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Emerging and Novel Elicitors of Anaphylaxis: Collegium Internationale Allergologicum Update 2024

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Abstract
Background: Anaphylaxis represents the most severe end of the spectrum of allergic reactions. Frequent elicitors of anaphylaxis are insects, foods, and drugs. This paper summarizes recent development with regard to emerging and novel elicitors of anaphylaxis. ***Summary:*** Food allergens on the rise include pulses (like pea, chickpea), seeds (hemp, chia), nuts (cashew), pseudograins (buckwheat, quinoa), fruits, and microalgae. Novel foods are foods that were not consumed to any significant extent in the European Union before May 1997, which includes four edible insects (mealworm, migratory locust, house cricket, and buffalo worm). Recent investigations have pointed out the risk of anaphylaxis associated with the consumption of yellow mealworm for people allergic to shellfish and house dust mites. In Europe, fire ants (mostly *Solenopsis invicta*) *and Vespa velutina nigrithorax* represent invasive species, which account for increasing numbers of anaphylactic reactions. Also, several new drugs, especially biologicals, have been associated with anaphylaxis. ***Key Messages:*** Elicitors of anaphylaxis are changing as a result of (i) increase in demand for plant-based food, (ii) introduction of novel foods, (iii) spreading of allergens by climate changes and globalization, or (iv) due to exposure to newly developed drugs.

Introduction

Anaphylaxis represents the most severe end of the spectrum of allergic reactions [1]. The EAACI/WAO definitions of anaphylaxis are as follows: "a serious (WAO)/severe (EAACI) life-threatening generalized or systemic hypersensitivity reaction" [2]. There is no gold-standard definition for anaphylaxis, which is a clinical diagnosis. Diagnostic criteria adopted by WAO are given in Table 1 [2]. Certain endogenous and exogenous factors can promote the occurrence of severe anaphylaxis. Such risk factors, which exist regardless of the trigger, are old age, severe cardiovascular diseases, existing and, in particular, poorly controlled bronchial asthma, taking certain medications that promote mast cell activation or leukotriene formation and mastocytosis [1]. Current data from the European Anaphylaxis Register confirm that the use of β-adrenoceptor antagonists is associated with an increased risk of severe anaphylaxis [1, 3].

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Table 1. Amended criteria for the diagnosis of anaphylaxis

Anaphylaxis is highly likely when any one of the following 2 criteria is fulfilled
1. Acute onset of an illness (minutes to several hours) with simultaneous involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) *And at least one of the following:* a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak flow, hypoxemia) b. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence) c. Severe gastrointestinal symptoms (e.g., severe crampy abdominal pain, repetitive vomiting), especially after exposure to nonfood allergens
2. Acute onset of hypotension[a] or bronchospasm[b] or laryngeal involvement[c] after exposure to a known or highly probable allergen[d] for that patient (minutes to several hours), even in the absence of typical skin involvement.

[a]Hypotension defined as a decrease in systolic BP greater than 30% from that person's baseline, OR. (i) Infants and children under 10 years: systolic BP less than (70 mm Hg + [2 x age in years]). (ii) Adults and children over 10 years: systolic BP less than <90 mm Hg. [b]Excluding lower respiratory symptoms triggered by common inhalant allergens or food allergens perceived to cause "inhalational" reactions in the absence of ingestion. [c]Laryngeal symptoms include stridor, vocal changes, odynophagia. [d]An allergen is a substance (usually a protein) capable of triggering an immune response that can result in an allergic reaction. Most allergens act through an IgE-mediated pathway, but some non-allergen triggers can act independent of IgE (e.g., via direct activation of mast cells).

The most common triggers of severe anaphylactic reactions are insect venoms, foods, and drugs [1, 3]. The ranking of triggers is influenced by various factors, including survey type, age group, and geographical region [1]. Within the European Anaphylaxis Registry, in adults, most frequent elicitors of anaphylaxis were wasps and bees followed by foods and drugs, while in children, foods were most frequently responsible for eliciting anaphylaxis, followed by wasps and bees and drugs [3–7]. Registry data showed an age-dependent ranking of food-eliciting anaphylaxis. In children, peanut was followed by cow's milk, cashew, and hen's egg, while in adults wheat flour was followed by shellfish, hazelnut, and soy [8–10].

Among the eliciting groups of drugs, analgesics and antibiotics were far most often reported. Female and senior patients were more frequently affected, while the number of children with drug-induced anaphylaxis was low [11].

During the last years, some allergens were reported to be of increasing importance. This may be due to a change of dietary habits [12], novel foods, spreading of allergens by climate changes and globalization [13], or due to exposure to newly developed drugs. This paper aimed at giving an overview of emerging and novel elicitors of anaphylaxis.

Food

There is an increasing trend for a diet based on plants, in which animal products are mostly or completely avoided, often for health and environmental reasons. The menu is supplemented with pulses (e.g., soy, lentils, peas), nuts (e.g., cashew, macadamia, almond, pecan, para, walnut), and seeds (e.g., chia, flaxseed) or pseudograins (quinoa, buckwheat). Indeed, the product range is expanding to include vegan foods such as milk alternatives (e.g., oat, almond, soy drinks) and cheese or meat substitutes (e.g., soy-based) [12, 14].

There are increasing reports on allergies to seeds and legumes, which may result from their use in concentrated form in vegan or health foods [12, 15]. Also, with migration of different population groups (e.g., from Near and Middle East or from Africa) to Central Europe, food patterns in the European population are changing. Typical foods from Africa are couscous which is made from wheat, barley, or panic grass, and bulgur which is made from wheat. In Arabian diet, pulses play a great role; e.g., chickpea is found in falafel and hummus [12, 16].

There exist several reports on anaphylaxis elicited by pulses [9, 16, 17], nuts [9, 16], seeds [9, 16, 18–22] as well as by pseudograins [9, 16, 23]. A review of selected plant allergen sources and significant allergens for vegan nutrition is given by Präger et al. [12]. Co-sensitization between 7S and 11S globulins was observed [24].

Novel foods are foods that were not consumed to any significant extent in the European Union before May 15, 1997 (Regulation (EU) No 2015/2283) [25]. The category covers new foods, food from new sources, new substances used in food as well as new ways and technologies for producing food [25, 26].

Table 2. Allergens in selected plant foods with increasing importance in anaphylaxis cases

Source	Botanical name	Allergens identified	References
Fenugreek	*Trigonella foenum-graecum*	Tri fg 1 (7S vicilin) Tri fg 2 (2S albumin) Tri fg 3 (7S globulin) Tri fg 4 (Bet v 1-like)	[16]
Chickpea	*Cicer arietinum*	Cic a 1 (7S vicilin) Cic a 2 (2S albumin) Cic a 3 (LTP) Cic a 6 (11S globulin)	[16, 31]
Lupine	Lupinus albus Lupinus angustifolius	Lup a 1/Lup an 1 (7S vicilin) Lup an 3 + isoform (LTP) Lup a 4 (Bet v 1-like) Lup a 5 + isoform (profilin) Lup an delta conglutin (2S albumin)	[16, 32, 33]
Pea	*Pisum sativum*	Pis s 2 + isoforms (vicilin) Pis s 27S + isoforms (vicilin/convicilin) Pis s 3 +isoform (LTP) Pis s 5 (profilin) Pis s 6 (Bet v 1-like)	[16]
Natto	*Glycine max* (fermented)	Gly m 4 (Bet v 1-like) Gly m 5 + isoforms (7S vicilin) Gly m 6 + isoforms (11S globulin) Gly m 7 (seed biotinylated protein) Gly m 8 (2S albumin) poly-c-glutamic acid (PGA) Nattokinase (serine protease)	[16, 34, 35]
Chia seeds	*Salvia hispanica*	Lectin Elongation factor 11S globulin	[18, 36]
Hemp seeds	*Cannabis sativa* (variant)	Can s 2 (profilin, aeroallergen) Can s 3 (LTP, aeroallergen) Can s 4 (oxygen-evolving enhancer protein 2, aeroallergen) Can s 5: Bet v 1-like (aeroallergen)	[16, 37–39]
Flaxseed	*Linum usitatissimum*	Lin u 1 (S2 albumin)	[16, 40, 41]
Poppy seed	*Papaver somniferum*	Pap s 1 (Bet v 1-like) Pap s 2 (profilin) Pap s 34	[42–45]
Sesame	*Sesamum indicum*	Ses i 1 + isoform, Ses i 2 + isoform (2S albumins) Ses i 3 + isoform (7S vicilin) Ses I 4, Ses i 5 + isoforms (oleosin) Ses I 6, Ses I 7 + isoforms (11S globulins)	[16, 46–49]
Cashew	*Anacardium occidentale*	Ana o 1 (7S globulin) Ana o 2 (11S globulin) Ana o 3 (2S albumin) Bet v 1-like isoform	[16, 26]
Quinoa	*Chenopodium quinoa*	Che qu	[50–52]
Buckwheat	*Fagopyrum esculentum*	Fag e 1 (13S globulin) Fag e 2 (2S albumin) Fag e 3 (7S-vicilin) Fag e 4 (antimicrobial peptide) Fag e 5 (vicilin-like protein)	[16, 53–57]

Novel plant food allergens such as gibberellin-regulated proteins, e.g., Pru p 7 from peach, and thaumatin-like proteins, e.g., Pru p 2 from peach, are increasingly being reported as significant causes of severe reactions to fruits [14]. Here, selected food allergens with recent growing importance shall be presented in detail.

Plant Food Allergens (Pulses, Seeds, Nuts, Pseudograins, Fruits)

Most frequent trigger of food-induced anaphylaxis in the legume group (pulses) was soy, followed by lupine and pea, while anaphylaxis to lens, bean, fenugreek, and chickpea was rarely reported [27]. Seeds from chia, hemp, linum, sesame, poppy, pumpkin, and sunflower as well as pseudograins may also elicit anaphylaxis. The following allergen sources (Table 2) are expected to be of growing importance with regard to anaphylaxis.

- *Fenugreek* (*Trigonella foenum-graecum*) is used as herb and can also be found in natural remedies, artificial maple syrup, coffee substitute, cheese, and supplement in baked goods. Allergic reactions to fenugreek are rare and may appear as cross-reactions in patients sensitized to peanut allergens Ara h 1 and Ara h 3 [5].
- *Chickpea* (*Cicer arietinum*): Hummus and falafel are main dishes containing chickpeas. Anaphylaxis to chickpea has been described, frequently in combination with exercise [28–30]. Certain chickpea allergens (e.g., pathogenesis-related protein/PR-10 and a vicilin-containing fraction) may cross-react with birch and peanut allergens [31].
- *Lupine*: Foods containing lupine (*Lupinus angustifolius*) are on the rise, e.g., flour, spreads, pasta, protein powder, coffee, milk and meat substitutes. Widespread use carries the risk of unintentional ingestion of lupine allergens in the sense of "hidden allergens," e.g., eliciting anaphylaxis by consumption of ice cream [15, 32, 33].
- *Pea (Pisum sativum)*: As an ingredient that does not require declaration, peas are of interest to the food industry. Pea protein is increasingly being used in highly processed vegan foods, and anaphylaxis has been reported [27]. The storage proteins Pis s 1 and 2 are probably the main allergens in pea [16].
- *Natto* is a *Bacillus subtilis* fermented soybean (*Glycine max*) in a mucilage. Anaphylactic reactions, also of delayed type, are increasingly being reported in adults. In addition to soybean allergens, allergens were identified in the mucilage [34, 35].
- *Chia seeds* (*Salvia hispanica*) are a "trend food" and are consumed neat in muesli, or in combination with plant drinks as an alternative to conventional puddings made from milk and eggs. They are also found as chia seed flour in baked goods. Anaphylactic reactions after consumption of chia seeds have been reported [18]. Cross-reactivity with sesame is being discussed [12, 36].
- *Hemp seed* is a variety of *Cannabis sativa* which is utilized in a number of food products including energy bars, yogurt, and baked goods. Sensitization to hemp can occur from prior marijuana handling, smoking, and ingestion. Anaphylaxis and IgE reactivity to various *C. sativa* components have been described, and several allergens are already characterized, mostly aeroallergens [37–39].
- *Flaxseed* (linseed, *Linum usitatissimum*) can be ground into a meal or turned into linseed oil. Anaphylaxis was mostly reported after ingestion of linseed flour [20, 40]. Storage proteins have been identified as potential allergens [41].
- *Poppy seeds:* Anaphylaxis to these seeds is rare and may be linked with sensitization/allergy to buckwheat and hazelnut [42–45].
- *Sesame* (*Sesamum indicum*) is a seed which is traditionally consumed as a paste (tahini) or as a sweet (halva). It may also be used as toppings on breads and crackers or as an ingredient for breads, pastries, salads, potato, and pasta dishes [46–49].
- *Cashew nuts* (*Anacardium occidentale*) are becoming increasingly popular, e.g., in pastes, spreads, or plant-derived drinks [16]. Meanwhile, cashews have become the fourth most frequent trigger for anaphylactic reactions in children [8, 12].
- *Quinoa* (*Chenopodium quinoa*): The mineral-rich leaves are eaten as a vegetable or salad. The seeds have a grain-like composition, which is why quinoa is referred to as a gluten-free pseudograin. Quinoa is popular as a health food. Anaphylaxis to quinoa seems to be rare with very few case reports in the literature [50–53].
- *Buckwheat* (*Fagopyrum esculentum*) is often linked to anaphylactic reactions in Asia, where it is eaten regularly [23, 54]. Foods involved in buckwheat anaphylaxis include buckwheat in pancakes, pizza dough, bread, cakes, and noodles [23]. An oleosin has been identified as a potential causative allergen for reactions to Tartary buckwheat (*Fagopyrum tataricum*) [55]. Buckwheat allergy is less common in Europe [56, 57].

Some nutritional supplements are marketed as "superfood." This term usually refers to foods that are associated with greater health benefits than other foods due to their nutrient content, e.g., fruits, seeds, microalgae, berries (Table 3).

Table 3. Selected foods that are marketed as "superfoods" may elicit anaphylaxis

Name	Anaphylaxis reports	Dishes consumed	Allergens (according to Allergome.org)
Pomegranate (*Punica granatum*)	[86, 87]	Fruit	Pun g, Pun g 1, Pun g 14, Pun g 5, Pun 7
Moringa (*Moringa oleifera*)	[88]	Seeds provide behen oil, which is used as salad oil, young, fleshy roots are used as a vegetable	n.d.
Goji (*Lycium barbarum*)	[89, 90]	Berries	Lyc ba, Lyc ba 3, Lyc ba enolase, Lyc ba glucosidase
Spirulina (*Arthrospira platensis, A. maxima*)	[91–93]	Microalgae in sushi, as a salad and as a dietary supplement	Art pl, Spi mx
Chlorella (*Chlorella vulgaris*)			Chl s

Edible Insects

Great attention has been paid to the utilization and production of edible insects as it could provide large amounts of multiple nutrients rapidly. Eating insects has so far been rather unusual in Europe. This could change if more insects are gradually allowed on the European market. So far, the European Commission has authorized four insects in different dosage forms as food (Table 4) [25].

Foods that contain insects must clearly and understandably list this in their list of ingredients [25]. The European Food Safety Authority concluded that consumption of the insect proteins evaluated could potentially lead to allergic reactions [58]. In addition, allergens from the food (e.g., gluten) may have gotten into the eaten insect [25, 26].

Recent investigations have pointed out the risk of allergic reactions associated with the consumption of yellow mealworm (*Tenebrio molitor*), for people allergic to shellfish and house dust mites [59]. Different IgE-binding cross-reacting allergens including tropomyosin, α-amylase, arginine kinase, and hexamerin have been identified as the major offending allergens. In patients primarily sensitized to mealworm, larval cuticle protein seems to play a major role [60].

Stinging Insects

Formicidae (Ants)

The family Formicidae contains all ants within the Hymenoptera order of stinging insects. Several genera have been reported in the literature as associated with systemic immediate type reactions [61, 62]. The most important are listed in Table 5. Similar to other Hymenoptera, ant species have been spread by humans beyond their native range, are now "exotic" or invasive in many regions [63, 64], and may continue to spread over time, especially with climate change. Hypersensitivity reactions caused by ant stings are increasingly recognized as an important cause of death by anaphylaxis [61].

Fire ants (Myrmicinae) do not need to be provoked to attack, and their venom is capable of causing a painful local reaction and, in some instances, results in life-threatening anaphylaxis. Most sting reactions are attributed to *Solenopsis invicta*, the red imported fire ant, and the second most important is the black imported fire ant, *Solenopsis richteri*. Bites can occur year-round but are most common in the summer months [65, 66]. In less than a century, they have spread via human trade throughout much of the USA, Mexico, the Caribbean, China, Taiwan, and Australia. *S. invicta* is already listed as a "species of concern" on the EU's invasive species list. Fire ants have previously been documented in imported soil and plants in Spain, Finland, and the Netherlands but not in the wild as seen in Sicily, where 88 nests bordering a river estuary have been found recently [67].

Fatal and near-fatal fire ant sting reactions were reported by the Fire Ant Subcommittee of the American Academy of Allergy, Asthma, and Immunology in 1989 [68]. In South America, fire ants were the most frequent insect triggers of anaphylaxis, and they induced significantly more often severe reactions than triggers of food-induced or drug-induced reactions [69]. Recently, an inverse relationship was reported between imported anaphylaxis cases to fire ants and α-Gal which was associated with fire ants being predators of ticks [70].

Table 4. Edible insects and their allergens

Common name and year of allowance	Anaphylaxis reports	Dishes (examples)	Allergens (according to Allergome.org)
Mealworm (*Tenebrio molitor*), 2021	[59, 94–96]	As a whole (snacks) or as flour/powder in bread, rolls, pastries pasta, in patties or chocolate	Ten m Ten m7
Migratory locust (*Locusta migratoria*), 2021	n.d.		Loc m, Loc m 7
House cricket (*Acheta domesticus*), 2022/2023	n.d.		Ach d
Buffalo worm (*Alphitobius diaperinus*), 2023	n.d.		n.d.

n.d., no data.

Table 5. Overview of allergens in venoms of ants according to the WHO/IUIS allergen nomenclature official database [61]

Allergen source	Allergen name	Allergen family
Solenopsis invicta	Sol i 1	Phospholipase
Solenopsis geminata	Sol i 2, Sol g 2, Sol r 2, Sol s 2	Unknown
Solenopsis richteri	Sol i 3, Sol r 3	Antigen 5
Solenopsis saevissima	Sol g 3, Sol s 3 Sol I 4, Sol g 4	Unknown Unknown
Myrmecia pilosula	Myr p 1 Myr p 2 Myr p 3	Pilosulin 1 Pilosulin 3 Pilosulin 4.1
Brachyponera chinensis (formerly *Pachycondyla chinensis)*	Pac c 3	Antigen 5

Fire ant venom is known as solenopsin, an alkaloid that burns and induces local erythema and the formation of pustules. Potent allergens in fire ant venoms are listed in Table 3 [71]. Imported fire ant venoms are cross-reactive with other Hymenoptera venoms; e.g., the Sol i 1 allergen from *S. invicta* has cross-reactivity with yellow jacket phospholipase. The Sol i 3 allergen is a member of the antigen 5 family that has amino acid sequence identity with vespid antigen 5 [72].

For allergy diagnostics, specific IgE and, in the USA, skin test preparations are available [61]. Fire ant whole-body extract subcutaneous immunotherapy was reported to be a safe and effective treatment for fire ant hypersensitivity [73].

Regarding other ants, anaphylaxis to Samsun ant (*Pachycondyla chinensis*), which is a species similar to *S. invicta,* has been reported in a case series from Iran [74]. Myrmecia ants (*Myrmecia pilosula, Myrmecia pyriformis*) are native to Southeastern Australia, and several species have been associated with allergic reactions and anaphylaxis [61]. Diagnostics are available locally in specialized centers [61].

Vespa velutina

Vespa velutina nigrithorax (VVN), commonly known as Asian wasp because endemic in Asia, represents an invasive species in Europe [75–77]. VVN can induce allergic reactions similar to those caused by other Hymenoptera, and death after VVN stings, presumably due to fatal allergic reactions, has been reported [76]. VVN has become the most common cause of Hymenoptera anaphylaxis in patient cohort in Spain [77]. The main allergen components identified in the venom of VVN are Vesp v 1 (phospholipase A1) and Vesp v 5 (antigen 5), but only Ves v 5 may be considered a dominant allergen. Both allergens Vesp v 5 and Vesp v 1 share a high level of cross-reactivity with their counterparts in *Vespula* spp. and *Vespa crabro* (VC) [78]. Since there is no specific available VIT for VVN yet, *Vespula*

spp. immunotherapy may be a valid option for patients allergic to VVN; when available, venom immunotherapy with VC venom may be more effective [79, 80].

Drugs

Several drugs, especially biologicals, have been associated with anaphylaxis [81]. Although the risks associated with these agents are overall low, hypersensitivity reactions have been described and are reported more frequently with increased use [82]. Omalizumab (anti-IgE) and reslizumab (anti-IL 5) product labels feature black box warnings for anaphylaxis. The overall rate of anaphylaxis caused by omalizumab, reslizumab, and other biologics utilized for allergic diseases is low, occurring in approximately 0%–0.3% of patients. The overall risk of omalizumab-related anaphylaxis is approximately 0.1%–0.2% [82, 83]. Checkpoint inhibitors, a promising drug class in oncology, have only rarely been associated with anaphylaxis [84].

Conclusion

The world is changing and so are elicitors of anaphylaxis. Diets are becoming more complex, novel foods are being introduced, and dietary trends have changed. The expanding market for vegan and vegetarian diet as well as changing dietary patterns due to migration is bolstering this effect [12, 16]. Most notably, plant food allergens are on the rise. Also, the recent allowance of edible insects on the European market may soon become a problem for people sensitized to shellfish and/or to house dust mites [59]. Special warnings on food stuff containing edible insects should therefore be mandatory. For allergologists, it is important in dietary history to take into consideration novel foods as potential triggers for food allergy [14].

Ants represent another potential allergen on the rise as they have already invaded several European countries [72]. The same holds true for *V. velutina* [75]. Last but not least, the modern drugs, especially biologicals, bear the risk of eliciting anaphylaxis [81].

All allergologists should be aware of these and other emerging and novel allergens. Clinical studies will allow to better characterize these allergens, and diagnostic as well as therapeutic measurements have to be installed. Acute therapeutical interventions will follow current anaphylaxis guidelines, and possibilities for allergen immunotherapy have to be investigated [1, 85].

Conflict of Interest Statement

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R.T. did literature research and wrote the manuscript.

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