

Contact dermatitis as an adverse reaction to some topically used European herbal medicinal products – part 4: *Solidago virgaurea*–*Vitis vinifera**

Paola L. Minciullo^{1,2}, Gioacchino Calapai¹, Marco Miroddi¹, Carmen Mannucci¹, Ioanna Chinou³, Sebastiano Gangemi^{1,2,4} and Richard J. Schmidt⁵

¹Department of Clinical and Experimental Medicine, University of Messina, Via Consolare Valeria, 98125 Messina, Italy, ²Operative Unit of Allergy and Clinical Immunology, Azienda Ospedaliera Universitaria Policlinico 'G. Martino', Via Consolare Valeria, 98125 Messina, Italy, ³Division of Pharmacognosy & Chemistry of Natural Products, Department of Pharmacy, University of Athens, 157 71 Zografou, Athens, Greece, ⁴Institute of Clinical Physiology, IFC CNR, Messina Unit, Via Consolare Valeria, 98125 Messina, Italy, and ⁵BoDD – Botanical Dermatology Database, Penarth, UK

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Summary

This review focuses on contact dermatitis as an adverse effect of a selection of topically used herbal medicinal products for which the European Medicines Agency has completed an evaluation up to the end of November 2013 and for which a Community herbal monograph – now (since 2014)† called a 'European Union herbal monograph' – has been produced. The present part 4 addresses species from *Solidago virgaurea* L. to *Vitis vinifera* L.

Key words: contact allergy; contact dermatitis; herbal medicine; phytodermatitis; *Solidago virgaurea*; *Syzygium aromaticum*; *Tanacetum parthenium*; *Taraxacum officinale*; *Thymus vulgaris*; *Trigonella foenum-graecum*; *Viola* spp.; *Vitis vinifera*.

Solidago virgaurea L.; family Compositae (or Asteraceae)

Now known by the common names Aaron's rod and European goldenrod, this medicinal plant was known in medieval times to Arnaud de Villeneuve as la verge d'or or *virga aurea* ('*Virga aurea Arnoldi Villanovani*') (1, 2), which may explain why the incorrect botanical name '*Solidago virga-aurea* Linn.' is often seen. Numerous subspecies and varieties of *Solidago virgaurea*, which were

previously regarded as distinct species of *Solidago*, are now recognized.

The dried flowering aerial parts, which constitute the subject of a European Pharmacopoeia monograph, are the source of the crude drug *Solidaginis Virgaureae Herba* (3). Although the ethnobotanical literature records the external use of *Solidago virgaurea* preparations in the treatment of wounds (see, for example, 4), no dermatological uses are recognized in the EU herbal monograph, which recognizes only the traditional use of herbal preparations and extracts of the crude drug taken orally to increase the amount of urine as an adjuvant in the treatment of minor urinary complaints (3). *Solidago Virgaurea* Extract (CAS no. 85117-06-2) is also a recognized cosmetic products ingredient to which 'skin-conditioning' properties are ascribed (5).

Solidago virgaurea yields a volatile oil, the main constituents of which are α -pinene, myrcene, β -pinene, limonene, sabinene, and germacrene-D (2, 6). Notwithstanding the classification of the genus *Solidago* in the Compositae, the plant appears not to produce sesquiterpene lactones. However, various flavonoids (quercetin,

Correspondence: Paola Lucia Minciullo, Dipartimento di Medicina Clinica e Sperimentale - UOC di Allergologia e Immunologia Clinica Policlinico Universitario Via Consolare Valeria 98125 Messina. Tel: +39 090 2212049; Fax: +39 090 2217231. E-mail: pminciullo@unime.it

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†http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2015/02/WC500181862.pdf (last accessed 10 May 2017).

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kaempferol and isorhamnetin and their glycosides, including astragalin and rutoside) have been reported to be produced by the plant, together with triterpene saponins of the oleanane type, the bisdesmosidic phenol glycosides leiocarposide and virgaureoside-A, diterpenoid lactones of the *cis*-clerodane type, and various phenolic acids (caffeic acid, chlorogenic acid, ferulic acid, synapic acid, and vanillic acid) (2).

Because the plant or extracts prepared from it are not commonly encountered as articles of commerce, wild-growing or cultivated plants, and in particular their pollen, are the most likely sources of adverse reactions. Although goldenrod is not considered to be an important source of airborne allergens, exposure can trigger respiratory symptoms and contact-allergic/urticarial symptoms, especially in occupationally exposed subjects. Thus, in 1919, Sutton (7) wrote: 'About seven years ago, I had an opportunity to study a case of goldenrod dermatitis, with an associated asthmatic disorder, due to the same agent. The patient was a little girl, and direct exposure to even small amounts of goldenrod pollen invariably and promptly produced a severe dermatitis, which quickly became generalized, and an asthma of varying degree, which persisted for 24 h or more and then gradually subsided. Examples of dermatitis from this source are rare, however, probably owing to the fact that the flower is insect pollinated, and direct inhalation or direct contact must necessarily precede absorption.' Schwartz et al. (8) later observed that '*Solidago virga aurea* ... has produced a maculo-papular dermatitis accompanied by itching and burning among field workers following three to twelve hours' work at haymaking', adding that 'The irritant is said to be carried by the pollen.'

IgE-mediated occupational allergy to the pollen of flowers, including *Solidago virgaurea*, has been shown in a series of 14 consecutive patients who presented with complaints associated with the handling of flowers. Extensive cross-sensitization was seen to pollen of several members of the Compositae family and to the pollen of *Alstroemeria* and *Narcissus*. Most of the patients had to find alternative employment (9). A 42-year-old female florist presented with a history of itching, burning and redness of the skin after contact with freshly picked dandelions (*Taraxacum officinale* F. H. Wigg.). Several weeks later, whealing not confined to the site of contact alone, conjunctival itching and sneezing were induced by pollen from *Solidago virgaurea* and from a number of other species of Compositae. Symptoms slowly progressed to bronchial asthma, but eczematous lesions never developed at the site of contact. The patient had to give up working in the flower shop (10). In a study of florists and healthcare workers with immediate hypersensitivity reactions to both latex

(from *Hevea brasiliensis* Müll. Arg., family Euphorbiaceae) and goldenrod, the possibility of cross-reactivity between *Hevea* latex and goldenrod antigens was explored. A number of latex-allergic individuals with evidence of goldenrod sensitization were identified (11).

Underwood & Gaul (12) observed three reactions to goldenrod (an unspecified species of *Solidago*) in a group of 29 patients with "dermatitis venenata" resembling "neurodermatitis". Patch tests gave characteristic flaring reactions, indicating a high degree of sensitization. Seven patients in Denmark believed to be suffering from photodermatitis were subsequently shown to be suffering from airborne Compositae oleoresin-induced contact dermatitis. One of the patients reacted when patch tested with a goldenrod extract in pet. (13). In Scotland, 8 of 55 patients with photosensitivity dermatitis and actinic reticuloid syndrome reacted when patch tested with an extract of *Solidago virgaurea*. Multiple positive reactions to extracts from a number of other Compositae plants were noted in the majority (14). One patient in a series of 14 elderly male patients with persistent light reactivity patch tested with plant extracts and fragrances reacted to an extract of *Solidago virgaurea*. The reaction was deemed to be a toxic rather than an allergic reaction (15). In a series of 6 patients investigated in Portugal for suspected airborne contact dermatitis, multiple reactions to lichens, liverworts and Compositae oleoresins were observed. However, none of the 6 reacted to goldenrod (16). A 46-year-old farmer in Spain presented with dermatitis of 3 years' duration. Patch testing showed multiple sensitization to lichens, liverworts, various sesquiterpene lactone-containing plants, etc., but no reaction to *Solidago virgaurea* (17). By contrast, in an earlier study reported by the same investigator (18), 1 patient, a 48-year-old male farmer, from a series of 12 with multiple sensitization to sesquiterpene lactone-containing Compositae and Magnoliaceae species, reacted strongly when patch tested with *Solidago virgaurea*. In another study carried out in Austria, a 69-year-old retired teacher, who had been a hobby gardener for ~30 years, developed facial eczema. On patch testing, he reacted strongly to *Solidago virgaurea* and to *Arnica montana*, and less strongly to some other members of the Compositae, including a *Tagetes* cultivar (19). Moreover, a 49-year-old female farmer in Finland, with a 21-year history of hand and face dermatitis, reacted strongly when patch tested with lichens, *Solidago virgaurea* 1% pet., and *Arnica montana* 0.5% pet. (20).

In a series of 81 patients in Denmark with suspected plant-induced dermatitis, none of 18 patients tested with a goldenrod extract in pet. reacted (21). In a series of 74 patients suspected of having allergic contact dermatitis caused by wild vegetation in the United States, 8% reacted

to an ether extract of goldenrod (22), Mitchell (23) cautioned – but provided no evidence for the claim – that a complicating feature of *Solidago virgaurea* is that the flower heads tend to accumulate extraneous pollen from other plants. Accordingly, it is possible that the higher incidence of apparent sensitization to *Solidago* species in the United States might be explained by Mitchell's observation.

Allergic dermatitis after systemic exposure to goldenrod has also been reported. A 52-year-old man presented with generalized very itchy maculopapular eczema, which disappeared following topical treatment with corticosteroids for 10 days. The skin lesions had begun 6 days after the intake of oral medication containing a goldenrod fluid extract for epididymitis. Patch testing showed positive reactions to the goldenrod medicament (24). Lundh et al. (25) observed positive patch test reactions to a number of commercially available herbal teas produced from Compositae species, including goldenrod (*Solidago virgaurea*) tea. The persons tested had all previously been shown to be sensitive to sesquiterpene lactone mix.

A 'short ether extract' of the whole plant was found to have a medium capacity to sensitize guinea-pigs (26). However, the contact allergens remain to be identified.

***Syzygium aromaticum* Merr. & L.M.Perry (syns *Eugenia aromatica* Baill., *Eugenia caryophyllata* Thunb., *Eugenia caryophyllus* Bullock & S.G.Harrison); family Myrtaceae**

Commonly known as the clove tree, this a native of the Maluku Islands ('the Moluccas') in East Indonesia, but is grown commercially in tropical regions around the world, including Madagascar, East Africa, Asia, and South America. Cloves, which are the sun-dried flower buds from the clove tree, are valued as a culinary spice and have been an article of commerce for centuries (27). They also provide the crude drug historically known as Caryophyllus (28) but now described more precisely as Flos Caryophylli, from which a volatile oil, clove oil (Oleum Caryophylli, or more precisely Caryophylli Floris Aetheroleum), may be distilled (29). Because of the pleasantly aromatic volatile oil contained not only in the flower buds but also in the leaves and stems, a variety of clove tree-derived extracts are also used in cosmetic products (see below).

The sun-dried flower buds are most commonly encountered as a culinary spice, whereas the distilled volatile oil is mostly used medicinally, especially in dentistry. Recorded traditional uses of the oil include the local treatment of toothache and minor infections of the mouth and skin, minor wounds, sore throats and coughs associated with the common cold, myalgia, rheumatic complaints, and

insect bites, and oral administration in the treatment of flatulent colic or nausea (29–31). A recent ethnopharmacological study in India (32) noted the use of clove preparations for treating dandruff, pruritus, scabies, eczema, and bed sores.

Eugenia Caryophyllus Bud Oil (or Clove Bud Oil), *Eugenia Caryophyllus* Stem Oil (or Clove Stem Oil), *Eugenia Caryophyllus* Leaf Oil (or Clove Leaf Oil) and a number of other distillates, waters and extracts referring to *Eugenia caryophyllus* rather than to *Syzygium aromaticum* are INCI names applied to cosmetic product raw materials. The CAS nos. 8000-34-8, 8015-97-2 and 8015-98-3 have been assigned to volatile oils distilled from clove flowers, leaves, and stems, respectively. However, CAS no. 84961-50-2, which refers to various extracts prepared from parts of the clove tree, may also be applied to these distilled oils. In addition to the use of the oils as fragrance materials, clove-derived oils, waters and extracts used in cosmetic products are variously described as having antioxidant, antimicrobial, antiplaque, astringent, humectant, 'masking', 'skin-conditioning' and 'tonic' properties (5, 33).

Clove oil (but not the herbal substance cloves) is the subject of an EU herbal monograph (34). It is recognized as a traditional herbal medicinal product for the symptomatic treatment of minor inflammations in the mouth or the throat. For this indication, mouthwashes containing 1–5% clove oil may be used several times a day for no more than 1 week. It is also recognized as a traditional herbal medicinal product for the temporary relief of toothache resulting from a dental cavity. For this indication, clove oil may be used undiluted, or in solutions containing a minimum of 50% of the oil, or in gels containing 20% of the oil, for no more than 1 week. No dermatological uses are recognized, but the EU herbal monograph does acknowledge that contact hypersensitivity to clove oil may occur with possible cross-reaction to balsam of Peru (from *Myroxylon balsamum* var. *pereirae* Harms, syn. *Myroxylon pereirae* Klotzsch, family Leguminosae).

In addition to its uses as described in the EU herbal monograph (34), clove oil originally, but now eugenol – its principal component – alone, is widely used in dentistry mixed with zinc oxide and certain other substances, for example colophony, as a temporary filling material (35–38).

Clove oil (from the flower buds) comprises mainly eugenol (72–88%), acetyl eugenol (4–21%), and β -caryophyllene (3–14%). Some minor constituents have also been reported, including chavicol, (Z)-isoeugenol, (E)-isoeugenol, benzyl acetate, α -pinene, β -pinene, limonene, α -ylangene, γ -caryophyllene, α -caryophyllene (=humulene), and caryophyllene epoxide, but these

together constitute only ~1% of the oil (29, 39, 40). Clove leaf oil has been reported to contain eugenol (75–84%), β -caryophyllene (12–20%) and α -humulene (1–2%) as the main components, with a small amount of acetyl eugenol (0–1.5%) (40–42). Clove stem oil comprises mainly eugenol (88–97%) and β -caryophyllene (2–10%), with a small amount of acetyl eugenol (0.1–2.5%) (40, 43). Eugenol is also present as a major constituent of other volatile oils used as fragrance raw materials in perfumery and cosmetic product manufacture, including carnation oil/carnation absolute (*Dianthus caryophyllus* L., family Caryophyllaceae) (44), African basil oil (*Ocimum gratissimum* L., family Labiatae) (45, 46), holy basil oil (*Ocimum tenuiflorum* L., syn. *Ocimum sanctum* L., family Labiatae) (47), pimento oil (*Pimenta dioica* Merr., syn. *Pimenta officinalis* Lindl., family Myrtaceae) (48), West Indian bay oil or myrcia oil (*Pimenta racemosa* J.W.Moore, syns *Pimenta acris* Kostel. and *Myrcia acris* DC.) (49), and cinnamon leaf oil (*Cinnamomum zeylanicum* Blume, family Lauraceae) (50); and as a minor constituent of others, including jasmine absolute (*Jasminum grandiflorum* L., syn. *Jasminum officinale* L. var. *grandiflorum* Stokes, family Oleaceae) (51–54), oils of Brazilian sassafras (*Ocotea odorifera* Rohwer, syn. *Ocotea pretiosa* Mez, family Lauraceae) and American sassafras (*Sassafras albidum* Nees, family Lauraceae) (55), citronella oil (*Cymbopogon nardus* Rendle, family Graminae) (56), and ylang-ylang oil (*Cananga odorata* Hook.f. & Thomson, family Annonaceae) (53, 57).

Cloves also constitute a source of phenolic compounds, including a variety of flavonoids (quercetin, kaempferol, kaempferol and rhamnetin and their glycosides), ellagitannins (eugenin), and phenolic acids (gallic acid, ellagic acid, 3-caffeoylquinic acid, 4-caffeoylquinic acid, 3-*p*-coumaroylquinic acid, 3-feruloylquinic acid, ferulic acid, *p*-hydroxybenzoic acid, caffeic acid, salicylic acid, syringic acid, vanillic acid, gentisic acid, protocatechuic acid, and *p*-coumaric acid) (29). Depending on the solvent used, these may be present in clove extracts prepared for use in cosmetic products, but would not be present in any significant amounts in distilled clove oils.

Clove oil used in the mouth, either as the diluted or undiluted oil applied to cavities in teeth to relieve toothache, or as an ingredient of a mouthwash or other form of oral medication, has been reported to cause adverse reactions in and around the mouth. Patch testing can be used to identify relevant allergens (58–63). Permanent local anaesthesia and anhidrosis developed in a patient who spilled clove oil on the face while trying to treat a carious tooth (64). Eugenol is a local anaesthetic, and high concentrations of eugenol are reportedly neurotoxic (65). This neurotoxicity could

account for the reported permanent local anaesthesia. However, β -caryophyllene present in clove oil also contributes local anaesthetic activity (66). A 53-year-old woman with dental problems complained of a burning sensation in the mouth and on the tongue, which became inflamed. She had been using Vectorident™, a mouthwash containing eucalyptus, clove, anise, and mint oils, for 3 months (67). Patch testing showed that she had become sensitized to eugenol. A 66-year-old male patient suffering from painful erosions on the lips and buccal mucosa became sensitized to eugenol present in an ointment mixture (Solcoseryl® + Xylocaine® + eugenol) prescribed for the treatment of the symptoms of oral lichen planus, the condition being exacerbated as a result (68). In another patient, a 53-year-old female who had been fitted with a new dental bridge, eugenol leaching from a zinc oxide–eugenol-based temporary cement was reported to produce oral lichen planus (69). The sensitizing capacity of two eugenol-containing root canal sealers (Endomethasone™ and Proco-Sol™) has been shown in a guinea-pig maximization test (70).

Adverse effects of eugenol in the oral cavity are often reported in association with its use in eugenol-containing, including zinc oxide–eugenol-based, surgical and periodontal packing and sealing materials/impression pastes (38, 70–76). The majority of patients who experienced stomatitis following the placement of a dental dressing containing eugenol were found to be sensitized to eugenol and/or colophony on patch testing (73). In further studies (77), the risk of inducing sensitization to eugenol secondary to the placement of a dental dressing containing eugenol was assessed. Of 133 patients who had shown negative patch test results with eugenol prior to periodontal surgery, 12 reacted positively postoperatively. The results indicated a sensitization rate of almost 10%. Most reactions to zinc oxide–eugenol are type IV delayed contact hypersensitivity reactions. However, a type I hypersensitivity reaction producing erythema on the face, neck, torso, upper limbs, and lower limbs, and itchiness and redness extending behind the ear, together with extensive wheals of various sizes, was reported in an 8-year-old boy in India (78). Chronic urticaria associated with oral exposure to eugenol (79–81) has also been reported.

In a study in the United Kingdom over the period 1984–1998, healthcare workers (including doctors, dentists, veterinarians, and nurses), together with metalworkers, were found to have significantly higher prevalences of allergy to eugenol than workers in other occupations (82). These occupational reactions typically present as allergic contact dermatitis of the fingers and palms (75, 83–86). A physiotherapist who used a massage cream

containing cinnamon and clove oils developed eczema of the hands as a result of becoming occupationally sensitized to eugenol (87).

Clove as spice can elicit occupational contact dermatitis, usually localized to the hands or fingers, in food-handlers, chefs, and kitchen, coffee room and restaurant workers (88–90). Of ~1000 patients investigated for occupational skin disease from 1991 to 1995 in a study in Finland, 5 had occupational allergic contact dermatitis (of the hands of fingers) caused by spices. Of these, only 1 reacted when patch tested with powdered cloves (89). However, in a study of hand eczema in 45 bakers, none was found to react when patch tested with eugenol 2% pet. although one reaction to isoeugenol 2% pet. was observed (91).

Oral exposure to clove oil or eugenol in food is potentially capable of inducing contact or systemic sensitivity. In an investigation of allergy to spices in 78 *Myroxylon pereirae* (balsam of Peru)-allergic patients in Finland, 36 reacted when patch tested with powdered cloves; none of 156 control patients not allergic to balsam of Peru reacted (92). A similarly designed study on contact allergy to spices carried out in The Netherlands identified only 4 patients in a selected group of 32 tested who reacted (1+) when patch tested with powdered cloves (93).

Eugenol and isoeugenol have long been recognized as sensitizers in fragrances/perfumes, and are therefore included in fragrance mix I used for patch testing in dermatology clinics. In the context of suspected contact dermatitis caused by cosmetics, eugenol rather than cloves or clove oil is generally used for patch testing. Interestingly, fragrance mix containing eugenol does not detect all cases of hypersensitivity to eugenol (94). The prevalence of sensitivity to eugenol in the general population is ~0.2% across five European countries: only 6 individuals of 3119 tested (0.2%) reacted when patch tested with eugenol 2% pet. (95). This is perhaps consistent with the conclusion of a survey reported in 1983 that, at the concentrations present in consumer products, eugenol alone or as part of clove leaf oil has a very low potential either to elicit pre-existing sensitization or to induce hypersensitivity (96). However, the prevalence of positive patch test reactions to eugenol in patients with suspected cosmetics intolerance patch tested with fragrance mix I is 1–2% (97–99). In a retrospective analysis involving 15 682 patients patch tested between 2000 and 2008 with at least one essential oil, 637 reacted positively to at least one of the essential oils, most commonly to ylang-ylang oil (3.1%), lemongrass oil (1.8%), jasmine absolute (1.6%), sandalwood oil (1.5%), and clove oil (1.5%) (53).

***Tanacetum parthenium* Sch.Bip. (syns *Chrysanthemum parthenium* Bernh., *Matricaria parthenium* L., *Pyrethrum parthenium* Sm.); family Compositae (or Asteraceae)**

The whole or fragmented aerial parts of the plant, which is commonly known as feverfew, provide the crude drug *Tanacetum Parthenii* Herba. The plant should not be confused with *Parthenium hysterophorus* L., which is also known as feverfew (100).

Traditionally, *Tanacetum parthenium* has been used as a remedy for fever, psoriasis, inflammation, toothache, rheumatism, asthma, insect bites, and stomach-ache, but, in recent years, it has become best known as a folk remedy for migraine prophylaxis (101–103). The EU herbal monograph only recognizes the oral use of the powdered herbal substance for the prophylaxis of migraine headaches after serious conditions have been excluded by a medical doctor (104). The sesquiterpene lactone parthenolide is considered to be the main active constituent (103). No dermatological uses are recognized. Inflammation of the oral mucosa and tongue, accompanied by swelling of the lips and occasionally loss of taste, has been experienced by migraine sufferers who chewed feverfew leaves. In a survey of ~300 feverfew users carried out in 1983, aphthous ulcers after chewing fresh leaves was reported by 11% of users, prompting discontinuance of treatment by some (101). Mouth ulceration is a systemic reaction to feverfew herb, and requires discontinuation of use of the product. Inflammation of the mouth and tongue with swelling of the lips appears to be a local reaction that may be overcome by using encapsulated herb products (105).

Parthenolide is present in the oleoresin fraction of the leaf, the stem, and the flower, and also in the pollen. In addition to parthenolide, which is the principal sesquiterpene lactone present in feverfew, a number of other sesquiterpene lactones are present, including several bearing peroxide and epoxide functional groups. These include 3 β -hydroxyparthenolide, costunolide, 3 β -hydroxycostunolide, artemorin, 3 β -hydroxyanhydroverlolorin, epoxyartemorin, and anhydroverlolorin-4 α ,5 β -epoxide. Costic acid methyl ester and reynosin have also been found in small quantities (103, 106). However, geographical variability has been reported: whereas parthenolide is the predominant sesquiterpene lactone found in British-grown and German-grown feverfew, no parthenolide was found in Mexican-grown or in Yugoslavian-grown feverfew. The Mexican-grown and Yugoslavian-grown feverfew contained mainly santamarin and reynosin (107, 108).

Feverfew also yields a volatile oil containing monoterpenes and sesquiterpenes, predominantly camphor and *trans*-chrysanthenyl acetate. Other reported constituents of the oil include β -farnesene, β -caryophyllene, germacrene-D, linalool, linalyl acetate, camphene, δ -cadinene, *p*-cymene, eugenol, and bornyl acetate (103, 106).

In the 1930s, *Chrysanthemum parthenium* was included in a list of "irritating plants" in the United States (109, 110). The plant has long been recognized as an important sensitizer in European Compositae-allergic patients (21, 111), this plant being the main cause in Europe of 'weed dermatitis', a condition that may be considered analogous to North American 'ragweed dermatitis', Australian 'bush dermatitis' and Indian 'parthenium dermatitis' in having an airborne aetiology (100). An early report of airborne sensitization to a plant identified as *Pyrethrum parthenium* in New South Wales, Australia was provided by Maiden in 1909, who referred to a gardener who could not tolerate being in the proximity of this plant because it caused 'eczematic swelling' on his face (112). Also in Australia, Burry described a case of a 75-year-old woman who had been diagnosed as having photodermatitis for 4 years prior to seeing a dermatologist. She was found to be hypersensitive to a plant growing in her garden, which was identified as *Chrysanthemum parthenium* (113). A similar case has been reported of a 63-year-old man in Germany with dermatitis of the hands, forearms, and face, mainly around the eyes. It transpired that he had become sensitized to *Tanacetum parthenium* growing as a weed in his and his neighbour's garden. Cross-reactions were observed to tansy (*Tanacetum vulgare* L.), yarrow (*Achillea millefolium* L.), marguerite (*Leucanthemum vulgare* Lam., syn. *Chrysanthemum leucanthemum* L.), aster (*Aster* sp.), sunflower (*Helianthus annuus* L.), laurel (*Laurus nobilis* L., family Lauraceae), and liverwort (*Frullania dilatata* Dumort., family Frullaniaceae) (111). After breeding and selling a new ornamental form of feverfew (*Tanacetum parthenium*), sold to the flower markets under the misleading name 'chamomile', a 40-year-old female florist developed, after half a year of handling, recurrent dermatitis of the face, neck, hands, and forearms (107). Further similar cases, including occupational cases of feverfew dermatitis presenting with a photodermatitis-like distribution of eczema on the face and V of the neck, with involvement of the upper eyelids, retroauricular regions, and the area under the chin, have been reported from Germany and Denmark. Again, patch tests showed not only strong reactions to feverfew and parthenolide, but also a number of cross-reactions to related species (114–116). On the other hand, of 16 floral shop workers tested in the United

States, none was found to react to a *Tanacetum parthenium* extract 1% in pet. (117).

Experimental studies using high-volume air sampler and dynamic headspace techniques around feverfew plants failed to detect either particle-bound or volatile parthenolide (118). The volatiles emitted from feverfew plants were mainly monoterpenes, but, as only a minority of feverfew-allergic patients reacted positively to these, their contribution to airborne Compositae dermatitis seemed to be of small significance (119). Further studies showed that 8 of 12 feverfew-allergic patients were so sensitive to parthenolide that even the minute quantity trapped in the filter of a high-volume air sampler operating in the vicinity of feverfew plants was sufficient to elicit a positive patch test reaction, with no reaction being seen in 10 control subjects. None of the feverfew-allergic patients reacted to monoterpenes or sesquiterpenes captured with a dynamic headspace extraction technique, and nor did these patients react to oxidized monoterpenes (120).

Chrysanthemum Parthenium Extract (CAS no. 89997-65-9) is a recognized cosmetic product ingredient purported to have a 'skin-conditioning' function (5). Two cases of contact dermatitis caused by cosmetic products containing a feverfew extract have been reported. A 45-year-old woman developed an eruption involving her scalp and face, including her eyelids and behind her ears, which was provisionally identified as seborrhoeic eczema with a seasonal airborne Compositae dermatitis component, which flared after she used a 'calming moisturizer' containing a feverfew extract for 2 weeks. A second patient, a 25-year-old woman, presented with a complaint of a 1-month history of an eruption around the eyes that started after she began using an 'eye cream' containing a feverfew extract. Both patients were patch tested with cosmetic and plant series and their own skin care products. The first patient had positive reactions to sesquiterpene lactone mix, to Compositae mix, to parthenolide, to *Tanacetum vulgare*, and to the 'calming moisturizer'. The second patient showed positive reactions to sesquiterpene lactone mix, Compositae mix, and the same calming moisturizer (121). It was noted in 2007 that parthenolide had been removed from the then currently available skin care products on the market that contained a feverfew extract (122). The parthenolide-depleted feverfew extracts that had been developed have been shown to have antioxidant and anti-inflammatory activity in *in vitro* models, and have therefore been incorporated into creams for use in the treatment and prevention of irritation caused by shaving (123). Studies involving 1000 subjects showed that these formulations did not

induce contact sensitization or phototoxic or photallergic reactions (124). It was subsequently concluded that parthenolide-depleted extract of feverfew may protect the skin and reduce the damage to oxidatively challenged skin (125). However, patch test reactivity to parthenolide-depleted feverfew extract-containing creams in feverfew/parthenolide-allergic patients has been shown (126), further confirming that feverfew-allergic patients can be so exquisitely sensitive to parthenolide that they may react to cosmetic products containing parthenolide-depleted feverfew extract.

In 1972, Mitchell (127) proposed the preparation of a 'sesquiterpene lactone mix' for patch testing to increase the likelihood of detecting contact allergy to Compositae species. Alantolactone and parthenolide from *Tanacetum parthenium* were initially considered to be the best indicators of Compositae contact allergy (107, 128, 129). In due course, a sesquiterpene lactone mix was formulated to contain equimolar concentrations of alantolactone, costunolide, and dehydrocostus lactone (130), but no parthenolide. It was soon recognized that this sesquiterpene lactone mix was failing to detect cases of sensitivity to members of the Compositae (131–134), and preference shifted to the use of a Compositae mix prepared from simple plant extracts. *Tanacetum parthenium* 1% is a component of a Compositae mix that has been in use since approximately 1980 (135–139). Testing with the individual ingredients of Compositae mix showed the most frequent reactions with *Tanacetum parthenium* extract (140). It should be noted that Compositae mix is both more likely to produce irritant reactions (134) and more likely to actively sensitize than sesquiterpene lactone mix (130, 131, 139), perhaps because of the parthenolide and other sesquiterpene lactones that it contains bearing peroxide and epoxide functional groups.

Patients who react to *Tanacetum parthenium* extract also often react to *Tanacetum vulgare* extract, and to parthenolide if it is included in the test tray. Thus, a patient in Canada with chronic lichenified dermatitis of exposed skin reacted to both *Chrysanthemum parthenium* and to *Tanacetum vulgare*, as well as to unspecified *Chrysanthemum* and *Gaillardia* species (141). Five of 15 forest workers sensitized to sesquiterpene lactones from the liverwort *Frullania nisquallensis* Sull. (family Frullaniaceae) had positive patch test reactions to extracts of various Compositae species. All 5 reacted to extracts of *Chrysanthemum parthenium* and *Tanacetum vulgare* in acetone (128). Also, a further 6 patients, possibly including cases previously reported, reacted to both feverfew (*Tanacetum parthenium*) and tansy (*Tanacetum vulgare*) (127). More recently, a 50-year-old metalworker who had become sensitized to German chamomile tea (*Matricaria chamomilla*) applied

externally on compresses was found, on patch testing, to react to both *Tanacetum parthenium* extract and *Tanacetum vulgare* extract, each 1% pet. (142). Further cases of concomitant positive patch test reactions to *Tanacetum parthenium* and *Tanacetum vulgare* extracts have been reported in a 10-year-old atopic boy (143), in a 41-year-old atopic woman (144), and in a 47-year-old atopic woman (145). In contrast, a 69-year-old male hobby gardener with facial eczema, when patch tested, reacted strongly to *Arnica montana* and to *Solidago virgaurea* extracts, and less strongly to extracts of unspecified cultivars of *Tagetes* and chrysanthemum extract and to *Tanacetum vulgare*, but did not react to *Tanacetum parthenium* (19).

All 3 patients with ragweed (*Ambrosia* spp.) dermatitis reacted, on patch testing, to *Chrysanthemum parthenium* (feverfew) and to an unspecified liverwort (*Frullania* sp., family Frullaniaceae) (146). Similarly, positive patch test reactions to feverfew were observed in nearly all patients with contact dermatitis caused by liverworts of the genus *Frullania* and various sesquiterpene lactone-containing plants of the families Magnoliaceae, Lauraceae, and Compositae. It was concluded from this study that *Tanacetum parthenium* was a better screening allergen for Compositae sensitivity than alantolactone (helenin) (18). Patch testing with a *Tanacetum parthenium* extract was also found to be more likely to detect contact sensitivity to autumn-flowering chrysanthemums (*Chrysanthemum*, formerly *Dendranthema* cultivars) than patch testing with an extract prepared from a randomly selected chrysanthemum, these chrysanthemums being a group of plants in which patch testing shows marked cultivar specificity (147).

***Taraxacum officinale* F. H. Wigg.; family Compositae (or Asteraceae)**

This, the common dandelion, is an almost stemless, lactiferous, perennial herb that is widely distributed in almost every temperate and subtropical region of the world (148). The plants are genetically rather more variable than is suggested by the botanical name, comprising overlapping populations of diploid sexuals and triploid or tetraploid apomicts, suggesting that hybridization occurs between sexual and apomictic individuals (149). This has led to the proposal that the dandelion is more appropriately described botanically as '*Taraxacum officinale* complex' (150). In turn, genetic variability may lead to phytochemical variability and therefore uncertainty in the interpretation of results from phytochemical and clinical studies involving dandelions and extracts prepared from them.

The dandelion is the source of the crude drugs *Taraxaci Folium* ('dandelion leaf') and *Taraxaci Radix cum Herba*

(‘dandelion root with herb’). The EU herbal monographs recognize the traditional use of herbal preparations of these two crude drugs ‘to increase the amount of urine [in order to] achieve flushing of the urinary tract as an adjuvant in minor urinary complaints.’ Dandelion root with herb is also recognized as a traditional herbal medicinal product ‘for the relief of symptoms related to mild digestive disorders (such as feeling of abdominal fullness, flatulence, and slow digestion) and temporary loss of appetite’ (151, 152). No dermatological uses are recognized, or mentioned in recent reviews of the literature (153–155).

Whereas skin exposure to herbal preparations of dandelion is likely to be only accidental, exposure to the fresh plant, and in particular to its milky sap, occurs commonly in gardeners and children who come into contact with mowings from dandelion-infested lawns, and in those who pull the plant by hand when weeding or when picking the leaves for a pet rabbit, tortoise, etc. (156, 157). It has been noted that the milky sap has been used in France (folklore; 16th century) to treat warts (158), this use also being mentioned, together with use in the treatment of chronic eczema, in a review of contact sensitization from Compositae-containing herbal remedies and cosmetics (159). Paulsen (159) reported seeing 2 cases of dandelion sensitization in younger males who had treated their warts with the milky plant juice, one of whom had handled dandelions for years because he used them as a pet food. Although exposure to dandelion may occur through the use of cosmetic products – *Taraxacum Officinale* Extract (CAS no. 68990-74-9) is a recognized cosmetic raw material (of unspecified composition but seemingly used for its flavonoid content) that is purported to have ‘soothing/skin-conditioning’ properties (5) – no reports of adverse skin reactions to cosmetic products containing a dandelion extract have been found. However, in the United Kingdom, 4 of 17 patients with dermatitis caused by cosmetic products has positive patch test reactions to a dandelion (2.5% pet.) extract. All had failed to react to sesquiterpene lactone mix (160). In a US study estimating the prevalence of botanical extract allergy in patients with contact dermatitis, a positive patch test reaction to dandelion was observed in 3 of 21 patients who were using botanical extracts but whose contact dermatitis was not fully explained by testing with standard allergens (161).

In addition to a high concentration of potassium, the main chemical constituents of the leaves of the plant are flavonoids, coumarin glycosides (luteolin-7-glucoside, luteolin-7-*O*-rutinoside, isorhamnetin-3-*O*-glucoside, quercetin-7-*O*-glucoside, apigenin-7-*O*-glucoside, two different luteolin-7-diglucosides, cichoriin, and aesculin),

triterpenoids, phytosterols (stigmasterol, campesterol, cycloartenol, 24-methylene-cycloartanol, and β -sitosterol), sesquiterpene lactones (taraxinic acid *D*-glucopyranoside and 11 β ,13-dihydrotaraxinic acid *D*-glucopyranoside), and phenolic acids (*p*-hydroxyphenylacetic acid, and hydroxycinnamic acid derivatives, in particular caffeic acid esters such as chlorogenic, dicaffeoyltartaric and monocaffeoyltartaric acids). The root has been reported to contain the eudesmanolides tetrahydroidentatin-B and taraxacolide-*O*-glucopyranoside, the guaianolides 11 β ,13-dihydrolactucin and ixerin-D, the germacranolides taraxinic acid *D*-glucopyranoside and its 11 β ,13-dihydro derivative and ainslioside, and the phenolics and coumarins dicaffeoyltartaric (chicoric) acid and its isomer, monocaffeoyltartaric, 4-caffeoylquinic, chlorogenic, caffeic, *p*-coumaric, ferulic, *p*-hydroxybenzoic, protocatechuic, vanillic, syringic and *p*-hydroxyphenylacetic acids, umbelliferone, esculetin, scopoletin, benzyl-*O*- β -glucopyranoside, dihydroconiferin, syringin, and dihydrosyringin. It is also rich in inulin (153, 154, 162, 163).

An early report of itching and tingling, erythema, papules and wheals followed by desquamation seemingly caused by the oral use for a medicinal purpose of a dandelion preparation known as Hooper’s Fluid Extract of *Taraxacum* over a period of ~7 days was provided by Smyth (164). Since 2000, 9 further sporadic cases of angioedema, urticaria, skin necrosis, erythematous rash, maculopapular rash, pruritus and alopecia have been reported to the World Health Organization’s Uppsala Monitoring Centre (165).

The dandelion has also been reported to elicit allergic contact dermatitis (156, 157, 166–169). Taraxinic acid 1’-*O*- β -*D*-glucopyranoside, a sesquiterpene lactone, has been identified as the contact sensitizer (170). A patient who was contact-sensitive to a dandelion extract was thought to have contact dermatitis with an airborne aetiology during the summer that persisted into the winter because the patient habitually drank dandelion tea (171). Twenty patients known to be contact-sensitive to sesquiterpene lactones were patch tested with various teas derived from Compositae plants. Twelve reacted to dandelion tea (25). A 56-year-old man presented with black discolouration of his fingertips associated with severe pain and loss of function for 8 weeks. He had been drinking 10–15 cups of dandelion tea daily for 6 months, and had developed renal failure. A diagnosis of secondary hyperoxalaemia resulting from high dietary oxalate with reduced renal clearance was made. The patient died 9 months after diagnosis (172).

However, dandelion has been described as a weak and rare sensitizer (26, 143, 173). Indeed, in a study of

656 consecutive unselected patients patch tested with sesquiterpene lactone mix and Compositae mix, only 1 patient reacted to dandelion extract, but reacted neither to Compositae mix nor to the sesquiterpene lactone mix (134). Whereas 20 of 22 dandelion-sensitive patients in one study reacted to both a Compositae mix and sesquiterpene lactone mix containing dehydrocostus lactone, alantolactone, and costunolide (173), other studies have reported the absence of patch test reactivity to sesquiterpene lactone mix in dandelion-sensitive patients (18, 157, 174, 175). Similarly, patients who react to dandelion extracts on patch testing may also react to various other members of the Compositae and to other sesquiterpene-lactone containing plants and liverworts (18, 167–169, 173, 176). Accordingly, we may infer that these reactions will usually be concomitant sensitization reactions rather than cross-reactions.

Dandelion seems to be an important plant allergen in Europe (173, 174, 177) but not in the United States (22, 178). In Australia, it is one of the weeds implicated in 'bush dermatitis' (179, 180) but, in Portugal, none of 6 patients (4 men and 2 women, none of whom were atopic) with suspected airborne contact dermatitis reacted to *Taraxacum officinale*, while they did react to some other members of the Compositae and to a sesquiterpene lactone-containing liverwort (*Frullania* sp., family Frullaniaceae) (16). Dandelion contact dermatitis is more common in hot weather (157, 175), but is more commonly reported in northern and central Europe than in southern Europe (181). Furthermore, dandelion seems to be an important allergen in atopic subjects, and especially in children with a personal or family history of atopy and hand eczema (143, 144, 176, 182–186).

The dandelion is one of several members of the Compositae to which patients with photosensitivity dermatitis and actinic reticuloid syndrome may react (185). An unusual case has also been reported in a 52-year-old woman who had a 13-year history of recurrent erythema multiforme affecting exposed skin, seemingly following exposure to common chickweed (*Stellaria media* Vill., Caryophyllaceae) early in the spring while she was home gardening. She then started gardening occupationally. Soon, she developed widespread severe haemorrhagic target lesions symmetrically distributed on the face, forearms, hands, wrists, palms, and knees. After complete resolution, she underwent patch testing. Eczematous patch test reactions were obtained with alantolactone and with fresh leaves of common chickweed, dandelion, field-milk thistle (*Sonchus arvensis* L., Compositae), and white clover (*Trifolium repens* L., Leguminosae). Photoaggravation caused by common chickweed and dandelion was seen. By the day 4 reading,

a typical erythema multiforme had commenced, as seen on admission (186).

Several reports have appeared of contact or generalized urticaria/asthma/conjunctivitis in patients with pollen allergy in which sensitivity to dandelion pollen and cross-reactivity to pollens from other members of the Compositae have been shown (10, 187–191).

***Thymus vulgaris* L.; family Labiatae (or Lamiaceae)**

Commonly known as thyme, this is an aromatic perennial sub-shrub, 20–30 cm in height, that is indigenous to southern Europe but is widely cultivated in Europe, the United States, and other parts of the world (192). It is the source of the crude drug *Thymi Herba* and a volatile oil known as *Thymi Aetheroleum* or thyme oil, which is obtained by steam distillation of the fresh flowering aerial parts. Both *Thymi Herba* and *Thymi Aetheroleum* may also be produced from the closely related species *Thymus zygis* L. (193, 194).

In the 1920s, thyme oil, and in particular its principal component, thymol, gained a reputation as a useful treatment for superficial fungal infections of the skin and scalp (195, 196), representing, at that time, a significant advance on standard treatments involving X-rays and thallium acetate. In a more recent study, 4% thymol in chloroform was evaluated as a remedy for paronychia (197). Considerable improvement was seen in 24 of 41 patients, whereas undesirable effects were seen in 4 cases (burning sensation and pruritus in all of these cases; erythema in 2). In the wider literature, reported dermatological uses of thyme or thyme oil (or its principal ingredient thymol) include application for the treatment of abscesses, acne, alopecia, bruises, burns/wounds, dermatitis/eczema, insect bites, paronychia, pruritis, stomatitis, and warts, and as a pediculicide and scabicide (193, 194, 198).

The EU herbal monograph on *Thymi Herba* recognizes the traditional use of a variety of herbal preparations only in the oral treatment of productive cough associated with a cold. No dermatological uses are recognized (199). The traditional use of orally administered *Thymi Aetheroleum* as an expectorant and for the relief of symptoms of coughs and colds is also recognized. For these symptoms, *Thymi Aetheroleum* is authorized for use as a bath additive, or for cutaneous application up to three times daily to the chest or back in liquid and semi-solid dosage forms in concentrations up to 10% (200).

The dried herbal substance contains up to 2.5% of a volatile oil, the main components of which are thymol, carvacrol, *p*-cymene, γ -terpinene, linalool, β -myrcene,

and terpinen-4-ol (193). However, it should be noted that there are at least seven chemotypes of *Thymus vulgaris* and of *Thymus zygis*, yielding volatile oils with different compositions (194, 201–204): borneol type, carvacrol type, geraniol type, linalool type, α -terpineol type, *trans*-4-thujanol and 4-terpinenol type, and thymol type. Only the thymol type with thymol as the predominant compound and containing a minimum of 40% thymol + carvacrol complies with the definition in the European Pharmacopoeia 'as is' required by the EU herbal monograph (193). In addition to the volatile oil, the herbal material contains flavones (including apigenin, luteolin, and 6-hydroxyluteolin) and their glycosides, methylated flavones (including cirsilineol, eriodictyol, and thymonin), and other phenolics, including caffeic acid and rosmarinic acid (193).

A variety of cosmetic product ingredients/fragrance raw materials are also derived from *Thymus vulgaris*, including Thymus Vulgaris Extract, Thymus Vulgaris Flower/Leaf Extract, Thymus Vulgaris Flower/Leaf/Stem Extract, Thymus Vulgaris Flower/Leaf Water, Thymus Vulgaris Flower Oil, and Thymus Vulgaris Leaf Oil. All have been assigned CAS no. 84929-51-1 (33). Thymus Vulgaris Leaf/Flower Oil has also been assigned CAS no. 8007-46-3 (5, 33). They are purported to have 'tonic/masking' properties (5). A fragrance raw material known commercially as Spanish thyme oil is also called 'red thyme oil' because of its deep colour (205). After redistillation, 'white thyme oil' is obtained, which is a less pungent oil with a light yellow colour (194). Clearly, and in the context of these materials potentially being derived from any of the chemotypes of *Thymus vulgaris* (see above), these cosmetic ingredient names and their associated CAS numbers convey little information on the actual chemical composition of any particular extract or distillate.

Undiluted thyme oil applied to the backs of hairless mice was severely irritating. Applied full strength to intact or abraded rabbit skin for 24 h under occlusion, it was again severely irritating. Tested 8% pet., it produced no irritation after a 48-h closed patch test on human subjects. A maximization test carried out on 25 human volunteers with thyme oil 8% pet. produced no sensitization reactions. Also, no phototoxic effects were reported for red thyme oil (205). In a carrageenan-induced pleurisy model in rats, thyme oil, carvacrol and thymol all significantly inhibited inflammatory oedema. In a mouse ear oedema model, carvacrol (10 mg/ear), applied topically, reduced oedema formation, exerting a topical anti-inflammatory effect, whereas thymol (10 mg/ear) did not reduce oedema formation but, rather, produced an irritant response. On gas chromatography–mass

spectrometry analysis of the sample of thyme oil, which had been hydrodistilled from *Thymus vulgaris* growing in Brazil, carvacrol was found to be the most abundant constituent (45.5%), followed by α -terpineol (23%) and endo-borneol (14%). Only 1% thymol was reported in the sample tested (206).

Clinically, hypersensitivity reactions and skin irritation have been observed after contact with thyme oil and/or thymol. An early report incriminated thymol in a toothpaste as the cause of cheilitis and glossitis in a patient (207). Of 450 patients with dermatitis, 4 had positive patch test reactions to oil of thyme (2% pet.) (208). In one study, patients allergic to oil of thyme were observed to also react to thymol and carvacrol (209). In another study, a patient who reacted to carvacrol (1% in eth.) failed to react to thymol (1% in eth.) (210). In an investigation of contact sensitivity in patients with ulcer cruris, thyme oil was one of the allergens most frequently encountered (211).

Thymol in Listerine® mouthwash used for home treatment of paronychia caused allergic contact dermatitis (212). A 70-year-old woman with chronic paronychia of the middle and ring fingers was prescribed a solution of 4% thymol in chloroform, to be applied once daily on the affected proximal nail folds. Six weeks after starting treatment, she developed severe erythema and oedema, with intense itching, in the treated areas. Patch tests with 4% thymol in chloroform and thymol 1% pet. gave positive reactions (213). Since 2000, 27 cases of angioedema, urticaria, lichenoid keratosis, bullous conditions, allergic dermatitis/rashes, pruritus and alopecia associated with 'Thymus vulgaris' have been reported to the World Health Organization's Uppsala Monitoring Centre (165).

Patients reacting to thyme extracts have also been reported to react to rosemary (*Rosmarinus officinalis* L., family Labiatae) extracts. One case involved a 45-year-old man who developed an acute, eczematous, vesicular, severely itching lesion on the thigh after a 24-h application of a herbal poultice prescribed and prepared by his physiotherapist. The poultice contained a mixture of rosemary, thyme, arnica (*Arnica montana* L., family Compositae), chamomile (identified, possibly incorrectly, as *Anthemis arvensis* L., family Compositae), and horsetail (*Equisetum arvense* L., family Equisetaceae). Sensitivity to rosemary and thyme, but not to arnica, chamomile, or horsetail, was confirmed by patch testing with the leaves 'as is'. Patch tests showed positive results for the poultice 'as is' (++) on days 2 and 4), rosemary (++) on days 2 and 4), and thyme (– on day 2 and ++ on day 4) (214). In another case, a woman developed an itchy hand and forearm with face dermatitis after picking rosemary on sunny days. She showed positive patch test reactions

to rosemary (++), and thyme (+), and a stronger reaction after photopatch tests with both plants (215). In a further case, a 53-year-old man experienced, over a period of 2 years, several episodes of pruritic erythema and severe swelling of the face, chest, and dorsal aspects of the arms, which resulted in peeling of the skin. These episodes were related to the application of home-made 'rosemary alcohol' to the chest as a balsam. Patch testing with leaves and flowers 'as is' showed sensitivity to rosemary and sage, with weaker reactions to lavender and thyme (216).

In an occupational setting, airborne contact dermatitis caused by thyme dust has been reported in farmers during the threshing of dried thyme. Of the 46 farmers studied, 4 showed skin symptoms after 5–30 min of exposure to thyme dust. The aetiology of thyme-related skin symptoms remains obscure, although an irritant mechanism (e.g. by mycotoxins) seems probable (217).

***Trigonella foenum-graecum* L.; family Leguminosae**

Commonly known as fenugreek, this is an annual plant that is widely cultivated as a semi-arid crop for its leaves and its seeds, which are used for both culinary and medicinal purposes (218). The dried seeds may be used whole or ground to a yellow powder after roasting; the leaves may be consumed fresh in salads or cooked as a vegetable. However, fenugreek is most commonly used as a spice in curries, seasoning blends, chutneys, pickles, and teas. Because of its maple aroma and flavour, fenugreek is also used as an ingredient in artificial maple syrup, artificial vanilla aroma, coffee substitute, liquorice, rum, cheese, butterscotch, confectionery, and baked goods (218, 219).

Numerous folkloric medicinal uses of fenugreek have been documented, including improving digestion, lowering blood cholesterol, improving appetite, decreasing blood glucose, decreasing blood pressure, reducing perspiration, inducing labour, and loosening mucus in the treatment of sinus and lung congestion. Diuretic, anti-inflammatory, antibacterial, pain-reducing, aphrodisiac and antioxidant actions have also been documented (218, 220, 221). Fenugreek also has a reputation as a galactagogue (220, 222). Folkloric dermatological uses include poultices, cataplasms and extracts for the treatment of skin inflammation, rashes, wounds, and furuncles, and use as a hair tonic for treating baldness (218, 221, 223–225). However, the EU herbal monograph for the crude drug *Trigonellae Foenugraeci Semen* (fenugreek seed) recognizes only the traditional use of the herbal substance administered orally in the form of a tea for temporary loss of appetite, and of herbal preparations

in the form of extracts or infusions used on the skin for the short-term symptomatic treatment of minor skin inflammations (226).

Fenugreek seeds are rich in mucilaginous polysaccharides comprising mainly galactomannans. They also contain a small amount of volatile oil and a variety of secondary metabolites, including: the nitrogenous substances trigonelline, nicotinic acid, and choline; the free amino acid 4-hydroxyisoleucine, saponins ('trigoneosides') derived from diosgenin, yamogenin, tigogenin, and other furanostanols; sterols, including β -sitosterol; and flavonoids, including orientin, iso-orientin and isovitexin (220, 221, 227–229). The volatile oil is reputed to contain anethole (230), but formal studies of the volatile and flavour constituents of fenugreek suggest that anethole is no more than a minor component of the volatile oil, and that it, and indeed most of the other terpenes present in the oil, are odourless at the concentration(s) present in an aroma extract of the seeds (231, 232).

Fenugreek extracts may also be encountered in cosmetic products: Fenugreek Absolute is a fragrance raw material (233); and *Trigonella Foenum Graecum* Extract (CAS no. 84625-40-1) is an extract of the seeds of fenugreek that is purported to have skin-conditioning activity (5). Its chemical composition will depend on the process/solvent used to prepare the extract. Also, it should not be assumed that similarly named extracts sold as food supplements or 'nutriceuticals' for, for example, their supposed antidiabetic and libido-enhancing properties have the same chemical composition as extracts sold for use in cosmetic products.

Dermatological testing of herbal preparations and extracts of fenugreek for use in medicinal or cosmetic products appears not to have been reported. However, the fragrance raw material Fenugreek Absolute, when applied undiluted to the backs of hairless mice and swine, was found not to be irritating. When it was applied full strength to intact or abraded rabbit skin for 24 h under occlusion, it was moderately irritating. Tested at 2% in pet., it produced no irritation after a 48-h closed-patch test on human subjects. A maximization test carried out on 27 volunteers at a concentration of 2% in pet. produced no sensitization reactions. No phototoxic effects were reported for undiluted fenugreek absolute on hairless mice and swine (233).

Adverse dermatological reactions following the use of fenugreek-containing products are only rarely reported. These are usually IgE-mediated reactions (219, 234, 235) that occur after ingestion or inhalation. Cross-reactions between fenugreek and other plants from the legume family, such as peanut, soy, lupin, lentil, pea, bean, and chick-pea (219, 234), have been shown, as has sensitization

to both fenugreek and coriander (*Elettaria cardamomum* Maton, family Zingiberaceae) (235, 236). Sensitization to fenugreek has also occurred after skin application of a fenugreek-containing product. The patient, who was affected by chronic asthma, developed numbness of the head, facial angioedema and wheezing after application of a fenugreek paste to her scalp as a treatment for dandruff (234). A 32-year-old female who was taking a herbal preparation made from fenugreek seeds to improve lactation developed toxic epidermal necrolysis (237). She had taken fenugreek for a similar purpose after the birth of her previous child, without incident.

***Viola* spp.; family Violaceae**

The wild pansy, also known as heartsease, is the source of the crude drug *Violae Herba cum Flore*. This is described somewhat confusingly in the EU herbal monograph (238) as being derived from '*Viola tricolor* L. and/or subspecies *Viola arvensis* Murray (Gaud) and *Viola vulgaris* Koch (Oborny)'. The common name wild pansy usually refers to *Viola tricolor* L.; the common name for *Viola arvensis* Murray [syn. *Viola tricolor* L. var. *arvensis* (Murray) DC.] is field pansy, but the names wild pansy and heartsease are also sometimes applied to this species (239). *Viola vulgaris* (Koch) Oborny, which appears to refer to the 'common pansy', is a name of no botanical standing, and probably refers to a plant name originally published as *Viola tricolor* L. ssp. *vulgaris* (Koch) Oborny, which is now regarded as a synonym of *Viola tricolor* L. ssp. *tricolor* (240). *Viola Tricolor* Extract (CAS no. 84012-42-0) is a recognized cosmetic product ingredient, of unspecified composition, that is purported to have emollient, skin-protecting and soothing properties (5).

Heartsease has a long history of use in Europe for the treatment of respiratory tract disorders, gastrointestinal disorders, as a diuretic, and inflammatory skin disorders, especially those of a seborrhoeal nature, but also weeping and dry eczema, including atopic dermatitis, impetigo, acne, pruritus, including vulval itching, psoriasis, varicose ulcers, haemorrhoids, and burn injuries (241–244). The use of the comminuted herbal substance as a herbal tea for oral use or for infusion preparation for cutaneous use is recognized in the EU herbal monograph as a herbal tea, wet dressing or bath additive only for the symptomatic treatment of mild seborrhoeic skin conditions (238).

Viola tricolor contains a variety of catechins/flavonoids, including rutin (quercetin-3-rutinoside; at one time called violaquercitrin), quercetin, luteolin, and luteolin-7-glucoside. The plant also contains: mucilaginous polysaccharides; phenolic acids, including *trans*-caffeic, *p*-coumaric, gentisic, protocatechuic, *p*-hydroxybenzoic,

p-hydroxyphenylacetic and vanillic acids; salicylic acid and derivatives such as methyl salicylate and monotropitoside (also known as violutoside); coumarins; saponins; and ascorbic acid and tocopherol (244). *Viola tricolor* and *V. arvensis* have also been reported to contain macrocyclic polypeptides known as cyclotides, which have been shown to have a variety of biological activities *in vitro*, including cytotoxic activity (244–246).

Adverse reactions to *Viola tricolor*/heartsease are very rarely reported. A case of haemolysis in a 9-month-old infant with glucose-6-phosphate dehydrogenase deficiency has been reported from Iran. Haemolysis occurred after oral administration of an aqueous extract of wild pansy to relieve restlessness (247). In another case, a 56-year-old farmer developed extensive photo-induced dermatitis after ingesting a herbal decoction prescribed for his chronic hand dermatitis (248). The herbal mixture from which the decoction had been prepared contained various plant species, including *Viola tricolor*. However, the role played by *Viola tricolor*, if any, in this patient's photo-induced dermatitis was not established.

***Vitis vinifera* L.; family Vitaceae**

This, the common grapevine, is a woody climbing plant that can reach a length of 30 m, and that has long been cultivated for its fruit, the grape, which is eaten fresh or dried, or is fermented to produce an alcoholic drink (249). The leaves are also eaten as a vegetable – 'stuffed vine leaves'.

Cultivated grapevines, often identified as *Vitis vinifera* L. ssp. *sativa* Hegi, a name that is now understood to be a synonym of *Vitis vinifera* L. ssp. *vinifera* (250), are thought to have been domesticated from wild populations of *Vitis vinifera* L. ssp. *sylvestris* Hegi (251). However, many thousands of botanical subspecies, varieties and cultivars of *Vitis vinifera* have been described, including interspecific hybrids/cultivars, some arising spontaneously when *Vitis vinifera* is grown in the vicinity of other *Vitis* species (252–254). In turn, these have to be regarded as 'chemovars', as shown by the wide range of colour, flavour and other usage-related characteristics shown by grapes. It follows that grapevines have to be identified to the cultivar/chemovar level in order to ensure suitability for their intended use. Thus, although '*Vitis vinifera* L.' is identified as the botanical source of the crude drug *Vitis Viniferae Folium*, the EU herbal monograph (255) does not explicitly specify any particular subspecies, variety or cultivar, noting in a footnote only that the crude drug has to comply with the requirements of a monograph in the Pharmacopée Française, 10th edn, 1996. The monograph in question is that for 'Vigne Rouge' ('Red

Vine'), in which the botanical source is described as '... la vigne rouge dite à cépage « teinturier » ... provenant de variétés à raisin noir et à pulpe rouge, de *Vitis vinifera* L'. This has been interpreted (256), possibly inappropriately, as signifying that the botanical source is *Vitis vinifera* L. var. *tinctoria* Raf. – the 'colouring grape' – when it actually appears to mean 'the black grape variety known as "the dyer" or "teinturier" or "teinturier du Cher" or "teinturier du Bordelais" with red flesh and with leaves that turn red in the autumn, that is used to enhance the red colour of wines' (257, 258).

Vitis vinifera L. (subspecies/variety/cultivar/chemovar not being specified) is also identified as the botanical source material used in the production of various cosmetic product ingredients, including *Vitis Vinifera* Distillate (purported to have 'tonic/masking' properties), *Vitis Vinifera* Extract, *Vitis Vinifera* Juice, *Vitis Vinifera* Leaf Extract, *Vitis Vinifera* Root Extract, *Vitis Vinifera* Seed Extract (all assigned CAS no. 84929-27-1, notwithstanding their chemical dissimilarities; purported to have skin-conditioning or skin-protecting properties), and *Vitis Vinifera* Seed Oil (CAS no. 8024-22-4), which has emollient properties (5).

Both vine fruits (grapes) and vine leaves contain a wide range of anthocyanins and other flavonoids/polyphenols, varying in composition with grape variety and viticultural conditions. These include: the flavonoids quercetin-3-O- β -D-glucuronide (miquelianin), quercetin-3-O- β -D-glucoside (isoquercitrin), kaempferol-3-glucoside (astragalin), kaempferol-3-galactoside, eucryphin, astilbin, and engeletin; flavan-3-ols (catechin, epicatechin, and procyanidin-B1) (256, 259); anthocyanins (including malvidin-3-O- β -glucoside) (256, 260–262); oligomeric proanthocyanidins; and gallic acid and gallic acid 3- β -glucosides and 4- β -glucosides (256, 259). Grapes also contain tartaric esters of hydroxycinnamic and caffeic acids (including *trans*-caftaric acid and *trans*-coutaric acid) (259, 261, 263), and resveratrol, viniferins, astringins, and piceid, which are polyphenolic stilbenes (256, 264). Potassium hydrogen tartrate is present in significant quantities in grapes, often crystallizing out of wines as 'cream of tartar' during their production (265). Malic, oxalic, citric, fumaric and succinic acids and their salts can also be detected in both grapes and vine leaves (256). The monograph in the Pharmacopée Française, 10th edn, 1996 for 'Vigne Rouge', the botanical source of *Vitis Viniferae Folium*, specifies a minimum content of 4% total polyphenols and 0.2% anthocyanins, expressed as cyanidin-3-glucoside (chrysanthemin).

In Europe, the leaves of *Vitis vinifera* have long been used as a traditional medicine for their astringent and homeostatic properties in the treatment of diarrhoea,

bleeding, haemorrhoids, varicose veins, and other circulatory and venous diseases (256). The EU herbal monograph on *Vitis Viniferae Folium* (255) recognizes as well established the use of grapevine leaf products orally for the treatment of chronic venous insufficiency. The monograph also recognizes the traditional use orally and topically for the symptomatic relief of discomfort and heaviness of the legs related to "minor venous circulatory disturbances", for the symptomatic relief of itching and burning associated with haemorrhoids, and for the symptomatic treatment of cutaneous capillary fragility.

Although very few case reports describing adverse skin reactions to pharmaceuticals/botanicals derived from *Vitis vinifera* are to be found in the medical literature, the VigAccess™ database (165) currently includes 253 records of 'skin and subcutaneous tissue disorders' ascribed to *Vitis vinifera*. These include cases of angioedema, urticaria, bullous eruptions, including erythema multiforme, cutaneous lupus erythematosus, allergic dermatitis, erythemas, exfoliative/macular/papular/morbilliform/vesicular rashes, alopecia, etc. Reports published in the medical literature mostly describe urticarial/anaphylactic reactions following ingestion of grapes/grape juice/raisins/sultanas/stuffed vine leaves/wine vinegar (266–270), but sensitization to grapes may also be asymptomatic (271). An early report of a skin reaction following contact with crushed grapes of the variety 'Concord' described initial itching, followed within 24 h by a red macular rash. Concord appears to be a hybrid between *Vitis vinifera* L. and *Vitis labrusca* L. (254). Marmalade prepared from the grape skins, when eaten, caused the itching to become more severe. This was followed by infiltration of the skin and small vesicles at the original site of the itching. Preliminary investigations suggested that the reaction had been caused by some substance in the grapes rather than by a foreign substance sprayed on the grapes (272). In another case, a 46-year-old female who had worked for 10 years raising seedless grapes in Japan developed miliaria-sized red papules on the fingertips, which became lichenoid and spread to the dorsa of her fingers and hands. They disappeared spontaneously in the autumn, reappearing from March to July every year. Her work involved removal of excess buds on the vines with her bare hands almost daily. Patch and photopatch testing showed sensitivity to a grape bud extract but not to grape leaf or other extracts/materials tested. Ultraviolet light increased the erythema and oedema caused by the grape bud extract. The reaction lasted for at least 96 h. A weak positive reaction to grape bud extract was observed in 6 of 22 other farmers tested who raised grapes (273). Grape farmers also constituted the subject of a study measuring

the prevalence of skin symptoms carried out in the Malevisi region of Crete. The incidence of self-reported and work-related itchy rashes was significantly greater in

grape farmers than in controls. Sensitization to pollens and allergic rhinitis were also significantly associated with self-reported itchy rash in grape farmers (274).

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