

Contact sensitisation to fragrance allergen: A 5-year retrospective study of patients in the Department of Dermatology, Hospital Kuala Lumpur

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ABSTRACT

Introduction: Fragrance allergy remains an important cause of contact dermatitis. We aim to describe the characteristics of patients with contact sensitisation to fragrances who underwent patch testing in the Department of Dermatology Hospital Kuala Lumpur.

Materials and Methods: This is a 5-year retrospective study of patients who developed positive reactions to fragrance allergens at the Department of Dermatology, Hospital Kuala Lumpur, Malaysia between January 2017 and December 2021. Patch tests were performed with European Baseline Series and relevant extended series. Patch test readings were recorded according to the International Contact Dermatitis Research Group recommendation.

Results: A total of 854 patients underwent patch test during the study period with 133 (15.6%) patients developing at least one positive reaction to fragrance allergens. The median age of patients at presentation was 40 years (range 16-79) old with 78.2% females. The most common initial presentation was hand eczema (55.6%). Other commonly involved sites include face (38.3%), leg (35.3%) and trunk (22.6%). The most frequent sensitising fragrance allergens were Fragrance Mix I (10.5%), Balsam of Peru (7.1%) and Fragrance Mix II (4.9%). Sixty patients (45%) developed positive reaction to more than one fragrance allergens. Twelve patients (9%) developed positive patch test reactions to their own products such as skincare, hair dye and hand wash. Current relevance was recorded in 96 patients (72.2%).

Conclusion: Contact sensitisation to fragrance allergens was detected in about 15% of our patients who underwent patch test. The most common sensitising allergens were Fragrance Mix I and II and Balsam of Peru.

KEYWORDS:

Fragrances, allergic contact dermatitis, contact sensitisation to fragrances, patch test, Balsam of Peru

INTRODUCTION

Contact dermatitis is defined as inflammation of the dermis and epidermis resulting from direct contact between a substance and the surface of the skin. It is the result of a type

IV hypersensitivity reaction involving the T lymphocytes of immune system. It can arise from exposure to various allergens which include metals, preservatives, woods and plants, plastic, rubber, medicines, medical devices, cosmetics and fragrances.¹

According to International Fragrance Association (IFRA), fragrance ingredient is "any basic substance used for its odour properties or malodour coverage."² Fragrances are frequently present in a variety of products for instance cosmetics (fine fragrances and aftershaves, lip balms, lipsticks, deodorants), household products (detergents), toiletries (shampoos, soaps, lotions, creams, sunscreens), wet wipes, baby products, paper products, fabric and clothes, topical pharmaceuticals, essential oils, industrial products (paints, rubber, plastic, insecticides, herbicides), and even flavouring agents in oral hygiene products, foods or drinks.^{3,4} Patch testing remains pivotal in diagnosing fragrance allergy.

This study aims to describe the characteristics of patients who have contact allergy to fragrances in Hospital Kuala Lumpur, Malaysia.

MATERIALS AND METHODS

This is a 5-year retrospective study of patients who developed positive reactions to fragrance allergens upon patch testing at the Department of Dermatology, Hospital Kuala Lumpur, Malaysia between January 2017 and December 2021.

Patch tests were performed with European Standard Series and relevant extended series from Chemotechnique Diagnostics using IQ chambersTM. Extended series used include cosmetic series, metal series, rubber series, dental series, medicament series, textile series, shoe series, plastic and glue series and hairdressing series. Fragrance allergens that were tested in the study included Fragrance Mix I, Fragrance Mix II, Balsam of Peru, and hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC) (Lyrall) in the European baseline series, as well as tea tree oil (oxidised), peppermint oil, benzyl alcohol, musk mix and benzyl salicylate in the cosmetic series. Patients were also tested with their own products, including hair dye, hair shampoo, cosmetics, skin care products, soap and toothpaste. Toothpaste and leave-on cosmetics such as lipstick, facial powder, facial foundation

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Table I: Characteristics of patients who developed positive reaction to fragrance allergens in patch testing

Characteristics		n = 133 (%)
Median age in years (range)		40 (16 – 79)
Male:female ratio		1:3.6
Ethnicity, n (%)	Malay	75 (56.4)
	Chinese	41 (30.8)
	Indian	13 (9.8)
	Others	4 (3.0)
Occupations, n (%)	White collar workers	32 (24.1)
	Healthcare workers	30 (22.5)
	Blue Collar workers	15 (11.3)
	Pink collar workers	11 (8.3)
	Housewife	22 (16.5)
	Unemployed	23 (17.3)
Patch test series used, n (%)	European baseline	133 (100)
	Cosmetic	45 (33.8)
	Rubber	34 (25.6)
	Dental	18 (13.5)
	Metal	18 (13.5)
	Shoes	14 (10.5)
	Hairdressing	9 (6.8)
	Textile	8 (6)
	Medicaments	8 (6)
	Plastic and glue	4 (3)
	Own products	65 (48.9)

Table II: Sites of lesions in 133 patients who were sensitized to fragrance allergens

Sites		n (%)
Hand		74 (55.6)
Face		51 (38.3)
	Not otherwise specified	33 (24.8)
	Lips	17 (12.8)
	Ears	11 (8.3)
	Eyelids	8 (6.0)
	Nose	3 (2.3)
Leg		47 (35.3)
Trunk		30 (22.6)
Arm		17 (12.8)
Neck		12 (9.0)
Anal/genital		11 (8.3)
Scalp		8 (6.0)
Scattered generalised		8 (6.0)

Table III: The sensitisation pattern of current cohort

Allergens		Number of patient positive to allergen (Sensitisation rate %)
European baseline series n =854	Fragrance mix I	90 (10.5)
	Balsam of Peru	61 (7.1)
	Fragrance mix II	42 (4.9)
Cosmetic series n=242	Tea tree oil oxidised	7 (2.9)
	Peppermint oil	5 (2.4)
	Lyril	10 (1.2)
	Musk mix	1 (0.5)
	Benzyl alcohol	1 (0.4)
	Benzyl salicylate	0 (0)

Table IV: Combined cross-reactivity (CR) rates

Compound 1	Compound 2	CR, %
Fragrance Mix I	Colophony	12.2
	Propolis	3.3
	Sesquiterpene lactone mix	2.2
Fragrance Mix II	Colophony	9.5
	Propolis	0
	Sesquiterpene lactone mix	0
Balsam of Peru	Colophony	13.1
	Propolis	4.9
	Sesquiterpene lactone mix	1.6

Table V: Worldwide studies on contact sensitisation to fragrances

Author country	Study period	n	Common age group (years)	Positive patch test reaction (%)	Top two allergens
Frosch et al., Germany ¹¹	2009 to 2012	56813	>40	NA	1) Fragrance mix I 2) Balsam of Peru
Cuesta et al., Spain ¹³	2004 to 2008	1253	>40	9.3	1) Balsam of Peru 2) Fragrance mix I
Vejanurug et al., Thailand ¹⁵	2013 to 2014	312	>40	26.9%	1) Fragrance mix I 2) Fragrance mix II
Hafner et al., Brazil ¹⁶	2000 to 2015	1870	40	13.8%	1) Fragrance mix I 2) Colophony

and deodorants were tested "as is". Cleaning products such as facial wash, shampoo and shower gel were diluted with water to 10% (w/w).

Patches were applied to the patients and removed after 48 hours. Initial reading was recorded at 48 hours and final reading was noted at 96 hours after patch application. The parameters studied include positive patch test reactions and the source of allergens. Readings were recorded according to the International Contact Dermatitis Research Group recommendation.^{5,6} A positive patch test reaction is defined as a reaction that fulfils at least a 1+ reaction (i.e., +, ++ or +++). Other reactions that can be found during patch tests are irritant reaction (IR), doubtful reaction (+?) and angry back reaction, but these are not considered as a positive patch test reaction.

RESULTS

There was a total of 854 patients who underwent patch test between January 2017 and December 2021 at Department of Dermatology, Hospital Kuala Lumpur. Out of these, 133 (15.6%) patients developed at least one positive reaction to fragrance allergens. The demographic data was shown in Table I. The median age of patients was 40 years (range 17 to 79) and 78.2% of patients were female. The initial presentations include allergic contact dermatitis (18.8%), hand eczema (14.3%), contact dermatitis (12%), discoid eczema (10.5%), atopic eczema (7.5%), cheilitis (7.5%), hand and feet eczema (6.8%) and lichen planus/lichenoid reaction of oral mucosa (6.8%). Other less frequent presentations include face eczema, oral ulcer, papular eczema, stasis eczema, allergic contact gingivitis, chronic urticaria, contact urticaria, papular urticaria, feet eczema, insect bite dermatitis, irritant contact dermatitis, metal allergy, palmoplantar eczema, photoaggravated dermatitis, seborrheic dermatitis and ashy dermatoses.

The most common sites of involvement were hands (55.6%), face (38.3%), legs (35.3%) and trunk (22.6%) as shown in Table II. As shown in Table III, the most frequent sensitising allergens were Fragrance Mix I (10.5%), balsam of Peru (7.1%) and Fragrance Mix II (4.9%). Other sensitising allergens included tea tree oil oxidised (2.9%), peppermint oil (2.4%), Lyra (1.2%), musk mix (0.5%) and benzyl alcohol (0.4%). None of our patients were sensitised to benzyl salicylate. There were 60 (45%) patients who developed positive reaction to more than one fragrance allergen. For our patients who were sensitised to fragrance mix I, cross-reactivity (CR) rate to colophony was 12.2% (Table IV). In

patients who were allergic to balsam of Peru, CR rate to colophony was 13.1%. Around 9% of patients who were sensitised to Fragrance Mix II also cross-sensitised with colophony. None of the patients who were sensitized to Fragrance Mix II cross-reacted with propolis and sesquiterpene lactones (SQL) mix.

There were 12 patients (9%) who developed positive patch test reactions to their own products such as skin care products (n = 4), hair dye (n = 3), hand wash (n = 3), hair shampoo (n = 1) and cosmetic (n = 1). Relevance of positive patch test reaction was assessed in all and 96 patients (72.2%) were found to have current relevance, mostly to their own toiletries (46.6%), followed by their household products (15.5%), cosmetics (9.5%), gloves (9.5%), footwear (6.9%), hair dye (3.4%) and food or flavouring (2.6%).

DISCUSSION

Fragrances represent the second most common cause of allergic contact dermatitis (ACD) after nickel.^{7,8} It is known to be the most common cause of allergies to cosmetics.⁹ The prevalence of contact sensitisation to fragrances differs worldwide and the most common contributing allergens were Fragrance mix I, Balsam of Peru and Fragrance mix II (Table V).^{11,13,15,16} The prevalence of fragrance contact allergy in the general population is 0.7–2.6%.¹⁰ A study across 12 European countries from 2009 to 2012 showed that 12.7% out of more than 50,000 patients patch tested revealed positive reactions to Fragrance Mix I, Fragrance Mix II, Lyril, balsam of Peru, oil of turpentine, or a combination of these.¹¹ In Spain, positive patch test reactions towards fragrance allergens were found in 1.7 to 15.1% of study population.¹²⁻¹⁴ A smaller study in Thailand showed that 22.1% of 312 patients reacted to Fragrance Mix I, Fragrance Mix II, Balsam of Peru, or combinations.¹⁵ Our study which showed a prevalence of 15.6% of fragrance allergy was similar to other studies to date.^{10,16}

In a study of 3119 patients patch-tested in 2008 to 2011 across five European countries, women were found to be affected twice as often as men.^{16,17} Our study presented similar characteristics. Typically, women in their mid-40s, commonly present with facial or hand eczema due to fragrance allergy,^{10,16,18-20} likely due to increased use of fragranced products among women. Sensitisation is more common at an older age likely due to age-related poor skin barrier function from asteatotic eczema,²⁰ and increased use of, as well as cumulative exposure with age to, products with fragrance.²¹ Face is commonly affected likely due to the direct

application of cosmetics, indirect transfer from contaminated hands, or airborne contact (mists, sprays, and aerosols).¹⁰ Eyelids are the most susceptible area to fragrance allergy as it has the thinnest epidermis.²² The other commonly involved area is the lips, especially the unkeratinised epithelium.²³ When it comes to lips involvement, food flavourings are frequently the contributor. Hands are commonly involved owing to the use of fragrance containing household products, cosmetics and topical medications.²¹ It is apparent that from our study there is a significant number of our patients who had dermatitis at the groin, pruritus ani or pruritus vulva (8.3%). This could be due to the fact that topical medicaments used in these areas also contained fragrances. These areas may also develop ectopic contact dermatitis from the transfer of fragrance allergens from the hands to these sensitive areas.

Cheng et al. reported a common presentation of papular/vesicular lesions or patchy dermatitis with eczematous papules among patients presented with fragrance allergy. Chronic lichenified pruritic plaques may also be seen.³ Our study showed similar findings where the initial presentations of fragrance allergy include eczematous lesions, papular lesions or lichen planus or lichenoid reaction of oral mucosa.

Our study revealed that Fragrance Mix I is the most common sensitising allergen (10.5%), which is similar to other studies.^{3,10,18,24} Fragrance Mix I consisted of 8 fragrance chemicals including cinnamyl alcohol, cinnamal, hydroxycitronellal, amyl cinnamal, geraniol, eugenol, isoeugenol and oak moss absolute. Oak moss absolute is the most common individual allergen contributing to fragrance allergy while amyl cinnamal is the least frequent contributor of fragrance allergy.⁹ Oak moss absolute is an extract derived from lichen growing on oak trees in the Mediterranean area, and it has a complex composition and has been used in many fragrance products, including perfumes, colognes and aftershaves.⁸ Geraniol is a commonly used fragrance terpene (appreciated for its fresh, flowery odour), occurring naturally in many flowers and plants, and is present in high concentrations in essential oils of rose and geranium.⁸ Hydroxycitronellal and geraniol are the fragrances most widely found in perfumes.²⁵ Cinnamal, hydroxycitronellal and isoeugenol are commonly present in deodorants. Isoeugenol can also be found in lip products, hydroalcoholics, aftershaves, women's facial and hand creams, intimate wipes, and make-up removers.

The rate of sensitisation of Balsam of Peru was comparable to previous studies.^{3,10} Balsam of Peru, also known as *Myroxylon pereirae*, is a natural complex resin derived from a Central American tree (or *Myroxylon pereirae* tree).^{9,26} It is frequently present in a wide variety of products ranging from drugs, perfumes, aroma compounds, cleaning products, dental cement and liquids, cosmetic products to foods. Balsam of Peru is used in topical medicaments to treat wounds as it has antibacterial properties. Its most important allergen is formed by the polymerisation of an ester of benzoic acid or cinnamic acid and coniferyl alcohol.²⁷ Its crude use in perfumes has been banned by International Fragrance Association (IFRA) since 1982 but its extracts and distillates can still be used in manufacturing of perfumes.²⁶

The third most frequent sensitising allergen is Fragrance Mix II (4.9%), similar to previous studies.²⁴ Fragrance Mix II consists of hexyl cinnamic aldehyde, hydroxyisohexyl 3-cyclohexene carboxaldehyde, farnesol, coumarin, citral and citronellol. The most frequent sensitising individual allergen is hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC), also known as Lyrall; the least frequent one is citronellol. Since the addition of Fragrance Mix II as standard test for fragrance allergy, there has been an increase in the sensitivity for detection of fragrance sensitisation with respect to traditional markers for fragrances (Fragrance Mix I and Balsam of Peru).⁹ Citronellol is most widely found in hygiene products and daily moisturizers.²⁵ Lyrall contributes to 1.2% of positive patch test result in our cohort, similar to other study.¹⁰ Lyrall is more commonly found in deodorants.²⁸ It is interesting to note that not all our patients who were positive to Lyrall were also positive to Fragrance Mix II. This could be due to the higher concentration of Lyrall when tested as an individual allergen compared to its concentration in the Fragrance Mix II. Of note, Lyrall has been banned from cosmetics products in EU since August 2021 hence it will be interesting to observe if the trend of Lyrall sensitivity decreases subsequently.

A total of 45% of our patients developed positive reaction to more than one fragrance allergens in our study, likened to another study.²⁴ There are more than 2500 existing fragrance ingredients and at least 100 ingredients are known contact allergens.¹² Hence, it is crucial to supplement standard patch testing with patients' own products. Hair care products commonly contain a great amount of fragrances. For instance, only 2.8% of 324 styling products were free of fragrances.¹⁰ Studies have shown significant cross sensitization between colophony, propolis and fragrance. In subjects who are allergic to colophony; fragrance and propolis may be significant cross-reactors. Similarly, in subjects who are allergic to propolis; fragrance and colophony are considered to be significant cross-reactors.²⁹ However, for patients allergic to fragrance, cross sensitisation to propolis or colophony is not significant in terms of cross-reactivity rate.²⁹ A 10% CR rate was considered to be significant enough to recommend avoidance of a potential cross-reacting allergen based on the American Contact Dermatitis Society's Contact Allergy Management Program (CAMP) recommendations.³⁰ Nonetheless, our study showed otherwise (Table V). For our patients who were sensitive to Fragrance Mix I, colophony may be a significant cross-reactor with a CR rate of 10.5%, but not propolis and SQL mix. Patients allergic to Balsam of Peru also showed a significant cross sensitisation to colophony (13.1%) but not to propolis and SQL Mix. We therefore recommend our patients who develop contact sensitisation to Fragrance Mix I and Balsam of Peru to also avoid colophony, in view of the CR rate of more than 10%.

Clinical relevance is crucial to translating research results into clinical use. The rate of currently relevant sensitisations reflect the extent of current exposure and the consequent disease state. This may rise or decline with time, hence showing the direct effect of a fragrance contact allergy to the individual.²⁶ It is believed that a strong positive reaction is more likely to have clinical relevance than a weak positive reaction. The recorded relevance in our study was high

(72.2%), similar to another study.³¹ This is likely due to fragrance sensitisation acting as a provoking factor for a spectrum of dermatoses. Unless fragrance-containing products are avoided, previous dermatoses will not improve despite appropriate treatment and protective measures.¹³

Contact allergy to fragrance is mostly not related to occupation³², but more commonly originates from personal use of scented cosmetics. However, secondary occupational exposure to fragrance ingredients may happen at workplace. Previous literature showed a high prevalence of allergy to Fragrance Mix I among healthcare workers due to irritant hand contact dermatitis from repeated washing disrupting the skin barrier, allowing better allergen penetration, hence subsequent application of products containing fragrances introduces a source for allergen exposure.³ Sensitivity to Balsam of Peru has been found to be more common among healthcare workers especially dentists.³³ Dentists also have a higher risk for allergy to eugenol (one of the components of Fragrance Mix I) due to exposure from mouthwashes, dressings, impression materials, and periodontal packings.¹⁹ About a fifth of our cohort were healthcare workers. Out of these, eight out of 30 healthcare workers (26.7%) had fragrance allergy related to work. Food handlers may be frequently exposed to components of Fragrance Mix I (cinnamal and cinnamic alcohol) and Balsam of Peru due to handling of spices and essential oils.³ Hairdressers, beauticians and aromatherapists are also particularly at risk for fragrance allergy.¹⁰ Overall, our study has shown a fairly equal distribution of fragrance allergy across different occupations.

As fragrances are widely used in daily products, it is extremely difficult for sensitized patients to avoid them completely without limiting their daily activities. Some products may also omit labelling fragrance in their ingredient if it was used for masking odour instead of imparting pleasant odour. Regulations have been imposed to safeguard consumer's health and safety including mandatory labelling of fragrance ingredients on products' ingredient label if products sold contained any of the 26 fragrances governed by EU regulations.^{12,31} Unfortunately, neither Balsam of Peru nor the extracts and distillates are included in the mandatory labelling as yet. Hence, there should be continuous efforts in identifying common fragrance allergens and they should be regulated continuously by authority bodies. Tighter regulations should be enforced to ensure that fragrance ingredients are labelled accordingly and correctly.¹⁰

Essential oils are sources of fragrance allergens and expanded patch testing involving essential oils may be considered in patients suspected to have fragrance allergy. So far, our study included few individual ingredients of essential oils which are present in the cosmetic series, namely the tea tree oxidized extract and peppermint oil. From our study, there were 2.9% and 2.4% of our patients who were sensitized to tea tree oil oxidized and peppermint oil respectively, hence it is essential to monitor these fragrance allergens in our populations. Since fragrance series was not available in our setting at present, we may include cosmetic series if we are investigating patients for fragrance allergy, as it contains a

few essential oils. Cosmetic series also contains sorbitan sesquileate, which is the dispersing agent used in Fragrance mix I hence testing for this will help to differentiate between true Fragrance mix I allergy and sorbitan sesquileate allergy.

Management of patients with fragrance allergic contact dermatitis includes avoidance of products with labelled known sensitising fragrances. Clinicians may advise patients to fully avoid the use of fragrance-containing products such as perfumes and toiletries. If patients need to use such products, they should be advised to avoid applying these products at areas of skin that are potentially traumatized (beard region, hands, and shaved areas) or occluded (axilla), as well as areas of high absorption (eyelids, genitals, and axilla) and areas of chronic dermatitis (e.g., stasis dermatitis). Exposure to air and oxidation of products should be prevented by replacing lid between uses. Household products such as dishwashing liquid, clothes detergent, toilet cleaners or floor cleaners also contain fragrance and patients should avoid skin contact with these products by using gloves or boots as protection as these household products usually have no fragrance-free alternatives. We should also educate our patients to avoid using products out of its shelf life (commonly 1 year) as certain fragrance ingredients autoxidise into allergenic products.³⁴ Patients with sensitisation to Balsam of Peru may benefit from a balsam-restricted diet, as Balsam of Peru has been associated with systemic contact dermatitis if ingested.³⁵ Examples of foods and drinks rich in Balsam of Peru include citrus fruit, spices such as vanilla and cinnamon, chocolate, cola, and tomatoes.³⁶ In general, avoiding exposure in infants and young children is ideal as sensitisation to an allergen is lifelong once acquired.

There is limitation to this study. Individual ingredients of fragrance mix I and fragrance mix II were not tested in all subjects showing positive reaction to the mixes. We should consider to purchase the fragrance allergy series which contains more fragrance allergens in order to detect more cases of fragrance allergy. Our findings may not be representative of the whole Malaysian population as this is only a single centre study.

CONCLUSION

Contact sensitisation to fragrance allergens was detected in about 15% of our patients who underwent patch test. It is more prevalent in women and commonly involves hands and face. The most common sensitising allergens were Fragrance Mix I, Fragrance Mix II and Balsam of Peru. Current relevance of positive patch test reaction was found in almost three quarter of our patients and these were mostly towards their own toiletries, household products and cosmetics. It is crucial to test patients' own products during workup for allergen sensitisation to ensure that these relevant reactions are not missed.

CONFLICT OF INTEREST DECLARATION

The authors have no conflict of interest to declare.

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