

Plant Allergen-Induced Contact Dermatitis

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ABSTRACT

Although manifold beneficial effects of plant compounds for the treatment of skin disorders are known, cutaneous exposure to plants can also result in various types of incompatibility reactions such as contact dermatitis. In this mini-review, we briefly describe the different clinical forms of contact dermatitis (photoinduced, irritative, and allergic form) and highlight recent publications in the field of contact dermatitis. Major topics are recent recommendations regarding testing for plant contact dermatitis, advances in understanding the immunological mechanisms of plant contact dermatitis, and case reports for plant contact dermatitis. Unfortunately, most people still associate the terms “healthy and safe to use” with plant compounds due to their natural origin, leading to an increased utilization, be it for home-made remedies or as cosmetics. Therefore, it is on the one hand important to raise awareness in a broad audience that plants may cause contact dermatitis and on the other hand to indicate to clinicians that plants should be included in a patch test if a history of plant exposure exists.

Introduction

Plants and plant products are ubiquitous in our daily life, be it at homes, in gardens, at workplaces, or in nature. Despite the broad applicability of different plant compounds in the treatment of (skin) diseases (see further articles in this issue), as well as most plants being harmless on contact with the skin or ingestion, cutaneous exposure to plants can also cause incompatibility reactions such as contact dermatitis. This observation is also true for the due to their perceived safety–increasing use of essential oils and botanical products that are included for example in cosmetics [1, 2]. Importantly, the risk of sensitization to essential oils increases with the concentration of the oil as well as with the presence of oxidation products such as epoxides or peroxides in the oil [3–5]. This indicates that these oils might become a stronger sensitizer with increasing age/autoxidation [6]. At least limonene seemed to be astonishingly stable under real-life conditions in a study ana-

lyzing the formation of primary and secondary oxidation products in consumer products that were used for over 2 y [7]

The age distribution of patients with positive patch tests to topical herbal remedies (1.4% patients with positive reactions out of the contact allergic subjects studied; 0.8% of the total study population) indicates that patients below 20 and over 69 y old seem to be slightly less affected and that the majority of positive patients were female (93 compared to 34 men) [8]. Unfortunately, due to the limited number of commercially available standardized patch test substances and the risk of *de novo* sensitization when directly applying (parts of) plants or extracts, testing for plant-induced allergic contact dermatitis (ACD) still remains difficult.

Sensitization in higher numbers seems to occur only to a few plant families, with about 250 recognized contact-sensitizing plant families with medicinal properties in Europe [9] and more than 10 000 species causing irritative or ACD worldwide [10]. The

high relevance of plant-mediated contact dermatitis is underlined by data provided by the Information Network of Departments of Dermatology (IVDK), where fragrance mix (9.1%), balsam of peru (7.2%), fragrance mix II (4.6%), rosin (3.9%), ylang-ylang oil (2.4%), compositae mix II (1.2%), and sandal wood oil (2.2%) were among the top 25 “hit list” of contact allergens in the patch test cohort 2012 [11]. ► **Table 1** provides a selected overview of sensitizing plant compounds and prevalence data. Apart from direct contact with plants/extracts mentioned above, even not so obvious routes of contact with sensitizing plant compounds may play a role in the development of skin reactions in extremely sensitive patients, as recently shown for the highly sensitizing sesquiterpene lactone (SL) parthenolide, occurring in plants of the Asteraceae family, which was found in Danish biodynamic and organic milk [12].

As indicated by a recent approach to develop a quantitative risk assessment model for skin sensitizing plant protection products [16], not only plants or plant compounds themselves but also plant protection products need to be taken into account regarding the elicitation of contact dermatitis after plant contact.

Clinical Forms of Plant-Induced Contact Dermatitis

Apart from mechanical injury due to splinters or abrasions, which usually do not come to the attention of physicians, although they represent a frequent cause of plant dermatitis, plants can cause more severe skin dermatoses. Co-exposure of the skin with plant compounds and UV-light may lead to phototoxic/irritative or photoallergic reactions. Toxic/irritative reactions result from an activation of the innate immune response while photoallergic reactions require the activation of the adaptive immune response. Both irritative-, immediate-, or late-type ACD reactions can occur even without UV radiation of the skin just by contact to the plant, analogous to the irritative or ACD observed after contact with irritative or sensitizing chemicals. A special form of contact dermatitis, the airborne contact dermatitis (ABCD), is induced by exposure to particles suspended in the air. Due to the general difficulty to prove the diagnosis, it is difficult to determine the exact prevalence of ABCD. Again, ABCD can be classified either as allergic or as irritative contact dermatitis, depending on the etiology and mechanism of inflammation. A recent case of ABCD in 2 patients showing allergic reactions to *Eucalyptus* L’Her. was published by Paulsen et al., also indicating that the exact identification of an ABCD was difficult [17].

A rare non-eczematous form of contact dermatitis was reported in a patient receiving acupoint herbal patch therapy with Semen Sinapis Albae (SSA) from *Sinapis alba* L. [18]. In this patient, patches were applied twice in an interval of 10 d with no cutaneous abnormalities observed 24 h after removal of the second patches. However, 1 mo later, pruritic erythema and pin-sized papules appeared at the application site; a skin biopsy showed parakeratosis, acanthosis, and focal spongiosis in the epidermis. The patient was diagnosed with lichenoid contact dermatitis induced by SSA [18].

Recent Recommendations Regarding Testing for Plant Contact Dermatitis and Novel Classifications

While contact dermatitis to plants has been well known for a long time and been extensively documented in several impressive works such as the book by Mitchell and Rook [10], it is still of relevance nowadays. In general, the prevalence for contact dermatitis is 20.1% [19], while for plant-induced contact dermatitis a retrospective study (2006–2009) from the Dermatology Department “St. Spiridon” Hospital, Iasi in Romania, included 9059 patients with 353 patients being diagnosed with contact dermatitis (i.e., showing a rather low overall prevalence of 3.89%); of these patients, 92 (i.e., 26.14%) showed a contact dermatitis reaction to plants (marigold 30%, chamomile 20%, and comfrey 17.5%) [20]. In a retrospective study analyzing patch test data of the IVDK from 2007 to 2016, Bauer et al. revealed that florists reacted significantly more frequently to Compositae Mix I and II (CM I: 8.7%; CM II 10.6%) than cooks (CM I: 2.1%; CM II: 0.8%) or controls (CM I: 1.3%; CM II: 1.2%) [13]. They concluded that florists and related occupations such as gardeners, horticultural workers, flower binders, and seller of fruits, vegetables, and flowers are at considerable risk to acquire occupational contact allergy to Asteraceae plants, fruits, and vegetables [13].

If patient history suggests exposure to plants, additional patch testing for plant compounds (compositae mix) in children was even recommended in a recent EAACI position paper [21], though it was also strongly advised against patch testing of plants known to be irritants such as the Brassicaceae family [21]. The compositae mix has a higher efficacy regarding the detection rate of Asteraceae allergy compared to the previously used SL mix [22]. However, as indicated by Jacob et al., it needs to be kept in mind that the compositae mix consists of short ether extracts of 5 plants (*Arnica montana* L., Asteraceae, *Matricaria chamomilla* L., Asteraceae, *Tanacetum parthenium* L., Asteraceae, *Tanacetum vulgare* L., Asteraceae, and *Achillea millefolium* L., Asteraceae) being produced without a standardized manufacturing protocol and chemical profile and thus reproducibility is not guaranteed. Therefore, the development, validation, and commercial marketing of an Asteraceae mix based on pure and standardized ingredients such as the SL Mix II proposed by Jacob et al. [23] might help to further improve the diagnostic in the future.

One elegant approach to review ACD to plants and to classify the most relevant chemical allergens contributing to plant-induced ACD was provided by Rozas-Muñoz et al. and is based on the 5 major families of chemical sensitizers: alpha-methylene-gamma-butyrolactones, quinones, phenol derivatives, terpenes, and miscellaneous structures (disulfides, isothiocyanates, and polyacetylenic derivatives) [24]. To classify the sensitizers according to their chemical structure might help to provide a more rationale understanding of cross-reactions between apparently unrelated plant genera.

► **Table 1** Sensitizing plant compounds (selected).

Patch test compound (= not plant derived)	Plant family	Plant species	Prevalence (%) according to NACDG 2011–12 [13] or (*) 2013–2014 [14] or (+) IVDK [11] or (#) de Groot [15]
Fragrance mix I			12.1 * 11.9 (+ 9.1)
▪ Amyl cinnamal	e.g., <i>Cinnamomum verum</i> J.Presl (Lauraceae)		
▪ Cinnamyl alcohol	e.g., <i>Styrax</i> L. (Styracaceae)		
▪ Cinnamal	e.g., <i>Cinnamomum verum</i> J.Presl (Lauraceae)		
▪ Eugenol	e.g., <i>Syzygium aromaticum</i> (L.) Merr. & L. M.Perry (Myrtaceae)		
▪ Geraniol	e.g., <i>Cymbopogon martini</i> (Roxb.) Wats. (Poaceae)		
▪ Hydroxycitronellal	e.g., <i>Piper nigrum</i> L. (Piperaceae)		
▪ Isoeugenol	e.g., <i>Myristica fragrans</i> Houtt. (Myristicaceae)		
▪ Oak moss absolute	<i>Evernia prunastri</i> (L.) Ach. (Parmeliaceae)		
Peru balsam	Fabaceae	<i>Myroxylon balsamum</i> (L.) Harms	7.9 * 7.2 (+ 7.2)
Fragrance mix II			5.2 * 5.7 (+ 4.6)
▪ Citronellol	e.g., <i>Rosa</i> L. (Rosaceae)		
▪ Citral	<i>Solanum lycopersicum</i> L. (Solanaceae) + <i>Cymbopogon citratus</i> (DC.) Stapf (Poaceae)		
▪ Coumarin			
▪ (Hydroxyisohexyl 3-cyclohexene carboxaldehyde)	e.g., <i>Dipteryx odorata</i> (Aubl.) Willd. (Fabaceae)		
▪ Farnesol	e.g., <i>Vachellia farnesiana</i> (L.) Wight & Arn. (Fabaceae)		
▪ Alpha-hexyl-cinnamal	e.g., <i>Matricaria chamomilla</i> L. (Asteraceae)		
Cinnamic aldehyde	Lauraceae	<i>Cinnamomum verum</i> J.Presl	3.9 * 4.2
Colophony	Sap of coniferous trees such as pines, junipers, firs, and cedars		2.3 * 1.9
Compositae mix	Asteraceae	<i>Tanacetum vulgare</i> (L.) <i>Arnica montana</i> (L.) <i>Tanacetum parthenium</i> (L.) Sch. Bip. <i>Matricaria chamomilla</i> (L.) <i>Achillea millefolium</i> (L.)	1.9 * 1.7
Cocamidopropyl betaine	Arecaceae	<i>Cocos nucifera</i> (L.)	1.4 * 1.6
Majantole	Asparagaceae	<i>Convallaria majalis</i> L.	1.3
Cocamide DEA	Arecaceae	<i>Cocos nucifera</i> (L.)	0.9 * 0.9
Tea tree oil	Myrtaceae	<i>Melaleuca alternifolia</i> (Maiden & Betche) Cheel	0.9 * 0.9 (# 2.7)
Canaga odorata oil (ylang ylang)	Annonaceae	<i>Cananga odorata</i> (Lam.) Hook.f. & Thomson	0.7 * 1.2 (+ 2.4) (# 2.6)

continued

► **Table 1** *Continued*

Patch test compound (= not plant derived)	Plant family	Plant species	Prevalence (%) according to NACDG 2011–12 [13] or (*) 2013–2014 [14] or (+) IVDK [11] or (#) de Groot [15]
Sesquiterpene lactone mix			0.7
▪ Alantolactone	Asteraceae	e.g., <i>Inula helenium</i> L.	*0.9
▪ Dehydrocostuslactone		e.g., <i>Saussurea costus</i> (Falc.) Lipsch.	
▪ Costunolide		e.g., <i>Saussurea costus</i> (Falc.) Lipsch.	
Carvone	Essential oil found e.g., in <i>Carum carvi</i> L. (Apiaceae), <i>Mentha spicata</i> L. (Lamiaceae), <i>Anethum graveolens</i> L. (Apiaceae)		0.6 *0.7
Jasminum officinale oil	Oleaceae	<i>Jasminum grandiflorum</i> L.	0.4 *0.5
Mentha piperita oil	Lamiaceae	<i>Mentha</i> × <i>piperita</i> L.	0.4 *0.6
Lavandula angustifolia oil	Lamiaceae	<i>Lavandula angustifolia</i> Mill.	0.4 *0.3
D-Limonene (precursor to carvone)	Rutaceae	Citrus trees	0.2

Recent Advances in Understanding the Immunological Mechanisms Underlying Plant Contact Dermatitis

The pathomechanisms involved in the development of ACD in general have recently been reviewed in more detail [25,26]. In brief, contact sensitizers are of low molecular weight (so-called haptens) and therefore need to bind to proteins to become immunogenic. Due to their low molecular weight (MW), they usually easily penetrate the epidermis, where they activate keratinocytes and innate immune cells to generate a pro-inflammatory cytokine milieu. After uptake of the sensitizer by immature dendritic cells (DCs), the DCs start to mature and migrate to the local lymph node, where the antigen is presented in the context of MHC-1 and co-stimulatory molecules to naive T cells. The T cells start to mature, proliferate, and migrate back into the skin. A second contact with the same sensitizer leads to the activation of the primed CD8+ T cells and the killing of cells that present the sensitizer in the context of MHC-1 such as keratinocytes. The clinical symptoms are erythema and eczema formation.

Regarding the mechanism underlying the inflammatory response to lattices of plants from the Euphorbiaceae family, a recent study showed that the serine protease mauritanicin and phorbol-12-myristate-13-acetate (PMA) modulate the release of the pro-inflammatory cytokine IL-8 in fibroblasts and the human keratinocyte cell line HaCaT in a protease activated receptor-dependent manner after *in vitro* stimulation for 60 min [27]. This study is in line with a previous work by Domsalla and Melzig, who showed that a combination of proteases and PMA promotes inflammatory responses in the human monocyte-like cell line U937

[28]. This indicates that plant compounds can even enhance the pro-inflammatory cytokine milieu necessary for the initial maturation of DCs and thereby promote the sensitization process.

Interestingly, the bioactive plant compound magnoflorine, isolated from *Tinospora crispa* L., Menispermaceae, was recently reported to enhance lipopolysaccharide (LPS) mediated pro-inflammatory responses in U937-macrophages via a MyD88-dependent pathway [29]. Treatment of U937 cells with magnoflorine alone had no effect on cytokine production (tumor necrosis factor alpha, interleukin 1 beta, prostaglandin E2). However, synergistically upregulated toll-like receptor 4 (TLR4), and MyD88 expression levels, mitogen-activated protein kinase/phosphoinositide 3-kinase (MAPK/PI3K) induced upregulation of NF-κB signaling and enhanced cytokine production was observed when LPS was added to magnoflorine treatment [29]. In addition, *T. crispa* extract was shown to enhance neutrophil migration and activation as well as T cell proliferation and pro-inflammatory cytokine production [30]. This indicates that while *T. crispa* extract is used orally for the treatment of diabetes type II [31], magnoflorine might also enhance the sensitization process in contact dermatitis if mixed with sensitizing plant compounds and applied topically, since both neutrophils [32] and macrophages [33] as well as the TLR4 pathway [34,35] are known to be crucially involved in the initial generation of a pro-inflammatory cytokine microenvironment resulting in enhanced sensitization and ACD.

Case Reports for Plant Contact Dermatitis

Recently, one of the few worksite-based studies addressing contact dermatitis to tulips was published [36], showing that of the 164 workers tested, 29.3% (i.e., 48 workers), were clinically suspected to have contact dermatitis with hand eczema being the most common clinical pattern identified. Interestingly, 17 of these workers showed positive reactions to patch tests with tulip plant (bulb) extracts or alpha-methylene-gamma-butyrolactone, with 12 reacting to both, 3 to alpha-methylene-gamma-butyrolactone only, and 2 to tulip bulb extract only. Importantly, healthy controls were negative for the patch test, ruling out irritancy of the patch test substances. This indicates that tulipalin A (alpha-methylene-gamma-butyrolactone) is the main antigen responsible for the dermatitis. In addition, the 2 workers reacting only to the tulip bulb extract show that further studies are still necessary to determine the exact chemical composition of tulip plants and their sensitizing agents [36].

One example of ABCD reaction to tulips was reported in an early publication by Hausen et al. [37]. A seedsman showing a sensitization against tulip bulbs presented with an initial reaction restricted to the fingers but then developed dermatitis spread over the whole body despite strict avoidance of direct contact with tulips. Despite clearance of the dermatitis, he suffered from a recurrence of ABCD after being in a room for 1 h with a vase of tulip flowers in a side room, indicating that he developed an ACBD to tulips [37].

Another—so far rare (only 2 cases reported)—case of ACD was attributed to jagua dye used for temporary tattoos [38,39]. Up to now, mostly beneficial effects of extracts from the Amazonian *Genipa americana* L., Rubiaceae, fruit and especially of its bioactive compound genipin (e.g., as an alternative to synthetic food dye) [40] or in traditional medicine to treat small wounds, skin disorders, anemia, and to induce abortions but also as insect repellent, have been reported in South America and China [39]. In 2 cases, the nontoxic fruit extract, which is long used in the indigenous population for body tattoos (both permanent and temporary) without known cases of adverse reactions, was reported to induce ACD after repeated application of jagua tattoo dye preparations on the skin. This indicates that although jagua dye is claimed to be a “safe and natural” replacement for henna dyes, the incidence of patients suffering from ACD to nonpermanent tattoos might increase with the rising use of these dyes. Interestingly, henna dyes, which are also known to result in ACD when used for nonpermanent tattoos, are usually problematic due to the addition of the sensitizer para-phenylene diamine, which is used to enhance the black coloring of henna [41], while pure henna itself seems to be non-sensitizing with rare cases showing sensitization to lawsone (2-hydroxy-1,3-naphthoquinone) [42].

In a 12-y-old girl, the first nonoccupational-induced contact dermatitis to *Verbascum thapsus* L., Scrophulariaceae, was recently described by Echaiz et al. [43]. Though the authors could not exclude that the dermatitis was attributable to the irritant properties of *V. thapsus*, they also reported a simultaneous ACD reaction to members of the Asteraceae family and a positive patch test to the compositae mix [43].



► **Fig. 1** An example of occupational contact dermatitis to plants in a 56-year old gardener.

An article reviewing the common causes of ABCD in the USA with the Asteraceae and Anacardiaceae family being the major plant related causes was recently published by Schloemer et al. [44]. The exposure to toxic, phototoxic, and allergic SLs in Asteraceae is known to result in allergic dermatitis (also known as compositae dermatitis), while constant exposure in horticulture leads to occupational dermatitis (see ► **Fig. 1** for an example of occupational contact dermatitis to plants in a 56-y-old gardener). For *Jacobaea vulgaris* Gaertn., syn. *Senecio jacobaea* L., a prominent member of the family of Asteraceae and known by many names like common ragwort, ragweed, St. James wort, Stinking Willy, cushag, or tansy ragwort, a case of contact dermatitis was reported by Pietkiewicz et al. [45]. In addition, as reported by Paulsen and Andersen, 4% (i.e., 529 of 13,139 patients tested) were sensitized to Asteraceae, and 95 (18% of these) were monosensitized [46]. Interestingly, when comparing the periods from 2002–2008 and 2009–2015, the prevalence of Asteraceae sensitization in the latter was significantly lower [46].

Conclusion

While the beneficial effects of plant compounds for the treatment of skin disorders are manifold as shown in the other articles of this issue, they can also result in different types of contact dermatitis. This is especially relevant as most people associate the terms “healthy and safe to use” with plant compounds due to their natural origin, leading to an increased utilization be it for homemade remedies or as cosmetics. Thus, plants should be taken into consideration especially when testing for contact sensitizers if a history of plant exposure exists. In addition, since several plant compounds show no positive patch test results when using the standard patch test series or commercial plant extracts, it is important to also test extracts/whole parts of the suspected causative plants directly provided by the respective patient whenever possible.

Conflict of Interest

The authors declare no conflicts of interest.

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