

A 6-Year Experience With Compositae Mix

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A Compositae plant mixture consisting of short ether extracts of arnica, German chamomile, feverfew, tansy, and yarrow has been included in the standard series for several years (1985 to 1990) to study the frequency of allergic reactions to Compositae (Asteraceae) species. One hundred eighteen of 3,851 tested individuals gave a positive response (3.1%). Further tests with the single species of the mixture and some additionally tested extracts of chrysanthemums and laurel oil (bay leaf; Lauraceae) revealed a high percentage of reactions to feverfew (70.1%) and lower responses to chrysanthemums (63.6%), tansy (60.8%), chamomile

(56.5%), arnica (51.8%), yarrow (51.8%), and the cross-reacting laurel oil (50.5%). Ten of 85 reacted to arnica alone. The results show that it is important to test Compositae extracts in patients with allergic contact dermatitis because these contain (in contrast to a mixture of pure sesquiterpene lactones) other constituents (eg, polyacetylenes, thiophenes) that may also contribute to the acquired hypersensitivity. Unrevealed sources of hand and face eczema (including airborne contact dermatitis) might be diagnosed more frequently.

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RECENT REPORTS have discussed whether a crude extract of the entire plant (named Compositae mix) or a mixture of distinctive sesquiterpene lactones (named SL mix) is preferred to detect Compositae contact allergy in humans.¹⁻³ Certain reports give the impression that no serious attempts have previously been made to indicate Compositae allergy in any other way than by the use of SL mix, which was introduced in 1987 and since then used mainly in England and the United States.⁴⁻⁶ In fact, it has not been possible to prepare a mixture of pure SLs before this because no compounds of this class were commercially available except santonin (nonsensitizer) and helenin (a mixture of three SLs from *Inula helenium*). However, it was not mentioned in the above-cited reports³⁻⁶ that an alternative Compositae test method was in use in the 1970s and 1980s, long before the SL mix became available. This Compositae mix was initiated by a discussion with Niels Hjorth (Gentofte, Denmark) in 1975 and based on the observation that short ether extracts (60 to 90 seconds) of Compositae plants contain more than 90% of the sensitizers but few of the contaminating by-products, eg, chlorophylls.^{7,8} In the late 1970s, tests were started with a mix of various Compositae species that soon became a routine procedure in the Department of Dermatology of the University Hospital in Hamburg (Germany). Some interested investigators in Denmark, England, Finland, France,

Spain, and the United States were supplied with the same material for comparison.

In middle Europe, more than 180 species of the Compositae family are abundant, of which at least 100 have been described or suspected to contain sensitizing constituents.⁹ In the first step of the investigation, 12 species (arnica, German chamomile, sunflower, yarrow, common daisy, feverfew, Roman chamomile, marguerite, cornflower, calendula, and the non-Compositae plant laurel [bay leaf; Lauraceae]) were added as a mix to the standard series and tested single when the mix became positive. During this step of the study, we noticed that only six of the species were of importance, whereas laurel (bay leaf) seemed to function as an indicator. These experiences, gathered in the first years, finally resulted in the preparation of a mix consisting of only five important and relevant species that were combined to give the so-called Compositae mix (see Materials and Methods).

Since 1985, this mixture of Compositae plant extracts has been continuously used as an optional addition to the standard series. The results of the patch tests, performed between 1985 and 1990, are reported here. Because the conditions of patch testing changed after 1990 in the Department of Dermatology in Hamburg, the results of the subsequent years could not be followed up and used for comparison.

MATERIALS AND METHODS

To prepare the Compositae mix, the following five species were used: arnica, German chamomile, yarrow, tansy, and feverfew. Table 1 gives their vernacular names, botanical names, and authors as well as the concentration used for patch testing.

Feverfew, yarrow, and tansy were either collected during the summer in the surrounding fields and meadows of Pinneberg (30 km north of Hamburg, Germany) or the gardens of the neighbors (feverfew) and inspected for their identity by a skilled

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Table 1. Vernacular and Botanical Names and Patch Test Concentrations of the Species Used in the Compositae Mix

Vernacular Name	Botanical Name	Test Concentration (%)
Arnica	<i>Arnica montana</i> L.	.5
German chamomile	<i>Chamomilla recutita</i> (L.) Rauschert	2.5
Feverfew	<i>Tanacetum parthenium</i> (L.) Schulz-Bip.	1.0
Tansy	<i>Tanacetum vulgare</i> L.	1.0
Yarrow	<i>Achillea millefolium</i> L.	1.0

botanist (Dr. H. Nothdurft). German chamomile and arnica were purchased from a local drug company (Caesar and Loretz, Hilden, Germany).

Short ether extracts were performed by cutting the fresh plant material (all above-ground parts) into 20-cm long pieces and extracting them for 90 seconds with peroxide-free ether (diethyl ether; Merck, Darmstadt, Germany) at room temperature. The predried commercial plant material of arnica and German chamomile was extracted for 2 to 3 minutes. After drying of the short ether extract over sodium sulfate for 1 hour and evaporation of the solvent at 39°C under reduced pressure (water pump vacuum), the extracts were incorporated into white petrolatum and combined in such a manner that the mix contained the five plant extracts in the concentrations given in Table 1. Before patch testing, the irritancy threshold had been determined by epicutaneous tests on 20 controls, including the author. Over the years, this determination has been repeated any time fresh plant material was collected during the summer. Thin-layer chromatography served as a control for the qualitative determination of the sensitizing constituents. This was done by separating the short ether extracts with chloroform-methanol

(100 + 1) as eluent and detection of the SLs by spraying the thin-layer chromatography plates with 50% sulfuric acid and heating them for 90 seconds at 180°C. After development of gray, violet, red, and/or brown spots, it was determined that the extracts contained sufficient amounts of the sensitizing SL to elicit positive reactions in Compositae-sensitive patients. A comparison with another color reagent (cerium sulfate in 2 N sulfuric acid, heating to 110°C for 10 minutes) brought no different results; the same SLs were detected. A chromatographic search for pesticides remained negative.

The Compositae mix has been used as an addition to the standard series since 1985. It was tested when there was the slightest hint of contact with plants in the case history. Patch tests were performed on the back of the patient for 24 hours using Finn chambers on Scanpor (Epitest, Finland) and self-adhesive tape (Fixomull, Beiersdorf, Germany) for securing the patches.

Reading was performed according to the rules of the International Contact Dermatitis Research Group. In case of a positive reaction to the mix (+ + or higher), the extracts of the five species were tested singly 1 week later. Relevant test reactions to other extracts and plant allergens are given in the last row of Table 2. Results of the standard series are not included.

Chrysanthemums (2.5%) and laurel oil (bay leaf; family Lauraceae) (2%) were tested separately for comparison. Laurel oil (purchased from Caesar and Loretz) had been recommended for many years in Europe as a natural remedy for cellulitis and self-medication of rheumatic complaints, sometimes resulting in severe allergic contact dermatitis.¹⁰

RESULTS

Between 1985 and 1990, 3,851 patients were patch tested with the Compositae mix in the

Table 2. Number of Positive Patch Test Reactions to the Compositae Mix and Single Compositae Species in Hamburg (1985 to 1990)

Year	No. of Patients Tested With Compositae Mix	Positive Reactions to the Single Species								Additionally Tested Species		Airborne Contact Dermatitis	Remarks/Positive Reactions to Other Allergens
		Positive	%	Arnica (arnica alone)	German Chamomile	Yarrow	Tansy	Feverfew	Chrysanthemums	Laurel Oil			
1985	537	15 (11/4)	2.8	4/12 [0/12] (2/2)	5/10 (3/2)	7/10 (6/1)	6/10 (4/2)	5/8 (3/2)	8/19 (6/2)	8/12 (4/4)	2/15	Actinic reticuloid (1x) Tincture of myrrh (1x)	
1986	705	16 (9/7)	2.3	10/14 [2/14] (5/5)	10/15 (6/4)	7/14 (3/4)	9/14 (5/4)	10/14 (5/5)	6/9 (2/4)	10/14 (5/5)	3/16	Ulcus cruris (1x)	
1987	710	19 (14/5)	2.7	4/9 [2/9] (4/—)	4/9 (3/1)	6/10 (5/1)	3/6 (2/1)	5/8 (4/1)	5/9 (4/1)	6/15 (5/1)	1/19	Ulcus cruris (2x) Eczema of the auditory canal (1x)	
1988	722	22 (14/13)	3.0	6/14 [2/14] (3/3)	8/14 (5/3)	10/15 (6/4)	5/6 (2/3)	10/13 (5/5)	8/15 (5/3)	10/20 (7/3)	2/22	Ulcus cruris (2x) Primin (1x) Tuliposid A (1x)	
1989	648	27 (14/13)	4.2	11/21 [2/21] (5/6)	12/21 (6/6)	10/23 (5/5)	7/12 (4/3)	14/20 (6/8)	12/20 (5/7)	7/22 (3/4)	1/27	Ulcus cruris (1x) Primin (2x) Tuliposid A (1x) Tincture of myrrh (1x) Patchouli oil (1x)	
1990	529	19 (12/7)	3.6	9/15 [2/15] (6/3)	9/15 (4/5)	5/13 (1/4)	4/8 (2/2)	10/14 (5/5)	10/14 (5/5)	9/16 (5/4)	2/19		
Total	3,851	118 (74/44)	3.1	44/85 [10/85] (25/19)	45/85 (27/21)	45/85 (26/19)	34/56 (19/15)	54/77 (28/26)	49/77 (27/22)	50/99 (29/21)	11/118		

NOTE. Numbers in brackets indicate the ratio of females to males.

Department of Dermatology of the University Hospital in Hamburg. One hundred eighteen patients developed a distinct positive reaction (at least ++) (3.1%). More than half of the patients with a positive reaction (62.7%) were women (Table 2).

Patch testing with the five single species showed some interesting aspects. A positive reaction was obtained most often with feverfew (70.1%). In decreasing order, the other species became positive: tansy (60.6%), German chamomile (56.5%), yarrow (51.8%), and arnica (51.8%). Ten of 85 Compositae-sensitive patients responded solely to arnica (Table 2). Chrysanthemums and laurel oil, tested separately, gave results of 63.6% and 50.5%, respectively.

Clinically the patients most often showed a contact dermatitis of the face, fingers, both hands, and forearms. In florists, sometimes the skin of the inner side of only the left forearm was involved due to the habit of cutting the flowers with the right hand and leaning the collected plants to the left forearm.

A third (33 of 118) had acquired their specific hypersensitivity occupationally (Table 3). The remaining 85 individuals had had multiple possibilities of contact with Compositae plants. Extensive questioning into their case histories finally allowed us to determine their present or former professions and to solve nearly all sources of their Compositae plant allergy. Most of them had their own gardens where they spent a remarkable part of their leisure time. Another group had used "natural" cosmetics extensively. The remaining patients (10%) were elderly individuals that spent a lot of their time outdoors. Clinically these 10% (11 of 118) displayed the picture of an airborne contact dermatitis. Five of them had worked as a florist in a flower booth, in the fields, or in the flower market. The other six were older than 60 years of age and had worked outdoors mainly in their own gardens as hobby gardeners. The lesions were typically distributed on the face, neck, décolleté, hands, and forearms, usually beginning in April and lasting approximately until October. Table 3 gives a survey of the professions of the patients and the way (if detected) they became sensitized. Only four cases remained unsolved.

DISCUSSION

Based on the knowledge that the Compositae are by far the most widely distributed plant family

Table 3. Professions and Ways Showing How Specific Hypersensitivity in 118 Compositae-Sensitive Patients Was Acquired

Profession	Known or Possible Contact With Plants	No.
Flower trade	Florists, flower sellers (market), preparing of festoons and bouquets, horticulture, flower nurseries	33
Retired persons*	Frequently busy in own garden, hobby gardeners	20
Housewives*	Own garden	18
Office workers (merchant, bookkeeping, insurance, bank)	Own garden	10
Civil servant (post office, railroad)	Own garden	5
Cook, housekeeper, kitchen aide	Kitchen work (vegetables, spices, fruits, salad making, sandwich making)	5
Mechanical engineer/ metal work	"Natural" ointment	3
Students	Flower decoration in restaurant	2
Farmer	Wild flowers (mowing, weeding)	2
Nurse	Herbal medicine, herbal remedies	1
Pediatric	Own garden	1
Lawyer	Own garden	1
Caretaker	Trimming of plants in the playground	1
Concrete worker	Probably herbal shampoo, soap, ointment	1
Beekeeper	Propolis, plants around the beehive	1
Agricultural assistant	Frequent staying outdoors	1
Masseur	Herbal massage oils	1
Dental assistant	"Natural cosmetic"	1
Butcher	Spices, lettuce	1
Grocer	Vegetable, flowers	1
Shop assistant	"Natural cosmetic"	1
Packer	"Natural cosmetic"	1
Teacher (female)	Specialized in farmwork	1
Computer specialist (female)	"Natural cosmetic"	1
Commander of a fire brigade	Own garden	1
Unsolved		4

*Formerly in other professions.

with sensitizing constituents in middle Europe,⁹ we chose at first 12 species for preparing the mix because they had been most often associated with positive reactions in epicutaneous testing and/or

could be shown to possess a strong or at least moderate sensitizing potency in guinea pig sensitization experiments.^{11,12}

However, the experiences during the first years taught us to reduce the composition finally to five species, which would be sufficient to detect the majority of Compositae-sensitive individuals. This decision was based on three reasons. (1) Due to cross-reactivity abundantly recognized in Compositae allergy,¹¹ the mix becomes positive in most Compositae-sensitive patients, even when the patient is allergic to only a single species. (2) The species selected comprise all groups of known SL structures, eg, guaianolides, pseudguaianolides, eudesmanolides, etc, and even a very rare one, the anthecotulid, a linear SL occurring in chamomile, because the ether extract grips more than 90% of the lipophilic constituents available on the plant surface. (3) The various possibilities of contact of human beings with Compositae plants caused us to consider two main groups: those that are used for topical remedies and in herbal cosmetics, ie, arnica (eg, tincture of arnica) and chamomile, and those mainly responsible for airborne contact dermatitis (feverfew, tansy, and yarrow).

Additional testing of chrysanthemums and laurel oil for 6 years corroborated our decision to omit these species from the mixture because every second patient reacted to laurel oil and nearly 64% to chrysanthemums. Although laurel oil seems to be less important as an indicator, chrysanthemum should be tested additionally any time an occupational Compositae hypersensitivity is suspected. Patch testing with the concentrations given in Table 1 has shown no case of patch test sensitization since 1985. Here we are in good agreement with Paulsen et al¹ and Wrangsjö et al,¹³ who used our extracts as well. We could not show any phototoxic or photoallergic reactions either. The results of photopatch testing with the Compositae mix in 1,129 patients have been reported.¹⁴

Among the three wild growing species, feverfew plays the most important role because it shows the strongest sensitizing capacity.¹⁵ Its position is shown by the order of positive reactions to the five species and will remain there in the near future because the dried leaves of feverfew are increasingly used in Europe and the United States as a remedy against arthritis and migraine.^{16,17} As expected by our knowledge of the sensitizing capacity of parthenolide (the main constituent of feverfew),¹⁵

chewing of the leaves caused side effects in more than 11% of the consumers.¹⁶ Its high concentration of parthenolide and wide distribution in private gardens in Germany as well as in Denmark¹ may be another point for explanation of its leading role in the frequency of positive test reactions.

German chamomile and arnica are very popular plants used in soaps, ointments, lotions, and shampoos. The use of tincture of arnica as an old folk remedy might explain the observation that specific hypersensitivity to arnica developed in 10 patients solely to this species. Our former experience with the mix showed that epicutaneous testing with a single Compositae species in Compositae mix-positive patients can be extended up to 35 members.¹¹ Due to their known cross-reactivity, we often observed positive reactions to sunflower, dandelion, marguerite, golden rod, stinking mayweed, blanket flower, and zinnia,¹¹ showing that hypersensitivity is by no means restricted to the five species discussed above. However, these five species seem to be, at least in Europe, the most important and thus will do for the purpose of screening Compositae plant allergy.

Chemically a short ether extract does comprise all lipophilic constituents occurring abundantly in a species of this plant family, ie, not only the huge class of SLs but also the second great class of Compositae constituents, the polyines (polyacetylenes/thiophene),¹⁸ ignored to date as equal sensitizers. Although the sensitizing capacity of SLs has been shown in human patch tests and guinea pig sensitization experiments during the last 20 years, that of the polyacetylenes was completely neglected. However, recent studies show that a short ether extract contains both materials: sensitizing SLs and important polyacetylenes/thiophenes. Although only four polyacetylenes and thiophenes have been identified thus far as contact sensitizers,^{19,20} we believe that further research on their sensitizing capacity will provide further convincing results.

It thus becomes clear that comparison of a mix consisting of pure SLs and a mix consisting of ether extracts of Compositae plants cannot give the same results in patch testing because the latter contains not only the SLs but additionally the second group (polyacetylenes/thiophenes), which probably is responsible for most of the observed cross-reactions that are not explainable by the lacking SL content of these species.

The consequence of using a short ether extract and not an ethanol, acetone, or chloroform extract was based on preliminary experiments performed in 1977⁸ showing that dipping of the fresh above-ground part of Compositae plants into ether will release more than 90% of its sensitizing constituents within 60 to 90 seconds and retain most of the contaminating nonallergenic compounds in the plant material. This corresponds well with the observation that a relatively short-lasting but repeated contact of the human skin with the plant will finally result in contact dermatitis. This again confirms former observations and statements reported in the literature that the allergenic contactants must be localized in the peripheral parts of the plants, eg, in their trichomes.²¹ In other words, preparation of Compositae plant extracts is not dependent on breaking complex plant cell structures. On the contrary, numerous observations and descriptions show that the greater part of the Compositae species possesses sensitive visible trichomes on their leaves and stems that break down on the slightest touch.²¹ In other species of this family, such trichomes seem to be lacking because they are not visible with the naked eye. However, under the microscope, different and fine textured trichomes and vessels will be discovered coating the surface and backside of the leaves such as those found typically on sunflower.²²

Attempts to introduce a Compositae mix commercially were started in Europe by two companies 4 years ago. However, comparison of test results obtained with these commercial mixtures and the Compositae mix from Hamburg revealed too many false-negative responses. Thin-layer chromatographic separation of the commercial extracts showed lesser amounts or no traces of the relevant SLs (data to be published). A comparison of the Compositae mix and the SL mix is being performed at present by some selected departments of dermatology belonging to the German contact allergy group. The results of this investigation will be published in a forthcoming report. Preliminary testing of the Compositae mix from Hamburg in different dermatology centers and private practices in the United States have shown results comparable with those obtained in Europe.^{1,13} If the commercially prepared Compositae mix improves in the near future by using freshly collected plant material instead of plants dried in a rotating oven, which destroys most of the allergenic constituents,

this mix will hopefully become available for interested investigators abroad. In contrast to feverfew, tansy, and yarrow, the commercial extracts of arnica and chamomile showed no reduction of the sensitizing constituents by drying in the mentioned oven.

In this study, special attention was paid to the question of how the patients had become sensitized to the Compositae. Most information was attained by extensive repeated questioning or telephone interviews. In most cases, delving into the case history of each individual finally disclosed the source of his/her hypersensitivity to Compositae species (Table 3). Some patients worked frequently in their own gardens, and others had contact with Compositae vegetables in their kitchen. A greater number showed a special liking for the use of "natural" cosmetics. Another group even prepared their own ointments and remedies by collecting or purchasing the flowers in special "alternative shops." Extracts were made following instructions from the currently popular pocket books on "natural cosmetics." It is no wonder that more women than men acquired Compositae hypersensitivity (Table 3; ratio, 74/44), as also noticed by Wrangsjö et al.¹³ One patient preferred handmade dried flower bouquets using yarrow, tansy, artichoke, and sea lavender; another handled dandelion to feed his rabbits; a third (woman) developed dermatitis of the auditory canal after washing her hair with an arnica-containing shampoo. In another case, a woman developed airborne contact dermatitis after years of sitting at the grave of her late husband for 2 hours a day. Although the grave itself and its surrounding space was clean, the neighboring graves had become a wilderness consisting mostly of Compositae species and especially of feverfew.

CONCLUSION

Experiments and consecutive experiences by patch testing of the Compositae mix for more than 10 years (beginning in 1982; it is still being tested but under altered conditions) reveals the possibility of detecting potential sources of observed contact dermatitis neither suggested by the patient nor by the questioning physician. In view of the difficulties in predicting plant hypersensitivity, the Compositae mix should be included in the standard series. Because the search for other additional sensitizers (eg, polyines) in the Compositae plant family must be continued, we believe, in agreement with Green

and Ferguson,³ that a simple SL mix containing only three of the at least six-membered class of SLs is not sufficient for screening Compositae contact allergy. However, we are aware of the fact that neither a mixture of five ether extracts (or more) nor a mixture of selected SLs will provide the chance of detecting 100% of all cases caused by members of a plant family in which far more than

1,350 SLs²³ and more than 1,000 polyines¹⁸ of different structures, different configurations, and biological activities have been identified to date.

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