Allergic Reactions to Pine Nut: A Review

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Abstract

Pine nut is a nutrient-rich food with a beneficial impact on human health. The many bioactive constituents of pine nut interact synergistically to affect human physiology in a favorable way. However, pine nut can trigger dangerous allergic reactions. Severe anaphylactic reactions to pine nut accounted for most of the 45 cases reported in the scientific literature. Pine nut allergy seems to be characterized by low IgE cross-reactivity with other commonly consumed nuts and a high monosensitization rate. The present review provides updated information on allergic reactions to pine nut, molecular characterization of its allergens, and potential homologies with other nut allergens.

Key words: Allergen. Anaphylaxis. Food allergy. Pine nut allergy. Tree nut allergy.

Resumen

El piñón es un alimento rico en nutrientes con un impacto beneficioso en la salud. Los componentes bioactivos del piñón interaccionan de forma sinérgica para influir en la fisiología humana de una forma favorable. Sin embargo el piñón puede producir reacciones alérgicas graves. Del total de los casos publicados, las reacciones anafilácticas severas representan la mayoría de las reacciones descritas. La alergia a piñón, además, parece estar caracterizada por una baja reactividad cruzada a nivel de anticuerpos IgE con otros frutos secos consumidos habitualmente y por un elevado porcentaje de monosensibilización. El propósito de esta revisión es dar una visión actualizada de las reacciones alérgicas a piñón, la caracterización de sus alérgenos a nivel molecular y sus homologías con otros alérgenos de frutos secos.

Palabras clave: Alérgeno. Anafilaxia. Alergia alimentaria. Alergia a piñón. Alergia a frutos secos.

Pine Nut Composition, Nutritional Value, and Health Benefits

Pines (genus *Pinus*) are evergreen trees belonging to the conifers division, the largest and most successful group of living gymnosperms. Gymnosperms first appeared 300 million years ago. Conifers separated from angiosperms (flowering plants) about 100 million years ago and thus constitute an ancient branch in the evolutionary tree (Figure). Conifers differ from flowering plants, since the seeds are not enclosed in an ovary but are exposed within structures such as cones (Figure) [1,2]. *Pinus pinea* is the largest producer of commercial pine nuts, although seeds from other species, such as *Pinus koraiensis* and *Pinus gerardiana*, are also eaten throughout the world. Pine nuts have been consumed for over 2000 years in the Mediterranean region. Today, they are frequently used in raw or roasted form and as ingredients in breads, cakes, cookies, sauces, candies, and vegetable and meat dishes. Although the composition of pine nuts varies between species, the scientific literature confirms that this nut is a valuable source of important nutrients. The investigations of Nergiz and Dönmez [3] with *Pinus pinea* L. seeds grown in Turkey revealed an average protein content of 31.6%. The average oil content was 44.9%, with a high proportion of unsaturated fatty acids. Saturated fatty acids account for 13%. Potassium was the most abundant mineral, followed by phosphorus and magnesium, and vitamin B_1 and B_2 content was high. Vitamin B_1 accounted for 1.5 mg/100 g of the edible portion, which corresponds to the daily requirement for adults. The seeds also had appreciable amounts of zinc and iron. Their energy value was 583 kcal/100 g.

Frequent intake of nuts has been associated with reduced risk of fatal coronary heart disease and nonfatal myocardial infarction. Nuts are included in the American Heart Association dietary metrics in the report on setting goals for health promotion and disease reduction for 2020 [4]. In the specific case of pine nut, the fatty acid composition has proven to be beneficial owing to the low saturated fatty acid content and high unsaturated fatty acid content. Linoleic acid, which is abundant in pine nuts, is thought to have beneficial effects on blood lipids, blood pressure, and serum cholesterol [3]. Pine nuts may also act as an appetite suppressant through their effect

on satiety hormones and reduced prospective food intake [5]. In addition to their favorable fatty acid profile, pine nuts contain tocopherol, an antioxidant with cardioprotective effects [6].

Allergy to Pine Nuts

Pine nut allergy was first described in 1958 by Santos and Unger [7]. Since then, numerous reports describing allergic reactions to pine nuts have been published (Table). Of the 45 cases reported to date (age range, 2-87 years; female-to-male ratio, 1.25), 34 (75.5%) involved severe anaphylactic reactions (Table). Moreover, it has been reported that even small amounts of pine nut can induce dangerous allergic reactions in sensitized patients. For instance, Van de Scheur et al [8] described the first case of acute anaphylaxis to pine nut following a prick-to-prick test with the fresh nut in a patient who had collapsed after eating a salad containing pine nuts. Reactions have been reported after consumption of pine nuts as part of pesto sauce [9,10], salads [8,10], meatballs and meat [11], and in cakes, candies, or cookies [12-14]. They have also been reported after consumption of pine nuts alone [15-18]. Interestingly, Jansen et al [19] reported an anaphylactic reaction in a patient with bird-egg syndrome after intake of a single nut of the patient's parrot's food, which proved to be *P pinea* seed.

Allergic reactions to pine nuts might also be stimulated by certain drugs, as described by Moneret-Vautrin et al [12] in 1998. The authors reported the case of an 87-year-old woman with no previous history of allergy who was diagnosed with hypertension. The patient started to take an angiotensin-converting enzyme (ACE) inhibitor and experienced severe anaphylactic shock after eating a cake containing pine nuts and walnuts. It is well established that anaphylactic reactions are associated with the release of mediators that induce the vasopermeability and vasodilation responsible for the collapse. Angiotensin II is a powerful vasoconstrictor, and the inhibition of its conversion from angiotensin I by ACE inhibitors may increase the severity of anaphylactic reactions by enhancing vascular permeability and vasodilatation [12].

In 2012, Cabanillas et al [18] reported their findings from a large case series of allergy to pine nuts (Table) [18]. The study included 10 consecutive teenagers and adults diagnosed with IgE-mediated clinical allergy to pine nut in Madrid, Spain. The reactions were severe in 8 patients, and 7 patients were monosensitized. A recent study confirmed high monosensitization rates among patients with pine nut allergy [20].

Pine Nut Allergens

Several studies have investigated the IgE-binding proteins of pine nuts, although no official allergen names have been registered by the Allergen Nomenclature Subcommittee of the International Union of Immunological Societies. Most nut allergens are seed storage proteins, such as vicilins (7S globulins), legumins (11S globulins), and 2S albumins. Seed storage proteins provide the essential nutrients required during germination and growth of the new plant [21]. Other nut allergens are homologous to proteins of the pathogenesis-related (PR) protein families, a group of unrelated families of proteins with the function of defending plants against pathogens and adverse environmental conditions [22]. Profilins, class I chitinases, and lipid transfer proteins (LTP) are examples of allergens that are homologous to PR proteins in nuts.

In the specific case of pine nut, Garcia-Menaya et al [15] characterized a protein—under nonreducing conditions—with a molecular weight of 15-17 kDa that was recognized by the serum IgE of a patient with severe clinical allergic symptoms after consumption of pine nut. Similarly, Ibañez et al [16] identified—again, under nonreducing conditions—a 17-kDa allergen that was recognized by the IgE of 2 patients with severe anaphylaxis caused by small amounts of pine nut. Both patients were monosensitized to pine nut. In both studies, the authors hypothesized that the recognition of this single IgE-binding protein was associated with the severe symptoms observed after pine nut intake. In 2012, Cabanillas et al [18] identified—under reducing conditions—a 6-kDa pine nut protein that was strongly recognized by the sera from 5 out of 9 (55%) pine nut–allergic patients. Analysis of the protein under nonreducing conditions revealed a band of around 16 kDa. Interestingly, most of the patients whose serum IgE recognized this allergen had a history of severe anaphylaxis to pine nut. Therefore, it seems that the 3 studies mentioned above uncovered the same major allergen from pine nut. However, Cabanillas et al went 1 step further and purified the main pine nut allergen by ion exchange chromatography. Mass spectrometry analysis and database searches revealed the allergen to be an albumin, ie, a seed storage protein. A partial nucleotide sequence for this allergen was also obtained. Interestingly, the authors found a domain with a trypsin/α-amylase–inhibiting function in the protein sequence that correlated with the high resistance of this allergen to degradation by digestive enzymes [18]. 2S albumins have also been described as major allergens in peanut (Ara h 2, Ara h 6), walnut (Jug r 1), and cashew (Ana o 3), all of which are characterized by high resistance to extreme pH, heat, or proteolysis [23]. Thus, this resistant major pine nut allergen may be directly implicated in the severe reactions that the nut caused in the cases reported above.

A second IgE-binding pine nut protein with a molecular weight of 50 kDa was described in 3 studies [11,18,24]. The protein was also identified as a major allergen. Mass spectrometry analysis revealed the allergen to be a vicilin, ie, a seed storage protein from the cupin family characterized by a β-barrel secondary structure. Resistance of the allergen to peptic and tryptic digestion was weaker than that of the 6-kDa allergen (albumin) [18]. Vicilins have been reported to be major allergens in several nuts, such as peanut (Ara h 1), walnut (Jug r 4), and pistachio (Pis v 3).

Although other IgE-binding proteins (such as 30 kDa and 44 kDa proteins) have also been detected by IgE-immunoblot in pine nut protein extracts [13,17,20], further studies are necessary to identify, purify, and characterize the IgE-binding proteins in pine nuts and to elucidate their implication in the severe allergic reactions pine nuts can cause.

IgE Cross-reactivity Between Pine Nuts and Other Nuts

The presence of IgE–cross-reactive allergens in nuts is a common finding. For instance, IgE cross-reactivity between peanut,

Table. Clinical and Immunological Findings of Published Cases of Pine Nut Allergy

Study	Number of Patients	No./Age, y/ Sex	Clinical Findings	Specific IgE, kU_A/L	Skin Test, mm	Other Nut Allergies
Santos and Unger, 1958 [7]	1	1/32/Female	Anaphylaxis	ND	Rub test	ND
Fine, 1987 [29]	2	1/13/Female	Anaphylaxis	ND	10 × 15	ND
		2/21/Male	Urticaria	ND	4 × 4	ND
Falliers, 1989 [30]	1	1/43/Female	Anaphylaxis	ND	8 × 24	ND
Koepke et al, 1990 [14]	1	1/21/Male	Anaphylaxis	ND	Positive	ND
Jansen et al, 1996 [19]	1	1/54/Female	Anaphylaxis	44.6	7	None; monosensitized to pine nuts
de las Marinas et al, 1998 [11]	1	1/28/Male	Anaphylaxis	5.27	6 × 6	Almond
Beyer et al, 1998 [9]	1	1/53/Male	Anaphylaxis	Positive	Positive	ND
Moneret-Vautrin et al, 1998 [12]	1	1/87/Female	Anaphylaxis	Negative	10	Walnut
Roux et al, 1998 [10]	3	1/28/Male	Anaphylaxis	11	11	None; monosensitized to pine nuts
		2/35/Male	Anaphylaxis	6.25	10	Brazil nut
		3/19/Male	Anaphylaxis	79.9	12	None; monosensitized to pine nuts
Garcia-Menaya et al, 2000 [15]	1	1/22/Male	Anaphylaxis	0.79	12	ND
Año et al, 2002 [13]	1	1/10/Male	Anaphylaxis	8.32	12	Peanut
Ibañez et al, 2003 [16]	2	1/2/Female	Anaphylaxis	7	12 × 16	None; monosensitized to pine nuts
		2/15/Female	Anaphylaxis	1.7	9 × 17	None; monosensitized to pine nuts
van de Scheur et al, 2004 [8]	1	1/20/Female	Anaphylaxis	ND	Positive	ND
Novembre et al, 2012 [24]	5	1/13/Female	Anaphylaxis	5.3	12	None; monosensitized to pine nuts
		2/13/Male	Urticaria, angioedema	4.5	5	None; monosensitized to pine nuts
		3/13/Male	Urticaria, angioedema	0.79	10	None; monosensitized to pine nuts
		4/13/Male	Anaphylaxis to pine nuts	27	5	None; monosensitized
		5/5/Female	Urticaria, angioedema	12.1	15	None; monosensitized to pine nuts
Cabanillas et al, 2012 [18]	10	1/30/Female	OAS	0.8	4.5	None; monosensitized to pine nuts
		2/38/Female	Anaphylaxis	0.9	11.5	None; monosensitized to pine nuts
		3/36/Male	Anaphylaxis	1.82	8.5	Pistachio, peanut
		4/34/Male	Anaphylaxis	2.27	12	None; monosensitized to pine nuts
		5/26/Male	Anaphylaxis	48	17.5	None; monosensitized to pine nuts
		6/39/Female	Anaphylaxis	0.02	10	None; monosensitized to pine nuts
		7/35/Female	Anaphylaxis	7.08	11	None; monosensitized to pine nuts
		8/17/Male	OAS	19.3	5.5	None; monosensitized to pine nuts
		9/18/Female	Anaphylaxis	2.2	15.5	None; monosensitized to pine nuts
		10/24/Male	Anaphylaxis	35.3	20	Hazelnut, peanut
Barbarroja-Escudero et al, 2014 [17]	1	1/19/Female	Anaphylaxis	16.2	Positive	None; monosensitized to pine nuts
Asero et al, 2014 [20]	12	Aged 3-71/9 female and 3 male	7 anaphylaxis; 3 urticaria/angioedema; 1 asthma, and 1 laryngeal edema	—	Positive	10 monosensitized to pine nuts; 1 to walnut; and 1 to walnut, hazelnut, and peanut

Abbreviations: F, female; M, male; ND, not determined; OAS, oral allergy syndrome.

almond, Brazil nut, and hazelnut has been demonstrated using ELISA [25]. Homology between allergens such as 2S albumins, vicilins, legumins, and profilins can explain this cross-reactivity.

However, pine nut is of particular interest, since allergic monosensitization to it is very common (Table). As explained above, pine nuts, the seeds of pines (gymnosperms), are evolutionally separated from flowering plants (angiosperms), to which all other nuts belong (eg, peanut, walnut, hazelnut, cashew, and pistachio) (Figure, A). This fact seems to have a direct impact on the homology of allergens from both groups and on their IgE cross-reactivity. In the scientific literature, immunological cross-reactivity can be found between nuts from species of gymnosperms; however, a lack of or low cross-reactivity between nuts from gymnosperms and angiosperms has been demonstrated. Jansen et al [19] showed that IgE-binding to proteins from *P pinea* seeds were completely inhibited by proteins from *Pinus cembra* seeds, while hazelnut and peanut did not show any inhibitory capacity. De las Marinas et al [11] showed low inhibition of IgE-binding (37%) of pine nut over almond using CAP inhibition with sera from a patient who was allergic to pine nut and almond. Moreover, Cabanillas et al [18] showed that the amino acid sequence described for the pine nut allergen albumin had high homology with albumins from *Pinus strobus* (81%), *Picea glauca* (68%), and *Pseudotsuga menziesii* (69%), all of which are gymnosperms. However, low homology (28%) was detected with 2S albumin from angiosperms, such as peanut. Similarly, the pine nut allergen vicilin showed high homology with the vicilin from *P glauca* and values lower than 40% with vicilins from angiosperm species.

Therefore, plant evolution can explain in part the singular features of pine nut allergy, which seems to be characterized by a high monosensitization rate, low IgE cross-reactivity with other commonly consumed nuts, and severe allergic symptoms.

Syndromes Associated With Pine Nut Intake: "Pine Mouth" Syndrome

Metallogeusia, a metallic or bitter taste perceived after consumption of pine nut, was first described in 2001 [26]. Since then, several cases of the so-called pine mouth syndrome have been reported. Patients describe a persistent metallic or bitter taste within 48 hours of eating pine nut that can last for up to 2 weeks [27]. Symptoms are self-limiting, with no adverse health effects. Both raw and processed pine nuts have been implicated in the syndrome. No mechanism has been described for pine mouth syndrome, and no pine nut compounds have been considered the cause of the disturbance. Initial studies suggested pine nuts from China as the symptom-inducing nuts, but pine nuts from other areas have also been implicated. Furthermore, it has been suggested that symptoms can be caused by decomposing lipids from the seed, although the role of seed contaminants in the syndrome has not yet been investigated [28].

Conclusion

Pine nuts are nutrient-rich foods with a beneficial effect on human health. However, they are also responsible for severe allergic reactions and other health problems.

Further studies are needed to characterize the singularity of pine nuts, the least evolved of the commonly consumed nuts, in triggering allergic reactions characterized by severe symptoms, low IgE cross-reactivity, and a high monosensitization rate.

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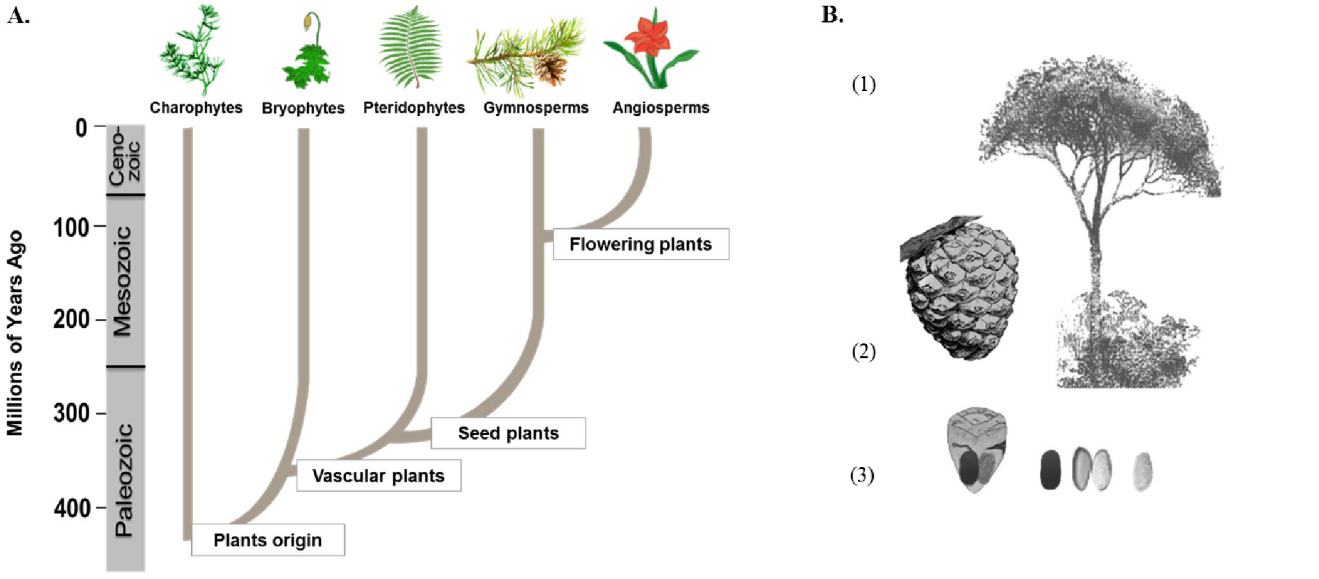

Figure. A, Graphic representation of the evolution of plants. Conifers separated from angiosperms (flowering plants) about 100 million years ago, thus constituting a relatively ancient branch in the evolution tree. B, *Pinus pinea* trees are about 12-25 m tall with a globose crown (1). The seeds are borne in cones, which mature in the third year (2). The cone scales can carry 2 seeds, which may be released from the cone or remain on the scale until the cone has fallen (3).

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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