Propolis: A Review of Properties, Applications, Chemical Composition, Contact Allergy, and Other Adverse Effects

Anton C. de Groot, MD, PhD

Abstract: **Propolis (bee glue) is the resinous substance that bees collect from living plants for the construction and adaptation of their nests. It has antibacterial, antifungal, and antiviral properties and may have a wide range of other beneficial biological activities. Propolis is available as a dietary supplement, in products for the protection of health and prevention of diseases, in biopharmaceuticals, and as a constituent of (bio)cosmetics. In this article, the following aspects of propolis are reviewed: the nature and chemical composition, its biological properties and applications, contact allergy and allergic contact dermatitis (sensitizing potential, products causing contact allergy, clinical picture, frequency of sensitization, coreactivity and cross-reactivity, the allergens in propolis), and other adverse effects.**

Propolis is the resinous substance that bees collect from living plants for the construction and adaptation of their nests. It has many beneficial biological activities; therefore, it is widely used in folk medicine in some countries and is available in various forms as food supplement, in biopharmaceuticals and in (bio)cosmetics. Although these "natural" products are perceived by most consumers as safe, adverse effects do occur, notably allergic contact dermatitis. This article provides a review of the nature, chemical composition, biological properties, applications, and adverse effects of propolis. The literature on contact allergy to propolis up to 1987 has been reviewed by Hausen et al.[1] A very useful more recent review article has been provided by Walgrave et al[2] in this journal in 2005.

WHAT IS PROPOLIS?

Propolis (bee glue) is a lipophilic resinous material that honeybees (*Apis mellifera* L.) collect from living plants. The materials available to bees for "manufacturing" propolis are produced by a variety of botanical processes in different parts of the plants. These substances may be actively secreted by plants or exuded from wounds: lipophilic materials on leaves and leaf buds, mucilages, gums, resins, lattices, and so on. The collected materials are mixed with the enzyme β-glycosidase present in the bees' saliva, partially digested and added to beeswax to form the final product (raw propolis, propolis *in natura*). Raw propolis is hard and wax-like when cool, but soft and very sticky when warm (hence the name *bee glue*). The material has a pleasant aromatic smell; its color varies from yellow, green, or red to dark brown, depending on its source and age.

The word "propolis" is derived from the Greek "προ" (pro: *in front of, at the entrance to*) and "πολις" (polis: *city* or *community*) and means a substance that is for or in defense of the city (*in casu* the hive). The bees use propolis in the construction and adaptation of their nests and apply it in a thin layer on the internal walls of their hive or other cavities they inhabit. It is used to block holes and cracks, to repair combs, to strengthen the thin borders of the comb, as a thermal insulator, to exclude draft, to protect against external invaders by narrowing the openings into their "city,"[2] and to mummify carcasses of creatures that have been killed by the bees after an invasion of the hive to prevent their decomposition. Bees also make use of the biological activities of propolis. Thus, the material is responsible for the lower incidence of bacteria and molds within the hive than in the atmosphere outside, resulting from propolis' antibacterial and antimycotic properties.[3]

BOTANICAL SOURCES OF PROPOLIS

It is generally accepted and chemically demonstrated that in temperate zones the bud exudates of species and their hybrids of the genus *Populus* (poplars) are the main source of propolis, notably species of the section *Aigeiros*. The most common species of this section is *Populus nigra* L. (black poplar), the other 2 are *Populus deltoides* L. and *Populus fremontii*; other former species are now considered subspecies of *P. deltoides*. Poplars (notably *P. nigra*) being the main source for propolis ("poplar-type propolis") is true for Europe (except some Mediterranean parts such as southern Greece, Crete, Malta, Cyprus, southern Italy), North America,

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Address reprint requests to Anton C. de Groot, MD, PhD, Acdegroot Publishing, Schipslootweg 5, 8351 HV Wapserveen, the Netherlands. E-mail: antondegroot@planet.nl; www.patchtesting.info.

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and the nontropical regions of Asia, including China, which is the main producer of commercial propolis. In New Zealand, introduced poplar species are also the source plants. In some parts of Canada, where no poplars of the section *Aigeiros* grow, the sources for honeybees to produce propolis include poplars of other sections such as *Populus trichocarpa* (section *Tacamahaca*) and *Populus tremuloides* (section *Populus*).[4] In Northern Russia, the birch *Betula verrucosa* and trembling aspen *P. tremuloides* are documented as propolis plant sources.[3,4] Despite the honeybees' preference for section *Aigeiros* poplars, exudates are also collected from other trees, for example, eucalyptus, birch, beech, alder, oak, willow, horse chestnut, pine, various conifers, and fruit trees.[5–7]

In tropical regions, there are no poplars and birches, and bees have to use other plant sources of bee glue. These can be identified by comparing the chemical profiles of the propolis in the region concerned and the suspected plant sources by chromatographic investigations. Examples of plant species that serve as botanical source for tropical propolis include *Baccharis* species, predominantly *Baccharis dracunculifolia* DC (Brazil, green propolis), *Dalbergia* species (Cuba, Brazil, Mexico, red propolis),[8] *Clusia major* and *Clusia minor* (Venezuela, Cuba), *Macaranga tanarius* (Pacific region),[9] *Cistus* species (Tunisia), *Ambrosia deltoidea* (Sonora desert [United States, Mexico]), *Larrea nitida* Cav. (Argentinan Andean propolis),[10] *Acacia paradoxa* DC (Kangaroo Island, Australia),[11] *Mangifera indica* L. (Indonesia),[12] and possibly *Araucaria* species (Brazil) and *Xanthorrhoea* species in Australia.[3,13]

The plant origin of propolis is not always certain. On the Canary Islands, for example, a propolis type is found with high content of furofuran lignans, but its plant origin is unknown. In Mediterranean countries and islands such as Sicily, Greece, Crete, and Malta, bees use plants of the Cupressaceae family as source for propolis, but the exact species have not been properly identified[3]; however, the main source of Mediterranean propolis may be *Cupressus sempervirens*.[14] The plant origin of the most widespread propolis types and their major constituents (*vide infra*) are shown in Table 1.[3,13]

PROPERTIES AND APPLICATIONS

Propolis has been used by humans for thousands of years for its pharmaceutical properties. In ancient Egypt, it was used for embalming the dead. Aristotle (around 330 BC) reported the first use in medicine, but it took more than 350 more years until the Roman scholar, Caius Plinius Secundus (23–79 AD), and the Greek, Pedanios Dioscorides (around 50 AD), continued with the medical uses of the substance. Records from the 12th century describe medicinal preparations with propolis for treating mouth and throat infections as well as dental caries, and propolis was documented as a medication in the 1600s in London. It was often used to treat skin wounds and to protect raw skin before bandages were available.[2] In the 17th century, Stradivarius used varnish containing propolis on his violins.[2,17]

Raw propolis is washed with water, solubilized in 95% ethanol, and repeatedly filtered to remove the wax and organic debris, creating "propolis balsam" or "propolis tincture."[18] The balsam possesses antibacterial, antifungal, and antiviral properties and may have a wide range of other beneficial biological activities:

TABLE 1. Most Widespread Propolis Types: Plant Origin and Major Constituents

Propolis Type	Geographic Origin	Plant Sources	Major (Typical) Constituents
Poplar	Europe, North America, nontropical regions of Asia, New Zealand, China	*Populus* species of section *Aigeiros*, most often *P. nigra* L.	Flavones and flavanones (pinocembrin, pinobanksin, pinobanksin-3-*O*-acetate, chrysin, galangin), cinnamic acids (notably caffeic acid) and their benzyl-, phenethyl-, and prenyl esters
Green (alecrim) Brazilian	Brazil	*Baccharis* species, predominantly *B. dracunculifolia* DC	Prenylated *p*-coumaric acids, diterpenic acids, prenylated acetophenones
Birch	Russia	*Betula verrucosa* Ehrh.	Flavones and flavonols (not the same as in poplar type): acacetin, apigenin, ermanin, rhamnocitrin, kaempferid, α-acetoxybetulenol
Red propolis	Cuba, Brazil, Mexico	*D. ecastophyllum* and other *Dalbergia* species	Isoflavonoids (isoflavans, terocarpans)
Mediterranean	Sicily, Greece, Crete, Malta	Cupressaceae (species unidentified, possibly *C. sempervirens*) and Pinaceae	Diterpenes (mainly acids of labdane type), anthraquinones[15,16]
"Clusia"	Cuba, Venezuela	*Clusia* species including *C. major, C. minor*	Polyprenylated benzophenones
"Pacific"	Pacific region (Okinawa, Taiwan, Indonesia)	*Macaranga tanarius*	C-prenyl-flavanones

Adapted from Bankova et al[3] and Sforcin and Bankova.[13]

anti-inflammatory, antioxidant, antiulcerogenic, local anesthetic, hepatoprotective, antitumor (cytotoxic),[19,20] immune-stimulating/modulatory,[19,21] cariostatic, spasmolytic, and many other biological properties.[2,3,13,19,20,22,23] These effects are attributed to the organic substances in propolis extracted with ethanol. The composition of the plant source determines the chemical composition of the propolis and its balsam dependent on its geographical location; as a result, its biological activity is closely related to the vegetation native to the site of collection.

In European-type (poplar) propolis, the chemical constituents responsible for its beneficial biological activities, and especially for its antibacterial and antifungal properties, are flavonoids and other (poly)phenolics, mainly substituted cinnamic acids and their esters.[24] In Brazilian propolis, such activities are due to prenylated *p*-coumaric acids (also substituted cinnamic acids) and diterpenes.[25] The amount of balsam extracted from crude propolis is an important characteristic, because high percentage of balsam means the propolis contains a higher content of biologically active components and a low percentage of wax and insoluble matter.[24]

Although scientific evaluation has provided substantial information on the biological activity and toxicity of propolis and indicates that the substance has indeed antibiotic, antifungal, antiviral, and antitumor properties, no propolis-containing preparation has yet found a place as accepted treatment in mainstream, Western medicine.[13] This is partly due to the extreme chemical diversity of propolis and, inherently, problems with standardization.[25] Nevertheless, propolis is widely used as a popular remedy in folk medicine (especially in the Balkan states, the former USSR, Germany, and Austria) and in apitherapy (the medical use of honeybee products such as honey, pollen, bee bread, propolis, royal jelly, and bee venom). It is also a constituent of "biocosmetics" and is sold in many health food stores as a dietary supplement, as "over-the-counter" products for the protection of health and prevention of diseases, and as biopharmaceuticals for self-treatment of various diseases. In dermatology, it has been used, for example, for burns,[26] leg ulcers,[27] psoriasis,[28] atopic dermatitis, recurrent aphthous ulcers,[29] warts,[30] herpes labialis, herpes genitalis,[31] and for wound healing and tissue regeneration.[22]

Propolis products are marketed in various forms such as creams, ointments, tablets, capsules, ampoules, syrups, sprays (for the oral and nasal cavities), and lozenges, and it may be found in cosmetics including shampoos, conditioners, ointments, lotions, lipsticks, toothpastes, and nail varnishes.[2,22]

Propolis can also be used as a food additive for preserving and for flavoring at the same time. For example, in Brazil, propolis is used to pickle meat and fish to keep these foodstuffs fresh and palatable.[32] Other applications include its use as an adhesive, to seal cracks, to protect wooden and other surfaces, as varnish for violins and other instruments[1] and for numerous other purposes.[3] Beekeepers themselves generally dislike propolis, because it causes difficulty when frames are removed from the hive, necessitates a great deal of labor to remove from comb honey sections before marketing, is a contaminant of beeswax, and sticks to hands and clothing.

Many producers of propolis claim their products to be "all natural," which consumers often equate with safety.

Indeed, systemic toxicity appears to be exceptional,[18,33–37] but propolis is a potent contact sensitizer,[38,39] and the use of propolis products not infrequently leads to sensitization and allergic contact dermatitis (discussed below).

CHEMICAL COMPOSITION

The compounds identified in propolis originate from 3 sources: plant exudate collected by bees, substances secreted from bee metabolism (including beeswax), and materials that are introduced during propolis elaboration. In general, propolis composition is directly related to that of bud exudates collected by honeybees from poplars[1] and other trees.[3] The chemical composition of propolis is highly variable, mainly due to the variability of plant species growing around the hive, from which the bees collect the exudates. Geographic location therefore is a major determinant of the composition. Propolis from temperate regions (poplar-type propolis), for example, contains mainly phenolics: flavonoids aglycone, aromatic acids, and their esters.[3,13] Brazilian propolis is significantly different from propolis found in the temperate zones. The Brazilian green propolis is rich in prenylated *p*-coumaric acid derivatives (notably artepillin C), diterpenic acids, and prenylated acetophenones and is found only in Brazil. Flavonoids are present in small quantities only. Red propolis from Brazil (which is also found in Cuba and Mexico and is acquired by the bees from *Dalbergia ecastophyllum* and other *Dalbergia* species) contains isoflavonoids (isoflavans, terocarpans) as important constituents. Moreover, the propolis from different regions of Brazil still displays significant variation in its chemical compositions, and 13 types of propolis have been classified according to its geographical origin, chemical composition, and source plants.[40]

Propolis from the Canary Islands contains lignans (eg, aschantin, sesamin, sesartenin), various terpenoids (eg, geraniol, germacrene D, isospathulenol, ledene, linalyl propionate, palustrol, and spathulenol), and certain sugars (such as galactose, maltose, mannose, melobiose, xylose) not found in poplar-type propolis.[41,42] Mediterranean-type propolis contains many diterpenes, mainly acids of the labdane type and anthraquinones, possibly derived from Cupressaceae and/or Pinaceae.[15,16,43] But even the poplar-type propolis composition may vary considerably, depending on the species of *Populus* or hybrids. The exudates may contain several hundreds of phenolic compounds, and each poplar type exudes a characteristic mixture of compounds.[44] In addition, propolis composition can vary depending on the seasonality,[45] illumination, altitude, race of honeybees,[7] method of harvesting the propolis,[46] and food availability and activity developed during propolis exploitation.

Despite these differences, most propolis samples share considerable similarities in their overall chemical nature. In general, crude propolis is composed of 50% resin and vegetable balsam (which contains the biologically active compounds), 35% waxes (mainly beeswax, some vegetable waxes), 5% to 10% aromatic oils, 5% pollen,

TABLE 2. Classes and Examples of Chemicals Identified in Poplar-Type Propolis[3,4,7,23,32,44,47–58,60–64]

Aromatic acids	
	(Substituted) cinnamic acids: cinnamic acid, caffeic acid, coumaric acid, dihydrocinnamic acid, ferulic acid
	(Substituted) benzoic acids: benzoic acid, gentisic acid, salicylic acid, vanillic acid, veratric acid
Aromatic esters	
	Benzyl, butyl, cinnamyl, ethyl, methyl-butenyl (prenyl, isoprenyl), methyl, pentyl, pentenyl and phenethyl esters of aromatic acids
Flavanones	
	Alpinetin, isosakuranetin, naringenin, pinobanksin (and esters and ethers), pincembrin, pinostrobin, sakuranetin
Flavones and flavonols	
	Acacetin, apigenin, chrysin, galangin, kaempferide, kaempferol, quercetin, rhamnetin, tectochrysin
Chalcones and dihydrochalcones	
	Alpinetin chalcone, 2′,6′-dihydroxy-4′,4′-dimethoxydihydrochalcone, isosakuranetin chalcone, naringenin chalcone, pinobanksin chalcone, pinocembrin chalcone, pinostrobin chalcone, sakuranetin chalcone
Terpenoids	
	β-Bisabolol, γ- and δ-cadinene, Δ3-carene, calamenene, caryophyllene, cymene, β-eudesmol, limonene, linalyl acetate, α- and γ-muurolene, β-selinene
Acyclic hydrocarbons and esters	
	Dotriacontanyl hexadecanoate, heneicosane, heptacosane, pentacosane, triacontyl hexadecanoate, triacontyl octadecenoate, tricosane, tripentacontane, tritriacontane
Alcohols	
	Benzyl alcohol, cinnamyl alcohol, isobutyl alcohol, 3-methyl-2-buten-1-ol (prenyl alcohol), phenethyl alcohol, 1-tetracosanol
Aldehydes	
	Benzaldehyde, 3,4-dihydroxybenzaldehyde, *n*-hexanal, isovanillin, propionaldehyde, vanillin
Aliphatic acids (short-chain)	
	Acetic acid, butanoic acid, citric acid, fumaric acid, malic acid, 4-pentenoic acid, 2,3,4-trihydroxybutanoic acid
Aliphatic esters	
	Benzyl, butyl, ethyl, isoamyl, isobutyl, methyl-butenyl, methyl and phenethyl esters of the aliphatic acids (notably acetic acid)
Aliphatic fatty acids (long-chain) and esters	
	Arachidic acid, cerotic acid, lauric acid, linoleic acid, myristic acid, oleic acid, palmitic acid, pelargonic acid, stearic acid and esters of some (eg, ethyl palmitate, ethyl stearate)
Amino acids	
	Alanine, arginine, glutamic acid, leucine, methionine, phenylalanine, proline, pyroglutamic acid, tryptophan, tyrosine
Aromatic hydrocarbons	
	3,4-Dihydroxystyrene, naphthalene, styrene
Acetophenones and other ketones	
	Acetophenone, dihydroxyacetophenone, methylacetophenone, 6-methyl-5-hepten-2-one
Glycerol derivatives	
	2-Acetyl-1-coumaroyl-3-cinnamoylglycerol, 2-acetyl-1-(*E*)-coumaroyl-3-(*E*)-feruloylglycerol, 2-acetyl-1,3-di[(*E*)-*p*-coumaroyl]glycerol, glyceryl phosphate, monoacetyl glycerine
Steroids	
	Chalinasterol acetate, β-dihydrofucosterol acetate, fucosterol acetate, stigmasterol acetate
Sugars and sugar alcohols	
	Fructose, glucose, glycerol, inositol, salicin, sorbitol, sucrose
Miscellaneous ingredients	
	N-carboxypyrrolidine-2-carboxylic acid, guaiacol, elemicin, eugenol, 5-hepten-2-one, hydroquinone

and minor other substances including organic debris.[18,23] Some essential elements such as magnesium, calcium, iron, nickel, and zinc as well as vitamins have also been found in propolis.[47] Not only the qualitative but also the quantitative composition of propolis constituents—even in the same type of propolis—varies considerably. For example, caffeic acid and its ester comprised 20% of propolis balsam from hives at the Zoology Department, Oxford, United Kingdom, but only 2% of propolis balsam from hives at the University Museum, about 400 m distant.[44]

Constituents of Poplar-Type Propolis

Poplar propolis is the most widely used and the most investigated type of propolis. More than 400 constituents have been identified in this propolis-type balsam from various geographical locations.[3,4,23,32,44,47–58]

These compounds can be grouped as follows:

(a) free aromatic (phenolic) acids
(b) esters of these acids

(c) flavonoids (flavanones, flavones, flavonols)
(d) chalcones and dihydrochalcones
(e) terpenoids
(f) others (acyclic hydrocarbons and esters, alcohols, aldehydes, aliphatic acids and esters, amino acids, aromatic hydrocarbons, glycerol derivatives, ketones, steroids, sugars and sugar alcohols, miscellaneous)

Long-chain fatty acids and their esters (in the wax component) and phenolic compounds are the main constituents.[3,12,23] The compounds identified in poplar-type propolis may stem from poplar exudate (aromatic acids and esters, flavonoids), from beeswax (fatty acids and esters, glycerol), from bee metabolism (amino acids, glyceryl phosphate), from contamination by honey (sugars), or formed during propolis "manufacture" and during preparation and analysis of samples (some chalcones).[44] In 1 investigation, the content of resin in poplar-type propolis samples of different geographic origin ranged from 18% to 82% with a mean of 57%[24]; the concentration of phenolics ranged from 8% to 46% (mean, 28%); flavones and flavonols were present in a 1.3% to 17.9% concentration (mean, 8%), and flavanones and dihydroflavonols accounted for 1.5% to 15.2% (mean, 6%) of the total composition.[24]

The active polyphenols/phenolics structurally have 1 or more aromatic rings with hydroxyl groups and can occur as simple and as complex molecules. Polyphenols can be subdivided into 2 major groups: hydroxybenzoic acids and hydroxycinnamic acids. Examples of hydroxybenzoic acids include gallic acid, gentisic acid, protocatechuic acid, salicylic acid, and vanillic acids. Hydroxycinnamic acid examples include *p*-coumaric, caffeic, ferulic, and isoferulic acids. Propolis also contains benzyl, methylbutenyl, phenylethyl, cinnamyl and other esters of these acids. A subcategory of *p*-coumaric acid derivatives is the flavonoids. Flavonoids can be classified into various subclasses. Flavonoids can undergo hydroxylation, methylation, glycosylation, acylation, prenylation, and sulfonation; these basic chemical metabolic substitutions generate the different subclasses: flavanols, flavanones, flavones, isoflavones, flavonols, and dihydroflavonols.[59]

Table 2 provides classes and examples of chemicals identified in poplar-type propolis samples from various locations. Because of space limitations, only a limited number of compounds identified in poplar-type propolis are mentioned here; a full list with synonyms, CAS numbers, and individual references will be published elsewhere (in nonmedical literature).

Constituents of Other Types of Propolis

It falls outside the scope of this article to give full listings of the chemicals found in propolis other than the poplar type. Most recent research has focused on Brazilian propolis (notably the red variety).[8,45,65,66–69] Other countries from which analyses of propolis samples have been published since 2005 include Algeria,[70] Argentina,[10] Cuba,[71,72] Dubai,[73] Egypt,[73] Honduras,[74] India,[75] Indonesia,[12] Iran,[76] Iraq,[6,77] Japan,[78] Jeju Island, Korea,[79] Jordan,[80] Kangaroo Island, Australia,[11,81] Kenya,[82] Mexico,[83,84] Myanmar,[85] Nepal,[86,87] Solomon Islands,[88] Turkey,[89] and the United Arab Emirates[73] (for a brief review, see Miguel and Antunes[90]). It may be assumed that these propolis types contain several hundreds of ingredients other than those found in poplar propolis (Table 2), some of which are fairly, highly, or even completely characteristic for certain geographical locations. In almost every analytical study, 1 or more ingredients not previously found in propolis samples are being detected. Most of these propolis types, however, are not very important as global source for propolis consumer products.

CONTACT ALLERGY

Sensitizing Potential

Petersen in 1977 found propolis to be a potent contact sensitizer in animal experiments with 19 of 25 animals being sensitized in the guinea pig maximization test.[39] Hausen et al,[38] using Freund's complete adjuvant test in guinea pigs, demonstrated that both propolis and "LB-1," a major constituent of poplar buds and poplar-type propolis, are strong sensitizers. At that moment, LB-1, also termed 1,1-dimethylallyl caffeic acid (synonym: 1,1-dimethylallyl caffeate), was thought to be 1 chemical: 3-methyl-2-butenyl caffeate. In a later study however, Hausen and Wollenweber[91] found LB-1 to consist of a mixture of 3-methyl-2-butenyl caffeate (54.2%), 3-methyl-3-butenyl caffeate (28.3%), 2-methyl-2-butenyl caffeate (4.3%), phenethyl caffeate (7.9%), caffeic acid (1.3%), and benzyl caffeate (1.0%).

The same group of German investigators[92] examined the sensitizing capacity of 26 compounds known to be present in propolis and/or poplar buds and a number of closely related substances. Strong sensitizing capacities were found for 3-methyl-2-butenyl caffeate, farnesyl caffeate, geranyl caffeate, benzyl caffeate, and benzyl isoferulate. Compounds with moderate sensitizing capacity were coniferyl benzoate, resorcinol monobenzoate, cinnamyl caffeate, methyl caffeate, coniferyl alcohol, phenethyl caffeate acetate, and phenethyl isoferulate.[92] In a similar study, phenethyl caffeate was found to be a strong sensitizer, benzyl salicylate a moderate, and benzyl cinnamate a very weak sensitizer.[91] Hashimoto et al[93] verified the allergenic properties of phenylethyl and prenyl (3-methyl-2-butenyl) esters of caffeic acids from propolis. The important flavonoids in poplar-type propolis, however, were found experimentally to have weak (rhamnetin, quercetin, naringenin, acacetin, chrysin) or no (galangin, kaempferol, apigenin, tectochrysin, ermanin) sensitizing capacity.[94]

Contact Allergy and Allergic Contact Dermatitis

The first description of contact dermatitis due to propolis was published in 1915, a case of occupational contact allergy in a beekeeper.[95] Cases of allergic contact dermatitis to propolis began to emerge with increasing frequency in the 1970s,[96,97] and at that time, it was already predicted that the incidence of allergy to propolis would rise with the increasing use of the strong sensitizer propolis in biocosmetics and in biopharmaceuticals for self-treatment of various diseases.[39]

TABLE 3. Results of Patch Testing With Propolis in Consecutive Dermatitis Patients

Years and Country	Test Concentration and Vehicle	No. Patients Tested	No. Patients Positive (%)	Relevance (R) and Comments (C)	Reference
2007 and 2011 Lithuania	10% Petrolatum	380	11 (2.9)	R: 7/11 (64%) current clinical relevance from topical remedies for stasis dermatitis, leg ulcers, mycoses etc.; C: overrepresentation of patients with leg dermatitis	138
2009–2010 United States, Canada	10% Petrolatum	4304	90 (2.1)	R: definite + probable relevance 35%	144
2008 Poland	?	275	42 (15)	R: not stated	137
2007–2008 Seven European countries*	10% Petrolatum	12350	270 (2.2)†	R: not stated; C: frequencies of sensitization ranged from 0.7% (Spain) to 4.0% (Austria), median 2.2	145
Austria		678	(4.0)		
Germany		2694	(2.2)		
Italy		984	(1.5)		
Lithuania		223	(2.3)		
Spain		372	(0.7)		
Switzerland		2402	(3.8)		
United Kingdom		4997	(1.4)		
2007–2008 United Kingdom	10% Petrolatum	2828	55 (1.9)	R: 13/55 (24%) current relevance, 4/55 (7%) past, 21/55 (38%) relevance uncertain, 17/55 (31%) due to cross-sensitivity to other allergens; C: >50% caused by cosmetics; 7% coreactivity to beeswax, 11% to fragrance mix I, 27% to colophonium and 40% to *M. pereirae* resin	119
2007–2008 United States, Canada	10% Petrolatum	5067	248 (4.9)	R: definite + probable relevance 19%	140
2001–2007 Czech Rep.	10% Petrolatum	462	35 (7.6)	9 Reactions (26%) were relevant	116
2007 United Kingdom	10% Petrolatum	684	24 (3.5)	R: not stated; C: only one patient coreacted to beeswax	111
2000–2007 United States	10% Petrolatum	500	26 (5.2)	R: 100%; C: high rate of macular erythema and weak reactions; relevance figures include ''questionable'' and ''past'' relevance	141
1995–2005 Germany	?	4242	59 (1.4)	R: not stated; C: the prevalence rose from 0.5% in 1995 to 2.0% in 2005	22
2004 Germany, Austria	10% Petrolatum	?	? (3.5)	R: not stated	136
2003 IVDK	10% Petrolatum	1831	34 (1.9)	R: not stated; C: frequency of propolis allergy was elevated in patients allergic to farnesol, which may be present in poplar buds	146
2002 Austria	?	443	29 (6.5)	R: not stated	139
2000–2002 Finland	?	5130	72 (1.4)	R: not stated; C: rise in prevalence from 0.5% in 1995–1996 (see below in this table) to 1.4% in 2000–2002 (significant)	134

TABLE 3. *(Continued)*

Years and Country	Test Concentration and Vehicle	No. Patients Tested	No. Patients Positive (%)	Relevance (R) and Comments (C)	Reference
1997–2000 Austria	10% Petrolatum	2660	35 (1.3)	R: not stated; C: significant association with fragrance mix I, colophony and *M. pereirae* resin; probably the same population as Reference [147] (below)	142
1997–2000 Austria	10% Petrolatum	2766	36 (1.3)	R: not stated; C: probably the same population as ref. 142 (above)	147
1996–1999 IVDK	?	20363	554 (2.7)	R: not stated; C: there was a significant increase in the frequency of positive patch test reactions with increasing age: 60 y and younger: 2%; 71–75 y: 4.4%, >75 y: 5.3%, indicating the relevance of topical leg ulcer/lower-leg dermatitis for the induction of sensitization	115
1998 Poland	10% Petrolatum	1830	(1.4–1.8)	R: not mentioned; C: 3 different samples of propolis from various parts of Poland were used for patch testing; 64%–79% of patients reacting to one or more propolis samples coreacted to *M. pereirae* resin	143
1995–1996 Finland	?	3885	19 (0.5)	R: not stated	134
1988–1990 Germany	10% Petrolatum	3199	39 (1.2)	R: 50% had used "biocosmetics" or "natural cosmetics" and 20% had used propolis capsules	92
1988 Czechoslovakia	10% Alcohol solution	605	25 (4.1)	R: previous contact was confirmed in 16/25 (64%), all folk remedies for various diseases; C: 52% coreacted to *M. pereirae* resin	114
1981–7 Slovakia	5% alcohol	7383	136 (1.8)	R: not stated; C: yearly range: 0.44%–3.32%; rise in frequency in 1985–1987	148
<1987				See the review of Hausen et al[1]	1

**Study of ESSCA (European Surveillance System on Contact Allergy network).*
†Age-standardized and sex-standardized proportions.
IVDK indicates Informationsverbund Dermatologischer Kliniken (Germany, Switzerland, Austria).

Occupational contact allergy to propolis in beekeepers is well known (mainly from collecting honey and cleaning hives, where contact with propolis is inevitable) and may lead to both contact dermatitis and airborne allergic contact dermatitis.[38,97–104] Airborne contact dermatitis may sometimes also be observed in neighbors of beekeepers.[105,106] Occupational contact allergy to propolis also occurs, albeit far less frequently, in musicians and people who make stringed musical instruments[107–109] and has been observed in farmers.[110] One case in a dental technician was caused by hand molding (propolis-contaminated) beeswax products in the manufacture of prosthetic components.[111] A shoemaker may have reacted to beeswax contaminated with propolis.[112] A worker in a retail store had contact dermatitis which was—unconvincingly—ascribed to beeswax[a] in wood varnish.[113]

Whereas formerly most cases were (thought to be) caused by occupational exposure in beekeepers, currently most are caused (or at least the cases being published) by the topical use of propolis for medicinal purposes.[92,114] Thus, propolis is an important allergen in patients with leg ulcers/lower-leg dermatitis,[115–117] and the frequency of sensitization is greater than 5% in patients with anal dermatoses.[118] Other sources of sensitization to propolis include cosmetics[119] and "biocosmetics" or "natural cosmetics."[92] In a number of cases, a positive patch test reaction to propolis can be explained by the previous use of preparations with poplar extract.[38,91]

Chewing propolis or chewing gum with propolis and the use of toothpastes, lozenges, powders, mouthwashes, and various remedies for intraoral uses containing propolis have been reported to cause allergic stomatitis (sometimes with ulcers), labial and oral

[a]Bee *glue* (synonym for propolis) is often confused with bees*wax* (which is part of raw propolis). It is assumed that beeswax may often contain small amounts of propolis, but this will not be the case in highly purified beeswax products such as pharmaceutical grade cera alba. It cannot be excluded that these facts may have led to mistakes in certain publications cited here.

swelling, dyspnea, cheilitis, and perioral eczema.[107,120–127] Oral administration of honey or propolis-containing products (capsules, tablet, powders, sprays) by patients allergic to propolis may cause generalized skin eruptions,[128,129] fixed drug eruption,[130] and erythroderma.[131]

It should be realized that occupational contact allergy in beekeepers may still be a major problem. More than 3.5% of German beekeepers may suffer from it,[132] with an estimated number of 2900 propolis sensitive beekeepers in Germany. However, they do not seem to recognize the problem and continue their hobby without protecting themselves from contact with the substance. On the contrary, many use propolis as medication for other disorders. This means that very few will be seen by a dermatologist, and the problem goes unrecognized (and unreported).[132] Previously, in Bologna, Italy, 5% to 6% of beekeepers were suspected to be allergic to propolis based on a questionnaire analysis of 153 apiarists.[133]

Frequency of Sensitization

The predicted rise in cases of contact allergy appears to have occurred. Between 1997 and 2002, a Finnish center observed an increase in positive patch test reactions to propolis from 0.5% to 1.4%.[134] In Italy, there was a linear increase in the frequency of sensitization from 2% in 1995 to 13.7% in 2002 in children with dermatitis.[135] In Germany, the prevalence rose from 0.5% in 1995 to 2% in 2005.[22] Propolis became part of the standard battery in Germany and Austria in 2004, and an average of 3.5% positive reactions were observed.[136] Reports of routine testing with propolis are summarized in Table 3. In the 22 studies reviewed, prevalence of positive patch test reactions ranged from 0.5% in Finland[134] from 1995 to 1996 to 15% in a small 2008 Polish study.[137] In general, the higher frequencies were observed in mid- and eastern European countries such as Poland, Lithuania, Czech Republic, Switzerland, Austria, and Germany, where the extensive use of propolis, usually for biopharmaceutical purposes, is well

TABLE 4. Results of Patch Testing With Propolis in Groups of Selected Patients

Years and Country	Test Concentration and Vehicle	No. Patients Tested	No. Patients Positive (%)	Selection of Patients (S), Relevance (R), Comments (C)	Reference
2008–2009 Poland	10% Petrolatum	103	17 (17)	S: consecutive children 7–8 y old with chronic recurrent eczema and atopy; R: not stated; C: 2nd most frequent allergen after nickel	149
		93	5 (5)	S: consecutive adolescents 16–17 y old with chronic recurrent eczema and atopy; R: not stated; C: 4th most common allergen after nickel, thimerosal and cobalt	149
1998–2002 IVDK	10% Petrolatum	42	3 (7)	S: patients with positive patch test reactions to their own shaving products/eaux de toilette/perfumes; C: statistically significant association with propolis contact allergy	152
1995–2002 Italy	20% Petrolatum	1255	74 (5.9)	S: consecutive children seen for patch testing aged 7 mo to 12 y; R: 75% relevancy; C: linear increase in the frequency of sensitization from 2% in 1995 to 13.7% in 2002; significant association with *M. pereirae* resin	135
1995–2002 IVDK	10% Petrolatum	164	5 (3.0)	S: patients with rosacea; R: not stated; C: the frequency was significantly higher than in patients with dermatitis	155
1996–1997 United Kingdom	10% Petrolatum	27	4 (15)	S: patients suspected of cosmetic dermatitis; R: not specified, one had taken propolis tablets; coreactivity to the fragrance mix in all cases	153
1996 Italy	20% Petrolatum	305	1 (0.3)	S: consecutive patients with psoriasis; R: not stated	154
1988–1994 Italy	?	670	5 (0.7)	S: children aged 6 mo—12 y; R: not stated	151
1970–1994 Poland	?	626	8 (1.3)	S: consecutive children seen for patch testing aged 3–16 y; R: not stated	150
<1987				See the review of Hausen et al[1]	1

IVDK indicates Informationsverbund Dermatologischer Kliniken (Germany, Switzerland, Austria).

TABLE 5. Case Reports of Patients Allergic to Propolis*

Country	Year	No. Patients	Exposures and Clinical Data	Reference
Croatia	2012	1	Lip edema with erosions in the corners of the lips, and perioral erythema caused by propolis spray used for gingival swelling	127
United States	2012	1	Fixed drug eruption from propolis food supplement	130
Korea	2011	1	Systemic contact dermatitis from oral propolis solution	128
United States	2011	1	Perioral dermatitis and eczema in a child allergic to propolis and cinnamal, improving after avoidance of topical products containing fragrances and beeswax and clearing after stopping the use of gummy multivitamins containing propolis	156
Belgium	2000–2010	2	Skin care products	157
Korea	2009	1	Cheilitis and oral mucositis from propolis solution used for the treatment of aphthous ulcers	158
Austria	2009	1	Maculopapular exanthema from propolis capsules	129
United States	2008	1	Chewable multivitamins containing beeswax† causing cheilitis and dermatitis	159
United Kingdom	2007	1	Occupational contact dermatitis in a dental technician from molding beeswax† products in the manufacture of prosthetic components	111
Serbia and Montenegro	2006	1	Antihemorrhoidal ointment containing propolis	160
United Kingdom	2006	1	Vulval eczema ascribed to the presence of propolis in topical corticosteroid preparations; however, these topical medications contained highly purified beeswax, unlikely to be contaminated with propolis†	161
Croatia	2006	1	Erosions of the lips and mouth from propolis solution	124
Korea	2006	1	Propolis ointment	162
Germany	1995–2005	19	Propolis products used for medicinal purposes	22
		1	Occupational exposure to propolis-containing ointment in a nurse	
		1	Occupational exposure to honey in a laboratory analyst†	
		1	Occupational exposure to beeswax in making candles†	
		1	Eating honey daily resulted in persistent exanthema†	
		1	Natural cosmetics provided by a beekeeper	
		1	Sunscreens containing beeswax contaminated with propolis†	
Canada	2004	1	Propolis ointment	163
Italy	2004	1	Contact cheilitis from eating (propolis enriched?) honey†	125
Spain	2004	1	Alcoholic solution of propolis used as mouthwash caused labial edema, oral pain, dysphonia, and dyspnea; 1 lozenge caused pain and swelling of the tongue with dyspnea	121
United States	2002	1	Occupational contact dermatitis from Italian varnish in a violin maker	108
Germany	2002	1	Occupational contact dermatitis from beeswax in a shoe maker†	112
Germany	2002	1	Unguentum leniens containing beeswax, supposedly contaminated with propolis†; the authors cite 3 similar cases in 2 German articles[165,166]	164
Japan	2001	1	Erythroderma from oral propolis powder (patch test with the powder was negative)	131

(Continued on next page)

TABLE 5. *(Continued)*

Country	Year	No. Patients	Exposures and Clinical Data	Reference
Czechia	2000	?	Cosmetic products; "several" patients	167
Germany	1998	1	Lip balm and an ointment caused contact cheilitis mimicking pemphigus vulgaris	168
Italy	1997–1998	2	Toothpastes containing propolis or ingredients thereof or cross-reacting substances	169
		1	Lip cream	
Italy	1997	2	Propolis (hand) cream used for psoriasis; labial edema after chewing propolis tablets in one patient	126
Italy	1996	1	Labial and oral swelling, dyspnea, oral mucosal ulcers, cheilitis, and perioral dermatitis from propolis tincture	120
Spain	1990	1	Propolis ointment and tincture	170
New Zealand	1990	1	Acute oral mucositis with ulceration from propolis lozenges	123
Germany	1988	3	Propolis ointment (n = 1), ointment prepared from poplar buds (n = 1), *Populus* Fluid (homeopathic preparation) (n = 1)	91
		1	Lipstick	
Germany	1988	1	Cosmetic ointments	171
		2	Therapeutic ointment	
Germany	1987	4	Propolis ointment	38
		2	Poplar bud ointment	
		1	Cream and face lotion	
		1	"Natural products" used as cosmetics	
The Netherlands	1987	1	Stomatitis and throat complaints from propolis tablet and toothpaste	172
Italy	1987	1	Allergic contact dermatitis superimposed on psoriasis from propolis containing creams	173
The Netherlands	1987	1	Cosmetic cream	104
Case reports from before 1987			See Reference [1]	1

** Cases of propolis allergy in beekeepers are not included.*

† Honey and beeswax are frequently contaminated with small amounts of propolis,[18,22] but is should be realized that in no single case-report analytical investigations have been performed to verify this, so some reports may not have been accurate.

known.[114,116,136–139] However, high frequencies of sensitization have also been observed in the United States and Canada in 2007 to 2008 (4.9%[140]) and the United Kingdom in 2007 (3.5%[111]). Generally speaking, the studies from after 2002 show higher sensitization rates than the older ones. In fact, of the 13 reports since 2002, only 2 had frequencies lower than 2% (1.4%,[22] 1.9%[119]), whereas 7 had prevalences (far) higher than 3%. Thus, it is not surprising that some investigators have suggested routine testing of propolis in the European baseline series; at this moment, it is part of the British Contact Dermatitis Society baseline series.[119] Unfortunately, as is the case in many such studies, data on relevance of the observed positive patch test reactions were often not provided. In the studies that commented on relevance, percentages ranged from 24% current relevance[119] to 64%.[138] In a US study, relevance was scored as 100%, but this included "past relevance" and "questionable relevance."[141] Incriminated products were propolis-containing pharmaceuticals,[92,138] cosmetics,[119] and "biocosmetics/natural cosmetics."[92]

In many reports, there was an overrepresentation of coreactivity to indicators of fragrance contact allergy, notably *Myroxylon pereirae* resin, in patients with positive patch test reactions to propolis[114,119,142,143]; this is further discussed in the Coreactions and Cross-reactions section.

Table 4 shows the results of testing with propolis in groups of selected patients, including children[135,149–151] and patients with fragrance allergy,[152] suspected cosmetic allergy,[153] psoriasis,[154] and rosacea.[155] Remarkably high frequencies were observed in 2008 to 2009 in Polish children of 7 to 8 years old (16.5%), propolis being the second most frequent allergen after nickel.[149] Also in Italian children, high frequencies of sensitization were observed (mean, 5.9% in the period 1995–2002), and there was a linear increase in the frequency of sensitization from 2% in 1995 to 13.7% in 2002.[135] In the Italian study, relevance was said to be 75%, but no details on the incriminated products were provided.[135] In earlier studies in both Polish and Italian children, sensitization rates had been far lower (0.7%–1.3%).[150,151] In 42 patients with positive patch test reactions to their own shaving products/eaux de toilette/perfumes, a frequency of 7% positive patch test reactions to propolis 10% was observed; the association was statistically significant.[152]

CASE REPORTS

Case reports of sensitization to propolis-containing products are shown in Table 5 (excluding cases of occupational contact allergy in beekeepers). The relevant literature from before 1987 has been reviewed by Hausen et al.[1]

It is clear that most cases are caused by the use of propolis for medicinal purposes and that cosmetics containing propolis constitute a small minority. Unusual contact dermatitis cases have included granulomatous allergic contact dermatitis accompanied by marked lymphadenopathy from the application of a 20% lotion made from Brazilian propolis to an abrasion[174] and contact cheilitis from a lip balm and an ointment mimicking pemphigus vulgaris.[168]

COREACTIONS AND CROSS-REACTIONS

Propolis and Myroxylon Pereirae

The association between positive patch test reactions to propolis and *M. pereirae* has been noted for decades (Table 6). From 9% to 90% of propolis-sensitive patients also react to *M. pereirae* resin (mean, in all studies: 43%, without a large study in children[135]: 54%; median, 55%).

Both substances are extremely complex materials, and patch testing with (some of) their ingredients is rarely performed. At least 26 chemicals may be present in both propolis and *M. pereirae* resin[1,91,92,175–177] (Table 7), and 9 of these have caused positive patch test reactions both in patients allergic to propolis and in patients allergic to *M. pereirae* resin.

TABLE 6. Coreactivity to *M. pereirae* (MP) Resin in Propolis-Positive Patients

No. Patients Positive to Propolis	No. Patients Co-Reacting to MP (%)	Comments	Reference
82	45 (55%)	Summary of literature from before 1987; range coreactivity 0%–91%	1
74	7 (9%)	"Significant association with MP"	135
55	22 (40%)		119
35		"Significant association with MP"	142
33	(64–79%)	Patients reacting to 1, 2, or 3 samples of MP	143
27	12 (44%)		22
25	13 (52%)		114
20	18 (90%)		175
7	6 (86%)		92
7	3 (43%)		142
6	4 (67%)		171
3	2 (67%)		91
Total 306	132 (43%)		

TABLE 7. Chemicals Which May Be Present in Both Propolis and *M. pereirae* Resin[1,91,92,175–177]

Aromatic acids	
Benzoic acid*†	*Fatty acids*
Caffeic acid (3,4-dihydroxycinnamic acid)*	Docosanoic acid
Cinnamic acid*†	Dodecanoic acid (lauric acid)
Ferulic acid (3-methoxy-4-hydroxycinnamic acid)*	Eicosanoic acid (arachidic acid)
Isoferulic acid (3-hydroxy-4-methoxycinnamic acid)†	Hexacosanoic acid (cerotic acid)
Vanillic acid (3-methoxy-4-hydroxybenzoic acid)	Octadecanoic acid (stearic acid)
	Tetradecanoic acid (myristic acid)
Aromatic esters	
Benzyl benzoate*†	*Others (terpenoids, alcohols, aldehydes)*
Benzyl cinnamate*†	Benzyl alcohol†
Benzyl ferulate	Cinnamyl alcohol*†
Benzyl isoferulate*†	Eugenol (terpenoid)†
Benzyl salicylate*†	1-Tetracosanol (lignoceryl alcohol)
Cinnamyl cinnamate*†	Nerolidol (terpenoid)†
Coniferyl benzoate*†	Vanillin (aldehyde)*
Methyl benzoate	

**Has caused positive patch test reactions in patients allergic to propolis (vide infra).*
†Has caused positive patch test reactions in patients allergic to M. pereirae resin.[176]

Thus, there are ample opportunities that positive patch test reactions to both propolis and *M. pereirae* resin are caused by common ingredients (which may be called "pseudo–cross-reactions"). On the other hand, by far the most important sensitizers in propolis (discussed below) are esters of caffeic acid. As caffeic acid is a substituted cinnamic acid (3,4-dihydroxycinnamic acid), such patients may well have real cross-sensitivity to other cinnamic acids (cinnamic acid, ferulic acid, isoferulic acid) and their aromatic esters such as benzyl cinnamate, benzyl ferulate, benzyl isoferulate, or cinnamyl cinnamate. Indeed, cinnamic acid and other cinnamates comprise about one third of *M. pereirae* resin, and of patients allergic to the substance, in 1 study, 38% reacted to cinnamyl alcohol, 33% to cinnamic acid, and 20% to cinnamyl cinnamate, so the cinnamates are the most important sensitizers in *M. pereirae* resin.[176]

Interestingly, the reverse situation may be different. Of 102 patients allergic to *M. pereirae* resin, only 9 (9%) coreacted to propolis.[179] This may indicate that the main sensitizers in propolis, the caffeates (caffeic acid = 3,4-dihydroxycinnamic acid), cross-react to the related cinnamates in *M. pereirae* (which are present there in high concentrations), but that the main sensitizers in *M. pereirae* less often induce reactions from their presence in propolis. However, in another—albeit far smaller—study, of 11 patients allergic to *M. pereirae* resin who had, according to their histories, never

come into contact with propolis, 5 (45%) coreacted to propolis,[175] so cross-sensitivity may be more common than described above.[176]

Other Coreactions

Coreactions to substances other than *M. pereirae* resin in propolis-sensitive patients are summarized in Table 8. The fragrance mix I and propolis may have cinnamyl alcohol and eugenol in common, but there appears to be no clear relationship between the 2.[119,135] Patch tests to colophony, however, are overrepresented; common ingredients may include resin acids such as (dehydro)abietic acid and certain monoterpenes.[119,142] Most concurrent reactions to yellow beeswax (cera flava, the least purified beeswax) may conveniently be explained by contamination of the beeswax with propolis, although analytical investigations to prove this in actual cases of contact allergy have not been performed.[99,119,178,179]

A high degree of coreactivity to poplar buds and extracts is to be expected, poplar buds being the most important source of propolis.[1,123,148] Coreactivity to (a number of) essential oils does not come unexpected, the highest degree being seen with clove oil (11/16 positive reactions, 69%[175]). Clove oil may contain up to 88% eugenol and 34% benzyl alcohol[180]; these compounds can

TABLE 8. Coreactivity in Patients Allergic to Propolis (Other Than *M. pereirae* resin)

No. Positive to Propolis	Coreacting Substance	No. Coreactions (%)	Comments	Reference
Fragrance mix I				
74	Fragrance mix I	3 (4%)	No significant association	135
55	Fragrance mix I	6 (11%)	No significant association	119
7	Fragrance mix I	5 (71%)		142
Colophony				
55	Colophony	15 (27%)		119
7	Colophony	3 (43%)		142
6	Colophony	3 (50%)		171
Beeswax				
55	Beeswax (yellow, cera flava)	4 (7%)	Probably due to propolis contamination	119
5	Beeswax	4 (80%)	Probably due to propolis contamination	178
3	Beeswax	1 (33%)		99
4	Beeswax (cera alba)	2 (50%)		171
4	Beeswax (cera flava)	2 (50%)		171
1	Beeswax (yellow and white, cera flava and cera alba)	1 (100%)	The patient was sensitized from cera alba (a purified beeswax) in a cosmetic product	179
Poplar bud (extracts)				
19	Poplar bud extracts	15 (79%)		148
1	Poplar buds and extract	1 (100%)		123
3	Poplar buds	3 (100%)	The patients did *not* react to a coca solution extract of poplar buds	171
Essential oils				
16	*Eugenia caryophyllus* (clove) oil	11 (69%)	The 16 patients were allergic to both propolis and *M. pereirae* resin	175
16	*Coriandrum sativum* (coriander) oil	4 (25%)	The 16 patients were allergic to both propolis and *M. pereirae* resin	175
16	*Cananga odorata* flower oil	3 (19%)	The 16 patients were allergic to both propolis and *M. pereirae* resin	175
16	*Cinnamomum cassia* (cassia) oil	3 (19%)	The 16 patients were allergic to both propolis and *M. pereirae* resin	175
16	*Mentha piperita* (peppermint) oil	3 (19%)	The 16 patients were allergic to both propolis and *M. pereirae* resin	175
16	*Salvia sclarea* (clary) oil	3 (19%)	The 16 patients were allergic to both propolis and *M. pereirae* resin	175
Miscellaneous				
16	Eugenol	6 (38%)	The 16 patients were allergic to both propolis and *M. pereirae* resin	175
26	Chamomile extract	4 (15%)		148
1	*Copernicia cerifera* (carnauba) wax	1 (100%)	Carnauba wax may contain 10% cinnamic acid	159

also be present in propolis and in *M. pereirae* resin (Table 7). However, of the 16 patients allergic to propolis, 11 (69%) also reacted to clove oil, but only 6 of the 16 (not known how many in the group of 11 reacting to clove oil) coreacted to eugenol, which means that eugenol cannot explain all coreactivity to clove oil.[175]

Conversely, positive patch tests to propolis may be overrepresented in patients with contact allergy to certain plants. Thus, 3 (60%) of 5 patients with positive patch test reactions to an extract of *Arnica montana* and 5 (56%) of 9 patients with positive patch test reactions to extract of *Calendula officinalis* (true marigold) coreacted to propolis 10% petrolatum.[139] Of 22 patients allergic to farnesol, 2 (9%; odds ratio: 6.2; 95% confidence interval, 1.4–27.7) coreacted to propolis.[146] Farnesol has not been demonstrated in propolis, but has been found in poplar buds.[146]

THE ALLERGENS IN PROPOLIS

In a (limited) number of studies, patients allergic to propolis have been tested with a (limited) number of its ingredients. The relevant data of these investigations, aimed at finding the responsible allergens, are shown in Table 9.

It is clear that the most important sensitizers—at least of the ones that have been tested—are the esters of caffeic acid: "LB1" (a mixture of 3-methyl-2-butenyl caffeate (54.2%), 3-methyl-3-butenyl caffeate (28.3%), 2-methyl-2-butenyl caffeate (4.3%), phenethyl caffeate (7.9%), caffeic acid (1.3%) and benzyl caffeate (1.0%)) (86% positive reactions), phenethyl caffeate (80% positive reactions), benzyl caffeate (69%), 3-methyl-2-butenyl caffeate (64%), geranyl caffeate (41%), and 2 mixtures of caffeates (27% and 26%). Caffeic acid itself scored 15% positive reactions in 55 patients tested in 3 studies. Caffeic acid is a substituted cinnamic acid: 3,4-dihydroxycinnamic acid. Cinnamic acid and its esters (cinnamyl, benzyl, methyl) also scored some positive reactions, but far less, and this also applies to other substituted cinnamic acids (ferulic acid, isoferulic acid, coumaric acid, 3,4-dimethoxycinnamic acid) and their esters. Benzoic acid, another important aromatic acid in propolis, and benzyl benzoate are not important sensitizers. Its ester coniferyl benzoate had a 50% score of positive reactions, but was tested in 2 patients in only 1 study. Eugenol, which has structural similarities to ferulic acid (3-methoxy-4-hydroxycinnamic acid) was positive in 6 of 16 patients in 1 study; many coreactions were observed to clove oil, which consists of 60% to 88% eugenol[180]; in another study, none of 3 propolis-allergic patients reacted to it.[171]

In general, the terpinoids are—confirming their weak or absent sensitizing potential in animal experiments (*vide supra*)—not important sensitizers in propolis. Most have caused no positive patch test reactions at all; a few reactions have been observed to apigenin, kaempferol, quercetin, quercetin 3-methyl ether, tectochrysin, and aesculetin (with the exception of tectochrysin tested in only 1 study[148]).

The allergen in commercial propolis creams may in some cases be other constituents of the product such as lanolin alcohol.[183]

Presence of Allergens in Raw Propolis, Hydroalcoholic Extracts, and Propolis Tablets

Gardana and Simonetti[50] determined the amounts of allergens in raw propolis samples from various countries (Europe, China, Uruguay, Nepal, Brazil), hydroalcoholic solutions, and propolis tablets with the aid of ultraperformance liquid chromatography/tandem mass spectrometry. The substances investigated were caffeic acid, 3-methyl-3-butenyl caffeate, 3-methyl-2-butenyl caffeate, 2 methyl-2-butenyl caffeate, benzyl caffeate, and phenethyl caffeate. In European (n = 7), Chinese (n = 2), and Uruguayan (n = 1) samples (probably poplar-type propolis), 1.37% (China) to 4.99% (Macedonia) of the raw propolis consisted of caffeic acid and its esters (mean for 10 samples, 3.50%; median, 3.78%). In the hydroalcoholic extracts and the tablets, the percentages were far lower: extracts 0.09% to 1.01% (mean, 0.44%; median, 0.38%), tablets 0.06% to 0.55% (mean, 0.16%; median, 0.09%).

In all 3 product samples, the highest concentrations were found for benzyl caffeate, followed by 3-methyl-2-butenyl caffeate, phenethyl caffeate, 3-methyl-3-butenyl caffeate, and caffeic acid. The lowest concentrations were found for 2-methyl-2-butenyl caffeate. In raw propolis, the amounts found (amounts in mg/g, range, followed by mean in parentheses) were as follows: benzyl caffeate 3.5 to 13.0 (9.3), 3-methyl-2-butenyl caffeate 2.7 to 10.5 (7.0), phenethyl caffeate 2.6 to 9.7 (6.6), 3-methyl-3-butenyl caffeate 2.2 to 9.3 (5.9), caffeic acid 1.7 to 7.6 (4.4), and 2-methyl-2-butenyl caffeate 0.4 to 3.4 (2.0). The amounts found in hydroalcoholic extracts were 7 to 13 times lower than in the raw propolis, and the amounts in tablets were factors 1.9 to 2.8 lower than in the extracts. As the profile of the chemicals in the hydroalcoholic extracts and the tablets is the same as in the raw material, it may be assumed that both were prepared from European or Chinese propolis. Five of the 6 chemicals were also found in Nepalese raw propolis, but in far lower concentrations. As expected—poplars do not grow in tropical regions—none of the chemicals was found in either green or red propolis from Brazil.[50]

Aliboni et al[184] determined the amounts of a number of cinnamic acids (caffeic acid, *p*-coumaric acid, ferulic acid), a number of flavonoids (quercetin, apigenin, kaempferol, chrysin, galangin), and benzyl cinnamate and benzyl salicylate in 5 samples of solid Italian poplar-type propolis. The results were as follows (amounts in mg/g, range, followed by mean in brackets): caffeic acid 2.6 to 25 (15), *p*-coumaric acid 1.9 to 5.4 (3.2), ferulic acid 3.1 to 5.2 (3.9), quercetin 0.6 to 8.5 (4.6), apigenin 1.3 to 8.0 (3.8), kaempferol 1.4 to 8.5 (4.5), chrysin 6 to 50 (32), galangin 4.7 to 30 (17.4), benzyl salicylate 0.015 to 0.08 (0.045), and benzyl cinnamate 0.02 to 1.03 (0.3).

PROPOLIS PATCH TEST MATERIALS

All 3 major suppliers of patch test allergens (Chemotechnique, Brial/Allergeaze, Almirall Hermal [Trolab]) provide propolis 10% in petrolatum. The propolis from Chemotechnique comes from China (probably poplar-type propolis) and contains 13% flavonoids.

TABLE 9. Testing of Propolis Allergic Patients With Selected Ingredients

Propolis Allergen	No. Positive/ No. Tested (%)	No. Positive/ No. Tested (%)	No. Positive/ No. Tested (%)	No. Positive/ No. Tested (%)	No. Positive/ No. Tested (%) Total
LB1*	8/9 (89%)[92]	2/3 (67%)[91]	8/9 (89%)[38]		18/21 (86%)
Phenethyl caffeate	20/27 (74%)[22]	10/10 (100%)[92]	2/3 (67%)[91]		32/40 (80%)
Benzyl caffeate	18/27 (67%)[22]	2/2 (100%)[92]			20/29 (69%)
3-Methyl-2-butenyl caffeate†	17/27 (63%)[22] 1/1 (100%)[99]	2/3 (67%)[171]	7/7 (100%)[92]	3/9 (33%)[181]	30/47 (64%)
Coniferyl benzoate	1/2 (50%)[92]				1/2 (50%)
Geranyl caffeate	11/27 (41%)[22]				11/27 (41%)
Ferulic acid dimethylallyl ester	3/9 (33%)[181]				3/9 (33%)
Eugenol	6/16 (38%)[175]‡	0/3 (0%)[171]			6/19 (32%)
3-Methyl-2-butenyl caffeate + 3-methyl-3-butenyl caffeate	7/26 (27%)[148]				7/26 (27%)
3-Methyl-2-butenyl diacetylcaffeate + 3-methyl-3-butenyl caffeate-	5/19 (26%)[148]				5/19 (26%)
Cinnamyl cinnamate	3/12 (25%)[175]‡				3/12 (25%)
Benzyl isoferulate	1/4 (25%)[92]				1/4 (25%)
Benzyl salicylate	2/8 (25%)[92]	0/2 (0%)[91]			2/10 (20%)
Apigenin	3/19 (16%)[148]				3/19 (16%)
3,4-Dimethoxycinnamic acid	3/19 (16%)[148]				3/19 (16%)
Kaempferol	3/19 (16%)[148]				3/19 (16%)
Methyl coumarate	3/19 (16%)[148]				3/19 (16%)
Quercetin	3/19 (16%)[148]				3/19 (16%)
Quercetin 3-methyl ether	3/19 (16%)[148]				3/19 (16%)
Caffeic acid	0/27 (0%)[22]	4/19 (21%)[148]	4/9 (44%)[92]		8/55 (15%)
Cinnamic acid	0/27 (0%)[22]	4/19 (21%)[148]	4/9 (44%)[92]	0/3 (0%)[171]	8/58 (14%)
Coumaric acid	3/27 (11%)[22]	3/19 (16%)[148]			6/46 (13%)
Tectochrysin	2/27 (7%)[22]	1/7 (14%)[182] 0/1 (0%)[91]	0/3 (0%)[171] 3/5 (60%)[38]	0/6 (0%)[92]	6/49 (12%)
Aesculetin	2/19 (11%)[148]				2/19 (11%)
Cinnamylideneacetic acid	2/19 (11%)[148]				2/19 (11%)
Ferulic acid	1/27 (4%)[22]	3/19 (16%)[148]			4/46 (9%)
Benzyl cinnamate	0/27 (0%)[22] 1/1 (100%)[121]	1/12 (8%)[175]‡ 0/3 (0%)[100]	2/9 (22%)[92]	0/1 (0%)[91]	4/53 (8%)
Vanillin	0/27 (0%)[22] 0/3 (0%)[171]	2/12 (17%)[175]‡	0/1 (0%)[121]	0/3 (0%)[100]	2/46 (4%)
Methyl cinnamate	1/27 (4%)[22]				1/27 (4%)
Benzoic acid	0/27 (0%)[22]	1/3 (33%)[92]	0/3 (0%)[171]		1/33 (3%)
Cinnamyl alcohol	0/27 (0%)[22] 0/3 (0%)[100]	0/12 (0%)[175]‡ 0/3 (0%)[171]	1/7 (14%)[92]	0/1 (0%)[121]	1/53 (2%)
Benzyl benzoate	0/27 (0%)[22]	0/12 (0%)[175]‡	1/8 (13%)[92]	0/3 (0%)[171]	1/50 (2%)
Benzyl alcohol	0/27 (0%)[22]				0/27 (0%)
Cinnamyl isoferulate	0/27 (0%)[22]				0/27 (0%)
Rhamnetin	0/27 (0%)[22]				0/27 (0%)
Chrysin	0/7 (0%)[63]	0/3 (0%)[171]	0/9 (0%)[38]		0/19 (0%)
Galangin	0/7 (0%)[182]	0/3 (0%)[171]	0/9 (0%)[38]		0/19 (0%)
Isalpinin	0/7 (0%)[182]	0/3 (0%)[171]	0/9 (0%)[38]		0/19 (0%)
Pinocembrin	0/7 (0%)[182]	0/3 (0%)[171]	0/9 (0%)[38]		0/19 (0%)
Pinostrobin	0/7 (0%)[182]	0/3 (0%)[171]	0/9 (0%)[38]		0/19 (0%)
Pinobanksin-3-acetate	0/7 (0%)[182]	0/3 (0%)[171]			0/10 (0%)
3,4-Dimethoxycinnamic acid dimethylallyl ester	0/9 (0%)[181]				0/9 (0%)
Acacetin	0/7 (0%)[182]				0/7 (0%)
Alpinone	0/7 (0%)[182]				0/7 (0%)
Alpinone-3-acetate	0/7 (0%)[182]				0/7 (0%)

TABLE 9. *(Continued)*

Propolis Allergen	No. Positive/ No. Tested (%)	No. Positive/ No. Tested (%)	No. Positive/ No. Tested (%)	No. Positive/ No. Tested (%)	No. Positive/ No. Tested (%) Total
7-Methylapigenin (genkwanin)	0/7 (0%)[182]				0/7 (0%)
Farnesyl caffeate	0/6 (0%)[92]				0/6 (0%)
Benzaldehyde	0/3 (0%)[171]				0/3 (0%)
2',6'-Dihydroxy-4'-methoxy-dihydrochalcone	0/3 (0%)[171]				0/3 (0%)
Galangin 3-methyl ether	0/3 (0%)[171]				0/3 (0%)

**LB1 is a mixture of 3-methyl-2-butenyl caffeate (54.2%), 3-methyl-3-butenyl caffeate (28.3%), 2-methyl-2-butenyl caffeate (4.3%), phenethyl caffeate (7.9%), caffeic acid (1.3%), and benzyl caffeate (1.0%).*[91]

†Synonyms: 1,1-dimethylallyl caffeate, prenyl caffeate.

‡These patients were also allergic to M. pereirae resin and were tested with a number of common ingredients.

Information on other ingredients is not available (Bo Niklasson, Chemotechnique, e-mail communication, June 2013). Brial makes its test material from propolis extract from Latin America, where the native plant species are poplar, eucalyptus, acacia, and pine; there is no information on the constituents (Jürgen Brinkmann, Brial, e-mail communication, June 2013). Almirall Hermal has not responded to repeated requests for information.

Unfortunately, the most important sensitizers, the esters of caffeic acid (caffeates), are not available for patch testing. Given the frequent occurrence of sensitization to propolis, we suggest that the providers investigate the possibilities to develop patch test materials with the caffeates (realizing their strong sensitizing properties, of course). Several other (possible) ingredients of propolis are commercially available and can be tested in propolis-sensitive patients: abietic acid, benzoic acid, benzyl alcohol, benzyl benzoate, benzyl cinnamate, benzyl salicylate, cinnamyl alcohol, eugenol, hydroquinone, limonene, methyl salicylate, α-pinene, salicylic acid, and vanillin. To detect sensitization to 1,8-cineole (eucalyptol, which is not available), *Eucalyptus globulus* (eucalyptus) oil can be tested, and for detecting allergy to γ-terpinene, *Melaleuca alternifolia* (tea tree) oil (which contains up to 25% of this terpene) can be used. Oil of turpentine may be tested as a substitute for β-pinene, which is a major constituent. It should be realized that these components may be minor allergens in propolis. In addition, it may be useful to test other essential oils in propolis-sensitive patients, notably *Eugenia caryophyllus* (clove) oil.

OTHER ADVERSE EFFECTS

Immediate Allergic Reactions

There are few documented cases of immediate reactions to propolis.[185,186] A 10-year-old boy had previously suffered an immediate systemic reaction within 5 minutes after a honeybee sting. Sensitization to honeybee venom was demonstrated by skin prick test and specific serum immunoglobulin E (IgE). The patient also displayed angioedema each time he had contact with beehive products (honey, propolis, beeswax, and pollen) while helping his father, a beekeeper. A prick-to-prick test was positive for propolis and negative for beeswax and honey, and both IgE and IgG against propolis extract were demonstrated.[185]

A 48-year-old man treated his sore throat with topical propolis. After 6 hours, the patient complained of dysphagia and saliva drooling. Dyspnea later occurred, and he soon lost consciousness with cyanosis and a generalized seizure attack, after which the patient became apneic and developed cardiac arrest. Severe larynx angioedema resulted in difficult airway intubation. The patient later developed multiorgan failure and adult respiratory distress syndrome and died of intractable sepsis after 50 days. No diagnostic tests to prove the causal relationship with propolis and to demonstrate the mechanism of the reaction were performed.[186]

Between 1991 and 1995, the National Poisons Information Service (London, United Kingdom) received 2 reports from allergic reactions to oral "royal jelly and propolis products" with symptoms ranging from crushing chest pains to severe bronchospasm and angioneurotic edema. No skin tests were performed. Similar cases from previous investigations were cited, which concerned type I reactions to royal jelly rather than to propolis.[187]

Systemic Adverse Effects

Oral propolis seems relatively harmless, with a calculated safe dose of 1.4 mg/kg body weight per day in humans (applying the safety factor of 1000).[18] Nevertheless, oral administration has been (tentatively) linked to seizures,[33] gastrointestinal symptoms,[34] and (suspicion of) acute renal failure.[35,36] Chronic aspiration from instillation of propolis to the nasal mucosa was suspected to have caused a benign tumor composed of foreign bodies.[37]

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. There were 4 "allergic" reactions of the airways (3 acute asthma, 1 breath impairment), 6 cases of "allergic" skin reactions, and 6 "allergic" reactions of the oral mucosa and/or uvula and/or tongue, notably edema. Two patients had gastrointestinal problems associated with propolis preparations, 1 digestive difficulty with stomach ache, and the other gastroesophageal reflux with heartburn. The suspected

product types were spray/aerosol (n = 7), tablets (n = 3), drops for oral use (n = 2), mouthwash (n = 1), tincture (n = 1), pomade (n = 1), and topical products, not specified (n = 3). Some of the reactions were serious: 6 patients were admitted to hospital or visited an emergency department, and in 2 of these, a life-threatening event was reported.[188] It should be realized that a causal association between propolis and these reactions was not verified, and the mechanism of action not investigated.[188]

Life-threatening descending necrotizing mediastinitis superimposed on concomitant aspiration pneumonia from inappropriate use of propolis has been reported; however, the causal relationship can be doubted.[189]

CONCLUSIONS

Propolis (bee glue, not to be confused with beeswax [propolis cera]) is a resinous substance collected by honeybees for the construction and adaptation of their nests. It has antibacterial, antifungal, and antiviral properties and possibly other beneficial biological activities, but propolis-containing preparations have not yet found a place as accepted treatment in mainstream, Western medicine. The chemical composition of propolis is highly variable, depending on the plant species from which the bees collect the exudates; therefore, geographic location is a major determinant. The most widely used propolis, that from moderate climates (poplar-type propolis), contains mainly phenolics: flavonoids aglycone, aromatic acids (substituted benzoic acids and cinnamic acids including caffeic acid, ferulic acid, and coumaric acid), and their esters. Propolis and some of its ingredients (notably the caffeic acid esters) are strong sensitizers. Contact allergy is not infrequent; in routine testing of patients with suspected contact dermatitis, frequencies of sensitization are usually 2% and often greater than 3%, notably in mid-European and eastern European countries; however, also in the United Kingdom and the United States (where it is routinely tested), patients often react to propolis. A rise in the prevalence has been observed since the mid-1990s. In many countries, it may well be worthwhile to add propolis to the (national) baseline series.

The allergens are mainly the esters of caffeic acid such as 3-methyl-2-butenyl caffeate, benzyl caffeate, phenethyl caffeate, and geranyl caffeate, which are also present in poplar buds. Contact allergy may be frequent as occupational disease in beekeepers; in consumers, biopharmaceuticals and (bio)cosmetics are the main sensitizing products. About half of the patients also react to *M. pereirae* resin (balsam of Peru), which may be due either to cross-reactivity or to the presence of common allergens (pseudo–cross-reactivity). A higher than expected number of coreactions is also observed to colophony, beeswax (presumably from contamination with propolis), poplar bud extracts (which has a similar chemical composition and is the main plant source for propolis), and certain essential oils, notably clove oil. Other adverse effects of topical application of propolis include rare cases of immediate type reactions. Oral application is largely safe. It has been linked to seizures, gastrointestinal symptoms, and acute renal failure, but the causal association remained unproven.

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