

REVIEW

Lupin allergy: a hidden killer in the home

M. L. Sanz¹, M. D. de las Marinas², J. Fernández³ and P. M. Gamboa⁴

¹Department of Allergology and Clinical Immunology, School of Medicine, University Clinic of Navarra, Pamplona, Spain, ²Unidad de Alergología, Policlínico Valencia, Consulta privada, Valencia, Spain, ³Allergy Department, Elche Hospital, Elche, Spain and ⁴Allergy Unit, Basurto Hospital, Bilbao, Spain

Clinical & Experimental Allergy

Summary

This review addresses the problem of lupin sensitization in the home environment. We summarize the data currently available on allergy to lupin, which has become, in recent years, a hidden killer in our homes. Since 2006, when lupin was included in European regulations as a food whose presence must be declared, the situation may have changed. Nevertheless, we must take into account the possibility of undeclared allergenic ingredients or the presence of 'hidden' allergens, given that contamination during food production processes may be a great risk for sensitized individuals. Furthermore, the United States, Japan, Australia and New Zealand still do not include lupin among the ingredients that must be listed on foodstuff labelling. Our responsibility is to educate the public so that they are aware of the danger and look for lupin in the labels of products that run the risk of containing it. Lupin allergy can manifest itself in isolation or in parallel to peanut allergy. Identification of the proteins causing possible cross-reactivity is complicated, and new structural studies are needed. To date, it has not been possible to clearly identify the allergens responsible for isolated lupin sensitization in relation to parallel and/or cross-sensitization between lupin and peanut. Most of the allergenic proteins of lupin are α - and β -conglutins, with a lesser presence of γ - and δ -conglutins. A β -conglutin corresponding to Lup an 1, with a sequence similar to Ara h 1, has been identified as a major allergen of lupin in patients with allergy following lupin ingestion.

Correspondence:

Dr Maria L. Sanz, Department of Allergology and Clinical Immunology, School of Medicine, University Clinic of Navarra, Apartado 4209, 31080 Pamplona, Spain.
E-mail: mlsanzlar@unav.es

Introduction

Lupins are legumes of the *Fabaceae* family, extensively grown and known in the Mediterranean region since ancient times. There are 450 species, of which the following are of agricultural interest: *Lupinus albus*, *Lupinus angustifolius*, *Lupinus luteus* and *Lupinus mutabilis*, which are commonly known as 'sweet lupins'. Lupins are usually consumed as appetizers, and are frequently found as snacks in the Mediterranean countries and in Australia. In addition, their flour is commonly used in many European countries as an 'improving' ingredient in the production of bread, biscuits, crusts, pasta and other bakery products and/or as soya substitutes [1].

In recent years, it has increasingly been suggested that lupins should be regarded as hidden allergens, to the extent that on the basis of findings from published studies of allergy and anaphylaxis [2], it was decided that lupin should be included in the list of food allergen whose presence must be declared as regulated by the European Directive on foodstuff labelling (Annex III bis) [3].

The prevalence of sensitization to lupin varies: in a recent study of 1160 patients in the Mediterranean area [4], a lupin sensitization rate of 4.1% was reported among atopic patients, while in the north of Europe, in a study involving 1522 patients clinically suspected of having food allergies, the figure was 1.6% [5], which can still be considered high, given the traditionally infrequent use of lupin in the diets of these patients.

A recent prospective study that analysed the prevalence of lupin allergy in France and Belgium [6] in patients presenting to allergy departments showed sensitization rates of 2.5% in the case of patients with manifest latent atopy. The corresponding sensitivity of patients sensitized to peanut was 17.1%. It is particularly significant that of all the patients studied (5366), only one was previously aware of being allergic to lupin. The authors proposed that sensitization to lupin should be investigated in all cases of patients with peanut allergy and that lupin be included in the battery of allergens to be tested in patients with a clinical picture of food allergy with no identified allergen.

In Denmark, sensitization to lupin was found in 82% of 39 patients allergic to peanut, of whom 35% showed clinically relevant symptoms after challenge. None of the patients was aware of the presence of lupin in the food-stuffs they consumed [7].

Allergenic proteins of lupin

The major protein component of the *Lupinus* species are storage proteins, the conglutins. The two main fractions are α - and β -conglutins, with a lesser presence of γ - and δ -conglutins [8].

The α -conglutinin protein belongs to the family of 11S globulins or 'legumin-like' globulins. This protein is composed of a heterogeneous mixture of subunits linked by two disulphide bridges. Their molecular weight ranges from 47 to 54 kDa, with basic units of 20 kDa.

As for β -conglutinin, this belongs to the family of acid 7S globulins or vicilin-like globulins. These have a trimeric structure consisting of over 20 polypeptide chains of 20–80 kDa without sulphide bridges according to Jappe and Vieths [8] and of 15–65 kDa according to Guillaman and colleagues [20 bis]; γ -conglutinin is a basic tetrameric 7S protein consisting of two polypeptides linked by disulphide bridges (17 and 30 kDa polypeptides).

All of these globulins (7S and 11S) belong to the cupin superfamily.

δ -conglutinin is a 2S monomeric minor protein and a member of the prolamine family.

The structure of all these proteins is complex, with variations among different cultivars and species of lupin [9, 10].

As regards the allergenicity of the lupin conglutins, Holden et al. [11] reported specific IgE-binding bands with a molecular weight of 10–80 kDa in the serum of 6 patients with lupin allergy. Most corresponded to α -conglutinin, and some to β -conglutinin. In no case was binding to δ -conglutinin observed, and most of the patients presented specific IgE targeted to more than one conglutinin. In any case, the authors pointed to increased allergenicity on the part of the α - and β -conglutins.

Goggin et al. [12] have identified a majority allergen of *L. angustifolius*, corresponding to Lup an 1, a β -conglutinin, with a sequence similar to that of Ara h 1 [13], in patients with allergy following lupin ingestion. Both Ara h 1 and β -conglutinin are vicilins.

In addition, other protein bands have been described in patients with lupin allergy. Rojas-Hijazo et al. have described a 14 kDa lupin allergen that is strongly heat resistant, in a patient monosensitized to lupin [14]. We have also described, in a woman with monosensitization to lupin, a 29 kDa IgE-binding band that failed to bind either peanut or lentil [15].

Other authors have also reported IgE-binding bands of different molecular weights both in patients monosensi-

tized to lupin [16–19] and in patients sensitized to other legumes [20].

Recently, Guillaumon et al. [21] have identified the major allergens for *L. albus*, which they have called Lup-1 y Lup-2. These correspond to a β conglutinin polypeptide and the basic subunit of α conglutinin, respectively. Work by these authors has shown a very high homology between Lup-1 and Lup an 1 from *L. angustifolius*.

Cross-reactivity

Lupin allergy can manifest itself in isolation or in parallel to peanut allergy [8]. Identification of the proteins causing possible cross-reactivity is complicated, and new structural studies are needed in this area.

To date, structural homology is known to exist between lupin α -conglutinin and peanut Ara h 3, as well as between β -conglutinin and Ara h 1, which has been shown both for *L. angustifolius* [13, 22] and for *L. albus*, which furthermore shows considerable homology with allergens from other legumes: Len c1 from *Lens culinaris*, Pis s1 from *Pisum sativum*, for con Lup-1, and y glycin G1 from soybean, for Lup-2 [21].

These proteins could be responsible for lupin cross-reactivity phenomena in patients with allergy to peanut and/or other legumes. However, to confirm this, IgE-binding studies with purified peanut allergens (Ara h 1 and Ara h 3) should be performed with sera from the lupin-allergic patients.

In addition, there appears to be a structural similarity between Ara h 8 and some lupin PR-10 proteins [13] – the latter being analogues of Bet v 1, and thus not responsible for systemic reactions.

To date, it has not been possible to clearly identify the allergens responsible for isolated lupin sensitization, in relation to parallel and/or cross-sensitization between lupin and peanut (where primary sensitization appears to be due to peanut), and it is also not known which lupin proteins are correlated to the severity of the clinical reaction.

Goggin et al. [12], assuming that the patients in their study showed primary sensitization to lupin even with positive but low levels of peanut specific IgE, considered that although a structural similarity exists between Ara h 1 and β -conglutinin, this fact is unlikely to explain the cross-reactivity between lupin and peanut – because none of the patients reacting to β -conglutinin showed clinical manifestations after consuming peanut. It is possible that individuals reacting to both peanut and lupin react to different lupin allergens or that they react to different IgE epitopes on β -conglutinin, compared with individuals who react to lupin alone.

Clinical implications

As the consumption of lupin has increased, so has the number of clinical cases reported in the literature

(Table 1). In this context, two possible lupin sensitization pathways exist: a primary pathway involving ingestion [14–19, 23–30] or the inhalation of lupin flour [31–34], which is more common among allergic patients living in Mediterranean countries, where the diet typically comprises a great variety of legumes, and among these, lupin [33, 35], and in Australia [33], and a secondary pathway resulting from cross-reactivity with the rest of the leguminous species, and particularly peanut [11, 16, 20, 36–41], soya [16] and peas [42] – this presentation being more frequent in North America [20] and in northern Europe [16, 36–39, 41]. Based on this secondary

pathway, the percentages of clinical reactivity to lupin in patients with peanut allergy have varied depending on the methodology used and the patients studied, with figures ranging from 4% [41, 43] to 17.1% [6] or 37% [7].

Regardless of the sensitization pathway involved, the most clinical common conditions reported in the literature are anaphylaxis, and generally appear following the ingestion of some commercial product in which the presence of lupin flour has gone unnoticed [15, 16, 18, 19, 23–28, 30, 36, 38, 39]. In addition, there have been several reports of asthma induced as a result of ingestion [25, 38] and/or inhalation [31, 33, 34, 40].

Table 1. Lupin allergy: published references

Author	No. patients, country	Known allergy	Food trigger	Symptoms
Hefle et al. [20]	1, United States	Peanut	Noodles	Urticaria, angioedema
Romano et al. [23]	3, Italy	Not known	Lupin seeds	Oral allergy syndrome
Matheu et al. [42]	1, Spain	Peas	Lupin seeds	Anaphylaxis, urticaria, angioedema,
Kanny et al. [36]	1, France	Peanut	Lupin flour	Acute asthma
Crespo et al. [31]	3, Spain	Lupin seed	Lupin flour inhalation	Asthma, rhinitis
Parisot et al. [32]	1, France	Grass pollen, D pt	Lupin flour inhalation	Rhinitis, conjunctivitis, oedema
Leduc et al. [24]	1, France	Not known	Pizza with lupin flour	Anaphylaxis
Faeste et al. [37]	1, Norway	Peanut	Bread	Urticaria, angioedema
Smith et al. [25]	3, Austria	Hayfever (pollen)	Bread with lupin grain	Urticaria, angioedema, asthma, abdominal pain
Wüthrich et al. [38]	2, Switzerland	Peanut, hayfever (pollen)	Pizza Gingerbread	Severe asthma, oedema, abdominal pain
Radcliffe et al. [39]	1, Great Britain	Peanut	Lupin flour in dough	Oral allergy syndrome, anaphylaxis
Moreno-Ancillo et al. [41]	1, Spain	Peanut	Lupin seed handling/ inhalation	Asthma
Rojas-Hijazo et al. [14]	1, Spain	Not known	Cookies, chicken, Bouillon cube	Anaphylaxis, oral allergic syndrome
Rotiroti et al. [26]	1, Italy	Not known	Lupin flour	Anaphylaxis
Wassenberg et al. [27]	1, Switzerland	Not known	Industrial waffle	Anaphylaxis
Peeters et al. [16]	6, The Netherlands	Peanut (in 3 out of 6)	Lupin flour	Several allergic reactions
De las Marinas et al. [15]	1, Spain	Not known	Lupin beans, packed buns	Anaphylaxis
Brennecke et al. [28]	1, Germany	Birch pollen	Lupin flour (nut, croissant)	Anaphylaxis, asthma
Quaresma et al. [17]	2, Portugal	Mites, pollen	Lupin seeds	Oral allergy syndrome
Campbel et al. [33]	7, Australia	Not known	Lupin flour	Rhinitis, asthma
Shaw et al. [41]	2, United Kingdom	Peanut	Lupin flour (challenge)	Oral allergy syndrome, urticaria, 20% decline in PEF
Holden et al. [11]	6, Norway	All peanut, 1 fenugreek, 1 hazelnut, 1 egg, milk and nuts	Lupin flour in pancake or muffins (oral challenge)	Asthma anaphylaxis, oral allergy syndrome and abdominal pain
Castro et al. [18]	1, Spain	Drug allergy	Lupin flour in packed fried tomato	Anaphylaxis with oral syndrome
Santos S et al. [19]	1, Spain	Pollen, dog and cat dander	Lupin flour in brownie cake	Anaphylaxis
Rossi et al. [30]	1, Italy	Not known	Lupin flour (gluten free pasta)	Anaphylaxis
Prieto et al. [34]	1, Spain	Not known	Lupin flour inhalation and oral ingestion. Lupin seeds	Rhino-conjunctivitis and asthma (inhalation). Anaphylaxis (oral intake)

Diagnostic implications

The diagnosis of lupin allergy is based on the clinical history, which, in many cases, yields no evident clues, because the allergen behaves as a hidden trigger. It has therefore been proposed that lupin flour should be included in the standard allergen test battery in patients with a history of anaphylaxis after food ingestion [6].

Positive skin tests to lupin and possibly also to other leguminous species (particularly peanut, soya, peas, lentils or chickpeas) can be corroborated by *in vitro* tests such as specific IgE, basophil activation tests and immunoblotting.

On the other hand, with the exception of cases of anaphylaxis, oral challenge testing could be considered in order to prove or to exclude the clinical relevance of lupin sensitization. In patients with respiratory symptoms, an inhalatory [34] or an oral challenge could be used [7, 16]. In this sense, Peeters [7] found the lowest lupin flour dose capable of inducing a clinical reaction (eliciting dose) to be about 0.5 mg for subjective symptoms. This dose for lupin is low, and is only fivefold higher than that for peanut. No predictive factors for lupin allergy were found [7].

Sources of lupin exposure and allergen avoidance

Lupin may be present in many foods, often in small amounts as hidden allergens that can give rise to allergic reactions. The possible sources include the presence of lupin flour added to pasta [20, 24, 38], breadcrumb coatings, hotdog buns [37], biscuits [14], packed buns [15], fresh buns [25], pancakes, muffins, croissants [28], Brownie-type cakes [19], industrial waffles [27], sauces, etc., as well as dietary products sold as milk or soya substitutes [8], and in products for celiac patients [30]. Because of its emulsifying properties, lupin flour is also used in chicken broth cubes, dehydrated chicken soup [14] or in commercial fried tomato sauce brick packs [18].

A novel line of research is being conducted on the basis of precise methods for controlling the presence of lupin flour in industrial products [44, 45] and calculating the approximate amounts present [46].

It is not easy to define dietary recommendations for the patients. In our opinion, in the case of primary sensitization, the patient should avoid the consumption of lupin or products that may contain lupin, without avoiding the consumption of the rest of the previously tolerated legumes [15, 18, 19]. Should any doubt exist, controlled exposure testing should be considered.

In patients with initial clinical sensitization to a leguminous species (particularly peanut), greater caution is required, depending on the population involved. Thus, French and Danish authors report cross-reactivity percentages of 17% [6] to 68% [47], for French and Belgian

populations, and 32% [7] for Danish populations. In contrast, in British [41] or Norwegian populations, [11] the figures are only in the order of 5%. In the latter cases, systematic avoidance of the product is not advised. Nevertheless, each case should be considered individually, with due assessment of the severity of the clinical manifestations, and considering the possibility of controlled exposure testing to lupin flour, before dietary counselling of the patient [48]. However, legume sensitization may be a dynamic process, and there have been reports of patients who began to develop symptoms in response to a single legume (peas), gradually followed by symptoms also in response to lentils, beans, peanuts and lupins [42].

As future alternatives, almost total elimination of lupin allergenicity through autoclave processing at a pressure of 6 bar for three minutes has been suggested [49].

Regulations on food ingredient listing

Starting in Europe in 1985, the General Standard for the Labeling of Prepackaged Foods of the Codex Alimentarius specifies the obligation to report the following foods and ingredients that are known to cause hypersensitivity: cereals containing gluten (e.g. wheat, rye, barley, oats, spelt or their hybridized strains and their products); crustaceans and their products; eggs and egg products; fish and fish products; peanuts, soybeans and their products; milk and milk products (lactose included); tree nuts and nut products; and sulphite at concentrations of 10 mg/kg or more.

Five additional food groups have been added: celery, mustard, sesame seeds, lupins and mollusks. The latter two have been introduced with the latest 2006 regulations [3].

However, other countries such as the United States, Japan, Australia and New Zealand do not include lupin among the ingredients that must be listed in foodstuff labelling.

In conclusion, and in line with the opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies [2], it can be stated that lupin is responsible for an increasing number of allergic reactions – some of which are serious – and that it should be regarded as a potential hidden killer in the home. This situation must be addressed by the bodies responsible for foodstuff labelling throughout the world.

Acknowledgements

M. L. S., J. F. and P. M. G. are supported by grant RD07/0064 from the Spanish Research Network on Adverse Reactions to Allergens and Drugs (RIRAAF: Red de Investigación de Reacciones Adversas a Alérgenos y Fármacos) of the Carlos III Health Institute.

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