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Analysis of suspected adverse reactions to food supplements containing beehive products: an update from the Italian Phytovigilance System

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Abstract

Introduction. Beehive products are widely used in food supplements; however, their composition variability and allergenic components have raised some concerns. This work aims to provide information about the beehive products safety profile by evaluating the suspected adverse reactions (ARs).

Methods. The suspected report of ARs collected within the Italian Phytovigilance System (IPS) were evaluated. The clinical and demographic characteristics of the cases were described, and the causality assessment performed.

Results. 61 reports were analysed, mainly concerned women. Serious events were reported in 17 forms (28%). The ARs (n=116) referred to respiratory (25.0%), skin (24.1%), and gastrointestinal disorders (21.5%). Label warnings for atopic subjects were present only in 7 food supplements. The causality assessment was mostly probable (54.1%).

Conclusions. Present findings outline relevant information about the safety issues of beehive product consumption, especially in atopic or allergic subjects, and strengthen the importance of IPS to point out safety signals.

Key words
- allergy
- atopy
- safety
- dietary supplements
- honeybee products

INTRODUCTION

In the last years, beehive products, namely honey, propolis, and royal jelly, have attracted a great attention of the scientific community owing to their presumed beneficial effects on human health. Indeed, several studies have highlighted a plethora of biological properties of these products, including antiseptic, anti-inflammatory, wound-healing, antioxidant, antibacterial, antimycotic, antifungal, antiulcer, anticancer, anti-allergy, and immunomodulatory ones [1-3]. Therefore, some attempts have been made to exploit the benefits of these products at a clinical level, albeit with limited results. Indeed, the high variability at chemical level, makes difficult the standardization of their preparations and, consequently, the reproducibility of the expected effects [3]. Several parameters contribute to the composition variability, such as the honeybee varieties, the plant species, the geographical area, and the harvesting season. Therefore, currently, beehive products have few applications, mainly as dietary supplements to relief minor ailments, in both adults and children [4]. Particularly, people resort to them to counteract respiratory tract diseases, to boost the immune system, and to increase body energy. However, at present, no health claim have been attributed to dietary supplements containing beehive products due to the high variability of their composition [5].

Despite the potential beneficial properties ascribed

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to beehive products, some concerns have emerged with respect to their safety. Particularly, the esters of caffeic acid (phenylethyl caffeate and methylbutenyl caffeate) seem to be responsible for the strong sensitizing properties of propolis [6]. Indeed, contact dermatitis and severe systemic allergies have been reported [7, 8]. Accordingly, propolis has been recently added in Europe to the test battery of compounds used in routine diagnosis of allergic contact dermatitis (ACD) [8, 9]. However, also other substances, such as isoferulates, flavonoid aglycones, and free aromatic acids, may play a role in propolis allergy [7]. Some cases of ACD have been ascribed also to royal jelly and honey. In the latter case, the presence of propolis and pollen in honey could be the culprits. The presence of essential oils in beehive products contributes to the occurrence of allergic reactions, being contact allergens. Moreover, substances secreted by the bees themselves may be involved in allergies [7].

Currently, there is a lack of knowledge about the efficacy and safety profile of these products due to both the absence of clinical trial and pharmacoepidemiological studies. In fact, absence of information about their use in the population makes it impossible to conduct studies for risk quantification. Therefore, at the moment, spontaneous reports of adverse reactions (ARs) represent the only tool to collect information related to the safety profile of these natural products.

In this context, in the present paper, the suspected ARs associated with the consumption of products containing, among others, beehive ingredients, collected within the Italian Phytovigilance System (IPS), have been evaluated to monitor their safety profile. The paper represents an update and a widening of a previous work [10] in which reports of ARs to food supplements containing propolis were analysed.

METHODS

All spontaneous reports of ARs referred to beehive products gathered within the IPS were analysed. IPS was set up in 2002 to collect spontaneous reports of suspected ARs related to products of natural origin, so improving the information about the safety profile of dietary supplements, galenic and/or herbal preparations. IPS is coordinated by the Italian National Institute of Health (Istituto Superiore di Sanità, ISS) and operates separately from the Italian Pharmacovigilance network, which collects ADRs (adverse drug reactions) related to registered drugs. The ARs concerning products of natural origin can be reported online by health professionals, companies, and citizens through the website www.vigierbe.it. ARs are coded according to the medical dictionary of regulatory activities (MedDRA) and the composition of the product (ingredients and dosages) is verified trough the label notified to the Italian Ministry of Health.

In the present study, an in-depth analysis of ARs related to beehive products, collected within the IPS between March 2002 and August 2023, has been performed by excluding the reports that have been already analysed in the previous publication [10]. All available information on the reports was retrieved and the demographic, clinical and pharmacological characteristics of cases were collected and analysed. In particular, data referred to: 1) patient characteristics, namely age, sex, and clinical history or status; 2) suspected product information, such as product type, dosages, composition, duration and reason for use; 3) concomitant products and predisposing conditions (e.g., previous allergies); 4) ARs description (i.e., seriousness, dechallenge, rechallenge, and outcome).

A multidisciplinary group evaluated each report and estimated the causality assessment (categorized as certain/definite, probable/likely, possible, unlikely, or un-assessable/unclassifiable) according to the World Health Organization (WHO) system for standardized case causality assessment criteria. When more than one active compound was present in the suspected product, the attribution of causality concerned the whole commercial product. The composition of products was reported, excluding excipients, as on the label of the package. Continuous data were expressed as mean ± standard deviation (SD) and categorical variables were expressed as count or percentages.

RESULTS

From March 2002 to August 2023, 79 spontaneous reports of suspected ARs related to beehive products were collected. Excluding the 18 cases previously published [10], 61 reports were analysed in the present study. Clinical and demographic characteristics of cases are provided in *Table 1*. The median age of patients who experienced ARs was 37.5 years (Inter Quartile Range=9.75-53.25 years); women were involved in 32 cases (52%), men in 26 (43%) while in 3 cases (5%) the information was lacking. Serious reactions occurred in 17 cases (28%). The ARs reported (n=116) were mainly related to "Respiratory diseases" (n=29; 25.0%), "Skin and subcutaneous tissue" (n=28; 24.1%), and "Gastrointestinal disorders" (n=25; 21.5%), mostly not serious (*Figure 1* and *Figure 2*).

The products involved in ARs were food supplements (n=45; 72.6%), herbal products (n=5; 8.1%), medical devices (n=4; 6.4%), herbal medicinal products (n=3; 4.8%), food (n=1; 1.6%) and others (n=4; 6.4%). About the composition, propolis was present in 59.7% of products (n=37), honey in 32.3% (n=20), royal jelly in 29% (n=18), and pollen in 4.8% (n=3) (See *Supplementary Material* available online). In 18 products, a combination of these components was present; moreover, in most of the cases, suspected products also contained different herbal extracts. The reason of use referred to two main reasons: coughs/pharyngitis/colds (44.3%; n=27) and asthenia/tonic (16.4%; n=10); the information was unknown in 21 cases (34.4%) and in 3 (4.9%) cases "other reasons" were reported (See *Supplementary Material* available online). Predisposing conditions, as atopy or allergy, were indicated in 30% of reports. Concomitant products were reported in 35.4% (n=22) of cases, however, in 17 cases (27.9%) the information was not available. From the label analysis, only 7 suspected products carried warnings for atopic subjects. Healthcare professionals reporting the suspected ARs were mainly physicians (n=31; 50%) and pharmacists (n=22;

Table 1
Clinical and demographic characteristics of patients showing adverse reactions to dietary supplements containing beehive products collected from the Italian Phytovigilance System

Characteristics	Overall (61)	Serious (17)	Not serious (44)
Age median (range) (1 NR)	37.5 (2-94) IQR (9.75-53.25)	34 (4-71) IQR (10.25-57.25)	36.5 (2-94) IQR (10-54.25)
Sex			
Male	26	5	21
Female	32	9	23
Unknown	3	3	0
Predisposing conditions			
Yes	18	6	12
No	26	4	22
Unknown	17	7	10
Concomitant products	18	6	12
≥5	3	0	3
Between 1 and 4	19	8	11
No	22	3	19
Unknown	17	6	11
Reason of use			
Coughs/pharyngitis/colds	27	9	18
Asthenia/tonic	10	2	8
Other	3	0	3
Unknown	21	6	15
Type of product			
Food supplement	45	14	31
Herbal product	5	1	4
Medical device	4	1	3
Herbal drug	3	0	3
Food	1	0	1
Other	4*	1	3
Report qualification			
Physician	31	10	21
Pharmacist	22	4	18
Citizen	4	1	3
Other	3	1	2
Unknown	1	1	0
Outcome			
Recovered	30	6	24
In recovering	7	3	4
Improvement with sequalae	4	3	1
Not recovered	2	1	1
Unknown	18	4	14
Dechallenge			
Positive	30	9	21

Continues

Table 1
Continued

Characteristics	Overall (61)	Serious (17)	Not serious (44)
Negative	1	0	1
Unknown	30	8	22
Rechallenge			
Positive	2	0	2
Negative	2	0	2
Not executed	46	15	31
Unknown	11	2	9
Causality assessment	2	0	2
Probable	33	6	27
Possible	21	8	13
Unlikely	1	0	1
Not related	3	1	2
Unassessable	3	2	1

*One report contained two suspected products; NR: not reported; IQR: interquartile range.

35.5%). In term of outcome, the clinical condition was mostly "recovered" (n=30; 49.2%), "in recovering" (n=7; 11.5%), "improvement with sequelae" (n=4; 6.6%), and "not recovered" in 2 cases (3.3%); the information was lacking in 18 reports (29.5%). Dechallenge resulted positive in 49.2% of reports (n=30); rechallenge was positive in 2 cases (3.3%); however, in most cases it resulted as "not executed". The causality assessment performed was mostly probable (54.1%; n=33) and possible (n=21; 34.4%); in 7 cases (11.5%) the assessment resulted as unlikely (1 case), unrelated (3 cases) or unassessable (3 cases), detailed information is presented in *Table 1*.

DISCUSSION

Nowadays, beehive products are found in many commercial products, among which dietary supplements, resulting in a widespread human exposure and an increased risk of adverse reactions, particularly hypersensitivity [8, 11]. Propolis has been recognized as one of the most used honeybee allergenic products, causing symptoms ranging from mild to severe reactions, such as anaphylaxis [12-14]. Particularly, documented cases of oral sensitization to propolis are rare, while allergic reactions resulting from local administration of propolis are significantly more common [15]. Caffeic acid and its esters have been found as the primary chemical constituents responsible for haptenic activity and allergenicity [8]. Along with propolis products, some cases of suspected allergic reactions to honey and royal jelly, have been also reported [16, 17]. Honey allergy may be caused by pollen content (especially Compositae pollen) or bee-derived proteins, while in the case of royal jelly the major protein 3 (MRJP3) has been identified as the main culprit [16, 18]. Moreover, allergen cross-reactivity between bee products can also occur [18].

Overall, the study retrieved 61 reports of ARs related to the consumption of beehive-derived products. Particularly, 17 reports pointed out serious ARs, 12 of which were related to products containing propolis (n=12), so confirming the trend highlighted in the literature [11]. The symptoms were mostly related to an allergic condition exacerbated in respiratory, cutaneous, or gastrointestinal disorders.

Commonly, beehive-derived products are used to alleviate the inflammatory status of the upper airways or to decrease states of fatigue after flu [19]. This was confirmed by the analysis where the reason for use referred to coughs/pharyngitis/colds in 43.5% of cases and asthenia/tonic in 16.1%. The study, also highlights the short duration of use of these products, being the median of 2 days with an interquartile range between 1 day and 4 days. This brief duration of use could be also related to the occurrence of ARs, mostly acute reactions with short-term onset that required the discontinuation of the products. In support, dechallenge, when reported, resulted as positive in about 50% of cases, reinforcing this hypothesis. Details of the reports are described in *Supplementary Material* available online.

The present work offers several points for discussion. Firstly, in some cases the patients had only taken one product derived from bees, such as propolis (in cases 1, 10, 19 and 31) or royal jelly (in cases 12, 13, 18 and 29); furthermore, concomitant factors or predisposing conditions were absent: this fact makes the association between consumption of bee product and AR more likely. However, in most cases, several ingredients were present in the reported food supplements making it difficult to establish the role of the beehive products in the ARs. Furthermore, other dietary supplements or drugs were often assumed concomitantly, making the picture more complex. As an example, in the case 4, a 10-year-old child experienced toxic epidermal necrolysis, a type IV delayed hypersensitivity reaction [20], one day after consuming a supplement containing propolis and rose-

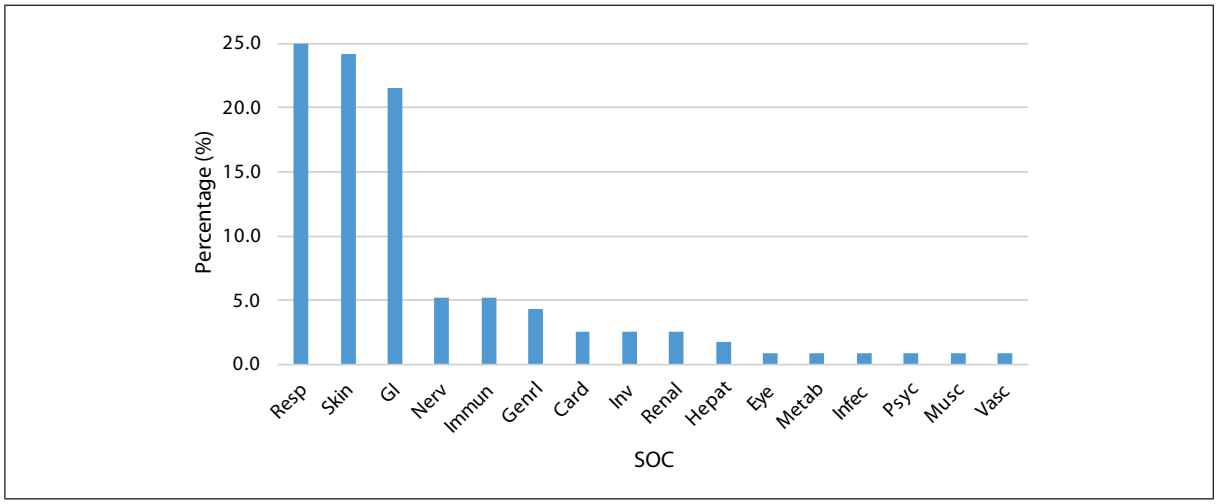

Figure 1
Frequency of system organ class (SOC) – overall.
Card: cardiac disorders; Eye: eye disorders; Genrl: general disorders and administration site conditions; GI: gastrointestinal disorders; Hepat: hepatobiliary disorders; Immun: immune system disorders; Infec: infections and infestations; Inv, investigations; Metab: metabolism and nutrition disorders; Musc: musculoskeletal and connective tissue disorders; Nerv: nervous system disorders; Psyc: psychiatric disorders; Renal: renal and urinary disorders; Resp: respiratory, thoracic and mediastinal diseases; Skin: skin and subcutaneous tissue disorders; Vasc: vascular disorders.

hip. He was also in therapy with gentamicin sulfate and betamethasone valerate for treating erythema and took another food supplement for pharyngolaryngeal pain. Moreover, about one week before the onset of the reaction, he was treated with the anesthetic lidocaine for the application of three stitches for a head wound. The AR was life-threatening and the patient did not recover yet, when the AR was reported. Previous evidence has shown that the intake of propolis can trigger skin reactions [9, 21]. However, the occurrence of toxic epidermal necrolysis has also been associated with products containing rose hips [22] and gentamicin, the antibiotic taken by the patient in addition to the food supplement [23]. Furthermore, lidocaine has also been reported to induce late hypersensitivity reactions [24]. Regarding the concomitant supplement, it was not possible to hypothesize its contribution to the AR, being its composition unknown. Therefore, although an association between product intake and onset of the AR has been highlighted, the actual contribution of the product to the reaction cannot be established owing to concomitant drugs/supplements taken by the patient whose

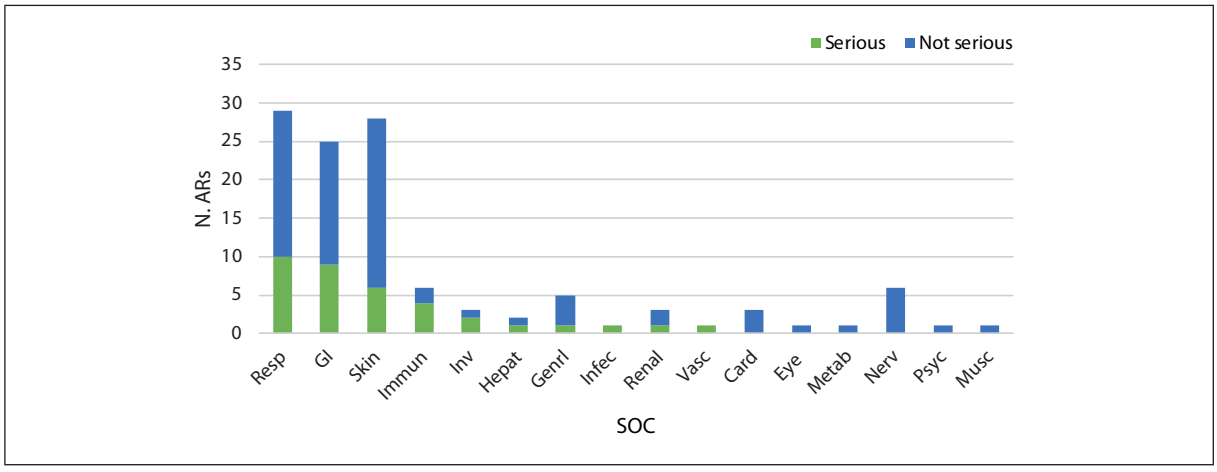

Figure 2
Number of adverse reactions (serious and not serious) grouped by system organ class (SOC).
Card: cardiac disorders; Eye: eye disorders; Genrl: general disorders and administration site conditions; GI: gastrointestinal disorders; Hepat: hepatobiliary disorders; Immun: immune system disorders; Infec: infections and infestations; Inv: investigations; Metab: metabolism and nutrition disorders; Musc: musculoskeletal and connective tissue disorders; Nerv: nervous system disorders; Psyc: psychiatric disorders; Renal: renal and urinary disorders; Resp: respiratory, thoracic and mediastinal diseases; Skin: skin and subcutaneous tissue disorders; Vasc: vascular disorders.

contribution in the AR cannot be excluded. As result the causality assessment resulted "possible".

Case 58, a 7-year-old child, experienced an allergic reaction characterized by generalized rash on the face, trunk, limbs, itchy and warm to the touch. She had assumed a food supplement containing concentrated apple juice, honey, fructose, ginger dry extract, and another food supplement based on agrimonia and tormentilla (See *Supplementary Material* available online). Honey consumption has been linked to several cases of allergic-type ARs, especially in children [16]. However, it should be also considered that plants of the Rosaceae family have recently emerged as the most frequent cause of allergic symptoms among foods, being responsible for the lipid transfer proteins (nsLTPs) syndrome, which may range from local manifestations (e.g., mild contact urticaria, oral allergy syndrome, gastrointestinal issues) up to anaphylaxis and even anaphylactic shock [25]. Therefore, in the present case, both supplements could have played a role in the triggering of ARs.

Sometimes, people who experienced ARs were also affected by serious conditions, thus making it difficult to establish whether the AR was due to the product consumption or to an exacerbation of the disease. For example, case 34, a 71-year-old woman, experienced oedema, ascites, oliguria, and toxic erythema after taking a supplement for flu syndrome with cough. The product contained propolis, thyme, rose hip, and echinacea. She was also assuming bisoprolol fumarate and was affected by liver cirrhosis. Hypersensitivity reactions and skin irritation have been reported for echinacea, propolis, and thyme [26-28]. However, liver cirrhosis worsening could explain to the occurrence of ascites and oliguria [29, 30]. Moreover, case 35, a 60-year-old female, experienced an allergic reaction characterized by acute respiratory failure after assuming a medical device syrup, containing propolis, which have been reported to cause ARs at respiratory levels [11]. However, the presence of goiter in the patient could have worsened the respiratory symptoms, due to the trachea compression. Another important aspect to consider is that the predisposing condition could be also represented by the reason for the use of the product such as sore throat or pharyngodynia. Therefore, it could be supposed that the beehive product intake worsens respiratory symptoms even if supporting literature is lacking. In addition to respiratory reactions, many skin events (mostly non-serious) have been collected in this study and have been already reported in numerous case reports [21, 31-36]. Even if these events are mostly not serious, it is desirable to consider the benefit-risk profile for these natural products, especially because they are usually used for minor ailments. Moreover, even if rarely, beehive products have been also associated with major dermatological adverse events, such as in the cases 4, 7, 12, 34, 49, 58 and 60.

Another important element of discussion is represented by the consumption of beehive-derived products by atopic subjects. In general, there is no evidence of toxicity of beehive products; however, numerous ARs appear in atopic subjects; therefore, they could be predisposed to allergic-type and inflammatory manifestations [37]. According to the most traditional classification [38], adverse reactions occur in individuals with a certain predisposition and are not readily anticipated; thus, from a pharmacological perspective, they are called "bizarre". Based on present results, it was found that in 30% of the reports (see cases 10, 11, 30, 40, 48, 49, 50, 53 and 55) predisposing conditions, such as atopy or previous allergy manifestation, were indicated (in 28% cases no information was reported). As an example, case 10, a 32-year-old woman, experienced pharyngodynia after taking a product containing propolis, to relieve dry cough due to pollen allergy. To be noted that in this case dechallenge was positive. In case 40, palate and tongue edema, and dyspnea affected a 65-year-old woman after assuming a supplement (propolis agrimony, rose hip, and zinc gluconate) for pharyngodynia. The patient's clinical history highlighted previous allergies to grasses, mites, mosquitoes and horseflies. Similar scenarios were also reported in cases 49 and 53. Therefore, atopic subjects should be discouraged from using beehive-derived products to avoid possible risk of allergic reactions.

Besides atopy, other predisposing conditions, such as autoimmune diseases, could represent an important factor in triggering the AR. For example, in case 56, the subject (a 36-years-old female) suffered of life-threatening sore throat and oedema after the intake of a supplement containing propolis (multifraction hydroalcoholic extract standardized on total flavonoids) and *Citrus limon* L. essential oil. Moreover, she presented several predisposing conditions, namely multiple sclerosis, fibromyalgia, osteoarthritis, and thyroiditis. These are immune-mediated diseases with an upper-activation of inflammatory mechanisms [39-41], so a condition which could possibly generate an inflammatory response after the intake of beehive-derived products. Each of these conditions requires a specific pharmacological treatment (although the concomitant medications were not specified in the report form); therefore, it is not possible to exclude a potential drug-natural product interaction. Both atopy and autoimmune diseases could be considered as predisposing the ARs due to their inflammatory physiopathology; however, up to now there is no evidence supporting this association; thus, this hypothesis is merely spurious and highlights the need to perform more studies aimed at analyzing the correlation between the inflammation in these pathologies and the response of the immune system to beehive products.

In this in-depth analysis it was observed that patients with predisposing conditions experienced more severe reactions. This issue should not be underestimated, considering that, very often, users do not receive adequate information about products of natural origin before their intake. Indeed, health professionals not always investigate the concomitant and/or predisposing conditions of patients; moreover, the operators of the food sector do not highlight on the product label the potential risks for predisposed individuals, perhaps for both marketing reasons and because there is no legal requirement to state such warnings. Nevertheless, this information would lead an increased consumer awareness, so guiding them in making the most targeted, safe, and conscious choice for the use of such products

and, thereby, stemming or limiting the ARs risk.

Noteworthy, Northern Italy was the area mostly involved in reporting the potential ARs to beehive products (51 cases); the Southern and Central areas contributed less, having only sent 5 and 4 reports, respectively, while in one case no information was reported. This disproportion in reporting between Italian areas could be due to the greater sensitivity of the North to report ARs related to natural products rather than by a greater frequency of events in these areas. However, it is also possible that the difference highlighted could be due to both a major consumption of natural products and a higher level of pollution which could be related to the highest frequency of respiratory problems [42].

At last, another point worthy of discussion is the large number of product categories in which beehive products can be found, thus causing some confusion among users. Indeed, in the reports analyzed within the analysis, beehive products were present in food, herbal products, herbal medicinal products, food supplements, and medical devices. Moreover, it should be outlined that suspected ARs to medical devices and herbal medicinal products are out of the scope of the IPS being a specific one already in place [43, 44]. However, to avoid losing information, we included them in the analysis. Therefore, it is important to increase the knowledge of health professionals and the general population on products of natural origin.

CONCLUSIONS

Based on the best available knowledge, the present study along with the previous published one [9] are the only focusing on the analysis of ARs to beehive products. Indeed, while some case reports are present in the literature, no clinical trials or observational studies, aimed at characterizing the safety profile of beehive products, were retrieved. Particularly, this study was conceived as an observational retrospective analysis of spontaneous reports collected from the IPS to characterize the safety profile of beehive products, thus allowing to: (a) identify safety issues; (b) highlight potential subgroup of people at major risk due to predisposing conditions, and (c) provide awareness of consumers concerning beehive products in a public health perspective. Present findings outline relevant information about the safety profile of beehive products consumption in atopic subjects. On the current legislation it is not mandatory to indicate beehive ingredients as allergic compounds. However, atopic or allergic people could take advantage on finding adequate information on the product label. The insertion of an information on the label could be an important help for at risk consumers who could consciously evaluate the benefit/risk profile of the beehive product consumption. Furthermore, several issues related to the complexity of natural products have been highlighted such as the fact that several ingredients were often present; thus, it is impossible to determine with certainty the role played by beehive products in the observed reactions. These results strengthen the importance of IPS as an irreplaceable method to monitor food supplements' risk signals, which otherwise would be lost, considering that safety studies are not required for their commercialization.

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Conflict of interest statement

The Authors declare no conflicts of interest.

Ethics approval

The present study does not require any institutional or national ethical committee approval. Moreover, personal data were processed according to the current legislation.

Availability of data and material

The Authors confirm that the data supporting the findings of this study are available within the article and the *Supplementary Materials* available online.

Authors' contributions

II: data analysis; investigation; writing; original draft. SDG: data analysis; investigation; writing; original draft. GM: supervision; writing; review and editing. MS: supervision; review and editing. FMI: supervision; writing; review and editing.

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