Plant Dermatitis: A Growing Problem

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The lectures from the Botanical Dermatology Course and workshop are described in detail below. This is a great opportunity for you who could not attend to learn more.

A "Botanical Dermatology Course and Workshop" was held in Odense, Denmark, on 27–29 August 2009. The course was organized by Klaus E. Andersen, Evy Paulsen (of the Department of Dermatology and Allergy Centre, Odense University Hospital, University of Southern Denmark) and Lars P. Christensen (of the Institute of Chemical Engineering, Biotechnology and Environmental Technology, University of Southern Denmark) as a European Society of Contact Dermatitis (ESCD) course. The aim was to provide participants with a basic and clinical understanding of dermatitis elicited by plants, with a focus on allergic contact dermatitis.

Field visits

The first afternoon was dedicated to field visits, first to the Research Centre Aarslev, Faculty of Agricultural Sciences, University of Aarhus. Senior scientist Kell Kristiansen informed participants about glasshouse research into breeding of asters (*Aster novii-belgii*) and growing genetically modified apple trees (Fig. 1). The aster plants are subjected to traditional breeding methods whereby cross-pollination creates new hybrids with, for example, more petals for ornamental use or longer stems for use in the cut-flower industry. The apple trees, on the other hand, are genetically modified to create hypoallergenic apples and are grown in pots in glasshouses to prevent "contamination" from outdoor unmodified pollens. Another important aspect of the work at the Research Centre is field experiments with medicinal plants. The main purpose is to grow medicinal plants that may be used in the treatment of some major diseases of Western society: diabetes, cardiovascular disease, cancer, and arthritis. The plants comprise both some traditional Western herbal remedies, such as willow (*Salix* species) and stinging nettle (*Urtica dioica*), and traditional plants of

Fig. 1. Participants in a glasshouse full of aster plants.

Chinese medicine, such as sweet wormwood (*Artemisia annua*), as well as the purple cone flower (*Echinacea purpurea*) used as a medicinal plant by North American Indians. Senior scientist Kai Grevsen showed the participants beds of fragrant herbs, such as thyme (*Thymus vulgaris*), oregano (*Origanum vulgare*), greek oregano (*Origanum vulgare* ssp. *hirtum*), and purple cone flower, and later lectured on the manipulation of secondary metabolites in plants by cultivation techniques. Many secondary metabolites, such as flavonoids, terpenoids, and polyacetylenes, constitute the defence system of plants, but are also biologically active (bioactive) in humans. The content and composition of bioactive compounds depend on both genetic variation within subspecies, clone, variety, etc., growing conditions (soil, climate, fertilizers, etc.), harvest time, and handling after harvest. For instance, in the cultivation of stinging nettles there appears to be an inverse relationship between a high yield of plant material and the content of bioactive compounds; high levels of nitrogen will promote plant growth, but significantly reduce the concentration of bioactive flavonoids.

Finally, the nursery Multigreen A/S opened its doors with great hospitality. The nursery is the second largest producer of ivy plants (*Hedera helix*) in Europe, the number of plants amounts to 8 million per year, 80% of which are exported. Production is mechanized to a large extent, thus probably reducing the prevalence of adverse effects from handling the ivy plants (Fig. 2).

Epidemiology of plant dermatitis

Christopher R. Lovell (UK) (Fig. 3) reviewed the worldwide distribution of plant dermatitis and the diversity of reactions, ranging from trivial urticaria from stinging nettles, to florid bullous dermatitis from phototoxic plants, to severe erythrodermia due to allergic contact dermatitis from *Parthenium hysterophorus* (wild feverfew). Irritant contact dermatitis can be caused by mechanical and/or chemical irritation of the skin, exemplified by the barbs (glochids) of prickly pear cactus *(Opuntia ficus-indica)* and by *Fremontodendron*, whose irritant spines cause an inflammatory response. In the occupational setting, irritant contact dermatitis is well-known among daffodil growers. The most important irritant plant family is the *Euphorbiaceae* (spurge family), which comprises popular pot plants, such as poinsettia *(Euphorbia pulcherrima)* and croton *(Codiaeum variegatum)*, but also the manchineel tree *(Hippocane mancinella)*, which causes major problems in the south-eastern USA. Phytophotodermatitis is classically caused by well-known members of the umbellifers (*Apiaceae*, formerly *Umbelliferae*), such as hogweed *(Heracleum sphondylium)*, giant Russian hogweed *(Heracleum mantegazzianum)*, wild carrot *(Daucus carota)*, and wild chervil *(Anthriscus sylvestris)*. Another important family is the *Rutaceae*, which includes *Citrus* species, the garden plant burning bush *(Dictamnus albus)*, and rue *(Ruta graveolens)*. String trimmers may spray plant sap on to the skin, resulting in a clinical pattern different from the streaky bullous eruption typical of phytophotodermatoses: a maculopapular dermatitis on exposed skin that may resemble pityriasis lichenoides. Phytophotodermatitis may leave the skin hypo- or hyperpigmented. Most cases of allergic contact dermatitis are caused by a relatively limited number of plant families (and species). Worldwide the poison ivy family *(Anacardiaceae)* is the most important. In Europe the daisy family *(Compositae/Asteraceae)* is the most frequently sensitizing, followed by the primula family *(Primulaceae)*.

Fig. 2. Henrik Bøg Madsen, Multigreen A/S, describing the large-scale production of *Hedera* plants.

Thomas Diepgen (Germany) outlined the hard epidemiological data on plant dermatitis: most of the studies are case reports or observational studies in patients. However, it is well-known that allergic contact dermatitis from *Toxicodendron* species – poison ivy, poison oak, poison sumac – affects millions of North Americans every year, with an estimated 50–78% of the adult population being sensitized.

Compositae allergy is among the top 10 contact sensitivities in Europe, and the prevalence of sensitization ranges between 1% and 4–5% in selected patient populations. However, there are no data on the prevalence in the general population.

Likewise, data on sensitization rates in occupationally plant-exposed individuals are scarce. The lifetime prevalence of occupational dermatitis was 19.6% in gardeners and greenhouse workers in the county of Funen, Denmark. In North Bavaria, florists had the third highest incidence rate of notified work-related contact dermatitis. In 77.4% a clinically relevant contact allergy could be identified, and the majority was also occupationally relevant. An allergic contact dermatitis was diagnosed in 68%, most often due to plant substances.

Fig. 3. Christopher Lovell lecturing on the worldwide problem of plant dermatitis.

Establishing botanical identity

Richard J. Schmidt (UK) described the importance of establishing correct botanical identity before patch-testing with plants "as is". Formerly, botanical nomenclature was based on the morphology of flowers/reproductive structures, whereas now genetic studies are used to classify, and re-classify, plants. This makes it difficult for lay people to identify plants correctly. The dermatologist should keep a "voucher sample", at least when a new plant sensitizer is suspected, for further studies, if necessary. Ideally, any plant eliciting positive patch-test reactions should be identified by a botanist familiar with the International Code of Botanical Nomenclature (ICBN): the correct botanical name is the key to a large amount of information about the plant in question.

Richard J. Schmidt has taken on the task of revising and updating the electronic incarnation of Mitchell and Rook's well-known book "Botanical Dermatology" (http://BoDD.cf.ac.uk), which is a useful database of dermatitic species.

Diagnostic patch-testing with plants

A limited number of plant allergens is available from the commercial patch-test material suppliers such as Hermal (Germany), Chemotechnique (Sweden) and Brial (Germany). Updated information and advice is available on their websites. Patch-testing with fresh and dried plant material is generally safe provided that the botanical identity is established. Avoid testing with irritant plants including *Euphorbiaceae* (spurge family), *Ranunculaceae* (buttercup family) and *Cruciferae* (cabbage or mustard family). Ask patients to bring photographs and samples of suspected plants to help identification. Comparison with photographs in books or on websites may help both the patient and the dermatologist. If fresh plant material is not available then advise the patient to press and dry the plant material between paper sheets for transportation or posting. Avoid sending plant material in air-tight plastic bags. The plant material will turn into a rotten smelly soup, which is useless for identification and testing.

Chemical sensitizers in plants and woods

Jean-Pierre Lepoittevin (France) presented a classification of the main types of chemical sensitizers responsible for the allergenicity of plants and woods based on their chemical nature.

Lactones: α-methylene-γ-butyrolactone is present in tulips and Peruvian lily (*Alstroemeria* spp.) or is included in sesquiterpene lactones characteristic of *Asteraceae* and many other plant families.

Quinones (ortho and para): Quinones are the main sensitizers in tropical woods, but are also present as such in for example *Primulaceae* (primin) and in more complex chemical structures.

Phenol derivatives (ortho- and para): Phenol derivatives are good examples of prohaptens needing to be metabolized to generate reactive intermediates. These relative lipohilic molecules can penetrate the skin generating quinone haptens *in situ*. Ortho-and para-phenol derivatives are found in plant species of the *Anacardiaceae, Ginkgoaceae, Primulaceae, Hydrophyllaceae* and *Proteaceae*. Smaller phenols are also involved in skin allergies; however, some of them, such as eugenol, need a demethylation step to become reactive, and hence can be characterized as prehaptens.

Terpenes: Terpenes are ubiquitous and are the main components of most essential oils. Terpenes are normally non-reactive, but when exposed to air-oxidation they can form highly reactive oxidation products and are also good examples of prehaptens.

Miscellaneous structures: Other types of natural products containing reactive functional groups have been associated with skin allergies. Examples of such natural products are alkyldisulfides (*Alliaceae*), isothiocyanates (*Cruciferae),* and aliphatic polyacetylenes (*Araliaceae, Apiaceae*).

Anti-microbial agents of plants causing contact allergy

Ann-Therese Karlberg (Sweden) described contact allergy from preservatives of natural origin. Difficulties in finding good commercial preservatives have resulted in an increased use of natural anti-microbial agents, such as tea tree oil, citrus oil, lavender oil, rose oil and colophony.

Tea tree oil comes from *Melaleuca alternifolia* and is very efficient against *Escherichia coli* and *Staphylococcus aureus* as well as *Candida albicans*. Tea tree oil is used as a traditional herbal remedy to treat, for example, acne and tinea. Tea tree oil can cause allergic contact dermatitis. The sensitizing agents are degradation products of monoterpenes, which are abundantly present in the oil.

Citrus oil from the peel of citrus fruits is used in various products due to its scent, but also as a disinfectant. Limonene is one of the major components of citrus oil that, when exposed to air-oxidation, can form highly reactive oxidation products that are strong allergens.

Lavender and rose oil are commonly used as fragrances and contain anti-microbial monoterpenes. The major components of these oils are synthesized, used as perfume ingredients, and analogous to limonene they are oxidized at air exposure forming allergenic compounds.

Colophony is obtained from pine trees and is the residue when the monoterpenes (the turpentine part) are distilled from the oleoresin of the trees. Colophony has many commercial applications due to its sticky and anti-microbial properties. Colophony is used as adhesive on plasters and to treat skin infections and is a well-known cause of contact dermatitis. The major components in colophony are diterpenes, such as abietic acid and dehydroabietic acid, which form allergenic compounds when oxidized and are considered as the major cause of contact allergy of colophony.

Cross-reactivity between plant chemical sensitizers

Jean-Pierre Lepoittevin (France) spoke on the cross-reactivity between plant chemical sensitizers. The factors that control molecular recognition during the elicitation stage depend on the nature of the chemical group and the compatibility of the spatial geometry. Thus, although tulipalin A (the allergen of tulips and *Alstroemeria*) and alantolactone (the allergen of *Inula helenium)* bear the same chemical group, α-methylene-γ-butyrolactone, they cannot give rise to cross-allergic reactions, as their spatial volumes are too different. In contrast, isoalantolactone and alantolactone produce a cross-allergic reaction, since they share both a homologous chemical group and spatial volume. The identification of cross-allergic responses can be especially difficult, as the metabolism of molecules can be very complex and two molecules with *a priori* little in common can be converted to derivatives that have a similar structure. The concept of pre/prohapten is also very important in the interpretation of results in allergic reactions. Miconidin from *Primula obconica* is easily oxidized to the allergen primin and is an example of a prohapten that cross-reacts with primin. On the other hand, miconidin methyl ether requires a demethylation step before it can be oxidized to primin and hence is an example of a prehapten that cross-reacts with primin. However, the structure of a modified/metabolized molecule can sometimes also be very different from that of the initial one, thus it can be difficult to establish similarities between chemical groups and structures. The term "cross-reaction" is often misused and should therefore be restricted to well-defined cases that can be called true cross-allergies.

Primula dermatitis

Christopher R. Lovell (UK) described primula dermatitis. *Primula obconica*, the greenhouse primula, has been recognized as an important cause of allergic plant dermatitis in Europe for over a century, although the main allergen, primin, was not identified until 1967. The primula dermatitis may present as a typical streaky vesiculobullous eruption, but the clinical features are variable and more unusual presentations have resembled erythema multiforme, herpes simplex, and lichen planus. Primin has been included in the European standard series for decades, but recent reports, including a large study from the UK, have shown a decline in the number of primin-positive patch-tests. Whether this is due to the introduction of primin-free *Primula obconica* cultivars is not clear. Contact dermatitis from hardy primula species, such as *P. auricula* and *P. denticulata*, has been described in enthusiastic primula growers.

The allergen, however, is not primin and the diagnosis rests on patch-testing with plants "as is". In conclusion, classical primula dermatitis may soon be a thing of the past.

Ivy dermatitis

Christopher R. Lovell (UK) also spoke on ivy dermatitis. Ivy *(Hedera helix)* is native to temperate regions and is absolutely unrelated to poison ivy. It is used widely as an ornamental plant both indoors and outdoors. Like *Primula obconica*, ivy has been a well-known cause of plant dermatitis for over a century, but contrary to *P. obconica*, ivy dermatitis may be an allergic plant dermatitis that is increasing, mainly because it has been previously underreported. The main allergen is the polyacetylene falcarinol, which occurs in other members of the ivy family *(Araliaceae)* as well as in the related *Apiaceae* family that includes carrots, coriander and other vegetables. Neither falcarinol nor the weaker allergen didehydrofalcarinol are commercially available, meaning that cases of ivy dermatitis may be missed. In view of the ubiquity of falcarinol, it would be a welcome addition to the plant series. Until this is available, diagnosis of ivy allergy rests on careful history-taking and patch-tests with plants "as is".

Compositae dermatitis

Evy Paulsen (Denmark) and ***Kerstin Lundh*** (Sweden) described *Compositae* dermatitis. Since the prevalence of *Compositae* sensitivity is high in Europe, it is important to screen with the sesquiterpene lactone mix and supplement with aimed testing using plant extracts and allergens based on the individual history. Important sensitizers in North Europe include cultivated plants, such as chrysanthemums, marguerite daisies (*Argyranthemum frutescens*), and feverfew (*Tanacetum parthenium*). The main allergen of feverfew grown in North and Central Europe is parthenolide, and this strong allergen has been shown, by High-Volume Air Sampler experiments, to be airborne on plant particles, thus eliciting airborne contact dermatitis. Other clinical features in European *Compositae*-sensitive patients include hand eczema, especially vesicular eczema of the palms and soles, and facial dermatitis. Concerning the alleged "sparing of woman and children" described in early reports, newer studies from both USA and Europe have shown a more equal sex distribution, depending on exposure. Likewise, recent studies have shown sensitization even in small children. Atopy may be a risk factor in these.

The sensitizing potential of *Compositae*-containing topical herbal remedies and cosmetics is probably low, but they may elicit dermatitis in *Compositae*-allergic individuals. Patch-testing with herbal teas derived from *Compositae* plants as, for example, German chamomile and dandelion, has shown a high prevalence of positive reactions in *Compositae*-sensitive persons; there seems to be more than one allergen in tea made from German chamomile.

Lichen contact allergy

Kristiina Aalto-Korte (Finland) spoke on lichen contact allergy. Strictly speaking, lichens are not plants, but comprise an algae and a fungus living symbiotically. They grow all over the world and are used ornamentally in flower arrangements, for toy trees, wool dyeing, and in the fragrance industry. The oak moss perfumes are extracted from *Evernia prunastri* (Oak Moss Absolute) and *Pseudevernia furfuracea* (tree moss). Lichen contact allergy may develop either from contact with lichens or fragrances. Allergic contact dermatitis from lichens is thought to be rare and occur mainly in an occupational setting among forestry and horticultural workers and lichen pickers. Fragrance allergy, on the other hand, is extremely common and the Oak Moss Absolute ingredient of Fragrance Mix I is the constituent eliciting positive patch reactions most frequently. However, people engaged in outdoor leisure activities in woodland may also be at risk from picking berries and mushrooms and cutting and handling barked wood. Lichen contact allergy is an old, partly forgotten, disease that may be relevant to test for in exposed persons.

Contact allergen release from plants

Airborne allergens may produce lesions in the exposed portions of the skin leading to an airborne contact dermatitis (ABCD), as described by ***Lars P. Christensen*** (Denmark). Plants are a rich source of airborne allergens that can be spread via indirect contact (e.g. hand-borne), direct release (emission) from plants, oxidation of non-allergenic volatiles to allergens in the air or on the skin, or by the release of small plant particles. The sensitizing properties of *Primula obconica* is primarily due to the accessibility of primin on the surface of the plant. Primin is formed in minute glandular hairs (trichomes). When the trichomes burst, the allergen accumulates on the top and sides of the hairs. Primin is volatile and released from intact plants in amounts high enough to elicit an allergic reaction in sensitized patients. Therefore, airborne primin is a possible cause of primula dermatitis. Examples of direct emission of strong allergens from plants are few, as many of these allergens are not volatile.

For many years, it has been debated whether non-volatile strong contact allergens, such as sesquiterpene lactones, can be spread via pollen or dust particles explaining the classical form of *Compositae* dermatitis with the typical airborne pattern eczema. Feverfew (*Tanacetum parthenium*) is allegedly an important cause of airborne *Compositae* dermatitis. The most important allergen of this plant is the sesquiterpene lactone parthenolide (PHL). By the use of a High-Volume Air Sampler (HIVAS) capable of capturing plant particles down to 4 µm in size it has been demonstrated that PHL is released from feverfew in a concentration of approximately 100 ng $plant^{-1}$ h^{-1} meaning that a border of feverfew plants may release milligrams of the allergen. Testing with a dilution series of PHL revealed positive reactions down to 8.1 ng/patch and confirmed the patch-test results on feverfew-allergic patients with HIVAS extracts. The detection of PHL in HIVAS extracts in allergenic amounts is strong evidence of PHL being the allergen responsible for airborne *Compositae* dermatitis caused by feverfew, and hence indicates that sesquiterpene lactones and other strong contact allergens may be airborne through plant particles being able to cause ABCD.

Plant allergens in type I allergy

Carsten Bindslev-Jensen (Denmark) spoke on plant allergens in type I allergy. Plants are well-known causes of immediate type skin and mucosal reactions, ranging from oral allergy syndrome to anaphylaxis. The former is often seen in patients with birch pollen allergy and the culprit proteins belong to the profilin family, whereas the latter primarily is mediated by heat-stable proteins from the so-called prolamin or cupin families of allergenic proteins. A useful database describing this is: www.meduniwien.ac.at/allergens.allfam. The most severe clinical reactions are elicited by nuts, especially Brazil nuts and hazelnuts, sesame and poppy seeds, and peanuts (which is a pea, not a nut – meaning that serving fresh peas instead of peanuts is not safe from an allergological point of view). In most cases freezing or heating will destroy the allergens, but this is not the case in peanut roasting. Despite the theoretically potential risk of introducing new and dangerous proteins into previously harmless foods, extensive studies of genetically modified plants used for food have not identified major problems. Finally, a new disease entity that is being diagnosed with increasing frequency was presented: food-dependent, exercise-induced anaphylaxis. Some of the gliadins from wheat, and especially ω-5 gliadin, can elicit anaphylaxis in combination, and only in combination, with physical exercise, aspirin and/or alcohol. Half of the patients have normal tryptase levels.

Plants in Denmark that cause skin diseases

With a series of excellent photographs of plants and patients ***Niels K. Veien*** (Denmark) reviewed problematic plants in Denmark. Allergic contact dermatitis is caused primarily by *Compositae* plants, such as dandelion (*Taraxacum officinale*), tansy (*Tanacetum vulgare)*, chrysanthemums, and lettuce (*Lactuca sativa*), while Peruvian lily is an occasional, and the greenhouse primula (*Primula obconica*) a rare, sensitizer. An exotic cause of contact allergy was the use of a wooden bracelet made of *Dalbergia retusa*. Chefs may be sensitized by garlic (*Allium sativum*), and in one example the preparation of a large quantity of Waldorf salad and later use of a tanning bed elicited a phototoxic reaction in a chef due to celery sap on the skin. Irritant contact dermatitis may be caused by the house plant *Dieffenbachia* (dumb cane) due to a combination of mechanical irritation from oxalate crystals and subsequent chemical irritation from a proteolytic enzyme and oxalic acid. Contact urticaria may be non-immunological, as in the case of stinging nettle, or immunological. Examples of the latter presented here included latex, wheat, potato, and Christmas cactus (*Schlumbergera*).

Plants and the poet – and a prize

Richard J. G. Rycroft (UK) presented an array of fascinating poems "that portray plants from towering trees to lowly weeds". The view that poetry can provide an exercise in paying attention to what is in front of us, and perhaps even make us acquire the same attitude to our own real-life surroundings, was conveyed to a very attentive audience. Finally, a book encompassing poetry, plants, and life itself in an almost miraculous way was recommended: "The Wild Braid" by the poet Stanley Kunitz with the writer Genine Lentine and the photographer Marnie Crawford Samuelson (New York: Norton; 2005).

Afterwards, Richard Rycroft was presented with the prestigious International League of Dermatological Societies (ILDS) Lifetime Award by Professor Kristian Thestrup-Pedersen (Denmark) as representative of the ILDS Board. The prize was awarded in acknowledgement of Richard Rycroft's lifetime achievement within dermatology and especially his years as Editor-in-Chief of *Contact Dermatitis* from 1987 to 2005.