



New arrivals in anaphylaxis to foods

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Purpose of review

More people are excluding wheat from their diet, or turning to a more sustainable diet in which includes meat substitutes or is mainly or wholly plant-based. This increases the availability of new foods and with it the increasing likelihood of novel allergens.

Recent findings

There is a growing body of evidence which suggests that allergies to seeds and legumes are increasing potentially due to their use in concentrated form in vegan or health foods. Insects can be a sustainable source of protein, but mealworm could provoke symptoms in individuals sensitized or allergic to shellfish or house dust mite. Novel plant food allergens such as gibberellin-regulated proteins and thaumatin-like proteins are increasingly being reported as significant causes of severe reactions to fruits.

Summary

these findings make it even more imperative to take a full dietary history to ensure apparent idiopathic anaphylaxis is not in reality due to a novel food, especially in cases where other forms of the food are tolerated. Given the lack of diagnostic tests for these novel foods, a prick-to-prick skin prick test should be performed with the suspected food. There is currently more work needed to define and sequence many of the allergens involved.

Keywords

anaphylaxis, fruits, hidden allergens, insects, legumes, seeds

INTRODUCTION

Food allergies are an increasingly important public health issue, especially due to emerging allergens in novel or substitute foods developed due to the growing trend of wheat exclusion, and adoption of sustainable food sources leading to changes in dietary patterns [1]. As a result, there has been an increase in the availability of plant-based foods and alternative wheat-free products in the market [2]. As the popularity of plant-based diets continues to rise, it is crucial to identify and understand these emerging allergens to prevent severe allergic reactions and ensure the safety of consumers with food allergies [3]. Unfortunately, mandatory and precautionary allergen labelling varies from country to country, may not include hidden or emerging food allergens and therefore can lead to confusion and misunderstandings among consumers [4,5]. This review will discuss some of these emerging allergens, (see Table 1) better understanding of which will help improve the diagnosis, prevention, and treatment of food allergies.

NOVEL FRUIT AND VEGETABLE ALLERGENS

Gibberellin-regulated proteins (GRPs), found in a wide range of plants, are resistant to heat and

proteolysis. The first GRP allergen described about 10 years ago was Pru p 7, (Peach lectin) in peaches [6]. Since then, other allergenic GRPs have been discovered in fruits such as pomegranates, oranges, sweet cherries and Japanese apricots [7,8]. Grapefruits, tangerines, and lemons also contain cross-reactive GRPs similar to those found in oranges [9]. A case of plum anaphylaxis induced by sensitization to GRP has also been reported [10] and a GRP allergen has been described from the bell pepper (*Capsicum annuum*), in a patient who was allergic to several GRPs, including peach, orange and Japanese cedar pollen (Cry j 7) [11].

Recently, a GRP allergen in strawberry was considered responsible for an exercise-induced systemic

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Curr Opin Allergy Clin Immunol 2023, 23:000–000

DOI:10.1097/ACI.0000000000000936

KEY POINTS

- Meat substitutes or vegetable-based foods may be responsible for allergic reactions to food.
- Allergens such as gibberellin-regulated proteins and thaumatin-like proteins are emerging allergens for fruit allergy.
- Allergy to seeds and legumes is increasing due to their use in concentrated form in vegan or health foods.
- Ingestion of mealworms could cause allergic symptoms in patients sensitised or allergic to crustaceans or house dust mites.
- It is important in dietary history to take into consideration novel foods as potential triggers for food allergy.

allergic reaction in a patient also allergic to Japanese cedar pollen, and a similar case caused by grape GRP has also been reported [12,13]. Sensitization to fruit GRP is often observed alongside sensitization to Cupressaceae pollen in both Europe and Japanese cedar pollen in Japan, however, it is unclear whether the primary sensitizer is the pollen or fruit [14]. Cross-reactivity may explain this associated sensitization; sequence identities within Cupressaceae are approximately 90% (fruits) and 60% (vegetables), however such sensitization is always clinically relevant [7[■]]. A pollen-food associated syndrome (PFAS) between peach and cypress pollen caused by allergens of the GRP family has also been described [15]. Reactions to GRPs may occur in a cofactor-dependent manner, making diagnosis difficult and increasing the risk of overlooking GRP allergies [16].

Thaumatococcus-like proteins (TLPs) are associated with plant defence mechanisms, found in pollens and plant foods and resistant to high temperatures and digestive enzymes [17]. TLPs were found in the pollen of Cupressaceae plants, but are only recognized by 40 to 60% of individuals with cypress pollinosis [18]. TLPs are also present as allergens in the pollen of plane trees, birch and mugwort, leading to cross-reactivity between these pollens and various fruits. TLPs have been identified in apple, peach, pear, plum, cherry, banana, kiwi, grape, melon, almond and olive [17,19–21]. The TLP in wheat has been linked to baker's asthma and TLP could also be relevant allergens in bell pepper, chestnut, lettuce, hazelnut, tomato and wine [17,22,23].

The routes and mechanisms of sensitisation for TLPs allergens are not yet fully known. A study in a mouse model showed that sensitisation to cherry TLP, Pru av 2, by the percutaneous route was

possible [24]. Most recently a TLP allergen was identified in the persimmon (sharon fruit) (*Diospyros kaki*) responsible for immediate systemic reactions in two patients [25]. Another report describes a child who experienced anaphylactic symptoms after ingesting heated winter melon. A TLP was identified as the causative allergen and the authors hypothesized that its development was due to cross-reactivity with ragweed pollen sensitisation [26]. A rare case of orange-induced FDEIA was also reported, with evidence of a possible underlying allergy to TLP, suggesting a potential role of cofactors in TLP allergy [27[■]].

INSECTS

Eating insects is a common practice in parts of Asia, Africa, and South America and increasing in popularity in Western countries as the need for sustainable food sources continues to grow. Food allergy to insects may occur due to primary sensitisation or cross-reactivity due to primary sensitisation to shellfish or house dust mite. Several insect allergens have been identified, including tropomyosin and arginine kinase, which are homologous proteins in crustaceans and house dust mites (HDM) [28,29].

Broekman *et al.* [30] reported that individuals allergic to shrimp are more at risk of developing food allergies related to mealworms and other insects, with tropomyosin and/or arginine kinase being the primary IgE binding proteins. In yellow mealworms (*Tenebrio molitor*), tropomyosin, α -amylase, arginine kinase, and hexamerin were identified as the major food allergens [31]. However, having a primary mealworm allergy does not necessarily indicate that the individual is likely to react to all insects [30]. Moreover, a recent case report demonstrated that specific cross-reactivities between cricket, mealworm, snail, and mussel can occur without cross-reactivity to shrimp or HDM [32]. Lamberti *et al.* [33] demonstrated that thermal processing may change the solubility of proteins, but the effects of processing appear to be protein-, species- and treatment-specific, so patients allergic to house dust mite, shrimp and mealworm should consume insects with caution, even after thermal processing.

Cases of food allergy to mealworms are being increasingly reported, especially in workers in edible insect factories or laboratories [34,35]. However, perhaps the most unusual case involved a patient who experienced anaphylactic shock after being bitten by a Japanese dwarf flying squirrel who had a positive immunoglobulin E (IgE) and Western blot to mealworm, but never ingested mealworms and had no known shrimp allergy [36]. The authors concluded that the patient developed skin

Table 1. Hidden allergens in foods

Type of food	Allergen	Foods in detail	Dish	References
Fruits	Gibberellin-regulated protein	Peach, pomegranate, orange, sweet cherry, Japanese apricot, grapefruit, tangerine, lemon, plum, strawberry, grape.	Umeboshi: Japanese apricots	[6,7 [■] ,8–10]
	Thaumatococcus-like proteins	Apple, peach, pear, plum, cherry, banana, kiwi, grape, melon, olive, chestnut.		[17,19–21]
Vegetables	Gibberellin-regulated protein	Bell pepper		[11]
	Thaumatococcus-like proteins	Bell pepper, lettuce, tomato		[17,23]
Tree nuts	Thaumatococcus-like proteins	Hazelnut, almond		[17,20]
Cereal	Thaumatococcus-like proteins	Wheat (baker's asthma)		[17]
Drinks	Thaumatococcus-like proteins	Wine		[22]
Insects	Tropomyosin, arginine kinase and others	Insects including mealworms, crickets	Insect-containing wax for fruit's peel.	[28–29,37]
Legumes	Poly-c-glutamic acid (PGA) and nattokinase (serine protease)	soya bean,	Natto (fermented soy bean)	[48–51,52 [■]]
		Pea, lentil, chickpea, fenugreek	Curry and other spicy dishes: fenugreek Prepackaged food, vegan meat substitutes, gluten-free pasta: peas, lentils and chickpea Nondairy yoghurt, pizza, milkshake, chicken burger: pea	[39 [■] ,40,44 [■] , 45–47]
Seeds	Cuc ma 5 (2S albumin) in pumpkin seeds 2S Albumins, nsLTP, oleosin in sunflower seeds Oleosins in Perilla seeds 2S albumin Pin p 1 in pine nuts 2S Albumin and an 11S globulin in flaxseed (linseed) Oleosin in buckwheat seed	Pumpkin, sunflower, flaxseed (linseed), pine nut, perilla seeds, hemp seed, buckwheat seed	Breakfast cereals, biscuits, crackers and protein powders Energy bars, yoghurt, and baked goods: hemp seed Pancakes, pizza dough, bread, cakes and noodles, buckwheat tea (Asia): buckwheat	[53–56,59,60, 69,71,74–76]

sensitization from handling mealworms as pet feed, and that the anaphylaxis had been due to the squirrel ingesting mealworms prior to biting the patient. Guillet *et al.* [37] reported a case of a patient with tropomyosin sensitization and seafood allergy who experienced anaphylaxis after ingesting orange peel. Skin prick testing confirmed causality between the anaphylaxis and orange peel ingestion, probably caused by the treatment of the orange peel with insect-containing wax, a potential source of insect tropomyosin.

LEGUMES

There is significant similarity between pea, lentil, peanut and soya bean [38], and a recent study of 195 peanut-allergic children found 64% were sensitized

and 17% had an allergy to one other legume, usually lentil, pea or lupine with severe reactions affecting 50% [39[■]]. Muller and colleagues also found that 20% of their cohort who were sensitized to fenugreek had experienced reactions to this legume [39[■]]. A recent case report highlighted the fact that allergy to fenugreek should be considered when individuals with a peanut allergy react to curry and other spicy dishes, rather than assuming peanut contamination is the cause [40]. However, sensitisation to other legumes is not universal in individuals with peanut allergy, with one study reporting that their cohort of peanut or soy allergic children had a much lower likelihood of co-sensitisation to other legumes, compared to those with a primary allergy to peas or lentils [41[■]]. A review of 120 children with a legume allergy from Turkey reported that lentils

were the most frequent trigger, followed by peanuts, chickpeas and peas, whereas reactions to beans was only reported in a minority [42]. In a systematic review, Hildebrand and colleagues found that increasingly legumes other than peanut and soy are reported to provoke reactions, especially lentils, pea and lupine [43].

Peas, lentils and chickpea protein is increasingly used in high concentrations in prepackaged food, and is a common constituent of vegan meat substitutes, vegan protein powders and gluten-free pasta. Studies on pasta made from lentils and chickpeas found that they retain important allergens after boiling [44,45]. A review of plant food proteins noted that pea protein use has been increasing, and reactions might be due to the concentration of protein in vegan products which may contain 60–70% protein, compared with 8% protein by weight in an average serving of plain cooked peas [46]. A case series reported that anaphylaxis to pea can occur, often due to pea protein being an added ingredient to composite foods such as nondairy yoghurt, pizza, milkshake and a chicken burger, and although some children also had a peanut allergy, this was not universal [47].

Although soy allergy is a well known to occur and often resolve in childhood, anaphylactic reactions are increasingly being reported in adults linked to natto, a fermented soybean. Natto, tempeh, miso and soy sauce are associated with numerous health benefits, thought to be due to the fermentation process increasing the amount of isoflavones which may protect against allergic inflammation [48]. The case reports usually describe Japanese adults who can tolerate soy products but have had anaphylactic reactions to natto, which is soybeans in a mucilage [49,50]. One allergen identified is poly-*c*-glutamic acid (PGA) in the mucilage, a substance also produced by jellyfish, meaning surfers and other regular sea bathers may be at a risk of developing reactions to natto if they become sensitised to PGA through jellyfish stings [51]. Suzuki *et al.* [52] found that only half of their case-series of patients reacting to natto were sensitized to PGA, with the rest reacting to a protein present in the mucilage, identified as nattokinase, a serine protease.

SEEDS

In the EU, only sesame and mustard seed have to be included as an allergen on food labels, however, other seeds such as pumpkin, sunflower, flaxseed and pine nuts are increasingly being utilised in breakfast cereals, biscuits, crackers and protein powders. Case reports of pumpkin seed allergy usually

find that the pumpkin flesh is tolerated but not the seeds [53]. A review of four patients reacting to pumpkin seeds but not the pulp, identified two allergens, although only Cuc ma 5 (2S albumin) was positive in all four cases [54]. Sunflower seeds contain both 2S Albumins and nonspecific Lipid Transfer Protein (nsLTP) allergens, but a lipoprotein such as an oleosin could also be responsible for severe reactions, especially to roasted seeds and in the absence of sensitisation or reactions to other foods [55,56]. A recent review by Majsiak and colleagues suggests oleosins could also be responsible for reactions to sunflower seeds when allergy tests were negative [57]. It appears that individuals reporting severe or anaphylactic reactions to sunflower seeds, might be sensitised only to these lipophilic proteins [58]. Recently oleosins have also been identified as an important allergen in perilla seeds [59].

Like other seeds, pine nut allergy often occurs as a stand-alone allergy, with individuals often mono-sensitised to pine nuts and the major 2S albumin Pin p 1, with up to one third of children with an allergy to pine nuts reporting severe or anaphylactic reactions [60]. Although the IgE-binding epitopes from peanut (Ara h 2 and Ara h 6) and Brazil nut (Ber e 1) do seem to share important similarities with epitopes in Pin p 1, it is not clear whether individuals with allergies to those foods are at a greater risk of developing an allergy to pine nuts [61]. A recent study from Mori and colleagues evaluated the efficacy of diagnostic tests for pine nut allergy in 91 children, 25 of whom had an allergy to pine nuts [62]. Their results suggested that the most effective diagnostic test is a prick-to-prick skin test with pine nuts, with a cut off of 4 mm having the best overall performance and positive likelihood ratio. A study from Korea reported that severe reactions in older children might be linked to pollen sensitisation [63].

Flaxseed (linseed) was originally utilised for its oil and was also a principal component of birdseed but is now consumed as a food and for medicinal/health purposes. Whilst earlier case reports involved individuals sensitised to flaxseed probably through handling of birdseed [64], more recent cases report reactions to flaxseed in foods [65–67]. Most recently, a case of a nonatopic male who had four episodes of unexplained anaphylaxis, found that the last episode was linked to the consumption of a flaxseed product [68]. In a review of five subjects with anaphylaxis to flaxseed, Bueno-Díaz *et al.* report that the allergens involved in severe reactions include a 2S Albumin and an 11S globulin [69]. Chia seed allergy is another seed eaten more often due to its health-related properties, but currently there is little evidence of allergic reactions being reported.

Albunni *et al.* [70] demonstrated cross-reactivity between the globulins of sesame seed and hazelnut, with the globulins in chia seed, suggesting a possible link.

Hemp seed is a variety of *Cannabis sativa*, grown for industrial use, is also utilized in a number of food products including energy bars, yoghurt, and baked goods, being high in protein and omega 3 fatty acids [71]. There is some evidence that cannabis and hemp can provoke allergic reactions when consumed in food products [72]. Alkhamash *et al.* [73], reported that 11/15 patients in a case series reported symptoms to hemp on the first ingestion, three of whom were non cannabis users, suggesting hemp can provoke symptoms in the absence of sensitisation to cannabis.

Allergy to quinoa seed seems to be rare with very few case reports in the literature, whereas common buckwheat is a known cause of allergy, being more prevalent in Asia where it is eaten regularly, and often linked to severe and anaphylactic reactions [74]. In addition, an oleosin has recently been identified as a potential causative allergen for reactions to tartary buckwheat (*Fagopyrum tataricum*), usually ingested in the form of buckwheat tea in North Asia and China [75]. Buckwheat allergy is less common in Europe, although a case report from Spain highlighted the issue that, due to its increasing use, buckwheat will undoubtedly become a growing cause of anaphylaxis in Western countries [76]. Foods involved in buckwheat anaphylaxis include, buckwheat in pancakes, pizza dough, bread, cakes and noodles [74]. Finally, although reactions to poppy seeds are rare, the spectrum of symptoms can range from mild oral symptoms to anaphylaxis and may be linked with sensitisation/allergy to hazelnuts [77].

CONCLUSION

Diets are becoming more complex, more new food allergens are being introduced and dietary trends have changed the paradigm of food allergy. Therefore, it is even more vital to obtain a full and detailed dietary history and keep an open mind about likely triggers. These could include foods not previously linked to allergic reactions, or foods tolerated in one form but not in other. Consideration must be made as to which tests are most useful, with prick-to-prick testing with the food appearing to be the best option currently. Anaphylaxis appears to be a frequent problem in these newer types of food allergies, and thus effective management is vital, although exclusion can be difficult as the foods containing these allergens are extremely varied and they do not have to be listed on labels. Eating a healthy diet is

important and a plant-based diet has been demonstrated to have anti-inflammatory effects [78]. Thus appropriate dietary advice must be available to support individuals with reactions to these novel allergens, ensuring substitute foods of equal nutritional value are advised, especially for those following a plant-based diet.

Acknowledgements

None.

Financial support and sponsorship

There was no financial support or sponsorship for this paper.

Conflicts of interest

There are no conflicts of interest.

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Good overview and introduction to the concepts of the role of food and nutrition in the inflammatory process.