

# Allergenic sesquiterpene lactones from cushion bush (*Leucophyta brownii* Cass.): new and old sensitizers in a shrub-turned-a-pot plant

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## Summary

**Background.** The Australian cushion bush (*Leucophyta brownii*) of the Compositae family of plants has become a popular pot and container plant. The plant produces the sesquiterpene lactone allergen calocephalin.

**Objectives.** To assess the sensitizing potential of sesquiterpene lactones from cushion bush.

**Patients/Materials/Methods.** Eleven Compositae-sensitive patients were patch tested with seven sesquiterpene lactones isolated from cushion bush.

**Results.** Six of seven sesquiterpene lactones elicited positive reactions in 4 of 11 patients.

**Conclusions.** The well-known sesquiterpene lactone pseudoivalin and its derivative pseudoivalin acetate, as well as calocephalin and tomentosin, were confirmed to be sensitizers, whereas leucophytalin A and 4 $\alpha$ -hydroxy-5 $\alpha$ H,10 $\alpha$ H-1,11(13)-guaidien-8 $\beta$ ,12-olide were shown to be allergenic for the first time. The patch test reaction patterns seem to follow the chemical patterns, which may eventually make it possible to trace primary sensitizers and advise patients more precisely.

**Key words:** Asteraceae; calocephalin; Compositae; cushion bush: *Leucophyta brownii*; leucophytalin A; pseudoivalin; tomentosin.

The endemic Australian cushion bush (*Leucophyta brownii* Cass., previously known as *Calocephalus brownii* F. Muell) belongs to the Compositae (= Asteraceae) family of plants. It was mentioned in a Danish gardener magazine as early as 1917, but it is only more recently that the shrub has become a popular pot and outdoor container plant in some Nordic countries (1) (Fig. 1).

In an Australian chemical study from the 1960s, Batterham et al. isolated guaianolide sesquiterpene

lactones from the leaf and stem wax of *C. brownii*. Two of these, pseudoivalin and pseudoivalin acetate, had been detected in *Iva microcephala* Nutt. previously, whereas a new, hitherto unknown, sesquiterpene lactone was named calocephalin by the authors (2). The structure of calocephalin was deduced from spectroscopic evidence (2). A renewed interest in calocephalin and related sesquiterpene lactones of cushion bush arose when a case of occupational sensitization to the plant and calocephalin in a Swedish gardener was published in 2004, followed by a clinical study in Swedish and Danish Compositae-sensitive patients, which showed a prevalence of calocephalin patch test positivity of up to 28% in aimed patch testing (1, 3).

Recently, Hyldgaard et al. published a detailed chemical investigation of the resinous exudate of cushion bush,

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**Fig. 1.** Cushion bush with silvery grey branchlets and yellow globular flower heads against a background of dark green leaves of another plant in an outdoor container.

and they detected two new 8,12-guaianolides, named leucophytalin A and B, one new 1,10-seco-eudesmane, named leucophytalin C, six known but rare 8,12-guaianolides, and the xanthanolide tomentosin (4). Furthermore, nuclear magnetic resonance (NMR) and X-ray crystallographic analysis of calocephalin revealed an epoxide group at C-1,2 and an acetoxy group at C-4 (Fig. 2), so the authors revised the structure of calocephalin as compared with the structure suggested by Batterham et al. (1, 2). As calocephalin, which belongs to the rarely occurring guaian-8,12-olide structural family, seems to be a potent contact allergen, and as pseudoivalin, pseudoivalin acetate and tomentosin have been detected in apparently allergenic plants, it was considered relevant to assess the sensitizing potential of selected sesquiterpene lactones, both common and rare, of cushion bush.

## Patients and Methods

Eleven patients, who had shown positive patch test reactions to Compositae in previous patch test sessions at our department, were recalled and patch tested with seven sesquiterpene lactones from cushion bush (Fig. 2). Fifteen microlitres of each allergen, 0.1% in eth., was placed in 8-mm Finn Chambers® on Scanpor® tape (SmartPractice, Phoenix, AZ, USA) and applied to the upper back for 2 days. Readings were performed on day (D) 3 according to ICDRG criteria (5). The sesquiterpene lactones used for patch testing were all isolated from a dichloromethane

extract of cushion bush in a purity of >98% (determined by NMR spectroscopy and high-performance liquid chromatography coupled with a diode array detector), as previously described (4). The study was approved by the local ethics committee (project ID: S-20150064).

## Results

Altogether, six of the seven sesquiterpene lactones gave positive patch test reactions in 4 patients: pseudoivalin and 4 $\alpha$ -hydroxy-5 $\alpha$ H,10 $\alpha$ H-1,11(13)-guaidien-8 $\beta$ ,12-olide elicited positive reactions most frequently (n = 4 each), followed by pseudoivalin acetate and leucophytalin A (n = 3 each), tomentosin (n = 2), and calocephalin (n = 1) (Table 1). Patient no. 3 presented a photograph of two crescendo (as compared with a photograph from D3) patch test reactions on D7, but, as the reactions were not assessed clinically, they were not recorded as positive reactions. There were no positive reactions in 9 controls, but one of the controls with a contact allergy to isocyanates had transient doubtful reactions to calocephalin and pseudoivalin acetate on D3.

The patients were broadly sensitized, with positive reactions also to the sesquiterpene lactone mix 0.1% pet., Compositae mix 6% and/or 5% pet., and parthenolide 0.1% pet., as well as most of the constituents of the two mixes (Table 1). Only 4 patients had been tested with calocephalin previously in 2004–2005: patients nos. 2, 4 and 10 had a ++ reaction at the time, considered to be of unknown relevance, whereas patient no. 8 had a doubtful follicular reaction, also of unknown relevance.

## Discussion

Cushion bush has not been reported as a cause of allergic plant dermatitis in Australian studies (6–8). However, Batterham et al. noticed ‘an interesting relationship’ between the sesquiterpene lactones of cushion bush and those of *I. microcephala* Nutt. (2). Species of the genus *Iva* – known by the colloquial name marsh elders – have been suspected sensitizers since the 1930s, notably *Iva angustifolia*, *Iva ciliata*, *Iva xanthiifolia*, and *I. microcephala* (9–11). *I. microcephala*, the piedmont marsh elder, was first reported as a sensitizer in 1960 by Williams et al.: a 37-year-old oil field worker with a history of recurrent, generalized dermatitis exacerbated in summer for 15 years was referred for further examination. After extensive patch testing with negative results, the patient mentioned a weed that seemed to make his hay fever worse, and patch testing with this weed elicited a bullous reaction within 24 h, even though the patch with the weed had to be removed after 6 h because of intense

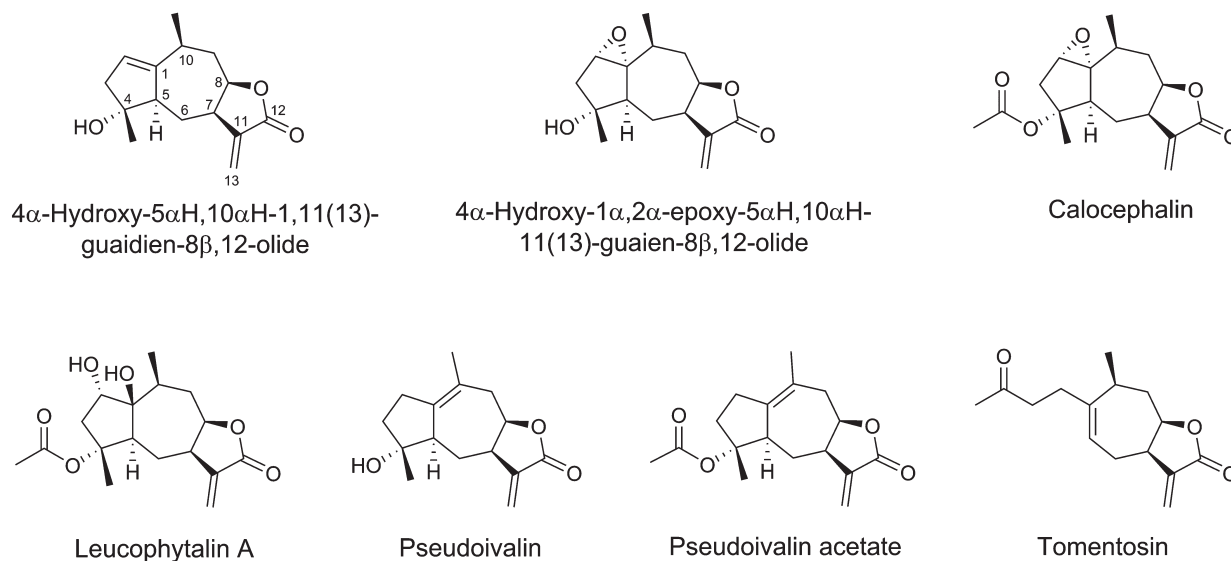


**Fig. 2.** Structures of sesquiterpene lactones isolated from cushion bush (*Leucophyta brownii*) and used for patch testing in the present investigation.

itching. The weed was identified as *I. microcephala* Nutt. The patient had a negative reaction to a commercial 'Marsh Elder' test kit, suggesting that he was sensitized to this species only. No controls were tested (12). Five years later, Herz et al. reported the detection of two new sesquiterpene lactones from *I. microcephala*: pseudoivalin and its 11,13-dihydro derivative (13). Mitchell and Dupuis, in their review of allergenic Compositae plants from 1971, stated that pseudoivalin in *I. microcephala* was reported to be allergenic, but details of patch test results have apparently not been published (14). At any rate, the present study confirms that pseudoivalin and pseudoivalin acetate are sensitizers, and thus indirectly proves the sensitizing potential of marsh elders, although it is likely that more than one allergen is present, in view of the case report by Williams et al. (12). Pseudoivalin occurs in species of different tribes (2, 4, 13, 15–18) (Table 2). In the present study, 4 of 5 patients with positive reactions to the eudesmanolide sesquiterpene lactone alantolactone also had positive reactions to pseudoivalin. However, Herz and Högenauer, in their chemical investigation of *I. microcephala* published in 1962, detected a new sesquiterpene lactone, which they named ivalin (19). Ivalin is structurally 2-hydroxyisoalantolactone, and thus belongs to the eudesmanolide group of sesquiterpene lactones. Herz et al. stated that *I. microcephala* was the first example of a plant that generated both eudesmanolides and guaianolides, possibly from a common germacranolide precursor (13). However, *Serratula latifolia* Boiss. contains alantolactone and pseudoivalin (18), and pseudoivalin and

eudesmanolides closely related to alantolactone have also been isolated from *Pulicaria crispera* Oliv. [syn. *Francoeuria crispera* Cass. (16, 20–22) and from *Pulicaria undulata* (L.) C.A.Mey.] (23). Although the genera *Pulicaria* and *Serratula* have pseudoivalin and eudesmanolides in common, they belong to different tribes (Table 2).

The patients in the present study may thus be concomitantly sensitized to plants containing both groups of sesquiterpene lactones or sensitized by different species containing either mainly guaianolides or mainly eudesmanolides. Only one species of the genus *Pulicaria* occurs in Denmark, common fleabane (*Pulicaria dysenterica*), and it is not common; likewise, the marsh elder *I. xanthiifolia* is rarely found in Denmark. Furthermore, 7 of 10 patients had positive patch test reactions to the 6,12-guaianolide dehydrocostus lactone of the sesquiterpene lactone mix (Table 1). Guaianolides are common in certain tribes in the Compositae and Apiaceae plant families. They exist in two forms, namely 6,12-guaianolides and 8,12-guaianolides. The difference between 6,12-guaianolides and 8,12-guaianolides lies in the  $\gamma$ -butyrolactone-ring position; thus, guaianolides with a C-6–C-12 lactone ring conjugation are referred to as 6,12-guaianolides (angular guaianolides), and guaianolides with a C-8–C-12 lactone ring conjugation are referred to as 8,12-guaianolides (linear guaianolides). The lactone ring is, in most guaianolides, *trans*-fused (6,7-*trans* or 7,8-*trans* configured) as in dehydrocostus lactone, whereas *cis*-fused guaianolides (6,7-*cis*-configured or 7,8-*cis*-configured), such as

**Table 1.** Results of patch testing with seven sesquiterpene lactones from cushion bush (*Leucophyta brownii*) on day (D) 3 in 11 Compositae-sensitive patients

| Allergen                                                                                                       | Patient no. |     |     |     |      |      |    |      |      |    |     |
|----------------------------------------------------------------------------------------------------------------|-------------|-----|-----|-----|------|------|----|------|------|----|-----|
|                                                                                                                | 1           | 2   | 3   | 4   | 5    | 6    | 7  | 8    | 9    | 10 | 11  |
| Pseudoivalin                                                                                                   | ++          | ++  | ?+* | +++ | –    | –    | –  | –    | –    | –  | +   |
| Pseudoivalin acetate                                                                                           | ++          | –   | ?+* | +++ | –    | –    | –  | –    | ?+   | –  | +   |
| Calocephalin                                                                                                   | ?+          | ++  | –   | ?+  | –    | –    | –  | –    | –    | –  | ?+  |
| Tomentosin                                                                                                     | ?+          | ++  | –   | –   | –    | –    | –  | –    | ?+   | –  | +   |
| Leucophytalin A                                                                                                | ++          | ++  | –   | ?+  | –    | –    | –  | –    | –    | –  | +   |
| 4 $\alpha$ -Hydroxy-1 $\alpha$ ,2 $\alpha$ -epoxy-5 $\alpha$ H,10 $\alpha$ H-11(13)-guaian-8 $\beta$ ,12-olide | –           | –   | –   | –   | –    | –    | –  | –    | –    | –  | –   |
| 4 $\alpha$ -Hydroxy-5 $\alpha$ H,10 $\alpha$ H-1,11(13)-guaidien-8 $\beta$ ,12-olide                           | ++          | ++  | –   | +++ | –    | –    | –  | ?+   | ?+   | ?+ | ++  |
| SL mix                                                                                                         | +++         | +++ | +++ | +++ | ++   | ++   | ++ | ++   | ++   | ++ | ++  |
| Comp. mix                                                                                                      | +++         | +++ | +++ | +++ | ++   | ++   | ++ | +++  | +++  | ++ | +++ |
| Parthenolide                                                                                                   | +++         | +++ | +   | +++ | ++   | ++   | ++ | ++   | +++  | ++ | +++ |
| Alantolactone                                                                                                  | ++          | ++  | –   | ++  | –    | –    | –  | ?+/F | –    | ++ | +   |
| Costunolide                                                                                                    | +++         | +++ | ++  | +++ | ++   | ++   | ++ | ++   | +++  | ++ | ++  |
| Dehydrocostus lactone                                                                                          | +++         | +++ | –   | +++ | ++   | –    | –  | +    | ++   | NT | ++  |
| Arnica                                                                                                         | ?+          | ++  | –   | –   | –    | –    | –  | ?+   | –    | –  | ++  |
| German chamomile                                                                                               | +           | +++ | –   | +++ | ?+/F | ?+/F | NT | ++   | +++  | ++ | ++  |
| Roman chamomile                                                                                                | ?+          | NT  | –   | NT  | NT   | NT   | –  | NT   | ?+/F | NT | NT  |
| Yarrow                                                                                                         | ++          | +++ | –   | ++  | –    | ?+   | ?+ | ++   | ++   | ++ | +   |
| Tansy                                                                                                          | ++          | +++ | –   | +++ | ++   | ++   | ++ | ++   | ++   | ++ | +++ |
| Feverfew                                                                                                       | NT          | +++ | –   | +++ | ++   | ++   | ++ | ++   | +++  | ++ | +++ |

\*, possibly positive on D7; –, negative reaction, + to +++, positive reactions; ?+, doubtful reaction; Comp. mix, Compositae mix 6% pet. from Trolab®, Hermal (Reinbek, Germany) consisting of arnica (*Arnica montana*) extract 0.5% pet., German chamomile (*Matricaria chamomilla*) extract 2.5% pet., yarrow (*Achillea millefolium*) extract 1% pet., tansy (*Tanacetum vulgare*) extract 1% pet. and feverfew (*Tanacetum parthenium*) 1% pet. and/or Compositae mix 5% pet. from Chemotechnique Diagnostics (Vellinge, Sweden) consisting of arnica 0.5% pet., Roman chamomile (*Anthemis nobilis*) extract 2.4% pet., yarrow extract 1% pet., tansy extract 1% pet., parthenolide 0.1% pet.; F, follicular reaction; NT, not tested; SL mix, sesquiterpene lactone mix 0.1% pet.

Two patients (nos. 1 and 3) were tested with Compositae mix II from Chemotechnique Diagnostics consisting of arnica extract 0.5% pet., German chamomile extract 1.2% pet., Roman chamomile extract 1.2% pet., yarrow extract 1% pet., tansy extract 1% pet., and parthenolide 0.1% pet.

**Table 2.** Examples of plants containing pseudoivalin

| Species                                | Plant family | Tribe       | References |
|----------------------------------------|--------------|-------------|------------|
| <i>Bedfordia arborescens</i> Hochr.    | Compositae   | Senecioneae | (15)       |
| <i>Iva microcephala</i> Nutt.          | Compositae   | Heliantheae | (13)       |
| <i>Leucophyta brownii</i> Cass.        | Compositae   | Gnaphalieae | (2, 4)     |
| <i>Pulicaria crispa</i> (Forssk) Oliv. | Compositae   | Inuleae     | (16)       |
| <i>Pulicaria sicula</i> (L.) Moris     | Compositae   | Inuleae     | (17)       |
| <i>Serratula latifolia</i> Boiss.      | Compositae   | Cynareae    | (18)       |

pseudoivalin, are rare (Fig. 2). The reactions to pseudoivalin and dehydrocostus lactone are less concordant than those to pseudoivalin and alantolactone, both with a linear chemical structure and *cis*-fused lactone ring, suggesting that the reactions to pseudoivalin are not caused by cross-reactions with dehydrocostus lactone, but by cross-reactions with guaianolides or other types of sesquiterpene lactones that, in their spatial structure and stereochemistry, are more closely related to pseudoivalin. The Danish patients are most likely not sensitized by the above-mentioned native species, but react because of

cross-reactivity with other plants of these tribes or closely related species. The clinical patch test reaction patterns seem to follow the chemical patterns, supporting the theory of concomitant sensitization.

Pseudoivalin acetate is a naturally occurring derivative of pseudoivalin. This explains why the two compounds elicit positive reactions in the same patients (with one exception). So far, pseudoivalin acetate has only been detected in cushion bush (4).

Tomentosin belongs to the xanthanolide group of sesquiterpene lactones. These occur in relatively few

**Table 3.** Examples of plants containing tomentosin

| Species/variety/subspecies                                              | Plant family | Tribe       | References |
|-------------------------------------------------------------------------|--------------|-------------|------------|
| <i>Arnica amplexicaulis</i> Nutt.                                       | Compositae   | Heliantheae | (24)       |
| <i>Arnica mollis</i> Hook.                                              | Compositae   | Heliantheae | (26)       |
| <i>Carpesium faberi</i> C.Winkl.                                        | Compositae   | Inuleae     | (27)       |
| <i>Carpesium macrocephalum</i> Franch. & Sav.                           | Compositae   | Inuleae     | (28)       |
| <i>Helianthopsis sagasteguii</i> H.Rob                                  | Compositae   | Heliantheae | (24)       |
| <i>Helianthopsis stuebelii</i> (Hieron.) H.Rob.                         | Compositae   | Heliantheae | (24)       |
| <i>Helianthus annuus</i> L.                                             | Compositae   | Heliantheae | (29)       |
| <i>Inula britannica</i> L. var. <i>chinensis</i> Regel                  | Compositae   | Inuleae     | (24)       |
| <i>Inula graveolens</i> L.                                              | Compositae   | Inuleae     | (30)       |
| <i>Inula helenium</i> L.                                                | Compositae   | Inuleae     | (31)       |
| <i>Inula hupehensis</i> (Ling) Ling                                     | Compositae   | Inuleae     | (32)       |
| <i>Inula japonica</i> Thunb.                                            | Compositae   | Inuleae     | (33)       |
| <i>Inula viscosa</i> (L.) Aiton                                         | Compositae   | Inuleae     | (24)       |
| <i>Leucophyta brownii</i> Cass.                                         | Compositae   | Gnaphalieae | (2, 4)     |
| <i>Parthenium tomentosum</i> L.                                         | Compositae   | Heliantheae | (25)       |
| <i>Postia bombycina</i> Boiss. & Hausskn.                               | Compositae   | Inuleae     | (24)       |
| <i>Pulicaria crispa</i> (Forssk) Oliv.                                  | Compositae   | Inuleae     | (20)       |
| <i>Pulicaria sicula</i> (L.) Moris                                      | Compositae   | Inuleae     | (17)       |
| <i>Scalesia baurii</i> B.L.Rob.& Greenm. ssp. <i>hopkinsii</i> Eliasson | Compositae   | Heliantheae | (24)       |
| <i>Scalesia stewartii</i> Riley                                         | Compositae   | Heliantheae | (24)       |
| <i>Viguiera tucumanensis</i> (Hook. & Arn.) Griseb.                     | Compositae   | Heliantheae | (24)       |
| <i>Xanthium pungens</i> Wallr.                                          | Compositae   | Heliantheae | (24)       |
| <i>Xanthium strumarium</i> L.                                           | Compositae   | Heliantheae | (24)       |

Compositae genera, including, among others, *Xanthium*, *Helianthus*, *Inula*, *Iva*, *Parthenium*, and *Telekia* (24). Tomentosin was first isolated from *Parthenium tomentosum* in 1971 (25). Examples of other Compositae plants containing tomentosin are shown in Table 3: they comprise a variety of (sub)species from the almost globally occurring common cocklebur (*Xanthium strumarium*) to a tree, Stewart's scalesia (*Scalesia stewartii*), which is found only in the Galápagos Islands (24, 27–29, 32, 33). Tomentosin has been reported to be a sensitizer once before: Rodríguez et al. tested 6 costus-sensitive volunteers with an acetone extract of 16 *Parthenium* taxa and 20 sesquiterpene lactones occurring in these species (34). Two of the 6 persons had positive patch test reactions to *P. tomentosum*, and 1 of the 2 had a 2–3+ reaction to tomentosin (34).

Some *Arnica* species contain tomentosin and closely related xanthanolides, and this seems to be in accordance with the findings of the present study, because 2 patients, nos. 2 and 11, had positive patch test reactions to both *Arnica* and tomentosin, and another had doubtful positive reactions to both (Table 1) (26, 35). Doubtful positive reactions to *Arnica* and tomentosin alone (individually) were seen in patients nos. 8 and 9, and thus the majority of the reactions to the two patch test preparations were concordant. The 2 patients with positive reactions to

tomentosin and patient no. 1 with a doubtful positive reaction also had positive reactions to alantolactone, and the two allergens are both present in *Inula* species (Table 3). The present study confirms the sensitizing potential of tomentosin, and its occurrence in some common plants suggests that it may be a more important allergen than previously suspected.

In contrast to tomentosin, calocephalin and leucophytalin A have only been isolated from cushion bush so far. Calocephalin has been reported to be a sensitizer, but only 1 of the 3 patients who had positive patch test reactions to this compound previously had positive reactions in the present study. The reason for this may be avoidance of contact with Compositae plants in the more than 10 years that have elapsed since the first calocephalin testing, making the patients less sensitive (1, 3). Leucophytalin A, on the other hand, is reported to be a sensitizer for the first time, with positive patch test reactions in 3 of 11 patients tested. Another patient had a doubtful reaction to leucophytalin A, and, altogether, these 4 patients are the patients who had positive/doubtful reactions to calocephalin. This suggests cross-reactivity between the two compounds, which both belong to the guaiane-8,12-olide structural family of guaianolides, as concomitant sensitization is less likely in Danish patients, who were probably not sensitized by cushion bush. According to

Batterham et al. *L. brownii* was apparently previously included in the Inuleae tribe, but it is now included in the Gnaphalieae (2). Two species of this tribe are common weeds in Denmark: wood cudweed (*Gnaphalium sylvaticum*) and marsh cudweed (*Gnaphalium uliginosum*). Whether they are inconspicuous sensitizers or whether the reactions to calocephalin and leucophytalin A represent cross-reactivity to guaianolides of these or other species has not been clarified.

The last compound, 4 $\alpha$ -hydroxy-5 $\alpha$ H,10 $\alpha$ H-1,11(13)-guaidien-8 $\beta$ ,12-olide, is a rarely occurring natural product that has been detected in *Pulicaria crispata* and *Pulicaria sicula* as well as in cushion bush (4, 16, 17, 36). The present study shows the compound to be a potent sensitizer, with four strong positive patch test reactions and three doubtful reactions. There is an association with the reactions to alantolactone: 4 of 5 patients with positive reactions to alantolactone also reacted positively to 4 $\alpha$ -hydroxy-5 $\alpha$ H,10 $\alpha$ H-1,11(13)-guaidien-8 $\beta$ ,12-olide, and the fifth had a doubtful reaction (Table 1). Another patient, no. 8, had doubtful reactions to both compounds. This may be caused by concomitant sensitization, as both compounds have been detected in species of the Inuleae tribe. As mentioned above, only one *Pulicaria* species, *Pulicaria dysenterica* (common fleabane), is found

in Denmark, and, as it is not common, is unlikely to be a primary sensitizer in Danish patients.

In conclusion, the present study has (i) proved that pseudoivalin and its derivative, pseudoivalin acetate, are sensitizers, (ii) confirmed the sensitizing potential of calocephalin and tomentosin, (iii) detected two new sesquiterpene lactone allergens, namely leucophytalin A and 4 $\alpha$ -hydroxy-5 $\alpha$ H, 10 $\alpha$ H-1,11(13)-guaidien-8 $\beta$ ,12-olide, and (iv) shown that the patch test reaction patterns seem to reflect chemical patterns within certain tribes, which may make it possible to trace primary sensitizers and advise patients more precisely.

In general, the worldwide web of sesquiterpene lactones in plants connects Compositae-sensitive patients on different continents through cross-reactivity. The mapping of the occurrence of sesquiterpene lactones in individual plant species is an ongoing process that helps clinicians to refine the diagnostic approach in Compositae contact allergy.

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