 7 of 7 patients (58). In another study, of 12 infants who had atopic dermatitis (AD) and were suspected of having adverse reactions to Potatoes, rubbing the skin with raw Potato resulted in skin reactions in 7 (58%), and oral challenge was positive in 8 (67%). One infant presented with an immediate reaction, and 7 with a delayed reaction, *i.e.*, exacerbation of AD, after oral challenge to cooked Potato. Nine (75%) infants were shown to have IgE antibodies to Sol t 1, and SPT to natural Sol t 1 were positive in 6 (50%) Potato-allergic infants (10). In a recent Australian study evaluating skin prick tests to 31 different food allergens in a selected population of predominantly breast-fed young infants who had moderate to severe generalised atopic dermatitis, of the 59 infants (mean age 26.5 weeks) tested, 54 (91.5%) had positive responses to 1 or more foods. Potato was positive in 12 (20%) and strongly positive in 1 (59).

Anaphylaxis may also occur as a result of contact with Potato (39,49). A report described a 4-year-old with raw Potato-induced anaphylaxis, in the absence of oral allergy syndrome. Rapidly developing urticaria, angioedema, respiratory distress, vomiting and diarrhoea occurred after biting into a raw Potato that was being used for painting in preschool (49).

Anaphylaxis in an 11-year-old girl, exclusively breastfed for her first 4 months, has been reported. She developed anaphylactic symptoms after ingestion of Potato at 5 months of age when she was fed Potato for the first time. Subsequently, she developed urticaria, angioedema, and respiratory and systemic symptoms on dermal contact with Potatoes, ingestion of Potatoes, and exposure to cooking Potatoes or Potato pollen (39).

Food-dependent exercise-induced anaphylaxis with Potato may occur (60-61).

Other reactions

Occupational contact dermatitis to raw Potato has been reported (62).

Skinned Potatoes or pre-cut French fries may be dipped in a sulphite or metabisulphite solution to prevent browning. The sulphite may trigger asthma in susceptible individuals (63-64).

Potato processing workers may be affected by organic dust, endotoxin or moulds (65-68). Hypersensitivity pneumonitis has been described (69).

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f225 Pumpkin



Cucurbita pepo

Family: *Cucurbitaceae*

Common names: Pumpkin, Field pumpkin, Naked-seeded pumpkin, Cheese pumpkin, Pimpkin

Source material: Peeled fresh fruit

Synonyms: *C. moschata*, *C. maxima*, *C. mixta*, *Cucumis pepo*

See also: Pumpkin seed f226

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and between the species can cross-pollinate to produce hybrids; hence the great number of shapes and sizes, and the difficulty of strict botanical distinctions.

Allergen Exposure

Geographical distribution

Pumpkin is a gourd-like squash of the genus *Cucurbita* and the family *Cucurbitaceae* (which also includes gourds). The Pumpkin is thought to have originated in Central America, possibly Mexico, but is now grown widely in temperate and tropical zones. It is an annual climber, typically with a large, round, ribbed, edible orange fruit. But Pumpkin comes in several other forms such as the finer-textured, straw-coloured Cheese Pumpkin.

The term “Pumpkin” is also sometimes applied to other squashes that have hard, smooth rinds (sometimes lightly ribbed) covering edible flesh and a central seed cavity; confusion is especially likely because some other squashes share the same botanical classifications as Pumpkins. Zucchini or courgette (also called “baby marrow”) is a small summer squash, but both Pumpkin and zucchini are known as *Cucurbita pepo*.

True Pumpkins can be differentiated from other squashes by their fruit stalk: it is hard and polygonal in Pumpkins, but soft and round in other squashes. But varieties within

Environment

Pumpkin is unknown in the wild. Traditional Pumpkin pie usually a mixture of Pumpkin, eggs, sugar and spice, all baked in a pastry shell. On its own, Pumpkin can be boiled, baked, roasted, mashed or made into soup. It is a good source of beta carotene and vitamin E.

The seed can be eaten raw or cooked, and oil can be extracted from it (see Pumpkin seed f226). The leaves and young stems can be cooked as a potherb, and the flowers and buds can be cooked or dried. The vines, leaves, flowers and fruits have decorative functions.

The seeds and pulp are often used for medicinal purposes. The leaves are applied externally to burns. The sap of the plant and the pulp of the fruit can also be employed in this way.

Allergens

No allergens from this plant have yet been characterised. Whether the allergens in Pumpkin pulp is similar to those present in Pumpkin seed has not yet been determined. See Pumpkin seed f226.

A Bet v 6-related food allergen, isoflavone reductase, phenylcoumaran benzylic ether reductase, has been detected in the closely related zucchini (1). Zucchini may also contain a profilin (2).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected, as well as to a certain degree among members of the family *Cucurbitaceae* (3). Clinical cross-reactivity has been demonstrated among Pumpkin, Pumpkin seed, muskmelon, Watermelon, Cucumber and zucchini (4).

A cDNA clone encoding a Soybean allergen, Gly m Bd 28K, has been isolated. The polypeptide for the cDNA clone exhibits high homology with the MP27/MP32 proteins in Pumpkin seeds, and with the Carrot globulin-like protein. The clinical significance of this has not yet been determined (5).

The closely related zucchini has been implicated in Latex-fruit syndrome. Cross-reactivity was demonstrated with Hev b6.01, the chitin-binding protein (6).

Clinical Experience

IgE-mediated reactions

Pumpkin can induce symptoms of food allergy in sensitised individuals (4). Dermatitis, asthma, rhinoconjunctivitis, itching of the mouth, angioedema of the face and lips, generalised itching and mild dyspnoea after eating Pumpkin soup or thin vermicelli containing Pumpkin have been reported in a patient (4).

IgE antibodies to Pumpkin have been measured using the Pharmacia CAP System in children with food allergies (7), adults with atopic dermatitis (8), and children with atopic dermatitis and respiratory allergy (9).

An immediate-type reaction after contact with the pulp of butternut squash (*Cucurbita moschata*), resulting in dermatitis, has been reported (10).

Other reactions

Pumpkin seeds may be aspirated into the trachea in young children (11).

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f343 Raspberry



Rubus idaeus

Family: *Rosaceae*

Common names: Raspberry, Red raspberry, Wild raspberry, Common red raspberry, European red raspberry, American red raspberry

Source material: Frozen fruit

Synonyms: *R. buschii*, *R. vulgatus* var. *buschii*

Important included species: *R. occidentalis* – Black raspberry/Thimbleberry

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Allergen Exposure

Geographical distribution

This plant is native (though in different types) to temperate regions of both Europe and North America. Technically, Raspberries are those brambles in which the small, knobby, thimble-shaped fruit separates readily from the core or receptacle, unlike the similar-looking Blackberry, of which the fruit is firmly attached to the receptacle. Raspberries are generally thought to be only bright red, but in reality can also be dark blue, yellow or white.

The brambles grow wild in neglected land, hedgerows and woodland edges in many regions of the world; they are also cultivated, but not on the scale of many other fruits, because the inputs per volume are high enough to make them a luxury food.

Environment

Delicious when eaten out of hand, the fruit is also used in pies, syrups, flavourings, jams, jellies and other preserves. A herb tea is made from the dried leaves. The shoots and roots are also edible. Raspberries are rich in phenolic phytochemicals.

The leaves and roots are said to be anti-inflammatory, astringent, decongestant, ophthalmic, oxytocic and stimulant. Teas from the leaves and roots are often taken for gynecological problems. Externally, the tea is used as a gargle to treat tonsillitis and mouth inflammations, and as a soothing poultice for several external ailments.

Unexpected exposure

A purple to dull blue dye is obtained from the fruit. A fibre obtained from the stems is used in making paper.

Allergens

Besides the allergens isolated and/or characterised, Raspberry also appears to contain high-molecular-weight proteins which appear to be allergenic (1).

The following allergens have been characterised:

Rub i 1, a Bet v 1 homologue (2-4).

Rub i 3, a lipid transfer protein (1-2,3-4).

A chitinase and a cyclophilin have also been isolated (4).

Detecting Rub i 1 using orthodox assays has been problematic and may indicate low levels of this allergen in Raspberry. The difficulty may also be due to the low sensitivity of alkaline phosphatase western blotting, or to reduced cross-reactivity (1). The characterisation of this allergen required, inter alia, PCR methods (4).

A Raspberry chitinase has been isolated and shown to react with more than 80% of Raspberry allergic patient sera tested. It has a high sequence homology with class III chitinases. The presence of cross-reacting carbohydrate determinants (CCDs) has been shown to be present in Raspberry chitinase (4).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the family could be expected (3) and has been documented between various members (*e.g.*, Apricot and Peach). Similarly, cross-reactivity between a number of berries belonging to the same genus can be expected but has not fully explored. Inhibition studies have demonstrated cross-reactivity between Currant and Raspberry, but in this instance, the patient evaluated, who was allergic to Red and Black currant, and Peach, Apricot, and Nectarine, was able to tolerate Raspberry, Plum, Apple, and Pear (6).

Members of the genus *Rubus* include:

Raspberry – *R. idaeus*

Black raspberry/Thimbleberry – *R. occidentalis*

Cloudberry – *R. chamaemorus* L.

Dewberry – *R. caesius*

Salmon berry – *R. spectabilis*

Blackberry f211 – *R. fruticosus*

Caneberry – *R. laciniatus*

Marionberry – *R. ursinus*

Loganberry – *R. Loganobaccus*

Boysenberry – *R. ursinus x idaeus*

Due to Rub i 1, a Bet v 1 homologue, and Rub i 3, a lipid transfer protein, cross-reactivity may occur between Raspberry and other fruit or vegetables containing these panallergens (4). Raspberry cyclophilin is homologous to Bet v 7 and may result in cross-reactivity with other cyclophilin containing foods. Raspberry chitinase may result in cross-reactivity with other chitinase-containing plants (4).

Clinical Experience

IgE-mediated reactions

Raspberry may rarely induce symptoms of food allergy in sensitised individuals (7).

A study was conducted at 17 clinics in 15 European cities to evaluate the differences among some Northern countries regarding what foods, according to the patients, elicit hypersensitivity symptoms. Questionnaires concerning 86 different foods were administered to food-allergic individuals. The foods most often reported as eliciting symptoms in Russia, Estonia, and Lithuania were citrus fruits, chocolate, honey, Apple, Hazelnut, Strawberry, Fish, Tomato, Egg, and Milk, which differed from the situation in Sweden and Denmark, where Birch pollen-related foods, such as nuts, Apple, Pear, Kiwi, stone fruits, and Carrot were the most common reported culprits. The most common symptoms reported were oral allergy syndrome and urticaria. Birch pollen-related foods dominated as reported allergens in Scandinavia, whereas some Mugwort-related foods were apparently of more importance in Russia and the Baltic States. Among 1,139 individuals, Raspberry was the 32nd most reported food resulting in adverse effects in 16% (8).

Occupational asthma due to the inhalation of Raspberry powder has occurred. A 35-year-old woman complained of hayfever symptoms, wheezing, and shortness of breath in association with coating a chewing gum with Raspberry powder. A 9-mm prick test result positive for Raspberry powder was seen, and a radioallergosorbent test for Raspberry was positive (0.84 kU_A/l). Her symptoms

f343 Raspberry

disappeared after she was moved to another part of the factory (9).

Other reactions

Food poisoning affected more than 200 people in the region of Quebec City, Canada, after they ate Raspberries imported from Bosnia. Viral studies indicated a virus of the Calicivirus family (10).

In April 1988, an outbreak of gastroenteritis occurred among employees in a large company in Helsinki, Finland. The research data suggest that the primary source of the outbreak was imported frozen Raspberries contaminated by calicivirus (11).

An outbreak of 24 cases of hepatitis A in Aberdeen, Scotland, was traced to a large hotel. Studies implicated Raspberry mousse prepared from frozen Raspberries. The Raspberries were probably contaminated at the time of picking (12).

An outbreak of cyclosporiasis occurred in guests of a wedding reception in Philadelphia, Pennsylvania. In a retrospective cohort study, 54 (68.4%) of the 79 interviewed guests and members of the wedding party met the case definition. The wedding cake had a cream filling that included Raspberries (13).

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f322 Red currant

Ribes sylvestre

Family: *Grossulariaceae*

Common names: Red currant, Cultivated currant, Repts, Ribs, Risp

Source material: Frozen fruit

Synonyms: *R. rubrum* var. *sativum*,
R. sativum,
R. schlechtendalii,
R. spicatum, *R. vulgare*
var. *macrocarpum*,
R. vulgare var. *sylvestre*

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Allergen Exposure

Geographical distribution

The Red currant is a member of the genus *Ribes* in the gooseberry family, *Grossulariaceae*. It is native to parts of western Europe (Belgium, France, Germany, the Netherlands, northern Italy, and northern Spain). There are many species of currants, the most common ones being Red currant and Black currant. They come from a deciduous shrub normally growing 1 to 1.5 m tall, occasionally 2 m, with 5-lobed leaves arranged spirally on the stems. The flowers are yellow-green and inconspicuous, appearing in pendulous 4 to 8 cm racemes and maturing into bright-red translucent edible berries about 8 to 12 mm in diameter, 3 to 10 berries on each raceme (1).

Currants are sometimes cultivated but often wild, and are found in many regions of the Northern Hemisphere. The Red currant is similar to the Black currant (or Blackcurrant) but differs mainly in colour, being bright red or white. Confusingly, a small, seedless raisin is also called a “currant”.

Environment

With its pleasant acid flavour, the fruit can be eaten out of hand but is more often cooked in pies, jams, etc. It is a good source of vitamin C and potassium.

The fruit is said to be depurative, digestive, diuretic, laxative, refrigerant and sialagogue. It is used cosmetically in face-masks.

The fresh leaves contain the toxin hydrogen cyanide, though details of quantities are not known. In small quantities, hydrogen cyanide has been shown to stimulate respiration and improve digestion (and may be of benefit in the treatment of cancer). In excess, however, it can cause respiratory failure and even death.

Unexpected exposure

A yellow dye is obtained from the leaves, and a black dye from the fruit.

f322 Red currant

Allergens

In an individual with allergy to grass pollen and allergy to Red currant, serum IgE protein bands of 37 and 26 kDa were demonstrated (2).

No allergens from this food have yet been characterised.

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected (3). but this possibility has not been explored, the following are of particular interest:

Gooseberry/English gooseberry – *R. grossularia*

Blackcurrant/black currant – *R. nigrum*

Clinical Experience

IgE-mediated reactions

Anecdotal evidence suggests that Red currant may, in rare instances, induce symptoms of food allergy in sensitised individuals; however, few studies have been reported to date (2,4-6).

The aim of a study conducted at 17 clinics in 15 European cities was to describe the differences among some northern countries regarding self-reported hypersensitivity symptoms from foods. Patients with a history of food hypersensitivity were asked to fill out a questionnaire in which 86 different foodstuffs were listed. "Slight symptoms" were most common with, among others, Red currant, which was the 49th most reported food resulting in adverse effects, affecting 9.2% of 1,139 individuals (6).

In a rare case of anaphylaxis, a 47-year-old woman presented with generalised urticaria, dysphagia, dyspnoea, pruritis of the palms and soles, hyponia, and tachycardia 2.5 hours after eating Red currants. A month later, she developed generalised urticaria after eating black-currant jam. Prick-to-prick SPT was positive to Red currant and black currant. Serum IgE antibodies were absent for both (4).

An earlier report of anaphylaxis to Red currant also lacked detectable IgE levels, but exhibited specific IgA and IgM antibodies instead (4).

A study reported on a 50-year-old woman with allergy to grass pollen and oral allergy syndrome involving several fruits. She presented with pruritus and pharyngeal occupation with dysphagia while eating fresh Red and black currant jam. She also reported similar episodes with Peach, Apricot, and nectarine (jam, juice, and fresh). She tolerated other fruits of the *Rosaceae* family (*i.e.*, Raspberry, Plum, Apple, and Pear). Skin prick-to-prick tests with fresh Red and Black currants were negative, and positive to Peach. IgE antibody level to Red currant was 5.7 kU_A/l, and 2.92 kU_A/l for Peach (2).

Other reactions

See under Environment.

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f330 Rose hip

Rosa spp.

Family: *Rosaceae*
Common names: Rose hip, Rosehip, Rose haw
Source material: Freeze-dried fruit
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Allergen Exposure

Geographical distribution

Rose hip, from a species of Rose flower, is a member of the *Rosaceae* family, which also includes fruit such as Apple, Peach and Apricot.

Rose hip is the edible ripe “fruit” of the Rose plant (usually the Dog or Wild rose), the pod and the base of the flower, and is typically red to orange, but might be dark purple to black in some varieties. Rose-hips (not true fruits, but enlarged floral cups, up to 30 mm in diameter) develop from Rose blossoms and are a popular natural remedy for many complaints, including osteoarthritis, rheumatoid arthritis, and lower back pain.

Environment

Rose hip is used to make jellies, jams, tea, wine and syrup (which is often added to cough mixtures and other medicines). Because of its tart taste, it is seldom eaten raw. Rose hips are typically gathered wild, dried, de-seeded, and shipped as dried pulp. They are often ground into powder and sold in health-food stores, or added to other foods as a supplement.

Rose hip is particularly high in Vitamin C and is a good source of lycopene, riboflavin, pectins, nicotinic acid, and malic acid (it is also a fairly good source of essential fatty acids, which is unusual for a plant food). Rose hip is being investigated as a treatment for osteoarthritis, cancer and other serious ailments.

Unexpected exposure

See under Environment.

Allergens

No allergens from this food have yet been characterised.

A 13 kDa lipid transfer protein-like protein has been isolated (1).

Potential cross-reactivity

An extensive cross-reactivity among the fruit of the different individual members of the *Rosaceae* family often occurs (2). Apple, Apricot and Peach, for example, are involved, but whether cross-reactivity between Rose hip and the fruit of the other members occurs has not yet been reported. Recently, the presence of a lipid transfer protein (LTP) has been reported (1), and this substance may cause cross-reactivity with other plants containing LTPs, including Apple, Apricot and Peach.

f330 Rose hip

Clinical Experience

IgE-mediated reactions

Anecdotal evidence suggests that Rose hip may uncommonly induce symptoms of food allergy in sensitised individuals; however, few studies have been reported to date (1,3).

A study was conducted at 17 clinics in 15 European cities to evaluate the differences among some Northern countries regarding what foods, according to the patients, elicit hypersensitivity symptoms. According to questionnaires administered to food-allergic individuals concerning 86 different foods, the foods that were most often elicited symptoms in Russia, Estonia, and Lithuania were citrus fruits, chocolate, honey, Apple, Hazelnut, Strawberry, Fish, Tomato, Hen's egg, and Cow's milk, a situation that differed from that of Sweden and Denmark, where Birch pollen-related foods such as nuts, Apple, Pear, Kiwi, stone fruits, and Carrot were the most common reported causes. The most common symptoms reported were oral allergy syndrome and urticaria. Birch pollen-related foods dominated as reported culprits in Scandinavia, whereas some Mugwort-related foods were of more importance in Russia and the Baltic States. Among 1,139 individuals, Rose hip was the 58th most often reported food, resulting in adverse effects in 8.1% (3).

In a 31-year-old man sensitised to *Rosaceae* without related pollen allergy, an anaphylactic reaction was reported to consumption of a fruit tea containing Rose hip. He presented with abdominal pain, pruritus and generalised urticaria 20 minutes after drinking fruit tea. He had previously reported oral allergy syndrome to related *Rosaceae* family foods, Peach and Almond, and anaphylaxis after consuming Cherry. The tea was a blend of Rose hip, hibiscus, Apple, Orange peel and Elderberry. The patient was shown to be sensitised to fruit tea extract and Rose hip extract. The presence of a lipid transfer protein in the extract was demonstrated (1).

Other reactions

The hairs on Rose hips and the seeds within them are usually removed, but if not they can pose a hazard. The hairs are mechanically irritating, and the seeds have been implicated in toxic reactions.

Reactive airway disease occurring in cultivators and processors of herbal teas, such as Sage, Chamomile, Dog rose and Mint, has been described (4).

Rose hip keratitis has been reported (5).

An evaluation was done of the rate of occupational asthma in workers at a Rose (*Rosa domescena*) oil extracting plant. This is a species closely related to the Dog rose. It was reported that a specifically prepared skin prick test using a Rose extract was positive for 53.8% of the test subjects. It was concluded that the workers in a Rose oil extracting plant are more susceptible to Rose pollens (6).

Respiratory changes have been reported in tea workers, including those processing Dog rose (7-9).

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Spinachia oleracea

Family: *Amaranthaceae*

Common names: Spinach, Savoy spinach

Source material: Freeze-dried spinach

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Allergen Exposure

Geographical distribution

The Spinach plant is indigenous to the Middle East. Spinach was subsequently grown in Spain from the 8th century, and it was the Spaniards who eventually introduced it to the United States. Spinach is now produced widely throughout the world for its edible leaves. It is the only edible vegetable in the *Chenopodiaceae* (Spinach) family. Two varieties exist: Savoy (wrinkled-leaf) and Semi-Savoy (flat-leaf).

The plants are grown from seed and harvested while young and tender. Varieties differ in their leaves from smooth and broad to arrow-shaped to savoyed or wrinkled, but all leaves are non-hairy. Their colour tends to be dark green. Since winter-hardy varieties of this annual are available, Spinach can be eaten year-round.

Environment

Spinach is not known in the wild. Large quantities are grown commercially for canning and freezing, as well as for fresh consumption. Spinach may be used raw in salads, or cooked (usually by boiling or sautéing) as a vegetable or as part of another dish. Many dishes that have Spinach as an integral ingredient are described with the phrase à la Florentine. The seeds can be eaten raw or cooked, or can be sprouted and added to salads. Spinach is a rich source of iron as well as of vitamins A and C. But because Spinach contains oxalic acid – which inhibits the body's absorption

of calcium and iron – the nutritional value is somewhat diminished. Some modern varieties have been developed that are low in oxalic acid. Spinach contains high levels of histamine; reactions may be indistinguishable from an IgE-mediated reaction.

The plant is carminative and laxative. In experiments, it has been shown to have hypoglycaemic properties. It has been used as a remedy for a variety of complaints.

Unexpected exposure

Chlorophyll extracted from the leaves is used as an edible green or yellow dye.

Allergens

Spinach extract contains a 20 and a 25 kDa protein, as well as 14-18 kDa proteins (minor bands on blot). One or more proteins appear to be heat-stable (1). A cross-reactive 30 kDa protein has also been detected (2).

The following allergen has been characterised:

Spi o 2, a profilin (3).

f214 Spinach

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected, as well as to a certain degree among members of the family *Amaranthaceae* (4). Cross-reactivity has been reported between Spinach and Chard, as might be expected (5, 6).

A single report was made of anaphylaxis to Spinach and concomitant oral allergy syndrome to Mushroom. Cross-reactivity was demonstrated between these 2 foods, and the authors suggest that this may be due to common epitopes (1). A subsequent study identified a 30 kDa protein in each food, which inhibition assays confirmed to be related and a relationship was demonstrated between allergy to moulds (*Alternaria alternata*, *Cladosporium herbarum* and/or *Aspergillus fumigatus*) and positive skin prick tests with Mushroom (*Agaricus bisporus*) and/or Spinach (2).

A study reports on the possible cross-reactivity between Spinach and Latex (two cases of cross-allergenicity between Latex and Spinach have been reported previously) (6-8). The authors suggest that there may be a common epitope (9-10).

Clinical Experience

IgE-mediated reactions

Spinach can induce symptoms of food allergy in sensitised individuals (1,5-6,10).

Oral allergy syndrome induced by Spinach has been reported (5).

Two anaphylactic episodes to Spinach occurring in a 31-year-old were reported. She also developed oral allergy syndrome to Mushroom, and cross-reactivity was demonstrated between these 2 foods. Skin reactivity was not detected to commercial extract of Spinach, but instead to fresh raw and boiled Spinach (1).

Exercise-induced anaphylaxis associated with food allergy to Spinach has been reported (10).

A 54-year-old female working as a vegetable farmer presented with painful pruritic skin lesions on both hands. Physical examination showed hyperkeratotic fissured eczema. RAST, prick, and patch testing revealed type I and IV hypersensitivity to Spinach, rucola, and chives, so that a protein contact dermatitis was diagnosed (11).

Other reactions

A 51-year-old woman developed hypersensitivity pneumonitis to Spinach powder used as a food dye (12). A 30-year-old man with chronic occupational rhinitis and asthma as a result of exposure to Spinach powder in a factory was described. Spinach-specific IgE was 15.4 kU_A/l. Ten minutes after handling the dried Spinach powder, he experienced the onset of dyspnoea. Eight hours later, there was recurrent dyspnoea and another decrease in FEV₁, accompanied by fever and arthralgia (13).

Phyto dermatitis due to contact with Spinach has been reported (14).

Spinach contains a high level of histamine, and the differentiation of IgE-mediated reactions from pseudoallergic reactions caused by the histamine is important (5).

Due to the presence of oxalates, people with a tendency to rheumatism, arthritis, gout, kidney stones or hyperacidity should use special caution if including this plant in their diet, since it can aggravate their condition.

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f44 Strawberry



Allergen Exposure

Geographical distribution

Strawberry plants make up about 12 species of low, runner-bearing perennial herbs. The Strawberry is the sweet red fruit borne on the runner. Most are native to northern temperate regions. Strawberry plants are cultivated as ornamentals and, especially, for their fruit. Strawberry was cultivated in the days of the Greeks and Romans, and commercial cultivation began about 250 years ago in France. Most cultivated Strawberries are derived from crosses between *F. chiloensis* and *F. virginiana*.

Environment

Both cultivated and wild Strawberries are eaten raw and used in desserts. They are often used to make preserves, and are even dried. The leaves are eaten raw and cooked and used as a tea substitute. The root is a coffee substitute in India.

The fruits contain salicylic acid. Both the fruits and leaves are used in a variety of herbal remedies. Externally applied, Strawberry is a remedy for chilblains and sunburn.

Fragaria vesca

Family: *Rosaceae*

Common name: Strawberry

Source material: Freeze-dried fruit

Other important Strawberry species:
F. alpina, *F. chiloensis*, *F. virginiana*

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Unexpected exposure

The fruit is also an ingredient in skin-care creams and tooth-whiteners. The flowers sometimes serve as a compost activator.

Allergens

A number of allergenic proteins have been detected, including a 30 kDa cross-reactive protein (1).

The following allergens have been characterised:

Fra a 1, a Bet v 1 homologue (2-7).

Fra a 3, a lipid transfer protein (2,6,8-10).

Fra a 4, a profilin (2,6,11).

Fra a 1 has been shown to vary among different Strawberry varieties. For 153 other proteins, biological variation is affected more by different growth conditions than by different taxonomical varieties. The allergen content was found to always be lower in colorless (white) Strawberry varieties than in the red ones (3).

Fra a 3 LTP gene expression in Strawberry is stimulated by wounding and repressed by cold stresses (9). Examination of Strawberry allergy in the Mediterranean area showed that, although Strawberry LTP (Fra a 3) is present in Strawberry extracts and is capable of eliciting histamine release in Peach LTP- (Pru p 3)-sensitised patients, the concentrations needed are much higher than for Pru p 3, so that these patients do not show clinical Strawberry allergy; therefore Fra a 3 does not seem to be clinically relevant (6).

A Bet v 6-related food allergen, PCBER (phenylcoumaran benzylic ether reductase), has been detected (7,12-13).

A beta-1,3-glucanase gene has been isolated from Strawberry; this enzyme has been shown to have allergenic potential in other plants (14-15). Its allergenic potential in this instance was not evaluated.

The pectolytic enzymes polygalacturonase, pectate lyase and pectin methylesterase (PMEs) have been isolated from Strawberry and are partly associated with a decrease in fruit firmness observed during ripening. Maximum PME activity was detected in green fruits and steadily decreased to a minimum in senescent fruits (16). Although these enzymes may be allergenic in other plants, their allergenic potential was not evaluated in the case of this one.

The white variety of Strawberries, known to be tolerated by individuals affected by allergy, were found to be virtually free from Strawberry allergens. Also, several enzymes in the pathway for biosynthesis of flavonoids, to which the red color pelargonidin belongs, have been shown to be down-regulated in these Strawberries (4).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected. Extensive cross-reactivity occurs among various members of the *Rosaceae* family, but, to date, the amount of cross-reactivity between Strawberry and other members of the family has not been evaluated (17).

Fra a 1 has a 54-61% and a 77-78% sequence identity with Bet v 1 and the homologous Apple allergen Mal d 1, respectively (4-5). Cross-reactivity with other plants containing a Bet v 1 homologue is therefore possible.

Allergy to *Rosaceae* fruit is frequently associated with Birch pollinosis in Central and Northern Europe, and with grass pollen allergy in central Spain. The main cross-reactive structures involved in individuals who have Birch pollen allergy are Bet v 1 and profilin; in grass pollen-allergic individuals,

profilin and carbohydrate determinants. *Rosaceae* fruit allergy can occasionally occur in patients without pollinosis. Eleven patients from central Spain allergic to Apples, Peaches, and/or Pears but not to pollen were compared with 22 control subjects with combined grass pollen and fruit allergy. *Rosaceae* fruit allergy without pollinosis was reported to be severe, with 82% of patients reporting systemic symptoms, mainly anaphylaxis (73%), whereas oral symptoms were less frequent (64%). Anaphylaxis was seen in 36% of patients. The fruit allergens involved showed cross-reactivity among *Rosaceae* species but were not related to profilin or Bet v 1. Ninety-one percent of patients with combined grass pollinosis and fruit allergy reported oral allergy, 45% reported systemic symptoms, 18% reported anaphylaxis, and 9% reported anaphylactic shock. The study concluded that allergy to *Rosaceae* fruits in patients without a related pollen allergy is a severe clinical entity. Profilin- and Bet v 1-related structures are not involved in *Rosaceae* fruit allergy without pollinosis (18).

A recent study concluded that in pollen-allergic patients who frequently present with allergic symptoms after ingestion of any of several kinds of plant-derived foods, the majority of these reactions is caused by 4 distinct cross-reactive structures that are present in Birch pollen. Proteins that share epitopes with Bet v 1, the major Birch pollen allergen, occur in pollens of several tree and other species: Apple, stone fruits, Celery, Carrot, nuts, and Soya beans. Approximately 70% of patients who are allergic to Birch pollen may experience symptoms after consumption of foods from these groups. In contrast, 2 minor allergenic structures, profilins and cross-reactive carbohydrate determinants (CCD), which sensitise approximately 10-20% of all pollen-allergic patients, are also present in grass pollen and weed pollen. IgE-binding proteins related to the Birch pollen minor allergen Bet v 6 (PCBER) are found in Apple, Peach, Orange, Lychee, Strawberry, Persimmon, zucchini, and Carrot. However, the occurrence of cross-reactive IgE antibodies often does not correlate with the development of clinical food allergy (12-13). For example, in a DBPCFC study, reactions to Peach occurred in 22 patients, in 6 to Apple, and in 5 to Apricot. The authors

f44 Strawberry

concluded that the presence of skin reactivity and IgE antibodies should not be taken as the only guide for multi-species dietary restrictions. Nevertheless, the possibility of clinical allergy to other *Rosaceae* should not be neglected. If the reported reaction is confirmed, current tolerance to other *Rosaceae* should be precisely established, unless there has been ingestion without symptoms after the reaction (19).

IgE antibodies were found to Peach, Guava, Banana, Mandarin and Strawberry in a patient experiencing anaphylaxis after eating Peach. The cross-reactive protein was identified as a 30 kDa protein occurring in all of the fruits (1,20).

In a study of 61 patients with a documented history of IgE-mediated reactions to Grape or its products (wine, juice, and wine vinegar), it was found that 82% were co-sensitised to Apple, 71% to Peach, 48% to Cherry, 33% to Strawberry, 49% to Peanut, 43% to Walnut, 31% to Hazelnut, 26% to Almond, and 29% to Pistachio. The high prevalence of concomitant reactivity to other fruits elicits interest in the clinical relevance of these findings among the Grape-allergic population (21).

A Mexican retrospective review of 232 patients with pollen allergy, among whom sensitisation to Olive tree pollen was found in 41.5%, 16.6% experienced symptoms of oral allergy syndrome, mainly related to Apple and Strawberry (22).

Clinical Experience

IgE-mediated reactions

Strawberry may commonly induce symptoms of food allergy in sensitised individuals, and was reported to be a common cause of allergy in children (6,23-26). Birch pollen-related foods appeared to dominate in Scandinavia, whereas some Mugwort-related foods were of more apparent importance in Russia and the Baltic States. Among 1,139 individuals, Strawberry was the 7th-most-reported allergenic food, resulting in adverse effects in 31% (25). According to a Polish study, most positive SPT to food allergens occurred with nuts, Celery, Rye flour, Carrot, Strawberry, Pork, and beans (27). In a Mexican study,

among 1,419 allergic patients aged between 1 and 18 years, 442 (31%) had positive SPT to 33 tested foods. Fish, Cow's milk, seafood, Soy, beans, Orange, Onion, Tomato, Chicken, nut, Lettuce and Strawberry were together responsible for 58% of all the allergic reactions (28).

A cross-sectional, descriptive, questionnaire-based survey was conducted in Toulouse schools to determine the prevalence of food allergies among schoolchildren. Of 2,716 questionnaires returned, 192 reported a food allergy. Eight reported allergy to Strawberry (29).

A study was conducted to evaluate the differences among some northern countries regarding what foods, according to the patients, elicit hypersensitivity symptoms: 1,139 patients with a history of food hypersensitivity filled out a questionnaire in which 86 different foodstuffs were listed. The foods reported as eliciting symptoms differed among countries. In Russia, Estonia, and Lithuania, citrus fruits, chocolate, honey, Apple, Hazelnut, Strawberry, fish, Tomato, Hen's egg, and Cow's milk were most often reported as causes of hypersensitivity. In Sweden and Denmark, Birch pollen-related foods, such as nuts, Apple, Pear, Kiwi, stone fruits, and Carrot, were the most common reported causes. In all countries, children, more often than adults, had symptoms of allergic reaction to citrus fruits, Tomato, Strawberry, Cow's milk, Hens egg, and fish. Most patients (95%) reported hypersensitivity to several foodstuffs (median: 8 foods). The most common symptoms were oral allergy syndrome and urticaria (25).

Reactions reported include symptoms of food allergy (abdominal pain and cramping, nausea and vomiting), atopic dermatitis, asthma, rhinitis, and symptoms of oral allergy syndrome. Allergy to Strawberry has also been reported as part of a true multifoody allergy in a 4-year-old child (30).

A study evaluating the role of profilin and lipid transfer protein was conducted; the subjects were 28 patients recruited from Spain and Italy who had a reported history of Strawberry allergy. Reported symptoms were oral allergy syndrome (n=26), asthma (n=1),

generalised urticaria (n=1), and pruritus (n=1). IgE antibodies were detected in 9 but were evaluated only in 16. Sixteen of the 17 skin prick tests performed were positive (6).

Food-dependant exercise-induced anaphylaxis attributed to Strawberry has been reported (31).

Other reactions

Contact urticaria to Strawberry has been documented (32-33). Contact urticaria to Cucumber pickle and Strawberry has been reported (34). A fixed-food-eruption to Strawberry was also reported (35).

Allergic contact dermatitis to Strawberry lip salve has been reported (36).

Strawberry contains a variety of aromatic and vasoactive substances, e.g., histamine, that may result in non-IgE-related reactions. For example, urticaria may occur as a result of excess production of histamine triggered by the fruit.

Unripe Strawberry fruit may produce a triterpene phytoalexin, which appears to be involved in the resistance of Strawberry to a particular fungus. Phytoalexin may result in photosensitivity dermatitis (37).

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f44 Strawberry

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f54 Sweet potato

Ipomoea batatas

Family: *Convolvulaceae*

Common names: Sweet potato, Sweetpotato, Yam, Batata

Source material: Fresh sweet potato

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Allergen Exposure

Geographical distribution

The Sweet potato, belonging to the Morning glory family and not related to Potatoes, is native to the West Indies and Central America, although early reports place it in Indonesia and Philippines too. It is a vine-like, perennial herb but is cultivated as an annual. It is now grown in more than 100 countries in tropical, sub-tropical and temperate climates. It is 1 of only 7 world food crops with an annual production of more than 100 million metric tons per year, and ranks thirteenth globally in production value among agricultural commodities. It is cultivated primarily for the enlarged edible storage roots, which provide large amounts of starch.

Although variation in storage root skin and flesh colour is abundant, there are 2 general types of Sweet potato: a dry, mealy, and a moist, seedy type. In most developing countries, the root has white to cream-coloured flesh and a bland, non-sweet flavor. In contrast, the type most used in developed countries has yellow or deep orange root flesh, a moist texture, a very distinct flavour, and high sugar content. This type is mistakenly referred to as “Yams” in the US, but the true Yam is of the family *Dioscorea*.

Environment

Sweet potatoes are a staple food of many peoples of the tropics, but in the industrialised world are principally a vegetable or a dessert. They are cooked, canned, frozen, dehydrated, and used as a source of flour, starch, glucose syrup and alcohol. Various products such as candy, pastas, flour, and drinks are produced in local industries. Both the starchy roots and vines can be used as animal feed. Nutrients supplied include vitamin C, iron, potassium, calcium, and fibre. The moist orange-fleshed variety is high in beta-carotene (a precursor of vitamin A).

Sweet potatoes contain trypsin inhibitors, and if eaten raw may reduce the ability to utilise protein. However, trypsin inhibitors do not survive cooking and are of no consequence in cooked roots.

f54 Sweet potato

Unexpected exposure

The starch is used commercially for sizing textiles and papers, for the manufacture of adhesives, and in laundries. In the US, large quantities of Sweet potatoes, either freshly harvested or shredded and dried, are used as feed for livestock.

Allergens

No allergens from this plant have yet been characterised.

A beta-amylase has been isolated. It showed 50-60% amino acid sequence identity with beta-amylases from Soybean and Barley, and about 25% with bacterial beta-amylases deduced from cDNA sequences (1). Its allergenic potential has not been evaluated.

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected, as well as to a certain degree among members of the family *Convolvulaceae* (2).

Clinical Experience

IgE-mediated reactions

Anecdotal evidence suggests that Sweet potato can occasionally induce symptoms of food allergy in sensitised individuals; however, no studies have been reported to date.

IgE antibodies to Sweet potato have been measured in children (3-4) and in adults (5) using the Pharmacia ImmunoCAP® System. Other species of *Ipomea* are involved in allergic pollinosis (6).

Other reactions

Sweet potato has been implicated as a cause of infantile food protein-induced enterocolitis syndrome (FPIES), a severe, cell-mediated gastrointestinal food hypersensitivity typically provoked by Cow's milk or Soy (7).

In a study of subjects with irritable bowel syndrome (IBS), 70 fresh food extracts were applied to the back by the prick-by-prick method. SPT was positive in 17 (38.6%) treated patients, in 5 (16.1%) untreated patients and in 1 (3.3%) control. Three of 44 (17.6) of the treated patients were skin prick test-positive for Sweet potato (8).

Sweet potato may be infected with the mould *Fusarium solani*, which produces a toxic substance, furanoterpenoid (9).

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Lycopersicon lycopersicum

Family:	<i>Solanaceae</i>
Common names:	Tomato, Garden Tomato, Love Apple
Source material:	Whole freeze-dried tomato
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**Allergen Exposure****Geographical distribution**

Tomato is a vine fruit of the Nightshade family. Tomatoes were used for food by the Indians of Peru before the arrival of Europeans. Tomato is the most universally accepted vegetable among all cultural groups, and second only to Potato as a vegetable in world food production. A great variety of cultivars exist, from the tiny Cherry tomato to giant prize varieties the size of Grapefruit; and though the stereotyped colour is red, colours can range from green to purple, and some varieties have stripes. Many wild forms are found, including a closely related species called Currant tomato (*L. pimpinellifolium*).

Environment

Wild forms are found, but are generally not good to eat. Tomato can be eaten raw or cooked, but is mostly processed into juice, canned goods, etc. It can be used as a savoury vegetable, especially in salads, and as a flavouring in soups and other cooked foods. The fruit can also be dried and ground into a powder to serve as a flavouring and thickening agent in soups, breads, pancakes, and so on. An edible oil can be obtained from the seed. The fruit is rich in vitamins A and C, calcium and potassium.

The skin of Tomato fruits is a good source of lycopine. Tomato is used as a herbal remedy for a variety of conditions. The pulped fruit is a wash for oily skin. The oil can be used in making soap.

All green parts of the plant are poisonous. A spray made from Tomato leaves is an effective but very toxic insecticide.

Allergens

Allergens began to be isolated around 4 decades ago (1) but have only recently been characterised.

In a study of 2 patients with significant immediate hypersensitivity reactions to Tomato, proteins similar to each other were detected in skin and seed extracts, with protein bands discernible at molecular weights of 21, 33, and 43 kDa. One band appeared to be a heat-stable allergen, as both patients in the study developed severe allergic reactions to both cooked and fresh Tomato. One patient reacted specifically to a 43 kDa protein band on IgE immunoblot (2).

The following allergens have been characterised:

Lyc e 1, a 14-16 kDa protein, a profilin (3-10).

Lyc e 2, a 50 kDa protein, a beta-fructofuranosidase (3,9,11-13).

Lyc e 3, a 8-10 kDa protein, a lipid transfer protein (3,8,14-17).

Lyc e Chitinase, a 31 kDa protein (18).

Lyc e Glucanase, a 55 kDa protein (19-21).

Lyc e Peroxidase, a 45 kDa protein (22).

Lyc e PME, a pectin methylesterase inhibitor (23).

Lyc e LAT52 from pollen (24).

f25 Tomato

Lyc e 1, a profilin, appears to be a minor allergen in Tomato. The recombinant Tomato profilin rLyc e 1 demonstrated high sequence identity to other allergenic food and pollen profilins and was reactive with 22% (11/50) of Tomato-allergic patients (5).

In another study of patients with adverse reactions to Tomato, 44% presented IgE antibodies to Tomato profilin and 35.5% to Cross-reactive Carbohydrate Determinants (CCDs). Two patients were sensitised to the lipid transfer protein Lyc e 3 (8).

Lyc e 3, a lipid transfer protein (LTP), is a potentially severe food allergen, in particular due to its extreme resistance to pepsin digestion. Cross-reactivity among foods containing LTPs is often accompanied by clinical food allergy, frequently including systemic reactions (17).

Specific allergens may be involved in specific adverse reactions. For example, Lyc e 3, a lipid transfer protein, appears to be involved in severe systemic reactions (17). In patients with oral allergy syndrome (OAS), 4 proteins binding with IgE from more than half of the patients' sera were found to be polygalacturonase 2A (Lyc e 2), [beta]-fructofuranosidase, superoxide dismutase (SOD) and pectinesterase (PE). The concentrations of PG2A, [beta]-fructofuranosidase and PE were highest in the red ripening stage (11).

The allergenicity of Tomato appears to be influenced by hormone treatment with ethylene and salicylic acid. In a report on 8 patients who experienced anaphylaxis after eating raw Tomato, the wheals obtained in prick tests were significantly more severe with the extracts of Tomato treated with ethylene and salicylic acid, and the patients who presented greater wheal diameters in skin tests were those who had more-severe episodes of anaphylaxis. Neither the protein stain nor the IgE immunodetection patterns clearly varied between the untreated and the hormone-treated samples. The study concluded that treatment with plant hormones induced a more intense cutaneous response (25).

A 2S storage albumin, named Lec2SA, has been isolated from the seed of Tomato. The sequence of Lec2SA was similar to that

of 2S albumins from different plants, such as Brazil nut and castor beans (26). The allergenic potential of the protein was not evaluated.

A cDNA clone encoding profilin from pollen grains (not fruit) of Tomato has been isolated (the clinical significance of this has not yet been determined). Sequence analysis of the insert shows 87% similarity to Tobacco, 78% to Timothy grass profilin, 77% to Arabidopsis profilin, 77% to Maize ZmPro3, and 73% to Birch profilin (27).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected, as well as to a certain degree among members of the family *Solanaceae* (28). This has been shown in IgE antibody inhibition experiments, where Tobacco, Mugwort pollen, and Tomato extracts inhibited the binding of a Tobacco-allergic patients' serum to Tobacco leaf. Tobacco (*Solanaceae* family) is often used as a contact insecticide in gardens (29).

In patients with Tomato allergy and multiple sensitisation to other foods and Birch pollen, IgE directed against Tomato profilin showed a strong cross-reactivity with profilins from plant food sources and Birch pollen (5). Bell pepper profilin (Cap a 2) and the Tomato profilin Lyc e 1 display 91% identity, whereas Tomato profilin from pollen shares only 75% identity with Tomato fruit profilin (6-7). Eleven out of 34 food-allergic patients (32%) display IgE binding to both purified profilins (6). An Italian study found that hypersensitivity to the profilin Bet v 2 was strongly associated with clinical allergy to citrus fruit (39% in patients monosensitised to Bet v 2), Melon or Watermelon (67%), Banana (66%), and Tomato (33%). The sensitivity of a history of allergy to gourd fruit, citrus fruit, Tomato, Banana, or a combination thereof as a means to detect profilin-hypersensitive patients was 85% (41/48). The authors suggested that in clinical settings in which laboratory investigations are not easily accessible, allergy to Melon, Watermelon, citrus fruit, Tomato, or Banana can be used as a marker of profilin hypersensitivity once a sensitisation to Latex and lipid transfer protein is ruled out (30).

Many earlier studies reported that patients with grass pollen-allergic respiratory disease report adverse food reactions more frequently than do patients allergic to House dust mite (31-32), probably as a result of the profilin panallergen. Positive SPT to food allergens was shown to be more frequent in children with allergy to grass pollen (59.8%) than in children with allergy to *Dermatophagoides* (9.4%). A considerably high frequency of positive reactions to Tomato (39.2%), Peanut (22.5%), Green pea (13.7%), and Wheat (11.7%) was observed in children with allergy to grass pollen (33). Other foods included Garlic, Onion, and fruits such as Peach (31-32). Whether this is due to a panallergen was not clearly established, but in inhibition studies with Tomato and extract from Birch pollen, Mugwort pollen, Apple, and Celery, significant inhibitions among all of these allergens were found. Epitopes exclusive to grass pollen and Tomato were not detected. Cross-reactivity between Tomato fruit and grass pollen allergens was confirmed by the EAST inhibition assay, the structures responsible being a 16 kDa protein, which was identified as profilin (9). Tomato profilin has also been shown to have a high degree of identity with profilin from Goosefoot pollen (34).

Other studies have reported an association between grass pollinosis and sensitisation to Tomato, Potato, Green pea, Peanut, Watermelon, Melon, Apple, Orange and Kiwi (35). A high frequency (50%) of food hypersensitivity occurs in patients with allergic rhinoconjunctivitis. Food allergens seen more frequently were shellfish, Tomato, Rice, and Peanut (36). A Polish study reported that 10-20% of children sensitised to grass pollens were also sensitised to Carrot, Celery, Apple, Tomato and nuts (37).

The lipid transfer protein (LTP) panallergen in Tomato (Lyc e 3) may result in cross-reactions with other foods containing this panallergen, e.g., *Rosaceae* fruit, tree nuts, Peanut, beer, Maize, Mustard, Asparagus, Grape, Mulberry, Cabbage, Date, Orange, Fig, Kiwi, Lupine, Fennel, Celery, Eggplant, Lettuce, Chestnut and Pineapple (17,38-39).

Approximately 50% of patients who are sensitised to Latex also show sensitisation to foods, most commonly fruit. These foods include Avocado, Potato, Banana, Tomato, Chestnut, and Kiwi (40-44). These individuals may report symptoms of oral allergy syndrome after ingestion of these foods (45). In a study of food allergy in Latex-allergic individuals, 18.4% (93 out of 505) were positive, and 69.9% of these positive cases were seen in a group of children with Latex-specific IgE antibodies, most frequently to Potato, Tomato, Sweet pepper, and Avocado (46). In 137 patients with Latex allergy, 49 potential allergic reactions to foods in 29 (21.1%) patients were reported. Foods responsible for these reactions included Tomato in 3 (6.1%) (47). Class I chitinases appear to be the relevant cross-reacting proteins in Latex-fruit allergy involving Cherimoya, Passion Fruit, Kiwi, Papaya, Mango, Tomato or Wheat. These allergens are activated by stress to the plant (18).

Tomato, Potato, and Latex contain a common protein of 44-46 kDa, probably corresponding to the proteins called patatins. Patatins are storage proteins found in plants such as Potato and Tomato. This protein could be implicated in the high degree of cross-reactivity among Tomato, Latex, and Potato observed in immunoblot and CAP inhibition studies (48). A 43 kDa Latex allergen, Hev b 7, has been purified from *Hevea brasiliensis* and shown to be highly homologous to patatins.

Tomato also contains a 1,3-beta-glucanase, which may result in cross-reactivity with other foods or plants containing this panallergen, e.g., Potato, Bell pepper, Banana, Latex and Olive tree pollen (Ole e 9) (20-21).

Japanese cedar (*Cryptomeria japonica*) pollinosis is among the most widespread diseases in Japan. Cross-reactivity between Japanese Cedar pollen and Tomato fruit could be demonstrated using RAST and immunoblot inhibition tests. IgE binding to Japanese cedar pollen in the sera of 4/5 subjects was inhibited by more than 50% by preincubation of the serum with Tomato fruit extracts. Likewise, IgE binding to Tomato fruit discs was inhibited by more than 50% by Japanese cedar pollen extracts in 3/5 sera (49).

f25 Tomato

Chao 2 from Japanese cypress (*Chamaecyparis obtuse*) has been shown to share significant identity with polygalacturonases of Avocado, Tomato, and Maize, as well as with Cry j 2 from Japanese cedar (*Cryptomeria japonica*) (50).

Clinical Experience

IgE-mediated reactions

Tomato is a common cause of symptoms of food allergy in sensitised individuals (2,5,13 51-60). For instance, the most common allergenic foods for 866 Finnish children aged between 1 and 6 years were citrus fruit, Tomato, Hen's Egg, Strawberry and fish (61). In Mexico, in 1,419 allergic patients aged between 1 year and 18 years, 442 (31%) had positive SPT to some 33 tested foods. Fish, milk, seafood, beans, Orange, Onion, Tomato, Chicken, nut, Lettuce and Strawberry were responsible for 58% of the total of allergic reactions (51).

In a study conducted at 17 clinics in 15 European cities to evaluate the differences between some Northern countries regarding what foods, according to the patients, elicit hypersensitivity symptoms, it was reported, after evaluation of questionnaires of food-allergic individuals concerning 86 different foods, that the foods most often reported as eliciting symptoms in Russia, Estonia, and Lithuania were citrus fruits, chocolate, honey, Apple, Hazelnut, Strawberry, Fish, Tomato, Egg, and Milk, which differed from Sweden and Denmark, where Birch pollen related foods, such as nuts, Apple, Pear, Kiwi, stone fruits, and Carrot, were the most common perceived causes. The most common symptoms reported were oral allergy syndrome and urticaria. Birch pollen-related foods apparently dominate in Scandinavia, whereas some Mugwort-related foods seemed to be of more importance in Russia and the Baltic States. Among 1,139 individuals, Tomato was the 8th most reported food, resulting in adverse effects in 29% (58).

In a cross-sectional questionnaire-based survey conducted in Toulouse schools in France, to determine the prevalence of food allergies among schoolchildren, 2,716 questionnaires were returned, of which

192 reported a food allergy. Tomato was implicated in 10 (62).

In a study of food hypersensitivity in Finnish University students, among 172 subjects, the most common foods causing symptoms were Kiwi (38.4%), Milk (32.6%), Apple (29.1%), and Tomato (27.9%) (63).

In a German study of 419 adults with suspected food allergy, 214 (51.1%) were found to have an IgE-mediated food allergy. One hundred and seventeen patients were shown to be sensitised to fruit and vegetables, which included Celery, Tomato, Carrot, Apple, and Banana (64).

In an evaluation of IgE antibody measurement in a Japanese population (n = 4,797,158), Japanese cedar pollen showed the highest number of IgE responses, followed by house dust and Dust mite. Among food allergens, Apple had the highest number of responses, followed by Sesame seed, Egg white, Potato, and Tomato (52).

Other allergic manifestations to Tomato include urticaria/angioedema, dermatitis, perioral dermatitis, oral allergy syndrome, asthma, rhinitis, and abdominal pain. Tomato pollen may trigger rhinitis and/or conjunctivitis (53,65). In particular, OAS appears to be a common symptom (5,53,66-67). Tomato-induced OAS has been reported in 33 of 50 patients with Tomato allergy (5). In a study of the relationship between sensitisation to major pollens (Japanese cedar, Orchard grass, Short ragweed, Alder) among 1,067 Japanese paediatric patients with allergic diseases, and the association with oral allergy syndrome, it was found that childhood OAS does not always accompany pollen allergy. The most frequent allergen responsible for OAS in the study was Kiwi fruit, followed by Tomato, Orange and Melon (68).

A report described a 12-year-old girl with abdominal pain, nausea, and general malaise after eating Tomato, symptoms which remitted completely with antihistamines. SPT and IgE antibody test to Tomato were negative, while the food challenge was positive. Tomato oral rush desensitisation resulted in the patient's ability to tolerate a maintenance dose of 100 g of Tomato daily with no side effects (69).

A study evaluating the Tomato lipid transfer protein *Lyc e 3* the the use of serum from 5 Tomato-allergic individuals, reported that the cohort's age ranged from 22 to 41 years of age. Five had experienced symptoms of oral allergy syndrome, 4 had skin reactions, 2 had respiratory tract symptoms, 3 had gastrointestinal symptoms, and 1 had cardiovascular symptoms. IgE antibody levels ranged from 1.6 to 51.5 kU_A/l. All were shown to have skin reactivity directed at Tomato (16).

Although Tomato is a commonly consumed food, severe allergic reactions to Tomato are unusual or rarely reported. A study reports on 2 adult patients with significant immediate hypersensitivity reactions to Tomato. Both experienced laryngeal oedema, and 1 had anaphylaxis (2). Eight patients aged between 12 and 27 years are described who experienced anaphylaxis after eating raw Tomato. The patients who presented greater wheal diameters in skin tests were those who had had more severe episodes of anaphylaxis (25).

Among 1734 individuals attending 6 allergy clinics in Spain and reporting respiratory and/or cutaneous symptoms, the prevalence of sensitisation to Tomato was 6.52%. The peel extract was positive in 110 of the 113 patients, and the pulp extract in 47 patients; 3 patients were positive exclusively to pulp. Only 1.8% of individuals reported symptoms with Tomato; 44% of them had negative skin tests to both extracts. Among Tomato-sensitised subjects, 16% reported symptoms with Tomato, and 97% were sensitised to inhalant aeroallergens, including 84% to pollens (mainly *Artemisia vulgaris* and *Platanus hybrida*), with differences between northern and southern regions. Most of the sensitised subjects were asymptomatic, and some patients reported symptoms without skin test sensitivity. Regional differences may exist, possibly related to the pattern of sensitisation to cross-reacting pollens (56).

In a study undertaken to investigate the relevance of Tomato allergy in 32 Birch pollen-allergic patients with a history of adverse reactions to Tomato, Tomato allergy had a prevalence of about 9%. Forty-four percent were sensitised to Tomato profilin, and 35.5%

had IgE antibodies to CCDs. Two patients were sensitised to the lipid transfer protein *Lyc e 3* (8).

Atopic dermatitis may be precipitated or aggravated by Tomato (70-72), and the condition has been reported to be among the commonest causes of contact dermatitis of the hands (73). In a study of 119 children (1.5 months to 12 years of age) with atopic dermatitis, Tomato was identified as an allergen in 29.4% (74). Urticaria has also been described in a 6 month-old girl (75). Phytodermatitis as a result of contact with green Tomato has been recorded (76).

In 25 patients with recurrent otitis media with effusion and food allergy demonstrated by positive skin testing, the most common foods found to be associated were Milk, Egg, beans, citrus, and Tomato. An elimination diet led to a significant amelioration of the otitis in 22 patients. A subsequent challenge with the suspected offending food provoked a recurrence of the problem (77).

Food-dependant exercise-induced anaphylaxis has also been commonly reported (78-84). Tomato, cereals and Peanuts were said to be the most common foods resulting in this condition (85).

Tomato has also been associated with eosinophilic oesophagitis (86).

Eosinophilic cystitis induced by the ingestion of specific foodstuffs (Tomato, Coffee, Carrot) has been reported (87). Interstitial cystitis has also been reported (88).

Of 26 individuals reporting clinical symptoms induced by Tomato contact or ingestion, 21 (81%) were prick-prick positive to freeze-dried extracts of Canary Islands Tomato. Twenty patients (77%) had positive skin prick test to peel extracts, and 12 (46%) to pulp extracts (55).

A 39-year-old atopic woman with 2-year history of fingertip dermatitis complained that rubber gloves irritated her hands and that handling uncooked Potato and Tomato aggravated her dermatitis. Uncooked but not cooked Tomato resulted in oral tingling and facial erythema. Cooked potato did not affect her. IgE antibody test was positive for Latex, Tomato and Potato (89).

f25 Tomato

IgE antibodies to Paprika pollen, but not to Tomato pollen, were detected in the sera from 2 greenhouse workers who worked with Paprika plants. A greenhouse worker who cultivated Tomato plants had IgE antibodies against both Tomato and Paprika pollen. The authors claim that the presence of IgE antibodies against Paprika or Tomato pollen is not restricted to workers in horticulture; IgE against this pollen can also be present in food-allergic patients who have serum IgE against Paprika and/or Tomato fruit (90).

Other reactions

In 33 patients with chronic urticaria as a pseudoallergic reaction to food (proved by means of an elimination diet and subsequent re-exposure with provocation meals), oral provocation tests were performed with field-grown Tomato. Of the group, 76% reacted to Tomato. The authors tested with salicylates, histamine, and other components, and attributed the reactions to aromatic volatile ingredients in food, which are novel agents that elicit pseudoallergic reactions. Histamine, salicylates, and a direct mast-cell histamine release proved not to be involved in this reactivity to naturally occurring pseudoallergens (91).

Occupational protein contact dermatitis to Coriander, Carrot and Potato occurred in a 22-year-old chef, who had developed pruritic hand dermatitis from handling raw Potato, Tomato, Carrot, and Curry. Dermatitis developed on his face if juice of these vegetables splashed on it (92).

Auriculotemporal syndrome (or gustatory flushing syndrome), has been reported to masquerade as food allergy (erythema alone) following ingestion of spicy food such as Tomato sauce (93).

Tomato has also been implicated as a factor in irritable bowel syndrome (IBS) (94).

Occupational asthma in greenhouse Tomato growers may occur as a result of Red spider mites, which inhabit the plant (95).

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Citrullus lanatus

Family: *Cucurbitaceae*

Common name: Watermelon

Source material: Fresh fruit

Synonym: *C. vulgaris*

See also: Melon f87

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Seven trypsin inhibitors were isolated from the seeds of *Cucurbitaceae* plants: 2 from Cucumber (*Cucumis sativus*) and Red bryony (*Bryonia diotica*) and 1 from Figleaf gourd (*Cucurbita ficifolia*), Spaghetti squash (*Cucurbita pepo var. vegetable spaghetti*), and Watermelon (*Citrullus vulgaris*) (4). Evaluation for allergenic potential was not conducted.

Allergen Exposure

Geographical distribution

This food is widely grown in tropical and sub-tropical climates, and is an especially popular seasonal fruit in the southern United States. The plant has trailing vines and very large fruit (commonly up to half a metre long) with smooth, thick green skin, and sometimes darker green stripes. The flesh is sweet, and pink, red or yellow in colour. It contains 95% water and has embedded brown or black seeds, although seedless varieties are available.

Environment

The fruit is commonly eaten in large slices, with the rind serving as a base, or in balls or cubes in fruit salads. The high water content makes the flesh impractical for cooking or preserving, but the rind is sometimes pickled.

Allergens

The following allergen has been characterised:

Cit la 2, a 13 kDa protein, a profilin (1-3).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected and has been reported (5). Cross-reactivity was demonstrated among Pumpkin, Pumpkin seed, Musk melon, Watermelon, Cucumber and Zucchini (6).

Cit la 2, a profilin, may result in cross-reactivity with other foods containing profilin. Profilins are cross-reactive allergens that bind IgE antibodies of almost 20% of plant-allergic patients (1). Profilin has been identified as a major IgE-binding component of Melon. Amino acid sequences of Melon profilin compared with other profilins showed the most identity in the case of Watermelon profilin. The Melon profilin showed substantial cross-reactivity with profilin from Tomato, Peach, Grape and Bermuda grass pollen. However, Cantaloupe, Watermelon, Banana and Kentucky blue grass displayed no notable cross-inhibition. The study suggests that IgE reactivity to Melon profilin strongly depends on the highly conserved conformational structure of the epitope, rather than on a high degree of amino acid sequence identity or even linear epitope identity (1). An earlier study reported that, as in Melon, the profilin of

Zucchini, Cucumber, and Watermelon extracts were strongly recognised by the IgE antibodies of the patients with Melon allergy (3).

Hypersensitivity to Bet v 2, a profilin, has been reported to be strongly associated with clinical allergy to citrus fruits (which occurs in 39% in patients monosensitised to Bet v 2 *vs.* 4% in patients monosensitised to Bet v 1), Melon or Watermelon (67% *vs.* 0%), Banana (66% *vs.* 8%), and Tomato (33% *vs.* 0%), whereas Bet v 1 sensitivity was associated with clinical allergy to Apple (100% *vs.* 39%) and Hazelnut (56% *vs.* 0%). The sensitivity of a history of allergy to gourd fruits, citrus fruits, Tomato, Banana, or a combination thereof as a means to detect profilin-hypersensitive patients was 85% (41/48). The specificity of an allergy to any of these fruits exceeded 85%, with positive predictive values ranging between 68% and 91%. The conclusion drawn was that in clinical settings in which laboratory investigations are not easily accessible, allergy to Melon, Watermelon, Citrus fruits, Tomato, or Banana can be used as a marker of profilin hypersensitivity once a sensitisation to Natural rubber latex and lipid transfer protein is ruled out (7).

In a subsequent study, 200 consecutive patients with pollen allergy underwent skin prick tests with purified natural Date palm profilin (Pho d 2). Sixty patients (30%) showed reactivity to this profilin. Thirty-four of 60 (57%) of profilin reactors had food allergy; 21 of these were monosensitised to profilin, 11 were sensitised to both profilin and Bet v 1-homologous protein, 1 to both profilin and LTP, and 1 to all of the 3 allergens. The large majority of profilin-allergic patients reported oral allergy syndrome as the only food-induced symptom and were able to tolerate the offending foods if they were cooked or otherwise processed. Twenty-eight of 34 reported reactivity to 2 or more plant-derived foods. *Rosaceae*, tree nuts, Melon and Watermelon, Tomato, Pineapple, citrus fruits and Banana were the more frequently offending foods. The authors reiterated that allergy to Melon, Watermelon, Tomato, Banana, Pineapple or Orange may be considered as a marker of profilin hypersensitivity (8).

In a study of the prevalence of and risk factors for Latex hypersensitivity among healthcare workers (HCW) in an Italian general hospital, 24 of 672 who responded to the questionnaire, out of a potential of 1,747 health care workers, reported oral allergy syndrome. It was most commonly related to Kiwi, Tomato, Peach and Melon/Watermelon. Latex-specific IgE was found in 62 out of 1,747 HCW (3.6%) (9).

ELISA inhibition assays demonstrated allergenic similarity among Celery, Cucumber, Carrot, and Watermelon. Immunoblots of individual sera showed a 15 kDa protein band common to all 4 foods. The authors conclude that these foods possess shared antigens that may account for clustering of allergies to them in patients (10). Cit la 2, a profilin, may have been the allergen responsible.

Allergy to Watermelon has been associated with other allergies, *e.g.*, to Melon and Latex. In a study, the most common foods associated with Melon allergy were Avocado (n=7), Banana (n=7), Kiwi (n=6), Watermelon (n=6), and Peach (n=5) (11).

An increased prevalence of food allergies in patients with Latex allergy occurs. Among a group of these patients, foods responsible for reactions included Banana (9, or 18.3%), Avocado (8, or 16.3%), shellfish (6, or 12.2%), fish (4, or 8.1%), Kiwi (6, or 12.2%), Tomato (3, or 6.1%), Watermelon, Peach, Carrot (2, or 4.1% each), and Apple, Chestnut, Cherry, Coconut, Apricot, Strawberry, and Loquat (1, or 2.0% each) (12).

Over the last 3 decades, several authors have described an association between sensitivity to diverse pollens and sensitivity to diverse plant foods. An association between Ragweed pollinosis and hypersensitivity to *Cucurbitaceae* foods (*e.g.*, Watermelon, Melon, Cucumber) and Banana has been reported (13). An association between grass pollinosis and sensitisation to Tomato, Potato, Green pea, Peanut, Watermelon, Melon, Apple, Orange and Kiwi has been reported (14).

Watermelon and Ragweed have been proposed as having similar allergens. Between 28% and 50% of 120 patients whose sera contained IgE antibodies to Ragweed also had IgE antibodies to 1 or more among the gourd family members

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studied (Watermelon, Cantaloupe, Honeydew melon, Zucchini, and Cucumber). In an ELISA system, the extracts of Watermelon and Ragweed inhibited each other in a dose-dependent manner (15).

Clinical Experience

IgE-mediated reactions

Watermelon may uncommonly induce symptoms of food allergy in sensitised individuals. Allergic reactions include oral allergy syndrome or oropharyngeal symptoms (itching and/or swelling of the lips, tongue, or throat), urticaria, dermatitis, angioedema, and dyspnoea (16-17).

In a study of 29 Watermelon-sensitive patients, 6 were symptomatic. Only about 25% of patients with IgE antibodies to Watermelon develop oropharyngeal symptoms. Symptoms include itching and/or swelling of the lips, tongue, or throat. Watermelon-specific IgE failed to predict an individual's symptoms or differentiate asymptomatic from symptomatic individuals (16).

In an Indian study of 24 children aged 3 to 15 years with documented deterioration in control of their perennial asthma during the months of August and September, it was reported that 19 (79%) were sensitised to Watermelon (18).

Contact urticaria from Watermelon in a 45-year-old woman with pollen allergy has been reported. She developed urticaria and swelling of her lips on eating Watermelon. Symptoms worsened every season and finally resulted in hospital admission following the onset of generalised urticaria, swelling of the lips and tongue, breathing difficulty, and hypotension (19).

Other reactions

Intestinal obstruction by a Watermelon seed has been reported (20).

Watermelon seeds, found in 414 (38.7%) children who had aspirated foreign bodies, were the most common foreign bodies aspirated (21).

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Mixes

These tests consist of a mixture of different allergens, related or unrelated. For specific information about the included allergens consult the separate descriptions.

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Refers to other books in the serie Allergy – Which Allergens?

¹Food of Plant Origin – Additives, Spices & Miscellaneous

²Food of Plant Origin – Legumes, Nuts & Seeds

³Food of Animal Origin

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Mandarin (f302)

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fx31

Apple (f49)
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fx77

Sesame seed (f10)²
Hazel nut (f17)²
Tomato (f25)
Kiwi (f84)
Cashew nut (f202)²

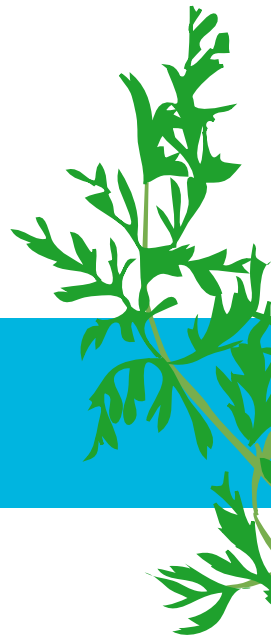
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