

Colophonium and Compositae mix as markers of fragrance allergy: Cross-reactivity between fragrance terpenes, colophonium and Compositae plant extracts

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The aim of this study was to assess the strength of any association between sensitization to 'new' fragrance compounds and sensitization to Compositae, fragrance mix, Myroxylon pereirae resin and colophonium, respectively.

Consecutive eczema patients were tested with a series of essential oils and selected fragrance compounds and another series of oxidized terpenes in connection with European multicentre fragrance projects. Contact allergy to either series was frequently detected, in 5% of 318 and 4.6% of 262 persons tested, and both had a statistically significant association with Compositae, colophonium and fragrance mix sensitization. The individual results indicated that simultaneously occurring positive reactions to essential oils, colophonium and Compositae were based on cross-reactivity rather than concomitant sensitization. Thus, all patients with positive reaction to the rare fragrance sensitizer β -caryophyllene had positive colophonium reactions, and cross-reactivity between essential oils and Compositae was related to the Compositae plant extracts of the Compositae mix and not the pure sesquiterpene lactones of the standard series. The implication is that Compositae mix and colophonium may be markers of fragrance allergy, which is important to know when assessing the relevance of positive reactions to Compositae plant extracts and colophonium.

Key words: β -caryophyllene; colophonium; Compositae mix; Compositae; contact dermatitis; essential oils; fragrance mix; oxidized terpenes; sesquiterpene lactones. © Blackwell Munksgaard, 2005.

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Fragrance allergens are the most frequent sensitizers in cosmetics (1). Plant compounds, especially essential oils, are often important constituents of the fragrance formulations, even though these volatiles may also be added for their allegedly therapeutic properties (1, 2). Recent research has pointed out that oxidized degradation products of some allergenic plant oils and terpenes are stronger sensitizers than the fresh unoxidized substances (3–5). Thus, oxidized R-limonene from citrus fruit peel oil, a widely used fragrance in Europe, has been shown to be an important sensitizer (4).

Compositae plant extracts comprise another frequently used group of ingredients in herbal cosmetics (6). On the basis of reports of sensitization to *Costus absolute*, a Compositae-derived fragrance material, which has now been largely abandoned, Fisher in 1980 suggested sesquiterpene lactones (SLs) as possible 'plant markers' of

perfume allergy (7, 8). The prevalence of Compositae sensitization in patients with fragrance allergy or cosmetic dermatitis is not negligible, and conversely, several studies on Compositae allergy have shown an association between Compositae sensitization and sensitization to fragrance mix (FM) and/or *Myroxylon pereirae* resin (balsam of Peru) and/or colophonium (1, 2, 9–12). However, the relative contribution of cross-reactivity, concomitant sensitization to allergenic cosmetic ingredients or sensitization to ubiquitous fragrance and plant allergens, acquired independently of each other, remains unknown.

At the Department of Dermatology in Odense, Denmark, we have screened for Compositae allergy since 1990 and together with other European clinics participated in a project on fragrance allergy within the European Union's 5th Framework from 1997 to 2003. The latter has implied sequential testing with

selected fragrance series in consecutive patients for longer or shorter periods.

Therefore, the aim of this retrospective study was to assess the strength of any association between sensitization to fragrance materials and Compositae sensitization, as well as sensitization to FM/Myroxylon pereirae resin/colophonium of the standard series.

Materials and Methods

In the first study, consecutive eczema patients were tested with a series of essential oils and selected fragrance compounds from January 1999 to February 2000 (Table 1). The overall results from this part of the European fragrance studies, including details on the fragrance materials used, have been reported previously (13). In the same period, the Compositae mix 6% pet. (CM) as well as the SL mix 0.1% pet. and the SL parthenolide 0.1% pet. were included in our standard series. The CM consists of short ether extracts of 5 European Compositae plants: arnica (*Arnica montana*) 0.5%, German chamomile (*Chamomilla recutita*) 2.5%, yarrow (*Achillea millefolium*) 1.0%, tansy (*Tanacetum vulgare*) 1.0% and feverfew flower extract (*Tanacetum parthenium*) 1.0% (14). The CM was provided by Trolab[®] (Hermal, Reinbek, Germany), whereas parthenolide was provided by Chemotechnique[®] Diagnostics (Malmö, Sweden) and SL mix by Trolab[®]. Prior to testing, the patients' history of fragrance allergy was recorded as certain, probable, questionable or none according to previous reports (15, 16).

Table 1. Essential oils and other fragrance compounds tested in the first part of this study

Fragrance compound	Test concentration (% pet.)
Patchouli oil	10
Dwarf pine needle oil	2
Ylang-ylang oil I	10
Ylang-ylang oil II	10
Sandalwood oil (East India)	2 and 10
Peppermint oil (American)	2
Spearmint oil (American)	2
Lemongrass oil (East India)	2
Cedarwood oil	10
(Moroccan and Chinese 1:1)	
Jasmine absolute	5
Narcissus absolute	2
Limonene	3
α -Damascone and β -damascone	0.2
α -Irene	10
Heliotropin	1 and 5
β -Caryophyllene	5
Hedione	5
α -Terpineol	5

In the second study, consecutive eczema patients were tested with a small series of oxidized terpenes from May 2002 to January 2003 (Table 2). In this period, the SL mix and parthenolide were the only screening allergens for Compositae sensitization.

All fragrance materials were applied to the back for 2 days, using Finn Chambers[®] (Epitest Ltd, Helsinki, Finland) and Scanpor[®] tape (Norgesplaster A/S, Oslo, Norway), and readings were taken on days (D)3 or 4 and 5–7 according to the ICDRG guidelines (17). Fisher's exact test was used to assess associations between prevalences, and the level of significance was chosen at 5%.

Results

Essential oils

A total of 318 patients were tested and 16 (5%) had one or more positive reactions to essential oils (EOS). The 16 persons comprised 13 females and 3 males and their mean age was 45 years. Table 3 shows the distribution of positive reactions to individual EOS.

Among 19 Compositae-sensitive persons tested with the series (59% of all Compositae-sensitive subjects detected in the period), 5 also had allergy to EOS, making the association statistically significant ($P = 0.0013$) (Table 4).

The 5 Compositae- and EOS-sensitive patients, 2 females and 3 males, had a mean age of 47 years.

For comparison, the remaining 14 Compositae-sensitive persons comprised 13 females and 1 male with a mean age of 44 years.

A total of 51 positive reactions from EOS were recorded in the 16 persons, with the majority (31 reactions) occurring in the 5 Compositae-sensitive subjects. Four of the 5 persons with concomitant Compositae and EOS allergy were SL mix-negative (Table 4).

Statistically significant associations were also found between allergy to EOS and FM ($P = 0.0017$) and EOS and colophonium ($P = 0.0010$) (Table 4).

Table 2. Oxidized terpenes tested in the second part of this study

Fragrance compound	Test concentration (% pet.)
Linalool hydroperoxide fraction	0.5
Oxidation mixture of linalool	2.0
Caryophyllene oxide	3.9
Oxidation mixture of β -caryophyllene	3.0
Oxidized β -myrcene	3.0

Table 3. Distribution of reactions to individual essential oils and other fragrance compounds in 16 patients positive to at least one of the compounds

Fragrance compounds	Numbers of positive reactions
Fragrance mix and ylang-ylang II	6 of each
Ylang-ylang I, sandalwood 10% and spearmint	5 of each
Sandalwood 2%, lemongrass, Narcissus absolute and β -caryophyllene	4 of each
Patchouli, cedarwood and limonene	3 of each
Dwarf pine needle and peppermint	2 of each
Jasmine absolute	1

Three of the 16 persons had 1 and another 3 had 2 other contact allergies while the remaining 10 persons had 3 or more (Table 5, Top 4).

Oxidized terpenes

262 persons were tested with the second series and 12 persons (4.6%), 10 females and 2 males, mean age 58.5 years, tested positive to 1 or more of the terpenes (Table 6). Among 22 persons with Compositae allergy tested in this period (76% of all Compositae-sensitive patients detected), 4 were also terpene-sensitive, and the association was statistically significant ($P = 0.01$) (Table 7). The 4 Compositae- and terpene-allergic persons were all females with a mean age of 73 years. In contrast to this, the mean age of the remaining 18 Compositae-sensitive subjects, 14 females and 4 males, was 48 years.

One of the 12 persons had no other contact allergy, another had 1, while the remaining 10 persons had 2 or more (Table 8, Top 4). Again,

a strong statistical association was seen between allergy to terpenes and colophonium ($P < 0.0001$), whereas the association between positive reactions to FM and terpenes was less significant ($P = 0.03$) (Table 7). Inclusion of other fragrance allergens such as citral and Lyrall[®] (hydroxyisohexyl 3-cyclohexene carboxaldehyde), however, made the association stronger. Because the association between allergy to both EOS and oxidized terpenes and colophonium allergy was highly significant, it was considered relevant to look for any specific allergens involved (Table 9).

Few patients tested positive to Myroxylon pereirae resin, and statistical analysis of any association was therefore left out.

Discussion

The prevalence of positive reactions to EOS is remarkably high, but still surpassed by that of Compositae, probably due to the inclusion of CM in the standard series. Even though the majority of positive reactions were seen in 5 patients only, some special patterns emerge: in accordance with the results of the European study, FM and ylang-ylang oil I and II were the top-ranking allergens, but it is surprising that sandalwood oil 10% and 2%, spearmint oil, caryophyllene, limonene and oil of Patchouli, cedarwood and dwarf pine needle elicit that many positive reactions (13). In the European study of 1606 consecutive patients, only 7 reactions were recorded to sandalwood oil 2%, and 4 of these

Table 4. Distribution of positive reactions to Compositae, standard fragrance allergens and colophonium in 16 patients with positive patch test reactions to one or more essential oils

Patient number	Sex/age	Essential oils (nos. pos.)	Compositae mix	SL	Fragrance mix	MPR	Colophonium	History	Comments
1	F/44	1	–	–	–	–	–	Probable	Pos. spearmint
2	F/64	1	–	–	–	–	–	None	Pos. YY II
3	F/52	1	–	–	+++	–	–	Probable	Pos. Narcissus absolute
4	F/44	12	+	–	–	–	++	None	Pos. tea tree Oil 100%
5	F/53	1	–	–	++	–	–	None	Pos. lemongrass
6	F/23	1	–	–	++	–	–	None	Pos. Jasmine absolute
7	F/22	4	0	–	0	–	++	Certain	Pos. sandalwood, cedarwood, caryophyllene
8	F/44	1	0	–	–	–	–	None	Pos. sandalwood 10%
9	F/35	2	–	–	0	–	+	None	Pos. own eau de toilette
10	M/64	12	+++	–	++	–	++	Probable	
11	M/34	1	++	–	0	–	–	None	Pos. Narcissus absolute
12	F/45	1	–	–	–	–	–	Questionable	Pos. spearmint and all toothpaste flavourings
13	F/31	6	–	–	+++	0	++	Probable	
14	F/74	1	–	–	–	–	–	Probable	Pos. lemongrass
15	M/59	5	++	–	+	–	0	Probable	
16	F/36	1	NT	NT	–	–	–	Probable	Pos. Narcissus absolute

SL, sesquiterpene lactone mix; MPR, myroxylon pereirae resin = balsam of Peru; nos. pos., numbers positive; NT, not tested, but positive to individual constituents of CM and SL; Pos., positive reaction to; History, history of fragrance allergy.

Table 5. 'Top 4' distribution of other contact allergies in 16 persons with one or more positive reactions to essential oils

Allergens	Number of positive reactions
Fragrance mix	6
Colophonium, Compositae and nickel sulphate	5 of each
Potassium dichromate and Germall 115	3 of each
Cobalt chloride, Quaternium 15, formaldehyde, Germall II, primin, <i>p</i> - <i>t</i> -butylphenol-formaldehyde resin	2 of each

came from Odense (13). Likewise, 10 positive reactions to β -caryophyllene and cedarwood oil, respectively, were seen in the European study compared with 4 and 3 reactions in our patients (13). The association between Compositae and EOS reactivity was slightly stronger than that between FM and EOS, and the strongest was found between colophonium and EOS.

Patient no. 4 (Table 4) reacted to tea tree oil (TTO) and possibly adhesive plaster and, not surprisingly, she tested positive to both colophonium and common fragrance allergens as ylang-ylang oil I and II and lemongrass oil, but also to more rare sensitizers as, e.g., limonene, cedarwood and dwarf pine needle oils and β -caryophyllene. Cross-reactions between TTO and colophonium have been reported previously (18). TTO of *Melaleuca alternifolia* contains a large number of mono- and sesquiterpenes, including *d*-limonene in a concentration from 0.4 to 3.1% (3). This explains the patient's limonene reaction and intuitively it would appear logical that the patient tested positive to other terpenes derived from woody oleoresins. Thus, β -caryophyllene is one of 2 terpenes comprising the majority of cortical oleoresin in silver fir (*Abies alba* Miller), and it is also detected in EOS of other species from the Pinaceae family (19–21). The patient had a 1+ reaction to CM of unknown relevance, which is most likely a cross-reaction between terpenes in TTO/colophonium and the Compositae plant extracts. This is in accordance with the suggestion of Storrs et al. (22) that cross-reactivity between SLs and distantly related diterpenes such as colophonium

occurs occasionally. Conversely, patient no.10 had strongly positive reactions to CM and FM of (possible) current and old relevance, respectively, as well as a strong reaction to colophonium of unknown relevance. The primary sensitizers were unknown, but the patient tested positive to both common fragrance allergens as FM, ylang-ylang I and II, lemongrass and Narcissus absolute and rarer sensitizers as Patchouli and dwarf pine needle oil, limonene and β -caryophyllene (Table 4). Patient no. 15, a male carpenter, had a relevant CM reaction, a weakly positive FM and a doubtful positive colophonium reaction. Because he reported dermatitis from contact with solvents and TTO-containing products, he was probably concomitantly sensitized to Compositae and TTO, explaining his strongly positive limonene reaction. However, cross-reactivity cannot be ruled out.

The remaining 2 Compositae-sensitive patients were both positive to Narcissus absolute only. Patient no. 11 had a 2+ reaction to CM of unknown relevance, a doubtful positive FM reaction and 1+ Narcissus absolute reaction, both of unknown relevance as his history of fragrance sensitivity was negative. Narcissus absolute contains several allergenic terpenes and other components, such as caryophyllene, cinnamic alcohol and coumarin (13). β -Caryophyllene is found in a multitude of EOS from different plant families, including some species of the Compositae genera *Achillea*, *Artemisia*, *Helichrysum* and *Eupatorium* (23–26). Cross-reactions between components of CM and Narcissus absolute is therefore a possibility. Patient no. 16 had a severe Compositae allergy and was the only patient of the 5 Compositae-sensitive patients who had positive reactions to ingredients of the SL mix. She had no fragrance reactions other than Narcissus absolute, and again cross-reactivity seems likely.

Altogether, the association between CM and specific EOS was difficult to assess because 2 of the 5 Compositae-sensitive patients were also colophonium-sensitive, but in the 3 persons without colophonium allergy, including one with a 1+ FM reaction, the pattern was more floral with reactions to Patchouli, ylang-ylang I and

Table 6. Distribution of reactions to individual oxidized terpenes in 12 persons positive to at least one of the compounds

Compound	Numbers positive	Numbers doubtful positive	Numbers negative
Linalool hydroperoxide fraction	5	5	2
Oxidation mixture of linalool	7	3	2
Caryophyllene oxide	1	4	7
Oxidation mixture of β -caryophyllene	3	2	7
Oxidized β -myrcene	0	1	11

Table 7. Distribution of positive reactions to Compositae, standard fragrance allergens and colophonium in 12 persons with positive patch test reactions to one or more oxidized terpenes

Patient number	Sex/age	Compositae mix	Sesquiterpene lactone mix	Fragrance mix	Myroxylon pereirae resin ¹	Colophonium	Comments
17	F/79	NT	+	0	–	+	Formerly positive fragrance reactions
18	F/67	++ (1994)	–	+++	++	+	
19	M/52	–	–	0	–	++	
20	F/47	NT	–	0	–	–	Exacerbation from spruce and tea tree oil
21	F/59	NT	–	++	–	+++	
22	F/64	++	–	+	–	0	
23	F/77	NT	–	0	–	–	Dermatitis from conifers
24	F/82	+++	++	++	+	–	
25	M/47	NT	0	–	–	–	
26	F/55	NT	–	0	–	–	Exacerbation of hand eczema when exposed to spruce
27	F/30	NT	–	0	–	–	
28	F/43	NT	–	–	–	++	

NT, not tested.

¹Balsam of Peru.

II, spearmint, limonene and Narcissus absolute. This seems to be in accordance with a previous report on possible cross-reactions between the monoterpene carvone and Compositae (27).

The 5 patients with concomitant Compositae and EOS allergy do not differ from the other 14 Compositae-sensitive patients tested in the same period as regards mean age and Compositae sensitization pattern: 11 of the 14 patients were tested with both CM and SL mix, and while all were positive to CM, only 3 were positive to SL mix. Inclusion in the standard series of the former will probably not only increase the number of Compositae-sensitive subjects detected, but also increase the risk of sensitization and false-positive reactions (28, 29). Indeed, 3 of the 11 positive CM reactions were 1+ reactions occurring on day 7. However, it is possible that concomitant testing with CM and EOS facilitates or enhances

their reactivity reciprocally. At any rate, if the association between positive reactions to EOS and Compositae is due to cross-reactivity, the results suggest that SLs are not the important allergens here, because 4 of the 5 patients were negative to both SL mix and parthenolide of the standard series, but rather other ingredients of the plant extracts. This is in accordance with the fact that EOS obtained by steam distillation contain fewer SLs than short ether plant extracts (personal communication Lars P. Christensen). Thus, a positive CM reaction may also be a marker of fragrance sensitivity rather than Compositae allergy as suggested before (10).

The prevalence of positive reactions to oxidized terpenes was also high and actually more than twice that observed in the European study of 1511 consecutively tested patients (5). Even though CM was not included in the standard series in this period, a high number of Compositae-sensitive persons were detected, and 22, which was 76% of all Compositae-sensitive subjects tested, were included in this study. The 4 females with concomitant allergy to Compositae and oxidized terpenes all had multiple contact allergies, and they were considerably older than the other 18 Compositae-sensitive patients. Three of the 4 women tested positive to CM (the fourth was not tested with the mix); 3 of the Compositae-sensitive were positive to oxidized linalool, but they were concomitantly positive to FM, Myroxylon pereirae resin or colophonium. Altogether, the association with Compositae was less convincing in terms of statistical significance and possible cross-reactivity patterns than with EOS.

Table 8. 'Top 4' distribution of other contact allergies in 12 persons with one or more positive reactions to oxidized terpenes

Allergens	Number of positive reactions
Colophonium, Euxyl K400 and MDBGN	5 of each
Compositae and fragrance mix	4 of each
Hydrocortison-17-butyrate	3 of each
MPR, citral, neomycin sulphate and caine mix, Kathon CG, budesonide, tixocortol pivalate, <i>p</i> - <i>t</i> -butylcatechol, epoxy resin, potassium dichromate, nickel sulphate, Germall II and carba mix	2 of each

MDBGN, methylidibromoglutaronitrile; MPR, Myroxylon pereirae resin.

Table 9. Positive reactions to essential oils, fragrance chemicals or oxidized terpenes in patients with concomitant positive colophonium reactions

Patient number	Positive reactions to
4	Patchouli, dwarf pine needle, ylang-ylang I and II, sandalwood 10% and 2%, peppermint, spearmint, lemongrass, cedarwood, limonene and β -caryophyllene
7	sandalwood 10% and 2%, cedarwood and β -caryophyllene
9	ylang-ylang I and II
10	Patchouli, dwarf pine needle, ylang-ylang I and II, sandalwood 10% and 2%, peppermint, spearmint, lemongrass, Narcissus absolute, limonene and β -caryophyllene
13	Ylang-ylang I and II, sandalwood 10% and 2%, cedarwood and β -caryophyllene
17	Linalool hydroperoxide, oxidation mixture of linalool (caryophyllene oxide and oxidation mixture of β -caryophyllene doubtful positive D3)
18	Caryophyllene oxide and oxidation mixture of β -caryophyllene
19	Linalool hydroperoxide
21	Oxidation mixture of β -caryophyllene (caryophyllene oxide doubtful positive D3)
28	Oxidation mixture of β -caryophyllene

The ranking of positive reactions to the 5 terpenes was similar to the overall ranking of the participating European clinics, but our patients had slightly more positive reactions to oxidized caryophyllene mixture and caryophyllene oxide (4 of a total of 10). As mentioned above, β -caryophyllene is found in EOS of conifers (19–21). Three of the 12 terpene-sensitive patients had exacerbation of their dermatitis from contact with spruce/conifers, and 2 of them were colophonium-sensitive (Table 7). Furthermore, among 5 colophonium-sensitive subjects, 3 were positive to oxidized caryophyllene and caryophyllene oxide (patients nos. 18, 21 and 28, Table 9). The fourth patient had doubtful positive reactions to both caryophyllene materials on day 3 (patient no. 17, Table 9). Patient no. 28 is especially interesting as regards cross-reactivity: she was sensitized to a colophonium-containing adhesive plaster (Tensoplast[®], BSN medical Ltd, Brierfield, England), and her only positive patch test reactions were Tensoplast[®], colophonium and oxidized caryophyllene mixture. This result is in accordance with most of the observations in the other colophonium- and terpene-sensitive patients. Matura et al. (5) state that caryophyllene oxide is a weak sensitizer and that the pure compound is nonsensitizing. Nevertheless, Frosch et al. (13) reported allergy to (non-oxidized?) β -caryophyllene, and in our EOS-sensitive patients, all β -caryophyllene positive were also colophonium positive (Table 9). The same applies to all patients with positive reactions to dwarf pine needle oil, sandalwood oil 2% and cedarwood oil. Furthermore, the majority of patients with positive reactions to Patchouli oil, ylang-ylang oil I and II, sandalwood oil 10% and limonene were colophonium-

sensitive. β -Caryophyllene is also found in ylang-ylang oil but is obviously not the most important allergen (13).

Altogether, positive colophonium reactions were associated with positive reactions to EOS of woody origin (Table 9).

Matura et al. (5) also reported statistically significant correlations between positive reactions to oxidized terpenes and colophonium. The most important allergens in colophonium are oxidized derivatives of the diterpenoid abietic acid (30). β -Caryophyllene, detected in EOS of both conifers and Compositae plants, could be another important allergen that through false or true cross-reactions may link colophonium, which is not a fragrance allergen per se, to fragrance sensitivity, and it also may be one of the links between sensitivity to CM, colophonium and terpenes of EOS.

Conclusions

Despite the shortcomings of this study such as the retrospective design, the relatively small number of patients, the multiple contact allergies in most of the patients, which increases the risk of finding coincidental associations, some conclusions may be drawn: contact allergy to EOS and selected oxidized and non-oxidized fragrance terpenes is frequently occurring, and both are significantly associated with Compositae allergy.

On the basis of the individual results from this study, the statistically significant association between positive reactions to EOS and positive reactions to colophonium and Compositae seems to originate from true or false cross-reactivity rather than concomitant sensitization to common allergens. Thus, colophonium-sensitive patients

were often allergic to EOS of woody origin as well as to the sesquiterpene β -caryophyllene, which is found in many EOS, including those from species of the Pinaceae and Compositae plant families. Cross-reactivity between EOS and Compositae was related to the Compositae plant extracts rather than pure SLs, which may be due to the more complex chemical composition of the plant ether extracts. A specific association between individual EOS and CM was difficult to assess because of concomitant colophonium allergy in 2 of 5 patients, but 2 CM-positive patients without fragrance or colophonium allergy had reactions to Narcissus absolute only.

CM may thus be a marker of fragrance allergy, and this should be borne in mind when assessing the relevance of positive reactions to Compositae plant extracts.

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