

The seamy side of natural medicines: contact sensitization to arnica (*Arnica montana* L.) and marigold (*Calendula officinalis* L.)

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Medical remedies of plant origin have gained increasing popularity in recent years. Both anaphylactic and eczematous allergic reactions are on the rise, accordingly. Arnica and marigold, both of the Compositae family, are in widespread use, but only limited data are available on their allergenic potential. We tested 443 consecutive patients, in addition to the European standard and other series, with Compositae mix, sesquiterpene lactone mix, arnica, marigold, and propolis. 5 subjects (~1.13%) reacted to arnica, 9 (~2.03%) to marigold. The Compositae mix was positive in 18 cases (~4.06%). Among them were 3 out of 5 individuals with a sensitization to arnica, and 4 out of 9 who reacted to marigold. Sensitization to arnica and marigold was often accompanied by reactions to nickel, Myroxylon Pereirae resin, fragrance mix, propolis, and colophonium. We conclude that Compositae allergy contributes significantly to the epidemiology of contact dermatitis and that sensitization to arnica and marigold cannot be assessed by testing with the Compositae or sesquiterpene mix alone. As extracts of these plants are frequently used in occupational and cosmetic products, patch testing with additional plant extracts or adjustment of the commercial Compositae mix to regional conditions is recommended.

Key words: arnica; marigold; *Calendula*; allergy; dermatitis; Compositae; sesquiterpene lactones; cross-reactions; plants; plant extracts; medicaments; herbal remedies; patch testing technique.
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The Compositae family comprises more than 20,000 species, distributed all over the world. It presents one of the largest families of flowering plants, including cultivated members of aster, dahlia, chrysanthemum, and gerbera, and wild flowers like thistles, dandelion, daisy, arnica, marigold, tansy, chamomile and yarrow. Ragweed, mugwort, and other wind-pollinated members cause pollinosis and asthma (1). Delayed-type hypersensitivity may arise from sesquiterpene lactones which are found in hundreds of different Compositae species (2–4). Herbal remedies have become very popular in recent years, and both anaphylactic (5) and eczematous allergic reactions increasingly observed. Among others, arnica (*Arnica montana* L.) and marigold (*Calendula officinalis* L.) are used as topical therapeutic agents in folk medicine. Although often suspected as causing allergic events, relatively few data are available on this issue. This prompted us to perform a prospective

study in order to determine the prevalence of delayed-type hypersensitivity to arnica and marigold in Austria, to demonstrate concomitant sensitizations, and to obtain information on the manifestations and clinical relevance of patch test results.

Patients and Methods

The study was performed from July to November 2000 at the Department of Environmental Dermatology, University of Graz, and the Allergy Unit of the Department of Dermatology and Venereology, University of Innsbruck. 443 consecutive patients, suspected of delayed-type hypersensitivity reactions, were patch tested with the European standard series, ether extracts of arnica (0.5%) and marigold (10%), Compositae mix (Comp mix), and propolis. 249 patients were, in addition, patch tested with sesquiterpene lactone mix (SL mix).

Short ether extracts of arnica and marigold were prepared as described previously (6). Briefly, arnica was purchased from a local drug company (Caesar & Loretz, Hilden, Germany). Marigold was collected in the surroundings of Buxtehude and inspected for its identity by a skilled botanist (H. Nothdurft). Short ether extracts were performed by cutting the plant material into 20 cm-long pieces and extracting for 90 s with peroxide-free ether at room temperature. After drying of the short ether extracts over sodium sulfate for 1 h and evaporation of the solvent at 39°C under reduced pressure (water pump vacuum), the extracts were incorporated into white petrolatum. Both arnica and marigold extracts had been tested in a control population of at least 50 subjects earlier and had not shown any irritant potential. All other test materials were obtained from Hermal (Germany). Tests were applied to the back of the patients for 2 days using Finn Chambers on Scanpor (Epitest, Finland; Norgesplaster, Norway) and then read 15 min and 1 day later. Readings were performed according to the International Contact Dermatitis Research Group (7). A specially-designed questionnaire was used to interview patients on the use of arnica and/or marigold, motives for and location of application, associated adverse effects, occupation, hobbies, and history of atopy.

Results

A total of 443 individuals with a mean age of 40.4 years were tested, comprising 311 women and 132 men. Table 1 shows the clinical characteristics of those reacting to arnica or marigold.

5 patients (~1.13%), referred to the departments for chronic hand or face dermatitis, showed positive reactions to arnica. Their ages ranged from 38 to 79 years, with a peak at age 56. 3 patients recalled the use of arnica as a topical remedy; 2 of

them were hobby-gardeners. One was not aware of adverse reactions to arnica, while the 2nd (no. 13) had developed dermatitis of face and arms after gardening.

9 subjects (~2.03%) proved to be sensitized to marigold. Their mean age was 51.9 years (range 21–87). They had been referred because of dermatitis of the hands or arms ($n=2$), legs ($n=2$), face ($n=3$), and face and arms ($n=1$). 6 remembered contacts with marigold as an ingredient of ointments, 2 had developed contact dermatitis shortly thereafter. 1 patient, the only person who proved sensitive to arnica as well, presented with a suspected photoallergic reaction on the face, neck, and arms, after application of a marigold-containing ointment and sunbathing afterwards.

The Comp mix revealed positive reactions in 18 cases (~4.06%), among them 3 of the 5 arnica-sensitive patients, and 4 of the 9 marigold-sensitive ones. Only 1 individual (a patient sensitive to arnica) reacted to the SL-mix. Concomitant reactions were observed to nickel ($n=95$; ~21.44%), thimerosal (40/199; ~20.01%), Myroxylon Pereirae resin ($n=57$; ~12.87%), fragrance mix ($n=52$; ~11.74%), propolis ($n=29$; ~6.55%), colophonium ($n=23$; ~5.19%), and rubber chemicals ($n=18$; ~4.06%). Among the 5 patients positive to arnica, 3 were sensitized to nickel, Myroxylon Pereirae resin, fragrance mix, and propolis. Among the 9 positive to marigold, 5 reacted to nickel, Myroxylon Pereirae resin, and propolis, and 4 to fragrance mix and colophonium. No active sensitization occurred during the test procedure.

Discussion

The increasing and widespread use of alternative substances and materials in the treatment of skin diseases is accompanied by heated discussions between representatives of orthodox academic

Table 1. Clinical characteristics of patients sensitized to arnica (A) or marigold (M): f=female, m=male

Patient (no.)	Sex	Age (years)	Sensitized to	Reason for patch testing (suspected allergenic material)	History of exposure to M or A
1	f	87	M	dermatitis, hands (latex gloves)	M, A
2	m	44	M	dermatitis, face (propolis)	A
3	m	41	M	dermatitis, hands (dichromate)	–
4	f	43	M	dermatitis, eyelids (?)	M
5	f	67	M	dermatitis, legs (marigold)	M, A
6	m	21	M	dermatitis, feet (?)	M
7	f	24	M	dermatitis, face (propolis)	–
8	m	60	M	dermatitis, face, arms (marigold)	M
9	m	76	M, A	photoallergic dermatitis (marigold)	M, A
10	f	49	A	dermatitis, hands (?)	–
11	f	38	A	dermatitis, hands (?)	M, A
12	f	51	A	dermatitis, feet (camomile)	–
13	f	79	A	dermatitis, face, arms (dandelion)	M, A

medicine, often claimed as being aggressive, toxic and harmful, and representatives of alternative medicine, condemned as unscientific and ineffective, but regarded as natural, bland, and free of side-effects. Among dermatologists, arnica is known as a potent contact sensitizer, while marigold is favoured for its beneficial effects with rare allergenic properties. However, for both plants, only limited data are available on the actual prevalence of delayed-type hypersensitivity reactions.

The sesquiterpene lactones of *Arnica montana* L. possess a strong sensitizing potency which explains a comparatively high sensitization rate (8, 9). However, recent studies showed divergent results. In 58 patients with positive patch tests to the Comp mix and/or the SL mix, 0 and 1 individual, respectively, showed a sensitization to arnica (10, 11). In another 6-year study with 3851 individuals tested, 118 reacted to the Comp mix and 51 were positive to arnica (~1.32 %) (12). Our results (5/443; ~1.13 %) are in good agreement with the latter study.

2 of our 5 patients would have been overlooked if they had been tested with the Comp mix or SL mix alone. Other authors have shown that the SL mix is an inadequate screen for Compositae allergy, and that the Comp mix is more sensitive (10, 13–17). In a recent multicentre study, Comp mix was shown to have a sensitivity rate of 76% (18). However, even the Comp mix, which contains arnica besides a mixture of short ether extracts of German chamomile, feverfew, tansy, and yarrow, also clearly failed to detect all arnica-sensitive patients in our series. This may be due to differences in the chemical composition of the SL, which varies remarkably with origin and provenance of the plants used for extraction (8). Thus, it has been argued that testing for Compositae allergy should be carried out at a phytoregional level (19).

Reports on sensitization to common or true marigold – *Calendula officinalis* L. –, are extremely rare (20). Only 4 cases have been observed (20, 21, 1 own observation in 2000 [B. M. Hausen]). In contrast to these data, 2.03% (9/443) of our patients showed positive patch test results to true marigold. Using the Comp mix alone, only 1/2 of this number would have been detected. Discrepancies in the chemical composition may explain this phenomenon. The Compositae family consists of 2 different classes of constituents: the sensitizing sesquiterpene lactones and the thiophenes/polyacetylenes. In the past, it was thought that the latter group elicits only phytophotodermatitis. However, today, we know that certain thiophenes also possess sensitizing properties (22). Common marigold contains neither sesquiterpene lactones nor thiophenes or polyacetylenes. The

only important constituent found is (–)-loliolide, which is identical with calendin. This bitter principle, formerly believed to be a SL, is an oxidation product of certain known plant carotinoids (23). Its allergenic properties have not yet been demonstrated. Due to differences in the local flora, a commercial Comp-mix should thus be manufactured in 2 brands: one for the use in northern European patients and another for those of the Mediterranean region, as suggested by Stingeni & Lici (19). Following this suggestion, a screening mix adjusted for Austria would be desirable as well.

Only a few of our patients who were sensitized to arnica or marigold were aware of having been in contact with these plants. It must be kept in mind, however, that the Austrian Medical Codex lists no less than 29 drugs containing up to 10% arnica montana, and 14 containing an average of 5% true marigold, mostly as local therapeutics and tea. Additionally, countless herbal cosmetics may be conducive to the sensitization rates observed. Consequently, at least the Comp mix or, preferably, different plant extracts should be patch tested routinely in patients with dermatitis of the hands, feet, and face, even if there is no history of exposure.

The 'hit list' of concomitant sensitizations detected in our patients correlated well with that observed in 40,000 patients from 26 centres in Germany and Austria (24). Previously-described local deviations (25–27) were confirmed, as for thimerosal, which was tested in 199 patients from Graz only, and revealed a frequency of 20.01% there. However, a significantly higher % of the Compositae-, arnica- or marigold-sensitized subjects showed sensitizations to propolis, fragrance mix, and Myroxylon Pereirae resin. This is in good agreement with other studies (11, 16–18, 28) and does not reflect true cross-reactivity, but rather, the occurrence of common chemical components which do not belong to the sesquiterpenes or thiophenes (28, 29). Moreover, Compositae-allergic patients have been described as being mostly elderly people (30), a finding also confirmed in our series. This may also contribute to the observed associations as the hit list of allergens changes with increasing age (31).

Conclusion

Delayed-type hypersensitivity reactions to Compositae plants present as chronic and, when untreated, gradually progressive disease. Several well-designed studies have shown that Compositae contribute significantly to the epidemiology of contact dermatitis, especially in the elderly. In con-

trast to the most common Compositae species, the Comp mix is not reliable for the detection of contact allergy to arnica and common marigold. Our study thus highlights the importance of testing additional plant extracts when there is persisting clinical suspicion of Compositae allergy in patients negative to the Comp mix. We therefore recommend the introduction of patch test mixes, comprising regionally important Compositae species.

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