

Do monoterpenes released from feverfew (*Tanacetum parthenium*) plants cause airborne Compositae dermatitis?

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The Compositae plant feverfew (*Tanacetum parthenium*) is an important sensitizer in Europe and has been suspected of causing airborne Compositae dermatitis. A previous investigation of substances emitted from feverfew plants detected no sesquiterpene lactones, however, but mainly monoterpenes. The aims of this study were to test whether feverfew-allergic patients were also sensitive to some of the above-mentioned monoterpenes and, if so, to study associations between sensitization patterns, relevance of feverfew allergy and clinical features. 17 patients with +++ reactions to feverfew and parthenolide were tested with 15 selected monoterpenes and 2 sesquiterpenes. Of the 17 persons, 13 had positive and/or doubtful positive reactions to 1 or more monoterpenes. Only 1 person was allergic to several monoterpenes. Her history of gradually worsening Compositae dermatitis culminating in a probable airborne dermatitis, mimicking photosensitivity, and the disappearance of symptoms upon removal of feverfew plants suggest monoterpenes as a possible contributing factor. Similar associations between doubtful positive monoterpene reactions and clinical patterns, fragrance/colophonium allergy and relevance of feverfew allergy were not established with certainty. In conclusion, sensitization to the sesquiterpene lactones of feverfew is not invariably accompanied by sensitization to its volatile monoterpenes. The presence of monoterpene allergy, however, may contribute to airborne Compositae dermatitis.

Key words: airborne contact dermatitis; allergic contact dermatitis; Asteraceae; colophonium; Compositae; feverfew; fragrance; monoterpenes; plants; sesquiterpene lactones. © Blackwell Munksgaard, 2002.

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The feverfew plant (*Tanacetum parthenium* (L.) Schulz-Bip.) is an ancient herbal remedy, probably native to South-east Europe, Asia Minor and the Caucasus (1). Due to its medicinal properties, however, it has been propagated throughout Europe, from gardens of medieval monasteries via herbaceous borders of private homes to its present state as a partly naturalized weed in several countries, including Denmark.

Feverfew's allegedly migraine-prophylactic effect rekindled a new scientific interest in the plant in the 1980s (2). At the same time, its well-known allergenic properties were further substantiated by clinical reports of feverfew contact dermatitis, and today the plant is considered an important sensitizer and marker of Compositae allergy in both Northern and Southern Europe (3–9). The airborne dermatitis attributed to feverfew (5) prompted an investigation of volatiles emitted

from flowering plants using dynamic headspace technique (10): the main volatiles released were monoterpenes, whereas no sesquiterpene lactones were detected (10). Flowering feverfew plants placed in natural surroundings were also investigated for the release of plant particles containing sesquiterpene lactones using a high-volume air sampler placed around the plants. Sesquiterpene lactones were not, however, detected in the filters from the sampler that was capable of capturing particles down to 0.01 µm in size (10). This suggested a possible rôle of monoterpenes rather than sesquiterpene lactones in airborne contact dermatitis from Compositae.

The aims of the present study were to investigate whether feverfew-allergic patients were also sensitive to monoterpenes released from intact feverfew plants and, if so, to study associations between sensitization patterns, relevance of feverfew allergy

Table 1. Volatiles emitted from flowering feverfew plants and selected for patch testing in feverfew-sensitive patients

	Patch test conc. (% pet.)	
1.	(-)- α -pinene	15%
2.	(+)- α -pinene	15%
3.	(-)- β -pinene	15%
4.	(+)- β -pinene	15%
5.	camphene	5%
6.	(+)-limonene	5%
7.	(-)-limonene	5%
8.	ocimene ^a	5%
9.	p-cymene	5%
10.	γ -terpinene	5%
11.	(\pm)-linalool	30%
12.	(+)-camphor	10%
13.	(-)-camphor	10%
14.	farnesene ^{a,c}	5% ^b
15.	(β)-caryophyllene ^c	5%
16.	(\pm)- α -phellandrene	5%
17.	?? α -terpinene	5%

^aMixture of isomers.

^bNo information on recommended patch test concentration available.

^cSesquiterpene.

Table 2. Results of patch testing with selected monoterpenes, sesquiterpenes, fragrance materials and colophonium in 17 feverfew-sensitive patients

rel., relevance of feverfew allergy. C, current. O, old. D, don't know. F, follicular reaction. FRAG, patch test results to fragrance materials. CO, patch test results to colophonium. (a) Possibly irritant reaction.

and clinical features in support of airborne Compositae dermatitis from monoterpenes.

Patients and methods

A total of 33 patients selected because of previous strongly positive (+ + or + + +) patch test reactions to feverfew 1% pet. and its most important sesquiterpene lactone allergen, parthenolide, 0.1% pet. were invited to participate. Patch testing with feverfew and parthenolide were repeated, unless performed within 3 months before inclusion, to confirm the plant allergy and supplemented with 15 monoterpenes and 2 sesquiterpenes (Table 1), selected from volatiles emitted from feverfew plants (10). The first 13 (Table 1, nos. 1–13) were selected mainly on the basis of yield exceeding 200 ng/g fresh plant/24 h. α -Terpinene and α -phellandrene, which were released in lesser amounts, were selected because of previously reported allergenicity (11). α -Pinene, which was released in approximately 130 ng/g fresh plant/24 h, was selected on the basis of its structural similarity to α -pinene, which is known to be allergenic and irritant (12). The substances used for patch testing were purchased from Fluka Chemie AG (Switzerland) and

TCI Tokyo Organic Chemicals (Japan). The purity (> 98%) of all substances was checked by GC and GC-MS (10) before use. GC-MS analysis furthermore revealed that the small amounts of impurities did not comprise oxidized products such as peroxides, aldehydes or peroxide degradation products. The impurities consisted in general of non-oxidized derivatives of the tested compounds, and were not supposed to be significantly more allergenic. Patch test concentrations were based on literature reports (11, 13). The substances were applied in Finn Chambers^R on Scanpor^R tape on the back for 2 days with reading on day 3 (D3) and possibly D5–D7 according to the ICDRG recommendations. Patch testing was performed in January and February 2001. The study was approved by the local ethics committee.

Results

The main findings are summarized in Table 2. Because of possible cross-reactions between monoterpenes and fragrance materials or colophonium, the result of the latest patch test with the last-mentioned substances are included. Of the 33 persons invited, 17 participated. Of these, 13 patients had positive and/or doubtful positive reactions to 1 or more monoterpenes. Only 1 person, however, was allergic to several monoterpenes and the details of her history are reported below (patient no. 1, Table 2 and case report). Patient no. 2 had a weak positive reaction to ocimene, but considering the irritant potential of this concentration (several doubtful positive reactions, at least 1 clinically irritant) and a slight eczema of the back of the patient, the reaction might as well be false-positive.

Facial involvement was seen in 15 patients: 6 had had patchy eczema that could be due to indirect allergen contact, while 9 had had a confluent facial dermatitis attributed to sun exposure and/or airborne allergens (Table 3). Of the 9 patients, 4 had unknown relevance of the feverfew allergy: in 2 of these patients the facial dermatitis was possibly related to photocontact allergy/irritancy and sun exposure (nos. 10 and 15) and in a third, a false positive monoterpene reaction could not be ruled out. The fourth patient had several doubtful positive monoterpene reactions and a recurrent facial eczema in the flowering season of dandelions.

Of the 5 persons with currently relevant feverfew reactions, 2 had had confluent facial dermatitis on a few occasions only and their monoterpene reactions were negative/doubtful positive (nos. 12 and 17). Patient no. 6 seemed to have been photosensitive previously, but she had several doubtful positive monoterpene reactions and no problems on sun exposure at present.

Table 3. Patients with facial dermatitis suggesting UV-sensitivity and/or contact with airborne allergens

Patient no.	Monoterpene reactions	Relevance of feverfew allergy	Comments
1	5 positive, 6?+	current	'UV-sensitivity' disappeared after plant removal
2	1 positive	don't know	probably false positive monoterpene reaction
4	4?+	don't know	facial dermatitis during flowering season of dandelions
6	4?+	current	probably PLE from PUVA, no problems on sun exposure now after PUVA treatments
10	1?+	don't know	previously photocontact allergy from PABA
11	1?+	current	itching of the skin when exposed to feverfew
12	0	current	sun exposure suspected on a few occasions only, once with facial involvement
15	0	don't know	slight PLE, no facial dermatitis after azathioprine treatment in the summer of 1998 and avoidance of plant contact
17	1?+	current	for years dermatitis of sun-exposed skin, but only 4 × severe facial dermatitis (outpatient clinic)

PLE, polymorphic light eruption.

2 persons with 5–6 doubtful positive monoterpene reactions were not included in the group with severe facial dermatitis. The first was a 76-year-old male hobby gardener with a summer-related eczema on hands, arms and sometimes periorbital area and legs (patient no. 3, Table 2). The second patient was a 59-year-old farmer's wife with summer-exacerbated vesicular hand and foot eczema and occasional involvement of arms and suspected UV-sensitivity (patient no. 5, Table 2).

Case Report

An 84-year-old woman with a hand eczema for 57 years, at first affecting the fingers, but for the last 25 years mainly localized to the palms of both hands (patient no. 1, Tables 2 and 3). In the last-mentioned period, the patient had summer exacerbation of her eczema, contrary to the previous exacerbation in autumn and winter. Standard patch testing at our department in 1977 showed positive reactions to oil of turpentine and formaldehyde, both of doubtful relevance. In 1987, the patient moved to a new house with feverfew plants in the garden. From 1990 she had flares of facial eczema and by the summer of 1994 she had developed instantaneous itching, erythema and oedema of face and neck on exposure to sun from June to September. Patch tests during these years were positive to colophonium, Myroxylon Pereirae Resin, nickel sulphate and cobalt chloride. After recurrence of the light-induced dermatitis in the summer of 1995, the patient was referred to our department again and patch testing revealed severe Compositae allergy as well as + reactions to colophonium, Germall II aq., an Aloe vera cream and a geranium plant as is. Photopatch testing was not performed. The +++ reactions to feverfew and parthenolide in particular were considered relevant because of the feverfew border close to her house and

because of the bunches of feverfew flowers she used to pick for her vases. In the summer of 1995, the patient avoided sun exposure as much as possible and she virtually only went out at night. After removal of Compositae plants, including chrysanthemum, marguerite and silver ragwort in addition to feverfew, from her garden, the patient has remained almost free of facial eczema and with only relatively slight exacerbations of vesicular palmar hand eczema in subsequent summer seasons in spite of persistent strongly positive Compositae patch test reactions (patient no. 1, Table 2). However, she has noticed a mild patchy facial dermatitis when travelling by car with open windows, especially during the flowering season of dandelions. On the other hand, she has no skin problems on sun exposure, contrary to the summers of 1994 and 1995.

Discussion

In 1986, Richard Schmidt stated that a European equivalent of the airborne sesquiterpene lactone-induced weed dermatitis, typically occurring in hot and dry climates, did not appear to exist (14). At the same time, however, he mentioned some cases of 'airborne contact dermatitis' described in Germany and attributed to feverfew (5, 14). Hausen, in his 6-year study of Compositae mix as an optional addition to the standard series, found that 11 of 118 Compositae-sensitive persons (10%) showed the airborne contact dermatitis pattern (15). Even if sensitization to sesquiterpene lactones in Europe rarely induces the clinical features of classical airborne Compositae dermatitis, about 1/2 of these 17 selected patients had had severe facial involvement, suggesting sensitivity to UV-radiation and/or airborne allergens. This group comprised the 2 persons with positive monoterpene reactions and 2 with 4 doubtful positive reactions, but also 5 per-

sons with no or only 1 doubtful positive reaction (Table 3). Obviously, sensitivity to the monoterpenes is not associated with the strength of the feverfew reactions, since almost all of the patients had +++ reactions. Also, there was no association with fragrance allergy, which was actually more prevalent in the (small) group with negative monoterpene reactions. Likewise, colophonium sensitivity occurred more frequently in the monoterpene-negative patients; on the other hand, both of the patients with monoterpene allergy were colophonium-positive. The number of patients, however, is too small to draw any conclusions.

An association with the clinical features was most apparent in the 1 patient with several positive monoterpene reactions (patient no. 1, Tables 2 and 3). She was the only one with consistently recurring facial dermatitis on sun exposure and disappearance of symptoms on removal of Compositae plants. The fact that the dermatitis developed immediately after sun exposure and that the patient tolerated the sun after plant removal points to airborne allergens as eliciting factors. It could be argued that the monoterpene reactions were of old relevance, because the patient had had a strongly positive reaction to oil of turpentine some 20 years ago. Oil of turpentine contains a mixture of α - and β -pinene, 3-carene and (+)- and (-)-limonene (16). The patient, however, tested positive to the pinenes, but only doubtful positive to the limonenes and, in addition, positive to terpenes not present in oil of turpentine. Her + reaction to colophonium could be a cross-reaction to the terpenes as could her reaction to geranium, which contains geraniol, a terpene alcohol, as suspected sensitizer.

Another patient (patient no. 6, Tables 2 and 3) with 4 doubtful positive monoterpene reactions developed dermatitis immediately after sun exposure, but she seemed to have had some degree of UV-sensitivity (Table 3). After PUVA treatments and removal of feverfew plants from her garden, she remained almost free of facial dermatitis and tolerated the sun. Otherwise, associations between clinical patterns and number of doubtful positive reactions were not obvious. Patient no. 4 had dermatitis of exposed skin of face and neck, 4 doubtful positive monoterpene reactions, but no relevance of the feverfew allergy. Other patients (nos. 11, 12 and 17, Table 3) with relevant feverfew allergy and occasional dermatitis of light- and/or air-exposed skin had negative or only 1 doubtful positive monoterpene reaction. Conversely, patients nos. 3 and 5 (Table 2) had several doubtful positive monoterpene reactions, but no or not convincing airborne dermatitis.

One important possible source of error is the patch test concentration of the selected monoterpenes.

The recommended concentration may vary considerably depending on whether the substances are commercially available or not. Monoterpenes nos. 5, 7, 8 and 10 and the sesquiterpene no. 15 (Table 1) were tested in a 5% pet. concentration based on information that a 4/5% concentration was non-irritant (13), but obviously the former may be too low. α -Phellandrene and α -terpinene 5% pet. tested positive in some patients as reported by Hausen et al., but no recommendations exist (11).

Though some of the emitted monoterpenes are allergens in their own right, it is possible that their oxidation products could be even more allergenic, as is the case with colophonium (17). Theoretically, this oxidation may occur in the air, perhaps induced by sunlight, or on/in the skin of the patients. The former hypothesis, however, was not supported by the findings in the headspace analysis (10).

We may conclude that sensitization to the sesquiterpene lactones of feverfew is not invariably accompanied by sensitization to the volatile monoterpenes of the plant. On the other hand, the history of patient no. 1, with her undoubtedly relevant feverfew allergy, her progressively developing Compositae dermatitis culminating in a probable airborne dermatitis, mimicking photosensitivity, her positive and doubtful positive reactions to more than 1/2 of the monoterpenes emitted from Danish feverfew plants and the disappearance of symptoms on removal of the plants, is suggestive of monoterpenes as a possible contributing factor in the 'photosensitivity' pattern.

The finding of sesquiterpene lactones in detached and dried plant parts (18) is circumstantial evidence of their rôle in airborne Compositae dermatitis, but the final proof is lacking. Likewise, the possible rôle of monoterpenes, emitted from flowering Compositae plants, and their allergenic oxidation products should be evaluated in larger clinical studies (19).

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