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Screening for Compositae contact sensitization with sesquiterpene lactones and Compositae mix 2.5% pet.

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Running head: Screening with SL mix and Compositae mix 2.5%

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ABSTRACT

Background: Compositae contact sensitization may be difficult to diagnose because of a lack of reliable screening allergens.
Objectives: To assess the suitability of Compositae mix II 2.5% pet. (CM2.5) as a screening mix in the baseline series combined with sesquiterpene lactone (SL) mix and parthenolide (PTH).
Methods: CM2.5 was added to the baseline series, which included SL mix and PTH 0.1% pet., in January 2015, and PTH was included in TRUE Test Panel 3 in October 2015. All Compositae-sensitive patients diagnosed or tested in the next 4 years were assessed.
Results: Altogether, 57 patients (2.7%) presented with Compositae allergy. At the primary testing in 53 newly diagnosed patients, SL mix elicited positive reactions most frequently (53% positive), followed by CM2.5 (47% positive), and PTH (45% positive). CM2.5 and PTH pet. elicited a few irritant reactions. Three patients had late reactions. Altogether, 16 patients (28%) were not detected by any of the 3 screening agents.
Conclusions: The SL mix is an indispensable, though insufficient, screening mixture in Denmark. It may be relatively safely supplemented with CM2.5 and PTH in the TRUE Test system for screening, but when Compositae sensitization is suspected, further extracts should be tested based on history.

Key words: allergic contact dermatitis; Asteraceae; Compositae mix II 2.5%; Compositae mix II 5%; sesquiterpene lactone mix; parthenolide; baseline series; patch testing

1. Introduction

Plants of the Compositae (Asteraceae) family are the most important causes of plant allergy in Europe today. The diagnosis is not always obvious because of the variable clinical pattern of Compositae dermatitis and the lack of reliable screening agents.[1-4] According to the literature, the commercial sesquiterpene lactone mix (SL mix), which is currently part of the European baseline series, detects between 35 and 65% of Compositae-sensitized patients.[3-6] The addition to the baseline series of another commercial SL allergen, parthenolide (PTH) 0.1% pet. may raise the detection rate another 10% in Northern Europe.[7] Mixtures of plant extracts or plants extracts with a SL allergen are commercially available. The original Compositae mix 6% pet. has a higher detection rate than the SL mix, but if it is applied for 48 hours instead of the 24 hours suggested in one of the first reports [8], it carries a risk of false positive reactions and allegedly active sensitization.[4,2,9]

In a Swedish multicentre study comparing the detection rate of SL mix and Compositae mix 5% pet. in 2818 patients,[10] 0.9% tested positive to SL mix compared to 1.1% positive to Compositae mix 5% pet.. The authors concluded that the difference was too small to justify the inclusion of Compositae mix in the baseline series in addition to the SL mix, but mentioned the possibility of substituting SL mix with the Compositae mix despite 2 cases of suspected active sensitization.[10]

The Compositae mix 5% pet. has been further developed to Compositae mix II, which is available at 2 concentrations (Table 1). The aim of this study is to assess the suitability of Compositae mix 2.5% pet. (CM2.5) as screening mix in the baseline series in its own right as well as combined with the SL mix and PTH.

2. Materials and Methods

The SL mix and PTH were included in the baseline series in 1990 and 1995, respectively. Furthermore, CM2.5 was added in January 2015, and True Test Panel 3, which includes PTH 3 µg/cm^2, in October 2015. Parthenolide was thus patch tested in duplicate in consecutive patients. The SL mix was obtained from Trolab (Almirall Hermal, Reinbek, Germany) and more recently from AllergEaze (SmartPractice, Phoenix, Arizona), which also supplied PTH in True Test Panel 3. Parthenolide 0.1% pet., the Compositae mixes II 2.5% and 5% pet. and the individual ingredients were obtained from Chemotechnique Diagnostics (Vellinge, Sweden). The patch testing was supplemented with Compositae mix II 5% pet. and selected allergens and extracts, where appropriate. The petrolatum-based allergens and mixtures were placed in 8 mm Finn Chambers on Scanpor (SmartPractice, Phoenix, Arizona) for 2 days. Readings were performed on day (D) 3/4 and D7 in accordance with the latest recommendations.[11] Reactions were recorded as irritant only if epidermal signs of irritancy such as a shiny stratum corneum were present.

3. Results

From January 2015 to March 2019, 2131 patients were patch tested with SL mix, 2075 with CM 2.5, and 1663 and 2057, respectively, with PTH 3µg/cm^2 and/or PTH 0.1% pet., respectively. The number of newly diagnosed Compositae-sensitive patients at this department was 57, making the

overall prevalence – on the basis of patients tested with the SL mix – 2.7%. Another 12 patients, who had been diagnosed with Compositae contact allergy previously at the department, were also patch tested in the period.

The newly diagnosed patients comprised 47 females (including 3 girls, 3, 5, and 17 years old) with a mean age of 50 years, and 10 males (including 2 boys, 14 and 17 years old) with a mean age of 51 years. In the majority of patients (91%), Compositae sensitization was considered to be of current or old relevance.

The results of patch testing with the 3 above-mentioned screening agents among the newly diagnosed patients are shown in Table 2. Four newly diagnosed patients were not tested with all 3 screening allergens and hence were not included in Table 2. The prevalence of positive reactions rose on subsequent patch testing, and if the 4 above-mentioned patients were included, the prevalence of positive reactions was 65% for SL mix, 61% for PTH and 57% for CM2.5 for all 57 (56 for PTH and CM2.5) patients. Altogether, 34 (64%) of the 53 newly diagnosed Compositae-allergic patients who were tested with all allergens at the primary testing were diagnosed by the 3 screening agents (Table 3). The 19 newly diagnosed Compositae-allergic patients, who were not detected by the screening allergens, included 3 patients with late reactions and 1 patient with doubtful reactions to both CM 2.5 and CM5. The positive Compositae reactions in the remaining 15 patients, not detected by any of the screening mixes or allergens, are presented in Table 4.

Among all consecutive patients tested in the study period, two irritant reactions to CM2.5 and 3 to PTH 0.1 pet., respectively, were recorded. No irritant reactions to the SL mix or PTH in the TRUE Test system were observed. Concerning patch testing with constituents of the Compositae mix II 5% pet., 40 patients (newly diagnosed as well as re-tested patients) were patch tested with the ingredients, and the results are shown in Table 5. The concordance between patch test reactions to PTH in pet. and PTH in the TRUE Test system in Compositae-sensitive patients tested with both preparations simultaneously is shown in Table 6. In general, however, the reactions to PTH in the TRUE Test were slightly weaker and developed more slowly compared to PTH in pet.

Three patients had late reactions, which were considered to be true, late positives of current and/or past relevance: a 22-year-old, atopic female with summer-exacerbated hand eczema since childhood (itching on the back from about D18), a 44-year-old, atopic female, who had worked as a sandwich maker many years ago (reactions noted on D12/13), and a 43-year-old, non-atopic female, who was seen on D19 because she had noticed a reaction on her back.

Overall, 15 of the 57 (26%) newly diagnosed patients had or had had atopic dermatitis, and another 11 had symptoms of mucosal atopy and/or a positive prick test to a standard inhalant allergen. All 5 patients younger than 18 years had atopic dermatitis. For comparison, the MOAHLFA index from January 2015 to March 2019 recorded atopic dermatitis in about 23% of all non-Compositae-sensitive patients tested. All atopic children and 6 of the 10 adults with current/previous atopic dermatitis had positive patch reactions to at least one of the 3 screening agents at the primary testing.

Possible/partly/definite occupational exposure, either currently or previously, was reported in 10 patients (17.5%); this is a low prevalence compared with patients without Compositae sensitization in the same period, 26.5% of whom, according to the MOAHLFA index, reported occupational dermatitis. At the primary testing, 50% of the occupationally exposed had positive patch test reactions to SL mix, whereas 30% were positive to PTH and CM2.5. For comparison, the corresponding figures in non-occupationally exposed were 53% positive to SL mix, 49% positive to PTH, and 51% positive to CM2.5. However, 6 of the 10 occupationally exposed had doubtful reactions to CM2.5%, including 4 with lettuce sensitization.

4. Discussion

The prevalence of Compositae sensitization in the general patch test population of our department of dermatology has been reported previously: in the first 8-year period, the prevalence was 4.3%, whereas a study of the first 26 years showed a prevalence of 4%.[2,6] The decline was statistically significant when comparing the prevalence of the period 2002-2008 with that of the period 2009-2015.[2] The present prevalence of 2.7% may thus reflect a further decline, or it may reflect random fluctuation in referral patterns in the last, shorter, study period of 4 years and 2 months. However, the prevalence is high enough to justify the inclusion of screening allergens in the baseline series. The percentage of females was 75% in the two above-mentioned studies, and is thus higher in the present study. [2,6]

The mean age of both sexes was slightly lower compared with a mean age of 51.5 years for females and 55 years for males in the 8-year study.[6] This reflects the 2 small children and 3 adolescents in the relatively small group of newly diagnosed Compositae-sensitive patients. The prevalence of atopic dermatitis does not differ much from that of the whole patch test population in the study period, whereas the prevalence of atopy, that is atopic dermatitis and/or hay fever and/or asthma and/or a positive prick test to a standard inhalant allergen, of 46% is higher than the 28% reported in the 8-year study.[6] Again this may be because of the shorter present study period with fewer patients.

In general, larger studies on SL mix as a screening mixture in consecutive eczema patients report SL mix reactions in 0.5-1.8% of patients. [12-16] There is considerable regional variability: in a European multicentre study[15] with a mean prevalence of 0.76% SL mix-patch test positive patients, a clinic in the UK had 2.2% positives to the SL mix. In a smaller study of 1354 Chinese patients[17], the SL mix elicited positive reactions in 7.5% of patients tested. The prevalence of positives in the present study of 37 of 2131 tested (1.7%) is thus rather high compared with more recent data form European and North American reports. [14-16]

Concerning the detection rate among Compositae-sensitive patients, studies in selected patient groups, with known or suspected Compositae contact allergy, have shown SL mix detection rates of 35-58% compared with oleoresins or extracts that detected the rest of the patients. [3, 5] The first study comparing the SL mix and Compositae mix 6% in a "general patch test population"[4] came to the same conclusion: SL mix detected 42% of Compositae-sensitive patients, whereas the Compositae mix 6% detected 90%, but the authors noted more irritant reactions to the latter. Geier and Hausen[18]

compared the detection rate of Compositae mix 6% pet. and the SL mix in 3703 patients, and the SL mix detected 47%, whereas the Compositae mix detected 92%. In our area, the study from an 8-year period in the 1990s reported a SL mix detection rate of 65% in 189 Compositae-sensitive patients.[6] In the present study, the SL mix detected only 53% in the first patch test session (Table 2). Nevertheless, the SL mix was the allergen eliciting most positive reactions among the 3 screening agents, followed by CM2.5, and parthenolide at the primary screening (Table 2). If all patch test results in the study period were included, the prevalence of positive SL mix reactions rose to 37 of the newly diagnosed 57 (65%), which is exactly the same figure as in the previous 8-year study. [6]

When the original Compositae mix 6% pet., consisting of ether extracts of arnica, German chamomile, yarrow , tansy and feverfew (*Tanacetum parthenium* (L.) Sch.Bip.) was added to the baseline series at clinics using 48 hours' exposure, the prevalence of positive reactions was high, ranging from 2.2 to 6.1%, but so was the prevalence of weak positive or irritant reactions and soon cases of sensitization were reported. [9,16,18,19] This prompted a study[20] on a lower, optimal concentration of the Compositae mix for screening purposes. However, in a British multicentre study [21], even a concentration as low as 3% was found to be sensitizing.

The Compositae mix 5% pet. originally consisted of arnica, Roman chamomile, yarrow, tansy, and parthenolide. It has also been used as a screening agent in both children and adults. The prevalence of positive reactions is typically lower than that of Compositae mix 6% pet.: the mean prevalence of positive reactions in a multicentre study of 2818 Swedish patients[10] was 1.1%, and, likewise, an Italian study[22] of 2614 children younger than 11 years old reported a prevalence of positive reactions of 1.6% . Compositae mix 5% pet. has been further developed to Compositae mix II 5% pet., where German chamomile is added, and this mixture is commercially available at 2 concentrations (Table 1). The CM2.5 has been used in the UK baseline series for at least 4 years without any unwanted effects, including no cases of active sensitization, and recently it was proposed as an addition to the European baseline series.[23] A British study[24] comparing CM2.5 with a dilution of the Compositae mix 6% from Trolab to 2% pet. in 1901 patients concluded that the latter elicited more positive reactions (1.3% positives) than CM2.5 (0.95% positives) and thus was a better screening agent. Even in this study 3 cases of suspected sensitization were reported.[24]

In the present study, CM2.5 was poorer than the SL mix as a screening agent. The prevalence rose on subsequent testing to 57%. However, in several cases, doubtful reactions to CM2.5 led to further patch testing with Compositae mix II 5% pet. which often detected sensitization (Table 4). The doubtful reactions to the low concentration were thus indicative of Compositae allergy.

Despite the fact that PTH is a commercially available SL allergen, very few studies on routine screening have been published. This probably will change as PTH has been included in TRUE Test Panel 3. A Danish 15-year study[7] on screening with SL mix and PTH 0.1% pet. showed an overall prevalence of positive patch test reactions of 2.19 and 2.25% , respectively. The conclusion was that although the inclusion of PTH increased the detection rate with 10%, it also carried a small risk of active sensitization. A more recent study from North America and Canada[16] reported a prevalence of 0.5%. In the present study, PTH had a detection rate on a par with that of CM2.5 at the primary

testing, but only 2 patients were diagnosed by the allergen on its own (Tables 2 and 3). The concordance between reactions to PTH in pet. and PTH in TRUE Test was fairly high (Table 6). As the reactions to PTH in the TRUE Test were slightly weaker and developed more slowly compared to PTH in pet., a D7 reading was important to record the maximum reaction and to not miss any positives on D7. In accordance with this, only 1 patient was detected by TRUE Test and not the pet. preparation.

The results of patch testing with the constituents of CM2.5 are presented in accordance with the time of testing. Even though the number of positive reactions was higher on subsequent testing for most of the allergens, as expected, both the ranking and the distribution of reactions to the individual allergens/extracts were very similar in the 2 groups. Parthenolide and the PTH-containing tansy extract elicited positive reactions most frequently, followed by yarrow and the same low number to Roman and German chamomile, whereas no one had positive reactions to arnica (Table 5). Only 2 patients had positive patch test reactions to Roman and German chamomile, and both were strongly sensitized with 3+ reactions to all 3 screening agents. In a study from the present department in the period 2006-2011[25], the distribution of positive reactions to constituents of the previous Compositae mix 5% pet. in 29 Compositae-sensitive patients showed 90% positive to PTH, followed by tansy (72% positive), and yarrow (34%), whereas no one tested positive to Roman chamomile and arnica . Likewise, Bauer et al.[26] reported the highest prevalence of positive reactions to PTH and tansy, followed by yarrow, and a smaller number to German chamomile, Roman chamomile, and arnica in both 249 florists and more than 3000 controls.

For comparison, patch testing with the extracts of the original Compositae mix 6% pet., 2 German[8,18] and 1 Danish study[27] (from the present department) showed similar results concerning the ranking of positive reactions: the feverfew extract elicited positive reactions most frequently, followed by tansy, German chamomile, yarrow, and arnica. At our department, the prevalence of positive reactions to German chamomile was as high as 64%, which makes the paucity of positive chamomile reactions in the present study all the more surprising.[27] German chamomile is considered to be a weak sensitizer, and the frequent positive reactions may be cross-reactions to other Compositae plants. [28] However, the concentration of German chamomile in both Compositae mix 6% pet. and the constituent test preparation was 2.5%, which is the recommended concentration for patch testing[28], whereas the corresponding concentrations in Compositae mix II 5% pet. and the constituent test preparation is 1.2% and 1%, respectively. This may explain the difference in test results in Germany and Denmark as well as the fact that only highly sensitive patients will react to the extract. [8, 18, 26, 27] In addition, the origin of the plant material may contribute: different chemotypes, that is groups of plants belonging to the same species, but producing different sets of secondary metabolites because of genetic variability, of chamomile exist, and this is also true of tansy, yarrow, and arnica. [29-32] Concerning yarrow, 1 patient had a negative reaction to yarrow when patch tested with constituents of Compositae mix II 5% pet., but a positive reaction to a yarrow extract from another supplier (Table 4). Roman chamomile was tested at the recommended concentration of 1% pet.[28] The low prevalence of positive reactions may be ascribed to it not being found and rarely used in Denmark, while it is traditionally the chamomile used in the UK, France, and Belgium.[33] In the first German study[8] of Compositae mix 6% pet., arnica elicited

positive reactions in 52% of the patients, in the second German study[18] only in 8%. The prevalence of positive reactions in the Danish 8-year study from the 1990s was 23%.[27] The lack of positive reactions now may reflect a declining use of sensitizing arnica preparations, such as arnica tincture, and/or a poorer quality of the plant material used. Arnica (*Arnica montana* L.) is a threatened species in Europe, and according to Hausen, another species of arnica (*Arnica chamissonis* Less.) may be used as a substitute as it contains the same active compounds.[28]

Taken together, patch testing with constituents of Compositae mix II 5% pet. does not provide much additional information, when PTH is tested routinely, as PTH and PTH-containing plant extracts elicit reactions most frequently -- and this information may already be available from the baseline series. Altogether, 19 Compositae-sensitive patients were not detected by any of the screening agents; if the 3 patients with late reactions are excluded, this means that 16 patients (28%) went undetected. Sometimes, patients occupationally exposed to Compositae are narrowly sensitized to a few species, and, of the 16 patients, 3 had had possible and 2 definite occupational exposure now or previously.[27] This means that half of the occupationally exposed was found in this subgroup. It is well-known that patients with lettuce sensitization may react to Compositae mix rather than SL mix.[34] The doubtful reactions to CM2.5 in our patients with occupational exposure lead to further patch testing with CM5% which was most often positive.

Active sensitization in the 3 patients with late reactions cannot be ruled out because the concentration of PTH, tested in duplicate as well as in CM2.5, may have reached a critical, sensitizing level. However, the Compositae sensitization could be relevant in all 3 patients, and we have previously reported on late reactions in patients with known Compositae sensitization, suggesting reactivation reactions may appear later than D7.[6]

5. Conclusions

Even though the detection rate of the SL mix was only up to 65%, it was the best screening agent among the 3 studied here. Both CM2.5 and PTH detected patients in their own right; the fact that PTH was tested in duplicate and at a higher concentration than that of CM2.5, of which it seemed to be the main allergen, may have led to a higher prevalence of positive reactions to PTH after repeated testing. However, CM2.5 performed slightly better than PTH at the primary testing, and it elicited doubtful reactions, which turned out to be indicators of Compositae sensitization: such reactions should be followed up by testing with Compositae mix II 5% and /or other allergens.

The TRUE Test preparation of PTH developed positive reactions that were slightly weaker and more slowly appearing than those of PTH in pet. On the other hand, no irritant reactions were recorded to the TRUE Test preparation. Reading at D7 is recommended when testing with CM2.5 and PTH in the TRUE Test system.

An important observation is that 28% of the Compositae-sensitized would not have been detected by the combination of the 3 screening agents. This emphasizes the importance of individual history taking and supplementary testing with relevant, often local, plant extracts. The findings also emphasize the difficulties in developing suitable Compositae screening allergens and extracts. In view of the safe and non-irritant nature of the SL mix, it seems to be an indispensable, though insufficient, screening mixture in Denmark. It may be relatively safely supplemented with CM2.5 and PTH in the TRUE Test system for screening purposes, or with Compositae mix II 5% pet., despite a small risk of sensitization, but when Compositae sensitization is suspected, further extracts should be tested based on the patient's history.

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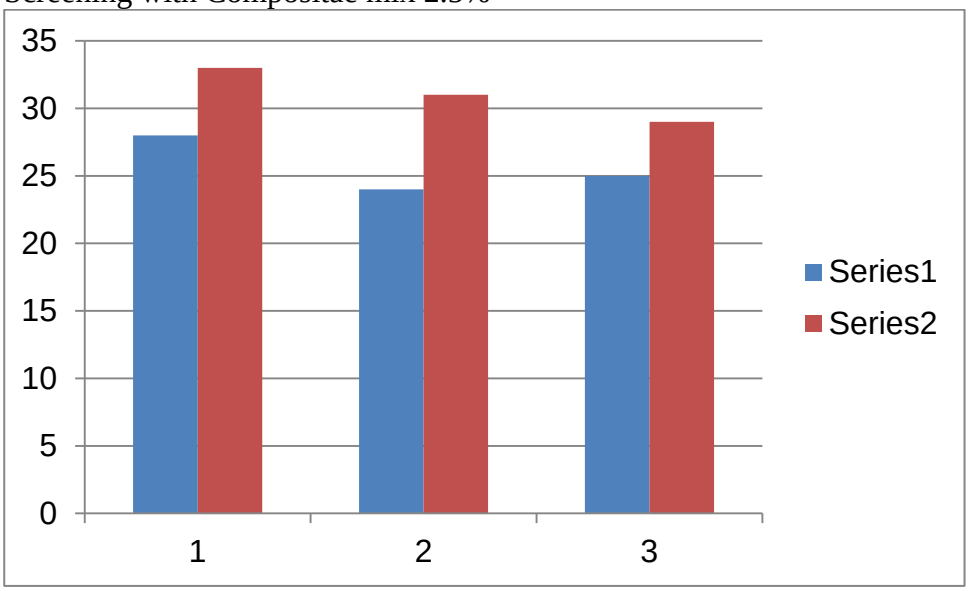
Screening with Compositae mix 2.5%



1= sesquiterpene lactone mix 0.1% pet. at primary and secondary testing
2= parthenolide 3µg/cm^2 and/or 0.1% pet. at primary and secondary testing
3= Compositae mix II 2.5% pet. at primary and secondary testing

Graphical abstract
Highlights

Screening with Compositae mix 2.5%

The Compositae mix 2.5% is a poorer screening mix than the sesquiterpene lactone mix and on a par with parthenolide in consecutive eczema patients.

Doubtful reactions to Compositae mix 2.5% may be markers of contact sensitization to Compositae.

The sesquiterpene lactone mix should be supplemented with Compositae mix 2.5% and parthenolide for screening.

Table 1. Concentration of the constituents of Compositae mix II 5% and 2.5% pet.

	Compositae mix 5% pet.	**Compositae mix 2.5% pet.**
Extract/allergen		
Roman chamomile (*Anthemis nobilis*) extract	1.2%	0.6%
German chamomile (*Chamomilla recutita*) extract	1.2%	0.6%
Milfoil (*Achillea millefolium*) extract	1.0%	0.5%
Tansy (*Tanacetum vulgare*) extract	1.0%	0.5%
Arnica (*Arnica montana*) extract	0.5%	0.25%
Parthenolide	0.1%	0.05%

Table 2. Distribution of positive reactions to Compositae screening allergens/extracts of the baseline series in 53 newly diagnosed Compositae-sensitive patients at the primary and possibly secondary testing (that is, re-testing with same allergens on a later occasion)

		No. of patients	
Mixture/allergen	**Tested**	**Positive primary (%)**	**Positive secondary testing (%)**
SL mix 0.1% pet.	53	28 (53%)	33 (62%)
Parthenolide 3 µg/cm^2 and/or 0.1% pet.	53	24 (45%)	31 (58%)
CM II 2.5% pet.	53	25 (47%)	29 (55%)

Table 3. Distribution of positive and negative reactions to Compositae screening allergens at the primary testing in 53 newly diagnosed Compositae-sensitive patients tested with all 3 allergens

Number positive to SL mix and parthenolide and Compositae mix 2.5%	21
Number positive SL mix or Compositae mix 2.5% or parthenolide	12
Number positive SL mix and parthenolide	1
Number negative SL mix, parthenolide and Compositae mix 2.5%	19

Table 4. List of Compositae extracts eliciting positive reactions in 15 patients* with negative reactions to Compositae screening agents of the baseline series

Compositae mix II 5% pet.(4 patients)
Compositae mix II 5% and feverfew (*Tanacetum parthenium* (L.) Sch.Bip.) 1% pet.
Compositae mix II 5% pet. and German chamomile (*Matricaria chamomilla* L.) extract 2.5% pet.
Compositae mix II 5% pet. and lettuce (*Lactuca sativa* L.) "as is"
Chrysanthemum extract 3% pet.
Milfoil (*Achillea millefolium* L.) extract 1% pet. (2 patients, different extracts)
Goldenrod (*Solidago virgaurea* L.) oleoresin
German chamomile extract 2.5% pet.
Mugwort (*Artemisia vulgaris* L.) leaf as is
Dandelion (*Taraxacum officinale* (L.)Weber ex F.H.Wigg.) 2.5% pet.
Dahlia oleoresin

*Of the 19 patients in Table 3, 3 patients with late reactions and 1 patient with a doubtful positive reaction to Compositae mix 2.5% pet. are not included in this table

Table 5. Distribution of positive reactions to constituents of Compositae mix II in 40 patients with positive reactions to Compositae mix 2.5% pet. and/or Compositae mix 5% pet. (newly diagnosed and re-tested patients)

Tested simultaneously with the mix (N=28)*	**Nos. positive/tested (%)**
Tansy 1% pet.	8/28 (28.5%)
Arnica 0.5% pet.	0/28
Parthenolide 0.1% pet.	18/28 (64%)
Roman chamomile 1% pet.	1/28 (3.5%)
German chamomile 1% pet.	1/28 (3.5%)
Milfoil 1% pet.	7/28 (25%)

Tested with constituents later (N=13)*	**Nos. positive/tested (%)**
Tansy 1% pet.	5/13 (38%)
Arnica 0.5% pet.	0/13
Parthenolide 0.1% pet.	12/13 (92%)
Roman chamomile 1% pet.	1/13 (8%)
German chamomile 1% pet.	1/13 (8%)
Milfoil 1% pet.	2/13 (15%)

- 1 patient was tested twice

Table 6. Concordance between patch test reactions to parthenolide 0.1% pet. (PET.) and parthenolide 3µg/cm^2 (TT) in 41 patients tested simultaneously with both preparations

TT/PET.	-	?+	+	++	+++
-	20	2		2	
?+			1	1	
+			2	3	
++		1		7	
+++					2