

The coumarin herniarin as a sensitizer in German chamomile [*Chamomilla recutita* (L.) Rauschert, Compositae]

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Background: Although German chamomile (*Chamomilla recutita*) is considered a weak sensitizer, recent studies have shown several possible non-sesquiterpene lactone allergens in tea (infusions) from the plant.

Objective: The aim of this study was to report the results of patch testing with herniarin (7-methoxycoumarin), which is one of the possible coumarin allergens in chamomile.

Patients/materials/methods: Between 1991 and 2009, selected patients with known or suspected Compositae contact allergy were patch tested with herniarin 1% petrolatum.

Results: Among 36 patients tested, there was one positive and three doubtful positive reactions to herniarin. All 4 patients had a relevant contact allergy to German chamomile, whereas the majority of the remaining 32 patients had chamomile allergy of unknown relevance.

Conclusions: The clinical results suggest that herniarin indeed is one of the non-sesquiterpene lactone sensitizers in German chamomile and that sensitization may occur through, for example, external use of chamomile tea or use of chamomile-containing topical herbal remedies.

Key words: allergic contact dermatitis; Asteraceae; chamomile tea; *Chamomilla recutita*; Compositae; coumarins; German chamomile; herniarin; 7-methoxycoumarin; patch test. © John Wiley & Sons A/S, 2010.

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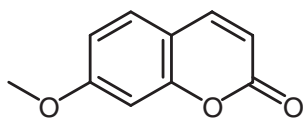
German chamomile (*Chamomilla recutita* (L.) Rauschert) has been used as a herbal remedy throughout large parts of the world for more than 2000 years (1). The allergenic potential of the plant is considered low (2), and this is in accordance with the scarcity of documented cases of contact sensitization from German chamomile (3). However, among persons with Compositae contact allergy, the prevalence of patch-test positivity to ether extracts of German chamomile is high, ranging between 57% and 64% (4, 5). Likewise, Lundh et al. found positive patch-test reactions to two different preparations of German chamomile tea (infusions) in 11 and 15 patients, respectively, of 19 Compositae-sensitive patients tested (6), and in a subsequent study, 15 of 35 previously sesquiterpene lactone mix-positive patients tested positive to at least one

compound of thin-layer chromatograms prepared from chamomile tea (7). The study detected several possible allergens in the tea, including the sesquiterpene lactone matricarin, but patch testing with the chromatographic spot containing the latter did not elicit positive reactions (8). Other potential allergens in German chamomile comprise, e.g. sesquiterpene alcohols, flavonoids, and coumarins (3).

The aim of this study was to report the results of aimed patch testing with herniarin (7-methoxycoumarin; Fig. 1), the main coumarin constituent in German chamomile.

Materials and Methods

From 1991 to 2009 selected patients with known or suspected Compositae allergy were patch tested



Herniarin (7-methoxycoumarin)

Fig. 1. Herniarin (7-methoxycoumarin).

with herniarin (CAS 531-59-9) 1% petrolatum, supplied by Professor Björn M. Hausen, Hamburg, Germany. Patch testing was performed with Finn Chambers® (Epitest Ltd Oy, Tuusula, Finland) on Scanpor® tape (Actavis Norway AS, Vennesla, Norway) for 2D with readings on D3–4 and possibly D7 according to the International Contact Dermatitis Research Group criteria (9).

Results

Between June 1991 and December 2009, a total of 36 patients were patch tested with herniarin from the same syringe, 31 patients in the years between 1991 and 1996, and 5 patients between 2007 and 2009. One tested positive, whereas the three had doubtful positive reactions, in one case of a follicular type (Table 1). The 36 patients tested included 4 with suspected plant allergy who turned out not to be Compositae-sensitive. Among the remaining 32 patients, 30 (94%) had positive patch-test reactions to ether extracts of German chamomile. Although the majority of the reactions (90%) were strongly positive, that is ++ or +++ reactions, the relevance was most frequently recorded as unknown, especially among the 26 Compositae-sensitive patients who tested negative to herniarin, 21 being of unknown relevance. In comparison with this, the relevance was current or old in the three patients who had doubtful positive reactions to herniarin. Details of patch-test reactions, relevance, and source of chamomile sensitization are shown in Table 2.

The history of the one individual with a positive herniarin reaction is described below.

Case Report

In June 2006, a 41-year-old atopic woman was referred with chronic relapsing vesicular palmar eczema. Her hand eczema first appeared when she was 19 years old. Although there had been

periods of remission, the eczema had never cleared completely. For 5–6 years, she had had a similar eczema of her soles and from time to time a more widespread dermatitis on her arms, legs, and trunk. According to the patient, she had contact allergy to nickel, perfume, leather, and rubber.

She had moved to a house with a garden 4 years before and had noticed summer exacerbation of her eczema since. There were no herbaceous borders in the garden, but there were marguerite daisies (*Argyranthemum frutescens*) in pots on the terrace. Past treatment included topical corticosteroids, antibiotics, and ciclosporin as well as herbal medicine. The patient had spent approximately €13 000 on plant-based medicines for internal and external use over the years.

The first patch testing in September 2006 showed positive reactions to nickel sulfate (down to 10 µg/cm²), potassium dichromate, methylchloroisothiazolinone (and) methylisothiazolinone, fragrance mix I and II, hydroxyisohexyl 3-cyclohexene carboxaldehyde, and Compositae (Table 3). The patient was not tested with other ingredients, especially coumarin, of fragrance mix II other than hydroxyisohexyl 3-cyclohexene carboxaldehyde. She tested negative to the corticosteroid series and her own topical products and gloves. Prick tests showed positive reactions to grass pollen and cat dander.

The patient was referred again in the summer of 2007 because she could not tolerate systemic corticosteroids or azathioprine and did not respond sufficiently to 15 mg methotrexate weekly. She was admitted and treated with bath-Psolarens plus Ultraviolet Light A (PUVA) to hands and feet as well as low-dose systemic corticosteroid, azathioprine, propantheline, and topical corticosteroids. Azathioprine was discontinued because of supposed side effects, and the patient was discharged with low-dose systemic corticosteroid to continue the treatment with bath-PUVA.

She was re-patch tested in November 2007, when systemic corticosteroids had been tapered off, and this time she also tested positive to cobalt chloride and thiuram mix of the baseline series in addition to the contact allergens previously found. The extended Compositae testing showed many strongly positive reactions as well as an unusual reaction to herniarin (Table 3). The patient denied using chamomile tea externally, but she had used the tea when treating her dog's inflamed eyes.

Table 1. Results of aimed patch testing with herniarin 1% pet. from June 1991 to December 2009

Allergen	Number of patients tested	Irritant reactions	Negative reactions	Doubtful positive reactions	Positive reactions
Herniarin 1% pet.	36	0	32	3	1 (2.78%)

pet., petrolatum.

Table 2. Distribution of (maximum) chamomile patch-test reactions, relevance and possible sources of chamomile sensitization in three Compositae-sensitive patients with doubtful positive reactions to herniarin

Patient number, sex/age	Occupation	German chamomile 2.5% pet. (Trolab®)	German chamomile 2.5% pet. (Hausen)	Relevance	Sources	Herniarin 1% pet.
1, F/37 years	Nurse	+	++	Old definite	Use of chamomile tea as eye wash	?+
2, F/61 years	Pensioner	++	NT	Current	Frequent contact with weeds	?+follicular
3, F/37 years	Nurse	++	NT	Current	Brewing of chamomile tea for and treatment of patients with herbal ointments	?+

NT, not tested; Trolab®, extract from Trolab® (Hermal, Reinbek, Germany); Hausen, extract delivered by Professor Björn M Hausen, Hamburg, Germany; F, female; pet., petrolatum.

Table 3. Results of patch testing with selected Compositae extracts and allergens in an atopic woman with severe recalcitrant hand eczema

Allergen	Reading	Reading
	September 2006	November 2007
Sesquiterpene lactone mix 0.1% pet.	+++	+++
Parthenolide 0.1% pet.	+++	+++
Compositae mix 6% pet.	+++	NT
Arnica (<i>Arnica montana</i>) 0.5% pet.	N	+
German chamomile (<i>Chamomilla recutita</i>) 2.5% pet. (Trolab®)	+? follicular	++
Yarrow (<i>Achillea millefolium</i>) 1% pet.	+? follicular	++
Tansy (<i>Tanacetum vulgare</i>) 1% pet.	++	+++
Feverfew (<i>Tanacetum parthenium</i>) 1% pet.	++	+++
Alantolactone 0.033% pet.	N	NT
Costunolide 0.1% pet.	++	NT
Dehydrocostus lactone 0.033% pet.	++	NT
Dandelion (<i>Taraxacum officinale</i>) 2.5% pet.	NT	++
German chamomile (<i>Chamomilla recutita</i>) 2.5% pet. (Hausen)	NT	++
Herniarin 1% pet.	NT	+
'Chrysanthemum' extract 3% pet.	NT	++
<i>Chrysanthemum cinerariifolium</i> 1% pet.	NT	+
Dog fennel (<i>Anthemis cotula</i>) 1% pet.	NT	++
Feverfew (<i>Tanacetum parthenium</i>) 1% pet. (Danish plants)	NT	+++
Marguerite daisy (<i>Argyranthemum frutescens</i>) 3% pet.	NT	++

N, negative; NT, not tested; pet., petrolatum.

Discussion

The coumarins are aromatic lactones that are widely distributed in the plant kingdom. Three major classes are recognized: the hydroxycoumarins, the furano- or furocoumarins (including psoralens and angelicins), and the pyranocoumarins (10). In contrast to the simple hydroxycoumarins and their glucosides that occur in about 100 plant families, the furo- and pyranocoumarins are mainly found in two large plant families, the Umbelliferae (Apiaceae) and Rutaceae, furocoumarins being well-known causes of phototoxicity in these families (10). Coumarins are used commercially in the fragrance industry, as flavouring agents, in sunscreens as well as in cosmetic and therapeutic ointments (11).

German chamomile flowers, especially the ligulate florets, contain the coumarins herniarin and umbelliferone (7-hydroxycoumarin) (12). These

two coumarins constitute about 0.1% of the more than 120 compounds detected in chamomile flowers, and as they are soluble in hot water, they will occur in chamomile tea as well (13). A group from the Ukraine isolated another four coumarins from chamomile flowers: coumarin, esculetin, scopoletin, and isoscoupoletin (12).

Positive patch-test reactions to simple hydroxycoumarins such as synthetic coumarin have been reported in persons with contact allergy from fragrances or cosmetics (14–16), although a more recent report suggests that the reactions are caused by contaminants rather than coumarin in itself (17). Hausen et al., in their second and third studies in the series on the sensitizing properties of simple coumarins, characterized isoscoupoletin as a weak sensitizer and esculetin as a strong sensitizer on the basis of a modified Freund's complete adjuvant test in guinea pigs (18, 19). In the first study,

using a slightly different elicitation technique, umbelliferone elicited only one doubtful positive reaction, whereas herniarin and coumarin in the open epicutaneous test in guinea pigs elicited two and one doubtful positive reactions, respectively. Like scopoletin, which elicited no positive reactions in either test, they were therefore considered to be non-sensitizers (11). However, this does not rule out sensitization in humans. Mutterer et al., in a case report of fragrance allergy, elegantly proved coumarin to be the original sensitizer through bio-assay guided chemical fractionation (20). However, testing with fragrance mix II in six European dermatological clinics ($N = 1701$) did not show any unequivocally positive reactions to coumarin (21).

Concerning sensitization to herniarin, the main coumarin in German chamomile, this has been documented in humans. In an experimental, clinical study from Bratislava, 5 of 28 patients with contact allergy to German chamomile tested positive to a 2% solution of herniarin (22). The incidence of sensitization to German chamomile in that area was rather high in the years between 1961 and 1984 with a maximum of 5.6% from 1977 to 1980 (22).

In this study, it is striking that all the four patients with positive and doubtful positive reactions to herniarin had a relevant chamomile contact allergy. Common features in three of the patients were the preparations of chamomile tea and/or contact with the tea or herbal remedies topically (Table 2). The fourth patient had frequent contact with weeds.

The patient with a positive reaction to herniarin first noticed summer exacerbation after she acquired a garden, but this does not fully explain the many positive reactions to rare plant sensitizers such as dandelion, *Chrysanthemum cinerariifolium*, and herniarin (Table 3) after a few years in a garden without herbaceous borders, especially because most of the reactions to the different species were of unknown relevance. Other possible sources of herniarin sensitization in this patient include the use of herbal remedies topically as well as systemically and contact with plants other than Compositae. Herniarin is one of the more common coumarins, occurring in several plant families, such as Caryophyllaceae, Gramineae, Labiatae, Leguminosae, Moraceae, Rosaceae, Rutaceae, and Solanaceae (10). Furthermore, it has antifungal and antibacterial properties and occurs as a phytoalexin in the leaves of celery (*Apium graveolens*, Apiaceae) (10). Its occurrence in Compositae is not restricted to German chamomile: it has been isolated from, e.g. *Eupatorium ayapana* (10), *Santolina oblongifolia* Boiss. (23), *Artemisia apiacea* (24), and *Matricaria discoides* (25).

The sensitization to German chamomile was considered relevant as the patient had actually used

German chamomile tea for the treatment of her dog. As mentioned earlier, coumarins occur in German chamomile tea, and according to McKay and Blumberg, the amounts of coumarins, flavonoids, and phenolics ingested by frequent tea consumption are not negligible (13). Therefore, direct contact with tea must involve a risk of sensitization to these rarer allergens. Thus, contact with both Compositae and other plants in the garden as well as chamomile tea may have sensitized this patient. The role of chamomile tea was further emphasized by one of the patients with a doubtful positive reaction to herniarin (patient 1; Table 2); she had noticed that using chamomile tea as eye wash would induce erythema and oedema of the rim of the eyelids.

The prevalence of sensitization is high in this study, perhaps because of a small number of patients tested. On the other hand, the prevalence was even higher in the Slovakian study paralleling a high incidence of sensitization to German chamomile (22). This may reflect a more widespread use of chamomile/chamomile tea in herbal medicine in Slovakia. The composition of the essential oil of chamomile flowers may vary significantly between growing regions and with processing conditions and in theory, this may also apply to the amounts of coumarins (13).

In conclusion, the results from the clinical studies suggest that true contact sensitization to German chamomile may be caused by herniarin—or in other words—that herniarin is indeed one of the non-sesquiterpene lactones allergens in German chamomile.

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