

Evaluation of the Main Contact Allergens in Propolis (1995 to 2005)

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Background: Propolis, the bee glue, is increasingly used in biocosmetics and for the self-treatment of various diseases.

Objective: Patients reacting to propolis were requested to participate in further testing with the breakdown constituents of the bee glue.

Methods: Twenty-seven patients agreed to be tested with 18 constituents, including four caffeates (the typical allergens of propolis) derived from the sticky exudates of poplar buds.

Results: Seven patients did not react to the propolis constituents tested. In the remaining 20 patients, the four caffeates produced strong reactions. Phenylethyl caffeate, which produced positive reactions in 20 patients, was the leading contact allergen. Benzyl caffeate elicited strong responses in 18 patients, and 3-methyl-2-butenyl caffeate produced reactions in 17 patients. Geranyl caffeate produced positive reactions in 11 patients. The flavonoid tectochrysin gave positive results in 2 patients; ferulic acid, coumaric acid, and methyl cinnamate produced weak responses.

Conclusions: In middle Europe, the caffeates are the responsible allergens in propolis allergy. Patients from other countries, where poplar trees do not grow, become allergic to other propolis constituents but not to the caffeates.

PROPOLIS, OR BEE GLUE, is a resinous beehive product that causes allergic contact dermatitis. Formerly, hypersensitivity was mostly observed in beekeepers, but propolis allergy today is increasingly seen in individuals who use propolis in biocosmetics and for self-treatment of various diseases. In ancient Egypt, propolis was used for embalming the dead. Violins made in Italy by the old masters (eg, Stradivari) were treated with polishes and varnishes containing propolis. In folk medicine, propolis served for a long time as an important remedy. In Eastern countries, it is still one of the most frequently used medicinal curatives. In dermatology, it has been used for the treatment of burns, leg ulcers, psoriasis, and atopic eczema and for wound healing and tissue regeneration. Since the beginning of the trend "back to nature" in the 1980s, propolis has also been found in toothpastes, creams, lotions, ointments, and chewing gums. Propolis is known for its antiseptic, antimycotic, antimicrobial, antitumor, antiinflammatory, and spasmolytic properties as well as for its effectiveness as an antioxidant, inhibitor of erythrocyte aggregation, and stimulant of the immune system. Bees produce propolis to seal hive walls, strengthen the borders of the combs and the

hive's entrance, embalm dead invaders, and prevent putrescence and microbial decomposition.

The allergens were detected in 1987. The responsible compounds were shown to be caffeic acid esters deriving from the sticky exudate of poplar buds.¹ Some of these caffeates were found to be strong sensitizers.^{2,3} Up to 11 caffeates have been identified in different *Populus* species.⁴ At the first peak of the popularity of propolis, between 1988 and 1990, propolis allergy reached a prevalence of 2.3% in Germany.³ Since 1995, propolis has been added to our standard series owing to renewed interest in Europe after a short decline in interest in the early 1990s. Results of patch tests with propolis in 4,242 patients over the last 10 years (January 1995 to May 2005) showed an increase in prevalence from 0.5% to 2.03%: 59 of the 4,242 patients reacted positively (median, 1.36%). Each patient reacting to propolis was requested to participate in further testing with the breakdown constituents of the bee glue (propolis series) that were still available from previous studies.^{2,3}

Twenty-seven patients (21 females and 6 males) agreed to be tested with the single allergens. Table 1 shows the results of the 72-hour readings. Seven patients did not react to the propolis constituents tested. The remaining 20 patients disclosed more or less frequent reactions. One patient reacted to 6 allergens, 3 patients to 5 allergens, 8 patients to 4 allergens, 6 patients to 3 allergens, and 1 patient to 2 compounds. Ten of the 18 allergens caused

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Table 1. Number of Patients Reacting to Breakdown Allergens from Propolis (1995 to 2005)

Propolis Allergen	Test Concentration (%)	No. of Patients Reacting (n = 27)	Reaction*		
			+++	++	+
Phenylethyl caffeate	0.1	20	11	6	3
Benzyl caffeate	1.0	18	8	6	4
3-Methyl-2-butenyl caffeate	0.1	17	9	5	3
Geranyl caffeate	1.0	11	4	5	2
Tectochrysin	5.0	2	1	1	—
Coumaric acid	5.0	3	—	1	2
Ferulic acid	5.0	1	—	—	1
Methyl cinnamate	10.0	1	—	—	1
Benzyl cinnamate	5.0	0	—	—	—
Benzyl benzoate	5.0	0	—	—	—
Benzyl alcohol	5.0	0	—	—	—
Benzoic acid	5.0	0	—	—	—
Caffeic acid	5.0	0	—	—	—
Cinnamic acid	5.0	0	—	—	—
Cinnamic alcohol	5.0	0	—	—	—
Cinnamyl isoferulate	1.0	0	—	—	—
Rhamnetin	5.0	0	—	—	—
Vanillin	10.0	0	—	—	—

*72-hour readings.

no responses; the four caffeates produced strong reactions. Phenylethyl caffeate was found to be the leading contact allergen, producing +++ reactions in 11 of 20 patients. Benzyl caffeate and 3-methyl-2-butenyl caffeate elicited strong reactions in 8 and 9 patients, respectively. Geranyl caffeate yielded strong reactions in 4 patients. The flavonoid tectochrysin elicited two reactions whereas ferulic acid, coumaric acid, and methyl cinnamate produced weak responses.

The order of frequency of reactions was in good accordance with the order of their sensitizing capacity obtained in guinea pigs sensitized experimentally.^{3,5}

Most of the patients had used propolis for medicinal purposes (for example, to treat eczematous lesions caused by hand eczema, atopic eczema, and perioral dermatitis). Others treated muscle pains, polymorphic light reactions, and pimples. One woman had treated elderly people in a nursing home with propolis-containing ointments; another had used cosmetics provided by a beekeeper.

One 20-year-old woman had been forced by her father, who kept bees as a hobby, to eat honey since early childhood. Her father also treated any lesion or injury of his children with propolis tincture. At 5 years of age, she

began to develop swelling of the throat after eating honey; however, the ingestion of honey and contact with propolis continued until she finally left home. Although all test material had been diluted providently (1:10), her patch-test reactions became so strong that the patches had to be removed after 6 hours. Propolis (1%) and phenylethyl caffeate (0.01%) produced strong reactions that were still visible after 4 weeks.

Another woman, born in 1935, consumed honey every day for years until it was recognized that her long lasting exanthema was due to propolis allergy. One 36-year-old sailor manufactured candles from beeswax for years while he was growing up in a nursing home; he reacted solely to propolis. A 62-year-old female secretary had used sunscreens containing beeswax contaminated with propolis. Her lesions developed only at those sites where the sunscreen had been applied. She reacted to propolis, but the sun protection factors remained negative. After his father retired, another patient, a 51-year-old mathematics teacher, had had to take over a factory that specialized in the bulk production of honey for supermarkets. After some years of being in contact with freshly harvested honey and frequently controlling its quality in the laboratory, he became allergic to propolis. He also reacted to honeycombs (honey and beeswax are always contaminated with small amounts of propolis).

The +++ reaction to tectochrysin in a 57-year-old lady was due to fresh spruce buds she continuously chewed when available. Tectochrysin occurs not only in poplar buds but also in *Pinus* and *Picea* species.

Among our 27 patients, only one was using cosmetics based on propolis. Goossens and colleagues found two propolis-sensitive patients among 475 individuals who used cosmetics that were partly of "herbal origin."⁶ Uter and colleagues, in a study of 20,363 elderly patients with and without dermatitis on the lower leg, found that 2.7% of the patients reacted to propolis. Among the various allergenic materials that yielded a significant increase of contact sensitivity with increasing age of the patient, propolis was the fifth most important one.⁷ In comparison with our patients, there were two patients who had treated their leg ulcers with propolis (a midwife born in 1919 and a female laboratory technician born in 1935). At last, with two patients, a 34-year-old shopgirl and a 41-year-old electrician, neither extensive questioning of the patients nor further discussion with them disclosed the source of their hypersensitivity to propolis.

Propolis contains more than 40 potential contact allergens. Most of them are identical with those known to occur in the bud secretion of poplars. As only 18 of

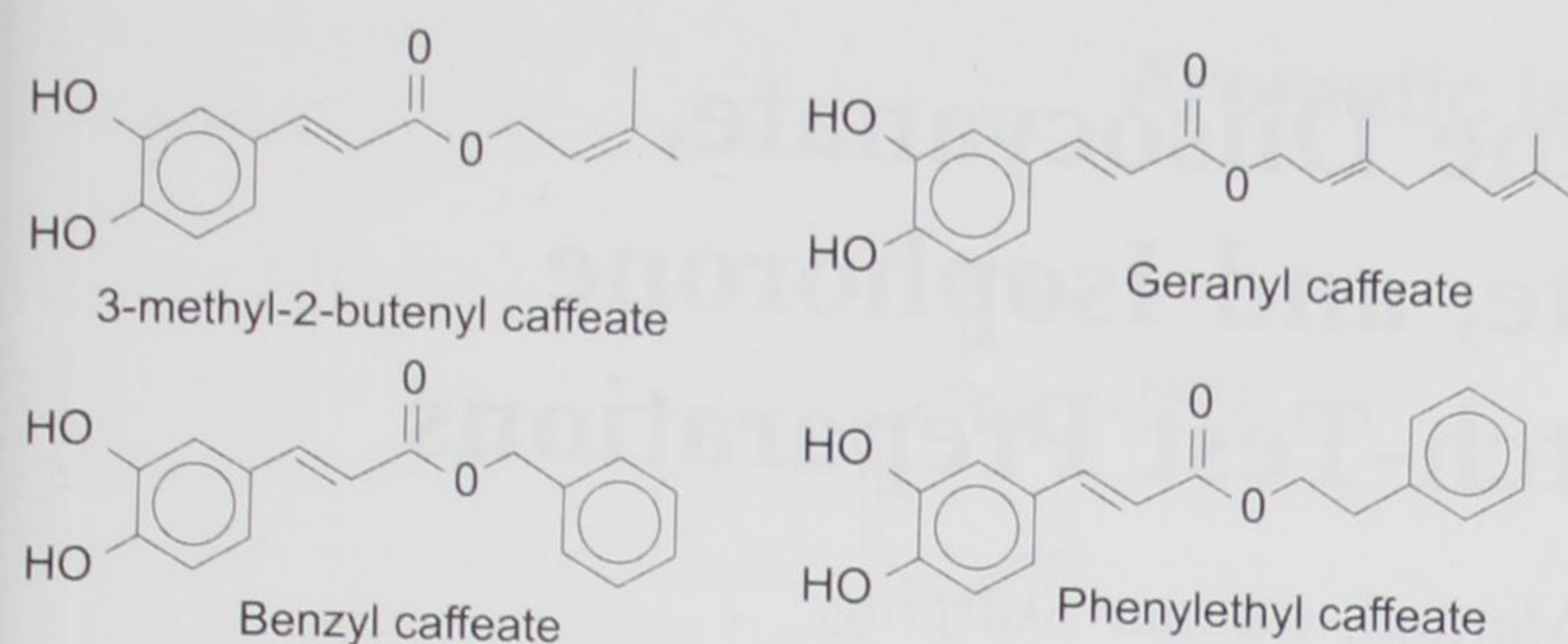


Figure 1. Structures of the four most important sensitizers of propolis.

them (but not all) were still available from previous studies, it is no wonder that some of our patients did in fact react to propolis itself but not to the available breakdown constituents. The missing constituents as well as the 10 compounds of our series provoking no reaction had shown a low sensitizing potency in guinea pigs.³ Eleven patients had a concomitant reaction to balsam of Peru (BP). Three of them who had a +++ reaction underwent a further test with the breakdown compounds of BP. One patient reacted to coniferyl benzoate and cinnamyl cinnamate, the second reacted to eugenol and isoeugenol, and the third remained "negative." Neither the patients who reacted to propolis nor those who reacted to BP reacted to vanillin or any of the other eight compounds common to both of the materials.³

As 20 of the 27 patients reacted more or less strongly to the caffeates, these constituents must be considered the main contact allergens of propolis in middle Europe (Fig 1).

As long as bees find a way to the buds of poplar trees, the caffeates will be substantial allergenic offenders. However, in propolis from countries where poplar trees do not grow, other still-unknown allergens seem to be the sensitizers. This may explain why two women who repatriated from Kazakhstan to Germany did not respond to the caffeates. One showed a weak reaction to ferulic acid; the other did not react at all.

References

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