

Review on perfume and present status of its associated allergens

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Abstract

Background: Perfume is basically a cosmetic product applied to human body for an amusing scent or the feeling of freshness. A certain amount of perfume penetrates and remains attached to the protein of the skin when perfume is applied on the body. It evokes a surge of events in human immune system which results with allergic symptoms. Fragrance ingredients are leading cause that can be responsible for the occurrence of allergic contact dermatitis that is recently studied under cosmetic adverse reaction.

Aim: The aim of this review article was to define the allergies that are caused by fragrance ingredients. This review highlights the various aspects of perfume with respect to its manufacturing process, compositions, and fragrance ingredients identified as allergens and its present regulatory status.

Method: There are 175 fragrance ingredients that are used in perfumes cause allergic reaction. Several studies were conducted on the patients. The study was conducted on four fragrance markers in the baseline series: fragrance mix I (FM I), Myroxylon pereirae, fragrance mix II (FM II), and hydroxyisohexyl 3-cyclohexene carboxaldehyde.

Result: Around 658 patients showed allergy due to fragrance ingredients when the patch test was performed. In other study, out of 1253 patients, 90% of the FM I and M. pereirae detected 90% of the cases.

Conclusion: Majority of the fragrance ingredients can cause allergic reactions and hence act as allergens and thus increase the risk of sensitization on activation. If any individual suffers from allergy or contact dermatitis on use of any perfume, he/she should be aware of it and should reduce or avoid its use to overcome such problems of hypersensitivity.

KEYWORDS

allergens, contact dermatitis, fragrance ingredients, perfumes, regulatory, sensitivity

1 | INTRODUCTION

The word perfume is originated from the Latin word “*perfumare*” which means “to smoke through”.¹ Perfume is composed of aromatic compounds, fragrant essential oils, solvents, and fixatives, used to provide the animal, food objects, and human body an engaging scent, mainly in the form of liquid.² Some of the fragrance ingredients used in the perfumes to give pleasant scent to human's body cause allergic reaction called fragrance allergen. This review article deals with fragrance ingredients that are used in perfume and allergic reactions that result from fragrance ingredients which are commonly used in the manufacturing of perfume.

2 | HISTORY OF PERFUMES

The use of perfume and perfumery in India was traced back between 3300 BC and 1300 BC in the Indus civilization. One of the earliest distillations of Ittar was mentioned in the Hindu Ayurvedic text *Charaka Samhita* and *Sushruta Samhita*.³ In 2004-2005, archaeologists believed that the world's oldest surviving perfumes were in Pyrgos, Cyprus. From 1221, the art of perfumery was known in Western Europe. Between the 16th and 17th centuries, body odors resulting from unusual bathing were primarily masked by the use of perfumes. The perfume industry developed partly due to this patronage.³

In 1693, Aqua Admirabilis also known as perfume water, Italian barber Giovanni Paolo Feminis created eau de cologne which is today considered as the best perfume.⁴ Evolution of perfume has a long history, and its present status is the result of contribution from many countries. As for example, Egyptians were the first, who used perfume for personal enjoyment, but the production of perfumes was reserved for the priests, and they used it for the religious purpose. Greek peoples used an extraordinary amount of perfumes, and each part of the body, they used different fragrance for hygiene and “cult of the body.” The perfume industry was established by two talented Arabian chemists named Jabir IbnHaygan and Al-Kindi. Perfumes were used as a part of luxury by Romans. France is considered the birthplace of modern perfumery and remains the center of the European perfume trade and design. However, the first modern perfume was introduced by Hungarians. England and Germany also contributed a lot in modernization of perfumery.⁵

3 | COMPOSITION

In general, perfume is prepared by combining 3 different ingredients as below:

Fragrant essential oils: They are obtained from synthetic aromatic plant and natural aromatic extract, for example, Citral, Jasmine, Rose, geranial, Sandal wood, and YlangYlang.⁶

Fixatives: To reduce the evaporation rate, natural and synthetic substances are mainly used, for example, benzyl alcohol and benzyl benzoate.

Solvents: 2% water and 98% ethanol used to dissolve perfume oil.⁷ Alcohol inhibits microbial growth, and it is most commonly used to spread the fragrance.

4 | NOTES IN PERFUME

Perfume has basically 3 sets of notes which are used for making the harmonious scent accord.^{8,9} They are Top notes, Middle notes, and Base notes (Figure 1). First impression is provided by the Top notes. Fragrance ingredients used in the Top notes are volatile in nature and fade away more quickly.¹⁰ Top note is the lightest of all notes and recognized after first application. It consists of small light molecules. Middle notes are considered the heart of a fragrance and take longer time to fade away. They are the main concept of scent and main function to veil the disagreeable initial application of base note, which set off more amiable with time. Base notes are long lasting and will remain on the skin. This note provides the solidity and depth to a perfume.

5 | MANUFACTURING OF PERFUME

Manufacturing of perfume consists of mainly four steps.¹¹ A flow-chart of the same is provided in (Figure 2). Individual step is further discussed in brief below:

- A Collection: The fragrance ingredients from the suitable source are collected in the manufacturing center, before manufacturing process begins.
- B Extraction: Fragrant essential oils are extracted from suitable plant by using various procedure or methods as discussed below:
 1. Steam Distillation: The fragrance ingredients that are present in the plants are held in still, and then, steam is passed through it, whereby fragrance oils convert into gas. Then, gas is passed through condenser, liquefied, and oils are collected.

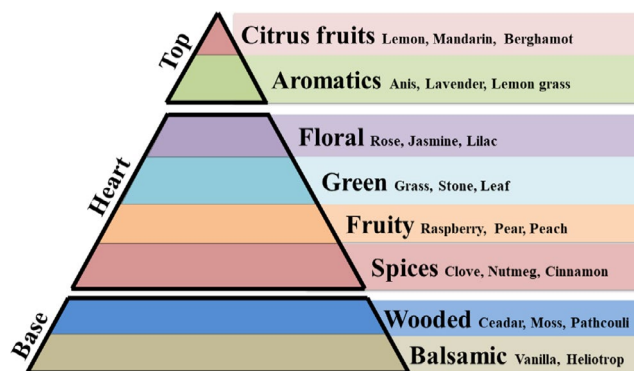
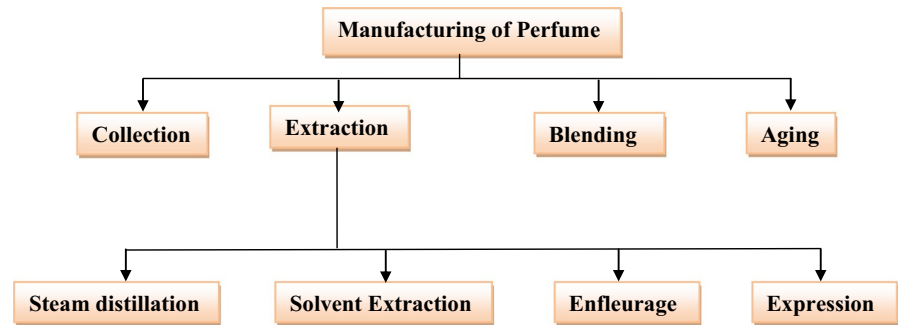


FIGURE 1 Three basic notes of perfumes

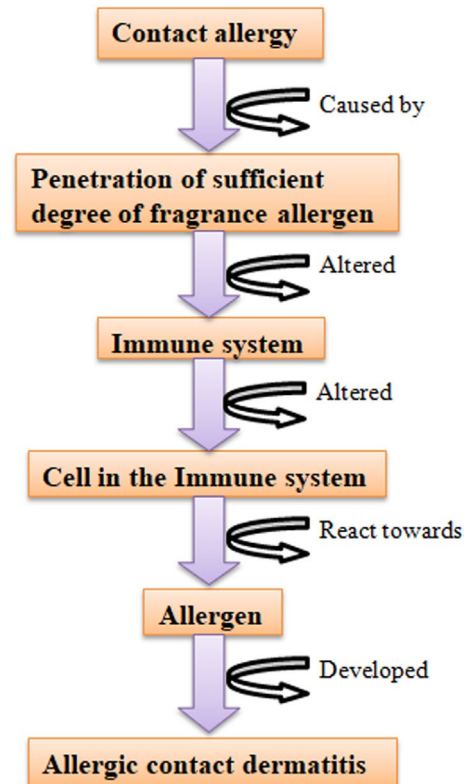
FIGURE 2 Manufacturing of Perfumes**TABLE 1** Classification of perfume on the basis of concentration of fragrance and duration of lasting⁹

Class	Percentage of aromatic compound	Duration of lasting (Hrs)
Parfume	20-30	6-8
Eau de perfume	5-20	4-5
Eau de toilette	5-15	2-3
Eau de cologne	2-4	2
Eau de fraiche	1-3	2

2. Solvent extraction: The flower parts are dissolved in appropriate solvents such as petroleum and benzene that are capable to retain the fragrance of the flower. Fragrances are dissolved in alcohol and then heated, and after evaporation of alcohol, fragrances are obtained.
 3. Enflourage: Flowers that contains fragrances are kept in glass sheet with grease that absorbs the fragrances.
 4. Expression: Manually or mechanically, the plants and citrus fruits are press down until all the fragrant essential oils are shoved out.
- C Blending: After extraction of various oils from plants or other sources, the oils are blended together. Most of the perfumes are prepared by dissolving 10%-20% of fragrant essential oil in water and alcohol.
- D Aging: Perfumes are matured for several months or even for years after blending, in order to check that the stability of fine perfume has been achieved.

6 | CLASSIFICATION OF PERFUMES

Perfumes are broadly classified in two different ways: on the basis of fragrance ingredients concentration and duration of lasting (Table 1) and on the basis of essence. Fragrance substances are the compounds which give amiable odors. They are ever present in various perfumed cosmetic products and in perfumes. Fragrance substances are also used in redolence therapy. It embellishes both emotional and physical health. Percentage of fragrance may vary from 1% to 3% (Eau de fraiche) to 20 to 30% (parfume) where it may last from 2

**FIGURE 3** Flowchart showing the development of allergic contact dermatitis

to 8 hours. On the basis of essence, perfumes are categorized into six groups. They are discussed below:

1. Bright floral: One or several flowers are responsible for such fragrance, for example, Estee lauder's beautiful
2. Green: Fragrance which mainly obtained from cut grass or leaf, for example, Calvin Klein's Eternity
3. Aquatic: A clean smell that is similar to ocean, for example, Davidoff cool water
4. Citrus: Citrus gives freshening effect, for example, Faberge Brut¹²
5. Fruity: Aromas that can be obtained from fruits other than citrus, for example, Ginestet Botrytis
6. Gourmand: Scent with safe to use or desert like qualities, for example, Thierry Mugler's Angel

7 | ALLERGY DUE TO FRAGRANCE INGREDIENTS

7.1 | Allergens

An allergen is commonly defined as “Any substance, often a protein that induces an allergy.” An allergen is an agent that is responsible for stimulating a response that initiates in immune system and results in an allergic reaction. While using perfume, contact allergens may occur when the skin of an individual has been exposed to fragrance ingredients. At the first place, it can affect the immune system of the user. Allergic contact dermatitis (ACD) is an inflammatory disease of skin characterized by skin redness (erythema), swelling, and vesicles in the acute phase. If any individual is exposed continuously to it, it may be converted into a chronic condition with scaling and painful fissures (is a cutaneous condition in which there is a linear-like cleavage of skin) of the skin. Fragrance ingredients that are used in cosmetics cause allergic contact dermatitis and usually involve on the hands and/or face. The development of allergic contact dermatitis due to fragrance is shown in Figure 3.

8 | HOW TO KNOW IF A FRAGRANCE INGREDIENT OR PRODUCT IS REGULATED AS A COSMETIC

Cosmetic can be defined as any product that can be used to enhance the attractiveness of individual. Accordingly, fragrance products such as perfumes, cologne, and aftershave lotions come under the purview of cosmetic. Some of the commonly used products, such as shower gels, shaving creams, and shampoo and body lotion, may also contain fragrance ingredients. Fragrance ingredients also present in those products that can be labeled as “unscented.” This is because the fragrances are added to mask the disagreeable smell of other ingredients by the manufacturer, without giving the product an observable scent.

Some of the fragrance products are used for preventing or treating disease, or affecting function of the body. These types of products are treated as drug under the law, or something as both cosmetic and drugs. Some examples of them are given below:

- Helping people sleep
- Treating colic
- Easing muscle aches

Many other consumer products that are not meant for application on the body but may contain fragrance ingredients are also regulated. Examples are as follows:

- Dryer sheets
- Fabric softener
- Laundry detergent
- Carpet fresheners

TABLE 2 Classification of perfume as allergens

Category	Number of individual fragrances	Number of natural extracts	Total no. of substances
Established in human	54	28	82
Established in animals	18	1	19
Likely	26	-	26
Possible	35	13	48

TABLE 3 Examples of Established Contact Allergen in Animals¹⁴

No. of individual chemicals	No. of natural extracts
AllylPhenoxyacetate, P-Tert. –	Jasminum
Butyldihydrocinnamaldehyd, Cyclamen	Sambac
Aldehyde, Dibenzyl Ether, 2,3-Dihydro-2,2,6	Flower
Trimethylbenzaldehyde, Trans-2-Hexenal,	Cera/
2-Hexylidene Cyclopentanone, Hexyl Salicylate,	Extract/
P-Isobutyl-A-Methyl Hydrocinnamaldehyde,	Water
Isocyclocitral, A-Methyl Cinnamic Aldehyde,	
MethylenedioxyphenylMethylpropanal,	
Methylundecanal, 2-Methoxy-4-Methylphenol,	
4-Methoxy-A-Methyl Benzenpropanal, Methyl	
Octine Carbonate, Perillaldehyde P-Mentha-1,8-	
Dien-7-Al, Phenylacetaldehyde	

- Room fresheners

Same requirement for safety is met by Fragrance ingredients as other cosmetics ingredients. Products that contained fragrance ingredients must be safe for the consumers, and before they go to the market, they do not require any approval of FDA. The cosmetic products should be safe for individual and should be properly labeled is a legal responsibility of companies and individual who manufacture or market cosmetics.

9 | CLASSIFICATION OF PERFUMES AS ALLERGENS

The Scientific Committee on Consumer Safety (SCCS) has announced that 1 to 3% of the European population have an allergy due to fragrance ingredients.¹³ Depending on the quality and strength of the available, dermatologist distinguishes among established (in human and animal) likely or possible contact allergen. SCCS has recognized 54 individual fragrance substances and 28 natural extracts (essential oil) which are categorized as “Established Contact Allergen in Human.” Among all the allergens, 1 natural extracts and 18 individual chemicals are categorized as “Established Contact Allergen in Animals,” 35 individual chemical along with 13 natural extract are categorized as “Possible Contact Allergens” and 26 individual chemicals are categorized as “Likely Contact Allergens” as considered by the committee. The list of commonly used allergens in perfume is presented below in Tables 2 to 7.

TABLE 4 Examples of Established Contact Allergens in Humans¹⁵

Individual chemicals	Natural extracts
Acetylcedrene, Amyl Cinnamal, Amyl Cinnamyl Alcohol, Amyl Salicylate, Trans-Anethole, Anise Alcohol, Benzaldehyde, Benzyl Alcohol, Benzyl Benzoate, Benzyl Cinnamate, Benzyl Salicylate, ButylphenylMethylpropional, Camphor, Beta-Caryophyllene, Carvone, Cinnamal, Cinnamyl Alcohol, Citral, Citronellol, Coumarin, (Damasconone) Rose Ketone-4, Alpha-Damascone (Tmchb), Cis-Beta-Damascone, Delta-Damascone, DimethylbenzylCarbinyl Acetate (Dmbca), Eugenol, Farnesol, Geraniol, Hexadecanolactone, Hexamethylindanopyran, Hexyl Cinnamal, Hydroxyisohexyl3-Cyclohexene Carboxaldehyde (Hicc),Hydroxycitronellal, Isoeugenol, Alpha-Isomethyl Ionone, (DI)-Limonene, Linalool, Linalyl Acetate, Menthol, 6-Methyl Coumarin, Methyl 2-Octynoate, Methyl Salicylate, 3-Methyl-5-(2,2,3-Trimethyl-3 Cyclopentenyl)Pent-4-En-2-Ol, Alpha-PineneAnd Beta-Pinene, PropylidenePhthalide, Salicylaldehyde,Alpha-Santalol And Beta-Santalol,Sclareol,Terpineol (Mixture Of Isomers), Alpha Terpineol,Terpinolene,Tetramethyl Acetyloctahydronaphthalenes, Trimethyl-Benzenepropanol (Majantol), Vanillin.	CanangaOdorata and 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 Expressed, Citrus Limonum Peel Oil Expressed,Citrus Sinensis (Syn.: Aurantium Dulcis) Peel Oil, Cymbopogon Citratus/ Schoenanthus Oils, Eucalyptus Spp Leaf Oil, Eugenia Caryophyllus Leaf/ Flower Oil, EverniaFurfuracea Extract, Evernia Prunastri Extract, Jasminum Grandiflorum/ Officinale, Juniperus Virginiana Laurus Nobilis, Lavandula Hybrida, Lavandula Officinalis, Mentha Piperita, Mentha Spicata, Myroxylon Pereirae, Narcissus Spp, Pelargonium Graveolens, Pinus Mugo/Pumila, Pogostemon Cablin, Rose Flower Oil (Rosa Spp), Santalum Album, Turpentine (Oil), Verbena Absolute.

TABLE 5 Fragrance substances categorized as likely contact allergens¹⁵

Ambrettolide, Carvacrol, Citrus Paradisi, Cuminaldehyde, Cyclopentadecanone, Trans-Trans-Delta-Damascone, 2,4-Dimethyl-3-Cyclohexen-1-Carboxaldehyde, Dimethyltetrahydro Benzaldehyde, Ethyl Vanillin, Heliotropine, Isoamyl Salicylate, Isolongifolene ketone, Longifolene, Mentha Arvensis, Methoxycitronellal, Methyl Cinnamate, Methylionantheme 5-Methyl-Alpha-Ionone, Myrcene Myrtenol Nerol, Nerolidol (Isomer Not Specified), Nopyl Acetate, Phytol, Rhodinol, Trans-Rose Ketone-5.

10 | MAIN MECHANISM OF ALLERGIES AND THEIR DISEASES

The main mechanisms of allergic reactions and their associated diseases are shown in Figure 4.

11 | ADVERSE REACTIONS DUE TO FRAGRANCES IN PERFUMES

Some of the important adverse reactions associated with the use of fragrances are irritant contact dermatitis, allergic contact dermatitis, immediate contact reactions (contact urticaria), connubial contact dermatitis and pigmented contact dermatitis. Further details of the same are given below:

Allergic contact dermatitis¹⁷:

- Specific T cells of allergen get activated.
- Nearly all allergens are chemically reactive in nature and are too small compound, hence act as heptans.
- Induction phase: The various events are included in the induction phase, starts with inceptive contact with the allergens and

TABLE 6 Examples of Possible Contact Allergens

No. of individual chemicals	No. of natural extracts
Cyclohexyl Acetate, Ethylene Dodecanedioate, Hydroxycitronellol, Methoxytrimethylheptano L,Methyl P-Anisate, Methyl Dihydrojasmonate, Phenethyl Alcohol, Phenylpropanol, Amylcyclopentanone, Benzyl Acetate,6-Ethylideneoctahydro-5,8-Methano-2h-Benzo-1-Pyran, 3 α ,4,5,6,7,7 α -Hexahydro-4,7-Methano-1h-Inden-5(Or 6)-Yl Acetate, Alpha-Ionone, Beta-Ionone, Methyl Ionone (Mixture Of Isomers), Terpeneol Acetate (Isomer Mixture), Alpha-Terpinyl Acetate, Citronellyl Nitrile, Alpha-Cyclohexylidene Benzeneacetoneitrile, Decanal, Dihydromyrcenol,3,7-Dimethyl-1,6-Nonadien-3-Ol, 2-Ethyl-4-(2,2,3-Trimethyl-3-Cyclopenten-1-Yl)-2-Buten-1-Ol, Geranyl Acetate, Hexahydro-Methanoindenyl Propionate, Ionone Isomeric Mixture, Isobergamate, Methyl Decenol, Tricyclodecanyl Propionate, Oxacyclohexadecenone, Verdyl Acetate, Trans-Beta-Damascone, Gamma-Damascone, Citronellal, Phenethyl Salicylate	Acorus Calamus Root Oil, Cedrus Deodara Wood Oil, Citrus Aurantium Amara Leaf Oil, Citrus Tangerina, CymbopogonNardus/ Winterianus Herb Oil, IlliciumVerum Fruit Oil, Lavandula Spica, Litsea Cubeba, Pelargonium Roseum, Salvia Spp, Tagetes Patula Thymus Spp, Vetiveria Zizanoides

completed when the individual is sensitized and giving a positive ACD reaction.

- Elicitation phase: Begins when allergens are re-exposure and results in clinical exhibition of ACD (within 1-2 days).
- For the development of ACD, the crucial factors are dendritic cells (DCs) and the local tissue microenvironment.

Ingredients	Use	Side effects
Sandal wood	Fragrance	Hypersensitivity
Limonene	Slightly astringent smell	Irritates the skin
Benzyl alcohol	Fixative	Skin irritation causing redness and pain
Benzyl benzoate	Fixative, Sweet, balsamic odor	Skin irritation like blister, itching, scaling, redness
Acetone	Solvent	Inhalation causes dryness of mouth and throat.
Ethyl acetate	Solvent	Defatting effect on skin and may cause dryness and cracking.

TABLE 7 Some commonly used fragrance ingredients with their allergic reaction

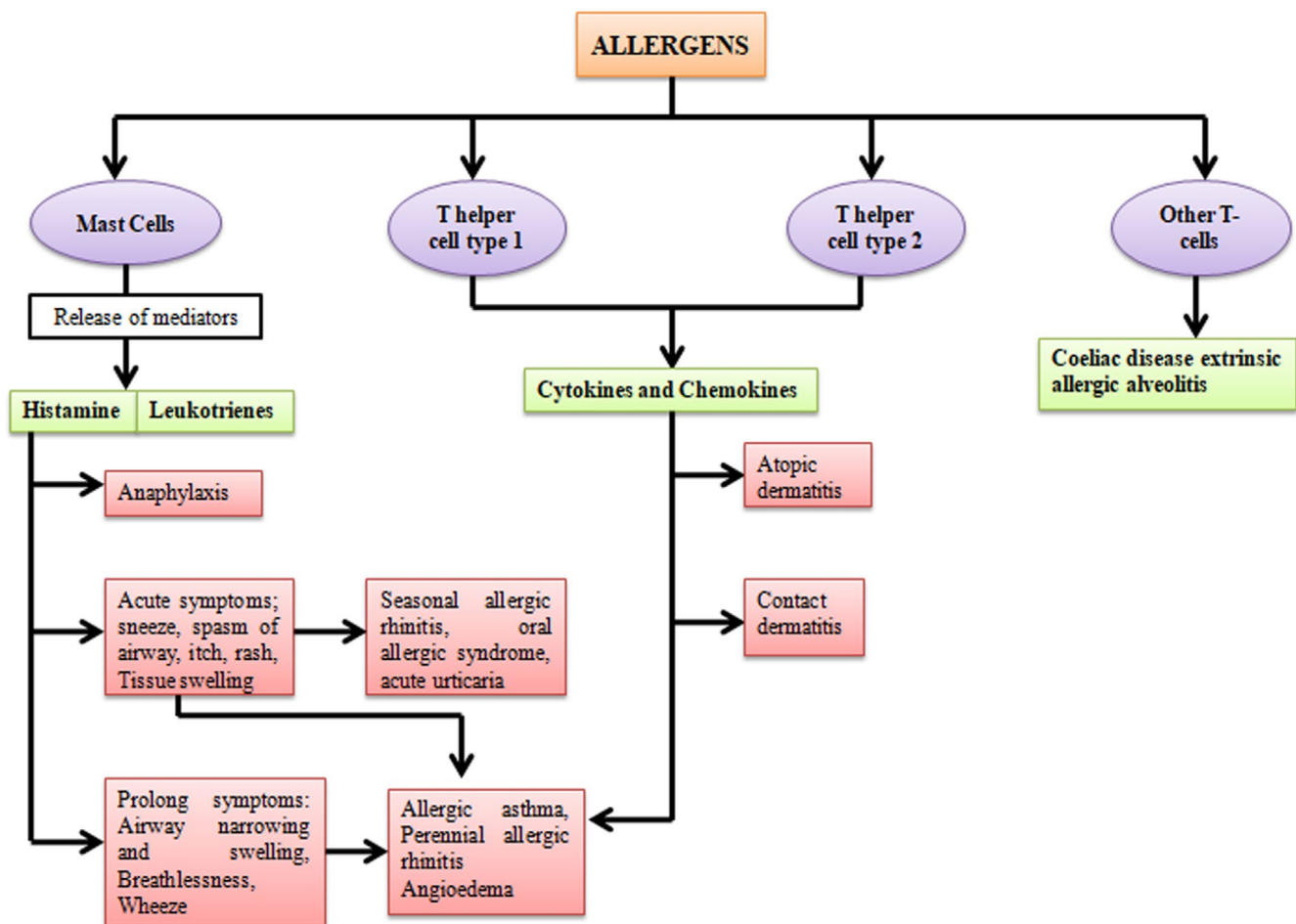


FIGURE 4 Schematic representations of the main mechanisms of allergies and their diseases¹⁶

Irritant reactions (including contact urticaria):

- Citral that can be used as individual fragrance ingredient causing irritant effect.
- Rashes or intolerance or rashes to perfume products/perfumes are shown to be allergic by testing.
- Cinnamon and *Myroxylonpereiarae* are well-recognized source of contact urticaria¹⁸.

Pigmentary anomalies:

- In 1973, the term "pigmented cosmetic dermatitis" was introduced which was previously known as melanosis faciei feminae.
- The increased pigmentation, mainly on the face or neck, often regarded as sub-clinical contact dermatitis. Most of the ingredients of fragrances showed pigmentation such as ylang-ylang oil, jasmine absolute, cananga oil, benzyl salicylate, hydroxyl citronellal,

TABLE 8 Positive patch-test reactions of some selected fragrances in 658 patients with hand eczema²⁶

Patch-test substances (CAS no.)	Patients with positive reactions [n (%)]
Citral 2% pet. (5392-40-5)	28 (4.3)
Hydroxycitronellal 5% pet. ^a (107-75-5)	20 (3.0)
Lyrall [®] 5% pet. (31906-04-4)	14 (2.1)
Eugenol 5% pet. ^a (97-53-0)	13 (2.0)
Oxidized L-limonene 3% pet. ^b (5989-54-8)	6 (0.9)
Geraniol 5% pet. ^a (106-24-1)	6 (0.9)
Citral 1% pet. ^c (5392-40-5)	3 (0.8)
Citral 0.5% pet. ^c (5392-40-5)	1 (0.3)
Oxidized D-limonene ^b 3% pet. (5989-27-5)	5 (0.8)
Lilial [®] 10% pet. (80-54-6)	3 (0.5)
Coumarin 5% pet. (91-64-5)	3 (0.5)
α-Hexylcinnamaldehyde 10% pet. (101-86-0)	3 (0.5)
Benzyl salicylate 5% pet. (118-58-1)	2 (0.3)
Galaxolide 10%, IPM 10% pet. (1222-05-5)	2 (0.3)
Citronellol 5% pet. (106-22-9)	2 (0.3)
Benzyl benzoate 5% pet. (120-51-4)	1 (0.2)

Note: IPM (isopropyl myristate) tested at 10% petrolatum (pet.) and was negative in those positive to Galaxolide[®]. Galaxolide[®] = 4,6,6,7,8,8-hexamethyl-1,3,4,6,7,8-hexahydrocyclopental[g] benzopyran; Lilial[®] = 2-methyl-3-(4-tert-butyl-phenyl) proanal; Lyrall[®] = 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene carbaldehyde and INCI (hydroxyisohexyl-3-cyclohexene carboxaldehyde).

^aPart of the fragrance mix.

^bn = 649.

^cn = 392.

sandalwood and geraniol.¹⁹

Photo-reactions:

- A number of allergic photo-contact reaction caused by Musk ambrette, and it was forbid from use in Europe in 1970s
- Nowadays, photoallergic contact dermatitis is not common.
- A few plant-derived fragrance ingredients such as furocoumarins (psoralens) cause phototoxic reactions.²⁰
- Phototoxic reactions still occur but are rare.

12 | SAFETY REGULATION

In United States, the perfume industry is not directly regulated by FDA (Food and Drug Administration), but the safety of perfume through their ingredients is controlled by FDA. The fragrance ingredients are tested and used in the preparation only when they comply generally recognized as safe (GRAS) criteria. In Europe, the fragrance ingredients and chemicals that are used in the manufacturing of perfume are listed along with their category of allergens.

TABLE 9 Constituents of the specific fragrance series, concentration used, and frequency of reactions found in the tested population (86 patients tested)²⁷

Components of the fragrance series	Concentration ^a (%)	Frequency n (%)
Geraniol	2.0	17 (19.7)
Eugenol	2.0	12 (13.9)
Ylang-ylang oil ^b	2.0	12 (13.9)
Cinnamyl alcohol	2.0	12 (13.9)
Isoeugenol	2.0	11 (12.8)
Geranium oil Bourbon ^b	2.0	8 (9.3)
Hydroxyisohexyl 3-cyclohexene carboxaldehyde	5.0	7 (8.1)
Cinnamal	2.0	7 (8.1)
Rose oil absolute ^b	2.0	6 (6.9)
Hydroxycitronellal ^b	5.0	6 (6.9)
Jasmine absolute, Egyptian	2.0	3 (3.5)
Cananga oil	2.0	3 (3.5)
Jasmine synthetic	2.0	3 (3.5)
<i>Evernia prunastri</i>	2.0	2 (2.3)
Benzyl alcohol	1.0	2 (2.3)
Benzyl salicylate	2.0	2 (2.3)
Lavender absolute ^b	2.0	2 (2.3)
Sandalwood oil	2.0	2 (2.3)
Citral	2.0	2 (2.3)
Farnesol	5.0	1 (1.2)
Coumarin	5.0	1 (1.2)
α-Amyl cinnamal	2.0	0
Narcissus absolute	2.0	0
Musk xylene	1.0	0
Musk moskene	1.0	0
Musk ketone	1.0	0
Vanillin	10	0
Methyl anthranilate	5	0
Citronellol ^b	1.0	0
α-Hexyl cinnamal	10	0

^aPetrolatum was used as the vehicle for all the constituents of the fragrance series.

^bFragrances that contain geraniol or that have cross reactions with geraniol.

13 | SCIENTIFIC COMMITTEE ON CONSUMER SAFETY (SCCS) OPINION ON FRAGRANCE ALLERGEN IN COSMETIC PRODUCT

In Europe, about 16% of eczema patients are sensitized to fragrance ingredients. In Europe, 1%-3% of population have allergy due to fragrance ingredients.¹³ One can aware with contact allergy to fragrance ingredients who cannot tolerate scented products on

skin. A set of 26 fragrance allergens with a well-recognized potential to cause allergy were identified by the Scientific Committee on Consumer products and Non-Food Products (SCCNFP). To decide whether safe threshold can be established for the fragrance allergens of concern, that is, those pose a high risk of sensitization to consumer; SCCS examined available elicitation dose-response data. The SCCS contemplates that elicitation level in sensitized individual will be adequately low, in order to protect both the majority of sensitized individual and almost all of the nonsensitized consumers from developing contact allergy. The accessible studies, however, indicate that a general level of exposure of upto $0.8 \mu\text{g}/\text{cm}^2$ (0.01% in cosmetic product) may be sanctioned by most consumers,¹⁴ including these with contact allergy to fragrance allergens. The SCCS has an opinion that this level of exposure (up to 0.01%) would be enough to avert elicitation for the greater part of allergic individual, unless there are any experimental data allowing the derivation of individual threshold.

The SCCP recommended that the safe concentration of hydroxyisohexyl 3-cyclohexene carboxaldehyde in cosmetics to 200 ppm. In 2004, SCCP concluded that atranol and chloroatranol which are the main constituents of allergy of *evernia furfuracea* and *evernia prunastri* should be avoided in the cosmetic products. The SCCS has an opinion that the existence of atranol and chloroatranol in cosmetic product is not safe.

14 | IN VIVO EXPERIMENTAL DATA

As per the 7th amendment of the European Union law on the safety of cosmetics, any animal testing for cosmetic products since 2004 and cosmetic ingredients since March 2009 has been prohibited. As such, there is no officially validated in vitro or in vivo test method for skin sensitization. However, for cosmetic ingredients, local lymph node assay (LLNA), guinea pig maximization test (GPMT) and Buehler test were used in risk assessment for regulatory purposes.²¹ These methods are used in hazard identification and risk assessment for regulatory purposes under REACH (Registration, Evaluation, Authorization and Restriction of Chemicals).²² Among these tests, LLNA is preferred over conventional guinea pig maximization test and the Buehler test as it is more scientific as well as less cruel with respect to regulatory and ethical consideration. According to the directives on classification and labeling,²³ substances and preparations meeting positive criteria in these tests shall be classified as "sensitizing" and assigned the symbol "Xi" and the "risk phrase (R43)" as "may cause sensitization by skin contact" or, according to the recent regulation on classification, labeling and packaging (CLP10) "H317" as "may cause an allergic skin reaction". The results from the OECD guidelines of animal tests are sufficient to classify a substance as a skin sensitizer (R43) when at least 30% of the animals have a positive response (by GPMT); when at least 15% of the animals have a positive response (by Buehler test); or when stimulation index (SI) value is equal to or greater than 3; that is, at least a threefold increase in lymph

node cell proliferative activity is induced as compared to vehicle-treated controls. For positive LLNAs, an EC3 value is calculated which gives the estimated concentration of a chemical necessary to give a threefold increase in proliferative activity compared to vehicle-treated controls. In recent past, the SCCS requested the International Fragrance Association (IFRA) to submit data on animal tests performed with fragrance substances, to be presented in a structured format. In response, industry submitted first a poster²⁴ and later a report consisting of LLNA protocol summaries on the 59 fragrance substances in the poster.²⁵ The SCCS reviewed and analyzed the report and the publications quoted in the report. In one study, Heydorn et al conducted a clinical study to investigate fragrance allergy on 658 patients with hand eczema.²⁶ The results of the study are summarized in Table 8. In another 4-year retrospective study, Cuesta et al studied the characteristics of the population allergic to perfumes; the study was conducted in Hospital General Universitario, Alicante, Spain.²⁷ The study was conducted on four fragrance markers in the baseline series: fragrance mix I (FM I), Myroxylon pereirae, fragrance mix II (FM II), and hydroxyisohexyl 3-cyclohexene carboxaldehyde. Out of 1253 patients studied, 90% of the FM I and M. pereirae detected 90% of the cases. The results of the study are summarized in Table 9.

15 | CONCLUSION

It is concluded that most fragrance ingredients act as allergens and thus increase the risk of sensitization on activation. SCCS suggests that the fragrance ingredients cause allergy or act as allergens if their concentration present is greater than 0.01% in rinse off products and 0.001% in leave on products. European Union Cosmetic Regulation 1223/2009 listed 26 allergens but no other regulatory agencies specify perfumes as allergens, they just describe perfumes as cosmetic products. If any individual suffering from allergy, or contact dermatitis on its application, he/she should be aware regarding it and should reduce or avoid the use of those ingredients to overcome such problems of hypersensitivity.

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How to cite this article: Kumar M, Devi A, Sharma M, Kaur P, Mandal UK. Review on perfume and present status of its associated allergens. *J Cosmet Dermatol*. 2021;20:391–399. <https://doi.org/10.1111/jocd.13507>