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Fenugreek: New Therapeutic Resource or Emerging Allergen?

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Abstract: Background: Fenugreek, or *Trigonella foenum greacum*, is an ancient medicinal plant native to the eastern Mediterranean that later spread to Asia; it is used as a medicinal herb, spice, or food. It is a component of spice mixes, such as curry, and it is also used as a supplement in wheat and corn flour for bread making. Fenugreek appears to have many health benefits and potential medicinal properties; for this reason, it is increasingly being used in nutraceutical formulations. This study aimed to describe patients who visited our operative unit for a suspected adverse reaction after ingestion of fenugreek and to highlight possible cross-reactivity between fenugreek and other legumes or other foods. Methods: A total of 13 patients (5 males and 8 females; mean age: 30.6; range: 20–42 years) visited our outpatient clinic with a clinical history suggestive of an allergic reaction to spices or legumes. They underwent a skin prick test for fenugreek, fresh foods, and food extracts. Results: A total of 6 out of 13 patients positive for fenugreek had experienced allergic symptoms after ingesting foods containing spices, and 10 patients presented polysensitization with other legumes, of which 8 also presented sensitization to pistachios. Conclusions: Given the increasing use of novel spices in Mediterranean cuisine and the possible spread of fenugreek-based nutraceuticals, it is relevant to draw attention to possible allergic reactions. Further studies are also needed to be able to establish its cross-reactivity pattern.

Keywords: fenugreek; pistachio; fabaceae; cross-reactivity; food allergy; nutraceuticals; diagnosis; trigonella; peanut; pathogenesis

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1. Introduction

Fenugreek, or *Trigonella foenum graecum*, is an ancient medicinal plant native to the eastern Mediterranean, which later spread to Asia (especially India); it belongs to the Rosaceae order, Leguminosae family, and Papilonaceae subfamily. The fenugreek plant is a short-lived annual angiosperm plant with a height of 50 cm height; it has green trifoliate leaves, white or yellow flowers, and thin curved pods containing about 10–20 golden yellow seeds. Its name is derived from the triangular shape of its flowers (from the Latin "trigonum").

Fenugreek is employed as a medicinal herb, spice, or food: its seeds (Figure 1) are ground, and the powder is used as a condiment or in traditional Ayurvedic and Chinese medicine. It is used in Indian cuisine as a component of spice mixes, such as curry; in Egypt, it is still employed as a supplement in wheat and corn flour for baking. It has also been shown to have many health benefits and potential medicinal properties (antioxidant, antidiabetic, hepatoprotective, hypocholesterolemic, antimicrobial, anti-inflammatory, neuroprotective, anticarcinogenic, antiulcer, and antilithigenic properties) in both in vitro and in vivo studies [1–4].

Figure 1. Dried fenugreek seeds.

There are many plant species that possess great biological activity [5–9]. Some pigments contained in plants play an important role in health [10]. Many foods on the market are defined as nutraceuticals because they are of plant origin [11]. Typical Mediterranean foodstuff, such as olive oil and wine, also contain very important biologically active molecules [12,13]. Fenugreek seeds contain soluble galactomannan, proteins, lipids, alkaloids (trigonelline), saponins (diosgenin and yamogenin-based saponins), 4-hydroxyisoleucine, volatile oils, C-glycosylflavones of apigenin, luteolin, and insoluble fiber [14]. In particular, it is mainly used to improve digestion, activate metabolism, facilitate childbirth, and increase milk flow. Trigonelline appears to be the most active metabolite of fenugreek; it is useful in treating diabetes, reducing cholesterolemia, and treating cancers (liver, breast, cervical, and pancreatic cancers) as a phytohormone [15,16]. Furthermore, fenugreek is used by chopping/crushing its seeds, or as an herbal preparation, dry or soft extract (preparations of intermediate consistency, between liquid and dry extracts, obtained by partial evaporation of the solvent used for preparation), powder, or in combination with other substances. Its main applications are appetite enhancement, topical treatment of localized skin and intestinal inflammation, and as an adjuvant in diabetes or hypercholesterolemia treatments [12–16].

It is considered nontoxic up to a maximum dose of 5 g/kg body weight. Side effects such as flatulence, diarrhea, abdominal distension, dyspepsia, hypokalemia, increased micturition frequency, and dizziness have been reported. Regarding adverse immunological reactions, the reports in the literature are mainly allergic reactions after contact with or ingestion of fenugreek, characterized by urticaria, angioedema, wheezing, cough, rhinorrhea, and itching. Type IV or delayed skin reactions after contact with fenugreek preparations are rare but possible. Finally, many authors have reported cross-reactivity between fenugreek and foods belonging to the Leguminosae (or Fabaceae) family [17–20].

As the use of fenugreek is increasing worldwide, both in diets and in nutraceuticals, an increase in adverse reactions can be expected in the coming years.

This study aimed to describe patients who visited our operative unit for a suspected adverse reaction after ingestion of fenugreek and to highlight possible cross-reactivities between fenugreek and other legumes or other foods.

2. Materials and Methods

2.1. Patients

We collected 13 cases of patients (5 males and 8 females; mean age: 30.6; range: 20–42 years) with a positive skin prick test for fenugreek seed powder. They visited our clinic as allergy outpatients of our hospital (Polyclinic "Gaetano Martino" of Messina) from March 2022 to December 2023 with a clinical history suggestive of allergic reactions to spices or legumes. Fenugreek seeds were also tested on 15 controls with negative results; the controls were subjects with a history of food allergy but not to spices or

any legumes, and were sex- and age-matched. All patients gave written informed consent for the anonymous use of their data and images for publication. The work was approved by the local bioethics committee (protocol number 3/24, 15 January 2024; ClinicalTrials ID registration: NCT06257797).

The detailed description of the medical history of the 13 patients is available in the Appendix A section.

2.2. Allergological Work-Up

The skin prick test (SPT) was performed on the volar face of the forearm in patients who were not receiving systemic therapy with antihistamines and corticosteroids for at least 7 days. Before allergen testing, SPT was performed with a positive control (histamine) and negative control (glycerol–saline solution).

Fenugreek was tested by mixing 120 mg of fenugreek seed powder with 1 mL saline at nonirritating doses, and this solution was tested using the SPT.

For other fresh foods (such as cashew, lupine, cumin, fennel, celery, and coriander), the same method as that described above was used.

SPTs for main foods and inhalants were performed using standardized extracts, commercially available and produced by the company Lofarma S.p. A., Milan, Italy. A distance of at least 2 cm was maintained between the SPTs to avoid false positives, and the drop of the extract was immediately pricked with a steel lancet (B-Lancet Steel, Benefits S.r.l., Genoa, Italy).

SPT was read 20 min after execution. The wheal diameter of 3 mm was evaluated as "+", 4 to 7 mm as "++", 7 to 10 mm as "+++", and a wheal with the presence of pseudopodia was evaluated as "++++".

Some patients also underwent food-specific IgE assay and ISAC or ALEX tests at other sites to better clarify the pattern.

2.3. Statistical Analysis

We carried out a descriptive analysis of the demographic and clinical characteristics of the subjects involved in the study. Categorical variables related to fenugreek-positive subjects and other possible cosensitizing allergens are expressed as absolute and/or relative frequencies.

3. Results

3.1. Patients with a History of Spice Allergy

Among the 13 patients with SPT positive for fenugreek, 6 patients (case nos. 1, 2, 3, 7, 9, 11) presented to an outpatient clinic because of allergic symptoms after ingesting chicken curry or other spicy foods from oriental cuisine (containing spice mix). They presented with anaphylaxis of varying degrees or IgE-mediated adverse reactions (type I immune-mediated reaction according to Gell–Coombs classification) according to the latency time between ingestion and onset of symptoms and based on reported symptoms. Among these six patients, half (case nos. 2, 3, 9) also tested positive for at least one legume (peanut, soy, and green bean).

3.2. Patients with a History of Legumes Allergy

Considering the high incidence of fenugreek positivity in patients who came to our observation for suspected spice allergy (6 out of 8) and in view of the known cross-reactivity between fenugreek and Leguminosae, we decided to test fenugreek in patients who visited our outpatient clinic at the same time with a history suggestive of allergic symptoms to at least one Leguminosae. In this way, we collected an additional seven fenugreek-positive patients (case nos. 4, 5, 6, 8, 10, 12, 13), who simultaneously tested positive for legumes and fenugreek.

3.3. Other Sensitizations in Patients with SPT Positive for Fenugreek and Legumes

In addition, we analyzed the positivity of patients at the same time sensitized to fenugreek and legumes and we observed that most of them were also positive for pistachio (case nos. 2, 4, 5, 6, 8, 10, 12, 13).

Table 1 shows our case series of allergic and sensitized patients to fenugreek.

Figure 2 illustrates SPT positive for fenugreek.

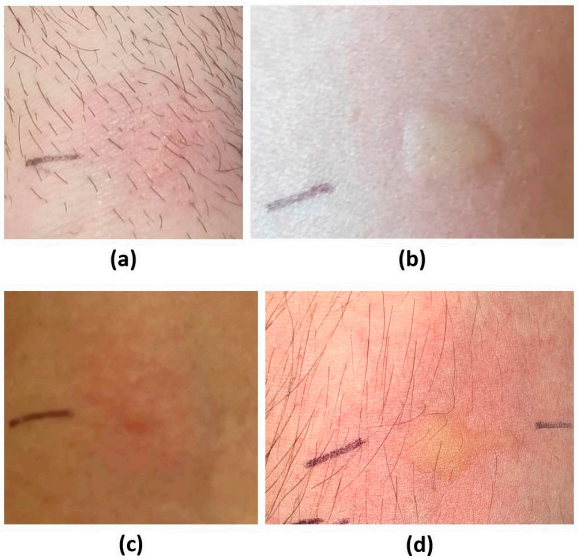

Figure 2. This figure shows the positive SPT for fenugreek in case no. 1 (**a**), case no. 2 (**b**), case no. 7 (**c**), and case no. 13 (**d**).

Figure 3 illustrates SPT positive for pistachios.

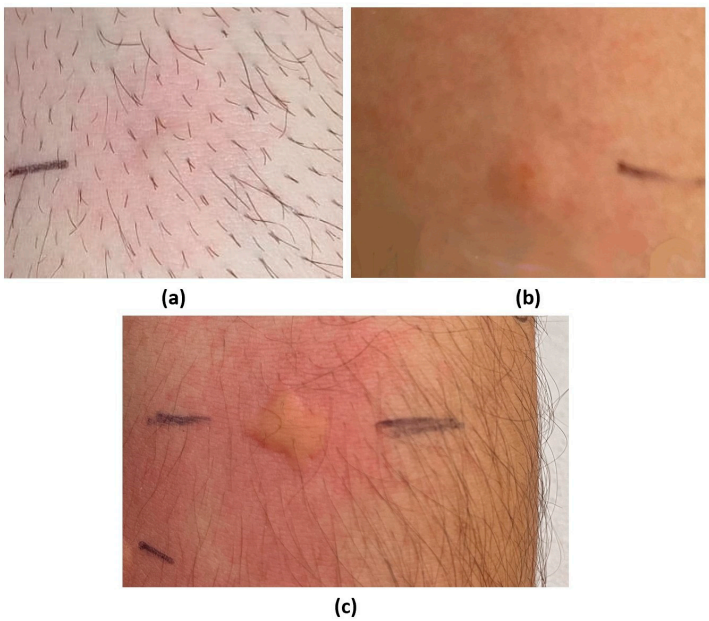

Figure 3. This figure shows the positive SPT for pistachios in case no. 1 (**a**), case no. 7 (**b**), and case no. 13 (**c**).

"+": Wheal's diameter of 3 mm; "++": wheal's diameter 4 to 7 mm; "+++": wheal's diameter 7 to 10 mm; "++++": a wheal with the presence of pseudopodia.

Table 1. This table shows the main sensitizations of our fenugreek-allergic patients, obtained by SPT and/or component resolved diagnosis (CRD) for foods and inhalants.

	Case series												
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
	Foods												
Fenugreek	++	++++	++	++	++	++	++	++	++++	++	+++	++++	++++
Cashew	-	++	<0.3 [1]	-	-	-	++	-	N.T. [3]	-	-	-	++
Pistachio	+++	++	-	++	++	+	+++	+++	-	++++	++	++++	++++
Peanut	-	+++	+	+	+++	+++	-	++	+	+++	-	+++	+
Other legumes	-	Lupine	-	-	Lentil	Lentil, soy	-	Lentil, lupine	Lentil	Pea	-	Bean	-
Other nuts	-	-	-	-	Walnut, hazelnut almond	Hazelnut	Hazelnut	Walnut, hazelnut	-	Walnut, hazelnut	-	Hazelnut	Hazelnut, almond
Apiaceae	Cumin, fennel, celery	Cumin, fennel, celery, coriander	Cumin	Fennel, celery	Fennel	Fennel, celery	-	Fennel, celery	Cumin, fennel, coriander	Celery	Cumin, coriander	-	-
Mustard	-	-	-	N.T. [3]	N.T. [3]	+	-	+++	+	<0.10 [2]	-	-	-
Peach	-	-	-	N.T. [3]	+++	++++	++	++	++++	++	+++	++++	++
	Inhalants												
Mugwort	+++	++	++	+++	+++	++	++++	9.91 [2]	-	0.86 [2]	-	-	++++
Other inhalants	Plantain, cypress	Birch, plantain	Birch, plantain, cypress	-	-	-	-	Cypress	-	-	-	-	Cypress

[1] This result was obtained by CRD (ISAC test) and it is expressed in ISU-E. [2] This result was obtained by CRD (ALEX test) and it is expressed in kUA/L. [3] The acronym "N.T." indicates "not tested".

4. Discussion

4.1. Fenugreek Is a Pharmaceutical Product

The advent of phytotherapeutic products is increasing the trade of substances for medicinal and preventive purposes and in daily and household use. Phytotherapeutic extracts, however, precisely because of their medicinal capabilities, are, to all intents and purposes, substances with their own pharmacodynamics and pharmacokinetics, with the possibility of drug interactions and the occurrence of adverse and undesirable reactions related to overdose and to the immunological setup of the person taking them.

Fenugreek appears to have health benefits, so it may be increasingly used as nutraceutical formulations (powder, herbal teas, tablets, and various combinations).

Recent studies have shown the promising uses of fenugreek as a medicinal herb, given the presence of seeds of simple alkaloids, including trigonelline, choline, gentianine, and carpaine. Trigonelline has antidiabetic, lipid-lowering, oestrogenic, neuroprotective, and anti-invasive properties [21,22]. Fenugreek also contains a significant amount of galactomannan and protein and various substances with antitumor action: diosgenin, which reduces cardiovascular risks [23] and has chemopreventive/therapeutic action against various tumors of different organs, such as gingerol, cedrene, zingerone, vanillin, squalene, naringenin, and eugenol. Finally, fenugreek contains substances with antioxidant action, such as vitamins, minerals, and antioxidants, which prevent free-radical-induced cellular damage [24]. Fenugreek extract induces apoptosis of human breast cancer cells expressing MCF-7. The inhibition of cell proliferation is time- and dose-dependent and could be the result of alterations in the cell death receptor (Fas) pathway [25].

A study on colon cancer cells showed that fenugreek extract exerted only antiproliferative effects on cancer cells, without affecting normal cells. This could be due to the fact that tumor cells express phosphatidylserine on the outer layer of the cell membrane, which acquires a net negative charge that allows electrostatic interaction with the positively charged antitumor peptides of fenugreek [26].

Sharma et al. reported that fenugreek has anti-inflammatory activity by reducing the cytotoxicity of fibroblasts via LPS-mediated mechanisms, restoring the levels of antioxidant enzymes such as glutathione and antioxidant enzymes such as glutathione peroxidase, glutathione-S transferase, catalase, and superoxide dismutase [27]. The antioxidant effects of fenugreek have also been demonstrated at cardiac, hepatic, renal, and plasma levels, resulting in improved antioxidant enzyme activity, and are enhanced by its association with onion [28,29].

The largest number of studies on the pharmacological properties of fenugreek have been conducted in patients with diabetes.

Diabetic patients treated with fenugreek showed a significant reduction in fasting blood glucose, blood pressure, and transaminase levels compared with controls. Therefore, fenugreek could promote better control of not only the glycemic profile but also the entire metabolic profile of patients with diabetes, helping to prevent chronic complications of diabetes mellitus, such as reduced renal function [30].

The administration of 25 g of fenugreek for 30 days in patients with type II diabetes resulted in a significant increase in HDL-C and a significant reduction in total cholesterol, LDL-C, and TGs [31]. Fenugreek, an add-on therapy to metformin, also showed greater results in improving glucose metabolism in patients with type II diabetes mellitus than sulfanilurea + metformin combination therapy. A statistically significant improvement in fasting insulin levels in the HOMA-IR and an increase in the HDL/LDL ratio were observed. In addition, a decrease, although not significant, in fasting blood glucose and glycated haemoglobin levels (which were outside the normal range) was observed after three months of combined fenugreek and metformin treatment. These improvements were not observed in patients treated with sulfanilurea or metformin [32].

A randomized, double-blind, placebo-controlled study was carried out to investigate the medicinal effects of fenugreek on postmenopausal syndrome. Treatment efficacy was assessed by the improvement in the menopause rating scale (MRS) score at day 1, day 28,

and day 42 of treatment and the improvement of hormonal balance. The MRS questionnaire assesses quality of life related to the severity of menopause-related symptoms and divides them into three categories: somatic, psychological, and urogenital factors [33].

Finally, according to Gaddam et al., fenugreek could be proposed as a supplement in patients with prediabetes, with the aim of slowing down the onset of diabetes. In patients with prediabetes, fenugreek caused a reduction in blood sugar levels and an increase in insulin levels, with an insulinotropic action, probably linked to the alkaloids it contains [34].

4.2. Allergic Reactions to Fenugreek

Allergic reactions to spices reported in the literature are not very numerous: to date, 10 cases have been recorded, and we have found 6 case reports and 2 clinical studies on 2 patients, respectively (Table 2). This is due to several factors. Until a few years ago, the use of spices was almost exclusively the prerogative of oriental cuisine, and exposure was mainly in the professional field (cooks and producers). In addition, spices are often used and sold as spice blends, and this also applies to fenugreek, whose presence in some dishes and foods is not clearly identifiable through labeling.

Table 2. Cases from the literature of fenugreek hypersensitivity.

Cases of Fenugreek Hypersensitivity							
Author	**Article Type**	**Year**	**Age**	**Sex**	**Symptoms Associated with Fenugreek**	**Previous Adverse Reactions**	**Other Cosensitizations**
Patil SP [35]	Clinical trial	1997	36	F	Sneezing, rhinorrhea, tearing, coughing, and wheezing after smelling.	Chickpeas ingestion.	/
			45	F	Nasal obstruction, hoarseness, angioedema, and wheezing after cutaneous contact.	Fenugreek ingestion.	/
Joseph NI [36]	Case report	2018	14	M	Urticaria, chest tightness, abdominal pain, and emesis after ingestion.	Fava bean and lentils ingestion.	/
Faeste CK [37]	Clinical study	2009	11	M	Anaphylaxis after the ingestion of curry mix.	/	Peanuts, lupin, pea, hazelnut, and almond.
			12	M	Anaphylaxis after eating prepacked Indian food.	/	Peanuts, lupin, pea, soy, hazelnut, and almond.
Che CT [19]	Case report	2017	14	M	Itching and lip tingling followed after several hours by chest heaviness, urticaria, and wheezing after ingestion of curry.	Peanuts, lentils, chickpea and peas ingestion.	Peanuts, Ara h2, lentil, chickpea and pea.
Aurich S [38]	Case report	2019	34	F	Flushing, angioedema, dyspnea, nausea, vomiting, and diarrhea after Chinese vegetable soup. Second similar episode after spicy sausage.	Peanuts.	Timothy grass, mugwort, and peanut, Ara h 1, Ara h 2, Ara h 3, Art v 3, and fenugreek seeds.
Ohnuma N [39]	Case report	1998	26	F	Itching, diarrhea and wheezing after curry ingestion	/	Wheat, apples, rice, peanuts, almond, and onions.
Ebo DG [40]	Case report	2006	25	M	Urticaria, conjunctivitis, oropharyngeal angioedema, and bronchospasm after eating pita bread.	Coriander and fenugreek after contact and inhalation at work.	Coriander.

Table 2. *Cont.*

Cases of Fenugreek Hypersensitivity							
Author	**Article Type**	**Year**	**Age**	**Sex**	**Symptoms Associated with Fenugreek**	**Previous Adverse Reactions**	**Other Cosensitizations**
Bentele-Jaberg N [41]	Case report	2015	32	F	Fever, headache and exanthema evolving towards TEN after regular ingestion of an herbal preparation made of pure fenugreek seeds to improve lactation.	/	/

Cases of fenugreek hypersensitivity in patients with peanuts allergy			
Author	Article type	Year	Outcomes
Namork E [42]	Retrospective study	2011	The Norwegian Food Allergy Register in 2000–2010 has received 877 reports, of which patients with a known peanut allergy had allergic reactions after spicy sauces and Indian dishes (the reactions were found to be caused by fenugreek seeds, commonly used in curry and other mixed spices).
Muller T [43]	Retrospective study	2022	A total of 195 children allergic to peanuts showed simultaneous sensitization to at least one other legume (fenugreek, soy, lupin and lentil; *n* = 122–69.7%); 10% of them were allergic to fenugreek. Main sensitizations were to fenugreek, followed by lentil, soy, pea, lupine, chickpea, broad bean, and bean.

F = female, M = male; Ara h = *Arachis hypogea* molecular allergen, Art v = *Artemisia vulgaris* molecular allergen; TEN = toxic epidermal necrolysis.

Based on data recorded on the Norwegian Food Allergy Register from 2000 to 2010, cases of allergy were reported after the ingestion of Indian foods and spices; this could represent a new hidden allergen introduced in recent years through fusion cuisines [42]. The adverse reactions reported to fenugreek appear predominantly as IgE-mediated reactions, ranging from milder forms to actual cases of anaphylaxis. In 2007, a case of biphasic anaphylaxis after curry ingestion was reported. The second curry exposure resulted in frank anaphylaxis a few minutes after consumption. The patient had known allergies to peanuts, in particular to Ara h2 (2s albumin belonging to the seed storage protein family), peas, chickpeas, and lentils [19].

In our case series, six patients (case nos. 1, 2, 3, 7, 9, and 11) came to our observation for suspected adverse reactions after the ingestion of spices. Skin tests confirmed the clinical suspicion of SPT positivity with fenugreek.

Furthermore, allergic reactions to fenugreek would be triggered not only by the ingestion of the spice but also by inhalation and/or contact with the spice. However, in our experience, all allergic reactions to fenugreek that came to our observation occurred after ingesting the spice. The first two cases of allergic reactions to fenugreek known to the scientific community date back to 1997 and were not caused by the ingestion of the spice. In the first case, a housewife with a positive history of mild asthma and chicken allergy developed sneezing, rhinorrhea, eye tearing, and wheezing after opening and smelling a container containing fenugreek. In the second case, a woman with rhinitis and allergic asthma and a previous episode of respiratory wheezing after the ingestion of fenugreek paste applied fenugreek paste to her scalp to treat dandruff. Nasal obstruction and hoarseness appeared after a few minutes, followed by angioedema and respiratory wheezing [35]. In the cases reported by Patil, the sensitization occurred at home and therefore had very low amounts of allergen indeed, compared to sensitizations that occur in the case described by Ebo in an occupational setting [40]. In addition, in the first case, the patient had a known allergy to chickpeas, so the adverse reaction to fenugreek could have resulted from cross-reactivity with chickpeas.

Rare type IV immune-mediated reactions following fenugreek ingestion have been reported. A lactating woman regularly consumed fenugreek seeds to stimulate milk production and developed toxic epidermal necrolysis. Skin patch tests were not performed due to their low sensitivity in cases of Stevens–Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN). An oral provocation test was not performed due to the risk of serious adverse reactions. Lymphocyte transformation tests (LTTs) were positive for fenugreek without any immune cell proliferation in the presence of metamizole, acetaminophen, and ibuprofen; therefore, based on the LTT results, fenugreek was identified as the most likely causative agent. However, the other drugs taken by the patient, namely, acetaminophen, ibuprofen, and metamizole, also taken after her previous pregnancy without any adverse reactions, were not ruled out with certainty as being responsible for the adverse reactions without provocation testing [41].

Cross-reactivity between fenugreek and other legumes has also been demonstrated in other clinical studies. A study of 195 peanut-allergic children showed simultaneous sensitization to at least one legume, namely, fenugreek, soy, lupin, and lentil, and 10% of the children were allergic to fenugreek. Children with fenugreek sensitization underwent OFC, and half of them tested positive despite never having ingested fenugreek. Moreover, although only one-third of OFC-positive children developed a severe anaphylactic reaction, all OFC-positive children developed the adverse reaction with low cumulative doses of the allergen [43].

Given the positivity found for fenugreek in the six patients, we decided to consider cross-reactivity with other legumes; three out of six patients resulted positive for other legumes (peanut, soy, and green bean). Furthermore, we tested for fenugreek in other patients who visited our operative unit in the same period and reported allergic symptoms after the ingestion of legumes (lupine, soy, peanut, lentil, green bean, pea, and chickpea). We found a further 7 patients positive for both trigonella and at least another Leguminosae, according to the literature, making 10 patients sensitized simultaneously to fenugreek and other legumes.

The SDS-PAGE study for the identification of fenugreek proteins showed that the pattern of the protein bands differed slightly from that of the other Leguminosae. However, an immunoblot study using rabbit-derived anti-fenugreek polyclonal antibody showed the ability of the antibody to bind at higher concentrations not only to most fenugreek proteins but also to the 22 kd bands of lupine, 30 kd of bean, 46 kd of peas, and 24 kd of chickpeas, demonstrating a potential cross-reactivity between fenugreek and these legumes [37]. In another case of allergic reaction after the ingestion of spreadable cream containing fenugreek, the patient had a positive history of lentil and fava bean allergy; in this case, appropriate in vitro diagnostic tests were performed using ImmunoCAP, which was positive for both fenugreek seeds and lentils [36]. In a 2009 clinical study, the specificity of fenugreek-specific polyclonal IgE at high concentrations was analyzed, and binding to proteins of different molecular weights from lupin, bean, pea, and chickpea was observed [37]. However, cross-reactivity between fenugreek and other legumes cannot yet be determined with certainty because there are few published cases of adverse cross-reactions, and fenugreek molecular allergens have only recently been characterized [44]. Four molecular allergens of fenugreek were characterized: Tri f1 (7S globulin or vicilin; homologous to Ara h1), Tri f2 (2S albumin), Tri f3 (11S globulin or legumin, homologous to Ara h3, Ara h4), and Tri f4 (Bet v 1-like or PR-10, homologous to Ara h8) [44,45]. The most dangerous protein could be 2S albumin, Tri f2, which is homologous to Ara h2, Ara h6, and Ara h7 and is an allergenic protein belonging to the seed storage protein family that is highly stable to cooking and digestion and is generally responsible for very severe anaphylactic reactions.

In most of the cases described in the literature, fenugreek sensitization occurs by cross-reactivity with other legumes, particularly peanuts. However, primary sensitization to fenugreek cannot be excluded. A Norwegian study involving 66 patients with fenugreek

allergy suggested this hypothesis. Eight of these patients had higher specific IgE for fenugreek than for peanuts, and five patients were not sensitized to peanuts [46].

Upon careful analysis of our data, we observed that of the 10 patients sensitized to fenugreek and legumes, 8 were also positive for pistachio. We also reported that some of these patients had allergic symptoms even after ingesting pistachio.

Our data confirmed the evidence reported in the literature about the known cross-reactivity between fenugreek and Leguminosae, but a possible cross-reactivity with pistachio also emerged.

The molecular allergens known to date from fenugreek are Tri f1, Tri f2, Tri f3, and Tri f4, as mentioned above. The known molecular allergens of pistachio, are Pis v1 (2S albumin), Pis v2 and Pis v5 (11S globulins or legumes), Pis v3 (7S globulin or vicilin), and Pis v4 (MnSOD) [45,47]. The potential allergens responsible could likely be storage proteins (2S albumin, 7S globulins, and 11S globulins) or yet-unknown allergens, which could explain the sensitization observed in our patients.

Our data concur with a recent study by Muller et al, which highlighted that peanut-allergic children also have sensitization to other legumes (including fenugreek) and pistachio. Among the 195 peanut-allergic children included, 63.9% (n = 122) were sensitized to at least one legume, and 23.7% (n = 28) were sensitized to pistachio. The main sensitizations were fenugreek, lentil, soy, and lupine [43].

However, our work has limitations and weaknesses. First, it was not possible to test the same panel of allergens for all included subjects since the idea of possible cross-reactivity arose later; second, it is not currently possible to search for antigenic determinants of fenugreek, although they have been characterized, so that further supporting data could be obtained. Third, more specific and extensive laboratory investigations are needed to characterize and confirm the suspicion of cross-reactivity between pistachio and fenugreek lack.

5. Conclusions

In conclusion, the analysis of our cases showed that fenugreek may be a major cause of allergic reaction to spices, even in the Western countries. The import of Eastern culinary traditions into our cuisine and the widespread use of spices in food preparations and herbal medicines could increase sensitization to fenugreek, which can be often found in hidden form. In addition, our study confirms cross-reactivities reported in the literature between fenugreek and other Leguminosae species, which are more commonly used in the Mediterranean area, suggesting that this is the sensitization route to fenugreek.

Finally, in a highly speculative manner, the existence of cross-reactivity between fenugreek and other foods not belonging to the Leguminosae family cannot be ruled out, because Trigonella is an emerging allergen that is still poorly understood and poorly investigated. In this case series, we observed a high incidence of patients cosensitized to fenugreek and pistachio. To date, no associations between these two families have been reported in the literature; however, this possible cross-reactivity is only a speculative hypothesis that needs to be confirmed by larger case series and adequate molecular and laboratory diagnostics.

Furthermore, care should be taken with the pharmaceutical use of fenugreek, especially in patients with known food allergies (peanuts and other legumes), to avoid the risk of allergic reactions.

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Data Availability Statement: The original contributions presented in the study are included in the article; further inquiries can be directed to the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

Appendix A

This section presents the detailed medical history of the 13 patients included in our case series (Table A1).

Table A1. Anamnesis and related allergy diagnostics.

Case	Age Sex	Symptoms Associated with Fenugreek	Symptoms Associated with Pistachio	Symptoms Associated with Other Legumes and Foods	Skin Prick Test for Food Allergens		Inhalant Sensitizations
					Positive	Negative	
1	37 M	Nasal obstruction, rhinorrhea, palmoplantar itching, and difficulty breathing after chicken curry ingestion.	Anaphylaxis after consuming pistachio ice cream and slush.	/	Fenugreek, pistachio (Figures 2 and 3), curry mix, cumin, mango, grapes, fennel, and celery.	Chicken, coconut milk, peanuts, and lupin.	Pellitory, grass, mugwort, plantain, ragweed, cat fur, dog coat, and house dust mites.
2	36 F	Itchy rash or urticaria, sometimes accompanied by lip angioedema after the ingestion of spice mixes.	/	Itchy rash or urticaria sometimes accompanied by lip angioedema after the ingestion of various foods on separate occasions (pomegranate, raw and cooked tomato, pumpkin, shellfish, chestnuts, mozzarella, aubergine, melon, watermelon, zucchini, nuts).	Fenugreek, pistachio (Figure 2), cumin, coriander, cashew, peanut, watermelon, mango, lupine, pomegranate, fennel, celery, pumpkin seed, yellow melon.	Other suspected food allergens.	Grass, mugwort, olea, plantain, and birch.
3	42 F	Sneezing blank, rhinorrhea, nasal obstruction, tightness in throat, tongue swelling, extremity itching after ingestion of soy snack (containing spices).	/	Sneezing blank, rhinorrhea, nasal obstruction, tight throat, tongue swelling, extremity itching after corn and onion ingestion.	Fenugreek, cumin, peanuts, and pomegranate. ISAC test: Ara h6. Ara h9.	Soy, corn.	Pellitory, grass, mugwort, olea, plantain, ragweed, and birch.
4	26 F	/	/	Episodes of lingual oedema, velvety, and urticarial rash after the ingestion of peach, melon, watermelon, and cherry juice; episodes of velvety oral cavity and pharynx after the ingestion of peanuts, walnuts, and fennel.	Fenugreek, pistachio, Peanuts, mango, strawberries, pomegranate fennel, celery, and yellow melon.	Other main suspected food allergens.	Pellitory, grass, mugwort, olea, cat fur, house dust mites.
5	22 M	/	Erythema on the face and trunk after consuming pistachios and beer.	Vomiting and diarrhea after eating peanuts; gut discomfort after eating lentils and strawberries; oral itching and throat constriction after eating peach and nuts; and rhinitis and erythema on the face and trunk after eating tomato.	Fenugreek, pistachio, tomato, lentil, peach, walnut, hazelnut, almond, mango, strawberries pomegranate, fennel.	Other suspected food allergens.	Pellitory, grass, mugwort.

Table A1. *Cont.*

Case	Age Sex	Symptoms Associated with Fenugreek	Symptoms Associated with Pistachio	Symptoms Associated with Other Legumes and Foods	Skin Prick Test for Food Allergens		Inhalant Sensitizations
					Positive	Negative	
6	28 F	/	/	Lip angioedema after peach ingestion; sore mouth and oral itching after eating hazelnut cream, zucchini, garlic, corn, and dragon fruit; throat constriction after lemon and red berries; episodes of oral itching after eating lettuce, arugula, radicchio, plum, pumpkin, eggplant, parsley, mushrooms, and potato.	Fenugreek, pistachio, mustard, soy, corn, rice, lentil, peach, hazelnut, peanut, strawberry, pomegranate, fennel, and celery.	Other suspected food allergens.	/
7	29 F	Nonitchy rash, diarrhea, abdominal cramps after the ingestion of spiced potatoes.	Tight throat, dyspnea, and swelling of the tongue after pistachios ingestion.	Tight throat, dyspnea, and swelling of the tongue after the ingestion of peach, walnut, and almond.	Fenugreek, pistachio (Figures 2 and 3), peach, hazelnut, cashew, mango, and pomegranate.	Other suspected food allergens.	Pellitory, grass, mugwort, and olea.
8	31 M	/	Constriction in throat after aperitif with alcohol, nuts and pizza with pistachios.	Nausea and vomiting after apple ingestion, constriction in throat after banana ingestion.	Fenugreek, pistachio, mustard, lentil, apple, mango, grapes, pomegranate, fennel, lupine, anise, banana, zucchini, and eggplant.	Other suspected food allergens.	Cypress.
9	36 M	Urticaria after ingestion of rice, mutton, fish, and a spice mixture including turmeric, coriander, ginger, chili pepper and other spices.	/	Angioedema and vomiting after corn ingestion; itching of the oral cavity after eggplant and green peas; urticaria, angioedema, and vomiting after zucchini, tuna, and mozzarella meal.	Fenugreek, cumin, turmeric, coriander, mustard, oat, rice, lentil, peach, peanut, pomegranate, fennel, anise, zucchini, eggplant, and rice.	Other suspected food allergens.	Olea, house dust mites.
10	42 F.	/	/	Itchy plantar palm and angioedema after hazelnut snack; anaphylaxis after eating a pizza with zucchini, Parma ham and maybe contaminated with arugula.	Fenugreek, pistachio, peanut, hazelnut, walnut, grape, celery, eggplant, pea, corn, sunflower seed, parsley, songino, onion, garlic, arugula, basil, strawberry, apricot, cherry, and apple. ISAC test: Corn, peanut, kiwi, apple, peach, grape, celery, hazelnut, walnut (Par j2, Can S3, Art v3, Pla a3, Zea m14, Ara h9, Act d10, Mal d3, Pru p3, Vit v1, Api g2, Cor a8, Jug r3).	Other suspected food allergens.	Pellitory, mugwort, hemp, plane tree.
11	26 F.	Episodes of tickling in the pharynx after curry ingestion.	Episodes of dyspnea and constriction in the throat after pistachios ingestion.	Various episodes of dyspnea and constriction in the throat after sesame ingestion.	Fenugreek, pistachio, cumin, coriander, peach, sesame, and pomegranate.	Nuts, mustard, bean, lentils.	Pellitory, grass, house dust mites cat fur, and dog coat.
12	20 F.	/	Urticaria and angioedema after pistachios ingestion.	Urticaria and angioedema after ingestion of peanuts, and peach; oral itching after green beans ingestion.	Fenugreek, pistachio, peanuts, bean, lentil, peach, apple, and hazelnut.	Other suspected food allergens.	/
13	23 M.	/	Episodes of velvety itchy scalp, and vomiting after pistachio ingestion.	Episodes of velvety itchy scalp, and vomiting after the ingestion of nuts (including peanut, almond, walnut, hazelnut) and apples.	Fenugreek, pistachio (Figures 2 and 3), Apricot, apple, peanut, peach, almond, hazelnut, mango, cashew.	Other suspected food allergens.	Pellitory, grass, house dust mites, cat fur, and dog coat.

Case 1

A 37-year-old male patient presented to our observation for anaphylaxis onset after ingesting homemade chicken curry. He reported eating this dish for the first time in the week before the reported episode without any symptoms. Five minutes after ingesting chicken curry, nasal obstruction, rhinorrhea, palmoplantar itching, and difficulty breathing appeared. He was treated with corticosteroids and systemic antihistamines after regression of the clinical picture. In addition, the patient reported two separate episodes of anaphylaxis after consuming pistachio ice cream and pistachio slush. He had a positive allergy history of rhinitis symptoms in spring and sporadic episodes of blank sneezing and urticaria after contact with dogs. SPT for inhalants produced positive results for pellitory, grass, mugwort, plantain, ragweed, cat fur, dog coat, and house dust mites. SPT for the main suspected food allergens performed using the commercial extracts was negative, whereas SPT with fresh food gave positive results for pistachio, curry mix, fenugreek (Figures 2 and 3), cumin, mango, grapes, fennel, and celery. Chicken, coconut milk, peanuts, and lupin tested negative. The patient no longer ingested pistachios and spice mixes containing fenugreek and cumin. He consumes and tolerates grapes. The epinephrine autoinjector was also prescribed due to the severity of reactions and the presence of premonitory symptoms of anaphylactic shock. In addition, the spices to which the patient was found to be positive could constitute a hidden allergen; therefore, avoiding these allergens may be difficult.

Case 2

A 36-year-old woman visited the outpatient clinic to investigate the appearance of multiple episodes of itchy skin rash or urticaria, sometimes accompanied by lip angioedema, after ingesting pomegranate, raw and cooked tomato, pumpkin, shellfish, chestnuts, mozzarella, eggplant, melon, watermelon, zucchini, nuts, and spice mixes. She also reported seasonal allergic rhinitis in spring, September, and October. The SPT for aeroallergens was positive for grass, mugwort, olea, plantain, and birch. The SPT for the main suspected foods made with allergenic commercial extracts was negative. SPT with fresh foods yielded positive results for pistachio, fenugreek (Figure 2), cumin, coriander, cashews, peanut, watermelon, mango, pomegranate, fennel, celery, lupine, pumpkin seed, and yellow melon.

Case 3

A 42-year-old woman came to our observation for the appearance of a sneezing blank, rhinorrhea, nasal obstruction, tightness in the throat, tongue swelling, and itching of extremities after ingesting corn, onion, and soy-containing snacks. The patient was administered oral antihistamine and intramuscular corticosteroids for persistent symptoms with resolution of oedema and facial erythema within 24 h. She also complained of rhinoconjunctivitis and perennial cough after exposure to environmental allergens. The SPT for inhalants was positive for pellitory, grass, mugwort, olea, plantain, ragweed, and birch. The SPT of the food extracts was positive only for peanuts. Soy and corn were negative. SPT with fresh foods was positive for fenugreek, cumin, and pomegranate. The patient also underwent molecular diagnostics using a multiplex panel (ISAC test by Thermofisher, Waltham, MA, USA), showing sensitization to Ara h6 in peanuts, which belongs to the 2S albumin storage protein family and Ara h9 (LTP family). Unfortunately, in the multiplex test, the study of fenugreek-specific IgE was not available. It is possible that the adverse reaction presented by the patient after ingesting the snack was due to the presence of spices not explicitly included in the food label, including fenugreek. In support of this hypothesis is the finding of skin positivity for fenugreek and sensitization to 2S albumin from peanuts, which could be derived from the presumed cross-reactivity between peanuts and fenugreek.

Case 4

A 36-year-old female visited our outpatient clinic complaining of episodes of lingual oedema, velvety, and urticarial rash after the ingestion of peach, melon, watermelon, and cherry juice. Subsequently, she eliminated these foods from her diet. Further episodes of

velvety oral cavity and pharynx appeared after the ingestion of peanuts, walnuts, and fennel. She reported ingesting peas, beans, chickpeas, and lentils without any adverse reaction.

SPT for inhalants was positive for pellitory, grass, mugwort, olea, cat fur, and house dust mites.

SPT for foods was positive for peanuts and strawberries. The SPTs for fresh foods were positive for pistachio, fenugreek, mango, pomegranate, fennel, celery, and yellow melon.

Case 5

A 22-year-old male underwent an allergy visit at our outpatient clinic to investigate several food allergy episodes: vomiting and diarrhea after peanuts; erythema on the face and trunk after pistachio and beer; gut discomfort after lentil and strawberry; oral itching and throat constriction after peach and nuts; and rhinitis and erythema on the face and trunk after tomato. We performed SPT for food allergens and found positive results for tomato, lentil, peach, walnut, hazelnut, almond, and strawberry. Fresh foods tested were positive for pistachio, fenugreek, mango, pomegranate, and fennel. The patient also reported rhinitis symptoms, and the SPT for aeroallergen was positive for pellitory, grass, and mugwort.

Case 6

A 38-year-old woman came to our observation following several episodes of food allergy: lip angioedema after peach; sore mouth and oral itching after a meal of hazelnut cream, zucchini, garlic, corn, and dragon fruit; throat constriction after lemon and red berries; and episodes of oral itching after a meal based on lettuce, arugula, radicchio, plum, pumpkin, eggplant, parsley, mushrooms, and potato. The patient also reported previous sensitization to soy. SPT for allergens in foods was positive for mustard, soy, corn, rice, lentil, peach, hazelnut, peanut, and strawberry. Fresh foods tested were positive for pistachio, fenugreek, pomegranate, fennel, and celery.

Case 7

A 29-year-old female visited the outpatient clinic with suspected food allergy. She reported an appearance of tightness in the throat, dyspnea, swelling of the tongue after peach, pistachio, and walnut ingestion, and an appearance of nonitchy rash, diarrhea, and abdominal cramps after ingestion of spiced potatoes. She also complained of rhinitis symptoms. The SPT for inhalants was positive for pellitory, grass, mugwort, and olea, and the SPTs for foods were positive for peach and hazelnut. We also tested fresh foods with positive results for pistachio, fenugreek (Figures 2 and 3), cashew, mango, and pomegranate.

Case 8

A 31-year-old male reported nausea and vomiting after ingesting apple, constriction in the throat after ingesting banana, and a second episode after aperitif with alcohol, nuts, and pizza with pistachio. He also reported rhinitis symptoms with positive SPTs for cypress. SPTs for foods were positive for mustard, lentil, and apple. SPTs for fresh foods were positive for pistachio, fenugreek, mango, pomegranate, grapes, fennel, lupine, anise, banana, zucchini, and eggplant.

Case 9

A 36-year-old male from Bangladesh reported several episodes of food allergy: angioedema and vomiting after corn ingestion; itching of the oral cavity after eggplant and green peas; urticaria, angioedema and vomiting after eating zucchini, tuna, and mozzarella; and urticaria after ingesting rice, mutton, fish, and a spice mix including turmeric, coriander, ginger, chili pepper, and maybe other unidentified spices. We performed SPT for foods with positive results for mustard, oat, rice, lentil, peach, and peanut. In consideration of the fact that due to eating habits, the patient consumed a lot of spices and that an episode occurred after a meal seasoned with various spices, we decided to test other spices not available as commercial extracts, with positive results for fenugreek, cumin, turmeric, and

coriander. The SPT for other fresh foods were positive for pomegranate, fennel, anise, zucchini, and eggplant.

History of allergy was positive for rhinitis and allergic asthma with sensitization to olea and house dust mites.

Case 10

A 42-year-old woman visited our observation with a history of multiple adverse food reactions, some of which characterized by anaphylaxis. The first episode was characterized by palmoplantar itching and angioedema after ingesting a hazelnut snack. The last episode was more severe and occurred after eating a pizza with zucchini, Parma ham, and possibly contaminated with rocket. Over the years, the patient has gradually eliminated foods that are positive for SPTs even in the absence of adverse reactions. We prescribed an ISAC test by Thermofisher, which showed sensitization towards LTP from pellitory, mugwort, hemp, plane tree, corn, peanut, kiwi, apple, peach, grape, celery, hazelnut, and walnut (Par j2, Can S3, Art v3, Pla a3, Zea m14, Ara h9, Act d10, Mal d3, Pru p3, Vit v1, Api g2, Cor a8, Jug r3). The ISAC test also highlighted sensitization towards sunflower seeds. The patient reported that she had ingested and tolerated kiwi, grape, and sunflower oil, despite the lack of positive results. Moreover, she tolerates chickpeas, beans, and lentils, but she has never eaten exotic spices because of fears of allergic reactions. We decided to perform SPTs on fresh foods and found positive results for pistachio, fenugreek, peanut, hazelnut, walnut, grape, celery, eggplant, pea, sunflower seed, corn, parsley, singing, onion, garlic, arugula, basil, strawberry, apricot, cherry, and apple.

Case 11

A 26-year-old woman presented to our observation for episodes of tickling in the pharynx after the ingestion of curry and for various episodes of dyspnea and feeling of tightness in the throat after ingesting sesame. Similar symptoms occurred after consuming pistachio. We performed SPTs on foods with positive results for peach sesame, fenugreek, cumin, coriander, pistachio, and pomegranate. Nuts, mustard, bean, and lentil were negative. Personal allergy history was positive for allergic asthma with sensitization to grasses, pellitory, house dust mites, cat fur, and dog coat.

Case 12

A 20-year-old woman visited the outpatient clinic for episodes of urticaria and angioedema after ingesting pistachio, peanuts, and peach on different occasions. She also complained of oral itching after ingesting green beans. She reported tolerating other legumes (such as lentil and bean), hazelnuts, almonds soy, cherries corn, and wheat.

We performed SPTs for foods with positive results for peanuts, bean, lentils, peaches, apples, and hazelnuts, and the SPT for fresh foods was positive for pistachios and fenugreek.

Case 13

A 23-year-old man presented to our observation for episodes of velvety, itchy scalp and vomiting after the ingestion of nuts, including almond, walnut, hazelnut, and peanut. He reported similar episodes after ingesting apple and sometimes after consuming pistachio. He tolerates cooked apples well. We performed SPTs for foods with positive results for apricot, apple, peanut, peach, almond, and hazelnut. The SPT for fresh foods was positive for pistachio, fenugreek (Figures 2 and 3), mango, and cashew. Personal allergy history was positive for allergic rhinitis and asthma with sensitization to grasses, pellitory, house dust mites, cat fur, and dog coat.

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