

Pink peppercorn: A cross-reactive risk for cashew- and pistachio-allergic patients

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Clinical Implications

- Allergen cross-reactivity occurs between cashew nut, pistachio nut, and pink peppercorn. Clinicians and cashew-allergic patients should be aware of the potential for cross-reactivity with related allergic triggers, some of which can be eaten as novel foods.

TO THE EDITOR:

Cashew nut allergy is a common food allergy capable of inducing anaphylactic reactions.¹ In cashew-allergic individuals, cosensitization with other allergens is common but does not always indicate co-allergy. This report summarizes 2 cases of reactions to pink peppercorn (ie, Peruvian peppers or Brazilian peppers) in cashew-allergic individuals and explores their immunologic cross-reactivity through ImmunoCAP inhibition.

Three major allergens have been identified for cashew nut, namely, Ana o 1, Ana o 2, and Ana o 3, or rather the 7S, 11S, and 2S seed storage proteins, respectively. The 2S albumin seed storage proteins in tree nuts, legumes, and seeds¹ are known to be highly allergenic because of their high stability to heat and digestion and their relatively high protein concentration.² Ana o 3 specifically has been shown to be a good predictor for clinically relevant cashew nut allergy in children.²

Within cashew's botanical *Anacardiaceae* family, cashew and pistachio cosensitization is well described, but cosensitization may also arise with other common related foods (eg, mango).^{3,4} The *Anacardiaceae* family belongs to the wider Sapindales order, of which the citrus *Rutaceae* family is also included and botanically closely related. Cases of allergy to the seeds of citrus fruits in cashew-allergic patients have previously been reported,^{5,6} as well as reactions with pectin—a food additive refined from dried citrus peels and apple skin, pulp, seeds, and stems.⁷ Despite high levels of cosensitization seen in cashew-sensitized children (pistachio 98% cosensitized and mango 21% cosensitized), van der Valk et al³ found that pistachio co-allergy existed in only 34% of children and no children challenged positive to mango.

A case of pink peppercorn allergy was first reported in a conference abstract by Kim and Minikes.⁸ They describe a 26-year-old woman with a history of cashew nut anaphylaxis, who experienced anaphylaxis after ingesting pink peppercorn. Food-specific IgE level for cashew and pistachio was 2.52 kU_A/L and 2.75 kU_A/L, respectively.⁸ We further report on 2 cases of allergic reactions to pink peppercorn and present evidence confirming cross-reactivity between cashew/pistachio and pink peppercorn.

This report is the result of 2 separate cases, seen in our UK clinic in late 2017 and early 2018, of allergic reactions to pink

peppercorn that were induced by eating a commercial brand of “Mediterranean Cracked Mixed Pepper” crisps, a new flavor introduced in the United Kingdom in February 2017.

Case 1: A 9-year-old female with a history of cashew nut allergy after skin contact, oral allergy syndrome, and sensitizations to pistachio, hazelnut, and grass pollen presented to our clinic after an acute allergic reaction to pink peppercorn-flavored crisps. She developed pruritus, urticaria, and an itchy tongue and mouth and began coughing within a few minutes after ingestion of the crisps. Her symptoms settled after the administration of chlorphenamine maleate. Her skin prick tests (using commercial extracts and prick-to-prick testing) showed wheals of the following size: cashew 17 mm, pistachio 14 mm, pink peppercorn 6 mm, Mediterranean Cracked Mixed Pepper crisps 3 mm (same brand as eaten at the time of the reaction), hazelnut 7 mm, orange pip/seed 4 mm, apple 3 mm, and milk 8 mm. Test results for lime seed, pomegranate, yellow melon, mango, peanut butter, and all other tree nuts were negative.

Case 2: A 3-year-old male with a history of food protein-induced enterocolitis syndrome (FPIES) and sensitization to milk, peanut, and tree nuts (including cashew and pistachio) presented to our clinic following perioral erythema, coughing, and vomiting 20 minutes after ingestion of pink peppercorn-flavored crisps. His symptoms resolved after administration of cetirizine. He had no history of clinical reactions to cashew. His skin prick tests showed wheals of the following size: cashew 6 mm, pistachio 15 mm, pink peppercorn 8 mm, and lemon pip 10 mm.

To establish whether cross-reactivity with cashew and pistachio was the mechanism for the observed sensitization to pink peppercorn, ImmunoCAP inhibition was carried out.⁹ For both patients, IgE binding to pink peppercorn was (almost) completely inhibited by both cashew and pistachio extracts (Figure 1). To establish whether Ana o 3 was involved in cross-reactivity, a single-point inhibition was carried out with 38 µg/mL of cashew extract and pink peppercorn extract (higher concentration was not available). With cashew 73% inhibition and with pink peppercorn 35% inhibition was reached, confirming involvement of 2S albumins in cross-reactivity. In conclusion, serum IgE analyses confirmed cross-reactivity between cashew, pistachio, and pink peppercorn, at least partly mediated by 2S albumins. This cross-reactivity is the immunologic basis for the clinical reactions to foods containing pink peppercorn in patients who have cashew and pistachio allergy.

Although little was known regarding pink peppercorn cross-reactivity with the *Anacardiaceae* family, the relationship with (seeds of) fruits of the closely related *Rutaceae* family has been studied. Figure E1 in this article's Online Repository at www.jaci-inpractice.org details cross-reactivity between these (and other) fruit seed allergens and cashew. Clinicians and cashew-allergic patients should be aware of the potential for cross-reactivity with related allergic triggers.

Despite this potential for cross-reactivity to allergens in a wide array of foods, reports of cross clinically relevant co-allergy in cosensitized individuals appear to be low. We demonstrate clinical and immunologic cross-reactivity between cashew/pistachio and pink peppercorn. Novel food preparations containing

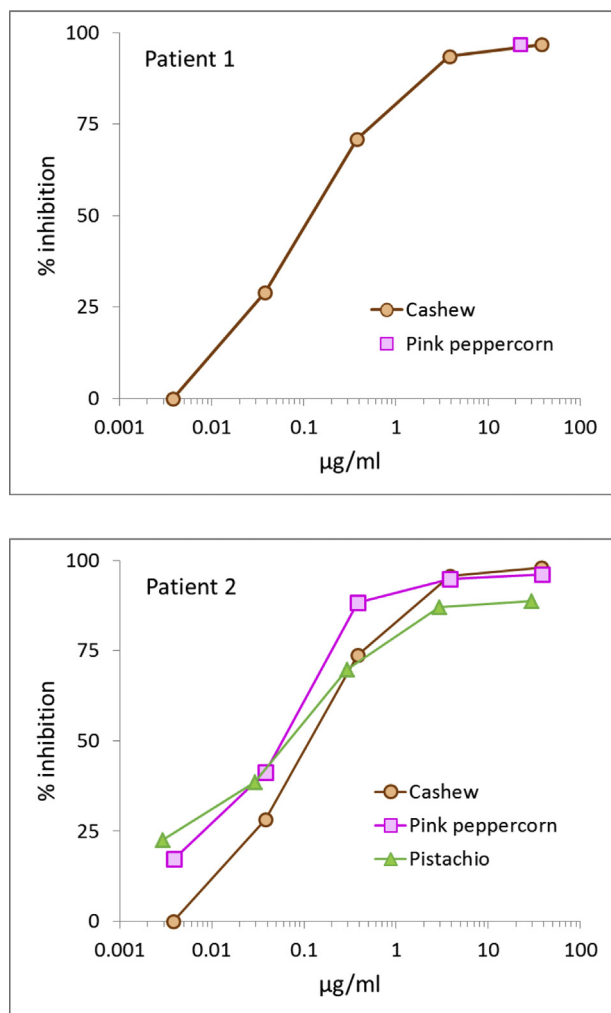


FIGURE 1. Pink peppercorn ImmunoCAP inhibition. Cross-reactivity of IgE antibodies against pink peppercorn was assessed by ImmunoCAP inhibition for both pink peppercorn allergic patients. Binding to ImmunoCAP-immobilized pink peppercorn extract was inhibited with pink peppercorn extract (only for patient 1 with a single high concentration) and with cashew nut extract. For patient 2, pistachio extract was also used as an inhibitor. At similar protein concentrations, maximal inhibition (close to 100%) is reached, supporting the highly cross-reactive nature of IgE antibodies against pink peppercorn and both tree nuts.

pink peppercorn may result in increased reporting of such reactions and represent a public health concern requiring appropriate cautionary labeling. In the United Kingdom, pink peppercorn is a constituent of at least 143 pre-prepared commercial foods (as searched on FoodMaestro). Clinicians and cashew-/pistachio-allergic patients should be aware of the potential for additional allergic triggers. Such knowledge will

TABLE I. ImmunoCAP analysis

Patient no.	Cashew	Pistachio	Pink peppercorn	Ana o 3
Patient 1	5.5 kU _A /L	8.0 kU _A /L	0.4 kU _A /L*	8.7 kU _A /L
Patient 2	43.8 kU _A /L	66.4 kU _A /L	9.8 kU _A /L	62.5 kU _A /L

*Skin prick test wheal to pink peppercorn (6 mm).

facilitate appropriate allergen testing and, if necessary, dietary modification.

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The authors received no specific funding for this work.

Conflicts of interest: G. Du Toit has received grants from the National Institute of Allergy and Infectious Diseases (National Institutes of Health), Food Allergy Research and Education, MRC & Asthma UK Centre, UK Department of Health through the National Institute for Health Research, Action Medical Research, and National Peanut Board; holds equities in FoodMaestro and DBV Technologies; is a Scientific Advisory Board member for Aimmune and Co; is an investigator on Aimmune-funded peanut immunotherapy trials; is on the DBV Technologies UK Advisory Board; is a lecturer at Allergy Symposia supported by pharma companies. R. van Ree has received consultancy fees from HAL Allergy BV and Citeq BV; and has received speaker fees from HAL Allergy BV and Thermo Fisher Scientific. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication October 1, 2018; revised November 14, 2018; accepted for publication November 18, 2018.

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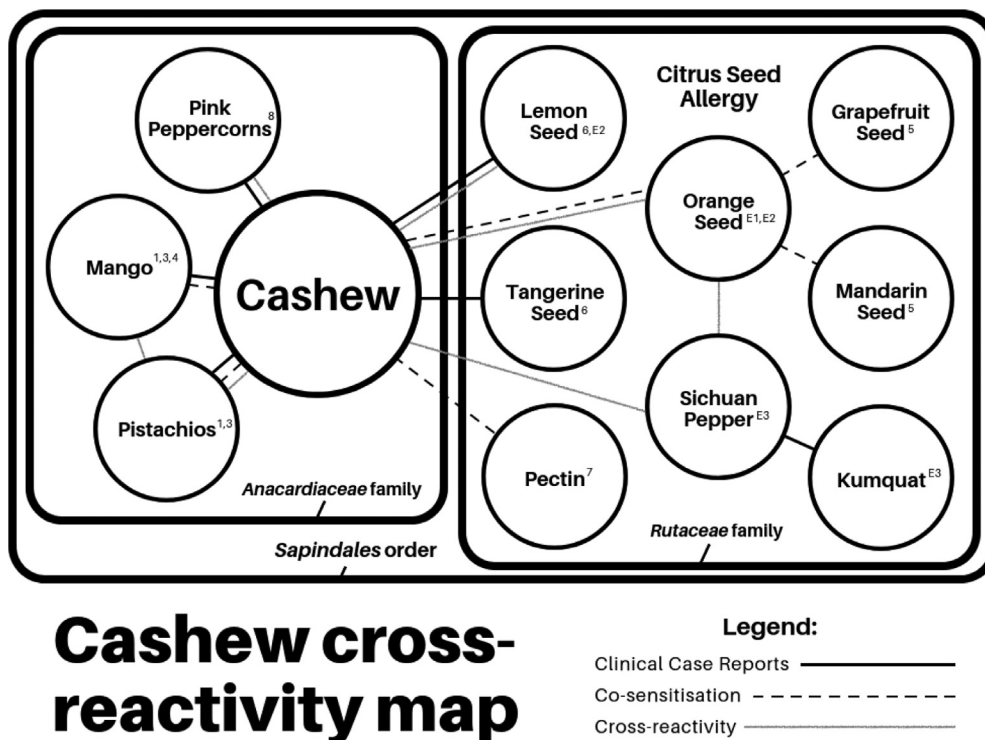
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<https://doi.org/10.1016/j.jaip.2018.11.051>

REFERENCES

- van der Valk JP, Dubois AE, Gerth van Wijk R, Wichers HJ, de Jong NW. Systematic review on cashew nut allergy. *Allergy* 2014;69:692-8.
- Lange L, Lasota L, Finger A, Vlainic D, Busing S, Meister J, et al. Ana o 3-specific IgE is a good predictor for clinically relevant cashew allergy in children. *Allergy* 2017;72:598-603.
- van der Valk JPM, el Bouche R, Gerth van Wijk R, de Groot H, Wichers HJ, Dubois AEJ, et al. Low percentage of clinically relevant pistachio nut and mango co-sensitisation in cashew nut sensitised children. *Clin Transl Allergy* 2017;7:8.
- Hegde VL, Venkatesh YP. Anaphylaxis following ingestion of mango fruit. *J Investig Allergol Clin Immunol* 2007;17:341-4.
- Turner PJ, Gray PE, Wong M, Varese N, Rolland JM, O'Hehir R, et al. Anaphylaxis to apple and orange seed. *J Allergy Clin Immunol* 2011;128:1363-5.
- Brandström J, Lilja G, Nilsson C, Ingemarsson N, Borres MP, Brostedt P, et al. IgE to novel citrus seed allergens among cashew-allergic children. *Pediatr Allergy Immunol* 2016;27:550-3.
- Ferdman RM, Ong PY, Church JA. Pectin anaphylaxis and possible association with cashew allergy. *Ann Allergy Asthma Immunol* 2006;97:759-60.
- Kim J, Minikes N. A rare case of food-induced anaphylaxis to pink peppercorns. *World Allergy Organ J* 2012;5:S152.
- Gao ZS, Zhou X, Yang ZW, Versteeg SA, Gao L, Fu WY, et al. IgE-binding potencies of three peach Pru p 1 isoforms. *Mol Nutr Food Res* 2016;60:2457-66.

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Cashew cross-reactivity map

FIGURE E1. Cashew allergy and associated seed and spice allergens.

REFERENCES

- E1. O'Sullivan MD, Somerville C. Cosensitization to orange seed and cashew nut. *Ann Allergy Asthma Immunol* 2011;107:282-3.
- E2. Savatianos SKA, Borga A, Ekoff H, Borres MP, Manousakis E, Papadopoulos NG. Cross-reactivity between Anacardiaceae (cashew/pistachio) and Rutaceae (orange/lemon) seeds. *Allergy* 2014;69:553.
- E3. Li H, Wang RQ, Cheng X, Zhou XP, Yin J. Anaphylaxis to *Pericarpium xanthoxyli* and its cross-reactivity between nuts and citrus. *J Allergy Clin Immunol* 2016;137:AB143.