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Editorial Open Access

Adverse Reactions Triggered by Amaranth Allergens-What We Know So Far from a Molecular Perspective

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Editorial

The genus *Amaranthus* contains 44 species and belongs to the family of Amaranthaceae classified within the order of Caryophyllales. Within this order a number of allergenic species including *Amaranthus retroflexus* (Redroot pigweed), *Beta vulgaris* (sugar beet), *Chenopodium album* (Lambsquaters), *Kochia scoparia* (Burning bush), and *Salsola kali* (Russian thistle) have been acknowledged by the WHO/IUIS allergen nomenclature subcommittee to contain clinically relevant inhalant allergens. Moreover, the seeds of two buckwheat species (*Fagopyrum esculentum* and *Fagopyrum tataricum*) are listed as allergens within the database.

The monoecious, wind-pollinated *Amaranthus retroflexus* is native to semi-desert regions of North America, however it was introduced into the flora of most continents within the last centuries and populates now a variety of habitats. Originally used as a medical plant, the leaves can also be harvested and consumed as vegetable. Allergic reactions to Amaranth pollen are frequently reported from Arab countries as well as the Mediterranean area, but also the Indian subcontinent [1,2]. In fact, 69% of allergic patients in Iran showed sensitization to Amaranth extracts [3]. The only allergen identified in *Amaranthus* pollen so far is the profilin Ama r 2 showing sensitization rates of 33% among allergic patients, whereas immunoblots using those sera also revealed a multitude of additional IgE-reactive bands in the extract [4]. In general, profilins are classified as panallergens indicating their ubiquitous distribution in all eukaryotic cells. These cytosolic proteins show a highly variable protein sequence but a strictly conserved structure, which is formed by a compact beta-sheet surrounded by several alpha-helices. The well-preserved structure may also explain the high levels of IgE cross-reactivity frequently reported on these allergens [5]. The actin-binding profilins have been described as allergenic molecules in 44 pollen as well as food sources and interestingly within all allergenic Caryophyllales pollen, a profilin allergen has been identified (Figure 1). Since panallergens are vastly cross-reactive also between species, patients sensitized to those allergens characteristically show multiple sensitizations to biologically unrelated sources [6]. Nevertheless, the clinical importance of profilin sensitization especially with pollen profilins is still heavily debated. Within the Amaranthaceae/Chenopodiaceae high levels of cross-reactivity have been reported. Of note, immunoblot analyses using sera of *Amaranthus* allergic patients revealed that there was massive IgE also directed against proteins from *Chenopodium, Kochia*, as well as *Salsola*, but almost all IgE reactive bands were found in the high molecular weight range of 30-45 kDa, excluding profilin as source of these cross-reactivities. The study further pointed out that the major IgE binding proteins of *Amaranthus* have not been identified yet. Moreover, inhibition experiments revealed that IgE binding to high molecular weight *Amaranthus* proteins could be substantially diminished by pre-incubation of the sera with either of the other Amaranthaceae/Chenopodiaceae pollen extracts [7]. Thus, it can be expected that the key-allergens responsible for the cross-reactivity within allergenic pollen of the Caryophyllales order need still to be described. Nevertheless, the profilin allergen Ama r 2 has also been implicated with cross-reactivity of *Amaranthus* with *Chenopodium* and *Salsola*, respectively, since the profilins Che a 2 and Sal k 4 could both inhibit serum IgE binding of *Amaranthus* allergic patients to Ama r 2 in immunoblot experiments [4].

Besides *Amaranthus* retroflexus, the pollen of *Amaranthus viridis* and *Amaranthus spinosis* has been described as allergen sources and moreover, *Amaranthus paniculatus* has been implicated with food allergies [1]. In fact, there are two case reports, one by Kasera et al. the other by Pföhler et al. showing that the ingestion of Amaranth grains or flour can induce severe anaphylactic reactions [8,9]. Unlike cereals, which are members of the monocot family of Poaceae, the Caryophyllales belong to the Magnoliopsida thus their grains are free from gluten proteins. This fact may have contributed to the increasing popularity of Amaranth and buckwheat products especially in Western societies. In the Indian culture Amaranth flour (also referred to as Rajgira and Ramdana) is consumed during fasting [8], whereas buckwheat is a staple food in many Asian countries [10]. So far, three allergens from buckwheat species have been acknowledged by the WHO/IUIS allergen nomenclature subcommittee. Fag e 2 (*Fagopyrum esculentum*) and Fag t 2 (*Fagopyrum tataricum*) are 2S albumins thus belonging to the prolamin superfamily, whereas Fag e 3 belongs to the vicilin family of seed storage proteins, which are integrated within the cupin superfamily (**www.allergen.org**). 2S albumins are widely distributed within mono- as well as dicotyledonous plants. As storage proteins they are deposited in protein bodies as nutrient source of the growing sprout during germination. Moreover, a function in plant defense against pathogens has been suggested. The structure of these methionine and cysteine rich, small proteins is dominated by alpha helices, which are linked by turns and variable regions. The very stable allergens are understood to sensitize atopic individuals directly via the gastro-intestinal route [11]. In buckwheat, more than 75% of allergic patients react with Fag e 2 [10]. Unlike 2S albumin, the structure of cupin allergens is characterized by beta sheets. Cupins can be either monomeric or form multimeric structures, whereas vicilins typically depict trimeric proteins [12]. The IgE reactivity of Fag e 3 was reported to be more than 80% among buckwheat allergic patients from Korea [13]. Moreover, several other IgE reactive bands have been identified in buckwheat extracts, among them the legumin-like proteins Fag e 1/Fag t 1, a 10 kDa allergen, and an allergen classified as trypsin inhibitor (www.allergome.org); however all these proteins are lacking an entry into the WHO/IUIS allergen nomenclature database. The prevalence of buckwheat allergy in some Asian countries may be very high, so reported in a study with Japanese students, where 11.5% of food allergic patients reacted with this grain [14]. In a clinical case of anaphylaxis caused by the ingestion of buckwheat-containing muesli, cross-reactivity of buckwheat with latex and fig have been reported [15], which is however only one of many reports of anaphylactic episodes caused by ingestion of grains from this weed [16-18]. Cross-reactivity could also be expected between Fag e 3 and the weakly homologous vicilin-like allergens from cashew and walnut; however, clinical proof is lacking [13].

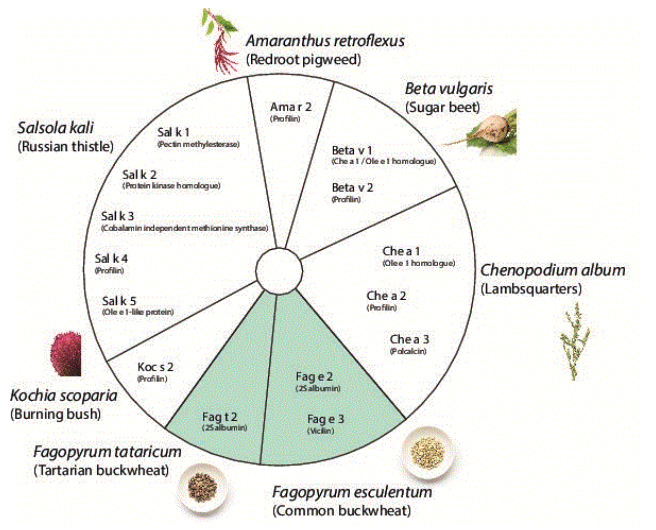

Figure 1: Schematic representation of Caryophyllales pollen and food allergens acknowledged by the WHO/IUIS allergen nomenclature subcommittee.

Buckwheat is becoming increasingly popular as a health food in the Western cuisine and obviously the plant has a high potential to induce anaphylactic reactions after ingestions. Similar might be true for *Amaranthus* and probably the anaphylactic potential of this plant may be considerable high. Despite a lack of knowledge on the allergens, especially food allergens, of *Amaranthus* sp. this topic requires careful research. Members of known food allergen families, among them seed storage proteins but also profilins, have been identified in members of the Caryophyllales order. Thus, it could be expected that these proteins might also play an important role in *Amaranthus*-associated food allergy. Moreover, cross-reactivity with related plants [i.e. buckwheat] seems probable and should be considered. The topic presents itself highly interesting and due to life-style changes will become more eminent within the next few years.

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