

Propolis, Colophony, and Fragrance Cross-Reactivity and Allergic Contact Dermatitis

Yiwen Shi, BA/BS, Susan Nedorost, MD, Loren Scheman, and Andrew Scheman, MD

Background: Colophony and propolis are among the complex plant resins used in a wide variety of medicinal and personal care products. A number of studies of colophony, propolis, and fragrance mixes suggest that contact with one of these allergens may increase the risk of delayed-type hypersensitivity reactions with additional compounds of significant cross-reactivity.

Objective: The aims of this study were to determine rates of cross-reactivity between propolis, colophony, and different fragrance mixes and to determine significant cross-reactivity thresholds for which to counsel patient avoidance.

Methods: Rates of cross-reactivity were calculated from the databases of 2 midwestern US patch testing centers. Rates were calculated both separately and collectively.

Conclusions: For patients allergic to colophony, fragrance and propolis may be considered significant cross-reactors. For patients allergic to propolis, fragrance and colophony may be considered significant cross-reactors. Cross-reactions between colophony, propolis, and fragrance mixes are unidirectional so, for patients allergic to fragrance, cross-reaction to propolis or colophony is not significant. Colophony allergy is found in only a small number of fragrance-allergic patients and is not a good indicator for fragrance allergy.

BACKGROUND

Colophony, also known as Rosin, is a natural resin derived from pines, cedars, spruce, firs, and junipers. It is used in both industrial settings, such as in electronic and rubber tire industries, and in nonindustrial settings as part of paper, glues, adhesives, and oils.^{1,2} There are 3 different methods of procuring colophony. Gum rosin, the most common form, is derived from live trees as tapped fresh resin oils; wood rosin is obtained from dead pine stumps; and tall oil rosin is derived from processed, liquefied tree pulp.³ A number of clinical cases related to colophony have been reported related to either bronchial asthma or dermatitis.⁴ One study of patch test clinics found a prevalence rate of 4.6% for colophony sensitivity.⁵ Colophony has sometimes been suggested as an indicator of fragrance sensitivity.

Propolis is a yellow-brown adhesive resin, also known as bee glue, used as a cementing substance in beehives after collection from poplar and conifer buds.⁶ Contact dermatitis from propolis is often an occupational hazard for beekeepers. However, beeswax purified from the honeycomb is also used in many cosmetics. In addition, propolis is sold in various forms as a topical ointment

and for ingestion in a number of health products, with its antiseptic and anti-inflammatory properties making it popular in both cosmetic and medicinal products. Like colophony, propolis has variable constituents depending on the location and variety of trees from which bees collect the resinous substance.^{2,7} Propolis derived from poplar and other tree resins contains well-known sensitizers such as cinnamic compounds and vanillin.⁶ The rate of sensitization to propolis, according to a number of patch test studies, varies from 1.2% to 6.6%.⁷

There are hundreds of potentially allergenic fragrances, including many of the constituents of the complex plant resins described previously. Fragrance mixes are commonly used to screen for fragrance allergy.⁶ Fragrance mix 1 consists of oak moss absolute, cinnamic aldehyde, cinnamic alcohol, α -amyl cinnamic alcohol, geraniol, hydroxycitronellal, isoeugenol, and eugenol.⁶ It is noteworthy that eugenol, found in oil of cloves, is used along with wood processing by-products (sawdust) to make vanillin. A more recent fragrance screen, fragrance mix 2, includes the different set of compounds citronellol, citral, coumarin, lylal, farnesol, and hexyl cinnamic aldehyde.⁶ Balsam of Peru, in contrast, is not a specific selection of distinct fragrances but consists of an aromatic liquid derived from the tree bark of *Myroxylon balsamum* that contains cinnamic aldehyde, cinnamic alcohol, eugenol, isoeugenol (all found in fragrance mix 1), and other compounds including vanillin and benzoic acid.⁸

OBJECTIVE

Dermatologists are often faced with a patient who desires to use scented personal care products but who has a positive patch test to

From the University Hospitals Case Medical Center, Cleveland, OH.

Address reprint requests to Susan Nedorost, MD, University Hospitals Case Medical Center, 11100 Euclid Ave, Cleveland, OH 44106.

E-mail: Susan.Nedorost@uhhospitals.org.

The authors have no funding or conflicts of interest to declare.

DOI: 10.1097/DER.0000000000000186

© 2016 American Contact Dermatitis Society. All Rights Reserved.

TABLE 1. Summary of Database Characteristics

Characteristics	Center 1, n (%)	Center 2, n (%)	Combined, n (%)	Combined, 95% CI, %
Total patients	2108	1909	4017	
Total patch tests				
Colophony	2062	1909	3971	
Positive reactions	65 (3.2)	17 (0.89)	82 (2.1)	1.7–2.6
Propolis	1312*	1909	3221	
Positive reactions	46 (3.5)	66 (3.5)	112 (3.5)	2.9–4.1
Fragrance mix 1	2071	1909	3980	
Positive reactions	241 (12)	252 (13)	493 (12)	11–13
Fragrance mix 2	1643†	1909	3552	
Positive reactions	132 (8.0)	104 (5.5)	236 (6.6)	5.8–7.4
Balsam of Peru	2064	1909	3973	
Positive reactions	228 (11)	239 (13)	467 (12)	11–13

*Patch test data collection began in 2008.

†Patch test data collection began in 2006.

colophony or propolis. By comparing rates of cross-reactivity between propolis, colophony, and fragrance mixes, we aim to provide some guidance to help the patient share decision making about the potential strategies for protection from future episodes of allergic contact dermatitis. The most conservative strategy is to avoid all fragrances in all products indefinitely; however, this is cumbersome, and many patients may wish to try a more liberal strategy if they understand the likelihood of cross-reacting substances causing a flare of dermatitis to be fairly low.

PATIENTS AND METHODS

As shown in Table 1, we performed a retrospective database analysis of patients presenting to 2 regional midwestern US patch testing centers. Data included patients from 1 center presenting between 2003 and 2015 and a similar number of patients from a second center presenting from June 2012 to December 2015. All patients who were simultaneously tested to colophony and/or rosin along with 3 fragrance screening allergens (fragrance mixes 1 and 2 and Balsam of Peru) were included. Reaction grades were documented according to the International Contact Dermatitis Research Group Criteria where “?” indicates a doubtful reaction, 1+ indicates a weak nonvesicular reaction, 2+ indicates a strong edematous/vesicular reaction, and 3+ indicates an extreme reaction. Center 1 included patch test responses of grade doubtful or higher at either the first or second reading, whereas center 2 included only reactions of at least 1+. Center 1 performed patch test readings at either 72 or 96 hours and at 1 week after patch application. All readings at center 2 were at 48 and 96 hours after patch application. Data from both centers were tabulated separately and also combined.

The number of cross-reactions (CRs) was determined to be the number of patients allergic to 1 compound who were also allergic to a second compound. Because CRs may be unidirectional, our search was conducted in both directions (ie, patients allergic to compound 1 who are allergic to compound 2 and vice versa). Per the American Contact Dermatitis Society's Contact

Allergy Management Program (CAMP) recommendations, we consider a 10% CR rate to be significant enough to recommend avoidance of a potential cross-reacting allergen.

RESULTS

As shown in Table 2, of 3971 patients tested for colophony sensitization, 82 patients (2.1%) were found to be sensitive to colophony. Of these 82 patients, 16 patients were also sensitive to fragrance mix 1 (CR, 20%), 11 patients were also sensitive to fragrance mix 2 (CR, 13%), and 19 patients were also sensitive to Balsam of Peru (CR, 23%). Of 56 patients sensitive to colophony who were also tested to propolis, 12 patients were also sensitive to propolis (CR, 21%). However, of 493 patients sensitive to fragrance mix 1, only 15 patients were also sensitive to colophony (CR, 3.0%); of 236 patients sensitive to fragrance mix 2, 9 patients were also sensitive to colophony (CR, 3.8%); and of 467 patients sensitive to Balsam of Peru, 15 patients were also sensitive to colophony (CR, 3.2%).

TABLE 2. Combined CR Rates

Compound 1	Compound 2	CR, %	95% CI
Colophony	Propolis	21	12–30
Colophony	Fragrance mix 1	20	11–29
Colophony	Fragrance mix 2	13	5.7–20
Colophony	Balsam of Peru	23	14–32
Propolis	Colophony	13	6.8–19
Propolis	Fragrance mix 1	25	17–33
Propolis	Fragrance mix 2	20	13–27
Propolis	Balsam of Peru	13	6.8–19
Fragrance mix 1	Colophony	3.0	1.5–4.5
Fragrance mix 1	Propolis	4.5	2.5–6.5
Fragrance mix 2	Colophony	3.8	1.4–6.2
Fragrance mix 2	Propolis	8.7	5.1–12
Balsam of Peru	Colophony	3.2	1.6–4.8
Balsam of Peru	Propolis	5.8	3.4–8.2

Of a total of 3221 patients tested to propolis, 112 (3.5%) had positive reactions. Fourteen of these patients were also sensitive to colophony (CR, 13%); however, there was divergence between the 2 testing centers. Center 1 found a 22% CR rate, but center 2 only found a 6.1% CR rate. Twenty-eight patients also had a reaction to fragrance mix 1 (CR, 25%), 22 patients were also sensitive to fragrance mix 2 (CR, 20%), and 15 patients were also sensitive to Balsam of Peru (CR, 13%). However, of 230 patients sensitive to fragrance mix 2 who were also tested to propolis, only 20 patients were also sensitive to propolis (CR, 8.7%); of 396 patients sensitive to fragrance mix 1, 18 patients were also sensitive to propolis (CR, 4.5%); and of 359 patients sensitive to Balsam of Peru, 21 patients were also sensitive to propolis (CR, 5.8%).

DISCUSSION

Allergic contact dermatitis to any one of these fragrance or resin mixes can be resolved simply through successful patient education and avoidance of the sensitizing compounds. However, these compounds appear in differing amounts in a multitude of products under numerous names. The list of potential CRs expands this pool to the extent that patients can rarely put forth the attention to avoid all of them. The information gleaned from patch test databases thus have utility as part of decision aids that patients can use to navigate compounds to which they may have allergic CRs. Patch test databases can be used to study the prevalence of CR for 2 given compounds, which can then be communicated to patients as probabilities. Some patients may then choose to only avoid products with compounds for which there is a higher potential for CR, whereas others may set a lower probability threshold, choosing to be more conservative in their avoidance particularly before significant events such as weddings or job interviews. More multifaceted decision aids may wish to include probabilities according to variables such as sex, race, age, and family history where relevant associations exist to produce a more sophisticated decision-making model.

Using the proposed CAMP CR threshold of 10%, the data from both patch testing centers suggest that, for patients allergic to propolis, it is reasonable to consider fragrance and colophony as significant cross-reactors. The CR with fragrance is not totally unexpected because of the presence of known fragrance allergens in propolis, such as cinnamic compounds. The only divergence between the data from the 2 centers concern whether patients allergic to propolis will cross-react with colophony; however, the combined data from both centers suggest that this is a significant CR. Using the proposed CAMP CR threshold, the data from both patch testing centers suggest that, for patients allergic to colophony, it is reasonable to consider fragrance and propolis as significant cross-reactors.

Using the proposed CAMP CR threshold, the data from both patch testing centers suggest that the abovementioned CRs are unidirectional and that, for patients allergic to fragrance, CR to propolis or colophony is infrequent, and these allergens are probably not necessary to avoid when fragrance allergy is present.

Colophony allergy is only found in a small number of fragrance-allergic patients and is clearly not a good indicator for fragrance allergy.

Our study has several limitations. Most of our conclusions regarding which CRs were significant (ie, >10% CR) reached a 95% statistical confidence level. A few CR conclusions did not reach this threshold, and further studies will be needed to confirm our findings. Our patch test database did not allow us to distinguish between CR and co-sensitization, which is especially difficult given the variety of fragrances. However, this distinction is not significant in the context of patient education and counseling because the end question in either situation is the same, which is whether the patient should make the decision to avoid certain compounds because of potential allergic reactions. Second, because of repeat testing on some patients, the number of patch tests performed in reality slightly exceeded the number of patients tested; hence, the denominator used to calculate the percentages of CRs is slightly overestimated. Nevertheless, this does not diminish the significance of these results because the rates of CR would in fact be underreported. Because fragrances tend to peak early and the initial read and final reads for testing center 1 were done at 3 to 4 days and 7 days respectively, later than in some earlier reading schedules, there was concern that our data may overlook fragrance reactions that peak earlier than our first read. However, when we compared the overall fragrance reaction rates at our clinic with the most recent North American Contact Dermatitis Group (NACDG) data,⁹ we found the rates to be fairly similar if not somewhat greater for some fragrances. NACDG reported a reaction rate of 12.1% for fragrance mix 1 and the range of 8.5% to 10.2% from previous years, compared with 12% from our results. For fragrance mix 2, the rate was 5.2%, and the range was 3.6% to 4.7% from previous years, which was lower than the 6.6% from our results. In fact, both testing centers in this study found higher rates of allergy to both fragrance mixes than those seen in the NACDG data. For Balsam of Peru, the NACDG recorded a rate of 7.9% and the range of 7.2% to 11.9% from previous years, compared with 12% from our results. Finally, for colophony, the NACDG rate was 2.3%, comparable with 3.2% from testing center 1 and 0.89% from testing center 2. The reason for the lower rate from testing center 2 may be because testing center 2 excludes questionable reactions in their data. However, overall, our reaction rates are comparable with NACDG data. Finally, although the results from the 2 test centers are very similar, variations that do exist may be influenced by testing methodology, technical preparation, score grading,¹⁰ and demographic differences in patient characteristics or regional levels of exposure to allergens.

On the basis of our results, we recommend that patients allergic to colophony be advised to avoid propolis and fragrance. For patients allergic to propolis, we recommend that patients be advised to avoid colophony and fragrance. However, the evidence does not support advising fragrance-allergic patients to avoid either colophony or propolis. The CAMP cross-reactor groups for propolis and fragrance already follow these recommendations.

However, we recommend that the CAMP database add propolis and fragrance as colophony cross-reactors. Finally, we recommend that further similar studies be done to explore CRs between other common allergens.

REFERENCES

1. Mariano A, Paredes I, Nuti R, et al. Occupational asthma due to colophony in non-industrial environments. *Med Lav* 1993;84:459–462.
2. Scheman A, Jacob S, Zirwas M, et al. Contact allergy: alternatives for the 2007 North American Contact Dermatitis Group (NACDG) standard screening tray. *Dis Mon* 2008;54:12–15.
3. Hamstra AA, Jacob SE. A review of colophonium. *The Dermatologist* 2015;23(8):38–41.
4. Keira T, Sundgren M, Levin JO, et al. Adverse effects of colophony. *Ind Health* 1997;35:1–7.
5. Kuiters GRR, Smitt JHS, Cohen EB, et al. Allergic contact dermatitis in children and young adults. *Arch Dermatology* 1989;125:1531–1533.
6. Rietschel R, Fowler J, Fisher A. *Fisher's contact dermatitis*. Philadelphia, PA: Lippincott Williams & Wilkins; 2001.
7. Walgrave SE, Warshaw EM, Glesne LA. Allergic contact dermatitis from propolis. *Dermatitis* 2005;16(4):209–215.
8. Scheman A, Rakowski EM, Chou V, et al. Balsam of Peru; past and future. *Dermatitis* 2013;24:153–160.
9. Warshaw EM, Maibach HI, Taylor JS, et al. North American Contact Dermatitis Group patch test results: 2011–2012. *Dermatitis* 2015;26(1):49–59.
10. Johansen JD, Aalto-Korte K, Agner T, et al. European Society of Contact Dermatitis guideline for diagnostic patch testing—recommendations on best practice. *Contact Dermatitis* 2015;73:195–221.