



Allergy to honeybee . . . not only stings

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Purpose of review

The purpose of this review is to provide a brief overview of the risks of consumption of bee products in honeybee venom allergic patients and compositae allergic patients, the potential allergens involved in these reactions, the advancement in solving diagnostic difficulties, and management of allergic reactions to bee products.

Recent findings

Allergic patients to bee venom and compositae allergic patients may be allergic to bee products. Several bee products allergens have been identified in bee venom.

Summary

Anaphylaxis to bee products is rare. Some studies show a clear association between some aeroallergens such as compositae with allergic reactions to bee products. Additionally, allergic reactions to bee products are associated with severe outcomes in atopic and patients with lung disorders and are a common occupational disease in beekeepers. Possible cross-reactivities have been suggested between bee components and bee venom. Furthermore some studies found patients with concomitant allergy to honey or to propolis and bee venom. Nevertheless a direct relationship between allergy to bee products and bee venom has not been shown. However, cross-reactivities between bee products and bee venom might be relevant in some cases.

Keywords

honeybee, insect stings, propolis

INTRODUCTION

Anaphylactic reactions to bee venom allergens are well known [1^{***}]. However, allergic reactions to products of beehives have been additionally reported. The primary products of beekeeping are the propolis, honey, royal jelly, and beepollen. Propolis is a mixture of beeswax and plant resins collected by worker bees. Royal jelly is a secretion produced by glands of worker honeybees used in the nutrition of adult queens. Because of the growth in the consumption of herbal medicine, the incidence of allergic reaction to bee products has increased. This correlates with reports of high rates of contact eczema caused by propolis and severe reactions after consumption of honey and royal jelly. Therefore, there should be an increased awareness about diagnosis and management of bee products-induced allergy. Although there are insufficient data supporting the relationship between atopy and contact dermatitis, factors that may influence contact dermatitis to propolis include atopy and lung diseases. Equally, the severity of allergic reactions to bee products is also influenced by atopy, lung disorders and in the case of bee venom acupuncture,

repetitive stings. Bee venom acupuncture consists of the injection of bee venom at specific sites.

Impaired skin barrier and loss of function mutations in the filaggrin gene have been reported to be a risk factor for nickel induced allergic contact dermatitis. This is especially true in patients with atopic dermatitis [2]. Although insect venom allergy has not been associated with common filaggrin null alleles [3], it remains unclear whether such mutations may contribute to either sensitization or severity of allergic reactions to bee-related products.

Diagnostic tests including skin tests and in-vitro tests are sensitive for confirming immediate reactions induced by honey and royal jelly. The inclusion of propolis in an extended standard patch

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KEY POINTS

- Bee product allergy should be disclosed in bee venom allergic patients with allergic reactions to 'natural herbal products'.
- Established risk factors for bee products allergy are atopy, lung disorders, beekeeping, whereas some reports suggest bee venom allergy and compositae allergy.
- The major royal jelly allergens 8 and 9 have been identified in bee venom.
- Compositae-allergic patients should be warned against use of compositae-containing products.
- There is not sufficient evidence to prevent patients suffering from bee venom allergy but not from bee product allergy to consume bee products.

test has improved the ability to diagnose delayed contact dermatitis to propolis. However, its major allergens are not available for routine incorporation into diagnostic tests. The latter is of utmost importance as some allergens are broadly present in a variety of products. Reports have also demonstrated the limitations of management of reactions to bee-related products due to the wrong assumption that 'natural products' do not have adverse effects, minimizing the label warning in the products and not reporting adverse reactions to the products.

Recent studies are attempting to clarify the specific composition of bee products, as well as their major and minor allergens responsible for the reaction and their cross-reactivities with bee venom and other food allergens. Additionally, studies have provided insight into the prevalence and characteristics of anaphylaxis and possible factors associated with the severity of reactions. Advances in the collection of detailed cases with specific phenotypes and IgE-specific patterns will lead to an improvement in the prevention and management of allergic reaction to bee products.

PROPOLIS

Both propolis and royal jelly have a long history of medicinal use and can be consumed fresh or taken in supplement form. Propolis is the resinous substance that bees collect from living plants for the construction and adaptation of their nests. Some therapeutic properties have been attributed to propolis such as: antiinflammatory, antioxidant, antiulcerogenic, local anesthetic, hepatoprotective, cytotoxic [4], immune-stimulating/modulatory [4], cariostatic, spasmolytic, and many other biological properties

[4–6]. Propolis is contained in tablets, toothpastes, gargles, syrups, and lozenges. Although systemic toxicity appears to be rare [7], propolis is a potent contact sensitizer. Studies on patients with contact allergy from unknown causes found that 1.2–6.6% of those who were patch-tested were sensitive to propolis [5]. Among 233 cases of suspected adverse reactions to natural health products, 12 patients that included three atopic children reported allergic reactions associated with propolis [8].

SENSITIZERS

Propolis constitutes an important cause of allergy with distinct clinical manifestations, depending on the sensitization route, leading to contact dermatitis, airborne allergic contact dermatitis, urticaria, rhinitis, conjunctivitis, angioedema, and anaphylactic shock [9]. Reactions are often triggered by topical application of propolis to at-risk populations: these include patients with leg ulcers/lower-leg dermatitis, chronic venous insufficiency (5.6%) [10], and anal dermatoses (5%). Moreover, hematogenous contact eczema has been reported after ingestion of propolis as a natural tonic [11]. The chemical composition of propolis is highly variable depending on its geographical area of origin. Twenty-six allergens have so far been identified. The major sensitizers are widespread and found in many other cross-reactive products of plant origin. Strong to moderate sensitization is caused by caffeic acid esters (such as 1,1-dimethylallyl ester of caffeic acid, benzyl caffeate, geranyl caffeate) and cinnamic acid esters (for example, cinnamyl cinnamate, benzyl cinnamate, cinnamyl alcohol), whereas benzyl cinnamate represents a weaker sensitizer.

Cera alba is a propolis-related substance that may be found in cosmetic products and as a food additive used as a coating and glazing agent, mostly for fresh fruits and candies. Facial and neck eczema associated with queilitis was observed after application of lip balm and consumption of wine gums containing cera alba as confirmed by a positive patch test to cera alba 20%. The patient had additional positive reactions to cera flava 30% and propolis 10% [12].

OCCUPATIONAL CONTACT ALLERGY TO PROPOLIS

Beekeepers are primarily affected by contact eczema to propolis within a range of 0.76–4.04% [13,14], but musicians, people who make stringed musical instruments and farmers [15,16] are also afflicted. Single cases of a dental technician and a shoemaker after manipulation of beeswax products contaminated with propolis have been also reported.

Additionally, airborne allergic contact dermatitis might affect beekeepers' neighbours. The most important contact allergen identified in propolis is a compound 1,1-dimethylallyl caffeic acid ester (LB-1) (consisting mainly of three pentenyl esters of caffeic acid) derived from the buds of poplar [17]. Other important contact allergens in propolis are caffeic acid phenethyl ester (phenethyl caffeate) and benzyl salicylate. The latter can also generate symptoms after the topical application of cosmetics containing benzyl salicylate. Because of the ubiquity of these proteins in the plant kingdom, patients frequently display symptoms induced by Peru balsam, rosin, turpentine, essential oils, and fragrances.

HONEY

Honey consists of nectar, honeydew, and a variable amount of pollen admixed during collection. Honey can be also consumed in chocolate bars, candies, and gingerbread. Both pollen content [18,19] and bee-derived proteins are relevant for honey allergy. In fact, bee body components, mould spores, algae, and other organic debris may be found in honey and theoretically mediate allergic reactions [20]. There are different types of honey depending on the floral source, offering a variety in colour and flavour, but also in protein content. Interestingly, despite the heterogeneous sources the antigen patterns remain remarkably constant between different honeys. However, there is a proportion of patients (around 9%) who might be allergic exclusively to specific proteins of one type of honey that allows them to consume other types of honey [21]. The main honey suppliers in the world are Argentina, China, and Mexico. The largest EU exporter is Germany, followed by Hungary and Spain. The symptoms range from itching in the mouth (52%), contact urticaria, and angioedema (9%), gastrointestinal symptoms (17%), and exacerbation of bronchial asthma (30%) to anaphylaxis (17%) [21]. Thirty percent of patients allergic to honey display sIgE antibodies to bee venom but also sIgE to hymenoptera venom can be demonstrated in around 20% of the general population [22].

ROYAL JELLY

Royal jelly is a thick, milky substance that is secreted by worker bees to feed the queen and her larvae. Manifestations vary from contact dermatitis, oral allergy syndrome, exacerbation of asthma, to anaphylactic shock [23–25], and fatal reactions have occurred [26].

RISK FACTORS

Propolis allergy used to be a predominant occupational disease affecting bee keepers. However, with the growing industry of 'natural products'

and the diversification of applications, the target population has been expanded. Although reaction to bee stings is not correlated with a reaction to propolis [27], the lack of bee stings in beekeeping in a period of time might be associated with a following severe reaction to insect sting and those patients were frequently found to suffer from propolis allergy [27]. Although, major royal jelly proteins 8 and 9 have been identified in honeybee venom and 38% of bee venom allergic patients were found to have sIgE reactivity to royal jelly using immunoblot analysis [28], a cross-reactivity between honeybee venom and royal jelly remains controversial. Royal jelly IgE reactivity has been detected in 52% of 75 patients allergic to inhalant and/or food allergens [24].

Atopic patients have been shown to be at higher risk of suffering from severe allergic reactions after ingestion of royal jelly [23,26]. A treatment resistant case of anaphylactic shock was seen in a Japanese atopic patient with asthma and atopic eczema after drinking a beverage of crude royal jelly [29]. Likewise, propolis contact allergy is significantly associated with lung diseases and allergic reactions to other sources [27]. Concerns have been raised regarding a possible association between allergy to bee venom and honey. Four of six patients who developed a systemic allergic reaction after ingestion of honey had positive sIgE against honey bee venom and two patients of those have experienced anaphylaxis after a bee sting [30²²]. In contrast, other studies have not confirmed allergenic cross-reactivities between bee venom and other bee products.

BEE VENOM ACUPUNCTURE

In the Far East, live bee venom acupuncture is a common practice. It consists of placing a living bee onto skin and applying downward pressure until the insect stings. Patients receiving live bee acupuncture depending on the number of occasions and the interval between the stings are at risk of suffering from (Bong-Chim) dermatitis [31], contact urticaria [32], foreign body granuloma or anaphylactic reactions.

NATURAL COURSE

The primary sensitization in patients allergic to honey and royal jelly might be due to the honey or royal jelly itself, to airborne compositae pollen or, as one study suggested, bee venom components. A 4-year-old boy who had an allergic reaction after the first ingestion of bee pollen without previous consumption of honey, bee pollen, royal jelly, or propolis, might have had the primary sensitization

towards airborne Asteraceae pollen (aster, daisy, composite, or sunflower family of plants) [33]. Interestingly, three out of seven patients who experienced severe allergic reaction after ingestion of royal jelly denied having consumed royal jelly before. In the same study [25], two out of seven patients consumed royal jelly for the first time 2 days before. Reports of allergic reactions after live bee acupuncture showed that the number and interval of bee stings may influence the outcome of the reaction. A singular sting or multiple stings at longer duration may cause foreign body granuloma [34,35] whereas patients with multiple stings within the short term are at risk of suffering from anaphylaxis.

DIAGNOSIS

In patients suffering from anaphylaxis after ingestion of honey, skin tests and in-vitro tests are highly sensitive. In 100% (six of six) and 70% (seven of 10) [21] of the patients a honey allergy was confirmed via serological sIgE antibodies and in 83% (five of six) the allergy was confirmed with skin tests [30²²]. Honey does not contain the main allergic components in propolis such as caffeic acid esters [36] but cross-reactivities have been found between honey and bee venom [20]. In fact, nine of 22 and four of six of honey allergic patients were sensitized to honey bee venom [20]. It is thought, however, that the majority of honey allergy cases are not related to cross-reactivity with bee venom, and rather caused by pollen contained in honey or other bee components. Additional cross-reactivities have been found between sunflower honey, sunflower pollen, and celery [37].

Royal jelly produced positive skin tests in all cases reported to date, providing a sensitivity of 100% [25,29]. None of the patients showed sIgE antibodies against venom from honey bee, wasp or hornet. Immunoblot analyses of the patients' sera with royal jelly-induced asthma or anaphylaxis revealed IgE binding to proteins at a molecular mass in the region between 25 and 55 kDa [25].

As 1.2–6.6% of the patients undergoing patch testing are sensitive to propolis. Although, in 2001, propolis sensitization was found in 1.3% adults [38], this increased in 2010 and was found to be the second commonest cause of sensitization in Polish children (16.5%) and the fourth in Polish adolescents (5.4%) with associated atopy and chronic recurrent eczema. The recommended patch test concentration is 10% propolis in petrolatum [5]. Although 3-methyl-2-butenyl caffeate is the most potent sensitizer, it is not reproduced synthetically and it is not used in the patch test. Several compounds of propolis are also found in balsam of Peru.

Some propolis-sensitive patients show a positive reaction to balsam of Peru and some *cera alba*-sensitive patients show a positive reaction to propolis.

One major concern dealing with the diagnosis of these rare cases of food allergy is the lack of cooperation with manufacturers who should label the specific ingredients of beverages in all the cases [29]. The second major concern is the contamination of bee products with compositae pollens. Contradictory information has been reported regarding the role of compositae pollen in the induction of allergic reactions induced by bee products. Only a minor role has been demonstrated in recent studies [39,40]. Although bees only use insect-pollinated (entomophilous) plants as pollen sources, at certain periods of the year such as early spring, wind-pollinated (anemophilous) trees represent pollen suppliers for honeybees. Some of the wind-pollinated trees known to belong to allergenic families are: ash (Oleaceae), oak (Fagaceae cross-reacting with Betulaceae), Willow and Poplar (Salicaceae). Corn pollen might be an additional important source in midsummer and fruit-bearing plants such as almonds might also grow near to beehives. However, wind-pollinated plants account for only 5% of the total content in honey and their relevance in honey allergy is controversial [21].

MANAGEMENT AND TREATMENT

In contrast to bee venom allergy, wherein venom immunotherapy is indicated, patients with allergy to bee products should avoid the source of the allergens. Patients at high risk should undertake protective measures. Unfortunately, only 30% of beekeepers allergic to propolis protected their hands despite contact allergy to propolis and from those 21.6% reported frequent use of propolis as a therapeutic product [27]. Despite knowing the possible adverse reactions, there is still no label warning on the packaging of some bee 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. It is well known that atopic and asthmatic individuals may be at an increased risk of allergic reactions after using these products.

CONCLUSION

Anaphylaxis to bee products is rare. The episodes have been associated to bee components itself, to airborne compositae pollen or, to bee venom components. However, there is not enough evidence to prevent patients with honeybee venom allergy without allergic symptoms to bee products from

the consumption of bee products. A comprehensive and detailed clinical description and antigenic characterization of large cohorts of patients allergic to bee products might help to define with precision further recommendations.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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