

Patch testing with constituents of Compositae mixes

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Summary

Background. The development of mixes containing Compositae plant extracts has improved the diagnosis of Compositae contact allergy, but none of them has fulfilled the criteria for an ideal European plant mix.

Objective. To evaluate which constituents of two commercial Compositae mixes were most useful as screening agents.

Patients. These comprised 76 patients testing positive to Compositae mix 6% in petrolatum and 29 patients testing positive to Compositae mix 5% pet., all of whom were tested with constituents of the respective mixes.

Results. The majority of patients tested positive to parthenolide or parthenolide-containing extracts, followed by German chamomile, yarrow, and arnica. As German chamomile is a weak sensitizer, the results suggest cross-reactions or reactions to unknown allergens. No one was positive to Roman chamomile.

Conclusions. Even though parthenolide seems to be a suitable supplement to the baseline series, the results emphasize that it is important to patch test with extracts of native or locally grown plants, not only because of the geographical variation, but also because of the potential unknown allergens contained in short ether preparations and the variability in the individual patient's exposure and cross-reaction patterns.

Key words: *Achillea millefolium*; allergic contact dermatitis; *Anthemis nobilis*; *Arnica montana*; Asteraceae; *Chamomilla recutita*; Compositae; patch testing; plants; *Tanacetum parthenium*; *Tanacetum vulgare*.

The sesquiterpene lactone mix is, at present, the only screening agent for Compositae contact allergy that is recommended in the European baseline series. Even though the development of mixes containing Compositae plant extracts (1–4) has been a diagnostic improvement, none of them has fulfilled the criteria for an ideal European Compositae mix in terms of reliability and safety.

On the basis of clinical studies, the Compositae mix 6% in petrolatum (CM 6%), originally developed by B. M. Hausen and previously available from Trolab® (Hermal,

Reinbek, Germany), seems to have a higher detection rate than that of the Compositae mix 5% pet. (CM 5%) available from Chemotechnique Diagnostics® (Vellinge, Sweden) (1, 3, 5), although direct comparative studies have not been carried out. The reason for this is not clear, but differences in climate, horticultural traditions, consumer habits and composition of the mixes may all be contributory factors.

The aim of this study was to evaluate which constituents of the two Compositae mixes were most useful in detecting Compositae contact allergy on the basis of distribution of positive reactions to the individual extracts and allergens.

Patients, Materials and Methods

Since 1990, the department has used the sesquiterpene lactone mix 0.1% pet. as a screening agent for Compositae

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Table 1. Constituents of two commercial Compositae mixes

Compositae mix 6% pet.	Compositae mix 5% pet.
Feverfew extract 1% pet. (<i>Tanacetum parthenium</i>)	Parthenolide 0.1% pet.
Tansy extract 1% pet. (<i>Tanacetum vulgare</i>)	Tansy extract 1% pet. (<i>Tanacetum vulgare</i>)
German chamomile extract 2.5% pet. (<i>Chamomilla recutita</i>)	Roman chamomile extract 2.4% pet. (<i>Anthemis nobilis</i> = <i>Chamaemelum nobile</i>)
Yarrow extract 1% pet. (<i>Achillea millefolium</i>)	Yarrow extract 1% pet. (<i>Achillea millefolium</i>)
Arnica extract 0.5% pet. (<i>Arnica montana</i>)	Arnica extract 0.5% pet. (<i>Arnica montana</i>)

sensitization in the baseline series, and from 1995 it was supplemented with parthenolide 0.1% pet. CM 6%, on the other hand, was used in aimed patch testing from 1990, except in a period from 1998 to 2001, when the mix was included in the baseline series. CM 5% has been applied in aimed patch testing since 2006.

A special subgroup of Compositae-sensitive patients were included in this study; namely, all consecutive Compositae-allergic patients who tested positive to CM 6% and/or CM 5% and were tested with their respective constituents. CM 6% pet. and the individual plant extracts of this mix were obtained from Trolab® (Table 1). CM 5% pet., parthenolide and the other four plant extracts of the mix (Table 1) were supplied by Chemotechnique Diagnostics®.

The plant extracts and allergens were applied to the back for 2 days with Finn Chambers® (Epitest Ltd, Oy, Tuusula, Finland) on Scanpor® tape (Actavis Norway AS, Vennesla, Norway), and readings were performed on D3–5 and possibly D7, according to the International Contact Dermatitis Research Group criteria (6).

The constituents were applied either: simultaneously with the mix(es), in cases of suspected Compositae contact allergy; or on D3–D5 or later, in cases of unexpectedly positive reactions to the mix(es). Testing on a later occasion was referred to as 'secondary testing'.

Results

Between July 2000 and March 2004, 76 patients with positive reactions to CM 6% were tested with the five constituents of the mix. Twelve patients tested positive to all constituents of the mix, whereas the other patients had varying patterns of positive reactions. The overall results of the primary and possible secondary testing are shown in Table 2. In 4 patients, the relevance was not recorded; of the remaining 72 patients, more than 80% were considered to have reactions of current and/or

Table 2. Distribution of positive reactions to the constituents of Compositae mix 6% pet. in 76 patients with positive reactions to the mix

Allergen	Number of patients positive in primary testing	Number of patients positive in secondary testing	% positive
Feverfew extract 1% pet.	52	56	74
Tansy extract 1% pet.	51	53	70
German chamomile extract 2.5% pet.	49	52	68
Yarrow extract 1% pet.	31	35	46
Arnica extract 0.5% pet.	18	20	26

Table 3. Distribution of positive reactions to the five constituents of Compositae mix 6% pet. in 76 patients [no. (%)] with varying degrees of sensitivity to the mix

Allergen	Strength of reaction to Compositae mix 6% pet.			Total number of positive reactions
	1+ (n = 21)	2+ (n = 32) ^a	3+ (n = 24) ^a	
Feverfew extract 1% pet.	7 (33)	27 (84)	23 (96)	57
Tansy extract 1% pet.	5 (24)	27 (84)	22 (92)	54
German chamomile extract 2.5% pet.	6 (29)	23 (72)	24 (100)	53
Yarrow extract 1% pet.	3 (14)	13 (41)	19 (79)	35
Arnica extract 0.5% pet.	2 (10)	10 (31)	8 (33)	20

^aOne patient was tested twice with the mix and constituents, and had 2+ and 3+ reactions to the former, making the number of patients with assessable reactions 77.

old relevance. The 76 patients comprised 62 females with a mean age of 49 years and 14 males with a mean age of 52 years. The majority of the patients had strongly positive reactions to the mix. Table 3 shows the distribution of reactions to constituents, depending on the degree of sensitivity to the mix.

Between November 2006 and July 2011, 29 patients with positive reactions to CM 5% were tested with constituents of the mix: they comprised 24 females (mean age 56 years) and 5 males (mean age 55 years). The overall results are shown in Table 4. All reactions were of current and/or old relevance. As one of the constituents, parthenolide 0.1% pet., was included in the baseline series in this period, testing with this compound was sometimes slightly displaced relative to testing with the other constituents: in the majority of cases, CM 5% and parthenolide were tested simultaneously. In 3 cases, however, parthenolide was re-applied along with the other constituents on a later occasion, because of negative reactions in the first testing. In 1 case, positive patch test reactions to parthenolide preceded testing with both CM 5% and the other constituents, and in 2 cases,

Table 4. Distribution of positive reactions to the constituents of Compositae mix 5% pet. in 29 Compositae mix-sensitive patients with varying degrees of sensitivity

Allergen	Strength of reaction to Compositae mix 5% pet.			Total number of positive reactions
	1+ (n = 1)	2+ (n = 25)	3+ (n = 3)	
Parthenolide 0.1% pet.	0	23	3	26
Tansy extract 1% pet.	0	18	3	21
Yarrow 1% pet.	0	8	2	10
Arnica extract 0.5% pet.	0	0	0	0
Roman chamomile 1% pet.	0	0	0	0

Table 5. Percentage of positive reactions to constituents of Compositae mix 6% pet. in two German studies and one Danish study

Study	German				
	Feverfew	Tansy	chamomile	Yarrow	Arnica
Germany 1985–1990 (n = 56–85) (1)	70	61	57	53	52
Germany 1996–1999 (n = 39) (7)	51	49	33	31	8
Denmark 1990–1998 (n = 129) (2)	81	77	64	41	23

parthenolide was tested 3–4 days prior to application of CM 5% and the other constituents. The majority of the reactions to the mix were 2+ reactions: only 1 patient had 1+ and three 3+ reactions. Thus, the results in Table 4 mainly reflect the results for patients with 2+ reactions to the mix.

Discussion

Previous studies on sensitization to CM 6% pet. and its constituents comprise two German and one Danish report, and the main results are presented in Table 5 (1, 2, 7). In the first and largest German study (1), the number of patients tested with the constituents varied from 56 to 85, and in the Danish study (2), the patients were tested with a Danish feverfew extract instead of the original feverfew extract used in the Compositae mix from Trolab®. Despite these methodological flaws, the results of the previous and present studies are similar as far as ranking of positive reactions is concerned: feverfew tested positive most frequently, followed by tansy, German chamomile, yarrow, and arnica.

Feverfew is native to the Balkan Peninsula, but has spread to most continents, including Australia, Asia, North Africa, Europe, and South and North America (8). It is a perennial plant that is fairly common in Danish

gardens and in the wild. Feverfew contains a variety of sesquiterpene lactones, representing three major structural groups, namely the eudesmanolides, the guaianolides, and the germacranolides (8). The composition in the individual plants varies according to the provenance. In western Europe, the germacranolide parthenolide is the main sesquiterpene lactone. Parthenolide may account for up to 85% of the total sesquiterpene lactone content, and its concentration may exceed 1.2% of the dry weight of post-flowering feverfew leaves, a figure that has been reported for a cultivar named *Tanacetum parthenium* f. *flosculosum* (D.C.) Beck (8, 9). As parthenolide is a strong sensitizer (10), the high concentration in feverfew confers strongly allergenic properties on the plant (10). Sensitization may occur through direct contact by gardening and weeding, and may be perpetuated by recurrent contact with airborne parthenolide-containing plant particles (11). However, even among the most sensitive feverfew-allergic persons, with positive reactions to a 0.01% extract of feverfew, the relevance of the reactions is unknown in about half of the cases (2). These results may be explained by the cross-reactivity that occurs regularly within the different structural groups, in this case the germacranolides (12). Notably, clinical and experimental studies provide evidence that feverfew and parthenolide cross-react with autumn-flowering chrysanthemums (*Chrysanthemum* cv., formerly described by some authorities as *Dendranthema* cv.) (2, 13, 14). This is probably an important primary sensitizer in Europe, considering its widespread use as an ornamental (10). Parthenolide has been detected not only in species of the genus *Tanacetum*, such as feverfew and tansy, but also in several species from other Compositae genera, such as *Ambrosia*, *Anthemis*, *Arctotis*, and *Inula*, as well as some Magnoliaceae genera (15), thus broadening the spectrum of possible cross-reactivity to plants containing parthenolide and other germacranolide sesquiterpene lactones. In theory, the inclusion of parthenolide in the baseline series since 1995 may have facilitated cross-reactivity to parthenolide-containing plant extracts, but the ranking of positive reactions was similar in the German studies (1, 7), and in a small Danish study conducted prior to 1995, feverfew tested positively most frequently, so any contribution by this facilitation seems to be less important (16).

Tansy is a common weed in Denmark, and even though it is probably handled less often than feverfew, its content of parthenolide will cause positive patch test reactions like feverfew, because of either primary sensitization or true cross-reactivity.

In contrast to tansy, German chamomile is not a common Danish weed: the plant is found in most of Europe,

but is probably native only in the south and east. German chamomile is considered to be a weak sensitizer (10), and it is therefore quite surprising that this plant comes third in the ranking. German chamomile has been used as a herbal drug worldwide for thousands of years by both laymen and physicians (17). In a recent German prospective study on prescribing patterns and adverse drug reactions, conducted among primary-care physicians who were members of the German National Association of Anthroposophic Physicians, 18 830 of 50 115 patients received Compositae-containing remedies, most frequently German chamomile (18). However, in accordance with other studies, the risk of adverse drug reactions was not high for remedies containing Compositae in general and German chamomile in particular (18, 19).

The most therapeutically important compounds of German chamomile are found in the essential oil and the flavonoid fraction (20). The former has been detected in all organs of the plant, and is most abundant in the flowers, which contain more than 120 compounds (20, 21). German chamomile flower oil consists mainly of sesquiterpene derivatives, including two sesquiterpene lactones, namely matricin and matricarin (15, 20). The essential oil of European German chamomile does not contain or contains only traces of the strong sesquiterpene lactone allergen anthecotulide, which has been detected in German chamomile preparations of South American origin (10, 22). Chamomile tea contains 10–15% of the essential oil in the flowers (21). In a Swedish study on contact allergy to German chamomile tea of Swedish origin, 30 of 35 Compositae-sensitive patients tested positive to the tea, and 15 were positive to different fractions of the tea tested with thin-layer chromatograms (23). The authors concluded that several sensitizers were present (23). In a subsequent study, no reactivity was detected to the spot containing matricarin, and, likewise, Hausen could not show any clinical reactivity to matricin (22, 24), suggesting that the primary sensitizers were not sesquiterpene lactones. Hausen mentioned coumarins and flavonoids from German chamomile as alternative sensitizers, and the coumarin herniarin has been reported to elicit positive reactions in clinical studies (10, 25, 26). Furthermore, the sesquiterpene alcohol bisabolol or one of its oxidation products has been reported as allergenic (27), and, more recently, clinical studies have suggested that bisabolol is an important chamomile allergen (28, 29). In an American study by Jacob et al., 4 of 7 children with self-reported intolerance to a moisturizer containing bisabolol tested positive to the moisturizer, bisabolol, and the sesquiterpene lactone mix and/or CM 6%, and improved clinically after avoidance of the cream (29).

Whichever allergens are most important, German chamomile is a weak sensitizer, and the high prevalence of positive reactions seems to be caused by cross-reactivity (10). The evidence is based on clinical observations suggesting cross-reactions between chrysanthemum and German chamomile (30).

Yarrow is a common weed in Denmark, and is native to Europe, western Asia, Caucasia, and northern Iran, and is naturalized as far away as Australia, New Zealand, and North America (10). Like feverfew and German chamomile, yarrow is an old medicinal plant (10). The main sesquiterpene lactone allergen is a guaianolide of peroxide character, α -peroxyachifolid, which is a strong sensitizer (31). Another weed of the genus *Achillea*, *Achillea ptarmica* (sneezewort or sneezewort yarrow), and the cultivated *Achillea filipendulina* (fernleaf yarrow), contain similar or closely related compounds (10). Contact dermatitis from yarrow has been known for more than 100 years, and Hausen et al. list at least 78 case reports, but, nevertheless, few cases of sensitization from yarrow-containing herbal remedies and/or cosmetics have been published (19, 31). Thus, it is likely that some persons are sensitized by gardening and weeding, whereas others test positive because of cross-reactivity. Primary sensitizers in humans are rarely found, but prevalences of positive yarrow reactions ranging between 33% and 79% among occupationally sensitized persons (especially to chrysanthemums) are suggestive of cross-reactivity (2, 30).

The fifth constituent of CM 6% is arnica, another medicinal plant that has been in use in Europe from the 16th century to the present day (10, 18). Arnica contains several strongly allergenic sesquiterpene lactones of the pseudoguaianolide type, including helenalin, which make both the fresh plant and the commercial drug preparations sensitizing (and irritant) (10, 32). Arnica is not a common weed in Denmark, and sensitization by direct contact is therefore less likely. Previously, sensitization occurred mainly from the topical use of tincture of arnica, but contact allergy has also been reported from arnica-based massage oils, and aqueous extract of arnica (2, 32, 33). The concentration of sesquiterpene lactones is highly variable in the different preparations: in a Danish study on Compositae-containing cosmetics and herbal remedies, the content of sesquiterpene lactones was higher in an arnica CO₂ extract than in the tincture and the infusion, where sesquiterpene lactones were detected in minute or trace amounts only (33). This suggests the presence of other allergens, as the infusion, and possibly also the tincture, elicited positive reactions (33). The prevalence of positive reactions in the present study may, of course, also reflect differences in the use of arnica preparations: in

the German study, 10 of 44 arnica-sensitive persons were mono-sensitized to this extract, indicating that arnica was the primary sensitizer, whereas only one person was mono-sensitized to arnica in this study (1).

According to Hausen, cross-reactions between arnica and tansy, yarrow, chrysanthemum and feverfew are frequently reported, and although 19 of the 20 arnica-allergic patients in the present study tested positive to at least one other constituent, the lower prevalence of positive arnica reactions shows that cross-reactivity is not obligatory and probably reflects the contribution of different primary sensitizers rather than the sesquiterpene lactones in the four above-mentioned plants. Generally speaking, the stronger the reactions to CM 6%, the higher the prevalence of positive reactions to any of the constituents, suggesting that persons with 2+ and 3+ reactions were broadly sensitized. However, even in these groups of patients, only one-third tested positive to arnica (Table 3).

A possible confounding factor when testing with CM 6% and constituents is sensitization to sorbitan sesquiolate, which is used in all preparations as an emulsifier. Screening for sorbitan sesquiolate contact allergy was not performed on a routine basis in this period. Typically, persons with sensitization to this emulsifier will show uniform positive reactions to all constituents. However, the 12 patients who tested positive to all ingredients had positive reactions to pure sesquiterpene lactones or/and Compositae extracts without sorbitan sesquiolate, indicating that the reactions are not attributable to sorbitan sesquiolate sensitization only.

Concerning CM 5% pet., no studies on patch testing with the constituents have been published. However, the pattern of reactivity to single components in the small group of patients in this study has some similarities to that of the CM 6% extracts: the majority of patients tested positive to parthenolide or the parthenolide-containing tansy extract. In a recent study, parthenolide was a slightly better screening agent for Compositae sensitization than the sesquiterpene lactone mix, and positive reactions to this baseline sesquiterpene lactone will therefore probably elicit positive reactions to CM 5% when tested simultaneously or a few days apart (34). The third in the ranking was yarrow, which tested positive in about one-third of the patients: this may be close to the prevalence in CM 6%-positive patients, taking into account the lower number of CM 5%-positive subjects.

The most surprising result is the lack of positive reactions to arnica and Roman chamomile. Concerning arnica, this may be caused by differences in the plant material used for the test preparations (2). The Roman chamomile extract from Chemotechnique Diagnostics[®],

on the other hand, tested positive in several patients in both a Swedish and a Danish study (23, 33). The recommended patch test concentration is 1% pet., but the concentration is more than double this in CM 5% (Table 1), which theoretically may contribute to the positive CM 5% reactions without this being recognized when testing with this constituent at the lower concentration. Roman chamomile is native to western Europe (Portugal, Spain, and France), North Africa, and the Azores, and is not found in Denmark (35). The plant contains germacranolide sesquiterpene lactones, the main one being nobilin, and, according to Hausen, positive reactions to Roman chamomile are occasionally seen in Compositae-sensitive persons (10, 35). Roman chamomile has been used as a medicinal plant since the 16th century, and is indicated for the same ailments as German chamomile, although they are chemically different (35). However, whereas German chamomile is used in central Europe, Roman chamomile is the chamomile used in the UK, France, and Belgium (35). This geographical difference may account for the lack of positive reactions in the present study. On the basis of this, it seems wise that a new version of CM 5% (Compositae mix II; Chemotechnique Diagnostics[®]), containing extracts of both German and Roman chamomile, was launched in 2011.

We know from the Swedish multicentre study on CM 5% that the detection prevalence of the sesquiterpene lactone mix as compared with CM 5% varies considerably, depending on the geographical location, probably reflecting differences in exposure to Compositae (5). Thus, some centres would benefit from inclusion of CM 5% in the baseline series, and others would not (5). This observation emphasizes the usefulness of plant extracts and the need for both a local and an individual approach when choosing Compositae patch test materials. As underlined by Geier and Hausen, the short ether extracts contain not only sesquiterpene lactones, but also other potential allergens (7). As mentioned above, clinical studies on German chamomile and, to a lesser degree, on arnica suggest the presence of allergens other than sesquiterpene lactones.

In conclusion, although the majority of patients test positive to parthenolide and/or parthenolide-containing plant extracts, and parthenolide may thus be a suitable supplement to the sesquiterpene lactone mix in the baseline series, it is important to patch test with extracts of native or locally grown plants, not just because of the geographical variation, but also because of the potential unknown allergens contained in short ether preparations and the variability in the individual patient's exposure and cross-reaction patterns.

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