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Contact Allergy Caused by Fragrance Mix and *Myroxylon pereirae* (Balsam Of Peru) – A Retrospective Study

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A B S T R A C T

Because of their widespread use, fragrances are among the most common causes of contact allergic dermatitis, second only to nickel. During a five-year period 3,065 patients with contact dermatitis were patch tested using a specific mix of fragrances. 509 (16.6%) patients were allergic to the fragrance mix, while 258 (8.4%) patients exhibited an allergic reaction to Myroxylon pereirae *(balsam of Peru). Between those 509 patients, 157 were patch tested with eight individual substances contained in the fragrance mix: cinnamal, cinnamyl alcohol, eugenol, isoeugenol, geraniol, hydroxycitronellal, alpha-amyl cinnamal and Evernia prunastri (oak moss). The most frequent allergens were isoeugenol 57.9% (91/157), eugenol 55.4% (87/157), cinnamyl alcohol 34.4% (54/157) and Evernia prunastri (oak moss) 24.2% (38/157). There were 62 patients (39.5%) who exhibited an allergic reaction to both the fragrance mix and* Myroxylon pereirae *(balsam of Peru). The results prove the importance of avoiding allergens in daily life, especially in industrial and cosmetic products. In order to prevent ACD, better cooperation between industry and dermatologists is needed.*

Key words: *fragrances, contact allergic dermatitis,* Myroxylon pereirae *(balsam of Peru), fragrance mix, fragrance ingredients*

Introduction

Allergy to fragrance materials was recognized at the beginning of the 20th century. It was first noticed in scabies patients treated with topical balsams containing fragrance materials[1]. Fragrances consist of many natural or chemical ingredients, as shown by results published in 1975 by Fisher, who composed a long list of fragrance ingredients and suggested concentrations for epicutaneous tests[2]. In 1977 Larsen developed a fragrance mixture (FM) which contained 8 ingredients (cinnamyl alcohol, cinnamal, alpha-amyl cinnamal, eugenol, isoeugenol, geraniol, *Evernia prunastri* (oak moss) absolute and hydroxycitronellal); the result was a screening patch-test substance for fragrance allergy[3]. Today we know that a single perfume may contain over 300 individual ingredients. For this reason, detection of allergy to one specific component is a difficult and complex matter. Another problem is presented by false negative/positive reactions to fragrance ingredients. For example, some studies have shown that eugenol and cinnamal are capable of inhibiting contact dermatitis and contact urticaria reaction. This is called the quenching phenomenon[4–6]. Fragrances are small-molecular-weight compounds of different chemical structures. All of the pure chemicals in the fragrance mix are phenolic in structure, except geraniol and hydroxycitronellal, which are terpenes. They can cause reactions by means of several mechanisms. For instance, reactive compounds bind directly to proteins, which are subsequently processed and presented to specific T lymphocytes[7,8] and nonreactive compounds gain their immunogenicity only after metabolic activation through oxidation of the parent compound[9]. Enzymes involved in this reaction are cytochrome P450 enzymes (CYPs)[10]. Next to nickel, fragrances are the most common cause of contact allergic dermatitis (CAD), which is a form of delayed-type hypersensitivity reaction mediated by T lymphocytes[11,12]. Allergy to fragrances can present a serious

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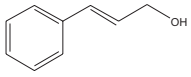
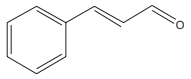
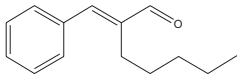
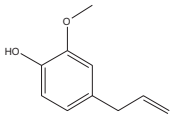
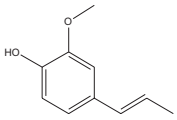
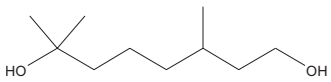
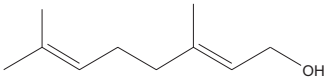
clinical problem for the population, especially for atopic individuals, because of widespread use of fragrance materials in creams, lotions, detergents and other personal and household products. In our study we also involved *Myroxylon pereirae* – balsam of Peru (MP) because it is the third most prevalent allergen and has a rather widespread use. MP is a sticky aromatic liquid that comes from cutting the bark of the *Myroxylon pereirae* tree, native to Central America. It contains a mixture of many substances generally related to cinnamon, vanilla, and clove fragrances and flavorings. Hjorth established that MP contained many potential allergens and it was considered the most important patch test indicator for fragrance allergy for a long time[13–15]. Many patients with a history of fragrance allergy may react to MP[16,17]. Concomitant reactions between FM and MP are well-known phenomena[15,18–20] because five of the FM components (cinnamyl alcohol, cinnamal, alpha-amyl cinnamal, euge-

TABLE 1
CHARACTERISTICS OF FRAGRANCE INGREDIENTS

Fragrance ingredient	Chemical formula	Structural formula	Characteristics
cinnamyl alcohol	$C_9H_{10}O$		White to slightly yellow solid, odor of hyacinth Phenol structure *Cinnamomum spp.*
cinnamal	C_9H_8O		A clear yellow to greenish yellow liquid with a pungent spicy note Phenol structure *Cinnamomum spp*
alpha-amyl cinnamal	$C_{14}H_{18}O$		Synthetic essential oil, intense odor of jasmine Phenol structure
eugenol	$C_{10}H_{12}O_2$		Clear to pale yellow oily liquid, powerful spicy odor of clove and a pungent taste Allyl chain-substituted guaiacol, phenol structure *Eugenia aromaticum; Eugenia caryophyllata*
isoeugenol	$C_{10}H_{12}O_2$		Colorless to light yellow-brown transparent liquid, odor of clove, weaker than eugenol Phenol structure Nutmeg oil and ylang ylang oil
hydroxycitronellal	$C_{10}H_{18}O_2$		Synthetic floral fragrance, sweet fresh odor of lily of the valley Non-cyclic primary alcohols
geraniol	$C_{10}H_{18}O$		Clear to pale-yellow oil insoluble in water Non-cyclic monoterpene alcohol *Rose oil; palmarosa oil; citronella oil*
Evernia prunastri (oak moss)	*Evernia prunastri*		Green to greenish-white and rough thalli – dry; dark olive-green to yellow-green and rubbery thalli – wet Contains: atranorin, chloroatranorin, everic acid, usnic acid, resin acid, dehydroabietic acid, abietic acid, diethyl phthalate, alpha-terpineol, cedrane, linalool etc.

nol, and isoeugenol) are found in MP. Therefore, a positive patch test to MP often indicates fragrance allergy.

The aim of the present study was to determine the incidence of fragrance-induced CAD using a specific fragrance mix. Patch testing according to the International Contact Dermatitis Research Group (ICDRG) system was conducted during 2001–2005 in Zagreb, Croatia.

Materials and Methods

Patients

A total of 27,815 patients with suspected CAD were included in the study. The epicutaneous (patch) tests and related data collection were carried out during a period of five consecutive years (2001–2005) at the Allergy Clinic of the Department of Dermatology and Venereology, Zagreb University Hospital Center and School of Medicine, Zagreb, Croatia.

Materials

Fragrances, *Myroxylon pereirae* (balsam of Peru) and fragrance mix 8% in petrolatum (consisting of cinnamal (cinnamal) – 1%; cinnamyl alcohol – 5%; alpha-amyl cinnamal – 5%; eugenol – 5%; isoeugenol – 5%; geraniol – 5%; hydroxycitronellal – 1%; and Evernia prunastri (oak moss) absolute – 2%) (Table 1), used for patch testing, were obtained from the Immunology Institute in Zagreb, Croatia.

Methods

Patch-test allergens were applied on the patients' upper back with 2-day occlusion. According to the International Contact Dermatitis Research Group (ICDRG) system, the tests were read 48 and 72 hours after their application[21,22]. The test results were interpreted using the following scale: negative reaction (0); macular erythema (?); erythema/in filtration and possibly papules (1+); erythematous papules and/or vesicles (2+); spreading blisters and/or crust with ulceration (3+); and irritant reaction (IR); whereby 1+, 2+ and 3+ were considered positive allergic reactions[21]. Statistical analysis was performed using the STATISTICA software, Version 7.1. (StatSoft, Inc.).

Results

Out of 27,815 patients, 3,065 (11%) patients with CAD were estimated; 509/3,065 (16.6%) were positive to FM, and 258/3,065 (8.4%) were positive to MP (Table 2). The fragrance series was tested on 157 (age range 7 – 78; mean age: 40.51; median: 40) patients: 113 female (71.97%; age range 7 – 74; mean age: 38.95; median: 39) and 44 male (28.0%; age range 10 – 78; mean age: 44.52; median: 48.5), who were chosen out of the 509 patients positive to fragrance allergens. The most frequent allergens were isoeugenol 57.9% (91/157), eugenol 55.4% (87/157), cinnamyl alcohol 34.4% (54/157) and *Evernia prunastri* (oak moss) 24.2% (38/157). There were 39.5% (62/157) patients positive to both MP and FM (Figures 1 and 2). Positive reactions to both MP and FM were calculated according to year: 2001 – 30% were patch test positive to FM and MP. From 10 subjects allergic to FM, 3 were also positive to MP (3/10); 2002 – 53.33% (16/30); 2003 – 46.15% (18/39); 2004 – 31.3% (9/29); 2005 – 32.65% (16/49).

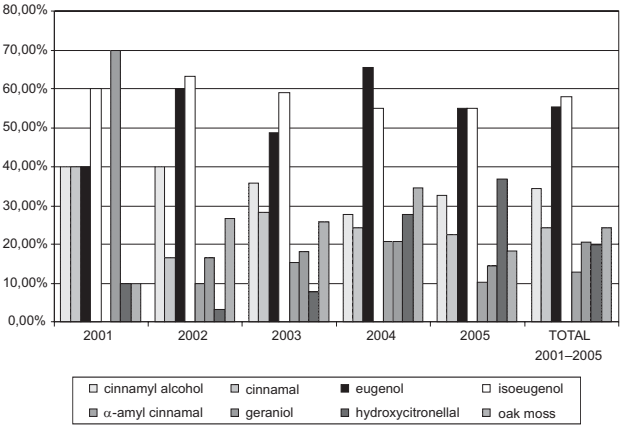


Fig. 1. Positive patch test reactions to individual components of the fragrance mix during a five-year period.

Discussion

Fragrances are ubiquitously used in cosmetics such as creams, lotions, medication, household and industrial products. They are also very common ingredients in food and paints[23]. Such a widespread distribution leads to unavoidable exposure, especially to those products that come into direct contact with the skin. Fragrances have become a major cause of CAD, which is a form of delayed-type hypersensitivity reaction[12]. A dramatic increase of adverse reactions to fragrances has been documented during the past 10 years. So far, our knowledge about CAD to fragrances arises from skin patch testing

TABLE 2
NUMBER OF PATIENTS HYPERSENSITIVE TO FRAGRANCE MIX AND MYROXYLON PEREIRAE (BALSAM OF PERU) DURING 2001–2005

YEAR	2001	2002	2003	2004	2005	TOTAL
Number of patch tested patients	5.654	5.617	5.514	5.540	5.490	27.815
CAD confirmed	736 (13.01%)	616 (10.96%)	602 (10.91%)	554 (10.00%)	557 (10.14%)	3065 (11%)
Fragrance mix positive	142 (19.29%)	96 (15.58%)	118 (19.60%)	80 (14.44%)	73 (13.10%)	509 (16.6%)
Myroxylon pereirae (balsam of Peru) positive	78 (10.59%)	45 (7.30%)	54 (8.97%)	42 (7.58%)	39 (7%)	258 (8.4%)

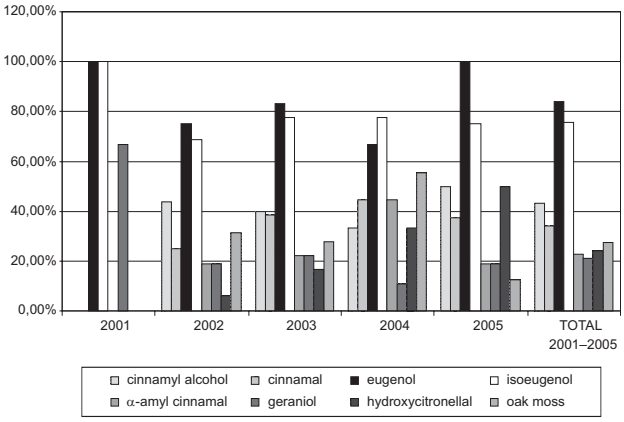


Fig. 2. Results of concomitant allergy to fragrance components in subjects allergic to Myroxylon pereirae *(balsam of Peru).*

using an FM composed of eight different substances. Recent data from the North American Contact Dermatitis Group (NACDG) indicate that 10.4% of tested patients were positive to the fragrance mix, while 11.6% of tested patients were positive to MP[24]. De Groot and Frosch published results for fragrance allergy in Europe, showing prevalence rates from 5 to 11%[12]. Our study shows slightly higher results: during a five-year period, 16.6% patients tested positive to FM, while 8.4% tested positive to MP. Our five-year study shows results similar to those of other studies (39.5% patients had positive reactions to both MP and FM). Furthermore, the results show that fragrance allergy increases with age and that it is more common in female than in male patients[25,26]. The mean age of patients with fragrance allergy in mixed patch tested populations was between 40 and 50, with males (44.5 mean age) being slightly older than females (38.9 mean age). Females were 2.57 times more likely to have an allergic reaction than males. This may be explained by their more frequent exposure to fragranced products (baths, lotions, make-up, hair care products, nail products and household products) and correlates with the findings of other studies[25–29]. In a study conducted on 176 patients, Larsen et al.[30] showed a co-reaction to FM and fragrance ingredients in 85.6% of patients. Our results showed that 90.4% of patients exhibited a co-reaction to FM and fragrance ingredients. If we take a look at every individual ingredient in FM, we can determine that some ingredients have a higher prevalence of allergy than others. By analyzing patch-test results for allergies concomitant to single fragrance ingredients and FM, we established that the most frequent allergens were isoeugenol (57.9%) and eugenol (55.4%). Isoeugenol and its isomer-eugenol are used in perfumes, flavorings, essential oils and in medicine (local antiseptics and analgesics). These data correlate with some other studies[31–34]. Schnuch reported that *Evernia prunastri* (oak moss) was the most frequent allergen, followed by isoeugenol as the second most frequent one[15]. The same result was obtained by Buckley et al.[26] *Evernia prunastri* (oak moss) is a natural fragrance derived from the lichen *Evernia prunastri* and widely used in fine perfumes, aftershave lotions and other cosmetic products. It has a very complex chemical composition which includes evernic and usnic acid, atranorin and chloroatranorin[26,35]. In our study *Evernia prunastri* (oak moss) (24.2%) came after cinnamyl alcohol (34.39%), sharing the fourth place with cinnamal (24.2%). Trattner and David showed that the most common allergens were cinnamal and *Evernia prunastri* (oak moss)[36]. Cinnamyl alcohol, which has a hyacinth-like odor, and cinnamal, which has a spicy aroma, are closely related chemicals. They naturally occur in cinnamon bark, leaf and oil, curry leaf and MP. Cinnamal, known to cause occupational allergic contact dermatitis (CAD) in bakers and candy makers, was established to be a cause of toothpaste-induced CAD[37]. Geraniol, an essential oil ingredient found in both jasmine and geranium oil and extensively used in household products and deodorants, caused 20.38% of allergic reactions. Hydroxycitronellal (sweet fresh odor of lily of the valley, synthetic floral fragrance) caused 19.75% of allergic reactions, while alpha-amyl cinnamal (intense odor of jasmine, synthetic essential oil) caused 12.74% of reactions, which means they induced less allergies in patients with a positive fragrance mix patch test. Similar results were given by other authors[15,30,31]. Theoretically, the ranking of the fragrance components may be due to differences in their exposure. Isoeugenol, eugenol and *Evernia prunastri* (oak moss) are frequently used, while geraniol, hydroxycitronellal and alpha-amyl cinnamalare rarely used. In his paper Schnuch analyzed 59 household products and 70 deodorants, establishing that 41% of household products and 76% of deodorants contained geraniol, whereas *Evernia prunastri* (oak moss) and isoeugenol very rarely appeared in household products[15,38–40]. When comparing the fragrance ingredients of the FM and MP, the most frequent allergens were eugenol (83.87%), isoeugenol (75.81%) and cinnamyl alcohol (43.55%).

Conclusion

Our study shows that fragrance allergy is fairly common. As we have demonstrated, the fragrance mix and MP are frequent contact allergens. It is also important to estimate fragrance ingredients and balsams that can cause contact urticaria. Persuading patients that fragrance allergy is a relevant issue and that it needs to be avoided presents a bigger problem than its actual diagnosis. Products labeled as »fragrance-free« may contain natural plant extracts, flower extracts or essential oils, all of which are actually fragrances. Natural products also present a serious problem for fragrance-sensitive patients, although this is often difficult to explain to them. Therefore, dermatologists, industry workers and pharmacists must work together to educate their clients and patients about fragrance allergy and products containing fragrances in order to successfully reduce the occurrence of fragrance-induced contact allergies in consumers.

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KONTAKTNA ALERGIJA NA SMJESU MIRISA I PERUVIJANSKI BALZAM; RETROSPEKTIVNA STUDIJA

SAŽETAK

Uz nikal, mirisi su zbog svoje široke uporabe najčešći uzrok alergijskog kontaktnog dermatitisa. Tijekom perioda od pet godina 3065 pacijenata s kontaktnim dermatitisom bilo je podvrgnuto testiranju na mješavinu mirisa. 509 (16,6%) pacijenata bilo je alergično na mješavinu mirisa, a 258 (8,4%) na peruvijanski balzam. Među njima, 157 pacijenata je testirano na pojedine komponente mirisa koje uključuju: cimetni aldehid, cimetni alkohol, eugenol, izoeugenol, geraniol, hidroksicitronelal, alfa-amil cimetni aldehid te ekstrakt hrastove mahovine. Najčešći alergeni bili su izoeugenol 57,9% (91/157), eugenol 55,4% (87/157), cimetni alkohol 34,4% (54/157) te ekstrakt hrastove mahovine 24,2% (38/157). 62 pacijenata (39,5%) imalo je pozitivnu reakciju na oba alergena – mješavinu mirisa i peruvijanski balzam. Rezultati upućuju na važnost izbjegavanja alergena u dnevnom životu, industriji i kozmetičkim pripravcima. Potrebna je bolja komunikacija između farmaceuta, dermatovenerologa i industrije zbog prevencije alergijskog kontaktnog dermatitisa.