

Systemic allergic dermatitis caused by sesquiterpene lactones

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Summary

Patients with Compositae sensitization are routinely warned against the ingestion of vegetables, spices, teas and herbal remedies from this family of plants. The evidence for the occurrence of systemic allergic dermatitis caused by sesquiterpene lactone-containing plants is mostly anecdotal and based on statements from patients rather than scientific data. However, a few clinical reports on accidental sensitization and exposure and oral challenge prove the existence of this kind of reaction, most convincingly for strong contact allergens such as costunolide in bay leaves, and less so for weak allergens such as those of lettuce. Other Compositae species suspected of causing systemic reactions are artichoke, mugwort, yarrow, dandelion, feverfew, and elecampane. Some Compositae vegetables and teas, such as lettuce and chamomile tea, may induce systemic reactions through both humoral and cell-mediated mechanisms. It is difficult to disentangle the contribution of these reactions to both local and systemic symptoms of skin and mucous membranes in, for example, lettuce contact allergy. Further studies are needed to assess the prevalence of systemic allergic dermatitis caused by sesquiterpene lactones, and to clarify the pathogenesis for individual haptens.

Key words: Asteraceae; challenge; Compositae; herbal tea; *Lactuca sativa*; *Laurus nobilis*; sesquiterpene lactones; systemic allergic dermatitis.

Sesquiterpene lactones (SLs) constitute one of the largest groups of secondary plant metabolites, with > 5000 compounds (1, 2). They are reactive low molecular weight substances with antimicrobial, antifeedant, growth-modifying and allelopathic properties in general, and are thus important for plant survival (2). SLs occur in at least 17 plant families, but most abundantly in the sunflower family (Asteraceae or Compositae), where they are important taxonomic markers (3). The ability of SLs to bind covalently with biological macromolecules is also the basis of their allergenicity, and the reason why the sunflower family contains so many sensitizing species (1, 4).

Contact sensitization to allergenic SLs may imply contact allergy to plants that are consumed either as

vegetables, spices, teas, or herbal remedies. This may cause systemic allergic contact dermatitis, which is most frequently reported to be caused by metals, drugs, and plants/herbals (5–9). However, reports on Compositae-related systemic allergic dermatitis are often anecdotal (10–13).

In contrast to immediate-type hypersensitivity reactions, which may be detected by serological and laboratory tests in addition to clinical tests, the diagnosis of systemic allergic dermatitis is based on clinical symptoms and signs, and possibly oral or other suitable challenges.

The aim of this article is to review the evidence for the occurrence of systemic allergic contact dermatitis caused by Compositae and other SL-containing plants.

Materials and Methods

The older literature was searched via textbooks and references from both old and new articles. The newer literature was searched via the Medline/PubMed database

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Table 1. Species of the Compositae (Asteraceae) family of plants used for food and/or beverages

Alpine chicory (<i>Cicerbita alpina</i> Wallr.) (syn. <i>Sonchus alpinus</i> L.)
Artichoke (<i>Cynara scolymus</i> L.)
Cardoon (<i>Cynara cardunculus</i> L.)
Chicory (<i>Cichorium species</i> , e.g., <i>C. intybus</i> L.var. <i>foliosum</i> Hegi, <i>C. endivia</i> L.)
Dandelion (<i>Taraxacum officinale</i> F.H. Wigg)
German chamomile (<i>Matricaria chamomilla</i> L.) (syn. <i>Chamomilla recutita</i> Rauschert, <i>Matricaria recutita</i> L.)
Goldenrod (<i>Solidago virgaurea</i> L.)
Jerusalem artichoke (<i>Helianthus tuberosus</i> L.)
Lettuce (<i>Lactuca species</i> , e.g. <i>Lactuca sativa</i> var. <i>capitata</i> L., <i>Lactuca sativa</i> L. var. <i>longifolia</i> Lam)
Marigold (<i>Calendula officinalis</i> L.)
Mary thistle (<i>Silybum marianum</i> Gaertn.) (syn. <i>Carduus marianus</i> L.)
Milfoil (<i>Achillea millefolium</i> L.)
Roman chamomile (<i>Anthemis nobilis</i> L.)
Salsify, common (<i>Tragopogon porrifolius</i> L.)
Salsify, black (<i>Scorzonera hispanica</i> L.)
Southern wormwood (<i>Artemisia abrotanum</i> L.)
Sunflower (<i>Helianthus annuus</i> L.)
Tarragon (<i>Artemisia drancunculus</i> L.)
Wormwood (<i>Artemisia absinthium</i> L.)

(<http://www.ncbi.nlm.nih.gov/pubmed>), combining SLs and the names of specific plant species with the different synonyms of systemic allergic dermatitis, notably systemic contact dermatitis, internal–external contact-type hypersensitivity, baboon syndrome, flexural drug eruption, and symmetric drug-related intertriginous and flexural exanthema.

Vegetables

The tribe Cichorieae of the Compositae family of plants contains some well-known root and leaf vegetables: common salsify (*Tragopogon porrifolius* L.), black salsify (*Scorzonera hispanica* L.), lettuce (*Lactuca species*), and chicory (*Cichorium species*) (14). Furthermore, dandelion (*Taraxacum officinale* F.H. Wigg) and *Cicerbita alpina* Wallr. of the same tribe may be used for salads or as vegetables (14). Other edible Compositae species include sunflower (seeds and oil) (*Helianthus annuus* L.), Jerusalem artichoke (*Helianthus tuberosus* L.), artichoke (*Cynara scolymus* L.), and cardoon (*Cynara cardunculus* L.) (Table 1).

Lettuce. The risk of induction of systemic dermatitis from ingestion of lettuce was noticed in some of the first case reports published in 1932 and 1945 (15, 16). Rinkel and Balyeat described occupational dermatitis of the hands, forearms, and neck, and around the nose and mouth,

in a non-atopic female salad maker, who also had occasional urticarial eruptions. She was patch test-positive to lettuce at first, but later, contact and scratch tests gave negative reactions, whereas an intradermal test to lettuce was positive (15). The authors pointed out 'the production of a typical contact type of dermatitis from the ingestion of lettuce' as noteworthy; however, the patient stated that ingestion of lettuce would produce a more marked urticarial eruption than would occur when she handled lettuce (15). Thus, it cannot be ruled out that the patient had concomitant immediate and delayed hypersensitivity reactions to lettuce. Likewise, Downing, in the discussion after Templeton's report on coexisting epidermal and dermal sensitization, mentioned that he had 'seen similar instances in salad makers' who reacted after both direct contact with and ingestion of lettuce (16). Whether such concomitant sensitizations are the pathogenesis of the additional urticarial features that are occasionally described in systematically induced contact dermatitis has not been clarified (17). Krook, on the other hand, reported that 3 of 4 patients in his case series with occupational lettuce/endive contact sensitization had no skin reactions after eating lettuce, in spite of the fact that all 3 patients had signs of immediate hypersensitivity to lettuce (two positive scratch test reactions, and two vesicular reactions in previously affected skin) (18).

A common clinical feature in patients with lettuce contact allergy is the occurrence of cheilitis and/or perioral eczema: Fregert and Sjöborg reported on 2 females with hand eczema, cheilitis and perioral eczema who had positive prick test reactions to lettuce, but one of whom had a negative lettuce patch test result (the other was not patch tested) (19). Oliwiecki et al. also described 2 housewives with positive patch test reactions to lettuce extracts or allergens: on dietary intake of lettuce, the first developed lip and facial swelling, and the other developed burning of the mouth and eczema around the lips. Neither of them was prick tested (11). Likewise, a male patient with a family history, but no personal history, of atopy, and with a positive patch test reaction to lettuce but a negative prick test result with lettuce reported that ingestion of lettuce would induce perioral dermatitis and swelling of the lateral aspects of his tongue (20). It is possible that all of these cases represent – at least partially – simple contact cheilitis or stomatitis of varying degrees. At any rate, for only 3 of the above-mentioned cases were clinical aspects described that were suggestive of systemically induced reactions to lettuce, that is, flaring of eczema in areas not in contact with lettuce. The first was the female salad maker, who reported more marked urticarial eruption on ingestion of lettuce; the second was one of the 2 housewives, who noticed that the dermatitis of the hands,

forearms, face and neck was aggravated by eating lettuce; and the last was the male, who, in addition to the oral symptoms, described either exacerbation of pre-existing eczema or induction of eczema on his back corresponding to previously affected sites (11, 15, 20). The common denominator of these cases is that the systemic allergic dermatitis was reported by the patients, and not by the dermatologists.

In connection with a PhD study, 3 patients with lettuce contact sensitization and 1 with suspected lettuce contact allergy, but an irritant patch test reaction to lettuce oleoresin, were orally challenged with ~45 g of lettuce (21). Two of the patients were atopics, and 1 possibly had atopic dermatitis; only 1 of the atopic patients had a positive prick test reaction to lettuce. This patient developed distinct immediate allergic reactions on challenge: oral allergy syndrome with blisters of the oral mucosa, cough, and nasal secretion, followed by facial oedema and itching of the face and hands, lasting for days. The other atopic patient had a transient prickly sensation on the tongue and inner aspects of lips after 10 min, and a tingling sensation on the tongue on the same evening. The third patient, with possible atopic dermatitis, developed a flare-up of vesicular hand eczema and itchy swelling and possibly blisters of the oral mucosa within 12 h, and it is thus likely that she had contact stomatitis rather than an immediate-type reaction. Her symptoms are in accordance with a systemically induced allergic reaction, as she avoided touching the lettuce during the challenge. The fourth patient had no personal or family history of atopy, and she was the only one without symptoms from the oral mucosa after the challenge; her symptom was a slight swelling under the lower lip, but no cheilitis as she had experienced previously. Thus, it is difficult, on the basis of the literature, to disentangle the contributions of immediate and delayed allergic reactions to both local and systemic symptoms of skin and mucous membranes in lettuce contact allergy. Systematic studies, including prick tests and patch tests with lettuce in atopics and non-atopics, are warranted to clarify this.

Chicory. Immediate systemic allergic reactions after the ingestion of different species of chicory are well documented (22–25). A few cases of occupational contact sensitization to *Cichorium intybus* var. *foliosum*, *C. intybus* and *Cichorium endivia* have been reported, but only 1 patient developed stomatitis on ingestion, and this may have represented contact stomatitis (26, 27). In 2 cases of immediate-type allergy to chicory, the patients also presented with contact dermatitis caused by chicory ascribed to protein contact dermatitis, which seemingly represents a combination of immediate and delayed allergy (24,

25). Neither of these patients developed systemic contact dermatitis on ingestion of chicory or inhalation of vapour from cooked chicory, but, rather, immediate reactions, such as generalized pruritus, facial erythema or angioedema, and dyspnoea (24, 25).

Artichoke. Occupationally and non-occupationally acquired contact sensitization, and immediate-type allergy, to artichoke have been reported, but there has been only 1 case of a possible systemic contact reaction (28–31): Meding described a 44-year-old male fish and vegetable seller with recurrent occupational facial and hand eczema, which was worse in summer (32). Despite extensive patch and scratch testing, including chrysanthemum and aster, vegetables, and food items, the cause remained obscure until he turned up with acute facial eczema and a feeling of obstruction in the throat, without visible oedema, which was ascribed to handling and eating artichoke the day before (32). Patch tests with a stem and an ethanol extract of the stem gave positive reactions on day (D) 3, whereas a patch test with leaf gave a negative result. Prick tests were not performed. Of course, airborne contact allergy to SLs, present in artichoke and released during handling of the vegetables, is a possible explanation, and, likewise, the mucosal symptoms could represent contact allergy, but a systemic contact reaction cannot be ruled out.

Jerusalem artichoke. Although the glandular hairs (trichomes) of the leaf surface contain 19 SLs, there are no reports of contact allergy to the subaerial parts of this root vegetable (33).

Common and black salsify. Neither of these root vegetables has been reported as a cause of contact sensitization. Chemical analysis of aerial and subaerial parts of black salsify has shown the occurrence of bisabolane-type sesquiterpenoids, but these are not SLs (34).

Alpine chicory. As suggested by its colloquial name, the young shoots of this plant are used as vegetables in Italian and Finnish kitchens. Contact allergy has not been reported, although roots and leaves from plants of different origin contain, among other things, lactucin and lactucin derivatives (14).

Herbal teas

Contact sensitization to herbal teas from Compositae plants occurs frequently among persons with Compositae allergy. This was shown in a Swedish study, which was inspired by Compositae-sensitive patients reporting

exacerbation of hand eczema after drinking herbal teas (35). Twenty patients with previous positive patch test reactions to the SL mix were recalled and patch tested with eight dilution series of aqueous extracts from six Compositae plants: among the 19 patients who were still allergic to SLs, 17 had positive patch test reactions to at least one herbal tea (35). Two different brands of German chamomile and milfoil tea were included, and, altogether, German chamomile teas elicited positive reactions most frequently, followed by wormwood, dandelion, milfoil, goldenrod and marigold teas (35). The majority of chamomile tea-sensitive patients had positive patch test reactions to an ether extract of German chamomile. Nine of the 20 patients recalled had some kind of atopic disease, including allergic rhinoconjunctivitis and/or asthma (35).

German chamomile tea. The first case of systemic contact dermatitis caused by chamomile tea was published in 1998: a 26-year-old female applied an antibacterial ointment and a chamomile poultice to itching erythema of her eyebrows after she had dyed these, and, after 4 days, the lesions turned into acute facial eczema (12). Patch testing gave positive results with, among other things, SL mix and chamomile tea. Fifteen days later, the patient had a flare-up of her lesions, accompanied by eczema of the arms and trunk, as well as itching and oedema of the oral mucosa and anal pruritus; the symptoms were ascribed to the drinking of a cup of chamomile tea the day before (12).

Another case was reported by Rycroft: a 25-year-old female, with a history of eczema in infancy, had recurrent dermatitis of the eyelids and face, despite avoidance of the known contact allergens colophonium, chromate, cobalt, and *Evernia prunastri* (oak moss) (36). When the patient was patch tested for the third time, she had positive reactions to an extract of German chamomile and Compositae mix, and she then remembered that at least some of the relapses of the oedematous facial eczema, occasionally including lip swelling, were preceded by her drinking steaming-hot chamomile tea, which she had been addicted to for ~1 year. On avoidance of chamomile tea, she was free of symptoms at a 4-month follow-up visit (36). A third case was reported by Wintzen et al.: a 35-year-old female with atopic dermatitis developed widespread dermatitis, including facial eczema, in two summer seasons, accompanied by malaise and fatigue (37). Although specific IgE antibodies against food items could not be detected, the patient suspected food allergy, and followed a self-devised diet until patch tests showed weak positive reactions to nickel, her own emollient cream, and Compositae mix 6% pet. She then realized that her diet consisted largely of food items from the

Compositae family of plants, and remembered that the eczema, itching and fatigue often increased after she had drunk chamomile tea (37). Prick testing with chamomile tea was not performed. Avoidance of her usual cream and Compositae food items resulted in fast and long-lasting improvement of both her skin and general condition. The authors concluded that the general symptoms and the appearance of eczema on previously unaffected skin, such as the face, were in accordance with systemic contact dermatitis caused by Compositae (37). This is a likely explanation, although summer-related facial involvement is not a rare occurrence. Likewise, the flare-up of eczema in previously unaffected sites combined with mucosal symptoms and anal pruritus in the patient reported by Rodríguez-Serna et al. are highly suggestive of systemic allergic dermatitis. In the second patient, the steam from the chamomile tea could, theoretically, have induced facial/eyelid dermatitis as suggested by Anzai et al. (38), but it is well known that, for example, cinnamon in cereal or cakes may induce eyelid dermatitis as the only manifestation of systemic contact dermatitis, and, as the patient also had lip swelling, it is likely that her symptoms were caused by a systemic reaction rather than an airborne reaction (39). Thus, all 3 cases are probably examples of a delayed allergic systemic reaction to German chamomile tea.

Experimental studies on oral challenge with chamomile tea are scarce: 3 females with strong positive patch test reactions to German chamomile extract, including 1 with suspected systemic contact dermatitis caused by chamomile tea, were challenged by drinking one or two cups of chamomile tea (21). After 3 days, only 1 patient had slight exacerbation of hand and neck dermatitis, but this was ascribed to ongoing worsening of her eczema; another patient with suspected systemic contact dermatitis did not react.

Other Compositae-based herbal teas. In the report by Kurz and Rapaport, a 44-year-old Japanese male treated his poison oak dermatitis with topical application of both a 'mugwort' plant and a brew of the same plant several times before he simultaneously ingested the brew and applied some of it to the affected skin; 2 days later, he was admitted to the hospital with a high fever, cheilitis, severe stomatitis, and vesicular/pustular eczema of the face, neck, and treated areas of the trunk and extremities (40). A skin biopsy was most consistent with erythema multiforme, and, because of the severity of the reaction, patch tests were not performed. The authors suggested that the patient sensitized himself by application of mugwort (*Artemisia vulgaris*) 'as is', and then developed an external/internal allergic reaction after ingestion of mugwort

'tea' (40). Mugwort is a weakly and rarely sensitizing plant, but it is possible that the poison oak rash paved the way for subsequent sensitization to mugwort (4). Incidentally, wormwood tea, from the same genus, elicited positive patch test reactions in 13 of 19 Compositae-allergic patients (35). Erythema multiforme, in this context with laboratory test results within normal limits, is probably an expression of a delayed hypersensitivity reaction, as described previously (41, 42).

Wrangsjö et al. mentioned that a 61-year-old female patient with atopic dermatitis and hand eczema had 'noted generalization of her dermatitis' after ingestion of yarrow tea, and she was patch test-positive to tea extract; however, apparently, oral challenge was not performed (43).

Mark et al. reported a case of possible systemic allergic dermatitis caused by dandelion tea: a 59-year-old woman had recurrent, summer-exacerbated facial dermatitis for 10 years. The results of phototests were normal, but she was patch test-positive to dandelion extract. She used to drink dandelion tea made from loose leaves, and, after she had stopped doing this, the dermatitis cleared; furthermore, a challenge with one cup of dandelion tea elicited a recurrence after 12 h. The conclusion was that the patient had airborne contact dermatitis caused by dandelions in summer. The persistence in winter could have resulted either from systemic allergic dermatitis or from airborne contact dermatitis caused by the steam from the tea or from the handling of the loose dandelion leaves (13). The clinical feature with facial involvement was in accordance with that described in 1 of the patients who were sensitive to chamomile tea (36).

Spices

Noble laurel (bay leaf) (Laurus nobilis L., Lauraceae). The dried leaves of the laurel tree are used as a spice (bay leaf). Both these, the fruits and the roots of the tree contain several SLs, including costunolide and laurenobiolide (44–46). Laurel oil (*Oleum Lauri*) is officinal, and was previously used in ointments for boils (in German, 'grüne Abszess-Salbe'; in French, 'Végebom'). The allergenic properties of laurel oil were recognized early on: Bandmann and Dohn quote Ehrmann as describing laurel oil – in 1902 – as a substance that had been long known to be capable of inducing 'erythema venenatum' (47). Another previously important source of sensitization to laurel oil was its use in the German felt industry, where it was used for glazing felt hats, thus causing hatband dermatitis (48). The prevalence of contact allergy to laurel oil was between 3% and 7% in some German and French clinics in the 1950s and 1960s (47, 48). In a

more recent Dutch study on contact allergy to spices, only 1 of 103 subjects reacted positively to laurel oil, whereas 2 had doubtful positive reactions (49). Thus, much of the information on systemic allergic dermatitis caused by bay leaf dates back to the early reports.

One of the first reports on systemic allergic dermatitis caused by laurel was quoted by Gronemeyer in his article on hatband dermatitis in 1953: he stated that Jaffé and Blumenthal, in their book from 1933, described a case of acute, generalized eczema after oral challenge with five drops of laurel oil (50). Gronemeyer also reported on a 25-year-old male, with a family history of atopy, who often developed transient, itching erythema after ingestion of pickled herrings. After wearing a new hat for 1 h, he developed severe vesicular eczema of the face in the following days, and patch testing confirmed contact allergy to the hatband and laurel oil. It is likely that the patient was previously sensitized to laurel, and that the erythema caused by pickled herrings might have been caused by bay leaf in the dressing (50). Bandmann and Dohn reported a convincing case in a male with recurrent, generalized eczema, which always occurred after holidays with fishing trips (47). Patch testing showed a positive reaction to laurel oil of unknown relevance, as the patient denied any contact with the oil. However, it turned out that the freshly caught fish were prepared with bay leaves. The patient refused oral challenge, but was free of symptoms after avoidance of the spice (47). Another case was reported by Brunner: a female hatter developed occupational hand eczema because of contact with laurel oil, and the allergy was confirmed by patch testing. A recurrence occurred after the use of laurel oil-containing ointment, and later a generalized eczema was ascribed to a spicy sauce containing bay leaves (51).

Another convincing case was reported by Hausen: a 53-year-old, non-atopic woman sensitized herself to laurel oil by using it twice daily as self-treatment for lipomas (52). In the following years, recurrences occurred several times. On one occasion, the patient developed burning, prickling and itching orally 4 h after eating sauerkraut, from which the bay leaves had been carefully removed before it was served. Within 4 days, dermatitis developed in all previously affected skin areas (52).

Dooms-Goossens et al. reported another 2 cases, emphasizing the importance of cross-reactivity between plants from the Compositae family and laurel (10). The first was a 26-year-old woman with recurrent widespread eczema after gardening, and, additionally, a 1-year history of periorbital and -oral eczema, dyshidrotic hand eczema, and, on at least one occasion, a prickling sensation and oedema on the tongue. The strongest patch test reaction was to laurel oil 2% pet., and, when the

patient stopped using bay leaves in her diet, her dermatitis cleared. The authors considered it probable that the patient was sensitized from her Compositae garden plants, with secondary systemic allergic dermatitis being induced by the ingestion of laurel-spiced dishes (10). The second case was a 61-year-old man with a 40-year history of dyshidrotic eczema of the hands and feet, and more generalized eczema in spring and summer. He was patch test-positive to, among other things, several Compositae plants, laurel, and a mixture of (unknown) spices that his wife used daily in cooking. When spices were omitted from his diet, his hand and foot eczema improved significantly, but he still suffered from flare-ups after gardening. Like the young woman, he was sensitized primarily to Compositae (dandelions in his case), and, on ingestion of strong cross-reacting SL allergens, he developed dyshidrotic hand and foot eczema, a well-known clinical entity that may be a manifestation of systemic allergic dermatitis (6, 10).

Foussereau et al. quoted a case of perioral dermatitis after ingestion of laurel as a spice; this may, however, reflect simple contact between the spice and skin, and not necessarily systemically reactivated contact dermatitis (48). Spier and Sixt, on the other hand, performed an oral challenge in 2 of their laurel-sensitive patients, with negative results (53). In conclusion, there is strong clinical evidence to support the occurrence of systemic allergic dermatitis induced by ingestion of bay leaves.

Chinese star anise (Illicium verum Hook f.). The fruits and oil of Chinese star anise are traditionally used as ingredients in both Chinese medicine and Chinese cuisine (54). Star anise is also an ingredient of five-spice powder. Although some sources report that the sesquiterpenes of star anise are SLs, they are more precisely described as seco-prezizaane-type sesquiterpenoids (54). According to a Polish study, star anise oil may be both sensitizing and irritant, but the essential oil does not apparently contain sesquiterpenoids (54, 55).

Tarragon (Artemisia drancunculus L., Compositae). Although tarragon allegedly contains sesquiterpenoids, no reports of contact allergy to this spice have been published (56). The essential oil of estragon did not elicit positive patch test reactions in either 3 Compositae-sensitive patients or 6 eczema patients (57).

Herbal remedies

Feverfew [Tanacetum parthenium (L.) Schultz Bip., Compositae]. Feverfew has been used as a medicinal plant for almost 2000 years, and, in view of its antipyretic and

anti-inflammatory properties, it is not surprising that it was known as the 'Medieval aspirin' (58). In the 1970s and 1980s, feverfew gained a reputation as a migraine prophylactic and a remedy for arthritis (59, 60). The main SL from feverfew, parthenolide, has strong cytotoxic properties, which have been tested in clinical cancer trials, and it is also a potent contact allergen (1, 4). Some of the migraine sufferers who chewed raw feverfew leaves developed oral ulcers that were considered to be caused by systemic absorption, as ingestion of dried feverfew leaves in capsules could not prevent the mouth ulcers (59). In contrast to this, the development of more widespread stomatitis, including on the surface of the tongue, and often with swelling of the lips, was interpreted as possibly being caused by direct contact with the plant (59). As the patients were not patch tested, the oral ulcers, described by Awang as 'recurrent, so-called aphthous ulcers', may not be a sign of systemic allergic contact dermatitis, although this cannot be ruled out (61).

In an experimental study, 10 feverfew-sensitive patients were orally challenged with 20 mg of dried feverfew leaves in a gelatine capsule, followed by – if there was no reaction after 1 week – 60 mg of dried leaves. As 9 of 10 patients had dermatitis despite being challenged in winter, the results were difficult to interpret, but 1 patient developed eczema on his leg after taking 60 mg, another patient with atopic dermatitis had a slight flare-up of her vesicular hand eczema and widespread itching after both challenges, and, finally, 2 patients developed an eczematous eruption on the neck and flare of vesicular hand eczema, respectively, after ingestion of 20 mg of feverfew leaves (21). The three last-mentioned challenges were considered to be (possibly) weak positive. It was concluded that it takes either a high single dose or possibly a longer period with a daily dose to provoke a systemic reaction (21).

Elecampane (Inula helenium L., Compositae). Like feverfew, elecampane is an ancient medicinal plant that was considered to be panacea in the Middle Ages (4). Elecampane contains several SLs, including the strong sensitizer alantolactone (4). Two cases of possibly systemic reactions to the plant have been reported. Pazzaglia et al. described a 32-year-old woman who developed contact dermatitis caused by a herbal massage liniment that contained elecampane and two other Compositae herbs, as well as laurel. She had positive patch test reactions to the liniment 'as is', the SL mix, and alantolactone. On questioning, she remembered that she had developed facial eczema when she, 1 year before, had ingested an elecampane-containing herbal remedy (62). Gil Mateo et al. reported on a 31-year-old woman who was

sensitized to a 'herbal bag' containing elecampane; the eczema appeared 2 weeks after the application, and cleared after 1 week of treatment with a topical corticosteroid and oral antihistamine. However, 2 weeks after the appearance of the eczema, new lesions developed in previously affected sites, spreading centrifugally. The clinical and histopathological features were consistent with erythema multiforme. Patch tests showed positive reactions to SL mix and alantolactone (63). Although strong contact allergens may induce 'contact erythema multiforme', which typically occurs 1–15 days after the initial eczematous lesions, the delay and extent of the secondary lesions in this case may represent systemic contact dermatitis, as suggested by White (41, 64).

Purple coneflower [Echinacea purpurea (L.) Moench, Compositae]. This plant, which was originally a herbal remedy used by the North American Plains Indians, is considered to be a non-specific immunostimulant. Taken orally, pressed juice from the aerial plant parts may be used as supportive treatment of, for example, recurrent infections of the upper respiratory tract (61, 65). Purple coneflower may induce contact dermatitis as well as immediate-type reactions (66–68). Engebretsen et al. reported a systemic reaction ascribed to SLs of purple coneflower: a 61-year-old, non-atopic male developed recurrent facial oedema and also, occasionally, itchy dermatitis on the legs when weeding the garden while wearing shorts. After developing pneumonia, he repeatedly ingested a liquid herbal medicine containing extract of purple coneflower, and, in the same (winter) period, he had increasingly frequent attacks of facial oedema, lasting for 7–14 days, with erythema and burning, but no itching. Prick testing with the standard inhalant, latex and food allergens showed negative reactions, whereas patch tests showed a positive reaction to SL mix. The authors concluded that the patient was most likely sensitized to SLs from gardening, and developed facial oedema 'owing to oral intake of herbal medicine containing SL' (69). There was a temporal and probably also causal connection between oral intake of the extract and the oedema, but the nature of the systemic reaction was not clarified, although it was probably systemic allergic dermatitis. However, as SLs have apparently not been isolated from purple coneflower, other constituents may be involved (70).

Discussion

As shown in this review, the evidence for systemic allergic dermatitis is more convincing for plants or plant products that contain potent contact allergens such as bay leaves than for plants containing weak allergens, for example

lettuce. This is in accordance with the statement that probably all contact allergens may cause this type of reaction, provided that the degree of sensitivity and dose administered are sufficiently high (17). Despite the lack of robust scientific data, there is no doubt that SLs are capable of inducing systemic allergic dermatitis: this was clearly shown in a case report of a chemistry student who was inadvertently sensitized to an SL through laboratory work with costus resinoid (71). The student had a personal history of atopy, and her initial reaction, which occurred 10 days after cutaneous exposure, was a vesicular–bullous erythema multiforme-like dermatitis on the hands, forearms, and retroauricular areas. A patch test showed a 2+ reaction to SL mix after 24 h. Three months later, the student had to work with β -cyclocostunolide, and, despite performing analyses under the laboratory hood and wearing a mask, glasses, and gloves, she had a severe relapse affecting the upper limbs and axillary, antecubital, and popliteal areas within 48 h. As she had noticed a smell of β -cyclocostunolide in the laboratory, and as she had a positive patch test reaction to β -cyclocostunolide, which is closely related to costunolide, the flare-up was considered to be systemic allergic dermatitis caused by inhalation of an SL (71).

A similar mechanism was suspected in a male Indian office worker with *Parthenium* sensitization, who developed recurrent widespread papulo-squamous to eczematous lesions in a non-airborne pattern (72). He lived in an area with abundant growth of *Parthenium hysterophorus*, but allegedly never touched the weed. On challenge, when he was asked to inhale five times from a polythene bag containing fresh, whole *Parthenium* plants, his pruritic dermatitis worsened after 8–10 h (72). In connection with attempts at oral hyposensitization in patients with *Parthenium* dermatitis, 6 of 20 patients had to discontinue the treatment because of exacerbation of dermatitis: the strong contact allergens of *P. hysterophorus* are thus capable of inducing systemic allergic dermatitis through both oral and airway exposure (73).

In view of the worldwide consumption of chamomile tea and lettuce, systemic contact dermatitis caused by these products is rarely reported. Although this may be because of relatively weak haptens, another possibility is oral tolerance to these common allergens (4, 74). White et al. suggested, on the basis of clinical and experimental data, that oral exposure to a hapten prior to cutaneous exposure might induce tolerance or diminished responsiveness to the allergen in question (74). Concerning Compositae plants, the paucity of chrysanthemum dermatitis in Japan has been ascribed to the consumption of chrysanthemum leaves in salads (4). However, patch testing with an extract of fresh leaves in Japanese

chrysanthemum growers showed positive reactions in 27.3% in 1976 and in 43.3% in 1982, and heavy exposure is thus also a risk factor in Japan (75).

A study that compared the prevalence of patch test positivity to SL mix in London and Singapore from 1998 to 2004 showed a significantly lower prevalence in Singapore: the authors suggested that the difference could be attributable to the consumption of chrysanthemum tea in Singapore, inducing oral tolerance (76). Even though SL mix is a notoriously poor screening agent in some areas, and perhaps even more so when screening for chrysanthemum sensitization is performed, oral tolerance may be a possible, even likely, although unproven, explanation, provided that the lack of case reports and positive patch test reactions to SL mix reflects a (true) low prevalence of sensitization in Japan and Singapore (4, 21, 76). Likewise, oral exposure to lettuce, which, in the majority of individuals, will occur before any significant cutaneous exposure, may induce a tolerance that is insufficient in persons with heavy, typically occupational, exposure. As mentioned above, lettuce may induce reactions through both immediate (humoral), intermediate (protein contact der-

matitis) and delayed (T-cell-mediated) mechanisms, and the contribution of each of these in systemic reactions has not been clarified. Furthermore, experimental studies have even suggested that topical exposure to strong contact allergens may be associated with hapten-specific antibody production, and more than one mechanism may therefore be involved (77).

The clinical picture is highly variable, from localized eczema of the face or hands to generalized eczema or exanthema, sometimes with additional urticarial or erythema multiforme-like features and mucosal symptoms. The clinical features do not differ from those induced by other allergens that may cause systemic allergic dermatitis.

In conclusion, on the basis of anecdotal statements from patients and a few reports on accidental sensitization and exposure, epidemiology, and experimental oral challenges, there is sufficient evidence to confirm the existence of systemic allergic dermatitis caused by SLs. However, further studies are needed to assess the prevalence of reactions and clarify the pathogenesis for individual haptens.

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