

# Surveillance of Suspected Adverse Reactions to Natural Health Products

## The Case of Propolis

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### Abstract

Natural health products are promoted to the public as equally or more effective and less toxic than conventional drugs. However, some 'natural' medicines are known to have adverse effects.

From April 2002 to August 2007, 18 suspected adverse reactions associated with propolis-containing products were reported to the national surveillance system of natural health products, coordinated by the Italian National Health Institute. Sixteen reports concerned allergic reactions (with dermatological or respiratory symptoms), while two concerned the digestive tract. Some of the reactions were serious: six patients were admitted to hospital or visited an emergency department and in two of these a life-threatening event was reported. In seven patients (four of whom were children), an allergic predisposition was indicated.

Propolis, a resinous substance collected by honeybees from the buds of living plants, has been used for several purposes (dermatitis, laryngitis, oral ulcers) because of its wide range of suggested activities (antibacterial, antiviral, anti-fungal, anti-inflammatory, antioxidant and chemopreventive actions). However, propolis is also a potent sensitizer and should not be used in patients with an allergic predisposition, in particular an allergy to pollen.

In Italy, products containing bee derivatives (bee pollen, royal jelly or propolis) are available to the public as food supplements. No label warning of possible adverse reactions is found on the packaging, although it is well known that atopic and asthmatic individuals may be at an increased risk of allergic reactions after using these products. The public and healthcare practitioners should be aware of the risk of allergic reactions to products derived from bees and a warning should be added to the packaging of these products.

Propolis is the generic name of a natural dark-coloured resinous substance collected by honeybees from the buds of living plants, such as *Cistus* spp.,

*Clusia* spp. and *Populus* spp. Propolis is a mix of bee wax and salivary secretions. It has been used for several purposes (dermatitis, laryngitis, oral ul-

cers)<sup>[1]</sup> because of its wide range of suggested activities, which include antiviral, antifungal, antibacterial (Gram-positive and -negative bacteria), anti-inflammatory, antioxidant and chemopreventive actions.<sup>[2,3]</sup> The chemical composition of propolis varies depending on its geographic region, and it is very complex as >300 compounds have been identified. The general composition is 50% of resin and vegetable balsam, 30% of wax, 10% of essential oils, 5% of pollen and 5% of organic debris.<sup>[3]</sup> In Europe, the presence of polyphenols, coumarins, amino acids, steroids and inorganic compounds has been reported. The biological activities are mainly attributed to flavonoids (rutin, quercetin, galangin) and to phenolic acids with their esters (caffeic acid phenethyl ester as a major component).<sup>[2,4]</sup> Propolis seems relatively safe, with a calculated safe dose of 1.4 mg/kg bodyweight/day in humans (applying the safety factor of 1000).<sup>[5]</sup> Nevertheless, propolis is a potent sensitizer and is a well recognized cause of occupational allergic eczematous contact dermatitis in apiarists.<sup>[6]</sup> For this reason, propolis is contraindicated in patients with an allergic predisposition, in particular an allergy to pollen. The allergenic action seems to be due to caffeic acids derivatives.<sup>[7]</sup> In this paper, we present the suspected adverse reactions associated with propolis reported within the surveillance system of natural health products active in Italy since 2002.

## 1. Surveillance System

The Italian Pharmacovigilance System collects spontaneous reports of adverse reactions only for registered drugs; however, awareness of the need for surveillance of the safety of natural health products has stimulated the implementation of a suspected adverse reactions reporting system in Italy, set up by the Italian National Institute of Health (Istituto Superiore di Sanità).

An *ad hoc* reporting form, similar to that in use to collect spontaneous reports of suspected adverse reactions to conventional drugs, was defined. The form was adapted to reporting suspected adverse reactions to any kind of natural health product (raw

medicinal plants, dietary supplements, animal-derived products, minerals, homeopathic preparations, etc.), which are not included in the pharmacovigilance system.

Voluntary reports of suspected adverse reactions are sent by the reporters (hospital doctors, office-based specialists, general practitioners, pharmacists) to the National Institute of Health, where all the forms are collected and registered in a centralized database. All reports are individually evaluated by a multidisciplinary group of experts (in the fields of epidemiology, pharmacology, pharmacognosy, toxicology, phytotherapy, homeopathy, pharmacovigilance).

The serious clinical events (deaths, life-threatening events, requiring or prolonging hospitalization or significantly disabling) are analysed more in depth by the group and written reports are sent to the Italian Medicines Agency for possible regulatory actions.

## 2. Suspected Adverse Reactions

Eighteen suspected adverse reactions associated with propolis-containing products were reported from April 2002 to August 2007 (table I). Six cases involved children (aged 1–10 years). One patient was a pregnant woman who used the product for acute pharyngitis in the first weeks of pregnancy (15 weeks). Sixteen reports concerned allergic reactions (with dermatological or respiratory symptoms), while two concerned the digestive tract. Some of the reactions were serious: six patients were admitted to hospital or visited an emergency department and in two of these patients a life-threatening event was reported. In seven patients (four of whom were children), an allergic predisposition was indicated. A positive rechallenge was observed in a 63-year-old woman, who had experienced a similar reaction using a mouthwash some years earlier.

Propolis was used in almost all cases for upper respiratory tract infections, or as topical preparations (cream and mouthwash) for wound healing (in a 1-year-old child) or for mouth ulcers.

**Table I.** Clinical data of adverse reactions associated with the use of propolis products

| Age (y),<br>gender | Trade name <sup>a</sup>                                      | Product<br>components other<br>than Propolis                                                                                                                                           | Daily dose (route<br>of administration);<br>duration | Reason for use                                                   | Adverse reactions                                                                    | Positive<br>dechallenge;<br>positive<br>rechallenge | Hospitalization or ED<br>visit/applied therapy                               | Other medications/<br>conditions                             |
|--------------------|--------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------|------------------------------------------------------------------|--------------------------------------------------------------------------------------|-----------------------------------------------------|------------------------------------------------------------------------------|--------------------------------------------------------------|
| 1, M               | Galenic (10%<br>Propolis)                                    | NR                                                                                                                                                                                     | When needed<br>(topical); 14 d                       | Healing wounds<br>and itching relief<br>for atopic<br>dermatitis | Atopic and<br>generalized<br>eczema, with<br>impetigo                                | Yes; NR                                             | Yes/antibacterials<br>(PO) +<br>corticosteroids and<br>antibiotics (topical) | <i>Cedrus libani</i> , Sulphur 30<br>CH, and dropropizina/NR |
| 4, M               | Apropolis A <sup>®</sup> ,<br>Propoli EPID<br>C <sup>®</sup> | Ginkgo,<br><i>Helichrysum</i> sp.,<br><i>Ribes nigrum</i> , mint,<br>tea tree oil, thyme,<br>grapefruit, <i>Rosa</i><br><i>canina</i>                                                  | 2 vials/d (aerosol)<br>+ 2 tablets/d<br>(PO); 4 d    | Influenza                                                        | Acute asthma                                                                         | Yes; no                                             | No/corticosteroids                                                           | No/atopic patient                                            |
| 5, F               | Apropolis A <sup>®</sup> ,<br>Propoli EPID<br>C <sup>®</sup> | Ginkgo,<br><i>Helichrysum</i> sp.,<br><i>Ribes nigrum</i> , mint,<br>tea tree oil, thyme,<br>grapefruit, <i>Rosa</i><br><i>canina</i>                                                  | 2 vials/d (aerosol)<br>+ 2 tablets/d<br>(PO); 5 d    | Influenza                                                        | Acute asthma                                                                         | Yes; no                                             | No/corticosteroids                                                           | No/atopic patient                                            |
| 5, F               | Propolis spray                                               |                                                                                                                                                                                        | NR                                                   | Pharyngitis                                                      | Scattered anthema<br>with itch and<br>modest lower<br>and bilateral<br>blefaroeedema | Yes; no                                             | Yes/NR                                                                       | None/none                                                    |
| 10 M               | Gol-Natur<br>Lenigola <sup>®</sup>                           | Water, fructose,<br>concentrated apple<br>juice, povidone,<br>glycine, sorbitol,<br>silica, aroma,<br>cellulose,<br>potassium<br>sorbate, methyl<br>p-hydroxybenzoate,<br>acesulfame-K | 2 oral sprays,<br>twice/d; 2 d                       | Tonsil<br>inflammation                                           | Cutaneous rush                                                                       | No; no                                              | No/antihistaminics                                                           | No/familial atopia                                           |
| 10, M              | Propolis                                                     |                                                                                                                                                                                        | NR (oral spray);<br>2 d                              | Tonsils<br>hypertrophy                                           | Cutaneous rush                                                                       | No; no                                              | No/antihistaminics                                                           | NR/familial allergic<br>asthma                               |
| 30, M              | Propolis                                                     |                                                                                                                                                                                        | 2 tablets/d (PO);<br>2 d                             | Sore throat                                                      | Allergic reaction<br>(erythema)                                                      | Yes; no                                             | Yes/corticosteroids                                                          | Barbiturates/infant<br>epilepsy                              |

*Continued next page*

Table I. Contd

| Age (y), gender | Trade name <sup>a</sup>  | Product components other than Propolis                                     | Daily dose (route of administration); duration | Reason for use       | Adverse reactions                        | Positive dechallenge; positive rechallenge | Hospitalization or ED visit/applied therapy | Other medications/ conditions                                                        |
|-----------------|--------------------------|----------------------------------------------------------------------------|------------------------------------------------|----------------------|------------------------------------------|--------------------------------------------|---------------------------------------------|--------------------------------------------------------------------------------------|
| 34, F           | Propolis                 |                                                                            | Once/d (topical use); 2 d                      | Acute pharyngitis    | Labial oedema, with tongue paraesthesia  | No; NR                                     | Yes/corticosteroids                         | NR/pregnant woman (15 wk)                                                            |
| 35, M           | Propolis pomade          |                                                                            | NR (topical use), NR                           | NR                   | Toxic local dermatitis (chest and hands) | NR; NR                                     | No/NR                                       | NR/NR                                                                                |
| 36, F           | Propolis                 |                                                                            | 1 topical; 1 d                                 | Pharyngodynia        | Asthma episode                           | Yes; no                                    | Yes/corticosteroids + $\beta_2$ -agonists   | Propylthiouracil/allergy                                                             |
| 37, F           | Propolis mother tincture |                                                                            | 12–20 drops, 2–3 times/d (PO), for 4 mo        | Sore throat          | Gastroesophageal reflux with heartburn   | Yes; no                                    | No/protonic pump inhibitors                 | Occasionally, sodium ferrogluconate/allergic rhinitis                                |
| 40, F           | Lenigola Spray Forte®    | Alcohol (ethanol), water, glycerin, thyme and eucalyptus e.o.              | 1 oral spray, 3 times/d (PO); 1 d              | Tonsils inflammation | Breath impairment                        | Yes; no                                    | No/none                                     | NR/none                                                                              |
| 43, M           | Propolis mouthwash       |                                                                            | NR, 1 d                                        | Mouth aphtha         | Oedema of uvula and tongue               | NR; NR                                     | NR/corticosteroids + antihistaminics        | NR/NR                                                                                |
| 51, F           | PropolPur spray®         | Glycerin, water, <i>Citrus limonum</i> e.o.                                | 3 oral spray/d; 2 d                            | Pharyngitis          | Face oedema                              | NR; NR                                     | No/NR                                       | None/none                                                                            |
| 57, M           | Propolis                 |                                                                            | 20 drops/d (PO); 3 d                           | Sore throat          | Labial and tongue oedema                 | Yes; NR                                    | No/corticosteroids + antihistaminics        | NR/NR                                                                                |
| 61, F           | Propolis                 |                                                                            | 20 drops, twice/d (PO); 2 d                    | Common cold          | Digestive difficulties with stomach ache | Yes; NR                                    | No/yes, but the therapy was NR              | None/none                                                                            |
| 63, F           | Lenigola Propoltimo®     | Acerola, thyme e.o., sucrose, lactose, orange flavour                      | 1 tablet/d; 1 d                                | Pharyngitis          | Uvula and soft palate oedema             | Yes; yes                                   | Yes/corticosteroids + antihistaminics       | Flurbiprofen mouthwash/ previous allergic reaction to mouthwash, containing Propolis |
| 91, F           | Grindoral tablets®       | Brown sugar, milk powder, <i>Grindelia</i> sp., eucalyptus e.o., mint e.o. | NR                                             | NR                   | Labial, tongue and palate oedema         | Yes; NR                                    | No/NR                                       | Atorvastatin, pentoxifylline and indobufen/NR                                        |

<sup>a</sup> Where not differently specified trade name was NR.

ED = emergency department; e.o. = essential oil; F = female; M = male; NR = not reported; PO = oral administration.

### 3. Conclusion

In Italy, products containing bee derivatives (bee pollen, royal jelly or propolis) are available to the public as food supplements, without any label warning of possible adverse reaction, although it is well known that atopic and asthmatic individuals may be at an increased risk of allergic reactions after using these products.<sup>[8-10]</sup> Propolis-containing products are often a mixture of various components that could contribute to adverse events. In particular, when essential oils are involved, high doses of the potential active ingredients are present. Furthermore, spray formulations were often used from our cases and this way of administration is particularly dangerous when allergenic substances are inhaled.

The public and healthcare practitioners should be aware of the risk of allergic reactions to products derived from bees and a warning should be added on the packaging of these products.

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