Topical botanically derived products: use, skin reactions, and usefulness of patch tests. A multicentre Italian study

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Summary

Background. The evidence on the safety of topical preparations containing botanical extracts is limited.

Objectives. To assess (i) the use of botanically derived compounds in a large population, (ii) the incidence of cutaneous side-effects, and (iii) the diagnostic usefulness of patch testing.

Methods. A questionnaire was used in 2661 patients to assess both the prevalence and type of topical botanical preparations used, and the occurrence of adverse skin reactions. Patients declaring adverse reactions were patch tested with (i) the Italian (SIDAPA) baseline series, (ii) an additional botanical series, and (iii) the patients' own products.

Results. Of the patients, 1274 (48%) reported the use of topical botanical products; 139 patients (11%) commented on adverse cutaneous reactions; 75 (54%) showed positive reactions with the Italian baseline series. Among the 122 patients tested with the botanical series, 19 (16%) showed positive reactions, in many cases with concomitant relevant positivity to at least one allergen of the Italian series connected with cosmetics. The commonest botanically derived allergens were propolis, Compositae extracts, and *Melaleuca alternifolia* (tea tree) oil.

Conclusions. Contact allergy is a possible adverse effect of natural products. Baseline series supplemented with the commonest botanical allergens may be adequate for detecting most of the cases of contact allergy to natural topical products.

Key words: adverse effects; botanical products; contact dermatitis; herbal remedies; herbal therapies; patch test

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The use of cosmetics and topical remedies containing natural ingredients, mainly botanical extracts, is increasing (1-4). Many botanically derived principles are used in cosmetic formulations designed to moisturize, cleanse, or perfume. Moreover, plant extracts are included in various topical products marketed for their claimed antioxidant, anti-inflammatory, analgesic and antimicrobial properties.

Evidence on the efficacy of the medicinal herbs contained in many preparations is usually limited, and adequate scientific proof of their efficacy is lacking (5). Furthermore, despite the popular belief in the harmlessness of natural ingredients, several cases of adverse reactions to plant extracts have been reported, in particular cutaneous side-effects such as allergic contact dermatitis, irritant contact dermatitis, phototoxic reactions, and contact urticaria (6-13). However, the number of reported cases of contact dermatitis seems small when compared with the widespread use of botanical remedies, and little is known about the real incidence of adverse reactions to botanical extracts contained in cosmetic and topically used herbal products.

This Italian multicentre study aimed to analyse: (i) the popularity and use of topical products containing botanically derived components in a large population, (ii) the most commonly used botanical extracts, (iii) the purported function of these preparations, (iv) the reasons behind the choice of these non-conventional treatments, (v) the perceived tolerance and efficacy of such remedies, (vi) the incidence of possible cutaneous side-effects associated with their use, (vii) the frequency of true contact allergy to topical natural products, and (viii) the diagnostic usefulness of patch testing with both the baseline screening series and a specifically prepared additional botanical series.

Materials and Methods

Nine Italian cutaneous allergy units in different geographical areas [Bari, Bologna, Ferrara, Genova, Messina, Milano, Perugia, Verona, Zingonia-Osio Sotto (BG)] participated in the study between September 2011 and June 2012. A self-administered questionnaire was given to all consecutive outpatients presenting for allergological investigation. Patients were not subjected to any demographic or clinical selection. Refusal or inability to complete the questionnaire were the only exclusion criteria. The questionnaire was composed of two sections. The first section included nine items, which solicited the following information: demographics, use of topically applied botanical preparations (regular or occasional use), reasons for choosing natural products as opposed to conventional synthetic compounds, characteristics of the treatment employed [formulation, natural active principle(s), treated body surface(s), cosmetic and/or medical usage, perception of efficacy and tolerability], and the occurrence of adverse reactions.

Patients who declared adverse reactions were asked to fill in a second five-item section of the questionnaire, with the aim of investigating the responsible botanical

Table 1. Allergens of the botanical series with the concentrations and vehicles used for patch testing

| Allergen | Concentration and vehicle |
|---|---------------------------|
| Propolis | 20% pet. |
| Melaleuca alternifolia extract (tea tree oil) | 5% pet. |
| Compositae mix | 5% pet. |
| Calendula officinalis extract | 10% ether |
| Aloe vera | 5% pet. |
| Centella asiatica extract | 2% ethanol |
| Peppermint oil | 1% pet. |
| Chamomile oil | 1% pet. |
| Arnica montana extract | 0.5% pet. |
| Sesquiterpene lactone mix | 0.1% pet. |
| Achillea millefolium extract | 1% pet. |

ingredients, skin reactions, which body area was affected, how the adverse reaction had been managed (suspension of use of the natural product, general practitioner or dermatologist consultation), and which treatments had been performed.

All of the patients declaring adverse reactions were patch tested with the Società Italiana Dermatologia Allergologica Professionale ed Ambientale (SIDAPA) baseline series (Lofarma S.p.A., Milano, Italy) as well as an additional botanical series, supplied by FIRMA SpA, Florence, Italy (Table 1). When possible, the patients' own botanical products were also tested. Exclusion criteria for patch testing were: photo-exposure, application of topical corticosteroids to patch test sites, and systemic treatment with immunosuppressive drugs.

Patch tests were performed with Finn Chambers[®] (diameter, 8 mm; SmartPractice[®], Phoenix, AZ, USA) on Scanpor[®] tape (Norgesplaster A/S, Vennesla, Norway); allergens were applied on the upper back, and removed after 48 hrs. The sites were examined on removal and 24 or 48 hrs after removal, according to the recommended International Contact Dermatitis Research Group guidelines (14).

Reactions were interpreted as relevant on the basis of the identification of the allergen in a topical product or a highly suggestive history of cutaneous adverse reactions after contact with topical products containing the allergen.

The protocol was approved by the local research ethics committee, and written informed consent was obtained from all of the participants.

Results

A total of 2661 patients (1905 females and 756 males) were enrolled in the study. Demographic characteristics of the enrolled population are shown in Table 2.

| Table 2. Demographic characteristics of the study population, and the prevalence of botanical product use in the study group, according to |
|---|
| sex and age |

| | Demog | raphics | No | use | Spora | dic use | Regular use | | | |
|---------|-----------|--------------------|-----------|-----------|-----------|-----------|-------------|-----------|--|--|
| Age | Males, | Females, | Males, | Females, | Males, | Females, | Males, | Females, | | |
| (years) | no. (%) | %) no. (%) no. (%) | | no. (%) | no. (%) | no. (%) | no. (%) | no. (%) | | |
| < 14 | 34 (5) | 29 (1) | 24 (4) | 15 (2) | 8 (4) | 12 (2) | 2 (5) | 2 (1) | | |
| 15-20 | 34 (5) | 110 (6) | 24 (4) | 41 (5) | 9 (5) | 42 (6) | 1 (3) | 27 (9) | | |
| 21-30 | 114 (15) | 349 (18) | 72 (14) | 139 (16) | 34 (18) | 145 (19) | 8 (20) | 65 (21) | | |
| 31-40 | 148 (19) | 359 (19) | 94 (18) | 115 (13) | 46 (25) | 170 (23) | 8 (20) | 74 (24) | | |
| 41-50 | 138 (18) | 393 (21) | 96 (18) | 170 (20) | 35 (19) | 166 (22) | 7 (17) | 57 (18) | | |
| > 50 | 288 (38) | 665 (35) | 221 (42) | 376 (44) | 53 (29) | 205 (28) | 14 (35) | 84 (27) | | |
| Total | 756 (100) | 1905 (100) | 531 (100) | 856 (100) | 185 (100) | 740 (100) | 40 (100) | 309 (100) | | |

One thousand three hundred and eighty-seven (52%) of the 2661 patients questioned denied using herbal remedies. Of the 1274 users of the natural products (48%) of the enrolled population), 349 (27%) of users) reported use on a regular basis, and 925 (73%) reported sporadic use. The sex and age distribution of the users and non-users is shown in Table 2.

The motivations for use were found to be as follows: curiosity 665 (52% of the total) [122 (18%) males and 543 (82%) females]; perceived safety of botanical products with respect to synthetic preparations 490 (38%) [75 (15%) males and 415 (85%) females]; search for an alternative treatment as conventional therapies had failed 83 (7%) [20 (24%) males and 63 (76%) females]; and mistrust in traditional topical products and exclusive use of natural products 36 (3%) [8 (25%) males and 28 (75%) females].

The botanically derived products used were, in decreasing order: body lotions (677 users; 81 males and 596 females); face creams (592 users; 62 males and 530 females); shampoos, lotions, and hair products (504 users; 101 males and 403 females); detergents (384 users; 80 males and 304 females); perfumes and deodorants (258 users; 51 males and 207 females); lip balms (221 users; 11 males and 210 females); decorative cosmetics (217 users; 3 males and 214 females); and products to treat anogenital ailments (52 users; 1 male and 51 females).

The treated body areas were: limbs 1145 (39% of the total) [200 males (18%) and 945 females (82%)]; face 724 (25%) [84 males (12%) and 640 females (88%)]; scalp 477 (16%) [101 males (21%) and 376 females (79%)]; trunk 449 (15%) [89 males (20%) and 360 females (80%)]; and genitalia 119 (4%) [16 males (13%) and 103 females (87%)]. As patients could report multiple treated body areas, the total of treated areas was greater than the number of patients.

The cosmetic or medical reasons for using botanical products are shown in Table 3.

Table 3. Cosmetic and medical uses of botanical products

| Cosmetic and medical motivation for use | Males | Females | Total |
|---|-------|---------|-------|
| Moisturizing/hydration | 64 | 429 | 493 |
| Skin cleansing | 76 | 289 | 365 |
| Itching/prurigo | 42 | 199 | 241 |
| Eczema and other dermatoses | 60 | 159 | 219 |
| Anti-wrinkle creams | 14 | 131 | 145 |
| Cellulitis | 6 | 131 | 137 |
| Vasoprotection and venous insufficiency | 11 | 122 | 133 |
| Hair fragility/hair loss | 33 | 100 | 133 |
| Decorative cosmetics | 15 | 118 | 133 |
| Photoprotection | 10 | 90 | 100 |
| Genital ailments | 14 | 69 | 83 |
| Haematomas | 16 | 59 | 75 |
| Acne | 5 | 64 | 69 |
| Insect bites | 4 | 64 | 68 |
| Bacterial and fungal skin infections | 8 | 37 | 45 |
| Rosacea | 3 | 32 | 35 |
| Hyperpigmentation/skin macules | 6 | 29 | 35 |
| Oral mucosal disorders | 3 | 29 | 32 |
| Atopic dermatitis | 4 | 27 | 31 |
| Haemorrhoids and anal ailments | 6 | 18 | 24 |
| Hair dyes | 0 | 16 | 16 |
| Arthralgia/myalgia | 6 | 9 | 15 |
| Dandruff and seborrhoea | 9 | 4 | 13 |
| Psoriasis | 2 | 0 | 2 |
| Other | 93 | 409 | 502 |

The reported botanical extracts present in the used products were, in decreasing order: *Aloe vera* (516 cases), marigold (276 cases), chamomile (263 cases), *Arnica* (203), propolis (188 cases), stinging-nettle (100 cases), peppermint (99 cases), *Melaleuca alternifolia* (78 cases), *Echinacea* (60 cases), *Centella* (58 cases), horse chestnut (27 cases), St John's wort (*Hypericum*) (27 cases), burdock (19 cases), and other natural ingredients (196 cases); 171 patients did not remember the active herbal principle.

Table 4. Prevalence of adverse reactions to botanical topical products in different age groups

| | | | Age (years) | | | | | | | | | | | | | |
|---------|-------|------|-------------|-------|-------|-------|------|--|--|--|--|--|--|--|--|--|
| | Total | ≤ 14 | 15-20 | 21-30 | 31-40 | 41-50 | > 50 | | | | | | | | | |
| Males | 19 | 1 | 0 | 1 | 5 | 1 | 11 | | | | | | | | | |
| Females | 120 | 2 | 10 | 16 | 27 | 22 | 43 | | | | | | | | | |
| Total | 139 | 3 | 10 | 17 | 32 | 23 | 54 | | | | | | | | | |

A total of 742 patients (58%) considered the botanical products to be well tolerated and efficacious (119 males and 623 females); 349 (27%) considered the products to be well tolerated, but to have doubtful efficacy (70 males and 279 females); and 183 (15%) considered the products to be inefficacious and/or dangerous (36 males and 147 females).

Of the 1274 users, 139 (11%) reported cutaneous adverse reactions after botanical product application [19 males (14%) and 120 females (86%)]. Of the 139 patients with adverse effects, 93 (67%) reported sporadic use of botanical products (17 males and 76 females), and 46 (33%) (2 males and 44 females) reported regular use. Table 4 shows the prevalence of the adverse reactions to botanical products in different age groups.

The reported adverse reactions were described as a worsening of the previous dermatitis (23 patients), or the development of new, different cutaneous symptoms and/or signs such as itching, burning, erythema, swelling, and vesiculation. Some patients reported more than one adverse reaction.

The affected body areas are shown in Table 5.

The adverse reactions to the topical botanical products were variably managed: 53 patients (38%) (8 males and 45 females) self-managed the adverse reactions, 15 (11%) (2 males and 13 females) consulted their general practitioner, 9 (6%) (1 male and 8 females) consulted the emergency ward, and 62 (45%) (8 males and 54 females) considered a dermatological consultation.

The adverse reactions were managed by discontinuing use of the topical botanical product in 51 patients; 38 patients used topical corticosteroids; 22 patients applied emollients and soothing products; 19 patients used topical corticosteroids plus antihistamines; 11 patients

were treated with systemic corticosteroids; and other, unconventional, therapies were used by 18 patients.

All of the 139 patients who reported adverse reactions underwent patch testing with the SIDAPA series. Sixty-four patients did not show any positive reaction, and a total of 130 positive reactions were observed in 75 patients (54%). Of the 130 positive reactions, 55 were considered to be relevant, 49 not relevant, and 26 of doubtful relevance.

The six allergens most frequently found to be positive in the SIDAPA series were nickel sulfate (36 reactions), fragrance mix 1 (17 reactions), methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI) (15), cobalt chloride (13), *Myroxylon pereirae* (9), and potassium dichromate (6).

For the allergens strictly connected with topical products and cosmetic use [fragrance mix 1, MCI/MI, *M. pereirae*, formaldehyde, paraben mix, hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC), lanolin alcohols, and colophonium], 54 positive reactions were found, 42 of which were relevant, in 31/139 patients (22%).

Of the 139 patients reporting adverse reactions, 122 underwent patch testing with the botanical integrative series (Table 1). In fact, 17 patients did not give consent to be tested for this further integrative series. Among the 122 tested patients, 19 (16%) showed 29 positive reactions, all of which were relevant (Table 6); 10 patients showed concomitant relevant positivity to at least one allergen of the SIDAPA series connected with cosmetics (Table 6).

When possible, patch tests with patients' own botanical products were performed. A total of 98 patch tests were performed in 59 patients. A total of 14 positive reactions, all of which were relevant, were detected in 13 patients. Among the patients who showed a positive reaction to their own natural products, 2 also had a relevant sensitization to an allergen of the herbal integrative series, whereas 10 had a relevant sensitization to at least one cosmetic allergen in the SIDAPA series.

Discussion

The findings of the present Italian study confirm the great popularity of topical preparations containing botanical extracts, as 48% of the patients questioned used natural

Table 5. Body areas affected by cutaneous adverse reactions

| | | Scalp | Face/neck | Eyelids | Lips | Trunk | Upper limbs | Hands | Anogenital area | Lower limbs | Feet |
|---------|-----|-------|-----------|---------|------|-------|-------------|-------|-----------------|-------------|------|
| Males | 19 | 3 | 4 | 3 | 2 | 2 | 5 | 3 | 1 | 5 | 2 |
| Females | 120 | 14 | 53 | 15 | 8 | 21 | 23 | 27 | 6 | 21 | 4 |
| Total | 139 | 17 | 57 | 18 | 10 | 23 | 28 | 30 | 7 | 26 | 6 |

 Table 6.
 Positive reactions to allergens of the botanical series and concomitant positive reactions to cosmetic allergens of the SIDAPA series

| | n HICC | 1 | I | I | I | I | I | I | I | T | I | Ι | I | I | Ι | I | I | + | I | I |
|--|--|---|---|---|---|---|---|---|---|---|----|---|----|----|----|----|----|----|----|----|
| | Paraben mix | I | I | I | I | I | I | I | I | 1 | I | I | + | I | I | I | I | I | I | I |
| | Lanolin alcohols Formaldehyde | ı | I | Ι | I | I | I | I | ı | ı | ı | I | ı | I | I | I | ı | I | I | ı |
| Cosmetic allergens in the SIDAPA series | Lanolin alcohols | I | I | I | I | I | I | I | I | I | I | I | I | I | I | I | I | I | I | ı |
| netic a s SIDAI | MC MC | I | T | Ι | T | T | I | I | I | I | T | Ι | + | T | Ι | ı | I | Ι | ı | T |
| Cosr in the | Fragrance MCI/ Lanolin mix MI alcohols | ı | I | Ι | + | I | ı | + | I | ı | ı | I | ı | + | I | I | + | + | + | ı |
| | <i>Myroxylon</i> pereirae Colophonium | ı | I | I | Ι | I | I | ı | I | I | I | I | I | I | I | + | Ι | I | Ι | ı |
| | Myroxylon pereirae | ı | I | + | I | I | I | I | + | I | I | Ι | + | + | Ι | Ι | I | Ι | Ι | I |
| | Achillea millefolium | ı | ı | Ι | ı | ı | ı | ı | I | ı | ı | I | ı | ı | I | ı | ı | + | ı | I |
| | Amica Sesquiterpene Achillea Myroxylon nontana lactone millefolium pereirae | I | ı | I | Ι | ı | I | I | I | I | I | Ι | I | ı | Ι | Ι | ı | Ι | Ι | I |
| | _ | ı | I | Ι | ı | + | ı | ı | ı | ı | 1 | I | 1 | I | I | ı | ı | I | ı | I |
| | Centella asiatica Peppermint Chamomile | I | I | + | Ι | I | I | I | I | ı | ı | Ι | ı | I | Ι | I | Ι | Ι | I | I |
| of the series | Peppermint | ı | I | I | I | + | + | I | I | ı | ı | Ι | ı | + | Ι | I | I | Ι | I | I |
| Allergens of the botanical series | Centella asiatica F | ı | I | + | Ι | I | I | ı | I | + | + | I | I | I | I | I | I | I | I | I |
| | | 1 | ī | I | ı | + | ı | I | ı | I | ı | ı | ı | ī | ı | ı | ı | ı | ı | ı |
| | Calendula Aloe officinalis vera | ı | I | + | I | + | ı | ı | ı | ı | ı | I | ı | I | I | I | I | I | I | I |
| | Melaleuca Compositae Calendula Aloe Iternifolia oil mix officinalis vera | ı | I | Ι | I | + | ı | ı | ı | ı | ı | I | ı | I | I | I | I | I | I | ı |
| | Ø | ı | I | I | I | I | + | ı | ı | ı | ı | I | ı | + | I | I | I | I | I | I |
| | Propolis | + | + | + | + | ı | ı | + | + | ı | + | + | + | ı | + | + | + | Ι | + | + |
| | Patient no. | _ | 2 | М | 4 | 2 | 9 | 7 | ∞ | 6 | 10 | 1 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 |

HICC, hydroxyisohexyl 3-cyclohexene carboxaldehyde; MCI, methylchloroisothiazolinone; MI, methylisothiazolinone.

topical products. A higher prevalence was found in a previous single-centre observational study, as well as in European published estimates (5, 16). Concerning sex differences, as expected, botanical products were reported to be used more frequently by women (55% of the enrolled female population) than by men (30% of the male population). On comparison of the use (either regular or sporadic) of botanical preparations among the age groups, the highest prevalence was found in 31–40year-old patients (59%), and the lowest prevalence was found in > 50-year-old patients. The high prevalence found in the lowest age group (50% of < 21-year-old patients) seems to suggest a great interest in alternative natural remedies both among young subjects and as regards their use in children. Curiosity and the perception that herbal remedies are safer than synthetic alternatives have been found to be the main reasons for choosing natural products.

A great variety of natural products were found to be used by our study population; among these, dermatological 'leave-on' body lotions were the most widely used topical botanical preparations, although face creams, hair care products, cleansers and perfumes were also popular (Table 3). Likewise, almost all body areas were found to be treated with natural compounds, and natural products were employed for both cosmetic and medical purposes.

The most widely used plant in the study population was *Aloe vera*, as had been found previously (16). Compositae plants (marigold, chamomile, arnica) and propolis were the top five natural ingredients. Botanical compounds were judged to be both efficacious and well tolerated by the large majority of patients using these products.

In spite of the general belief, 11% of users reported one or more adverse cutaneous reactions to botanical products. This percentage was higher than previously observed (16). A slightly higher percentage of women (11%) than of men (8%) reported these side-effects. A higher rate of reported adverse reactions was found among patients aged > 50 years than in the other age groups. The reported adverse reactions were described mainly as worsening of a previous dermatitis or, to a lesser extent, the development of cutaneous symptoms consistent with contact dermatitis, especially on the face and neck, hands, and upper limbs.

The majority of patients consulted a dermatologist in order to resolve the cutaneous side-effects, probably because of the severity of symptoms, although a considerable number of the patients managed the skin disorder by themselves. Discontinuation of the use of topical botanical products was the main therapeutic approach for cutaneous side-effects; topical

corticosteroids and emollients were frequently used as well, and 11 patients (8%) required oral steroids.

It is of interest that, among the patients reporting cutaneous side-effects and who were patch tested with the SIDAPA series, 54% (75 of 139 tested) showed at least one positive reaction. Regarding the frequency of sensitization to the allergens included in the SIDAPA series that are typically found in cosmetics and topical medicaments, such as fragrance mix, MCI/MI, M. pereirae, formaldehyde, paraben mix, HICC, colophonium, and lanolin alcohols, 31 patients (22%) showed relevant positive sensitizations. This prevalence was higher than that of allergic contact dermatitis caused by cosmetic allergens detected in other series (15). As previously shown, fragrances were the most common ingredients causing contact allergy in our population, with positive reactions to fragrances being found in 12% of the patch tested patients (12, 17). This prevalence is difficult to compare with those of other studies in which only patients selected for suspected cosmetic allergic contact dermatitis were investigated (15, 18). It may be hypothesized that the rate of allergy to fragrances would have been increased if the additional allergen fragrance mix II had been used in our study (19).

Overall, our findings seem to suggest that a relevant proportion of patients reporting cutaneous side-effects of natural products are sensitized to cosmetic ingredients of the topical products. However, this does not reflect true sensitization to the botanical principles, but exclusively sensitization to a cosmetic product.

When the patients were also tested with an integrative botanical series, 29 relevant positive reactions were found in 19 patients (16% of the tested patients). This result seems to indicate that allergy to botanical ingredients is not uncommon in the case of adverse reactions.

Nevertheless, even though our botanical series matched the plants most frequently present in natural products used by the interviewed study population, the prevalence of positive reactions to at least one component of the plant series was lower than previously found. In a previous US study, 47.6% of patients of a selected high-risk group for botanical allergy developed a relevant positive reaction to botanical allergens, in comparison with 3.4% of a control group (13). In an earlier study, 59% of a small series of patients with a clinical diagnosis of cosmetic dermatitis had one or more positive patch test reactions to plant components (12). These discrepancies are probably attributable to differences in both patient selection criteria and the botanical series tested.

The most common natural allergen seen was propolis (14 cases detected) (Table 6). This result agrees with that

of other studies (13), and may be related to both the wellknown sensitizing property of propolis and its widespread use as a natural active principle in our population (20-22). Among the 14 patients with contact allergy to propolis, 4 showed a concomitant positive reaction to fragrance mix and 3 to M. pereirae, confirming possible cross-reactivity resulting from shared constituents (22). Surprisingly, although 78 subjects reported the use of formulations containing Me. alternifolia oil, only two positive reactions to this ingredient were found. This is not in line with the findings of previous studies, where tea tree oil has been found to be the most common plant allergen (12, 13, 23, 24), but it does reflect a low prevalence of sensitization in Italy (25). Even though the Compositae family is the most important allergenic plant family in Europe, in our series the prevalence of sensitization was low; chamomile and marigold were the most frequent culprits. No cases of contact allergy to sesquiterpene lactone (SL) have been observed. confirming that SL mix detects Compositae allergy with lower reliability than Compositae mix (26); therefore, SL mix allergen does not add significant diagnostic accuracy to a botanical integrative series. However, as already underlined, neither SL mix nor Compositae mix can be considered to be Compositae allergy screens (26, 27, 13). When a contact allergy to Compositae is suspected, it is important both to patch test with extracts of native or locally grown plants and to avoid simultaneous testing of mix and constituents, in order to obtain reliable patch test results (28, 29). Consistent with the weak allergenic potential of *Aloe vera* (30, 31), only one positive reaction to this extract was found in our population, even though this was the most used botanical ingredient declared by the enrolled subjects. Although Centella asiatica is regarded as a rare allergen (32), three reactions were found in our series, as well as three reactions to peppermint, a popular herbal ingredient (33).

Testing patients with their own commercial botanical products showed that, among the 13 patients (22% of total) who had at least one positive reaction, 10 had a concomitant relevant sensitization to cosmetic allergens in the SIDAPA series, whereas only 2 had a relevant sensitization to an allergen of the botanical integrative series (Table 6).

Carrying out patch tests with patients' own products may be useful for detecting relevant contact allergy, not only to botanical allergens but also to cosmetic ingredients. Testing with the single constituents supplied by the manufacturer may be the only way to detect unusual herbal culprits (34).

When contact dermatitis caused by topical products containing plant compounds is suspected, cosmetic

ingredients, such as fragrances and preservatives, may be the main culprit allergens, rather than plant ingredients as such. However, on the basis of our findings, contact allergy to botanically derived compounds is possible in $\sim 15\%$ of declared adverse skin reactions to natural topical products. An additional botanical series may be of questionable diagnostic usefulness, principally because of the difficulty in making it representative of the wide variety of herbal ingredients found in natural cosmetics. Indeed, only a limited number of standardized botanical allergens are commercially available, and numerous cases of contact allergy may therefore go unrecognized. Consistent with this, botanical allergens supplemental to the SIDAPA baseline series may not significantly enhance the diagnostic accuracy of patch testing. In our series, the addition of propolis, Me. alternifolia and Compositae mix alone to the baseline series would have allowed the detection of all but 2 of the patients with contact allergy to botanical ingredients (89.5%).

A limitation of our study is that both skin symptoms and causal relationships between exposure to botanical preparations and adverse skin reactions were retrospectively self-reported and not corroborated by clinical assessment by a dermatologist. Owing to the retrospective design of our analysis, we could not consider the clinical pattern of skin reactions. Possible risk factors for contact dermatitis, such as atopic background and previous documented skin sensitization, were not investigated in our population.

In spite of these limitations, a considerable number of adverse skin reactions to topically applied botanical preparations was found in our population. This confirms that there is a public misconception in Italy that 'if it is natural it must be safe'; this misconception is probably actively managed by the cosmetic industry. Our Italian multicentre study provides further evidence of adverse reactions to botanical extracts present in cosmetic and herbal products. Post-marketing surveillance of any undesirable effects possibly caused by the use of botanical products could provide more information. Baseline series supplemented with the most common botanically derived allergens, such as propolis, Compositae extracts, and *Me. alternifolia* oil, may be adequate for detecting the majority of cases of contact allergy to natural topical products.

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