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CLINICAL REPORT

Patch Testing with Main Sensitizers Does Not Detect All Cases of Contact Allergy to Oxidized Lavender Oil

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Lavender oil is an essential oil obtained from lavender (*Lavendula angustifolia*). The main components linalool and linalyl acetate have been shown to autoxidize in contact with oxygen in the air, forming sensitizing hydroperoxides. Patients with suspected allergic contact dermatitis were consecutively patch tested with oxidized lavender oil 6% pet., oxidized linalyl acetate 6% pet., and oxidized linalool 6% pet. to investigate the frequency of contact allergy to oxidized lavender oil, and the pattern of concomitant reactions to oxidized linalool and oxidized linalyl acetate. Positive reactions to oxidized lavender oil were found in 2.8% of the patients. Among those, 56% reacted to oxidized linalool and/or oxidized linalyl acetate, while 52% reacted to the fragrance markers of the baseline series. Oxidized lavender oil showed among the highest frequencies of contact allergy to studied essential oils. A well-standardized preparation of oxidized lavender oil could be a useful tool for diagnosis of contact allergy to fragrances. *Key words: allergic contact dermatitis; CAS 8000-28-0; essential oils; fragrances; Lavendula angustifolia; patch test; terpenes.*

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Lavender oil is the essential oil obtained from steam distillation of freshly cut flowering tops of lavender (*Lavendula angustifolia*). Like other essential oils, lavender oil has been used for centuries as a fragrance material and in traditional herbal medicine. Interest in essential oils is high, and studies from diverse fields on the properties of lavender oil are numerous (1–3). In these studies, formulations containing up to 30% of lavender oil are applied topically. The oil is also frequently used in aromatherapy, mainly for its anti-stress properties (4, 5). Lavender oil consists mainly of the terpenes linalool, linalyl acetate and caryophyllene in concentrations of approximately 50%, 40% and 2–5%, respectively (6, 7) (Fig. S1[1]) These terpenes autoxidize in contact with oxygen in the air (8–10). In this process, sensitizing hydroperoxides can be formed, and have been detected as autoxidation products of linalool and linalyl acetate (8, 9)[2].

Investigation of lavender oil with respect to contact allergy is important, since it is a commonly used essential oil and exposure to its components is frequent from multiple sources. The aim of the present study was therefore to investigate the frequency of contact allergy to oxidized lavender oil among patients with dermatitis, and to investigate the pattern of concomitant reactions to oxidized linalool and oxidized linalyl acetate, as well as to the fragrance markers of the baseline series.

METHODS

Chemicals

Linalyl acetate and linalool were purchased from Sigma Aldrich (Schnelldorf, Germany) and distilled under reduced pressure prior to the autoxidation experiments (>99%). Lavender oil 40/42 was obtained from Robert Bontoux (Clos d'Aguzon, France). White, non-stabilized petrolatum was purchased from VWR (Radnor, Pennsylvania, USA). Linalyl acetate hydroperoxides and linalool hydroperoxides were synthesized as described previously (8, 9).

Air exposure procedure

Samples of distilled linalyl acetate, distilled linalool and freshly obtained lavender oil were air-exposed as described previously (9). Lavender oil and linalyl acetate were air-exposed for 45 weeks as described previously (8). In the present experiments, linalool was air-exposed for 25 weeks, after which the concentration of linalool hydroperoxides corresponded to earlier used oxidation mixtures of linalool (8, 12).

Instrumentation and mode of analysis (see Appendix S1[1])

Patch test materials

Oxidized lavender oil was tested at 6.0% in petrolatum (pet.). The test concentration was chosen based on our previous concentration study of oxidized linalool (13) and the sensitization potency of oxidized lavender oil (11). Oxidized linalyl acetate

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[2]In studies of autoxidation of lavender oil, we found that the natural essential oil followed the same pattern of autoxidation as the synthetically produced terpenes linalool and linalyl acetate (8–11). We also found the non-oxidized oil to be a weak sensitizer, whereas the oil and its main components linalool and linalyl acetate are important sensitizers in oxidized form.

and oxidized linalool were tested at 6.0% pet. as previously described (12, 14). All patch test preparations were stored at –20°C until use. The patch test preparations were used for a maximum of 6 months. During the period of usage, patch test preparations were stored in the refrigerator.

Patients and patch testing

Patients tested with the Swedish baseline series at the Department of Dermatology, Sahlgrenska University Hospital during the period 2008 to 2010 were included in the study. A total of 1,693 patients was tested (517 males and 1,176 females). The mean age was 45.7 years with a standard deviation (SD) of 17.7 years.

Based on previous experience (15), non-stabilized petrolatum was used for all patch test preparations. Patch test materials were stored at –20°C until use. Small Finn chambers®, (8 mm, Epitest Ltd Oy, Tuusula, Finland) on Scanpor® tape (Norgesplaster A/S, Vennesla, Norway) were used for the study. Patches were applied to the upper back for 48 h. Readings were performed according to the International Contact Dermatitis Research Group recommendation (16) on days 3–4 and 7. Patch testing was performed at the Department of Dermatology, Sahlgrenska University Hospital, Gothenburg, Sweden.

Statistical analysis

Analyses were performed using R version 3.0.3 (The R foundation for Statistical Computing, Vienna, Austria). An exact McNemar test was used to test for differences in positive reactions between the test materials. All tests were 2-sided and $p < 0.05$ was considered statistically significant.

RESULTS

Analysis of patch test materials

Analysis of the oxidation mixtures was performed prior to preparation of the patch test materials. Freshly prepared patch test preparations were analysed using solid phase extraction (SPE) followed by high performance liquid chromatography (HPLC) (Appendix S1[1]). The composition of the 25 or 45 weeks oxidized samples of linalyl acetate, linalool and lavender oil are described below[3]. The results of the degradation study were in accordance with previous experience (12).

Patch testing

The frequency of positive patch test reactions to oxidized lavender oil was 2.8% during the test period, and the distribution of strength of positive patch test reactions is shown in Table I. Of the 47 cases with positive patch test reactions to oxidized lavender oil, 9 were men and 38 were women. The frequencies of positive reactions were 1.7% among men and 3.2% among women. The rate of doubtful reactions was 3.2%, which was similar to that of positive reactions.

During the study period, patients were also patch tested with oxidized linalool 6.0% pet. and oxidized linalyl acetate 6.0% pet. with an overall frequency of positive reactions of 3.3% and 2.2%, respectively (Table I) (12, 14). The frequency of positive reactions to oxidized linalool was found to be significantly higher than that of positive reactions to oxidized linalyl acetate ($p = 0.004$). No significant difference was seen between frequencies of positive reactions to oxidized lavender oil and to oxidized linalool or between frequencies of positive reactions to oxidized lavender oil and to oxidized linalyl acetate.

The pattern of concomitant reactions to oxidized lavender oil, oxidized linalool and oxidized linalyl acetate is shown in Fig. 1. In all, 93 of 1,693 patients reacted to any of the tested materials. Six patients with reactions to one of the study materials were not tested with all 3 preparations and were removed from the analysis of concomitant reactions. Of the patients showing a positive reaction to oxidized lavender oil, 44% (19 of 44) showed no concomitant reactions to either of the 2 main components of the essential oil, while 41% (18 of 44) also reacted to oxidized linalool. Furthermore, 34% (15 of 44) reacted to both oxidized lavender oil and oxidized linalyl acetate, while 20% (9 of 44) reacted to

[3]The 45-weeks sample of oxidized linalyl acetate contained 24.2% linalyl acetate and 35.3% linalyl acetate hydroperoxide. In the patch test preparation of oxidized linalyl acetate, with a total concentration of 6.0% pet., the concentration of linalyl acetate was found to be 1% and that of linalyl acetate hydroperoxides was found to be 2%. After 12 months, the degradation of linalyl acetate hydroperoxides in the patch test preparation was 5%, to a level of 1.9%. The 25-weeks sample of oxidized linalool contained 61% linalool and 14.6% linalool hydroperoxides. In the patch test preparation of oxidized linalool (6.0% pet.), the concentration of linalool was found to be 3.6% and that of linalool hydroperoxides was 1%. After 12 months, the degradation of linalool hydroperoxides in the patch test preparation was 9%, to a level of 0.91%. The 45-weeks sample of oxidized lavender oil contained 10.2% linalyl acetate, 5.7% linalool, 11.2% linalyl acetate hydroperoxide and 5.7% linalool hydroperoxide. In the patch test preparations of oxidized lavender oil (6.0% pet) 0.17% linalool, 0.4% linalyl acetate, 0.31% linalool hydroperoxides and 0.63% linalyl acetate hydroperoxides were detected.

Table I. *Frequencies of positive and doubtful patch test reactions and distribution of strength of positive reactions to oxidized lavender oil, oxidized linalyl acetate and oxidized linalool, all 6.0% pet*

Test material	Patients tested	Positive reactions *n* (%)	CI positive reactions *n* (%)	Doubtful reactions *n* (%)	Positive reactions + *n* (%)	Positive reactions ++/+++ *n* (%)
Oxidized lavender oil	1,693	47 (2.8)	2.0–3.7	55 (3.2)	30 (64)	17 (36)
Oxidized linalyl acetate[a]	1,717	37 (2.2)	1.5–3.0	28 (1.6)	28 (76)	9 (24)
Oxidized linalool[a]	1,674	56 (3.3)	2.5–4.3	61 (3.6)	38 (68)	18 (32)

[a]Data previously published (10). CI: confidence interval.

all 3 patch test materials. When studying only patients with strong reactions (++/+++) to one or more of the test materials, a higher proportion of the patients showed concomitant reactions to the tested patch test materials in the study (Fig. 1B).

Concomitant reactions to the fragrance markers of the baseline series are shown in Table II. We observed that 52% (23 of 44, with 3 patients not tested with the other fragrance markers) of the patients with positive reactions to oxidized lavender oil also showed reactions to at least one fragrance marker of the baseline series. High rates of concomitant reactions to lavender oil and *Myroxylon pereirae* and Fragrance Mix (FM) I, respectively, were observed. It should be noted that, among the patients with positive patch test reactions to oxidized lavender oil, 20% of patients (9 cases) reacted only to oxidized lavender oil, stressing the importance of testing with this preparation.

DISCUSSION

The present study indicates that oxidized lavender oil is a common cause of contact allergy, with a frequency of positive patch test reactions of 2.8% among the tested patients. This is in accordance with experimental data on the sensitization capacity of oxidized lavender oil, where pure lavender oil was shown to be a weak sensitizer, whereas the oxidized sample was classified as a moderate sensitizer in the local lymph node assay (11).

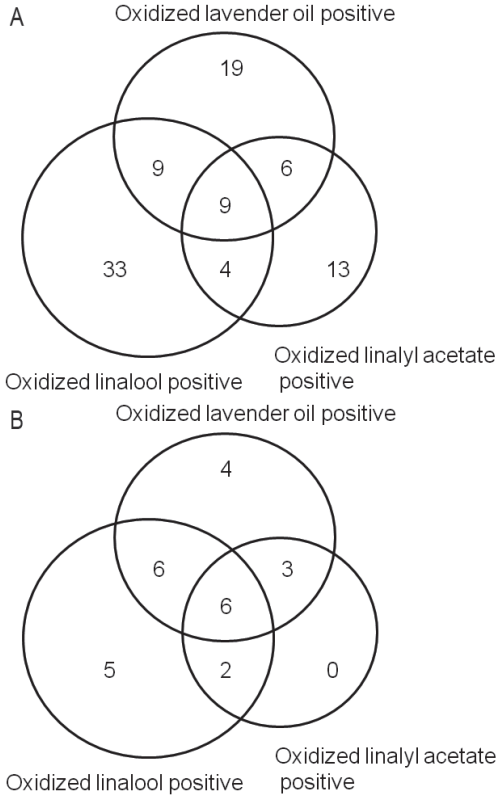

Fig. 1. Venn diagrams showing the pattern of concomitant reactions to oxidized linalyl acetate, oxidized linalool and oxidized lavender oil in the 93 patients with positive reactions to (A) at least 1 of the test substances and (B) in the 26 patients with ++/+++ reactions to at least 1 of the study materials. Six patients with reactions to one of the study materials were not tested with all 3 preparations and were removed from the analysis.

Table II. *Concomitant reactions to the fragrance markers of the baseline series among patients with positive patch test reactions to oxidized lavender oil 6.0% pet. (*n = *44[a])*

Concomitant reactions to:	*n* (%)
Fragrance mix I	16 (34)
Fragrance mix II	7 (15)
Myroxylon pereirae	14 (30)
HICC	1 (2.1)
Colophonium	6 (13)
≥1 fragrance marker or Colophonium	23 (52)

[a]Three of the 47 patients with positive reactions to oxidized lavender oil were not tested with the fragrance markers of the baseline series and were excluded from the analysis.
HICC: hydroxyisohexyl cyclohexene-3-carboxaldehyde.

As the frequency of doubtful reactions is similar to the frequency of positive reactions, the risk of false-positive reactions must be considered. However, more than 97% of the tested patients did not show positive reactions, and among reacting patients the sex distribution is clearly shifted towards women, contrary to false-positive reactions, which would have been found in equal distribution between men and women. Furthermore, among the reacting patients, many also reacted to other fragrance markers, a well-known phenomenon in fragrance contact allergy (12, 17, 18). The frequency of doubtful reactions is also similar to frequencies of doubtful reactions to oxidized linalool in a previous study (13). There, a large proportion of patients with doubtful reactions showed positive reactions to the next higher test concentration.

Patch testing with the oxidation mixtures of the main components (Fig. S1[1]) detected only 56% of the cases of contact allergy to oxidized lavender oil (Fig. 1), thus patch testing with oxidized lavender oil can be important. The same pattern has previously been observed for lemongrass oil, clove oil and ylang-ylang oil, where 48–72% of patients with positive reactions to the essential oil reacted only to the essential oil and not to the corresponding main component (19). One explanation may lie in the observation that mixtures of fragrance sensitizers display an increased potency, both in sensitization and in elicitation of a sensitizer (20). Studies have shown that the innate immune system is also activated in development and elicitation of contact allergy and it is thought that the activation of the innate immune system can be performed by other compounds than the sensitizer in question, such as irritants or other sensitizers (21). A European multicentre study has previously shown that patch testing with the oxidation mixture of *R*-limonene detected more cases of contact allergy than testing with the hydroperoxide fraction (22). Thus, a mixture of sensitizers could induce a

stronger inflammatory response than a single sensitizer. Another aspect that may contribute to the difference in results in testing with oxidation mixtures of essential oils and oxidation mixtures of the individual components lies in that essential oils are complex mixtures in which new sensitizing compounds could form over time in chemical reactions between the components of the mixture. Thus, well standardized preparations of oxidized essential oils could be useful additions to the existing toolbox for diagnosis of contact allergy to fragrances and to essential oils.

Few studies of patch testing with essential oils are reported in literature (19, 23, 24) and most have been performed with essential oils of unknown purity, where the oils have not been intentionally oxidized nor analysed for oxidation products. In European studies, investigating 12 and 6 essential oils, respectively, 0.4–2.6% of the patients showed positive reactions, with ylang-ylang (10% pet.) as the main cause of positive reactions (19, 23). In these studies, 54% of patients with positive reactions to at least one essential oil showed positive reactions to FM I (23) and, in the other study, 64% of patients with positive reactions to at least one essential oil showed positive reactions to FM I or FM II (19). This is in accordance with the results of the present study (Table II). As the fragrance chemicals present in FM I and FM II do not completely cover the chemical composition of the studied essential oils, these results are to be expected. For lavender oil, even fewer studies have been performed. Two studies report frequencies of 0.5% and 3.7%, respectively, of positive reactions to lavender oil of unknown purity (25, 26). The studies all add evidence that essential oils are not uncommon causes of contact allergy. Of the studied essential oils, oxidized lavender oil shows among the highest frequencies of positive patch test reactions in the tested patients.

The relevance of the positive reactions was not assessed specifically in this study; however, exposure assessments have been made elsewhere, calculating the highest maximum daily exposure of linalool and linalyl acetate. Here, linalool and linalyl acetate yielded the highest and similar dermal exposures among the compounds studied (27). In multicentre studies, we demonstrated oxidized linalool to be a common cause of contact allergy (12). A high proportion of the positive reactions were judged to be clinically relevant, by studying product labels. Exposures from lavender oil and handling of lavender flowers were also implicated. Chemical analysis of the patients' products was not performed. However, linalool hydroperoxides have been detected in consumer products using mass spectrometry (28), at a level 5 times below the reaction limit to linalool hydroperoxides in the repeated open application test (29), thus indicating that the reactions could be clinically relevant.

Detailed chemical analysis using sensitive and selective methods is important in patch testing with terpenes susceptible to autoxidation. The rates of sensitization to lavender oil in a Japanese study (26) showed a marked increase in the later part of the study, from 1.1% to 13.9%, 8 years later. The authors do not declare how the patch test materials were handled or for how long the same batch of essential oil was used. The results could thus indicate an oxidation of the patch test material used. In an Australian study of contact allergy to tea tree oil (10% pet.), the essential oil used was intentionally oxidized for a short time. In the study, 1.8% of patients showed positive patch test reactions to oxidized tea tree oil (24). Here, the oxidized oil was analysed using iodine titration for the peroxide value. This technique will give only a rough estimation of the degree of oxidation, since only peroxides and hydroperoxides contribute to the peroxide value. For example, the main sensitizers produced in oxidation of α-terpinene, 1 of the main components of tea tree oil, are epoxides, which do not contribute to the peroxide value (30). Thus, adequate chemical analysis should be performed in order to be able to perform reproducible patch testing with essential oils. There have been questions regarding when, during the process of storage and handling of essential oils, hydroperoxides would be formed. In recent investigations of petitgrain and sweet orange essential oils, hydroperoxides of limonene were detected in sweet orange oil at the opening of the bottle straight from the producer, and hydroperoxides of linalool and linalyl acetate were detected in petitgrain oil after 25 days of storage at room temperature (31, 32). Thus, the claims that naturally derived oils would form smaller amounts of sensitizers on autoxidation than industrially produced fragrances are misleading. In patch testing with essential oils and natural extracts, it is of great importance to investigate the chemical composition of the material and to consider degradation of the test material over time.

Lavender oil has been associated with allergic contact dermatitis of the hands in masseurs and beauticians (33–35). Airborne contact dermatitis caused by lavender oil used in aromatherapy has also been reported (36). In these cases, patch testing was performed using not intentionally oxidized lavender oils, sometimes the essential oils used by the patients at the workplace. Although cases were detected using lavender oil of unknown oxidation state, it is likely that cases of contact allergy to the hydroperoxides of linalool and linalyl acetate are largely missed when patch testing with not intentionally oxidized lavender oil, due to low concentrations of sensitizers in the test material.

Lavender oil is also used in topical drugs, such as ketoprofen ointments. As these ointments are applied frequently for medicinal purposes, the treatment can give rise to a high level of exposure to lavender oil. In

addition, photoallergic contact dermatitis to lavender oil in topical ketoprofen preparations has been reported (37). Also, the interest in essential oils, such as lavender oil, in alternative medicine is increasing (2, 3, 5) and several studies show that exposure to botanically derived products and natural drugs, based on plant extracts and essential oils can be causes of allergic contact dermatitis (38–40). Thus, allergic contact dermatitis to essential oils mirrors the broad spectrum of use of these plant extracts, and exposures beyond aromatherapy and fragranced cosmetic products are of importance.

Conclusion

Essential oils have previously been shown to be not uncommon causes of contact allergy, and the present study shows oxidized lavender oil to cause among the highest frequencies of positive patch test reactions to studied essential oils. Further studies of contact allergy to essential oils are needed, taking into account the importance of autoxidation of the essential oils. Moreover, further development of analytical methods for the detection of oxidation products of fragrance compounds in cosmetic products is necessary.

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