

Photoallergic contact dermatitis to 8-methoxypsoralen in *Ficus carica*

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Background: Photocontact dermatitis to *Ficus carica* is induced by furocoumarins present in sap. These substances are generally considered to cause phototoxic reactions.

Objectives: We conducted a patch test and histopathological study of patients with phytophoto contact dermatitis from the fig tree to evaluate the mechanism underlying the photoreaction.

Patients and Methods: Patch and photopatch testing with serial dilutions of two natural furocoumarins [5-methoxypsoralen and 8-methoxypsoralen (8-MOP)] contained in plant sap were performed in 47 patients. A synthetic furocoumarin, 4,5',8-trimethylpsoralen, was also tested. Histopathological analyses were made of some positive photoreactions.

Results: Positive photopatch tests reactions to 8-MOP were obtained in 12 of 47 patients, in 4 of them down to a concentration of 0.0001%. Patch tests and photopatch tests to the other two furocoumarins were negative. Histopathological findings on biopsies from positive photopatch tests to 8-MOP showed a dermatitis.

Conclusions: Allergic photoreactions induced by contact with plants containing coumarins are generally regarded as chance findings. This study has demonstrated that phytophoto allergic contact dermatitis resulting from furocoumarins is not an exceptional finding, and should be suspected in subjects with diffuse clinical manifestations in photo-exposed but also non-exposed sites. To differentiate allergic from toxic photoreactions, patch tests need to be performed with serial dilutions of furocoumarins. Histological analysis of a biopsy sample from a positive test site will reveal alterations compatible with a photoallergic contact dermatitis.

Key words: *Ficus carica*; furocoumarins; 5-methoxypsoralen; 8-methoxypsoralen; photoallergic contact dermatitis; phytophoto contact dermatitis; psoralens; 4,5'-8-trimethylpsoralen. © John Wiley & Sons A/S, 2010.

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Ficus carica L. (of the Moraceae family), the fig tree, is believed to be native to the Middle East (Syria) but is widely cultivated in the Mediterranean area and other warm zones worldwide, in some of which it also grows wild (Fig. 1). Individuals who come into contact with the plants and its fruit include cultivators, gatherers, packers, gardeners, and consumers. As the wood is little used because of its poor quality, carpenters are not generally affected.

The branches, leaves, and skin of the fruit, when cut, exude rubbery sap that contains many different compounds, such as various proteolytic

enzymes (ficin, triterpinoids, protease, lipodiastase, amylase) and furocoumarins. The enzymes have an irritant potential and so can aggravate the phototoxic effect of the coumarins (1–6). In the fig tree, the furocoumarins present include psoralen (7–9), 5-methoxypsoralen (5-MOP), 8-methoxypsoralen (8-MOP) (4, 8–11), and 4'-5'-dihydropsoalene (10).

Every year, in the late spring, summer, and early autumn we observe many cases of photo contact dermatitis from *F. carica*. In a sample of these patients, we conducted patch and photopatch tests with three furocoumarins to explore the pathogenic mechanism underlying these clinical pictures.



Fig. 1. *Ficus carica* L. Pear-shaped fruit ('syconiums') between lobed leaves of fig tree.

Materials and Methods

Study population

The study population consisted of 47 patients, 8 of whom have already been previously presented (12). There were 44 men (mean age 35.8, range 18–70 years) and 3 women (mean age 19.6, range 17–22 years). All the male patients were cultivators and had a positive history for contact with fig sap. The onset of the rash was generally about 10–15 hr after contact and reached a peak on the following days. Of the 44 men, 32 presented a modest erythematous-vesico-bullous contact dermatitis, manifesting as figured lesions localized only on the areas exposed to fig sap, such as the hands and forearms. Sometimes the trunk (some of these subjects had been bare-chested when the contact occurred) was also involved (Fig. 2). The remaining 12 males



Fig. 2. Figured lesions on the trunk (resulting from latex fluid running down), forearms, and hands.

presented with an intensely itchy severe erythematous-vesicular and bullous dermatitis not only on areas exposed to the fig sap, but also on non-exposed sites; the latter included both photo-exposed (face, neck) and non-photo-exposed areas (limbs). The three women had used a home-made preparation of fig leaves used as a tanning agent, and suffered extensive burns on photo-exposed sites, about 1 day after exposure to the sun for 30–60 min in the month of August. In these female patients and in the 12 affected males, the dermatitis was diffuse and so severe as to require hospitalization.

Treatment with wet compresses and topical corticosteroids resolved the complaint in some cases within a few days. The three women and eight of the men required systemic corticosteroids for 7–10 days. All patients developed hyperpigmented sequelae of varying intensity that lasted up to 2–3 months.

Patch and photopatch tests

All patients were tested at least 2–3 months after complete resolution of the reaction. Patch tests were performed with the SIDAPA (Società Italiana di Dermatologia Allergologica Professionale e Ambientale) baseline series (FIRMA Diagent, Florence, Italy). Patch and photopatch tests were also made with the ethanol extract of cut fig leaves and three pure psoralens, namely 5-MOP (bergapten), 8-MOP (xanthotoxin), and 4,5',8-trimethylpsoralen (trioxsalen; TMP) (Sigma Chemical Company, St Louis, MO, USA). The psoralens were dissolved in ethanol and serial dilutions were prepared; 5-MOP and 8-MOP were tested down to a concentration of 0.0001%, TMP at 0.1% only. The patch tests were carried out at two different times. Initially, patch testing with the baseline series of allergens was performed to reveal other possible sensitizations. The tests were applied on the back and left in occlusion for 2 days, using the Finn Chambers® (Ø 8 mm; Epitest Ltd, Tuusula, Finland) technique on Scampor® tape (Norgesplaster A/S, Vennesla, Norway). Readings of the patch tests were performed at D2 and D4. One month after patch testing with the baseline series, ethanol extracts of cut fig leaves and the three psoralens were applied in duplicate with the same method. Fifteen microlitres of the test solution of each psoralen were applied with a micropipette to the filter paper disc in each test chamber. One set of tests was irradiated on D2 with 5 J/cm² ultraviolet A (UV 801 KL, PUVA/TL 01, Photochemotherapy, Herbert Waldman, Werk für Lichttechnik, Germany), whereas the opposite side of the back was covered with a black cloth. Test reactions were read at D2, before and 30 min after irradiation, and at D3 and D4. A test was also

performed with UVA irradiation only; the test dose was 18 J/cm².

As controls, 20 healthy volunteers were photopatch tested with ethanol extract of cut fig leaves and the three psoralens at a dilution of 0.1% in ethanol. The reactions were scored according to the International Contact Dermatitis Research Group guidelines (13).

Histopathology

In four patients, biopsy samples were taken for histological examination from positive photopatch test reactions after 2 days to 8-MOP at 0.0001%, and stained with haematoxylin and eosin.

Results

Patch and photopatch testing

Patch tests with the baseline series of allergens were negative in all patients. The patch tests with the ethanol extract of cut fig leaves and with the three psoralens were negative in patients (thereby ruling out an ordinary contact allergy) and controls. In the latter, photopatch tests with the same substances also gave negative results.

However, 12 of the 47 patients (25.3%), namely the males with the severe clinical picture, had positive reactions to photopatch tests with the ethanol extract of cut fig leaves (++) in D4) and with 8-MOP, in all cases down to a concentration of 0.001% (++)/+++ in D4) and in 4 of them down to 0.0001% (++) in D2) (Table 1). In most cases, the reactions to 8-MOP showed an increasing crescendo pattern from D2 to D4, manifesting as increased blistering spreading beyond the site of application of the test chamber. Photopatch tests with 5-MOP and TMP were all negative, as was the test with UVA rays only.

Histopathology

The skin biopsies from positive phototest reactions (++) to 8-MOP at 0.0001% revealed changes consistent with an allergic picture: spongiosis, exocytosis, and spongiotic vesicles in the epidermis and a lymphohistiocytic infiltrate in the superficial dermis, mainly perivascularly. Parakeratosis and eosinophilic necrotic keratinocytes ('sunburn cells'), typical changes of phototoxic reactions, were not observed.

Discussion

Ficus carica L. is a tree-like shrub, growing from 2 to 5 m tall that has three to five lobed deciduous leaves. The fig tree is thought to be native to Western Asia and to have been imported later to the Mediterranean area. Since ancient times, the sap of the fig tree has been used as a medicine, especially to treat vitiligo, eczema, and psoriasis.

The sap of the fig tree contains various enzymes with irritant and pruritic properties, as well as furocoumarins. The latter are beneficial to the plant because they protect from attacks by fungal pathogens (14). In contact with the skin, furocoumarins bind to the DNA. Exposure to UV light causes cross-linking of the DNA that blocks cell division, DNA repair, DNA synthesis, and eventually causes cell death. This occurs mainly in epidermal DNA, leading to vesicle formation and blistering (15–17).

Various cases of photocontact dermatitis from fig plants (5, 7, 18–22) have been reported in the literature. The condition is frequent in southern Italy (12, 23, 24) and in the Lebanon (9), and in Turkey, where about 10% of fig pickers develop a contact dermatitis (25). The sap of the shoot or leaf of the fig tree can cause an itching or burning sensation, contact dermatitis, and lasting

Table 1. Results of photopatch testing with three psoralens and with an ethanol extract of cut fig leaves in 12 patients

Patient	8-MOP 0.1%		8-MOP 0.01%		8-MOP 0.001%		8-MOP 0.0001%		5-MOP 0.1 → 0.0001%			TMP 0.1%		Cut fig leaves	
	D2	D4	D2	D4	D2	D4	D2		D2	D4		D2	D4	D2	D4
1	++	+++	++	+++	++	++	–		–	–		–	–	+	++
2	+++	+++	++	+++	++	+++	++		–	–		–	–	+	++
3	++	+++	++	+++	+	++	–		–	–		–	–	+	++
4	+++	+++	++	+++	++	++	–		–	–		–	–	+	++
5	+++	+++	++	+++	++	+++	++		–	–		–	–	+	++
6	++	+++	++	+++	+	++	–		–	–		–	–	+	++
7	++	+++	++	+++	++	+++	++		–	–		–	–	+	++
8	+++	+++	++	+++	++	+++	++		–	–		–	–	+	++
9	+++	+++	++	+++	++	++	–		–	–		–	–	+	++
10	++	+++	++	+++	+	++	–		–	–		–	–	+	++
11	++	+++	++	+++	+	++	–		–	–		–	–	+	++
12	++	+++	++	+++	+	++	–		–	–		–	–	+	++

8-MOP, 8-methoxypsoralen; 5-MOP, 5-methoxypsoralen; TMP, 4–5', 8-trimethylpsoralen.

hyperpigmentation. Dermatitis can also be induced by a decoction of the leaves, which is sometimes used as a tanning agent, as observed in three of our patients and reported by other authors (17, 20, 26), or as a remedy for a pre-existing dermatosis (27). Cases induced by a tanning decoction are obviously more severe than those resulting from accidental contact with the plant, both because of the vast surface area exposed and of the deliberate exposure to the sun.

Each year, in late spring and especially the summer, we observe many of cases of erythematovesico-bullous photo contact dermatitis attributable to exposure to the fig tree. At these times, there is a higher concentration of furocoumarins in the plant (9), associated with other factors that can enhance photoreactivity, such as the greater sunlight, heat, and environmental humidity. The cases we observe in the autumn are more modest, because of the lower concentration of furocoumarins in the plant and the lesser intensity of the UV light in this season. In these autumnal cases, the condition presents with mildly erythematous lesions showing little or no exudation. In children, we sometimes observe a modest erythematovesicular dermatitis around the mouth, followed by pigmentation, resulting from contact with the sap that leaks from the peel when the fruit is detached from the plant and immediately eaten. It should be noted, however, that the fruit itself is not harmful as it does not contain furocoumarins (9).

The pathogenic mechanism underlying contact dermatitis to psoralens is still debatable. Phototoxic dermatitis is certainly the most frequent type of reaction resulting from psoralens. There are conflicting views about the possibility of photocontact sensitization. Many cases of contact allergy (28–31) and photocontact allergy (32–38) after exposure with furocoumarins, acquired during topical or systemic therapeutic procedures for eczema, psoriasis, vitiligo, and alopecia areata, have been reported in the literature. However, photoallergic reactions to psoralens resulting from contact with plants have rarely been described. Ljunggren reported a patient with a photocontact allergy to the psoralens xanthotoxin, bergapten, and imperatorin in parsley (*Petroselinum sativum*) (39). Kavli and Volden exposed themselves repeatedly to psoralens and plant parts from *Heracleum laciniatum*, and photocontact allergy was induced to the psoralens sphondin and isobergapten after five and six exposures, respectively (20). Goitre et al. reported two cases of occupational photocontact allergy to the leaf, stem, and latex of *Heracleum mantegazzianum* (40).

From the differential diagnosis standpoint, the clinical pictures of toxic and allergic photodermatitis are different, but in practice it still may not be

easy to differentiate between the two conditions. The pruritus is undoubtedly worse in allergic dermatitis, whereas in the toxic form pain and burning are the prevalent symptoms. Moreover, in allergic photodermatitis, the inflammatory skin reaction tends to reach a peak earlier (10–24 hr) than in phototoxic dermatitis, in which it usually takes 48–72 hr (39, 41). The difficulty in differentiating toxic from allergic photoreactions can be overcome by performing photopatch tests with serial dilutions of the incriminated substance (39, 42). A higher concentration of the compound or a higher UV energy is needed to elicit toxic than allergic reactions. This is demonstrated by the observation that a dilution of a 1000-fold that of the minimum phototoxic dose in normal subjects still elicits an eczematous response in patients. Of importance is the reading time of the phototests in relation to the minimal phototoxic dose (MPD): it must be extended up to 144 hr before excluding phototoxic reactions, as demonstrated in studies on the psoralen-UVA erythema induction by bath 8-MOP and TMP (43, 44). There is great variation in the MPD within each phototype as well as an overlap of the MPD in adjacent phototypes (45).

From the histopathological point of view, biopsy specimens from clinical lesions can sometimes be inconclusive, whereas histological examination of the reactions to photopatch tests can be helpful. Allergic photoreactions, which are quite similar to those observed in positive allergic patch test reactions, are characterized by the presence of epidermal spongiosis, the formation of vesicles, and exocytosis; in the superficial derma there is a focal, perivascular distribution of a lymphohistiocytic infiltrate, oedema, and sometimes eosinophils. Phototoxic reactions are characterized by the presence of parakeratosis, because of an increased cell turnover, and eosinophilic necrotic keratinocytes ('sunburn cells'). This may cause the formation of intra- or sub-epidermic vesicles and bullae, generally of an acantholytic and not a spongiotic nature. In such a damaged epidermis, exocytosis is largely of polymorphonuclear neutrophils; there is generally little or no oedema at the dermal level while there is a diffuse distribution of the inflammatory infiltrate, consisting mostly of polymorphonuclear neutrophils (46–51).

In this study, we report 47 cases of contact dermatitis to *F. carica*. In 12 subjects, photopatch tests revealed positive reactions to ethanol extracts of cut leaves and 8-MOP, in some cases down to a concentration of 0.0001%. All non-irradiated control tests were negative in these patients, thereby ruling out ordinary contact allergy. The histological picture of the positive photoreaction sites at 8-MOP at 0.0001% was strongly consistent with contact allergy, featuring spongiosis, and exocytosis in the

epidermis and a perivascular lymphohistiocytic infiltrate in the superficial dermis.

Psoralens have a variable sensitizing potential. It appears from the literature and our findings that of the various compounds, 8-MOP is the strongest agent (both when used for therapeutic purposes and after accidental contact with the plant), followed by 5-MOP. Both these psoralens are present in *F. carica* but our patients were positive only to 8-MOP and not to 5-MOP or TMP, a synthetic compound. This positivity only to 8-MOP could be linked to its higher photoreactivity when compared to the parent molecules. It is not possible to state for certain that negative photopatch tests to 5-MOP and TMP could exclude the possibility of a cross reaction with 8-MOP.

Conclusions

Photoallergy to furocoumarins has rarely been reported, especially in terms of sensitization acquired after contact with plants. There are a number of reports in the literature of allergy and photoallergy to psoralens acquired during therapeutic procedures. However, the frequency of plant-induced photoallergy to furocoumarins may well be underestimated because the resulting dermatitis is commonly considered to be of a toxic nature. Photopatch tests performed with serial dilutions of the compounds, together with histological examination of positive reactions, can provide useful elements helping to distinguish toxic from allergic photoreactions.

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