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A 21-year experience
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Contact sensitization to florists' chrysanthemums and marguerite daisies in Denmark: a 21-year experience.

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Running head: Chrysanthemum and marguerite allergy in Denmark
Summary

Background: Both florists’ chrysanthemums (*Chrysanthemum* cultivars) and marguerite daisies (*Argyranthemum frutescens* (L.) Sch.Bip. and its varieties and cultivars) are popular ornamental plants in Denmark.

Objectives: To present results of aimed patch testing with chrysanthemum and marguerite daisy extracts in Danish patients with Compositae sensitization.

Materials/Methods: The results of patch testing with chrysanthemum extract 3% pet. and marguerite daisy extract 3% pet. (and possibly 1% pet.) were analyzed.

Results: Altogether, 111/191 (58%) had positive patch test reactions to chrysanthemum extract and 104/179 (58%) tested positive to marguerite daisy. The majority was recreationally exposed, and most of the reactions were considered relevant. Feverfew extract 1% pet., Compositae mix 5 or 6% pet. or parthenolide 0.1% pet. may cross-react with chrysanthemum; Compositae mix seems to be best at detecting sensitization to marguerite daisy.

Conclusions: In areas where exposure to chrysanthemum or marguerite daisies is prevalent, it is suggested to include extracts of these plants in the plant series to improve diagnosis of, and advice to, Compositae-allergic patients.

Key words: allergic contact dermatitis; Asteraceae; Compositae; *Chrysanthemum*; marguerite daisy; *Argyranthemum frutescens*; patch testing
1. Introduction

Florists’ chrysanthemums are flowering plants of the genus *Chrysanthemum*, tribe Anthemideae, in the Compositae (Asteraceae) family (Fig.1). Originally native to East China and Japan, they are today popular ornamental plants in large parts of the world, notably Asia, Europe, and North America. Chrysanthemums are used both as cut flowers and potted plants as well as in gardening for herbaceous borders. Most chrysanthemum cultivars are hybrids/chimeras developed from *Chrysanthemum indicum* L. (formerly known as *Dendranthema indicum* (L.) Des Moul) and *Chrysanthemum morifolium* Ramat. (*Dendranthema morifolium* (Ramat.) Tzvelev). Owing to such biological variability, the phytochemical profile may differ between cultivars.

The first case of contact dermatitis from a *Chrysanthemum indicum* cultivar was reported in 1904 in a female gardener, whereas the first patch test with leaves and stem of the plant was performed in the 1930s. Several case reports followed, and later also more case series from both Europe and Japan. Hausen and Schulz reported that chrysanthemum was the most important sensitizer among occupationally exposed persons in Northern Germany, and McGovern and Barkley stated that chrysanthemums caused more occupational dermatitis than any other composite.

Marguerite daisy (*Argyranthemum frutescens* (L.) Sch. Bip.), native to the Macaronesian islands (found in Madeira, Selvagens and Canary archipelagos), has become a very popular summer plant in Denmark, where it is used both for pots, containers and window boxes. The first reports of contact sensitization appeared in 1998 and 2001 in occupationally and non-occupationally exposed persons in Denmark, respectively. Among 190 consecutively tested persons with Compositae sensitization, 89 were patch tested with a marguerite daisy extract, and 66 (74%) were patch test-positive.

As both chrysanthemums and marguerite daisies are commonly cultivated and may be important sensitizers, we report our results with aimed patch testing with extracts of these plants in Compositae-sensitive patients with special reference to cross-reactivity.

2. Materials and Methods

Short ether extracts of unidentified *Chrysanthemum indicum* and marguerite daisy cultivars were incorporated into petrolatum (pet.) in a concentration of 3% (and additionally 1% for marguerite daisy) at the pharmacy of Odense University Hospital and tested in controls as previously reported. The concentration of 3% was chosen because of our experience with a syringe of chrysanthemum cultivar extract 3% pet., kindly supplied by Professor B.M. Hausen and used prior to the making of our own extract.

The extracts were tested in patients with known Compositae sensitization as well as in patients with suspected Compositae contact allergy. Only results from the former group will be presented here. The baseline series included the following Compositae allergens and extracts: sesquiterpene lactone mix (SL mix) 0.1% pet. from February 1990 (Trolab, Hermal, Reinbek, Germany) and in recent years AllergEaze (SmartPractice, Phoenix, Arizona), parthenolide 0.1% pet. from January 1995 (first prepared at the hospital pharmacy in Odense, later provided by Chemotechnique Diagnostics (Vellinge, Sweden), parthenolide 3...
µg/cm² from October 2015 (AllergEaze), and Compositae mix II 2.5% pet. from January 2015 (AllergEaze). Furthermore, the original Compositae mix 6% pet., consisting of ether extracts of arnica (Arnica montana L.) 0.5% pet., German chamomile 2.5% pet. (Matricaria chamomilla L.), yarrow 1.0% pet. (Achillea millefolium L.), tansy 1.0% pet. (Tanacetum vulgare L.), and feverfew 1.0% pet. (Tanacetum parthenium (L.) Sch. Bip.) from Trolab was included in the baseline series from October 1998 to April 2001.

The patch test materials were applied to the back for 2 days using Finn Chambers (Epitest, Helsinki, Finland) on Scanpor (Norgesplaster, Oslo, Norway) and more recently Finn Chambers on Scanpor (SmartPractice). Readings were performed on day (D) 3-4 and D7 whenever possible, according to the latest guidelines. The chi square test and Fisher’s exact test were used for statistical comparisons between frequencies, and the level of significance was set at 0.01.

3. Results

In the period from February 1998 to February 2019, 191 Compositae-sensitive patients were patch tested with chrysanthemum extract 3% pet., and 111 (58%) had positive reactions. Likewise, 179 Compositae-sensitive patients were patch tested with the marguerite daisy extracts 3 and/or 1% pet. (only 13 patients were tested with the latter and 9 had positive reactions), and 104 (58%) were patch test-positive. Altogether, 108 patients were tested with both chrysanthemum and marguerite daisy extracts, and the majority (n=90, 83%) had positive patch test reactions to both.

The 111 chrysanthemum-positive patients comprised 94 females (85%) with a mean age of 55 years, and 17 males (15%) with a mean age of 60 years. The majority of the positive chrysanthemum-reactions (n=91, 82%) were considered to be of current/old relevance, whereas 7 were of unknown relevance, and 13 were not registered. The 80 chrysanthemum-negative patients comprised 62 females (77.5%) and 18 males (22.5%), and in both genders the mean age was 56 years. The results of patch testing with selected Compositae extracts and allergens in patients with positive and negative chrysanthemum reactions are presented in Table 1.

The 104 patients sensitized to marguerite daisy comprised 89 females (86%) with a mean age of 53 years, and 15 males (14%) with a mean age of 60 years. The patch test reactions were considered to be of current/old relevance in 80 patients (77%), unknown in 14 patients, and not registered in 10 patients.

Altogether, 28 patients were partly/possibly/definitely occupationally sensitized to Compositae, including 10 with lettuce exposure. However, only 5 were exposed mainly to marguerite daisies, and 3 were exposed to chrysanthemums, and another to chrysanthemum and marguerite daisies at a nursery and later at a flower shop. Several patients had a mixed Compositae exposure, being flower arrangers, florists, and persons working in gardens, parks, or in agriculture. Table 2 shows the results of patch testing with selected Compositae extracts and allergens in those exposed to marguerite daisies or chrysanthemums, respectively, and ,for comparison, some florists with a mixed exposure to Compositae plants.
4. Discussion

The prevalence of sensitization is high for both plant extracts. For chrysanthemum, a study of the first 8 years (1990-1998) with systematic Compositae screening at our department showed a prevalence of positive chrysanthemum reactions of 72% (83/115). The lower prevalence in the present study may reflect that comparatively fewer patients have been tested in the past 21 years. Reports on the prevalence of positive patch test reactions to chrysanthemums in a general patch test population are scarce: Roed-Petersen and Hjorth detected 1 positive reaction to Chrysanthemum spp. (oleoresin in pet.) tested in 23 persons as part of the baseline series. By aimed patch testing, the prevalence of positive chrysanthemum reactions – for both occupationally and recreationally exposed – have been reported to range between 45 and 72% in Europe. In an Indian study, 52% of 62 patients suspected of chrysanthemum contact dermatitis tested positive. In another Indian study of 75 patients suspected of contact dermatitis, 6 (8%) had positive patch test reactions to chrysanthemum, which placed the plant in top 5 of allergens eliciting positive reactions.

According to Hausen and Oestmann, chrysanthemum sesquiterpene lactones elicited positive reactions most frequently among 64 flower market vendors with occupational dermatitis. In a Danish study on 25 gardeners with Compositae sensitization, 13 of 16 (81%) were patch test positive to the German chrysanthemum extract and 6 of 7 positive to the Danish chrysanthemum extract. Previously, the paucity of reports on chrysanthemum dermatitis in Japan, where chrysanthemum is the national flower, has been ascribed to ingestion of young chrysanthemum plants as salad as well as floating the flower on soup, inducing oral tolerance. However, in a Japanese study on chrysanthemum growers, the prevalence of positive reactions to a chrysanthemum leaf extract rose form 27.3% in 1976 to 43.3% in 1982. On the other hand, Ueda et al, in their study on 58 male and 47 female chrysanthemum farmers in Japan, reported 5% positive reactions among males and 17% among females patch tested with 6 different chrysanthemum cultivars. As most of the Japanese cases seem to be occupational, the theory of oral tolerance may still be true: the balance between tolerance because of ingestion and cutaneous sensitization may be tipped in favour of sensitization when the exposure is heavy. In conclusion, despite differences in patch test materials, the prevalence of positive reactions seems to be high by aimed patch testing. This may reflect a high level of exposure, a strong sensitizing potential, a high degree of cross-reactivity or a combination of these three explanations. The numerous case reports from occupational settings – reviewed by Hausen and Schulz up to 1973 - and the fact that more than 30% of occupationally exposed become sensitized emphasizes the importance of intense exposure. As pointed out by Schmidt and Kingston, amateur gardeners may also be affected because of years of exposure; this is indeed the case for most patients in our study.

Concerning the sensitizing potential of chrysanthemum, there is experimental evidence to classify chrysanthemum as a strong sensitizer, surpassing both arnica and sunflower (Helianthus annuus L.). Several sesquiterpene lactones have been detected in chrysanthemum: the main allergen seems to be...
arteгласин A, a guaianolide sesquiterpene lactone with an epoxy group, isolated by Hausen et al. 1, 27-29 Incidentally, arteгласин A was suggested as one of the allergens for a new sesquiterpene lactone mix. 30

Concerning cross-reactivity, Schulz et al, in their combined experimental clinical and animal study on allergens from florists’ chrysanthemum, showed reciprocal cross-reactions between chrysanthemum and parthenolide, and cross-reactivity between chrysanthemum and alantolactone, but not reciprocally, although neither of these sesquiterpene lactones could be detected in the plants. 27 Thus, 10 of 15 guinea pigs sensitized to the florists’ chrysanthemum had positive patch test reactions to parthenolide, whereas only 2 tested positive to alantolactone. In 5 chrysanthemum-sensitive persons, 4 tested positive to parthenolide 0.1% eth. and 1 to 0.5% eth.; only 2 persons had positive patch test reactions to alantolactone 1% and 0.5% eth.. 27 These findings are in accordance with the clinical observations reviewed by Schmidt and Kingston 26: who report that cultivar specific sensitization, because of phytochemical variability, may cause false negative patch test reactions in chrysanthemum-allergic persons, and that this may be avoided by patch testing with an ether extract of the parthenolide-containing feverfew plant. In a previous study from our department 7, only 32% of chrysanthemum-negative individuals were positive to parthenolide compared with 85% of chrysanthemum-positive persons, which was a highly significant difference.

A similar difference was found in the present study, not only for parthenolide, but also for feverfew extract, Compositae mix (which contains either feverfew or parthenolide), and SL mix (Table 1). Even though the cross-reactivity between alantolactone and florists’ chrysanthemum was modest in experimental studies27, it may contribute to the cross-reactivity with SL mix together with cross-reactions between the guaianolides arteгласин A from chrysanthemum and dehydrocostus lactone from the SL mix, and cross-reactions between the germacranolides parthenolide and costunolide from the SL mix. Some of the patients were tested on separate occasions, and as patch testing may boost sensitivity, this could be a contributory factor to the high prevalence of positive reactions to the 4 allergens and extracts, respectively, in Table 1. Another explanation is that most Compositae-sensitive patients have been exposed to a wide range of Compositae species and are broadly sensitized in an individual pattern. Broadly sensitized persons will react to most allergens and extracts. A high concordance between positive reactions in clinical studies may thus reflect both cross-reactivity and co-sensitization. In general, the patients with negative chrysanthemum reactions seemed to be less sensitive. However, it may be concluded from Table 1 that Compositae mix, feverfew extract, parthenolide and to a lesser degree SL mix are most often positive in patients with chrysanthemum sensitization.

The preponderance of females is typical for Compositae-sensitive patients in our area. 31 Likewise, the mean age for both genders, although higher than those reported in the first 8 years32, is characteristic of Compositae-sensitive patients who are often middle-aged or elderly. 33 The slightly lower mean age in female patients sensitive to marigold probably reflects the inclusion of young gardeners and greenhouse workers occupationally exposed to this species.

The prevalence of positive patch test reactions to marigold is lower than that previously reported from our department. 7 However, it parallels the prevalence of positive reactions to the chrysanthemum extract, and most of the reactions were relevant. In occupationally sensitized, prevalences of 65-73% have
been reported. 7, 12 In the present study, most of the reactions were found in non-occupationally exposed, and the question is whether the reactions represent primary sensitization or cross-reactivity. Patients 1-5 in table 2 have worked primarily with marguerite daisies, which implies intense exposure to the plants: patient 2 reported that she handled 12000-14000 cuttings per day. Obviously, these patients are narrowly sensitized to marguerite daisies with sometimes strong reactions to both the 3% and 1% extracts, but few or weak reactions to other Compositae allergens and extracts, notably the screening allergens SL mix and parthenolide (Table 2). The Compositae mix was best at picking up sensitization, but in some cases this mix was negative as well, making it necessary to test with an extract of the plant to detect the sensitization. The allergens of marguerite daisy are unknown. Although sesquiterpene lactones have been isolated from other Argyranthemum species, no data on the occurrence in Argyranthemum frutescens (L.) Sch. Bip. have been published. 11 Cross-reactivity to chrysanthemum does not seem to be the rule based on our results (Table 2). Nevertheless, the number of individuals with marguerite daisy sensitization of unknown relevance was twice as high as that for chrysanthemum-sensitive individuals, so some of the reactions to marguerite daisy are probably caused by cross-reactivity. It is also evident from Table 2 that florists with mixed exposure and middle-aged or elderly gardeners, who are probably recreationally exposed as well, are broadly sensitized and hence have more positive reactions.

In conclusion, more than half of the Compositae-allergic patients were sensitized to chrysanthemum and/or marguerite daisy. Contrary to previous reports on chrysanthemum contact allergy, most of the patients were non-occupationally sensitized to both chrysanthemum and marguerite daisy. The majority of the reactions were considered relevant, which, combined with experimental studies on the sensitizing potential of chrysanthemums, and the fact that both plants need manual “disbudding”, suggests that both plants are important sensitizers. Chrysanthemum and marguerite daisy extracts are not commercially available; however, feverfew extract 1% pet., Compositae mix 5 or 6% pet., and to a lesser degree, parthenolide 0.1% pet. may cross-react with chrysanthemum, and Compositae mix 5 or 6 % pet. seems to be the best extract to detect sensitization to marguerite daisy. However, in occupationally exposed persons, it may be necessary to test with an ether extract of marguerite daisy 3% or 1% pet. as cross-reactions to other Compositae extracts and allergens are unreliable in narrowly sensitized individuals. In areas where exposure to chrysanthemums and marguerite daisies is prevalent, it is worthwhile to include extracts of these species in the plant series to improve the diagnosis of, and advice to, Compositae-sensitive patients.

References


Fig. 1. Cultivar of florists’ chrysanthemum. Photograph: Grafik og Klinisk Foto, Odense Universitetshospital, Odense, Denmark
Fig. 2. Marguerite daisy (*Argyranthemum frutescens* (L.) Sch. Bip.) cultivar. Photograph: Grafik og Klinisk Foto, Odense Universitetshospital, Odense, Denmark

Table 1. Results of patch testing with selected Compositae allergens and extracts in Compositae-sensitive patients with or without sensitization to chrysanthemum extract

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Feverfew 1% pet.</th>
<th>PTH 0.1% pet.</th>
<th>SL mix 0.1% pet.</th>
<th>CM 5 or 6% pet.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chrys. pos. patients</td>
<td>98/100 (98%)**</td>
<td>93/110 (85%)*</td>
<td>89/111 (80%)*</td>
<td>106/108 (98%)**</td>
</tr>
<tr>
<td>Chrys. neg. patients</td>
<td>36/71 (51%)**</td>
<td>31/80(39%)*</td>
<td>31/80 (39%)*</td>
<td>61/79(77%)**</td>
</tr>
</tbody>
</table>

Legend

PTH = parthenolide

SL mix = sesquiterpene lactone mix

CM = Compositae mix

*P < 0.00001 by Chi square test

**P<0.00001 by Fisher’s exact test

Table 2. Distribution of selected patch test results in persons occupationally sensitized to marguerite daisises, chrysanthemums, or mixed Compositae plants

<table>
<thead>
<tr>
<th>Pt.no</th>
<th>Sex/age</th>
<th>Occupation</th>
<th>Chrys.3% pet.</th>
<th>Marg.3% pet.</th>
<th>SL mix 0.1% pet.</th>
<th>PTH 0.1% pet.</th>
<th>CM 5 or 6% pet.</th>
<th>Feverfew 1% pet.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F/39</td>
<td>Gardener (M)</td>
<td>?+</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>2</td>
<td>F/21</td>
<td>Greenhouse worker (M)</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>?+</td>
</tr>
<tr>
<td>3</td>
<td>F/36</td>
<td>Home help (previous work with M)</td>
<td>NT</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>?+</td>
</tr>
<tr>
<td>4</td>
<td>F/28</td>
<td>Greenhouse worker (M)</td>
<td>-</td>
<td>++</td>
<td>++ 1% pet.</td>
<td>-</td>
<td>-</td>
<td>+?</td>
</tr>
<tr>
<td>5</td>
<td>F/55</td>
<td>Gardener (M)</td>
<td>-</td>
<td>++</td>
<td>+ 1% pet.</td>
<td>?+</td>
<td>+</td>
<td>+?</td>
</tr>
<tr>
<td>6</td>
<td>F/34</td>
<td>Gardener/florist (C and M)</td>
<td>++</td>
<td>+++</td>
<td>++ 1%</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>No.</td>
<td>Gender</td>
<td>Age</td>
<td>Occupation</td>
<td>Chrys.</td>
<td>Marg.</td>
<td>SL mix</td>
<td>PTH</td>
<td>CM</td>
</tr>
<tr>
<td>-----</td>
<td>--------</td>
<td>------</td>
<td>-----------------------------</td>
<td>--------</td>
<td>-------</td>
<td>--------</td>
<td>-----</td>
<td>----</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>55</td>
<td>Florist</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>42</td>
<td>Gardener (C)</td>
<td>++</td>
<td>+</td>
<td>?+ 1% pet.</td>
<td>?-</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>84</td>
<td>Pensioner/florist</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>48</td>
<td>Greenhouse worker (C)</td>
<td>++</td>
<td>+</td>
<td>?+</td>
<td>+?</td>
<td>+++</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>51</td>
<td>Florist</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>55</td>
<td>Florist</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>

**Legend**

Chrys. = chrysanthemum extract 3% pet.

Marg. = marguerite extract 3% pet.

SL mix = sesquiterpene lactone mix 0.1% pet.

PTH = parthenolide 0.1% pet.

CM = Compositae mix 5 or 6 % pet.

(C) or (M) means that the patient has been exposed mainly to chrysanthemum(C) or marguerite daisy (M)

- = negative reaction

?+ = doubtful positive reaction

NT = not tested