

Allergic Contact Dermatitis from Propolis

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Propolis is commonly used in cosmetic and medicinal preparations because of its antiseptic, antiinflammatory, and anesthetic properties. Its therapeutic qualities have been well documented. However, 1.2 to 6.6% of patients who are patch-tested for dermatitis are sensitive to propolis. The main allergens are 3-methyl-2-butenyl caffeate and phenylethyl caffeate. Benzyl salicylate and benzyl cinnamate are less frequent sensitizers. Propolis is found in a number of "natural" products, including lip balms, cosmetics, lotions and ointments, shampoos, conditioners, and toothpastes. Dermatologists should consider patch testing with propolis in users of such remedies.

THE TERM "PROPOLIS" comes from two Greek words: "pro," which means "before," and "polis," which means "city." This ancient term came into being centuries ago when an early Greek student of nature established the fact that honeybees use propolis to narrow the openings into their "cities," or hives.¹ Propolis, also known as bee glue, is a lipophilic brownish resinous substance collected by bees, mainly from poplar and conifer buds; it is mixed with wax to seal the hives and to protect the bees against invaders and cold weather. It is hard and waxlike when cool but soft and sticky when warm.² Bee glue is not the same as beeswax. Beeswax is secreted by bees and is also used widely in cosmetics. However, it is a rare sensitizer unless contaminated with propolis.³

Propolis has a long history of use in folk medicine. In fact, more than 15 Greek and Roman authors reported on the preparation and application of the so-called third natural product of bees (besides honey and wax).⁴ Records from the twelfth century describe medicinal preparations with propolis for treating mouth and throat infections as well as dental caries,⁵ and propolis was even documented as a medication in the 1600s in London.⁶ It was also often used to treat skin wounds and to protect raw skin before bandages were available. Today, propolis is used for many purposes and is sold in many health food stores as a remedy for many diseases.^{3,6} Propolis products are marketed in various forms such as oral pills and lozenges, and propolis

is often found in cough syrups, shampoos and conditioners, ointments, lotions, lipsticks, cosmetics, toothpastes, and varnishes.⁶ Many of these products claim to be "all natural," which consumers often equate with safety.

Composition of Propolis

The composition of propolis is variable, depending on the locale and variety of trees and other plant species used for collection. Unique constituents have been identified in propolis found in Cuba and Brazil.⁶ There are more than 180 propolis constituents that are identified by gas chromatography/mass spectrometry.⁷ Other reports estimate that there are more than 300 components.⁸

The main chemicals in propolis are resins, which constitute 45 to 55% of propolis and consist of free aromatic acids (eg, benzoic, caffeic, cinnamic, coumaric, and ferulic acids); benzyl, methylbutenyl, phenylethyl, cinnamyl, and other esters of these acids; chalcones and dihydrochalcones; and terpenes.⁹ Propolis also contains flavonoids, including quercetin, apigenin, galangin, kaempferol, luteolin, pinocembrin, pinostrobin, and pinobanksin. The phenolic ester caffeic acid phenethyl ester (CAPE) has been the subject of several clinical trials because of its potential for the treatment of a number of disorders.⁶

Responsible Allergens

The main allergens found in propolis are 3-methyl-2-butenyl caffeate and phenylethyl caffeate, both of which are constituents of LB-1 (Fig 1 and Table 1).^{9,10} LB-1 was the first allergen identified in propolis.² Chemical separation of different propolis samples and poplar bud extracts reveals that LB-1 is always present.¹¹ LB-1 was originally thought to consist solely of 1,1-dimethylallyl caffeic acid

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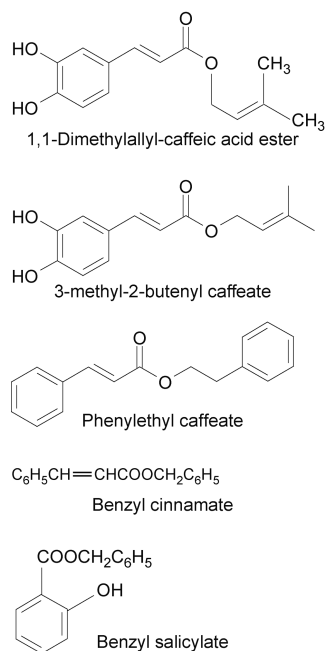


Figure 1. Structure of propolis allergens.

ester^{11,12} but more recently has been found to consist mainly (87%) of three isomeric pentenyl caffeates.¹⁰ 3-Methyl-2-butenyl caffeate, the main component of LB-1, has been identified as the strongest sensitizer^{9,10}; 2-methyl-2-butenyl caffeate and 3-methyl-3-butenyl caffeate are the other two pentenyl caffeates (pentenyl caffeates make up 87% of LB-1). Phenylethyl caffeate is a smaller component (7.9%) of LB-1 and elicits strong reactions in patients known to be sensitive to propolis.¹⁰ In general, esters of caffeic acid play an important role in sensitization. In one study, all caffeates tested showed a moderate to strong sensitizing capacity.⁹ Propolis is generally rich in these caffeates when bees have the opportunity to collect the sticky bud exudates of poplar species.^{13–20}

Benzyl salicylate and benzyl cinnamate (see Fig 1 and Table 1) are less frequent sensitizers.^{9,10} In guinea pigs, benzyl salicylate is a moderate sensitizer^{10,21} whereas benzyl cinnamate is a very weak¹⁰ to moderate²¹ sensitizer. Hausen and colleagues patch-tested three propolis-allergic patients; none reacted to either benzyl salicylate or benzyl cinnamate.¹⁰ In Europe and Japan, benzyl salicylate has been found to be a frequent sensitizer in cosmetic-sensitive patients^{22–27} whereas other studies have found fewer reactions from benzyl salicylate in similar patients.^{28,29} Regardless, propolis-sensitive patients should be counseled about potential cross-reactions to cosmetics or products containing benzyl salicylate and benzyl cinnamate.

When studied experimentally, flavonoids have generally shown a weak capability or no capability for sensitization.³⁰ Other compounds found in propolis include waxes (mostly beeswax) and fatty acids, essential oils, pollen, and other organics and minerals.^{2,5} None of these constituents have been found to be the responsible contact allergen.^{2,31–33}

Potential Medical Uses and Biologic Properties of Propolis

Several groups of researchers have focused their attention on the biologic activity of propolis and its active constituents.³⁴ General medicinal uses of propolis have included dental care and the treatment of anemia, ischemia, infections, cancer, and hepatitis. In regard to dermatology, propolis has been used in tissue regeneration, wound healing, and the treatment of ulcers and eczema.⁵

Several studies have shown that aqueous and alcohol extracts of propolis have hepatoprotective effects on both chemically induced (carbon tetrachloride, acetaminophen, and D-galactosamine [D-GalN]) and immunologically induced (D-GalN/lipopolysaccharide) liver toxicity.^{35–41} The antitumor activity of propolis, including cytotoxicity, has also been well documented.³⁴ A new clerodane diterpenoid called PMS-1, isolated from Brazilian propolis, exhibits cytotoxicity toward human hepatocellular carcinoma, human lung carcinoma, and skin tumors.^{42,43} Specifically, CAPE was shown to be cytotoxic to various tumor cell lines⁴⁴ and to have antitumor properties. Studies have shown that it can arrest the growth of human leukemia HL-60 cells⁴⁵ and different oral tumor cells.⁴⁶

The flavonoids and phenolic compounds of propolis have also been reported to have antioxidant properties that play a role in the antitumor and antihepatotoxic activities of propolis. Reactive oxidative species associated with tumor production are thought to act as second messengers for signal transduction pathways that regulate cell proliferation. The phenolic constituents of propolis reduce intracellular peroxides, thereby potentially inhibiting carcinogenesis. This activity also seems to be hepatoprotective.³⁴

Table 1. Responsible Allergens

Allergens	Role
LB-1	Major
3-Methyl-2-butenyl caffeate	Major
Phenylethyl caffeate	Major
Benzyl salicylate	Minor
Benzyl cinnamate	Minor

One of the most widely known and extensively researched properties of propolis is its antibacterial activity. Many research studies have been conducted with propolis on different species of bacteria, fungi, viruses, and other microorganisms.^{6,34,47–51} One study examined the antibacterial activity of different fractions of Brazilian propolis against *Staphylococcus aureus* and observed that the antibacterial activity is mainly due to polar phenolic compounds.⁴⁷

Propolis has also shown an antiinflammatory effect and has been used for the treatment of some skin inflammatory diseases.⁸ Mirzoeva and Calder studied the in vivo effect of dietary propolis and propolis components on arachidonic acid metabolism.⁵² The ethanol extract of propolis was found to suppress prostaglandin and leukotriene generation by murine peritoneal macrophages in vitro and during zymosan-induced acute inflammation in vivo. Propolis significantly suppressed the lipoxygenase pathway of arachidonic acid metabolism during inflammation. CAPE was the most potent modulator of the arachidonic acid cascade among the tested propolis components.⁵²

Many of the above-mentioned studies of the biologic activities of propolis were performed with mice and therefore may not be generalizable to humans. The few studies involving human subjects were limited by small sample sizes and nonrandomized noncontrolled study designs. More detailed studies are needed to determine the potential therapeutic benefits of propolis in humans.

Type IV Contact Dermatitis Reactions to Propolis

Although propolis sensitization was originally thought to be most commonly related to occupational exposure, most cases today result from use of propolis-containing products either applied topically (as with cosmetics) or ingested orally.⁵³ As shown in Table 2, the rate of sensitization to propolis among patients suffering from dermatitis has been reported to vary from 1.2 to about 6.6%. Hundreds of cases of contact dermatitis from propolis are now reported from all over the world.^{2,11,54–61} In a recent study looking at the frequency of contact sensitization to propolis in children, 5.9% of 1,255 patch-tested subjects reacted positively to propolis (20% in petrolatum [pet]) over an 8-year period. A linear increase in the annual frequency of propolis allergy was seen, possibly reflecting the increase in the use and popularity of propolis-containing products.⁵³ Popular products containing propolis include Burt's Bees (Burt's Bees, Inc., Durham, NC), Apivita Propoline products (Apivita S.A., Metamorfoosi, Greece), the BeeRich line (Eagle Marketing, Inc., Yukon, OK), ApiHealth products

(ApiHealth NZ Ltd., Auckland, New Zealand), P-Bee products (P-Bee Products, Inc., Laguna Hills, CA), and Beehive Botanicals (Beehive Botanicals, Inc., Hayward, WI).

Occupational Issues

The first report of a case of allergic contact dermatitis from propolis was published in 1915 and described a beekeeper with contact dermatitis on his fingers and wrist.⁶² Since that time, propolis has been recognized as an occupational contact allergen, mainly in beekeepers but also in musicians and people who make stringed musical instruments.^{2,63–69} It is the most common cause of occupational contact allergy in beekeepers and is a much more common sensitizer than beeswax.¹² For example, a young man aged 23 years was working as a beekeeper when he started having recurrent episodes of eczema on the back of his hands, with swelling of the eyelids and watering of the eyes. These flares occurred at work. A series of patch tests showed positive reactions to balsam of Peru, beeswax, propolis, and extracts of poplar leaves.⁷⁰

Occupational contact dermatitis may also be caused by airborne propolis emitted from nearby hives.^{69,71,72} Several cases have been reported, and all were related to the patients' being near bee hives. One patient developed repeated redness, swelling, and itching in the periorbital regions after he opened the beehives and removed the honey. Skin contact with honey and dead bees was tolerated, and no hand dermatitis was present. Patch-test reactions to propolis, allergen LB-1, and balsam of Peru were all positive, suggesting that the patient was reacting to an "odorous cloud" that was emitted from the hives, and his symptoms resolved upon avoidance.⁷¹ A similar case was seen in a 57-year-old beekeeper who had repeated episodes of erythema and facial itching and swelling after collecting honey but who also never developed hand dermatitis. He had positive patch-test reactions to honey, wax, and propolis.⁶⁹

In addition to cases related to beekeeping, several other cases of occupational propolis allergy have been described. Henschel and colleagues described a 50-year-old man with

Table 2. Sensitization Rates

Reference	Total Patients Patch-Tested	Positive Reactions to Propolis
Hausen BM et al ⁹	3,177	38 (1.2%)
Guisti F et al ⁵³	1,831	35 (1.9%)
Machackova J ⁸³	650	27 (4.2%)
Reider N et al ⁹²	433	28 (6.55%)

a 1-year history of hand dermatitis who worked in a retail store, handling everything from raw materials to manufactured goods, including untreated and finished wood products. Patch tests with the European Standard, facial, preservatives, rubber, and office worker series including propolis revealed a single ++ reaction to 10% propolis at 2 and 4 days. Wearing gloves at work improved his symptoms.⁶⁴ A positive reaction to propolis was also seen in a shoemaker with vesicular hand eczema who used beeswax in making shoes.⁶⁵

Unusual Presentations

Aside from the typical presentation of an erythematous vesiculopapular eczema, contact dermatitis from propolis can also result in some unusual clinical presentations. Two cases of propolis contact dermatitis presented in a setting of psoriasis. These patients applied a cream that contained propolis to their arms and/or active areas of psoriasis, resulting in exacerbation of the disease. Patch tests showed positive reactions to propolis.⁷³ Propolis-induced contact dermatitis can also mimic pemphigus vulgaris, which was the case in a patient who applied propolis-containing ointment and lip balm, resulting in blistering dermatitis of the lips and adjacent oral mucosa, leading to an initial misdiagnosis of pemphigus.⁷⁴ Another patient had treated an abrasion below the nose with a lotion containing 20% propolis. After a week, a papule appeared that later developed into an erythematous nodule, accompanied by fever and enlarged lymph nodes in the submental, submaxillary, and cervical regions. Antibiotics had little effect, and a skin biopsy specimen showed epidermal hyperplasia and granuloma formation. Cultures were negative, and patch testing with the propolis lotion resulted in a positive reaction. The lesion healed, and the lymphadenopathy resolved after topical application of the propolis solution was discontinued.⁷⁵

Type I Immunoglobulin E–Mediated Reactions to Propolis

Although type IV reactions are more prevalent, there have been several case reports of type I immediate hypersensitivity to propolis.^{76,77}

Hsu and colleagues described a 48-year-old man with cardiac arrest secondary to respiratory distress. The patient had applied topical propolis for the treatment of acute pharyngitis and developed dysphagia and drooling 6 hours after use. Respiratory distress ensued, with resultant hypoxia and shock. The patient eventually died from compli-

cations of repeated ventilator-associated pneumonias and sepsis. Although formal testing was not performed, propolis was thought to be responsible because of the temporal proximity of the symptoms to propolis use and because no other possible causes were identified.⁷⁶

Callejo and colleagues described a beekeeper's 10-year-old son who for years had had a history of angioedema associated with the manipulation of beehive products. Despite a history of tolerance to bee stings, he developed an immediate systemic reaction (with urticaria, angioedema, severe hypotension, and fecal and urinary incontinence) within 5 minutes of being stung by a honeybee. Skin-prick test results were positive for propolis but negative for beeswax and honey. The result of a propolis-specific immunoglobulin E (IgE) radioallergosorbent test (RAST) was also positive in this patient, indicating an adverse IgE-mediated reaction to propolis.⁷⁷

Reactions to Ingested Propolis

The ingestion of propolis can also have deleterious effects resulting in allergic contact cheilitis, stomatitis, perioral eczema, labial edema, oral pain, and dyspnea. Several cases have been described after patients have consumed various propolis products such as tablets, toothpaste,⁷⁸ mouthwash, and propolis lozenges.⁷⁹ Bellegrandi and colleagues described a patient infected with human immunodeficiency virus-1 (HIV-1) who developed painful ulcers of the mouth, followed by labial and oral swelling, dyspnea, and labial and perioral eczema. Treatments with antiviral and antifungal agents were unsuccessful. It was later determined that the patient had been taking propolis drops. Stopping this resulted in a remission of symptoms. The result of patch testing with propolis (20% pet) in this patient was positive. Eight healthy subjects and 10 HIV-positive patients without a history of allergy also underwent patch testing. None reacted to propolis.⁷⁹

Cross-Reactions

There are at least eight compounds^{10,33,80–82} and as many as 13 compounds⁹ that propolis and balsam of Peru have in common. Some of these compounds include benzyl benzoate, cinnamyl cinnamate, and benzyl cinnamate.³³ Several studies have suggested that patients who are sensitive to propolis also may react to balsam of Peru^{9,10,53,83} although these studies are not consistent, and not all patients who react to propolis react to balsam of Peru and vice versa. This is most likely due to the variability of the components contained in propolis, depending on where

the trees were grown and where the propolis was extracted. It is on the basis of the findings of common components that these reactions have been termed "pseudocross-reactions" and not true cross-reactions.³³

Patch Testing

Propolis is now part of the European Standard patch test series, having been incorporated over a period of 3 years (1988 to 1990).⁹ Propolis is generally patch-tested and is commercially available in a 10% concentration in petrolatum.^{84,85} However, in some countries (such as Italy), it is routinely tested at a 20% concentration.^{53,86–90} Several studies found that a 20% concentration did not provoke irritation.^{86–90} In their study, Hausen and colleagues also found that the threshold of irritation for propolis was higher than 20% and that the threshold for LB-1 was between 3% and 10%.¹¹ Despite these findings, the generally recommended patch-test concentration is 10%. 3-Methyl-2-butenyl caffeate, the strongest sensitizing component of LB-1 in propolis, cannot be used for patch tests at this time because it has been impossible to reproduce it synthetically.⁹

Management

Management of propolis allergy is avoidance of the allergen. Synonyms for propolis include bee glue, bee bread, hive dross, propolis balsam, propolis resin, and propolis wax.¹² Patients should also be counseled to exercise caution when using products containing beeswax because it may be contaminated with propolis. The American Contact Dermatitis Society Web site's Contact Allergen Replacement Database eliminates 771 cross-reacting substances, regardless of whether the terms "bee glue," "beeswax," or "propolis" are entered.⁹¹

Summary

Propolis is commonly used in cosmetic and medicinal preparations because of its antiseptic, antiinflammatory, and anesthetic properties. Its therapeutic qualities have been well documented. However, 1.2 to 6.6% of patients undergoing patch testing are sensitive to propolis.^{9,53,84,92} Therefore, dermatologists should be aware of this important allergen.

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