

Contact dermatitis as an adverse reaction to some topically used European herbal medicinal products – Part 2: *Echinacea purpurea*–*Lavandula angustifolia**

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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 has been produced. Part 2: *Echinacea purpurea* Moench–*Lavandula angustifolia* Mill.

Key words: adverse drug reaction; contact dermatitis; *Echinacea purpurea*; *Hamamelis virginiana*; *Hedera helix*; herbal medicine; *Humulus lupulus*; *Hypericum perforatum*; *Juniperus communis*; *Lavandula angustifolia*; phytodermatitis.

Plant Sources of Some European Herbal Medicinal Products and the Adverse Skin Reactions They May Elicit – Part 2: *Echinacea purpurea*–*Lavandula angustifolia*

Echinacea purpurea Moench (syn. *Rudbeckia purpurea* L.); family Compositae (or Asteraceae)

Known commonly as purple coneflower, the flowering aerial parts of this plant are the source of the crude drug Echinaceae Purpureae Herba. However, in Europe, the

crude drug itself is not normally encountered, but rather ethanolic extracts of the herb or root ('tinctures'), and products prepared from the dried expressed juice (1). Historically, at least two other species of *Echinacea* may have been collected and mislabelled as *E. purpurea*, namely *Echinacea angustifolia* DC. and *Echinacea pallida* Nutt, and much of the early research reported for *E. angustifolia* and *E. purpurea* was probably actually conducted on *E. pallida* (2). Furthermore, some authorities now believe *E. angustifolia* to be a variety of *E. pallida*, naming these two taxa as *E. pallida* Nutt. var. *angustifolia* Cronquist and *E. pallida* Nutt. var. *pallida*, respectively (3). Notwithstanding this confusion, these three taxa are now individually recognized as sources of crude drugs in Europe, providing Echinaceae Angustifoliae Radix, Echinaceae Pallidae Radix, Echinaceae Purpureae Herba, and Echinaceae Purpureae Radix, which have accordingly been made the subjects of individual Community herbal monographs (4).

Although indigenous to the United States and south central Canada, these plants, and *E. purpurea* in particular, are widely cultivated for medicinal use, as garden ornamentals, and for cut flowers. They were traditionally used as herbal remedies by the Great Plains Indian tribes of North America. Later, settlers from Europe also recognized *Echinacea* species as useful remedies both when

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taken internally and when applied externally for a variety of conditions, including rattlesnake bites and other venomous bites and stings, septic wounds, burns, abscesses, colds, catarrh, tonsillitis, pyorrhoea (periodontitis), and many other conditions (2, 5, 6). The Community herbal monographs now recognize the use of orally administered preparations only for the short-term supportive treatment of the common cold. However, it should be noted that the value of echinacea preparations in the treatment of colds has not been unequivocally established (7).

The Community herbal monograph on Echinaceae *Purpureae Herba* additionally recognizes a traditional use for the external treatment of small superficial wounds (1). Specifically, the monograph recognizes the use for no more than 1 week of an ointment containing the dried juice expressed from the fresh herb.

The Community herbal monograph (1) acknowledges that contact dermatitis may occur following cutaneous use of *E. purpurea* preparations. However, published case reports appear to be lacking. In a study of 1032 consecutive or randomly chosen patients in Dutch patch test clinics in 1988–1989, 2 patients reacted to a proprietary ointment containing 'Echinacea tincture 10%', reportedly prepared from *E. angustifolia* (8). The significance of this observation is diminished because proper authentication of the patch test material was seemingly not carried out, and nor were tests carried out with the Echinacea tincture alone.

In view of the claimed immune stimulant activity of echinacea products (2, 9), it is perhaps surprising that reports of allergic side-effects are not more commonly encountered either following topical exposure or following oral administration. A case of echinacea-associated anaphylaxis in an atopic woman in Australia was reported in 1998 (10). In a later report, 5 cases of adverse reactions to echinacea products in Australia were evaluated comparatively. Three of the patients had positive prick test results. A further 51 Australian adverse drug reports implicating echinacea were then reviewed. Observed reactions included cases of anaphylaxis, acute asthma, and urticaria/angioedema. Four patients were hospitalized, 4 reacted after their first known exposure, and 1 suffered multiple progressive systemic reactions. In a follow-on study, 20 of 100 atopic subjects who had never taken echinacea products also had positive prick test reactions. Atopic subjects were over-represented in those experiencing adverse reactions. Accordingly, it was concluded that atopic patients should be advised of the risks associated with oral exposure to echinacea products (11). In 2001, a case of recurrent erythema nodosum that was temporally and perhaps causally associated with the oral use of echinacea as a herbal therapy

was reported from Canada (12); and in 2004, a flare of pemphigus vulgaris in a 55-year-old male was correlated with ingestion of a herbal supplement containing echinacea that he began taking after he developed an upper respiratory tract infection (13).

It is generally thought that no single constituent or group of constituents is responsible for the activities of echinacea. Rather, several groups of constituents (the alkamides, caffeic acid derivatives, polysaccharides, and alkenes/polyenes) appear to contribute to activity (6). Similarly, the constituent(s) responsible for the adverse effects remain unidentified.

***Hamamelis virginiana* L.; family Hamamelidaceae**

This species, commonly known as witch hazel, forms a deciduous shrub or small tree. It is native to eastern North America from Nova Scotia to Florida and as far west as Texas, but is cultivated in Europe and elsewhere as a garden ornamental. The leaves and the bark are the source of the crude drugs *Hamamelidis Folium* (14) and *Hamamelidis Cortex* (15), respectively. A herbal preparation known as *Aqua* (or *Liquor*) *Hamamelidis*, hamamelis water, distilled witch hazel or just 'witch hazel', which is an aqueous ethanolic distillate prepared from the fresh leaves and bark or from the dried twigs, is also the subject of a Community herbal monograph (16). The plant material used commercially to prepare the crude drugs and herbal preparations is obtained mainly from the eastern United States and Canada (17).

The leaves contains 3–10% tannins (catechins and gallotannins, plus cyanidin and delphinidin-type proanthocyanidins), flavonoid galactosides and glucuronides, flavonoids including kaempferol, quercetin, quercitrin, and isoquercitrin, and 0.01–0.5% volatile oil. The bark contains 8–12% tannins, small amounts of flavonols, and ~0.1% volatile oil. It is richer in hydrolysable tannins, whereas the leaves mainly contain condensed tannins. *Hamamelis* water is a clear, colourless liquid containing 13–15% ethanol, and has the characteristic odour of the volatile oil distilled from the plant material. Thus, in addition to water and alcohol, hamamelis water contains steam-volatile substances, including α -ionones, β -ionones, hexen-2-al, and 6-methyl-3,5-heptadiene-2-one (18), which are known collectively as 'hamamelis ketone'. It contains no tannins (17), and therefore lacks the astringent properties of leaf and bark preparations.

Historically, decoctions prepared from hamamelis bark were used by North American Indians to prepare poultices for use on 'swellings and tumours of a painful character', as well as for 'external inflammations'. The decoction of the bark is astringent (because of the tannins

it contains), and has been used to treat 'haemoptysis, haematemesis and other haemorrhages', as well as 'diarrhoea, dysentery and excessive mucous discharges', haemorrhoids, 'old, flabby, fetid ulcers', 'sore mouth', and other such conditions (19).

It would appear that the supposed virtues of distilled witch hazel were invented by the pharmaceutical industry in the late 1800s, when a proprietary preparation was originally introduced (20). Subsequently, a non-proprietary preparation was made the subject of pharmacopoeial monographs in the United States and the United Kingdom (i.e. *Liquor Hamamelidis*), but then seemingly fell out of favour. The preparation appeared in a list of suggested deletions from the British Pharmacopoeia (21), because it was considered to be 'little more than a weak solution of alcohol'. Shortly thereafter, in 1918, the United States Dispensatory (22), in describing its uses, noted that 'This water was probably introduced into the British Pharmacopoeia and US Pharmacopoeia IX on account of the large demand for it which has grown out of the wide advertisements of a certain proprietary medicine, and the universally recognized need in American families for an embrocation which appeals to the psychic influence of faith. As the tannic acid of hamamelis bark does not come over into the distillate the water is therapeutically a mixture of water and alcohol, the volatile oil being found in too minute a proportion to possess any therapeutic value.' Nevertheless, this preparation continues to be widely recommended as a soothing, astringent application for sprains and bruises, as a haemostat for small superficial wounds, and as an application for minor skin irritation, authors [see, for example (18, 23)] inadvertently perpetuating the notion that distilled witch hazel is endowed with the healing properties associated with the tannin-containing preparations.

The Community herbal monograph (16) recognizes the traditional use of distilled witch hazel for relief of minor skin inflammation and dryness of the skin, and for the temporary relief of eye discomfort resulting from dryness of the eye or exposure to wind or sun. In both applications, the distillate is diluted before use, to a strength corresponding to 5–30% in a semi-solid preparation for cutaneous use, and 1:10 in eye drops for ocular use. In addition, the Community herbal monograph recognizes the traditional use of herbal preparations (variously: tinctures, decoctions, dry extracts, and liquid extracts) of hamamelis leaf (14) and hamamelis bark (15) for relief of minor skin inflammation and dryness of the skin, for symptomatic relief of itching and burning associated with haemorrhoids, and as a mouthwash and gargle for relief of minor inflammation of mucous membranes of the oral cavity.

'Hamamelis' has been described (24) as being one of the less common causes of allergic contact dermatitis-conjunctivitis. No positive patch test reactions to 'Hamamelis virg. 10% in petrolatum' were observed in a series of 280 consecutive eczema patients (25). In a series of 1032 consecutive or randomly chosen patients in Dutch patch test clinics in 1988–1989, 2 patients reacted on patch testing with Hamamelis™, a proprietary ointment containing 'Hamamelis extract 25%' used for treating haemorrhoids. A further 2 patients reacting to this ointment may have been reacting to the wool fat in the ointment base (8). A non-atopic woman who developed contact allergy to an unspecified proprietary 'eye gel' reacted when patch tested with the 'witch hazel distillate' that it contained. Five control subjects did not react to the eye gel (26). The identity of the sensitizer(s) in witch hazel preparations remains unknown.

***Hedera helix* L.; family Araliaceae**

This well-known plant is the common ivy, an evergreen ground covering and climbing woody vine. It is native to most of Europe and western Asia, but is found worldwide, becoming a noxious weed where conditions suit its growth (27). Selected cultivars are also widely grown as house plants and as garden ornamentals.

The leaves are the source of the crude drug *Hederae Helicis Folium*, otherwise known as *Herba Hederae Helicis*. Historically in the United States, the leaves and the berries have been used medicinally, applications of the leaves having been recommended for 'sanious ulcers' (i.e. those yielding a thin, fetid discharge of pus mixed with serum or blood), 'cutaneous eruptions', 'tetter', and itch, and the berries were said to be purgative and even emetic (22). In Europe, the internal use of the leaves has been deprecated, whereas the utility of a decoction prepared from the leaves for washing and in poultices against vermin, scabies, skin diseases, ulcers and abscesses has been acknowledged (28). More recently, however, the leaves and the berries have become recognized as a stimulating medicine for chronic catarrh, bronchitis, and, especially, whooping cough (29). Applied externally, ivy preparations are said to moderate the sensitivity of the peripheral nerves, thus finding a use in the external treatment of rheumatism, neuritis, neuralgia and particular 'cellulagias' (i.e. neurotrophic manifestations that include subcutaneous tenderness and thickening) (29).

The most important constituents of *H. helix* are bidesmosidic triterpene saponins based on hederagenin, 2 β -hydroxyhederagenin (also known as bayogenin), and oleanolic acid. The main saponin is hederasaponin C (also known as hederacoside C). Monodesmosides such as

α -hederin can develop by hydrolytic cleavage when fresh leaves are dried. In addition, *H. helix* leaves have been reported to contain flavonoids (quercetin, kaempferol, etc.), caffeic acid derivatives and other phenolics, such as caffeic acid and dihydroxy-benzoic acid, the coumarin glycoside scopolin, phytosterols (stigmasterol, sitosterol, cholesterol, campesterol, and α -spinasterol), and polyacetylenes, including falcarinone, falcarinol, dihydrofalcarinol, and dihydrofalcarinol (29–32).

The Community herbal monograph (33) recognizes a well-established and traditional use of various aqueous ethanolic extracts/preparations of the leaf of *H. helix* as expectorants 'in case of productive cough' and 'in cough associated with cold'. No external/dermatological uses are recognized, and listed undesirable effects include allergic skin reactions, that is, skin rashes and urticaria, and couperoses (i.e. broken capillaries and telangiectasia). Interestingly, various leaf and stem extracts of *H. helix* (CAS no. 84082-54-2) are recognized in Europe as cosmetic product ingredients with a skin-conditioning, hair-conditioning, astringent and/or antidandruff function (34). It follows that, in Europe, cosmetic products are more likely to be the cause of adverse reactions to *H. helix*-derived materials than herbal medicines. However, the dermatological literature describes almost exclusively reactions in gardeners, tree surgeons, horticulturalists and the like following contact with freshly damaged plant material (27, 35).

Leaves of the common ivy already had a reputation as a remedy for treating corns when a case was reported from Australia at the end of the 19th century of intense skin irritation developing after application of ivy leaves soaked in vinegar to a patient's toes each night for a week. Three further attacks of dermatitis occurred after she handled wet ivy leaves (36). The skin-irritating properties of common ivy were, at that time, already known to gardeners in England (37). Further reports quickly appeared in the Australian, French and German literature (38–41), and then sporadically over the next 40 years from the United States (42–44) and Spain (45). More recent patch test studies have shown sensitivity to *H. helix* in Australia (46), South Africa (47), and England (48, 49). Individual cases have been reported from Italy (50), England (51, 52), Switzerland (53), Denmark (54, 55), Spain (56, 57), and Germany (58). It has also been recognized that patients sensitized to Algerian ivy (*Hedera algeriensis* Hibberd) react similarly to *H. helix* (59, 60), and that patients sensitized to *H. helix* may react to several other plants in the family Araliaceae (56, 61, 62) and also to carrots (*Daucus carota* L., family Umbelliferae) (56, 63).

The contact allergens of *H. helix* have been identified in guinea-pigs (64) as the polyacetylenes falcarinol and

dihydrofalcarinol. Irritancy at higher concentrations was observed. The isolated substances elicited reactions in patients being investigated for sensitivity to *H. helix*. The allergenicity of falcarinol has also been shown in human volunteers (32). A number of patch test studies in patients being investigated for sensitivity to *H. helix* (32, 48, 56, 57, 64, 65) have now shown reactivity to falcarinol and to dihydrofalcarinol.

Rarely, urticarial reactions following skin contact with *H. helix* leaf extracts (54, 66) and anaphylaxis following ingestion of a commercial ivy syrup product (67) have also been reported, but the identity of the responsible agent(s) remains to be established. An intense scarlatiniform rash associated with hallucinations, and with delirium and clonic convulsions alternating with stupor, occurred in a 3.5-year-old boy who had eaten a quantity of ivy leaves (68).

It may be deduced from the literature that sensitization to *H. helix* is predominantly a hazard for gardeners, horticulturalists, and those involved in similar such occupations who come into contact with damaged plant material (35, 49, 51, 52, 65). However, falcarinol has been detected in a *H. helix* extract-containing cosmetic product, so it is possible that individuals who have become sensitized through contact with damaged *H. helix* (knowingly or unknowingly) could react to such products (64).

***Humulus lupulus* L.; family Cannabaceae**

This plant is the common hop, botanically a climbing bine, which is best known for its fragrant green-coloured flower cones (hop 'strobili' or 'strobiles') used in the brewing industry for making beers. The dried flower cones also provide the crude drug *Lupuli Flos* or *Flores Humuli Lupuli* (69). The Community herbal monograph (70) recognizes the traditional use of *Lupuli Flos*, administered orally, for the relief of mild symptoms of mental stress and to aid sleep. Historically, hops have also been applied topically in the form of a fomentation or poultice to treat 'painful swellings and tumours' (71, 22). Although no dermatological uses are recognized in the Community herbal monograph (70), various extracts and oils from *H. lupulus* (CAS no. 8060-28-4; CAS no. 8007-04-3) are recognized in Europe as cosmetic product ingredients with skin-conditioning, hair-conditioning, perfuming, masking and other functions (34). It follows that, in Europe, cosmetic products are more likely to be the cause of adverse skin reactions to *H. lupulus*-derived materials than herbal medicines.

The sedative properties of hops have been recognized for at least 180 years. An early report (72) described a case of a 14-year-old girl who had been engaged in hop-picking for a week. Because her hands were cold and

chapped, she placed them in the hop-bin to warm them. Shortly afterwards, she felt tingling and smarting on the hands. The affliction was spread to her face because of her habit of passing her hand over her forehead to arrange her hair. She became somnolent and had visual disturbances. Her face became deeply erythematous and swollen. By the next evening, her hands and face were covered with vesicles. Since that time, dermatoses associated with hop-picking have been described in many other reports. Systematic studies of occupational hop-related skin diseases have been carried out in the United Kingdom (73) and in eastern Europe (74, 75).

A case has been described of airborne dermatitis caused by hops in a 57-year-old female farmer (76) who also experienced acute dermatitis of the hands. Prick tests with saline and glycerol extracts of hop leaves and cones gave positive results, and a glycerol extract of the hop cones produced positive patch test reactions at 48 and 72 hr. Relapses of her dermatitis occurred upon connubial exposure to hop allergens on her husband, and to hop extract present in an externally applied beauty cream and in an orally administered herbal sedative.

A further case has been described (77) of a patient who complained of urticaria on both hands while working with ripe dried hops, although not with fresh ones. Type 1 allergy was confirmed by prick test and specific IgE. The patient also had a history of urticaria–angioedema immediately after oral peanut (*Arachis hypogaea* L., family Leguminosae), banana (probably a triploid, so-called AAA group cultivar of *Musa acuminata* Colla, family Musaceae) and chestnut (*Castanea sativa* L., family Fagaceae) intake.

The causative agents of hop-induced contact skin reactions remain to be established. However, it is evident that both irritant and allergic effects have been described. In hop pickers, the dermatitis has been attributed (78, 79) to mechanical abrasion by the rough hairs on the climbing stem. It has also been suggested (78) that lupulin, a yellow powdery secretion of the glandular hairs on the scales of the hop cones, may be responsible for the irritation. From a study carried out in a hop pickers' hospital, it was concluded that at least three distinct conditions were associated with hop-picking, namely 'hop rash', 'hop eye', and 'hop gout' (80). Hop rash was believed to arise from the inevitable inoculation into the innumerable scratches on the skin of hop pickers of proteins in hop juices and hop pollen. A study carried out in Herefordshire (United Kingdom) (73) obtained positive patch test reactions to fresh hop oil (in 6 of 18 tests), aged hop oil (in 1/18), hop cones (in 6/18), humulone (in 2/18), and lupulone (in 2/18). Fresh hop oil contains ~40% β -myrcene, but this compound disappears from aged hop oil (81). It is on

the basis of these observations that β -myrcene, humulone and lupulone have been assumed to be the low molecular weight allergens in hop oil.

***Hypericum perforatum* L.; family Hypericaceae**

This plant is commonly known as St John's wort, this name referring to the day, St John's day (i.e. midsummer day, June 24), on which the plant is normally seen to be flowering. It is a perennial herb with yellow flowers, and is indigenous to Europe and West Asia (82). The flowering tops of the plant, dried, provide the crude drug *Hyperici Herba* (83).

Both well-established and traditional uses of herbal substances/herbal preparations derived from St John's wort are recognized in Community herbal monographs. Thus, the oral use of herbal preparations of St John's wort for the treatment of mild to moderate depressive episodes is considered to be well established (84). In addition, three traditional uses are recognized, namely oral use of herbal preparations for the relief of temporary mental exhaustion, oral use for the symptomatic relief of mild gastrointestinal discomfort, and cutaneous use for the symptomatic treatment of minor inflammations of the skin (such as sunburn) and as an aid in healing of minor wounds (85). Interestingly, it is believed that use of St John's wort on wounds might have a basis in the doctrine of signatures, which suggested that a 'wounded' (perforated: *H. perforatum*) plant is intended by nature to cure wounds (86). Uses of externally applied St John's wort preparations for several other conditions, with a basis in folk tradition and medical experience, have been described in the popular and medico-scientific literature (83, 87). These other conditions include bruises, ulcers, varicose, haemorrhoids, myalgia, sciatica, rheumatism, lumbago, cramps, and keloid scars.

The phytochemistry of St John's wort is well documented. With reference to the dried drug, phloroglucinol derivatives, principally hyperforin, adhyperforin, and furanohyperforin, account for 0.2–4% by weight; naphthodianthrones, mainly pseudohypericin and hypericin, protohypericin, protopseudohypericin, cyclopseudohypericin, and skyrin derivatives, account for 0.06–0.4%; flavonoids, mainly quercetin glycosides, account for 2–4%; and procyanidines and tannins account for 6–15%. Also present are small quantities of caffeoylquinic and *p*-coumaroylquinic acids, and an essential oil containing, among other volatiles, 2-methyloctane and α -pinene (82, 83).

'Hypericum oil', otherwise known as *Hyperici Oleum*, is not the essential oil but a liquid extract of the crude drug prepared by using a vegetable oil such as olive oil, sunflower oil, linseed oil or wheat germ oil as a

solvent. The liquid extract is then allowed to ferment during storage in a warm sunny place for ~6 weeks until the oil is bright red. It has been reported that Hyperici Oleum does not contain hypericin, the red colour being ascribed to breakdown products of hypericin (88). Hypericum Perforatum Extract (CAS no. 84082-80-4) and Hypericum Perforatum Oil (CAS no. 68917-49-7; CAS 84082-80-4) are recognized in Europe as cosmetic product ingredients with 'astringent/soothing/skin protecting/tonic/antimicrobial/masking' and emollient functions, respectively (34). However, there is much confusion regarding the nature of various extracts and preparations described in the literature. Infusions of the herb or flowers in a bland fixed oil such as olive oil are sometimes described as Hypericum Perforatum Extract and sometimes as Hypericum Perforatum Oil. Furthermore, a fixed oil can be extracted or expressed from the seeds of the plant and, as noted above, a volatile oil can be distilled from the whole plant, each of these also being described as Hypericum Perforatum Oil. The term Hypericum Perforatum Extract may also refer to a product prepared by solvent (e.g. methanol or ethanol) extraction of the capsules, leaves, and stem heads, followed by evaporation of the solvent. Therefore, care has to be taken to determine exactly how extracts have been prepared when interpreting the literature on this subject.

The potential of St John's wort preparations to cause adverse skin reactions in humans has to be viewed in the context of the well-known propensity of several *Hypericum* species to, on ingestion by animals, produce primary photosensitization – a condition known as hypericism – following absorption of hypericin (89–92). Presumably because St John's wort is not eaten as a culinary herb, photosensitivity resulting from ingestion of the plants has not been observed in humans. Photosensitivity was also not observed in a prospective randomized study of patients taking *H. perforatum* extract at doses used for the treatment of depressive disorders (93). However, photosensitivity/skin reddening/erythroderma/itching has very occasionally been reported in patients taking St John's wort extracts medicinally (94–99).

In a report on the safety of Hypericum Perforatum Extract and Hypericum Perforatum Oil, produced for review by a self-styled Cosmetic Ingredient Review Expert Panel in the United States (100), the results of dermal irritation, sensitization and photosensitization tests were reported. The materials tested were described (unfortunately, rather inadequately) as 'a mixture of Hypericum Perforatum Extract (1–5%), olive (*Olea Europaea*) oil (>50%), and tocopherol (<0.1%)' and 'a mixture containing Hypericum Perforatum Oil, butylene glycol, and water (percentages not specified)'. These

preparations were found variously to be non-irritating, non-sensitizing and not phototoxic when applied to rabbit or guinea-pig skin. However, it was reported that Awassi sheep fed the flowers for 14 days did show signs of dermal and generalized toxicity.

A case of contact dermatitis has been reported in a trapper in Australia (101), who complained of extensive dermatitis of the exposed parts, which he suspected had been caused by (a botanically unidentified) St John's wort. He showed a blister-like reaction when patch tested with the plant. The reaction was very severe, and took several days to subside when the patch was removed. Contact phototoxicity of a 1% dispersion of hypericin has been shown on mouse ears; the activity of the hexa-acetate ester of hypericin was also investigated, this substance being found to be similarly active at 60-fold greater dilution (102).

A patient with multiple solar keratoses, after undergoing laser treatment with a Q-switched frequency doubled Nd:YAG laser at 532 nm, developed a severe phototoxic reaction to the laser light. She was also treated for facial telangiectasia by use of a pulsed dye laser emitting at 585 nm, to which she also developed an exaggerated and unexpectedly severe response. It transpired that the patient was taking St John's wort at the time of the laser treatment. Medication with St John's wort was stopped, and treatment with the same energy fluence and wavelength was carried out a month later, with no untoward effects. Also, potential problems with the copper vapour laser (578 nm) and with the krypton ion laser (532 and 568 nm) were considered to be likely in patients taking St John's wort (103). Similarly, orally administered St John's wort extract containing hypericin has been found to lower the erythema threshold to ultraviolet (UV) A (104) and UVB (105) irradiation. Finally, some success in the photochemotherapy of vitiligo by oral administration and topical application of St John's wort extracts has been claimed (106, 107). As photodynamic therapy is used as a treatment for psoriasis, a combination of phototherapy with St John's wort or purified/synthetic hypericin rather than psoralens might be an option, but clinical evidence for such the efficacy of such use is still missing (87). However, a study of the clinical effect of topical *H. perforatum* ointment without light exposure in 10 patients with plaque-type psoriasis has been undertaken. Erythema, scaling and thickness were evaluated; all were significantly lower where the formulated ointment had been applied (108).

***Juniperus communis* L.; family Cupressaceae**

This plant is the common juniper, an evergreen shrub or small tree that is widely distributed in the northern hemisphere, from Arctic to Mediterranean latitudes. It

has needle-like leaves and bears berry-like cones commonly known as juniper berries. These cones, dried, provide the crude drug *Juniperi Pseudo-fructus*. The essential oil obtained by steam distillation of the ripe cones is known as *Juniperi Aetheroleum*, *Juniperus Communis* Oil, juniper berry oil, or, simply, juniper oil (109). Both *Juniperi Pseudo-fructus* (110) and *Juniperi Aetheroleum* (111) are the subjects of Community herbal monographs.

In the field of cosmetics, *Juniperus Communis* Extract (otherwise known as *Juniperus Fruit Extract*; CAS no. 84603-69-0) and *Juniperus Communis* Oil [otherwise known as *Juniperus Communis Fruit Oil* (CAS no. 73049-62-4) and *Juniper Communis Berry Oil* (CAS no. 8002-68-4)] are recognized as cosmetic product ingredients with 'tonic/deodorant/masking' functions (34). Confusingly, in the context that wood and leaf oils are very different in *Juniperus* species (112), CAS no. 84603-69-0 also refers to other kinds of extracts from other parts of the *J. communis* plant, for example *Juniperus Communis* Wood Oil and *Juniperus Communis* Branch/Fruit/Leaf Extract. Therefore, CAS numbers cannot be relied upon as indicators of the chemical composition of these cosmetic products.

No well-established uses, but only traditional uses, of herbal substances/herbal preparations derived from *J. communis* are recognized in Community herbal monographs. As regards cutaneous use, the only indication recognized refers to the use of the essential oil (juniper berry oil) as an adjuvant in the relief of minor muscular and articular pain. For this indication, 1–1.5 g of juniper oil is used as a bath additive three or four times weekly in a full bath for 10–20 min at 35–38°C (111).

The composition of the essential oil is well documented. Over 100 constituents have been reported. As with all essential oils, the composition can vary with geographical source, but, typically, the oil comprises ~58% monoterpenes, these being mainly the monoterpene hydrocarbons α -pinene, β -pinene, β -myrcene, sabinene, and limonene. Monoterpene alcohols, including terpinene-4-ol and terpineol, are also present in the oil, together with various sesquiterpene hydrocarbons, including β -caryophyllene, α -muurolene, and γ -muurolene (109). Because these volatile oil constituents are found in a multitude of other plant-derived volatile oils/fragrances, the possibility of cross-reaction with juniper berry oil in patients who are contact-sensitive to one or other of those oils has to be expected.

Undiluted juniper berry oil applied to the backs of hairless mice and swine was not irritating, but was moderately irritating when applied to intact or abraded skin of rabbits for 24 hr under occlusion. No phototoxic effects were reported for undiluted juniper berry oil on hairless

mice and swine (113, 114). Juniper Extract (undiluted leaf extract) applied to the dorsal skin of 25 human volunteers in photopatch tests did not induce irritation, photoaggravation, or phototoxicity (115).

Skin irritation was observed in 2 of 20 subjects patch tested (24 hr of application) with an aged sample of juniper berry oil (116). Juniper berry oil (8% in petrolatum) produced no skin irritation after a 48-hr closed patch test on human subjects (113, 114).

In a human maximization test, no evidence of sensitization was observed in any of the 25 subjects tested with 8% juniper berry oil in pet. (113). In a more recent study, 86 of 299 patients with allergic reactions to an International Contact Dermatitis Research Group perfume mixture containing one essential oil and seven other fragrance substances were tested with juniper berry oil and 34 other essential oils. Six of the 86 subjects were found to be sensitive to juniper berry oil (117). The identity of the allergen(s) was not determined.

A 53-year-old aromatherapist with an acute bilateral hand eczema was patch tested with working dilutions of essential oils. 'Juniper essential oil' (which may or may not have been juniper berry oil) at a concentration of 1% in grape seed oil did not elicit any reactions at 48 or 96 hr (118). A 47-year-old patient who, over a period of 25 years, had to enter a smokehouse repeatedly during the transportation of meat and sausage products developed both eczema of the face and hands and occupational asthma in response to a spice used in the production of sausages (containing juniper berry oil) and to a smoking powder used in the smoking of sausages (containing juniper). No further skin reactions or respiratory problems were observed after the patient began working in an office (119).

***Lavandula angustifolia* Mill. ssp. *angustifolia* (syn. *Lavandula officinalis* Chaix); family Labiatae (or Lamiaceae)**

Lavender, also known as English lavender, garden lavender, or true lavender, is a low-growing shrub that is native to southern Europe but is extensively cultivated worldwide as an ornamental plant and for the production of its essential oil (lavender oil), which is used mainly as a fragrance in cosmetic, domestic and professional products (120), but is also in aromatherapy (121, 122). Both the flowering tops of the plant and the essential oil obtained by steam distillation from the flowering tops are also used as traditional herbal remedies in Europe for the treatment of anxious restlessness, agitation, insomnia, and similar such conditions. Furthermore, lavender oil has been used for local massage in cases of rheumatism, gout, neuralgia, sciatica, and scabies (122).

The common name lavender is used loosely to refer not only to the two currently recognized subspecies of *L. angustifolia* but also to *Lavandula latifolia* Medik. (syn. *Lavandula spica* var. *latifolia* L.; otherwise known as spike lavender) and to numerous cultivars/hybrids between these species, known as lavandins and referred to botanically as *Lavandula* × *intermedia* Emeric ex Loisel. Perhaps understandably, the botanical name '*Lavandula vera*' is commonly but unauthoritatively used for describing the botanical source of 'true' lavender or lavender oil. However, true lavender is not *L. vera* DC., this name now being considered to be a synonym of *L. angustifolia* ssp. *pyrenaica* Guinea (123), otherwise known as the Pyrenean lavender.

Strictly, the term 'lavender oil' refers to the essential oil obtained by steam distillation from the flowering tops of *L. angustifolia* ssp. *angustifolia*; 'spike lavender oil' refers to the oil distilled from *L. latifolia*; and 'lavandin oil' refers to oils distilled from *Lavandula* × *intermedia* cultivars. Confusingly, the cosmetics industry has referred to lavandin plants botanically as '*Lavandula hybrida*' (124), from which the cosmetics ingredients Lavandula Hybrida Extract (CAS no. 91722-69-9) and Lavandula Hybrida Oil (CAS no. 8022-15-9) are supposedly derived (34). '*L. hybrida*' is not an accepted botanical name: *L. hybrida* E.Rev. ex Briq. is now recognized as a synonym of *L. angustifolia* Mill., that is, true lavender, not lavandin, whereas *Lavandula* × *hybrida* Balb. ex Ging. is a synonym of *Lavandula* × *heterophylla* Viv. (123), the sweet lavender, a hybrid believed to be derived from crossing *Lavandula dentata* L. with *L. angustifolia* Mill. (Plant List). Lavandula Intermedia Oil (CAS no. 92623-76-2), that is, lavandin oil, is also a recognized cosmetics ingredient. Furthermore, (true) lavender oil may be referred to as Lavandula Angustifolia Oil (CAS no. 8000-28-0 or 90063-37-9) or as Lavandula Officinalis Flower Oil (CAS no. 84776-65-8). Thus, care has to be taken when interpreting the results of published investigations, because the essential oils derived from these various species and cultivars do differ in their composition.

The principal components of lavender oil are monoterpenic alcohols (60–65%) and esters, comprising mainly (–)-linalool and (–)-linalyl acetate. Also present are *cis*-ocimene (3–7%), terpinene-4-ol (3–5%), limonene, cineole, camphor, lavandulyl acetate, lavandulol, α -terpineol, β -caryophyllene, geraniol, and α -pinene. Non-terpenoid aliphatic components include 3-octanone, 1-octen-3-ol and its acetate, and 3-octanol (122).

Community herbal monographs recognize the traditional oral use of both lavender flower preparations, namely *Lavandulae Flos* (125), and of lavender oil, namely *Lavandulae Aetheroleum* (126). Dermatological

use is also recognized, but only for lavender oil used as a bath additive (1–3 g of oil per full bath) for relief of mild symptoms of mental stress and exhaustion and to aid sleep, with a recommendation that the temperature of the bath should be 35–38°C and its duration 10–20 min. Notwithstanding the extensive skin contact with lavender oil that occurs during such 'balneotherapy', contact dermatitis appears not to have been reported following such exposure. In a blind study involving 635 women who used, variously, 'pure lavender oil' (botanical source not specified), 'synthetic lavender oil' (of unspecified composition) or 'an inert substance' (2-isobutyl-3-methylpyrazine) as a bath additive (six drops per bath, daily for 10 days) postnatally to investigate the effectiveness of balneotherapy as a means of reducing perineal discomfort, no side-effects were reported (127). However, 2 cases of facial dermatitis have been described in patients who used lavender oil to refresh a 'lavender pillow' being used to aid sleep (128). Also, 3 cases of gynaecomastia in prepubertal boys occurred after topical application of products containing lavender and tea tree oils – a 'healing balm' containing lavender oil, a styling gel containing lavender and tea tree oils, and a lavender-scented soap. The boys were aged between 4 and 10 years. Gynaecomastia resolved after use of the lavender-containing products was discontinued. Anti-androgenic activity of both lavender oil and tea tree oil was demonstrated *in vitro* by the use of MDA-kb2 human breast cancer cells stably transfected with an androgen-inducible and glucocorticoid-inducible mouse mammary tumour virus–luciferase reporter plasmid (129).

Formal studies involving human test subjects suggest that lavender oil is benign upon skin contact. At a concentration of 16% in pet., lavender oil did not produce any irritation after 48 hr in a closed patch test and produced no sensitization reactions in a human maximization test (130). Similar negative results were obtained with 5% lavandin oil (124), 10% lavender absolute (131), and 8% spike lavender oil (132), each in pet. In a series of evaluations of linalool, linalyl acetate and a number of other linalyl esters for skin irritation in male and female volunteers, no irritation was observed in a 48-hr closed patch test with 20% linalool in pet. or in a 48-hr semi-occluded patch test with 32% linalyl acetate in acetone. However, mild irritation was observed in a 48-hr semi-occluded patch test with 32% linalool in acetone. No reactions were observed in the human maximization test with 20% linalool in pet. in 25 male volunteers, but 3 positive reactions were observed with some samples of linalyl acetate (10% in pet.) tested in a total of 131 volunteers. It should also be noted that linalool and

linalyl acetate (100% concentration) have both been shown to be irritant on prolonged contact (20 hr) with rabbit skin, but, inconsistently, some studies reported no irritation, whereas others reported mild or severe irritation (133).

Prospective testing with linalool, linalyl acetate and lavandin oil (each at 1% and 5%) in cohorts of 100 consecutive patients attending European patch test clinics failed to elicit any allergic reactions (134). However, in other similar prospective studies of consecutive patients, 6 of 1147 showed positive patch test reactions to 1% lavender oil in pet. (135), and 4 of 200 showed positive patch test reactions to 2% lavender oil in pet. (136). In investigations of patients presenting with cosmetic or medication use-related or occupationally acquired allergic contact dermatitis, lavender, spike lavender and lavandin oils and their components linalool, linalyl acetate, geraniol, etc. are often found to elicit positive patch test reactions in patients who have been exposed to these oils (137–150). A recent systematic review of case reports and case series of adverse effects associated with aromatherapy found that the most common adverse effect was dermatitis, and that lavender oil (and also peppermint, tea tree oil, and ylang-ylang oils) was found to be among the most common essential oils responsible for adverse effects (151). An epidemiological study conducted in Japan showed an increasing incidence of positive patch test reactions to lavender oil, with the incidence rising from 1% to 14% over a period of 9 years in patients being investigated for cosmetic use-related allergic contact dermatitis, this rise seemingly being associated with a similar rise in the use of lavender oil in aromatherapy (152). In a 6-year study of cosmetics product allergens in Japan (153), lavender oil (and also ylang-ylang, cananga and geranium oils,

and jasmine absolute) was found to be among the most common causative agents.

The inconsistency of findings in formal studies of irritancy and allergenicity and in multicentre prospective studies can now be explained in light of the finding that lavender oil (154) and its components linalool (155–158), linalyl acetate (159) and geraniol (160) are susceptible to autooxidation in air to form peroxides and hydroperoxides that have been shown to be potent contact allergens. In a recent multicentre study (161) involving 4731 consecutive patients in 13 UK dermatology departments who were patch tested with both stabilized limonene and linalool and with the hydroperoxides of these terpenes, 12 patients (0.3%) showed positive patch test reactions to stabilized linalool. In contrast, 281 (6%) reacted to linalool hydroperoxides, prompting the observation that non-oxidized linalool and, by extension, good-quality fresh lavender oils are liable to produce false-negative patch test reactions.

Because of this finding that is the air oxidation products of lavender oils that are mainly responsible for adverse skin reactions to the oils, the International Fragrance Association has, since 2009, recommended the addition of an antioxidant – 0.1% butylated hydroxytoluene or α -tocopherol – to lavender oil at the time of production of the raw material to limit the formation of sensitizing peroxides (162). Also, since the seventh Amendment to the Cosmetics Directive 76/768/EEC made in 2003 (163), and subsequently transposed into Regulation (EC) No. 1223/2009 (164), it has been mandatory in Europe to declare the presence of linalool and geraniol in the lists of ingredients on cosmetics products if their concentration exceeds 0.001% in leave-on products and 0.01% in rinse-off products.

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