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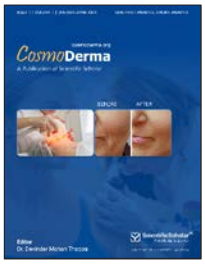

Review Article

Perfumes and associated allergens: A brief review

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Received : 22 January 2022
Accepted : 02 February 2022
Published : 23 February 2022

DOI
10.25259/CSDM_9_2022

Quick Response Code:

ABSTRACT

A perfume (Latin, *perfumare* for smoke through) is essentially a cosmetic product to be used on the human body for its pleasing scent to mask body odor and have a feeling of freshness. A perfume is composed of fragrances which are aromatic compounds and essential oils, and solvents and fixatives. These fragrances are chemicals or are derived mostly from botanical sources. A perfume that usually consists of a few to hundreds of fragrance materials remains a major source of contact allergy from them. Everyone comes in contact with fragrance materials in daily life either directly from the application of a product to the skin, mostly cosmetics, or occasionally after contact with fragrance-containing household or other personal care products. Cosmetics and personal care products such as personal perfume(s), deodorant, aftershave lotion/gel, eau de cologne, and eau de toilette with the highest ever concentrations of fragrances remain the major source of contact sensitivity from fragrances. The adverse effects associated with the use of perfumes are both allergic and irritant contact dermatitis, pigmented contact dermatitis, phototoxicity and photoallergy, and contact urticaria. Systemic toxicity may also occur following inhalation and ingestion of fragrance(s) causing respiratory illness, headache, and attacks of migraine. However, allergic contact dermatitis and pigmented contact dermatitis remain by far the commonest cutaneous adverse effects. Colophony, *Myroxylon pereirae*, lanolin, formaldehyde, vanillin, musk mix, rose oil, cetostearyl alcohol, and more than 160 fragrances, both single and complex mixtures of chemicals (methyl ionones), or essential oils (*Evernia furfuracea* (treemoss) extract, *E. prunastri* (oakmoss) extract, *Ferula galbaniflua* gum, *Narcissus poeticus* flower extract, and *Viola odorata* leaf extract) have caused cosmetic contact sensitivity in most instances. Ylang-ylang oil, jasmine absolute, Cananga oil, benzyl salicylate, hydroxyl citronellal, sandalwood, and geraniol are common fragrances to cause pigmentary changes. This review highlights the composition of perfumes and constituent fragrances identified commonly as allergens. A brief insight is also provided for the diagnosis of allergic contact sensitivity from fragrances and present safety regulatory status.

Keywords: Allergens, Allergic contact dermatitis, Cosmetics, Fragrance allergens, Fragrances markers, Patch test, Perfumes

INTRODUCTION

A perfume (Latin, *perfumare* for smoke through) is essentially a cosmetic product to be used on the human body for its pleasing scent to mask body odor and have a feeling of freshness. A perfume is composed of aromatic compounds, essential oils, solvents, and fixatives to give a pleasant fragrance to the human body or flavor to foods. There are about 2500 different fragrance ingredients used today to compose perfumes and a perfume which usually consists of 10–100 or even more fragrance ingredients remain a major source of contact allergy from them.[1] In day-to-day life, everyone comes in contact with fragrance materials either directly from the application of a product, mostly cosmetics, to the skin or occasionally from contact with fragrance containing household objects, or personal grooming products used by partners and peers.

Because of direct application and/or after contact with an allergen-contaminated surface, the fragrance ingredients, particularly in cosmetics, cause allergic contact dermatitis mostly involving the hands and /or face. The cosmetic allergens may also come in contact with the skin from a product used by the spouse or other person (connubial or consort dermatitis), airborne vapors or droplets (airborne contact dermatitis), or their accidental transfer via contaminated hands to more sensitive areas such as the eyelids (ectopic dermatitis). Sunscreen chemicals used as such or as ingredients in other cosmetics such as fairness cosmetics often interact with *Myroxylon pereirae* (balsam of Peru), cinnamic acid, cinnamic aldehyde, and cinnamon oils, the common fragrance additives, can lead to contact dermatitis.[2,3] Systemic exposure may also occur following inhalation or ingestion of fragrance fortified products of daily use or flavored foods and beverages.[4,5] However, most individuals can tolerate perfumes and perfumed products well without experiencing allergic reactions even after continuous exposure to fragrances with well-established potential to cause contact sensitivity and allergic contact dermatitis.[6] Herein, we briefly review the composition of perfumes and their fragrances commonly identified as allergens that have caused allergic contact reactions.

History of perfumes

The history of perfumes dates back to antiquity when scented balms and ointments were blended for Egyptian elites who otherwise routinely used fragrant oils, considered as the sweat of the sun God Ra, for cleansing and bathing. Ancient Romans used incense for religious ceremonies and sprinkled rose-scented water to mask the foul smell of city life. The ancient Greeks believed that fragrances improved health and vitality and wearing a sweet-smelling fragrance was pleasing to the Gods. The use of scents also spread throughout the ancient world and to other cultures including the Iranians and Chinese. The use of perfume and art of perfumery in India dates back to Indus civilization (3300–1300 BC) and finds mention of *Ittar* in ancient Indian texts of Charaka Samhita and Sushruta Samhita. Although Hungarians were first to introduce modern perfume, the modern-day perfumery evolved more in France that till date remains the center of the European perfume trade and design with significant contribution from Germany and England in the modernization of art of perfumery.

Composition of perfumes

A perfume is prepared by combining three different ingredients; synthetic or natural essential oils for fragrance (for instance, citral, jasmine, granial, sandalwood oil, ylang-ylang oil) constituting about 15–30% in a solvent (water 2% and alcohol 98%) to dissolve perfume oils. In general, the major constituent of a perfume is fragrance materials or substances having pleasant odors which are complex mixtures of natural or manmade chemical substances. Fragrances are added to a cosmetic product to impart a pleasant odor when applied to the body or to mask an unpleasant odor of some other ingredients to enhance acceptability and the experience of its usage by signaling cleanliness or freshness, creating a sense of well-being, and make it more pleasing to the user or the companions. Over the years there has been a significant advancement in the science of perfumery and fragrances sourced from plants and animals (e.g., musk deer) in more scientific ways for preparing new chemicals and controlling their quality and composition. The knowledge of the physical, chemical, biochemical, and biological properties of the various substances to be used as fragrances is imperative. Additionally, several other factors such as desired strength of the scent, degree of volatility, compatibility, interaction, and properties of each ingredient to produce the desired odor when applied to the skin, and the effect of heat, light, and packaging on its stability also need to be considered to formulate a fragrance.[7] The interplay of these properties is important to achieve a desired aesthetically pleasing final effect. Alcohol acts as a preservative and antimicrobial and helps in spreading the fragrance. The fixatives (benzyl alcohol, benzyl benzoate) are added to reduce the evaporation of volatile ingredients.[8,9] A fixative can be an odorless substance or the fragrance material itself characterized by low volatility.

Perfumes can be classified into two broad types depending on, (a) the concentration of fragrance ingredients and its lasting effect and, (b) the "perfume essence" or what actually makes the scent, usually a combination of essential oils (cedarwood, sandalwood, lime, etc), absolutes (jasmine, neroli, rose), animal extracts (musk, ambergris), and synthetic fragrances [Table 1].[8,9] A perfume generally constitutes a few to several hundred fragrance materials in a predetermined optimal strength of which 300–400 are of natural origin.[10] The volatility of all raw materials plays an important role as the fragrance character evolves over time after application. There are three essential parts of a perfume called "notes" used to formulate a scent that is more harmonious. The most volatile ingredients the "top notes" fade away quickly and are recognized first after the application. The middle notes, the "bouquet" or "heart notes" take a longer time to fade away and form the main concept of the perfume. They mainly conceal the displeasing initial "base notes" or "bottom" or the "dry out" which are long-lasting materials remaining on the skin and providing solidity and depth to a perfume.[10] However, perfume is usually developed for a particular purpose, to be used in cosmetics or household products, and to retain the same

fragrance its composition may need to be restructured depending on the type of product [Table 2].[10,11]

Epidemiology of perfume allergy

Although the exact prevalence of fragrance allergy in India remains understudied, up to 4.5% of the European adults have a contact allergy to one or more fragrances with an estimated prevalence of 1.9% for clinically relevant fragrance contact allergy.[12] Allergy to cosmetic ingredients, fragrances, in particular, is four times more prevalent in females than in males and most patients are between the age of 20 and 55 years.[13,14] This generally alludes to greater use of cosmetics by women and consequently the higher chances of exposure to many allergenic ingredients in cosmetics.

Perfume allergens and sources of their exposure

As stated earlier fragrances remain the major allergens in perfumes or other products of daily use including cosmetics. Since an extensive review on individual fragrances and essential oils is beyond the scope of this article, more details are available to the interested readers in an excellent review by deGroot.[4] Reportedly, there are about 162 fragrances, both single and complex mixtures of chemicals (methyl ionones), or essential oils (*Evernia furfuracea* (treemoss) extract, *E. prunastri* (oakmoss) extract, *Ferula gummosa* gum, *Narcissus poeticus* flower extract, *Viola odorata* leaf extract) that have caused contact allergy/allergic contact dermatitis.[9] Depending upon the evidence available these have been categorized as '*established,*" "*possible,*" or "*likely*" *contact allergens* on the basis of positive results in the general population and/or in patients/individuals with positive results in suspected contact dermatitis to fragrances [Table 3].[9,15]

Table 1: Classification of perfume on the basis of concentration of fragrance, lasting effect, and essence.

Class	Conc. of Aromatic compound (%)	Duration of lasting effect (hrs)
Parfum	20–30	6–8
Eau de parfum	5–20	4–5
Eau de toilette	5–15	2–3
Eau de toilette	2–4	2
Eau de fraiche	1–3	2
Essence	**Description**	**Example**
Bright floral	One or several flowers are responsible for such fragrance	Estee lauder's beautiful
Green	Fragrance which mainly obtained from cutgrass or leaf	Calvin Klein's Eternity
Aquatic	A clean smell that is similar to ocean	Davidoff cool water
Citrus	Citrus gives freshening effect	Faberge Brut
Fruity	Aromas that can be obtained from fruits other than citrus	Ginestet Botrytis
Gourmand	Scent with safe to use or desert like qualities	Thiersy Mugler's Angel

Cosmetics and personal care products such as personal perfume(s), deodorant, aftershave lotion/gel, eau de cologne, and eau de toilette with the highest concentrations of fragrances are complex mixtures of perfumes, emulsifiers, various lipids, preservatives, stabilizers, and higher alcohols. These may not be the only source but remain the major source of exposure to perfumes and fragrances. Additionally, many household products also contain fragrance materials unless specified otherwise. Even the so-called "fragrance free" products may contain perfume or essential oil to mask the unpleasant odor of an ingredient or the final product itself. Flavoring agents such as carvone and menthoxypropanediol in toothpaste or lip cosmetics are other considered contact sensitizers.[16,17] For the records, it may be mentioned here that a mixture of methylisothiazolinone and its chlorinated derivative methylchloroisothiazolinone (Kathon CG), a preservative, both in rinse-off (shampoos, liquid soaps) and leave-on (wet wipes facial skin-care products, body lotions, deodorants) cosmetic products have caused contact allergic reactions in epidemic proportions worldwide in recent years.[18,19] Polyhexamethylene biguanide (syn. polyaminopropyl biguanide, polyhexanide), a disinfectant and antiseptic, has shown to be another potential allergen in wet wipes and facial make-up cleansers, inducing both delayed-type eczematous and severe immediate-type reactions—contact urticaria syndrome.[20–22]

Adverse reactions due to fragrances in perfumes

[Table 4] lists various adverse effects and relevant fragrances in detail.[9,23] Exposure to fragrances in perfumes can cause a variety of adverse effects including irritant contact dermatitis, allergic contact dermatitis, contact urticaria, photoallergic reaction, pigmented contact (cosmetic) dermatitis, or systemic reactions such as respiratory symptoms, headache, and attacks of migraine in some individuals following systemic exposure.[10] Allergic contact dermatitis accounts for the most adverse effects related to fragrance ingredients in perfumes affecting 1–3% of the European population while 16% of eczema patients are sensitized to fragrance ingredients.[24,25] Colophony, *Myroxylon pereirae*, lanolin, formaldehyde, vanillin, musk mix, rose oil, cetostearyl alcohol, fragrances, and antiseptics such as cetrimide and triclosan in cosmetics have caused vide array of dermatological problems including primary irritant reactions, allergic contact dermatitis, photosensitivity and photodermatitis, contact urticaria, skin dyspigmentation, and brittle nails and hair.

Table 2: Perfume in cosmetics and other products of daily use.

Class	Product (Conc. of perfume)
Cosmetics	Body lotion (0.4%)
	Skincare product (0.3–0.5%)
	Lipstick (1%)
	Compressed powder (0.5%)
	Face cream (0.3%)
	Facial makeup (1%)
	Fragranced cream (4%)
Hair care products	Hair pomade (0.5%)
	Hair spray (0.1–0.3%)
	Shampoo, undiluted (0.5%)
Toiletry products	Bath product (0.2%)
	Soap, undiluted (0.5–2%)
	Shower gel (1.2%)
Perfumes	Perfume proper (15–30%)
	Masking Perfume (≤0.1%)
	Eau de cologne (3–5%)
	Eau de parfum (8–15%)
	Eau de toilette (4–8%)
	Deodorant/antiperspirant (1–3%)
Household products (Detergents, cleaners, softeners, fabric conditioners, polishes, fabric softeners, deodorizing sprays, carpet fresheners, room fresheners, diffusers, solvents, and waxes)	Dishwashing liquid (0.1–0.5%)
	Laundry powder (0.1–0.3%)
	Liquid detergent (0.1–1%)
	Bathroom cleaner (≤5%)
	Aerosol freshener (0.5–2%)
Flavors added to foods, soft drinks, lozenges, chewing gum, candies, ice cream, tobacco, etc.	Cinnamon, clove, vanilla, or cardamom extracts
Topical medicaments, aromatherapy	Essential oils such as tea tree oil, eucalyptus oil, oakmoss extract, treemoss extract, etc.
Flavors in dentistry and oral hygiene products (Toothpaste, mouth washes, dental floss)	Eugenol
Paper and paper products (Diapers, facial tissues, moist toilet paper, sanitary napkins)	
Industrial products (Paints, rubber, plastic, cutting fluids, electroplating fluids, insecticides, herbicides, air-conditioning additives)	

Ylang-ylang oil, jasmine absolute, Cananga oil, benzyl salicylate, hydroxyl citronellal, sandalwood, geraniol are common fragrances to cause pigmentary changes.[8,26] Bergamot oil in eau-de-cologne and tar derivatives in cosmetics have been implicated for hyperpigmentation in Riehl's melanosis, erythrosis pigmentata faciei of Brocq, poikiloderma of Civatte, and Berloque dermatitis.[27] A subclinical contact dermatitis and postinflammatory cytolysis of melanocytes have been implicated often for this increased pigmentation involving mainly the face or neck. Excipients, the inert substances used to solubilize, foam, lubricate, thicken, emulsify, sequester, or color the active component in a formulation, may act as irritants in higher concentrations or cause allergic contact dermatitis when applied directly with the allergen-containing formulation. Gallate mix (dodecyl gallate, octyl gallate, propyl gallate), used as antioxidant and preservative in leave-on creams, moisturizers, body lotions, and another rinse-off hair and body cleansers and topical formulations, has been implicated for rising propyl gallate allergy in recent years.[28,29]

Myroxylon pereirae and vanillin, the common additives to cosmetics and skincare products, are often considered markers of fragrance allergy and are known to induce contact sensitivity. Citral, used as an individual fragrance ingredient, is also a potential irritant. Musk ambrette and 6-methyl coumarin had been responsible for a number of photoallergic contact reactions with actinic reticuloid syndrome in Europe in the 1970s and mid-1980s.[30-32] Bergapten (5-methoxypsoralen) in citrus peel essential oils is a naturally occurring phototoxic furocoumarin that can cause phototoxic reactions.[33] Cinnamic acid, cinnamal, and *Myroxylon pereirae* are also well recognized among several other fragrance allergens to induce contact urticaria.[9]

Table 3: Categories of perfume allergens that have caused allergic contact dermatitis.

Category of allergens	Chemical allergens	Aromatic extracts of plants or other natural sources
Established contact allergens	Acetylcedrene, Amyl cinnamal, Amyl cinnamyl alcohol, Amyl salicylate, Anise alcohol, Benzyl alcohol, Anethole, Benzyl benzoate, Benzaldehyde, Benzyl cinnamate, Benzyl salicylate, β-Caryophyllene, Butylphenyl methylpropional, Camphor, Carvone, Cinnamal, Cinnamyl alcohol, Citral, Citronellol, Coumarin, α-Damascone, β-Damascone, Dimethylbenzyl carbonyl acetate, Eugenol, Farnesol, Geraniol, Hexadecanolactone, Hexamethylindanopyran, Hexyl cinnamal, Hydroxycitronellal, Hydroxyisohexyl 3- cyclohexene carboxaldehyde (Lyral), α-Irisone (Ionone) Isoeugenol, Limonene, Linalool, Linalyl acetate, Menthol, 6-Methyl coumarin, Methyl ionones, Methyl 2-octynoate, Methyl salicylate, 3- Methyl-5-(2,2,3-trimethyl-3 cyclopentenyl) pent-4-en-2-ol (Ebanol), α-Pinene, β-Pinene, Propylidene phthalide, Rose ketone-4, Salicylaldehyde, α-Santalol, β-Santalol, 4-Terpineol, α-Terpineol, Terpinolene, Trimethyl benzenepropanol (Majantol), Tetramethyl acetyloctahydronaphthalenes, Vanillin	*Cananga odorata*, (Ylang-Ylang Oil), *Cedrus Atlantica* (bark oil), *Cinnamomum cassia* (leaf oil), *Cinnamomum zeylanicum* (bark oil), *Citrus aurantium* Amara (flower/ peel oil), *Citrus bergamia* (peel oil), *Citrus limonum* (peel oil) *Citrus sinensis* (peel oil), *Cymbopogon citrates* (lemongrass oils), *Eucalyptus* spp. (leaf oil), *Eugenia caryophyllus* (clove flower/ leaf oil), *Evernia furfuracea* (treemoss extract), *E. prunastri* (oakmoss extract), *Jasminum officinale* sub sp. grandiflorum, *Juniperus virginiana Laurus nobilis* (Tej patta), *Lavandula hybrida*, *L. angustifolia*, *Mentha piperita* (peppermint), *Mentha spicata*, *Myroxylon pereirae*, *Narcissus Spp*., *Pelargonium graveolens* (geranium), *Pinus mugo* (mountain pine), *Pogostemon cablin*, Rose flower oil, *Santalum album* (Indian sandalwood), Turpentine oil, Verbena Absolute
Possible contact allergens	Amylcyclopentanone, Benzene acetonitrile, Benzyl acetate, 6-ethylideneoctahydro-5,8-methano2h-enzo-1-pyran, 3α, 4,5,6,7,7α-Hexahydro4,7-methano-1h-inden-5 (or 6)—yl acetate, Citronellal, Citronellyl nitrile, Cyclohexyl acetate, α-Cyclohexylidene, Decanal, Dihydromyrcenol, Ethylene dodecanedioate, Geranyl acetate, Hexahydro-ethmanoindenyl propionate, Hydroxycitronellal, α-Ionone, β-Ionone (Isomers mixture), Isobergamate, Methoxytrimethylheptanol, Methyl *p*-anisate, Methyl dihydrojasmonate (Hedione), Methyl decenol, Musk ambrette, Oxacyclo-hexadecenone, Phenethyl alcohol, Phenylpropanol, Terpineol acetate (Isomer), Terpinyl acetate, Tricyclodecenyl propionate, Verdyl acetate, Trans-β-damascone, γ-Damascone, Phenethyl salicylate	*Acorus calamus* (root oil), *Cedrus deodara* (wood oil), *Citrus tangerina* (leaf oil), *Cymbopogon nardus* / *C. winterianus* (oil), *Illicium verum* (star aniseed, fruit oil), *Lavandula spica*, *Litsea cubeba*, *Pelargonium roseum* (rose geranium), *Salvia spp*. (sage), *Tagetes patula* (French marigold), *Thymus spp*. (creeping red), *Viola odorata* (English violet), *Chrysopogon zizanoides* (Khus)
Likely contact allergens	Ambrettolide, Carvacrol, Cuminaldehyde, Cyclopentadecanone, 2,4-Dimethyl-3-cyclohexen-1-carboxaldehyde (Ligustral), Dimethyltetrahydro benzaldehyde, Ethyl vanillin, Heliotropine, Isoamyl salicylate, Isolongifolanone, Methoxycitronellal, Methyl cinnamate, 5-Methyl-α-ionone, Myrcene, Nerol, Nerolidol, Nopyl acetate, Rhodinol	*Citrus paradise* (Grapefruit peel extract), *Mentha arvensis* (Wild mint, peppermint oil)
Fragrance allergy indicators	**Fragrance Mix I** (1% each of Amylcinnamaldehyde, Cinnamic aldehyde, Cinnamyl alcohol, Eugenol, Geraniol, Hydroxicitronellal, Isoeugenol, Oakmoss absolute) **Fragrance Mix II** (Citral 1%, Citronellol 0.5%, Coumarin 2.5%, Farnesol 2.5%, Hexyl cinnamic aldehyde 5%, Lyral 2.5%) ***Myroxylon pereirae*** (balsam of Peru) resin	

Note: The list is by no means complete and requires updating as old allergens are replaced by new allergens discovered over time.

Diagnosis of allergic contact sensitivity from fragrances

The diagnosis of contact sensitivity from a fragrant ingredient in a perfume or perfumed product rests on the detailed clinical history of the patient, clinical picture, identification of putative allergenic ingredient by patch testing and careful interpretation of patch test results for their clinical relevance, and improvement/ healing of dermatitis after avoiding the culprit allergen. History of preexisting irritant dermatitis or atopic dermatitis is a predisposing factor for contact dermatitis from fragrances owing to their ubiquitous presence in topical formulations and other perfumed products of daily use. Microtrauma of shaving will facilitate contact sensitivity/dermatitis among men because of fragrances in aftershave or deodorants.

Clinically, after sensitization from cosmetics/products having fragrances in high concentration, new-onset dermatitis may appear or preexisting dermatitis worsens

Figure 1: A patch of acute allergic contact dermatitis in the axilla caused by fragrance ingredients in antiperspirant deodorant. Other axilla was also involved similarly.

Figure 2: Allergic contact dermatitis of the chest from a perfume spray.

Figure 3: Contact dermatitis over neck because of dabbed perfume.

Figure 4: Allergic contact dermatitis of face and eyelids from a perfume sprayed playfully by her grandchild.

(as in perianal or vulvar dermatitis) or gets perpetuated to become chronic (as in hand dermatitis) even from the use of cosmetics, household or industrial products, and flavors with low fragrance levels. While new-onset dermatitis varying in severity from mild to severe with dissemination is an important feature, contact sensitivity from fragrances usually aggravates preexisting dermatitis of the hands, axillae, face, and neck. The axillae remain the most significant area predisposed for dermatitis from

fragrances used in deodorants [Figure 1] as the skin is easily irritated due to occlusion and resultant warmth and moisture. Other sites where perfumes are dabbed directly (behind the ears, upper chest, cubital fossae, and wrists) or scented deodorant is applied (axillae) or sprayed (neck, chest, and axillae) will also develop patches of dermatitis [Figures 2–4] with a corroborating history of a similar rash previously. Pigmented contact (cosmetic) dermatitis [Figure 5] is another manifestation of contact allergy from above-stated fragrance ingredients in perfumes.

Figure 5: Pigmented contact dermatitis in the axilla caused by cologne spray.

Patches of dermatitis because of sensitivity from fragrances with oozing and crusting occur in the acute phase of contact dermatitis or can resemble nummular eczema, seborrheic dermatitis, sycosis barbae, pustular contact dermatitis (in atopic individuals particularly), and sometimes may even mimic atopic dermatitis, erythema multiforme, or lupus erythematosus and bullous impetigo or toxic epidermal necrolysis when irritant dermatitis is severe and extensive. Occasionally, patients may experience photo-reaction from contact with a photo-allergen present in perfumed cosmetics and exposure to sunlight especially ultraviolet—A light or numerous allergic reactions due to fragrant products of daily use. Dyshidrotic hand eczema and widespread id-eruptions are also ascribed to systemic contact dermatitis from ingestion of spices and flavored foods and beverages.

Although about 75% of patients with positive patch test from fragrances may not be aware of their allergy, anamnesis analysis will show that most patients with contact sensitivity to fragrance ingredients are aware of their intolerance and often recall the name of product especially deodorants, colognes, eau de toilette, or another perfumed cosmetic that had initiated their disease at first instance.[9,34] Nevertheless, many patients with positive patch test results seem to tolerate perfumes and scented products in daily life without developing allergic contact dermatitis from fragrance ingredients. It is also possible that individuals with positive results who are exposed to a putative allergen may not necessarily develop

Table 4: Fragrances that have caused pigmented cosmetic dermatitis, photosensitivity reactions, urticaria-type immediate reaction, and systemic adverse effects.

Adverse effect	Implicated fragrances
Pigmented cosmetic dermatitis	Benzaldehyde, Benzyl alcohol, Benzyl propionate, Benzyl salicylate, Cedrol methyl ether, Cinnamyl alcohol, Citral diethyl acetal, 5-Cyclohexadecenone, Eugenol, *E. prunastri* (oakmoss) extract, Geraniol, Germall, Geranium oil, 2-(2-hydroxy-5-methyl-phenyl) benzotriazole, Hydroxycitronellal, Ionone, α-Isomethyl ionone, Isosafrole, Jasmine synthetic, Methoxycitronellal, Methyl-α-ionone, Methyl isoeugenol, Musk ambrette, Musk moskene, Rose ketone-4, Tetramethyl acetyloctahydronaphthalene, 5,5,6-Trimethylbicyclohept-2-ylcyclohexanol, Vetiveryl acetate
Photosensitivity reaction	Acetyl hexamethyl indan, 3-Carene, Cinnamal, Cinnamyl alcohol, Coumarin, Eugenol, *E. prunastri* (oakmoss) extract, Fragrance, Mix I, Hydroxycitronellal, Methyl anthranilate, 6-Methyl coumarin, Musk ambrette, Musk ketone, Musk moskene, Musk tibetene, Musk xylene, *Myroxylon pereirae* resin
Contact urticaria and immediate-type reaction	Amyl cinnamal, Amylcinnamyl alcohol, Anise alcohol, Benzaldehyde, Benzyl alcohol, Benzyl benzoate, Camphor, Carvone, Cinnamal, Cinnamic acid, Cinnamyl alcohol, Coumarin, Ethyl vanillin, Eugenol, *E. prunastri* (oakmoss) extract, Fragrance Mix I and II, Geraniol, α-Isomethyl ionone, Limonene, Menthol, Methyl salicylate, *Myroxylon pereirae* resin Terpinyl acetate, Vanillin
Airway irritability, rhinitis/asthma and other systemic adverse effects	Benzyl alcohol, Benzyl benzoate, Benzyl salicylate; Camphor, Eucalyptol, Eugenol, Limonene, Menthol, Methyl salicylate, Vanillin, Thymol

Note: The causal relationship cannot be established always.

Table 5: Common fragrances and fragrance markers for patch testing.

Serial no.	Patch test allergen	Conc. (Pet.)	Remarks
1.	Amylcinnamaldehyde	2%	
2.	Amylcinnamyl alcohol	5%	
3.	Anise alcohol (anisyl alcohol)	10%	in Softisan veh
4.	Benzyl alcohol	10%	in Softisan veh
5.	Benzyl benzoate	10%	
6.	Benzyl cinnamate	10%	
7.	Benzyl salicylate	10%	
8.	Butylphenyl methylpropional (p-tert-butyl-α-methyl-hydrocinnamic aldehyde)	10%	
9.	Cananga oil	2%	
10.	Cinnamic aldehyde	1%	
11.	Cinnamic alcohol	2%	
12.	Citral	2%	
13.	Citronellol	1%	
14.	Coumarin	5%	
15.	Eugenol	2%	
16.	*Evernia furfuracea* extract (treemoss absolute)	1%	
17.	Farnesol	5%	
18.	Fragrance mix II	14%	Fragrance allergy indicator
19.	Geraniol	2%	
20.	Geranium oil Bourbon	2%	
21.	Hexyl cinnamic aldehyde	10%	
22.	Hydroxicitronellal	2%	
23.	Isoeugenol	2%	
24.	α-Isomethyl ionone	10%	
25.	Jasmine synthetic	2%	
26.	Jasmine absolute	2%	
27.	Lavender absolute	2%	
28.	d-Limonene	10%	
29.	Linalool	10%	
30.	Lyral (Hydroxyisohexyl 3-cyclohexene carboxaldehyde)	5%	
31.	Methyl anthranilate	5%	
32.	Methyl-2-octynoate	0.2%	
33.	Musk ketone	1%	constituents of Musk mix
34.	Musk moskene	1%	
35.	Musk xylene	1%	
36.	*Narcissus poeticus* absolute	2%	
37.	Oakmoss absolute	2%	in Sorbitan 5% (emulsifier)
38.	Rose oil	2%	
39.	Sandalwood oil	2%	
40.	Vanillin	10%	
41.	Ylang-Ylang oil	2%	
	Additional allergens other than suspected personal cosmetic products need to be tested		
1.	*Myroxylon pereirae* (balsam of Peru)		
2.	Carvone	5%	
3.	*E. prunastri* extract (oakmoss absolute)	2%	
4.	Lichen acid mix (0.1% each of Atranorin, Evernic acid, and Usnic acids)	0.3%	

(Cont...)

Table 5: *(Continued)*

Serial no.	Patch test allergen	Conc. (Pet.)	Remarks
5.	Limonene hydroperoxide	0.2, 0.3%	
6.	Linalool hydroperoxide	0.5%, 1%	
7.	Menthol	5%	
8.	Methyl salicylate		
9.	Musk ambrette		
10.	Trimethylbenzene propanol (Majantol)	5%	
11.	Perfume mix (containing 1% each of Cinnamic aldehyde, Cinnamic alcohol, Eugenol, Geraniol, Hydroxicitronellal, Isoeugenol)	6%	
12.	Fragrance mix I (Sorbitan 5% as emulsifier)	8%	Fragrance allergy indicator
13.	Anethole	5%	Fragrance allergy indicator
14.	Colophonium (colophony rosin)	20%	Fragrance allergy indicator

Note: Allergens 1 to 41 constitute "European Fragrance Series" (available from Chemotechnique Diagnostics (www.chemotechnique.se). Conc., concentration; Pet., petrolatum

Table 6: Indian Cosmetic and Fragrance Series*.

Sr. No.	Allergen	Conc. (Pet.)
1.	Abitol	10%
2.	Amerchol L 101	50%
3.	Benzyl alcohol	10%
4.	Benzyl salicylate	10%
5.	Bronopol	0.25%
6.	Butylated hydroxyanisole (BHA)	2.0%
7.	Butylated hydroxytoluene	2.0%
8.	Cetyl alcohol	5.0%
9.	Chloroacetamide	0.2%
10.	Chloroxylenol	0.5%
11.	Gallate Mix	1.5%
12.	Geranium oil	2%
13.	Benzophenone	10%
14.	Drometrizole	1.0%
15.	Imidazolidinylurea	2.0%
16.	Isopropyl myristate	2.0%
17.	Jasmine absolute Egyptican	2.0%
18.	Lavender absolute	2.0%
19.	Musk mix	3.0 %
20.	Phenyl salicylate	1.0%
21.	Polyoxyethylene sorbitan	5.0%
22.	Rose oil	2.0%
23.	Sorbic acid	2.0 %
24.	Sorbitan monooleate (Span 80)	5.0%
25.	Sorbitan sesquioleate (arlacel 83)	20.0%
26.	Stearyl alcohol	30.0%
27.	Tert–butyl hydroquinone	1.0%
28.	Thiomersal	0.1%
29.	Triclosan	2.0%
30.	Triethanolamine	2.0%
31.	Vanillin	2.0 %
32.	Oleamidopropyl dimethlamine	0.4%
33.	Cetrimide	0.5%
34.	Jasmine synthetic	2.0%
35.	Hexamine	2.0 %
36.	Chlorhexidine digluconate	0.5%
37.	Phenyl mercuric acetate	0.01%
38.	Cocamidopropyl betaine	1.0%
39.	Diazolidinylurea (germall II)	2.0%
40.	Ethylene diamine dihydrochloride	1.0%
41.	Quaternium 15 (Dowiell 200)	1.0 %
42.	Propylene glycol	5.0%
43.	Kathon CG	1.3%

*Approved by Contact Dermatitis and Occupational Dermatoses Forum of India and marketed by Systopic India Limited, New Delhi (India), Conc.: concentration, Pet.: petrolatum

hypersensitivity clinically while many others who develop a rash from perfumes or scented products are not allergic by patch testing.[35] This is perhaps because of false-positive (irritant effect) patch test reactions or immediate-type effects to fragrances, the relevant concentration of allergens is too low to elicit clinical contact reactions, allergens are not present in the products used, or simply because of technical limitations of patch testing procedures.[15,36] Adequate testing is further limited by the fact that a perfume may contain more than 250 individual ingredients and the sensitizing fragrance ingredient is not included in the used patch test series.[9]

The most baseline series, used routinely for patch testing in patients suspected of having contact dermatitis, contain the common fragrance allergens and the "indicators" of fragrance allergy that is fragrance mix I, fragrance mix II, and *Myroxylon pereirae* (balsam of Peru), and lichen acids indicative of allergy to treemoss and/or oakmoss extract (Indian baseline series has only fragrance mix I, *Myroxylon pereirae,* colophonium). Colophonium (rosin) was considered a marker for fragrance allergy previously is not an ideal fragrance allergy marker

Table 7: Fragrances allergens that need to be labeled on products in European Union in personal cosmetics and household products.

Serial number	Fragrances
1.	Alpha isomethylionone
2.	Amyl cinnamal (Jasmonal A)
3.	Amylcinnamyl alcohol
4.	Anisyl alcohol
5.	Benzyl alcohol
6.	Benzyl benzoate
7.	Benzyl cinnamate
8.	Benzyl salicylate
9.	Butylphenyl methylpropional (Lilial)
10.	Cinnamal
11.	Cinnamyl alcohol
12.	Citral
13.	Citronellol
14.	Coumarin
15.	Eugenol
16.	Evernia furfuracea (Treemoss) extract
17.	Evernia prunastri (Oakmoss) extract
18.	Farnesol
19.	Geraniol
20.	Hexyl cinnamal (Jasmonal h)
21.	Hydroxycitronellal
22.	Hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyral)
23.	Isoeugenol
24.	Limonene
25.	Linalool
26.	Methyl 2-octynoate

Note: These 26 substances have been identified by the European Commission under European Union Cosmetic Regulation and need be identified on products when present in concentrations greater than 0.01% (100ppm) in rinse-off products and 0.001% (10ppm) in leave-on products along with their category of allergens for the information of consumers.

as it identifies very few cases otherwise not detected by other markers.[34] However, when there is a strong clinical suspicion of fragrance allergy, testing with a "fragrance series" [Tables 5 and 6] along with additional fragrances and/or essential oils is strongly recommended to identify any additional cases of fragrance contact allergy. Patch testing with the patient's own cosmetic products suspected of causing contact sensitivity is also important as in nearly 50% of cases relevant allergic reactions to perfumes, deodorants, and shaving lotions are not identified by any fragrance indicator.[37] Furthermore, a much lower concentration of a contact sensitizer in end products may be another reason for a dissociation between the patch test results from individual ingredients and the tested product.[38] It is also possible that ascertaining the relevance of all positive results may remain difficult as the manufacturers usually do not label all ingredients over a cosmetic package. However, repeated open application tests (ROAT), repeat testing, or use tests remain important to confirm the allergic nature of the doubtful (?+) or weak-positive (+) patch test reaction and to establish the relevance of fragrances/markers or perfumed products causing contact sensitivity in a user.

Safety regulation

Products containing fragrance ingredients must be safe for the consumers and requires the same regulations for safety as for other cosmetics ingredients. The fragrance ingredients are used in the commercial product only after testing and are generally recognized as safe when they comply with recommended safety criteria. The cosmetic products need to be labeled properly for users' safety and is a legal responsibility of manufacturers and those who market them. However, there is usually incomplete or no labeling or declaration of the complete list of ingredients by the manufacturers on the pretext of proprietary/trade secret issues especially in countries where it is not binding legally. Although the safety of perfume ingredients is regulated by USFDA, it does not regulate the perfume industry *per se* and no approval is needed before their marketing. However, the scientific data on the safety of fragrances in consumer products generated by the Research Institute of Fragrance Materials, United States, is used by International Fragrance Association to monitor the safety of fragrances for use in consumer products, to create industry codes of practice and guidelines, to make recommendations on limiting or prohibiting the use of specific substances, and to test new fragrances to rule out toxicity before their marketing.[39] On the other hand, European Union Cosmetic Regulation lists 26 fragrance ingredients and chemicals including all the ingredients present in fragrance mix I and II for patch testing [Table 7][40] that need to be identified when present in concentrations greater than 0.01% (100 ppm) in rinse-off products and 0.001% (10 ppm) in leave-on products along with their category of allergens on cosmetics and detergent products. However, a general level of exposure of up to 0.8μg/cm^2 (0.01% in cosmetic products) for the fragrance of concern may be tolerated by most consumers including those with contact allergy to fragrance allergens.[8] Central Drugs Standard Control Organization in India has also laid out a set of protocols for import, manufacturing, labeling, packing, sale, and distribution of cosmetics (as defined by the Drugs & Cosmetics Act 1940) under Cosmetics Rules 2020. It has been made mandatory for manufacturers to declare all ingredients of their products including those with concentrations of less than 1% for consumers to make more informed choices. The addition of raw materials as specified in Annexure-A of the Indian Standard IS: 4707 Part 2 (amended from time to time) in the cosmetic product(s) is also prohibited. Import or manufacturing of cosmetics that contain dyes, colors, and pigments other than the one specified by the Bureau of Indian Standards is also prohibited under this law. However, most regulatory agencies only specify perfumes as cosmetic products and not as allergens.

CONCLUSION

A perfume is a complex mixture of aromatic compounds, essential oils, solvents, and fixatives to give a pleasant fragrance to the human body or flavor to foods. The major constituent of a perfume is fragrances or substances having pleasant odors which are complex mixtures of natural or manmade chemical substances. Perfume is basically a cosmetic product applied to the human body for an amusing scent or feeling of freshness. Its fragrance ingredients act as allergens and thus increase the risk of contact sensitization. Direct exposure of fragrances to the skin, nose, eyes, mouth, and respiratory system may result in adverse effects particularly allergic contact dermatitis of varying severity in the majority of the consumers while systemic adverse effects too are not uncommon.

The diagnosis of fragrance allergy rests on medical history, clinical presentation, and patch testing. It is highly desirable to understand the properties of chemicals and mixtures and their likely adverse effects seen in a sizable number of end-users which can be immediate, recurrent and chronic, mild, or potentially severe enough to lead to loss of workdays and wages, general ill health or psychosocial distress. While identification and future avoidance of product(s) containing a problematic fragrance ingredient is perhaps the first step in the prevention/treatment of fragrance-induced allergic reaction for the user, the requirement for safety parameters is as important as for other cosmetic ingredients. The regulatory bodies need to ensure adherence to the safety regulations of the day by the manufacturers of fragrances and cosmetics in general.

Declaration of patient consent

Patient's consent is not required as there are no patients in this study

Financial support and sponsorship

Nil.

Conflict of interest

There are no conflicts of interest.

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How to cite this article: Mahajan VK. Perfumes and associated allergens: A brief review. CosmoDerma 2022;2:21.