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Vegan diet—alternative protein sources as potential allergy risk

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Abstract
Background As a vegan diet is per definition a plant-based diet, consumers rely on plant protein sources in order to substitute animal proteins. Plant protein sources commonly used in this context are the following: cereals, like wheat (*Triticum aestivum, Triticum durum*), oat flakes; pseudo cereals like quinoa; nuts and oil seeds like cashew (*Anacardium occidentale*), hazelnut (*Corylus avellana*), walnut (*Juglans regia*); seeds like psyllium seeds (*Plantago ovata*), sesame (*Sesamum indicum*), and chia seed (*Salvia hispanica*).
Methods In order to assess the allergy risk posed by vegan diet, a literature search focusing on the composition of this particular diet and whether the respective foods are potentially allergenic was performed.
Results At first glance, it is evident for allergologists that these protein sources are well-known allergen sources. Particularly nuts and legumes harbour storage proteins, oleosins, and lipid transfer proteins that as such are associated with severe allergic reactions to food. In addition, there is increasing evidence that the simultaneous consumption of several of these foods may produce a summation effect where many single allergens of high allergenic potential sum up, thereby inducing anaphylaxis. Furthermore, food processing—or the lack of it—puts patients with pollen-associated food allergy at risk to react to some of the plant foods used in vegan diets.
Conclusion Therefore, individuals with a history of atopy should be educated regarding the allergy risk of a vegan diet.

Keywords Wheat · Lupine · Fenugreek · Pea · Sesame

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Introduction

A vegan diet, also referred to as plant-based or strict vegetarian diet, excludes *per definitionem* all animal-derived products, any kind of meat, dairy, eggs and seafood but also honey and animal-based food additives such as milk powder, lactose, gelatine or certain food colourings. Furthermore, this diet form is free from food that was processed with the help of animal products even if these are not contained in the final product, such as wine that was clarified through fish bladders [1, 2]. Essential nutritional requirements are not met which is why the consumers have to substitute animal proteins by plant proteins. This, however, bears the risk of food allergy as there are many foods of high nutritional value that are known to have a strong allergenic potential.

There are two main variants of IgE-mediated immediate type allergy to plant food, the primary (A) and the secondary food allergy (B). The class I food allergy (A) already occurs very early in life with a primary sensitization to foods like peanut, soy, wheat, fish, egg, milk, and (B) the pollen-associated food allergy (class II) for which the primary sensitizer is to be found in (mostly) tree pollen. Bet v 1, the major allergen from birch (*Betula verrucosa*) which in Northern Europe is the cross-reactive allergen with homologue proteins in many different plant foods. It is obvious that patients with the pollen allergy in question are at risk to develop symptoms to nuts and legumes when they switch to a vegetarian or vegan diet or may not be able to fully implement the substitution in cases of

pre-existing legume allergy. In addition, the declaration "vegan …" does not stand for "free of allergens" [3]!

Most common alternative plant protein sources in vegan diet

Plant protein sources commonly used by consumers of a vegan diet are the following: cereals, like wheat (*Triticum aestivum, Triticum durum*) (as seed, Seitan, and others), oat flakes; pseudo cereals like quinoa; nuts and oil seeds like cashew (*Anacardium occidentale*), hazelnut (*Corylus avellana*), walnut (*Juglans regia*); seeds like floseeds (*Plantago ovata*), sesame (*Sesamum indicum*), and chia seed (*Salvia hispanica*).

Very important protein sources chosen as substitutes are different legumes and protein isolates thereof: soybean (*Glycine maxima*) which is available as both processed and unprocessed food (tofu and tempeh), lupine (basically three different *Lupinus* species), peanut (*Arachis hypogaea*), pea *(Pisum sativum*), the latter also processed as well as unprocessed, chickpea (*Cicer arietinum*), lentils (*Lens culinaris*) and fenugreek (*Trigonella foenum-graecum*). The allergenic potential is altered with the method of food processing [3].

Table 1 Wheat allergens mainly associated with food allergy to wheat

	Biochemical name
Wheat (Tri a) allergens (food)	
Tri a 12	Profilin
Tri a 14	Lipid transfer protein
Tri a 17	Beta-amylase
Tri a 18	Agglutinin isolectin 1
Tri a 19	Omega-5-gliadin
Tri a 20	Gamma gliadin
Tri a 25	Thioredoxin
Tri a 26	High molecular weight (MW) glutenin
Tri a 36	Low MW glutenin GluB3-23
Tri a 37	Alpha purothionin
Tri a 41	Mitochondrial ubiquitin ligase activator of NF_KB 1
Tri a 42	Hypothetical protein from cDNA
Tri a 43	Hypothetical protein from cDNA
Tri a 44	Endosperm transfer cell-specific PR60 precursor
Tri a 45	Elongation factor 1 (EIF1)
Wheat (Tri tu) allergen	
Tri tu 14	ns Lipid transfer protein 1

Tri a Triticum aestivum, *Tri tu Triticum turgidum*, *MW* molecualr weight, *NFkB* nuclear factor kB, *ELF* elongation factor, *ns* non-specific

Allergenic potential of the alternative plant protein sources in vegan diet

Cereals

One of the most important plant protein sources are cereals. With regard to wheat the allergologist has to consider different wheat-associated diseases, basically the IgE- and non-IgE-mediated entities.

IgE-mediated entities are wheat allergy including wheat-dependent exercise-induced anaphylaxis (WDEIA) and the occupational disease bakers' asthma. Presently, there are 29 wheat (28 *Triticum aestivum* and one *Triticum turgidum ssp. durum* (Durum wheat)) allergens documented in the WHO/IUIS database, of which 15 (14 *Triticum aestivum* and 1 *Triticum turgidum ssp. durum*) are associated with food allergy (Table 1; [4]). The non-IgE-mediated entities consist of celiac disease and non-celiac wheat sensitivity.

Case report

A 65-year-old man who had experienced two anaphylactic reactions due to unknown causes with pruritus starting at the head with subsequent generalization, urticaria and drop of blood pressure presented in the Interdisciplinary Allergy Outpatient Clinic Lübeck/Borstel. During the described episode an adrenalin pen had been applied and development of further symptoms avoided.

So far, the history for type I allergy revealed an inhalant allergy to grass and rye pollen with seasonal rhinitis.

Allergy diagnostic test

IgE-antibody detection was performed (Table 2).

Skin prick test (prick-to-prick test) revealed a reaction to wheat flour of 10 mm, which was stronger than that to the positive control histamine (7 mm).

A wheat-dependent exercise-induced anaphylaxis (WDEIA) could not reliably be diagnosed because the patient could not undergo an oral challenge accompanied by standardized exercise due to a heart disease. However, the facts that there were only two in-

Table 2 In vitro allergy diagnostic test

	ImmunoCAP IgE [kU/L]	
Allergen extract		
Wheat flour	Negative	(CAP class 0)
Allergen component		
– Tri a 19 (omega 5-gliadin)	2.64	(CAP class 2)
– Tri a 14 (lipid transfer protein)	Negative	
Total IgE	99.1	
Serum tryptase	4.5 µg/l (normal: < 11.4 µg/l)	
Tri a Triticum aestivum		

Table 3 Single legume allergens from protein sources relevant in a vegan diet [4, 22, 23]

Plant food allergens (Protein families)	Peanut (*Arachis hypogaea*) Ara h x	Lupine (*Lupinus angustifolius*): Lup an x (*Lupinus albus*): Lup a x (*Lupinus luteus*): Lup l x	Soy bean (*Glycine maxima*) Gly m x	Pea (*Pisum sativum*) Pis s x	Lentil (*Lens culinaris*) Len c x	Chickpea (*Cicer arietinum*) Cic a x	Green Bean (*Phaseolus vulgaris*) Pha v x
Vicilin-like storage protein; 7S-globulin	**Ara h 1 (IUIS)**	**Lup an 1 β-conglutin (IUIS)** *Lup a 1*	**Gly m 5 (IUIS)** **Gly m Bd 28**	**Pis s 1 (IUIS)** **Pis s 2 (IUIS)** (Convicilin; α-subunit of vicilin)	**Len c 1 (IUIS)** (γ-vicilin subunit)	not published	*Pha v phaseolin*
Conglutin-like storage prot. 2S-albumin	**Ara h 2 (IUIS)**	δ-conglutin *Lup a δ-conglutin* *Lup an-δ-conglutin*	**Gly m 8 (IUIS)**	not published	not published	*Cic a 2S-albumin*	not published
Legumin; 11-S-globulin	**Ara h 3 (IUIS)**	α-conglutin *Lup a-α-conglutin* *Lup an-α-conglutin*	**Gly m 6 (IUIS)**	not published	not published	*Cic a 6*	not published
Profilin	**Ara h 5 (IUIS)**	**Lup a 5 (IUIS)**	**Gly m 3 (IUIS)**	*Pis s 5*	not published	not published	*Pha v 5*
Conglutin	**Ara h 6 (IUIS)**	not published	not published	not published	not published	not published	not published
Conglutin	**Ara h 7 (IUIS)**	*Lup a γ conglutin* ? *Lup an γ conglutin* ?	not published	not published	not published	not published	not published
PR-10 Bet v 1-super family	**Ara h 8 (IUIS)**	*Lup a 4* *Lup l 4*	**Gly m 4 (IUIS)**	*Pis s 6*	not published	*Cic a 4*	*Pha v 6*
Non-specific (ns) Lipid Transfer Proteins	**Ara h 9 (IUIS)** **Ara h 16 (IUIS)** **Ara h 17 (IUIS)**	**Lup an 3 (IUIS)** *L. luteus* LTP	not published	**Pis s 3 (IUIS)**	**Len c 3 (IUIS)**	*Cic a 3*	**Pha v 3 (IUIS)**
Defensins	**Ara h 12 (IUIS)** **Ara h 13 (IUIS)**	not published	**Gly m 2 (IUIS)**	not published	not published	not published	not published
Oleosins	**Ara h 10 (IUIS)** **Ara h 11 (IUIS)** **Ara h 14 (IUIS)** **Ara h 15 (IUIS)**	not published	17 kDa oleosin 18 kDa oleosin 24 kDa oleosin	not published	not published	not published	not published
Agglutinins	–	–	*Gly m agglutinin*	*Pis s agglutinin*	*Len c agglutinin*	–	*Pha v PHA*
Diverse	**Ara h 18 (IUIS) (cyclophilin)**	not published	**Gly m 1 (IUIS)** Hydrophobic protein from soybean **Gly m 7 (IUIS)** Seed biotinylated protein *Gly m TI (trypsin inhibitor)* *Gly m Bd 30 k (cysteine protease)* *Gly m CPI (cystatin)* *Gly m EAP (embyonic abundant protein)*	*Pis s albumin*	**Len c 2 (IUIS)** Seed-specific biotinylated protein	**Cic a 1 (IUIS)** Late embryogenesis protein 4 *Cic a 10* HSP-70 –	*Pha v alpha AI (alpha amylase inhibitor)* *Pha v chitinase*

abbreviations in **bold**: allergens accepted by and documented in the WHO/IUIS database; abbreviations in *italics*: Allergens taken from www.allergome.org

Fig. 1 Lupine plant (**a**), lupine seed and flour (**b**)

cidences and alpha-GAL syndrome could be excluded are highly suggestive for the effect of augmenting factors in addition to wheat consumption. At a follow-up visit 4 years later, he reported to be completely free of symptoms since avoidance of all wheat products. The peculiarity of this case is that it is an example for the value of molecular allergy diagnostics when patients are diagnosed with idiopathic anaphylaxis: The IgE-reaction to wheat extract was non-existent; however, when rTri a 19 was used, the strong skin test reaction to wheat flour was confirmed, and a reliable dietary recommendation could be given.

Legumes

Soybean

Soybean and products made thereof are an integral part of the vegan diet. Particularly birch pollen allergic individuals may react severely to soy milk, soy rice drinks, soy yoghurt, etc., based upon a pollen-associated food allergy for which the sequence and structural similarity between Bet v 1, the major allergen in birch pollen, and Gly m 4, the Bet v 1 homologue in soy are responsible [5]. In general, Bet v 1-associated food allergies present with mild to moderate symptoms, mostly with an oral allergy syndrome. However, this is often enough not the case with soy products: Here the reactions can be much more severe due to the amount of allergen consumed and the fact that the allergenic protein, normally destroyed by heat, had not been exposed to heat long enough during food processing (summarized in [3]). There are presently eight soybean allergens documented in the WHO/IUIS database (Table 3).

Lupine species

On the other hand, several consumers meanwhile try to substitute soy with lupine products (Fig. 1) because the latter is not genetically modified. Lupine serves as food as well as food additive. Lupine flour has favourable nutritional properties, it is gluten-free which makes it a valuable substitute for wheat in case of wheat allergy, and it is lactose-free. It is preferably used by vegetarians and in a vegan diet, and its consumption continues to increase! As an ingredient it is often used in wheat flour, however, there are lupine pasta, lupine sausages, lupine ice cream, lupine ketch up, etc. [6, 7]. Lupine allergy can be severe although it is not as potent as peanut [8]. It manifests itself as food allergy and, less often, as occupational disease (bakers' asthma with and without reaction to the ingestion of lupine containing food). Like soy, lupine has to be declared on ingredient lists [9]. The first description of a lupine allergy was in 1994, when a peanut allergic individual reacted severely to lupine pasta [10]. The potential to react to lupine via cross-reactivity to peanut should not be underestimated [8], because it makes lupine a "hidden allergen" for those who are not aware of the cross-reactivity. There is, however, a considerable number of lupine monosensitizations [6]. The first report on lupine allergy in Germany in 2006 was such a patient [11]. Only three allergens have so far been accepted and documented by the WHO/IUIS allergen nomenclature subcommittee: Lup an 1 (β-conglutin); Lup an 3 (lipid transfer protein), and Lup a 5 (profilin). Three different lupine species are dominant in foods: *Lupinus albus* (white lupine), *Lupinus angustifolius* (blue lupine), and *Lupinus luteus* (yellow lupine). One lupine species is not exactly like the other regarding the protein and allergen content and distribution [12]. A very recent study on cross-reactivity among legumes in 195 peanut-al-

Fig. 2 Fenugreek flour and seeds

lergic children showed sensitization to lupine, fenugreek, soy and lentils in descending order [13].

Fenugreek

Fenugreek (*Trigonella foenum graecum* of the *Fabaceae* family) also belongs to the legumes. It is consumed as dried and roasted seeds or as flour (Fig. 2), in the form of spices (e.g. curry), in cheese, baked goods, confectionery, and in coffee substitutes and herbal teas [14]. It serves as food and is an ingredient of traditional medicine as well. The first description as food allergen source dates back to 1997, when severe reactions after ingestion, inhalation and external application of fenugreek seed powder were published [15]. Anaphylaxis to fenugreek in curry spices has also become known since then [16, 17]. As has been observed for lupine, fenugreek induces not only food allergy and anaphylaxis but occupational asthma as well [18]. No single allergens of fenugreek have so far been accepted and documented by the WHO/IUIS allergen nomenclature subcommittee. A clinically most relevant aspect is that the data speak in favour of peanut being the primary sensitizer, as sensitization to fenugreek is mostly the result of a pre-existing peanut sensitization, and fenugreek monosensitization is very rarely observed [14].

Table 4 Oleosins as documented in the WHO/IUIS database ([23], modified)

Plant protein source	Oleosins (IUIS)	Molecular weight [kDa]
Peanut (*Arachis hypogaea*)	Ara h 10	16
	Ara h 11	14
	Ara h 14	17.5
	Ara h 15	17
Hazelnut (*Corylis avellana*)	Cor a 12	17
	Cor a 13	14–16
	Cor a 15	17
Sesame (*Sesamum indicum*)	Ses i 4	17
	Ses i 5	15
Buckwheat *(Fagopyrum tataricum)*	Fag t 6	18

kDa kilo Dalton

Pea

Some vegetarian and vegan dishes contain several food allergen sources with high allergenic potential in parallel. A case report on an anaphylactic reaction to “falafel” demonstrates this impressively [19]: A 28-year-old woman developed an anaphylactic reaction grade III after ingestion of falafel. Generally, falafel consists of mashed beans and/or chickpeas plus garlic, herbs and spices. Sometimes, wheat or pea flour or soy is additionally used. Falafel may be served together with tahini sauce, which consists of sesame. Taken together, falafel may present a highly allergenic food [19]. Although the exact content of the anaphylaxis-causing falafel dish remained obscure in the cited case report, allergy diagnostic tests including oral food challenge revealed an immediate type allergy to pea. In addition, the presentation of several highly allergenic foods in one meal may cause a summation effect via single allergens with similar structures that are ingested at one certain time point, which in the end is responsible for the severity of the reaction [19].

So far, three allergens in pea (*Pisum sativum*) are listed in the WHO/IUIS database. There is evidence that the storage proteins Pis s 1 and Pis s 2 are the major pea allergens [20].

Like fenugreek pea does not have to be documented on ingredient lists. With regard to pea an increase in reactions can be expected as pea is used more and more in highly processed vegan foods [21]. Apart from peanut and soy, single allergens from other legumes are not yet available for routine allergy diagnostic tests.

Lipophilic allergens in vegan diet-relevant food

Apart from storage proteins there are other protein families that are associated with severe allergic reactions. Those are lipophilic (oleosins) and lipid-associated proteins (lipid transfer proteins [LTP]). Particularly oleosins that are present in oil seeds and most probably absent in aqueous extract-based allergy diagnostic test solutions have been described as being responsible for severe reactions after ingestion of peanuts, hazelnut, sesame, soy, sunflower, walnut, and recently buckwheat [22, 23], and some have already been well characterized and documented in the WHO/IUIS database ([4]; Table 4; [23]). A study on 76 peanut allergic patients in Borstel/Lübeck showed that those sensitized to oleosins suffered severe symptoms ([24], updated).

Sesame

As mentioned above, we thought oleosins to be the cause of a severe reaction to sesame when a patient with a plausible history of an anaphylaxis after consumption of a bread roll with sesame was completely negative in routine allergy diagnostic tests. Total IgE: 11.6 IU/ml; serum tryptase 5.5 µg/L, specific IgE was negative to sesame extract, rSes i 1 (storage protein), apple extract, wheat extract, rTri a 19 (omega-5-gliadin), and marker allergens like rTri a 14 (LTP), rMal d 1 (Bet v 1-homologue), rMal d 3 (LTP). His serum was also IgE negative for peanut and lupine seed extracts, the latter being a common ingredient of wheat flour. The oral provocation was positive for sesame. In addition, our experimental investigation with whole sesame extract (obtained via acidic and alkaline extraction) revealed IgE-binding to sesame proteins—which based on their molecular weight were storage proteins—and to peanut oleosin-enriched extract of roasted sesame in immunoblot, which is also suggestive for an IgE-reaction to oleosins [25].

Conclusion

To the best of my knowledge there are no cohort studies on food allergy development in individuals who have switched to a vegan diet at a certain time point in their life, so at present there is no information on a "vegan host-specific" risk factor other than the augmenting factors known for the general population of atopic and food allergic patients. Individuals with atopic predisposition are predisposed to having or to developing a class I or class II food allergy either in the course of the "allergenic march" or via aimed exposition to "vegan" foods they include as "new" foods into their diet. The potential of cross-sensitivity is high. Whether this sensitization will be/become clinically relevant cannot be properly predicted yet.

However, case reports on occupational allergy to food allergen sources used in vegan and gluten-free diets are interesting in this context as they represent important examples for allergen exposure as a "risk factor" as such. One recent publication described a baker who developed an inhalant allergy also affecting the bronchial system to several foods after one year of work mainly with foods used in the vegan diet. She had no previous allergies. However, bakers use high amounts of certain foods (food allergen sources) which points to the allergen dose and exposure time as being of particular relevance [26].

For several food allergen sources relevant for the vegan diet the allergens have not been identified and characterized yet. Specific and sensitive diagnostic tools are, therefore, still lacking to a certain extent and will have to be developed further via molecular allergy research. Lipophilic allergens should be made available for routine diagnostic tests as they have been shown to be marker allergens for the severity of food allergy (summarized in [22–24]).

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