ORIGINAL ARTICLE

Goji Berries (*Lycium barbarum*): Risk of Allergic Reactions in Individuals With Food Allergy

CH Larramendi,[1,2] JL García-Abujeta,[1,2] S Vicario,[1,2] A García-Endrino,[1] MA López-Matas,[3] MD García-Sedeño,[1,2] J Carnés[3]

[1]Sección de Alergología, Hospital Marina Baixa, Villajoyosa, Alicante, Spain
[2]Centro de Especialidades Foietes, Benidorm, Alicante, Spain
[3]R&D Department, Laboratorios LETI S.L., Tres Cantos, Madrid, Spain

Abstract

Background: New foods are frequently introduced in Western diets for their healthy properties; however, they may produce adverse effects.
Objective: After attending a patient who experienced an allergic reaction to Goji berries, we evaluated the allergenic potential of this food in plant food–allergic individuals, a group that is considered to be at high risk of experiencing a reaction.
Methods: We recruited 30 additional plant food–allergic individuals in Spain during 3 months in 2010. Four patients reported symptoms on intake, 6 tolerated the berries, and 20 had never tried Goji berries. Patients underwent skin prick tests with Goji berries, as well as with peach peel and plant food panallergens as markers of cross-reactivity between unrelated foods. We carried out in vitro tests in symptomatic patients.
Results: Skin tests to Goji berries were positive in 24 patients (77%): 5 symptomatic patients and 19 asymptomatic patients. Positivity to Goji berries was associated with positivity to peach peel and to the panallergen nonspecific lipid transfer protein (LTP). Nearly half of the patients reported symptoms (45%), but 89% of the skin test–positive patients had never eaten Goji berries. We detected specific immunoglobulin E to Goji berries in all cases, and several individuals recognized 2 protein bands in the immunoblot. Addition of LTP to sera mostly inhibited immunoglobulin E binding to an LTP-like band, suggesting a role for this panallergen in sensitization to Goji berries.
Conclusions: Our results demonstrate the allergenic potential of Goji berries in high-risk individuals, which is probably due to cross-reactivity with LTP from other foods. The risks of Goji berries should be taken into consideration in individuals with food allergy, especially those who are allergic to LTP.

Key words: Food allergy. Functional foods. Novel foods. Goji berries. Panallergens. Lipid transfer proteins.

Resumen

Fundamento: La introducción de alimentos "nuevos", además de sus potenciales propiedades saludables, puede también tener efectos adversos.
Objetivo: Evaluar el potencial alergénico de las bayas de Goji en sujetos alérgicos a alimentos vegetales, tras atender a un paciente que presentó una reacción alérgica tras la ingestión de este alimento.
Métodos: Se incluyeron treinta individuos adicionales, alérgicos a alimentos vegetales, estudiados en un periodo de 3 meses en el año 2010. Cuatro sujetos referían síntomas al tomar las bayas, seis las toleraban y 20 no las habían probado nunca. A todos se les realizaron pruebas cutáneas con bayas de Goji, piel de melocotón y panalérgenos vegetales, como marcadores de reactividad cruzada. En aquellos individuos que refirieron síntomas se realizaron pruebas *in vitro*.
Resultados: Las pruebas cutáneas con bayas de Goji fueron positivas en 24 sujetos (77%), incluyendo los cinco que referían síntomas y 19 (73%) de los asintomáticos. La positividad a las bayas de Goji se asoció con positividad a la piel de melocotón y al panalérgeno LTP (proteínas transportadoras de lípidos). El 45% de los sujetos expuestos refirieron síntomas, pero la mayoría (89%) de los que tenían pruebas positivas, no las habían probado. En los cinco casos se encontró IgE especifica frente a bayas de Goji. Varios reconocieron 2 bandas (7 y 50 kDa) en el inmunoblot. La inhibición con LTP impidió la fijación de IgE a la banda de 7 kDa, sugiriendo el papel de este panalérgeno en la sensibilización a bayas de Goji.
Conclusiones: Se demuestra el potencial alergénico de las bayas de Goji en sujetos de alto riesgo, probablemente debido a reactividad cruzada con LTP de otros alimentos. Los riesgos del consumo de las bayas de Goji deben ser tenidos en cuenta en sujetos con alergia a alimentos, especialmente en los alérgicos a LTP.

Palabras clave: Alergia a alimentos. Alimentos funcionales. Alimentos nuevos. Bayas de Goji. Panalérgenos. Proteínas transportadoras de lípidos.

Introduction

New foods are increasingly common in Western diets. Globalization means that Western food is now available throughout the world and exotic foods are available in Western countries. The healthy properties of some of these new foods, frequently considered functional foods [1], have been stated in the media.

One such food is Goji berries (wolfberries, *Lycium barbarum*), for which pharmacological and immunological studies seem to support some of the claims made with regard to their healthy properties [2-5]. Goji berries have been consumed in Asia and used in traditional Chinese medicine for more than 2000 years [6,7]. Recently introduced in Western countries, their distribution and consumption are growing fast. Although Goji berries are not strictly a novel food [8], data on their consumption in Western countries prior to 1997 are scarce.

In the last few years, hepatotoxic effects [9] and interactions with anticoagulants [10] have been reported as adverse effects of Goji berries. Delayed-type allergic reactions (photodermatitis) [11] and immediate-type reactions [12,13] have also been described. In the case of immediate-type allergy, a role has been suggested for nonspecific lipid transfer proteins (LTPs) [12]. Asymptomatic sensitization, which is not unusual and not well understood [14], is frequently related to cross-reactivity and could explain why allergic reactions can occur after the first known exposure to a specific food [14]. While such findings are hard to demonstrate with commonly consumed foods, novel foods offer an opportunity to investigate the role of panallergens [16].

After an initial report of a patient who experienced an allergic reaction after eating Goji berries for the first time, a pilot observational study was subsequently undertaken to investigate the allergenic potential of Goji berries and the role of LTPs and other panallergens.

The objective of the study was to investigate the relevance of sensitization to Goji berries in individuals with food allergy in order to determine the potential risk of consumption in this group. We also collected data on the clinical and immunological characteristics of these individuals and on the allergens or panallergens involved.

Methods

Study Group

After attending a 40-year-old man who presented with facial angioedema and dyspnea while eating Goji berries for the first time, we recruited 30 additional individuals attending our outpatient allergy clinic in southeastern Spain during a 3-month period in 2010. All patients had a previous or recent diagnosis of plant food allergy and were asked to provide information about their consumption of Goji berries (knowledge, purpose of consumption, and eventual symptoms) (Table 1). After giving their oral consent, all patients underwent skin prick tests (SPTs) with Goji berry. Five patients who reported symptoms after ingestion (the index case and 4 additional patients) were included in the symptomatic (allergic) group and the rest in the control (nonallergic) group. Written consent was obtained from the individuals of the allergic group before a serum sample was obtained. In vitro tests were performed with individual serum samples and a pool of sera from these 5 patients.

Allergic Group

Case 1: A 40-year-old man complained of facial angioedema with dyspnea (requiring epinephrine) while eating Goji berries for the first time (30-40 berries). The patient previously reported 2 episodes of facial angioedema after eating walnut-containing snacks.

Case 2: A 31-year-old man with a history of allergic rhinitis and contact urticaria with *Cannabis sativa* reported pharyngeal itching lasting 30-60 minutes on 10-12 occasions, immediately after eating Goji berries (10-15 berries). Symptoms increased in intensity after each exposure, prompting the patient to avoid these berries thereafter.

Case 3: A 30-year-old woman with a history of hay fever, oral allergy syndrome (OAS) induced by nut consumption, skin sensitization to multiple vegetable foods, and several episodes of food-induced cofactor-related anaphylaxis (exercise, nonsteroidal anti-inflammatory drugs, and menstruation) had previously tolerated a whole pack of Goji berries but reported labial angioedema and perioral skin rash immediately after eating a new pack (20 berries). Symptoms lasted for 45 minutes without treatment. After a subsequent similar episode, the patient avoided Goji berries. The patient associated the symptoms with drier berries in the second pack.

Case 4: A 36-year-old man with a history of allergic rhinoconjunctivitis and urticaria due to peanut and date, OAS due to other nuts (walnut, hazelnut), episodic rhinitis, and sensitization to several inhalants and foods with no evident clinical relevance reported itching in the mouth, ears, and axilla lasting 10 minutes immediately after eating only 1 Goji berry.

Case 5: A 42-year-old woman reported a 2-month history of severe generalized itching that resolved after avoiding Goji berries (intake of 20-30 berries daily for several months). The patient had a history of perennial rhinoconjunctivitis that deteriorated in spring and was allergic to pollens and mites. She also had a long history of contact urticaria to peach, although she tolerated the peeled fruit. The patient had recently developed urticaria after ingestion of persimmon.

Control Group

The control group comprised 26 patients (8 males; mean [SD] age, 31.3 [11.7] years) who were sensitized to other plant allergens besides pollen (mainly foods, but also latex). Twenty had never tried Goji berries and 6 tolerated them.

Extract

A Goji berry extract was manufactured (Laboratorios LETI S.L.) [17]. Briefly, Goji berries (*L barbarum*) purchased at a local market were homogenized and extracted in buffer solution containing phosphate-buffered saline/polyvinylpolypyrrolidone 0.01M. The extracted material was centrifuged and the supernatant collected, dialyzed, filtered, and freeze-dried. The protein content of the extract was 482 μg/mg of freeze-dried material.

Protein Profile

Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) analysis was used to determine the protein profile of the extract. Briefly, 60 μg of Goji berry extract was run in SDS-PAGE gels (2.67% C, 15% T acrylamide). The sample was diluted in sample buffer containing 0.5 M Tris-HCl (pH 6.8), 10% SDS, 50% glycerol, bromophenol blue, and ß-mercaptoethanol (Bio-Rad Laboratories). The sample was denatured at 100ºC for 10 minutes and centrifuged for 1 minute at 16000*g*. Reference markers (Bio-Rad Laboratories) with a known molecular weight were run in the same gel as controls. After electrophoresis, the gel was stained with Coomassie dye.

Skin Prick Tests

All patients underwent skin testing with Goji berries, either by prick-prick, SPT with the manufactured extract (5 mg/mL, Laboratorios Leti S.L.), or both.

Patients also underwent SPT with peach peel extract (Laboratorios LETI S.L.) and several panallergens, such as purified LTP (containing 20 μg/mL Pru p 3, 20 μg/mL Cor a 8, and 5 μg/mL Par j1/2) (Laboratorios LETI S.L.), purified profilin from date palm pollen (containing 50 μg/m of Pho d 2), and a polcalcin-enriched extract from date palm pollen (Laboratorios ALK-Abelló).

Wheals greater than 7 mm^2 were considered positive [18]. The Fisher exact test was used to compare positivity between the extracts.

Specific Immunoglobulin E

Specific immunoglobulin (Ig) E to Goji berries was determined by ImmunoCAP (ThermoFisher Scientific) following the manufacturer's instructions. Briefly, Goji berry extracts were labelled with biotin and coated in solid phase by combination with streptavidin ImmunoCAP. Individual serum samples were then incubated in the previously Goji berry–coated UniCAP discs. The experiment was carried out using the ImmunoCAP 100E system (ThermoFisher Scientific). Positivity was obtained when the circulating Goji berry–specific IgE in sensitized patients recognized the Goji berry extract in the solid phase to provide a measurable fluorescent signal.

Immunoblot

The allergen profile was studied using immunoblot. Briefly, Goji berry proteins were electrophoretically separated according to their molecular weight and electrotransferred onto an Immulon-P membrane (Millipore). Serum samples from individuals were incubated overnight with membranes. Finally, the reaction was developed by chemiluminescence. Positivity was obtained when the circulating Goji berry–specific IgE in sensitized patients recognized the Goji berry extract fixed on the membranes.

Inhibition Experiments

Based on the assumption that the ability of one allergenic source to inhibit another is probably due to the existence of common or similar allergens in both of them, we conducted inhibition experiments to look for similarity between allergens.

Immunoblot inhibition: Serum samples from 3 individuals with positive IgE by immunoblot and the pool of sera were used for the inhibition experiments. Goji berry extract was used in the solid phase (as in immunoblot). Individual serum samples were previously incubated with Goji berry extract (1000 μg) and purified LTP from tomato (60 μg). After 2 hours, the complex was incubated again with membranes containing Goji berry extract in the solid phase. The reaction was developed by chemiluminescence.

CAP inhibition: Streptavidin ImmunoCAPs (ThermoFisher Scientific) were combined with biotinylated Goji berry extract in the solid phase. Individual serum samples and the pool of sera were previously incubated for 2 hours with 5 μg of purified LTP from peach. After incubation, the inhibited samples were combined with the solid phase and the reaction developed following the manufacturer's instructions (see above).

Results

Goji Berry Ingestion and Symptoms

Eleven patients (35.5%) had tried Goji berries at some time, and 5 of this group (45.5%) reported symptoms (allergic group) (Table 1). All patients tried the Goji berries for their supposed health benefits. The symptoms reported by the 5 allergic patients were mild to moderate. All 5 patients declined a controlled challenge test with Goji berries. In 3 cases, symptoms occurred after the first exposure to Goji berries. More than 16% of all the patients studied reported symptoms with the berries.

Table 1. Characteristics of the Study Population[a]

Participants (n)	Age, y	Sex, M/F	Symptoms	Consumption, No.	No. of Beries Ingested	Times Berries Were Ingested
Cases (5)	35.8 (5.3)	3/2	Yes	Yes (5 pts)	18.7 (12.8) (5 pts)	1- >60
Sensitized controls (19)	29.8 (9.8)	6/13	No	No (16 pts)	Unknown (3 pts)	Unknown (3 pts)
				Yes (3 pts)		
Negative controls (7)	35.3 (16.1)	2/5	No	No (4 pts)		
				Yes (3 pts)	Unknown (3 pts)	Unknown (3 pts)

Abbreviations: F, female; M, male; pts, patients.
[a]Values are expressed as mean (SD) unless otherwise indicated.

Table 2. Results of Skin Tests and In Vitro Tests

	CAP, kU_A/L	Immunoblot Bands, kDa	Skin Prick Test, mm^2	Skin Prick Test, mm^2			
	Goji Berries			Peach Peel	Panallergens		
					LTP Mix	Profilin	Polcalcin
Individual cases							
No 1	0.78	7	41.5	32.8	Negative	Negative	Negative
No 2	2.87	7-50	60	51.5	52.5	Negative	Negative
No 3	0.58	No	68	17	7.5	Negative	Negative
No 4	3.62	7-50	51	12.5	94	Negative	Negative
No 5	0.37	No	23	Negative	ND	Negative	12.5
Groups							
Cases (5)[a]	1.6 (1.5)	7 (3 positive) 50 (2 positive)	48.7 (17.4)	22.8 (19.9 (4 positive)	38.5 (43.7)) (3 positive)	0	2.5 (5.6) (1 positive)
Sensitized controls (19)[a]	ND	ND	39.9 (25.6)	46.5 (28.7) (15 positive)	32.6 (13.1) (14 positive)	2.2 (9.4) (1 positive)	20.7 (8.7) (4 positive)
Negative controls (7)[a]	ND	ND	0	0	4.8 (11.8) (1 positive)	0	0

Abbreviations: LTP, lipid transfer protein; ND, not determined.
[a]Values expressed as mean (SD) unless otherwise indicated.

Skin Prick Tests

Goji berries: SPTs with Goji berries were positive in the 5 patients (100%) of the allergic group and in 19 controls (73.1%, the sensitized group). Therefore, 24 patients (77.4%) were sensitized to Goji berries. Most of the nonexposed patients (16 out of 20, 80%) had a positive SPT result.

Panallergens: The SPT with LTP was positive in 3 cases, negative in 1 case, and not performed in 1 case. It was positive in 15 (65.2%) of 23 controls tested. The SPT with polcalcin was negative in 4 patients, positive in 1 patient (case 5), and positive in 4 of 22 controls (18.2%). The SPT with profilin was negative in all patients and positive in 1 of 26 controls (4%).

Foods: The SPT with peach peel was positive in 4 patients, negative in 1 patient, and positive in 15 of 26 controls (57.7%).

When all study participants were compared, a strong association was observed between positivity to peach peel and positivity to Goji berries (P=.0002) and between positivity to LTP and positivity to Goji berries (P=.008). Negative controls were less sensitized to LTP (P=.02) and peach peel (P=.0005) than positive controls.

Mean (SD) SPT values are expressed in Table 2.

Protein Profile

The protein profile of the Goji berry extract showed several bands with a molecular weight ranging between 7 kDa and 100 kDa. The most prominent bands corresponded to proteins at approximately 7, 25, 66, and 100 kDa (Figure 1A).

Specific Immunoglobulin E

All 5 cases had low but detectable levels of specific IgE against the extract (Table 2).

Immunoblot

A 7-kDa band was recognized in 3 patients and a band of approximately 50 kDa in 2 patients (Figure 1B). The serum pool recognized the same bands.

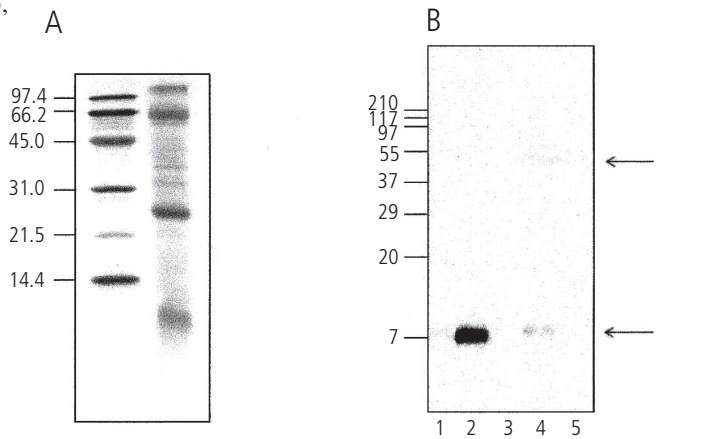

Figure 1. A, Sodium dodecyl sulfate polyacrylamide gel electrophoresis. Lane 1, molecular weight markers; lane 2, Goji berry extracts (60 µg of protein). B, Immnoblot. Lanes 1-5, immunoblot with the 5 individual sera (diluted 2/3). In the solid phase, 100 µg of protein of Goji berries extract. The arrows indicate the 7-kDa and 50-kDa bands.

Immunoblot Inhibition

Goji berry extract was totally inhibited by itself (positive control: autoinhibition). LTP from peach inhibited the 7-kDa band (in the molecular weight range of LTPs) in the pool of sera and in 2 individual sera but not completely in 1 of the individual sera, suggesting a high degree of cross-reactivity, but not 100%. The 50-kDa band was not inhibited by peach LTP in any case, indicating that this allergen may be specific and play an important role in sensitization to Goji berries (Figure 2).

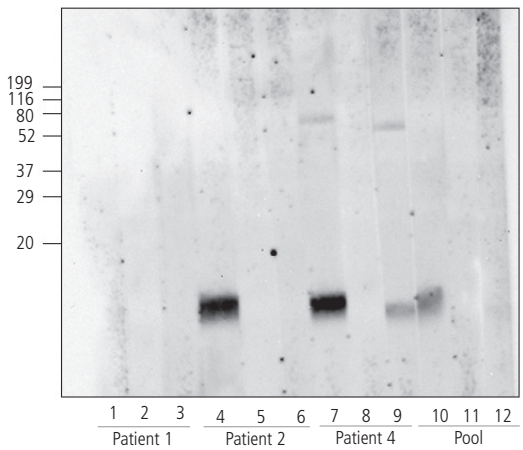

Figure 2. Immunoblot inhibition. In the solid phase, 100 µg of Goji berry protein. Lanes 1, 4, 7, and 10: no inhibition. Lanes 2, 5, 8, and 11: autoinhibition (inhibition with 1 mg of Goji berry protein). Lanes 3, 6, 9, and 12: inhibition with 60 µg of peach peel LTP.
The patient whose serum is used is indicated below the corresponding lanes.

CAP Inhibition

Adding 5 µg of peach LTP to the sera inhibited specific IgE binding to Goji berries by 95%, 62%, and 52% in serum samples from patients 2, 4, and 1, respectively. LTP inhibited IgE binding to the Goji berry extract by 75% when the pool was used.

Discussion

Our results suggest that Goji berries can cause allergic reactions in both exposed and unexposed food-allergic individuals.

We present 5 patients who experienced allergic reactions of differing severity after eating Goji berries. In this group, prick tests with Goji berries were positive and in vitro tests demonstrated the presence of specific IgE. Further characterization of allergenic proteins by immunoblot showed bands in the molecular weight range of the nonspecific LTPs and bands with a higher molecular weight in about half of the cases.

We also studied a group of asymptomatic plant food–allergic patients who, in most cases, had never tried Goji berries and who underwent skin prick testing with the fruit (some had tried the berries but had not experienced symptoms). More than 16% of the study population reported symptoms with the berries (nearly half of those who had tried them), and 77% were sensitized to Goji berries, even if many had never tried them (many patients had never seen or heard of Goji berries). In fact, most of the patients (80%) who had never tried the berries had a positive SPT result. Most of the symptoms affected the oral cavity (OAS) and the skin, but more severe symptoms (dyspnea) and high sensitivity (symptoms with only 1 berry) were also reported. The risk of new foods for food-allergic patients has previously been reported in unexposed individuals [19,20].

Plant food–allergic patients in Spain and elsewhere in southern Europe are frequently sensitized to nonspecific LTP [21], as were many of our controls. In fact, a strong association was found between sensitization to LTP and Goji berries, suggesting that Goji berries have an allergenic LTP and that this LTP cross-reacts with that of peach, the main allergenic source in our area. These in vivo data are consistent with the in vitro results, because immunoblot revealed that most of them recognized an LTP-like band. Cross-reactivity is further suggested in vivo by the fact that most unexposed and LTP-sensitized patients had a positive SPT result to the berries, 3 cases reported symptoms on first exposure, and IgE binding to the Goji berry extract was highly but not completely inhibited after LTP was added to the sera of the allergic patients. Skin reactions have been described [6], and a few cases of immediate-type allergy to Goji berries were recently reported in Spain [12,13]. While LTP is considered responsible for the reactions [12], our data suggest that other allergens, such as high-molecular-weight allergens, may also play a role.

Our study population comprised plant food–allergic patients. Therefore, the group is not a true control group, but a selection of potentially high-risk individuals. Although the high level of sensitization found in our study is striking, the small number of patients and the selection bias make it difficult to extrapolate the results to other populations.

As allergy is a reaction to proteins or allergens in the environment, allergens can vary greatly with geographic area, as both outdoor respiratory allergens and food intake habits differ around the world [22,23]. Allergy to peach and to nonspecific LTP is prevalent in southern Europe [21-23]. Consequently, patients from this area should be made aware of the potential risks of consuming Goji berries. In the present study, we address a specific food and a selected group of patients; however, other exotic foods may also be risky for selected populations [24,25]. Therefore, allergic reactions should be taken into consideration when analyzing the effects on health of novel and functional foods.

In summary, we show that Goji berries, an increasingly popular health food, may have adverse effects in food-allergic individuals. Clinically relevant allergic sensitization to Goji berries was observed in a high proportion of exposed individuals, and a high potential risk (sensitization) was observed among unexposed (plant food–allergic) individuals from Spain. LTP seems to play an important role, although it is not the only allergen involved. Further studies are needed to determine the real importance of Goji berries as an allergenic source, their complete allergenic profile, and the true risks of ingestion for different populations. Our results indicate that a risk of allergic reactions among food-allergic individuals in southern Europe (mainly sensitized to peach/LTP) should be expected.

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Carlos Hernando de Larramendi

Sección de Alergología
Hospital Marina Baixa
Avda. Alcalde Jaume Botella Mayor 5
03570 La Vila Joiosa, Alacant, Spain
E-mail: chernandol@coma.es

