

Contact dermatitis as an adverse reaction to some topically used European herbal medicinal products – Part 3:

Mentha × piperita – *Solanum dulcamara**

Gioacchino Calapai¹, Paola L. Minciullo^{1,2}, Marco Miroddi¹, 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 2015)[†] called a European Union herbal monograph – has been produced. Part 3: *Mentha × piperita* L. – *Solanum dulcamara* L.

Key words: adverse drug reaction; contact dermatitis; herbal medicine; *Mentha × piperita*; *Oenothera biennis*; phytodermatitis; *Pimpinella anisum*; *Quercus* spp.; *Rosmarinus officinalis*; *Ruscus aculeatus*; *Salvia officinalis*; *Solanum dulcamara*.

Plant Sources of Some European Herbal Medicinal Products and the Adverse Skin Reactions They May Elicit – Part 3: *Mentha × piperita* – *Solanum dulcamara*

Mentha × piperita L.; fam. Labiatae (or Lamiaceae)

Peppermint (*Mentha × piperita* L.) is a hybrid mint produced by crossing *Mentha aquatica* L., the water mint, and

Mentha spicata L., the spearmint (1). First described by the English naturalist John Ray in 1696, peppermint now grows all over the world. This popular herb is used in numerous forms (oil, leaf, leaf extract, and leaf water) in cosmetics, personal hygiene products, foods and pharmaceutical products for its flavouring, fragrance and therapeutic properties (2–4).

The EU herbal monograph on peppermint oil (5) recognizes the traditional use of the oil in liquid or semi-solid preparations for cutaneous and transdermal use, for inhalation, and for oromucosal use. The cutaneous and transdermal uses include the symptomatic relief of localized muscle pain, the symptomatic relief of localized pruritic conditions in intact skin, and the relief of symptoms of coughs and colds. The monograph also recognizes as well established the oral use of the oil in gastro-resistant capsules for the symptomatic relief of minor spasms of the gastrointestinal tract, flatulence, and abdominal pain, especially in patients with irritable bowel syndrome, and the cutaneous use of the oil for the symptomatic relief of mild tension-type headache.

Peppermint leaf is also the subject of an EU herbal monograph (6). However, no dermatological uses for teas

Correspondence: Paola L. Minciullo, UOC Allergologia e Immunologia Clinica Policlinico Universitario, Via Consolare Valeria, 98125 Messina, Italy. Tel: +39 090 2212049; Fax: +39 090 694773. E-mail: pminciullo@unime.it

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[†] [see http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000212.jsp (last accessed 29 July 2015)]

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or tinctures prepared from peppermint leaves are recognized in the monograph.

The major constituents of peppermint oil are L-(–)-menthol (30–60%), L-(–)-menthone (14–32%), and menthyl acetate (3–14%). Minor constituents include pulegone, menthyl isovalerate, limonene, α -pinene, acetaldehyde, phellandrene, cineole, cadinene, amyl alcohol, and dimethylsulfide (2, 3).

In tests carried out on intact and abraded rabbit skin, menthol (which is a solid at room/body temperature) applied at full strength for 24 hr under occlusion was found not to be irritating (7), whereas menthone (8) and menthyl acetate (9, 10) (which are liquids at room/body temperature) were found to be mildly irritating. Tested at 8% pet., menthol produced no irritation after a 48-hr closed patch test in human subjects, and nor was it sensitizing at this concentration in a human maximization test carried out on 24 volunteers (7). Studies carried out in Japan (11) had previously shown that menthone rather than menthol was responsible for the skin irritant properties of peppermint oil. In a more recent study in Japan, positive patch test reactions to menthol, menthyl acetate, piperitone, pulegone, menthofuran and dihydrocarveol were observed in 10 patients with allergic contact dermatitis who were tested with individual components of peppermint and spearmint (*M. spicata* L.) oils (12).

At low concentrations, menthol i.e. L-(–)-menthol, otherwise known as levomenthol, produces a cooling sensation when it comes into contact with the skin or mucous membranes (13, 14). Other isomers of menthol do not exert this cooling effect (13). The effect is mediated by a direct action at TRPM8 (Transient Receptor Potential Melastatin type 8), an ion channel gated by changes in temperature, which is involved in temperature sensing (15). Menthol at higher concentrations (5–10% concentration in mineral oil) caused a burning sensation when applied to the skin (13). Undiluted peppermint oil spilled on a previous skin graft on the dorsum of the hand of a pharmaceutical worker caused a chemical burn (16).

In the mouth, 40 drops of undiluted peppermint oil taken orally for medicinal purposes caused chemical burns in the entire oral cavity and pharynx, producing oedema of the upper and lower lips, and oedema of the tongue, uvula, and soft palate. Laryngoscopy revealed a cherry-red and swollen epiglottis, and hypopharyngeal and laryngeal mucosal burns (17). A case of a severe burning sensation in the anal canal on defaecation, persisting for 20 min before gradually subsiding, was reported in a man who was administered enteric-coated peppermint oil capsules while hospitalized with *Salmonella* enteritis and suffering with perianal soreness. After recovery, the patient was able to take

enteric-coated peppermint oil capsules with no ill-effects (18). A similar, although much less severe, burning sensation in the anal canal has previously been reported in some patients taking high doses of enteric-coated peppermint oil capsules (19).

Considering the widespread use of peppermint oil and menthol in pharmaceutical, cosmetic, culinary and confectionery products (2, 14), the incidence of allergic contact dermatitis caused by peppermint oil and its constituents is relatively low (2, 3, 20). Most commonly, reports of adverse effects refer to intraoral and perioral reactions following the use of toothpastes or other dental/oral products containing peppermint oil or menthol (21). Reactions elsewhere on the body are usually related to the use of cosmetic (22–25) or pharmaceutical products (26–30), or to aromatherapy (31).

Four of 1147 consecutive patients attending eight contact dermatitis clinics in Europe in 1969 were found to react to peppermint oil (1% pet.) on patch testing (32). In a clinic in Poland, 86 patients who had reacted to perfume mix were patch tested with a battery of 35 essential oils. Six reacted to peppermint oil (22). Positive reactions were noted in 3 of 1200 dermatitis patients patch tested with peppermint oil 2% pet. and in 1 tested with menthol 5% pet. (23). One of 75 patients with contact allergy to cosmetics from 1781 contact dermatitis cases studied at a clinic in The Netherlands in the period 1981–1986 reacted to peppermint oil (24). Also, in a clinic in Oregon in the USA, one positive patch test reaction to peppermint oil 2% pet. was observed in 21 patients who had been referred for patch testing for suspected allergy to botanical products (33).

Peppermint oil is considered to be one of the most common allergens in toothpastes, along with cinnamal and cinnamon oil (34). Presenting symptoms include stomatitis, cheilitis, glossitis, gingivitis, and perioral dermatitis. In a study of 4 patients who developed allergic contact cheilitis (oral eczematous dermatitis involving the lips and perioral skin) following the use of lip balms containing peppermint oil, all reacted to peppermint oil on patch testing (35). In another study, 12 cases of contact sensitivity to menthol and peppermint oil were reported in patients presenting with intraoral symptoms (burning mouth syndrome, recurrent oral ulceration, or a lichenoid reaction). The 5 patients with burning mouth syndrome showed contact sensitivity to menthol 5% pet. and/or peppermint oil 1% pet.: 1 patient was sensitive to both agents, 3 were sensitive to menthol but not to peppermint oil, and 1 was sensitive to peppermint oil but not to menthol. The 4 patients with recurrent intraoral ulceration were sensitive to both menthol and peppermint oil, and the 3 patients with an oral lichenoid reaction

were sensitive to menthol, but only 2 also reacted to peppermint oil (36). Other reports have described cases of stomatitis and perioral dermatitis (37–40), glossitis (40), and cheilitis (41–43), a case of recurrent mouth ulceration (44) and a case of orofacial granulomatosis of the lower lip (44) associated with exposure to peppermint oil and/or menthol. In a patient presenting with oral burning and discomfort associated with a lichenoid eruption in the mouth, which was exacerbated by mint-flavoured mouthwashes and foods, patch test reactions to menthol 5% pet. and to peppermint oil 1% pet. did not appear until D5. Repeat patch tests again showed a positive reaction on D5 with no earlier reaction on D2, suggesting a true late elicitation rather than active sensitization (45).

The consumption of food products containing peppermint oil can be a risk factor for sensitization. Even consumption of excessive amounts of mint-flavoured sweets can cause stomatitis and glossitis (40). Drinking vast amounts of peppermint tea every day for 6 years was the cause of chronic erythema and itching of the vulva with pigmentation disorders in a 43-year-old woman with a history of atopy and sensitization. Patch testing revealed a strong connection between peppermint oil and those reactions. In fact, after the patients avoided products containing peppermint oil, complete clinical recovery occurred. Further confirmation was provided when subsequent re-exposure to the same peppermint tea led to severe pruritus (46).

Cheilitis and perioral dermatitis associated with the smoking of menthol cigarettes has also been reported. The patient, who also suffered from dermatitis on the dorsal aspects of the central fingers of both hands, reacted on patch testing with menthol 1% pet. and 'essence of mint' 1% pet. (47). Also, cases of urticaria have been reported following oral exposure to peppermint oil coupled with cutaneous exposure and the smoking of menthol cigarettes (48, 49).

***Oenothera biennis* L.; fam. Onagraceae**

Native to North and South America and now widespread throughout Europe and parts of Asia, this biennial plant is also known by the names tree primrose, sun cups, sundrops, king's cure-all, fever plant, evening star, and night willow-herb (50). Native Americans used an ointment prepared from the stem and leaf of the plant as a topical remedy to soothe cutaneous affections of infants, and the bruised leaves were applied to ulcers (50, 51).

The oil obtained by cold expression or solvent extraction from the seeds of the plant is called evening primrose oil. It is a triglyceride oil, which, when it complies with the European Pharmacopoeia standard (eighth Edition,

Volume 2, 2014) for *Oenotherae Oleum Raffinatum*, yields, on saponification/hydrolysis, 65–85% linoleic acid [(9Z,12Z)-9,12-octadecadienoic acid], 7–14% γ -linolenic acid [(6Z,9Z,12Z)-6,9,12-octadecatrienoic acid], and a maximum of 0.5% of α -linolenic acid [(9Z,12Z,15Z)-9,12,15-octadecatrienoic acid]. Other fatty acids present are 5–12% oleic acid [(9Z)-9-octadecenoic acid], 1–4% stearic acid (octadecanoic acid), 4–10% palmitic acid (hexadecanoic acid), and a maximum of 0.3% saturated fatty acids of chain length less than C₁₆ (52, 53). The oil also contains 1.5–2% unsaponifiable matter, comprising mainly β -sitosterol and γ -tocopherol (54).

The EU herbal monograph for evening primrose oil (55) refers to two plant sources, namely *Oenothera biennis* L. and *Oenothera lamarckiana* L. The latter name has no botanical standing – the name *O. lamarckiana* was originally published by the French botanist Seringe, not by Linnaeus – and appears to have been included in the monograph in an attempt to acknowledge that the name *O. lamarckiana* is occasionally used (incorrectly) when referring to the related redsepal, tall or large-flowered evening primrose *Oenothera glazioviana* Micheli (synonyms *Oenothera erythrosepala* Borbás, *O. lamarckiana* auct.), a species that yields a seed oil that is very similar, or even superior, as regards its supposed medicinal properties, to that produced by *O. biennis* L. (56). Notwithstanding this nomenclatural confusion, the herbal monograph (55) recognizes the fatty oil obtained from seeds of *O. biennis* or *O. lamarckiana*, administered orally, as a traditional herbal medicinal product for the symptomatic relief of itching in acute and chronic dry skin conditions. No topical or other medicinal uses are recognized.

Evening primrose oil is also recognized as a cosmetic product ingredient with the INCI name *Oenothera Biennis* Oil and CAS no. 90028-66-3. A variety of other extracts have been assigned the same CAS number, including *Oenothera Biennis* Flower Extract, *Oenothera Biennis* Leaf Extract, *Oenothera Biennis* Root Extract, and *Oenothera Biennis* Sprout Extract (57), even though they have very different chemical constitutions.

However, evening primrose oil has been widely used in the treatment of systemic diseases characterized by chronic inflammation, including atopic eczema (50). Evening primrose oil was previously licensed as Epogam® and as Efamast® in the United Kingdom as a prescription treatment for atopic dermatitis and mastalgia, respectively. However, marketing authorizations were withdrawn in October 2002 because of a lack of clear evidence of clinical benefit for evening primrose oil in either atopic dermatitis or mastalgia (50, 58, 59).

Presumably in recognition of the effect that orally administered evening primrose may have on itching, aromatherapy formulas containing oils rich in γ -linolenic acid, such as evening primrose oil, have been recommended for psoriatic pruritus (60).

O. biennis has been listed as an 'irritant plant' on the basis of an earlier anecdotal report (61). Also, according to a different anecdotal source, it has been noted that *O. biennis* can produce eczema in humans (62). The VigAccess™ database provided by the World Health Organization's Uppsala Monitoring Centre includes 85 records of skin and subcutaneous tissue disorders out of 364 suspected adverse drug reaction reports for *O. biennis*. These include 15 'angioedema and urticaria' reports, 53 'epidermal and dermal conditions' reports, and 11 'skin appendage conditions' reports (63).

***Pimpinella anisum* L.; fam. Umbelliferae (or Apiaceae)**

The common name of this plant is anise. The material of interest for medicinal use is the fruit (i.e. whole cremocarp), which has an odour of anethole. In particular, the medicinal properties of the fruit (known as aniseed) are attributable to its content of essential oil (anise oil). The essential oil is a clear, colourless or pale yellow liquid, obtained by steam distillation of dry ripe fruits. It comprises 80–95% *trans*-anethole. The remainder includes the terpenoids α -terpineol, linalool, and β -farnesene, and various benzenoids, including estragole, *cis*-anethole, and anisaldehyde (64).

The EU herbal monographs recognize the traditional use of aniseed (Anisi Fructus) and anise oil (Anisi Aetheroleum) for the symptomatic treatment of mild, spasmodic gastrointestinal complaints, including bloating and flatulence, the relief of dyspeptic complaints, bloating, and flatulence, and as an expectorant for coughs associated with colds (65, 66). No dermatological uses are recognized. However, the possible occurrence of allergic reactions affecting the skin is acknowledged, as is the risk of hypersensitivity reactions associated with exposure to other sources of anethole, including caraway oil (*Carum carvi* L.) and fennel oil (*Foeniculum vulgare* Mill.).

In the cosmetics field, two INCI names have been registered for anise oil, namely Pimpinella Anisum Seed Oil and Pimpinella Anisum Fruit Oil. These and other extracts of anise, which may be rather different from anise oil in their chemical constitution, have been assigned CAS no. 84775-42-8. Interestingly, the alternative CAS number 8007-70-3 is also applied to Pimpinella Anisum Seed Oil. This is a CAS number that is used for *Illicium Verum* Fruit/Seed Oil, the volatile oil derived from the dried, ripe fruits and seeds of star anise, *Illicium verum* Hook. f., fam. Illiciaceae (57).

There appear to be no reports in the literature of adverse skin reactions attributable directly to contact with the anise plant or anise fruit (i.e. aniseed). Neither anise oil nor anethole, when tested at a concentration of 2% pet., produced any irritation after a 48-hr closed patch test in 25 human volunteers. Similarly, human maximization tests carried out with anise oil and with anethole produced no reactions (67, 68). However, both anise oil and anethole have occasionally been the subjects of adverse skin reaction reports. Perhaps the earliest report appeared in 1938. A 44-year-old female patient in the United States presented with stomatitis and an eruption on the fingers and left palm. Questioning showed that she had been using a denture cream to clean her dentures, holding the dentures in the left hand while doing so. Investigations showed that rinsing did not completely remove residues of the denture cream. The denture cream had a pleasantly aromatic odour, which was attributed to the inclusion of the essential oils of anise, wintergreen and cloves in the formulation. Oral challenge testing with anise oil-containing gums provoked a strong reaction in the patient's mouth. Patch testing showed that the patient was sensitive to both anise oil and anethole, each tested at a concentration of 1.1% in an alcohol/bland ointment base. Patch tests with all other constituents of the denture cream gave negative results, as did all tests in 30 control subjects (69). More recent cases of stomatitis associated with exposure to anise oil and/or anethole, with positive patch test reactions on the skin, have been reported from Denmark (70, 71, 38), Scotland (36), England (72, 73), Italy (43), and Australia (74). An interesting feature reported in two of these cases (69, 73) is that a loss of taste may be experienced by the patient.

In an occupational setting, sensitization to oil of anise has been reported in 2 female workers in a cake factory in Spain. The 2 women presented with dermatitis on the hands and forearms, which, in 1 of the patients, spread to the scalp and face. Rhinitis and blepharitis occurred whenever they entered the cake factory. Positive patch test reactions were observed with anise oil 5% in olive oil, and with anethole 5% pet. No studies in control subjects were reported (75).

A further report described 2 women who presented with eczema on the lower legs. Both had used a product marketed as Sanyrène™ and as Corpitol™, comprising 99% 'Corpitolinol 60' [further described as 'hyperoxygenated glycerides of essential fatty acids rich in linoleic acid (60%) and Vitamin E'] and 1% 'aniseed perfume'. The product is indicated for patients at risk of developing pressure ulcers. In both cases, patch tests showed a positive reaction to *trans*-anethole 5% pet. (76).

***Quercus* L. spp.; fam. Fagaceae**

Members of the genus *Quercus* are found naturally in temperate regions, where they grow to form large trees. The bark from three particular European species, namely the English oak (*Quercus robur* L.), the durmast oak (*Quercus petraea* Liebl., syn. *Quercus robur* L. var. *petraea* Matt.), and the downy oak (*Quercus pubescens* Willd.) is used to prepare the crude drug known as *Quercus Cortex*. Oak bark is harvested during March and April for its content of tannins (77).

The tannins in *Quercus Cortex* comprise a complex mixture of hydrolysable tannins and condensed tannins (which are proanthocyanidins). The principal types of hydrolysable tannin are gallotannins and elagitannins. The hydrolysable tannins contain a polyhydric alcohol (typically D-glucose) as the basic structural unit, the hydroxyl groups of which are esterified by gallic acid or hexahydroxydiphenic acid (77). The various constituents of oak tannin are not easily separated, and so are normally put to medicinal use as extracted.

In addition to its oral administration in the symptomatic treatment of mild diarrhoea, the EU herbal monograph recognizes as traditional the oromucosal use of *Quercus Cortex* as a decoction in the symptomatic treatment of minor inflammation of the oral mucosa or skin, and the use of a decoction in the bath (or as a topical rinse or poultice) for the symptomatic relief of itching and burning associated with haemorrhoids after serious conditions have been excluded by a medical doctor (78).

Reports of adverse skin reactions attributable to (oak) tannins have appeared only infrequently. A 30-year-old male patient with an eruption on the hands and body, which was diagnosed as contact dermatitis, was treated with 'tannic acid compresses' – tannic acid is also known as gallotannin or oak bark tannin. This resulted in a severe exacerbation and progression of all of his lesions (79). Patch tests with tannic acid in water elicited positive reactions down to a 0.25% concentration. He also reacted to ink (probably containing oak gall tannins), metol, and pyrogallol, chemicals used in photographic developer solutions that have structural similarities to the gallic acid that is released from tannic acid/gallotannin by hydrolysis. Two further cases involved female patients who had applied an ointment to the perianal area for treating haemorrhoids. The ointment contained 2% benzocaine, 2% butyl aminobenzoate, and 10% tannin. Positive patch test reactions to tannin (1–10% pet. and aq.) and to butyl aminobenzoate were observed in both patients; patch tests with tannin 10% pet. gave negative results in 24 controls (80).

Occupational exposure to oak in woodworkers has also been reported to produce dermatological symptoms.

A carpenter who developed dermatitis following contact with oak sawdust reacted on patch testing with tannin 2% aq. (81). In The Netherlands, 20 wood-sensitive patients were patch tested with ethanolic extracts of various woods (82). One patient reacted to oak (*Q. robur* L.).

A more complex picture of sensitivity to oak was reported from Italy. Three patients all reacted to an ethanolic extract of oak (prepared from finely chopped leaves, branches, and inner and outer bark). However, when tested separately with extracts of the various parts of the oak, 1 patient was found to be sensitive to the bark only, the second patient was sensitive only to an extract of the mosses and lichen growing on the bark, and the third was sensitive to the bark extract and to the moss and lichen extract. All 3 failed to react when patch tested with tannin 0.25% aq. In 2 of these patients, the eczema flared when they cut wood for a log fire. Patch tests in 12 controls all gave negative results (83).

***Rosmarinus officinalis* L.; fam. Labiatae (or Lamiaceae)**

Commonly known as rosemary, this shrubby plant originates from the Mediterranean region, but is now widely grown there and elsewhere as an ornamental plant and for medicinal, culinary and cosmetic use. It provides the crude drugs rosemary leaf and rosemary oil (an essential oil). Traditionally, the essential oil has been used in balneotherapy and aromatherapy, as well as being applied topically as an antiseptic and to aid wound healing, and as a rubefacient, mild analgesic, and parasiticide (84, 85). Rosemary oil, applied topically, also has a long-standing reputation as a hair growth promoter (84–87).

Various rosemary extracts are also used in cosmetic products for their preservative antioxidant and antimicrobial activities, including *Rosmarinus Officinalis* Extract, *Rosmarinus Officinalis* Leaf Extract, *Rosmarinus Officinalis* Flower Cera, *Rosmarinus Officinalis* Flower Extract, *Rosmarinus Officinalis* Flower Oil, and *Rosmarinus Officinalis* Water, all of which have been assigned CAS no. 84604-14-8. Rosmarinic Acid has been assigned CAS no. 20283-92-5 (57, 88, 89).

EU herbal monographs recognize the traditional use of rosemary leaf (*Rosmarini Folium*) and rosemary oil (*Rosmarini Aetheroleum* or *Oleum Rosmarini*) administered orally for the symptomatic relief of dyspepsia and mild spasmodic disorders of the gastrointestinal tract, and cutaneously as an adjuvant for the relief of minor muscular and articular pain, and in minor peripheral circulatory disorders. For cutaneous use, preparations of the leaf or the oil are used as a bath additive for balneotherapy. The oil may also be incorporated into a suitable vehicle at a concentration of 6–10% and applied topically two or three times daily (90, 91).

Chemically, rosemary oil (obtained by steam distillation) comprises 1,8-cineole (20–50%), α -pinene (15–25%), camphor (10–25%), bornyl acetate (1–5%), borneol (1–6%), camphene (5–10%), α -terpineol (12–24%), limonene, β -pinene, β -caryophyllene, and myrcene. Extracts produced by solvent extraction of the leaves will contain a greater or lesser quantity of the volatile components of the essential oil, together with non-steam-volatile extracts, including apigenin, betulin, carnosic acid, carnosol, hesperidin, oleanolic acid, rosmadial, rosmanol, and rosmarinic acid. It is important to recognize, however, that the composition of both the oil and the other extracts from the leaves, stems and flowers does vary significantly, not only because three chemotypes of the plant are recognized as regards the composition of the oil that they yield (namely the *cineoliferum*, *verbenoniferum* and *camphoriferum* chemotypes), but also because the compositions of extracts and steam distillates will vary with the methodology used to prepare the extract, and also with the season and with the geographical origin of the plant material (84, 92–94).

The risk of developing contact dermatitis will depend upon whether an individual has been exposed to the distilled essential oil or to an extract of the leaves, stems, or flowers. In turn, because the individual components of the essential oil and of solvent extracts are commonly found in many other plants, cross-reactivity may occur with those other plants and/or their essential oils or extracts. However, on the basis of the number of published reports of contact dermatitis attributable to rosemary, the incidence of adverse skin reactions is very low. But, the possibility of misdiagnosis or under-reporting cannot be ruled out (95).

When applied at full strength to intact or abraded rabbit skin for 24 hr under occlusion, rosemary oil was found to be moderately irritating (96), as were α -pinene (97), terpineol (98), and camphor (99). When tested at 10% pet., rosemary oil produced no irritation after a 48-hr closed patch test on human subjects (96), and neither did α -pinene 10% pet. (97) or camphor 4% pet. (99). When applied at full strength to intact or abraded rabbit skin for 24 hr under occlusion, 1,8-cineole was not irritating; nor was this substance irritating when applied to 25 human subjects at a concentration of 16% pet. in a 48-hr closed patch test (100). In sensitization studies, rosemary oil produced no sensitization in a human maximization test carried out on 25 volunteers (96). Human maximization tests carried out with 1,8-cineole 16% pet. (100), terpineol 12% pet. (98) and camphor 4% pet. (99) also produced no sensitization in 25 volunteers. However, a positive patch test reaction to 1,8-cineole (eucalyptol) was observed in a patient who had become sensitized to tea-tree oil (from *Melaleuca alternifolia* Cheel, fam.

Myrtaceae) applied to his atopic eczema (101). Also, of 2 aromatherapists who showed positive patch test reactions to α -pinene and to numerous essential oils, only 1 also reacted to rosemary oil (102). A subsequent study found 3 aromatherapists to be patch test-sensitive to rosemary oil (103).

Rosemary oil was mentioned in an article on 'cosmetic irritants' published in 1938 (104), but the author of the article merely included rosemary oil in a list of natural essential oils used in perfumes. Approximately 40 years later, in a study of 450 dermatitis patients in Poland, 3 were shown to react on patch testing with rosemary oil (105). A report from Japan described a case of contact dermatitis induced by a cleansing gel containing an extract of rosemary leaf (106). The patient, a 23-year-old woman, had been using the cleansing gel for ~2 months. Patch testing showed sensitivity to Rosemary Leaf Extract 0.1% aq. A 48-year-old woman, with a medical history including allergic rhinitis and asthmatic bronchitis, developed oedema and eczematous lesions on her hands, eyelids and face a few hours after taking a walk during which she touched several odorous plants. Patch testing showed sensitivity to rosemary extracts and to carnosol 0.1% alcohol. It was also noted that a photopatch test reaction to rosemary leaf as is was more intense than that observed with the closed patch test. The patient was not sensitive to either oregano or sage (107). Photo-aggravation of a reaction to rosemary was also observed in a 62-year-old non-atopic woman who had been affected by several episodes of itchy hand, forearm and face dermatitis after picking rosemary on sunny days. Lesions appeared hours after she handled rosemary leaves, and resolved within 7 days of treatment with a topical corticosteroid. Positive patch and photopatch test reactions were observed with rosemary and with thyme. Tests carried out on 5 control subjects all gave negative results (108).

In an occupational setting, an otherwise healthy 56-year-old man had been working for several years in a food (sausage) processing factory, where his job was to add spices and additives. He developed contact dermatitis on the hands, forearms and face after the introduction of a new herb extract, Rosmanox™, made from the leaves of rosemary. Patch tests with the rosemary extract 5% and 10% pet., and with carnosol 1% ethanol, a naturally occurring compound present in rosemary and in Rosmanox™, produced positive reactions. Patch testing in 226 control subjects produced no positive reactions (109). Another case of sensitization occurred in a 59-year-old male who regularly ate foods flavoured with rosemary. He presented with severe cheilitis 1 year in duration, which cleared within a few days after he avoided rosemary. Sensitivity to rosemary but not to spearmint

(*M. spicata* L.) or peppermint (*Mentha piperita* L.) was confirmed by patch testing with the leaves as is (110).

Home-made rosemary preparations applied to the skin for therapeutic purposes have also caused contact sensitization. A 56-year-old man applied rosemary leaf plasters for pain in his knee. He developed an acute vesicular exudative dermatitis in the area of application. Sensitivity to rosemary but not to thyme (*Thymus vulgaris* L.), 'origanum' (identified, possibly incorrectly, as *Origanum vulgare* L.) or mint (*M. piperita* L.), was confirmed by patch testing with leaves as is (111). In another 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 aspect 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. The involvement of the face suggested that the 'rosemary alcohol' had elicited an airborne contact dermatitis (112). A further case involved a 45-year-old man who developed an acute, eczematous, vesicular, severely itching lesion on the thigh after a 24-hr application of a herbal poultice prescribed and prepared by his physiotherapist. The poultice contained a mixture of rosemary, thyme (*T. vulgaris* L.), arnica (*Arnica montana* L., fam. Compositae), chamomile (identified, possibly incorrectly, as *Anthemis arvensis* L., fam. Compositae), and horsetail (*Equisetum arvense* L., fam. Equisetaceae). Sensitivity to rosemary and thyme, but not to arnica, chamomile, or horsetail, was confirmed by patch testing with the leaves as is (113).

***Ruscus aculeatus* L.; fam. Asparagaceae**

Known as butcher's broom, this plant is native to Mediterranean Europe and Africa, and is widely distributed in Europe. It is also cultivated by hobby gardeners and grown for the florist trade. The rhizome is the part of the plant used medicinally (114). Its main constituents are steroidal (or, more precisely, spirostanol) saponins based on the aglycones ruscogenin and neoruscogenin, and include ruscin, neoruscin, deglucoruscin, and ruscoid, with their various sulfated and acetylated derivatives, ruscozepines A and B, aculeosides A and B, and others. Coumarins, including esculin and esculetin, triterpenes, and flavonoids, are also present (114, 115).

There is some confusion in the published literature regarding the chemical composition of the rhizome and extracts prepared from it. The impression is held by some authors that the rhizome contains ruscogenins, and that ruscogenins are the active substances. Also, the word 'ruscogenin' is used (incorrectly) when referring to an

extract of *R. aculeatus* rhizome [see (114)]. In fact, the rhizome contains steroidal saponins (including ruscin and neoruscin), which, on hydrolysis, yield their aglycones (namely ruscogenin and neoruscogenin). Also, for practical reasons, when the crude drug extracts are being standardized, they are standardized for the content of the aglycones that they yield, and not for the saponins that they contain. A recently published study now suggests that the active substances in *R. aculeatus* rhizome are actually the spirostanol saponins ruscin and deglucoruscin, and the coumarin glucoside esculin (116).

The EU herbal monograph recognizes the traditional use of extracts prepared from the rhizome of butcher's broom (*Rusci Aculeati Rhizoma*) administered orally to relieve symptoms of discomfort and heaviness of legs related to minor venous circulatory disturbances, and for symptomatic relief of itching and burning associated with haemorrhoids. No topical use is recognized (117). However, *Ruscus Aculeatus* Root Extract (CAS no. 84012-38-4) is a recognized cosmetic product ingredients with 'astringent', 'refreshing', 'skin conditioning', 'soothing', 'stabilizing' and 'tonic' properties. Ruscogenin (CAS no. 472-11-7), and neoruscogenin (CAS no. 176-33-4) are also recognized as having 'skin conditioning' properties (57, 89).

Of those interviewed in a survey carried out in England, 46% of retail florists claimed to have had a rash at some time in their employment, and 84% of these thought that they knew the cause(s). Butcher's broom was identified as one of the offending plants (118). However, there appears to be little or no risk of an adverse reaction in those who receive bouquets of flowers containing butcher's broom.

Rather more likely to cause a reaction are topical products labelled as containing ruscogenins or *R. aculeatus* extract and sold as haemorrhoid treatments, anti-cellulite creams, and local treatments for varices. A 30-year-old non-atopic female, 7 months pregnant and with a previous history of nickel intolerance, was prescribed a vasoconstrictor cream (Fabrovén™) for the treatment of varices. After applying the cream for 2 months, she developed a papulo-erythematous pruriginous eruption on both legs, which spread within a few days to the entire skin, and produced oedema of the eyelids. She denied any preceding sun exposure. Patch tests with *R. aculeatus* extract (0.8%, 1% and 1.6% ethanol) produced positive reactions (119). Several further cases of contact sensitivity to *R. aculeatus* extract and/or to ruscogenins have been reported from France (120). A 34-year-old Caucasian woman presented with pruritic erythematous lesions following the local application of a haemorrhoid treatment cream (Proctolog™). She developed an eczematous

perianal rash, which cleared within several days following Proctolog™ withdrawal. Several months later, the patient experienced a generalized eczematous cutaneous eruption on the day after topical application of an anti-cellulite product on the lower limbs (RoC® Retinol Anti-Cellulite Modelling). Patch testing showed sensitivity to both products. Patch tests with individual ingredients of the creams showed sensitivity only to ruscogenin, which was present in both products. No reactions were observed in 20 control subjects (121). Similar reports from Spain (122, 123) implicated *Ruscus Llorens*™ rectal ointment.

***Salvia officinalis* L.; fam. Labiatae (or Lamiaceae)**

Commonly known as sage, true sage, garden sage, or Dalmatian sage, this plant originates from the Mediterranean region, but it is now cultivated in several European countries, principally in south-eastern Europe (124, 125). Like many other members of the Labiatae, it yields an aromatic essential oil, which is known as sage oil and accounts for the medicinal uses of the plant. Although best known as a culinary herb, sage has also been used in traditional medicine to treat pharyngitis, uvulitis, stomatitis, gingivitis, glossitis, flatulent dyspepsia, hyperhidrosis, and galactorrhoea (125).

The principal components of the essential oil are (–)- α -thujone (10–60%) and (+)- β -thujone (4–36%), with smaller quantities of 1,8-cineole (eucalyptol) (5–20%) and D-(+)-camphor, predominantly, but also L-(–)-camphor (1–15%). Smaller quantities of the sesquiterpenes α -humulene and β -caryophyllene, hydroxycinnamic acid derivatives, including rosmarinic acid, phenolic diterpenes, including carnosic acid, carnosol, and rosmanol, triterpenes, including ursolic acid, and flavonoids are also present in sage (124, 125). However, the composition of the essential oil can vary further depending on its geographical source, time of harvesting, and other factors, with several other components having been reported in different studies. Even leaves picked from different parts of the same plant, top to base, can vary in their relative contents of thujones and camphor (125, 126).

In addition to a monograph for sage leaf (*Salviae Officinalis Folium*), the European Pharmacopoeia (eighth Edition, Volume 1, 2014) includes a monograph for sage tincture (*Salviae Tinctura*) produced from 1 part of comminuted sage leaf and 10 parts of ethanol (70% vol/vol). The European Pharmacopoeia also includes a monograph for three-lobed sage leaf (*Salviae Trilobae Folium*), botanically identified as *Salvia fruticosa* Mill. (syn. *Salvia triloba* L.f.) – recent taxonomic studies having now established that *S. triloba* L.f. is a synonym of *S. fruticosa* Mill. (127). However, it is pertinent to record that, although it is often

claimed that commercial sage is Dalmatian sage, i.e. *S. officinalis* L., a study published in 1980 found that most commercial imported dried sage sold in the United States was 50–95% *S. triloba* L.f. (otherwise known as Greek sage, Greek oregano, or three-lobed sage) plus 5–50% *S. officinalis* L. However, commercial dried sage produced from plants grown domestically in the United States was 100% *S. officinalis* L. (128). To add to the confusion, a cross between *S. officinalis* L. and *S. fruticosa* Mill., which was developed in Israel at the Newe Ya'ar Agricultural Research Centre (129), has become an article of commerce, most probably being sold as culinary sage. This cultivar was reportedly found to be labelled as 'oregano' in a grocery store in San Antonio, United States (130). It was originally named silver sage or silver leaf sage, and is now being sold as Newe Ya'ar Sage, named botanically as *Salvia* cv Newe Ya'ar (128). Clearly, the identity of any fresh or dried plant material brought in to the clinic as true sage, namely *S. officinalis* L., or as three-lobed sage (i.e. *S. fruticosa* Mill.) should be questioned.

The EU herbal monograph on sage leaf (*Salviae Officinalis Folium*) recognizes the traditional use of herbal preparations, orally or oromucosally administered, for the symptomatic treatment of mild dyspeptic complaints such as heartburn and bloating, for the relief of excessive sweating, and for the symptomatic treatment of inflammation in the mouth or the throat. It also recognizes the traditional use of an infusion prepared from the comminuted herbal substance applied cutaneously for the relief of minor skin inflammation (131).

No EU herbal monograph has been prepared for sage oil (*Salviae Officinalis Aetheroleum*), because this oil is deemed to be potentially too toxic for oral use. A case of human poisoning has been reported following ingestion of sage oil for acne (132). After prolonged use of alcoholic extracts or of the pure essential oil, epileptiform convulsions can occur (125). Accordingly, the risk associated with exceeding the maximum recommended daily intake of thujone (5 mg daily for a maximum duration of 2 weeks) outweighs any potential benefit from taking the oil (133).

An old sample of Dalmatian sage oil applied undiluted to the skin of adult human volunteers, which was then covered with an adhesive bandage, produced a reaction in 1 of 20 subjects (134). It is not clear whether the observed reaction was of an irritant or an allergic aetiology. When applied at full strength to intact or abraded rabbit skin for 24 hr under occlusion, Dalmatian sage oil was found to be moderately irritating. A patch test with full-strength sage oil applied for 24 hr produced 1 irritant reaction in 20 subjects. When tested at 8% pet., the oil produced no irritation after a 48-hr close patch test on human subjects.

Also, in sensitization studies, sage oil 8% pet. produced no sensitization in a human maximization test carried out on 25 volunteers (135).

Despite the widespread use of sage leaf and its preparations, allergic reactions to sage have only very rarely been reported, and in most, if not all, of the few reported cases, we cannot be certain that it was true sage (i.e. *S. officinalis* L.) that was used in the investigation. Perhaps the earliest report of dermatitis attributable to sage appeared in 1931 (136). A case report published in 1978 noted that a patch test carried out with a commercially prepared extract of *S. officinalis* in a 65-year-old male gave a positive result (137). However, this result has to be regarded as unreliable, because the extract had seemingly been contaminated with alantolactone, with which the patient had also been tested and to which he also reacted. Alantolactone is not known to occur in members of the Labiatae. A 65-year-old aromatherapist reacted on patch testing with numerous essential oils, including the essential oil from 'sage' 1% and 5% pet. (138). This result has to be interpreted with caution, because it is not clear whether the authors were referring to Dalmatian sage oil (from *S. officinalis* L.) or to clary sage oil (from *Salvia sclarea* L.), or indeed to Spanish, Greek or any other 'sage' oil. Between October 1991 and August 1992, 2 patients from a series of 55 with suspected contact dermatitis reacted on patch testing with sage 25% pet. (139). Then, a report published in 2006 described a case of a 53-year-old male patient who had become sensitized to rosemary but who also reacted when patch tested with sage leaves applied as is. He denied any previous contact with sage (111). Also, a report published in 2011 described a case of an 83-year-old female patient who developed swelling and redness of the lips, followed by a burning sensation, after using a lip balm. She reacted on patch testing with the lip balm and with a *Salvia* extract (stated to be *S. officinalis*) provided by the manufacturer. Patch tests in 20 healthy control subjects gave negative results (140).

***Solanum dulcamara* L.; fam. Solanaceae**

The plant, commonly known as woody nightshade or bittersweet, is a sub-shrub or vine with a creeping, branched rhizome. Its stems, which are harvested either in the spring before leafing or (in order to comply with the requirements of various pharmacopoeias) in the autumn after the leaves have fallen, provide the crude drug *Solani Dulcamarae Stipites* or *Stipites Dulcamarae*. The plant has a long history of traditional use in temperate regions of Europe and Asia, and in North America down to Mexico and Venezuela, extracts being administered orally for the treatment of a variety of skin diseases (141–144).

Topical uses have also been recorded for skin conditions, including skin inflammation, acne, and common warts (143, 145).

The EU herbal monograph on woody nightshade stem (*Solani Dulcamarae Stipites*) recognizes the traditional use of the comminuted herbal substance in the form of an infusion or decoction applied cutaneously only for the symptomatic relief of mild recurrent eczema. The infusion or decoction (at room temperature) is applied to the affected area on a clean dressing (146). Oral use is not recognized, because of concerns about its toxicity (144).

Woody nightshade stems are also used to prepare the cosmetics ingredient *Solanum Dulcamara Stem Extract* (CAS no. 84696-50-4). This is regarded as having 'skin conditioning' properties (89).

So. dulcamara L. contains steroidal alkaloid glycosides (including α -solamarine, β -solamarine, solasonine, and solamargine), steroidal saponins (based on the aglycones yamogenin, tigogenin, and diosgenin), and polyhydroxynortropane alkaloids, including a family of calystegines. The contents of these various substances vary between different parts of the plant (144). Whether or how these substances are responsible for the supposed medicinal properties of the crude drug remains to be established. It may also be pertinent to observe that, in preparing a decoction by boiling the crude drug in water and reducing its volume, a greater degree of hydrolysis of the various glycosides can be expected than would occur with only a short period of exposure to boiling water in the preparation of an infusion. Accordingly, a decoction of woody nightshade stems is unlikely to be identical in its composition to that of an infusion.

Historical reports note that orally administered extracts of woody nightshade are diaphoretic (increase sweat production) and can produce adverse dermatological effects, including pruritus, erythematous scaly eruptions, and urticaria (141). There appear to be no published case reports of adverse skin reactions following the use of herbal preparations applied cutaneously. However, in an open study on 45 patients with chronic eczema, who were treated four times daily for 3 weeks with a proprietary ointment (Cefabene®) containing an ethanolic extract of the crude drug, 1 patient experienced a burning sensation in the skin after application. This was considered to possibly have been a reaction to the ethanol present in the ointment (147). In another open study involving 536 patients diagnosed with atopic eczema, contact dermatitis, or other types of eczema, who were treated with the same proprietary ointment, 23 patients experienced local side-effects, including a burning sensation in the skin and erythema; 1 patient developed urticaria (148).

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