



An overview of the toxic effects and allergic reactions caused by propolis

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Abstract

Natural, herbal, and organotherapeutic products can be as efficient as those synthesised in the laboratory, with the additional advantages of lower cost and greater accessibility. Among organotherapeutic products, propolis stands out for its diverse pharmaceutical properties and wide range of indications. Generally, propolis is a promising pharmacological substance, and it does not cause undesirable side effects in most people. Scientific research has shown that propolis produces no signs of tissue or organ toxicity when used at usual concentrations. However, it is capable of causing allergic reactions in heavy users with a history of previous allergies. Hence, the present literature review provides an overview of the toxic effects and allergic reactions caused by propolis.

KEY WORDS: PROPOLIS, APITHERAPY, TOXICITY, HYPERSENSITIVITY

Introduction

The World Health Organisation (WHO) defines health as a state of complete physical, mental and social well-being, not merely the absence of disease. Health is a broad goal that is difficult to address, and conventional allopathic medicine despite having technological advances has failed to achieve this goal completely because it treats symptoms rather than patients (1). Thus, there is room for natural therapies that employ organic, mineral, and spiritual (anthroposophic) elements and view human beings as complex entities requiring treatment that accounts for many variables that may interfere with their physical and mental integrity. This traditional form of medicine, which is experiencing a re-emergence is called alternative or natural medicine and has been practised for centuries in countries such as China and Japan (2).

Interest in natural medicine has gained strength worldwide since the 1st International Conference on Primary Health Care in Alma-Ata, Kazakhstan in 1978. A document that originated in this conference, known as the Declaration of Alma-Ata, stressed the importance of natural therapeutic resources and recommended the incorporation of proven traditional practices into primary health care activities. Influenced by this document, the WHO has pledged to encourage the implementation of public policies that facilitate the integration of traditional medicine and complementary/alternative medicine (integrative medicine) into the national health systems of its member states (3,4).

In Brazil, a country with rich biodiversity and popular culture influenced by Native Americans, Europeans and Africans, the knowledge and manipulation of plants with medicinal properties predates colonial times. These traditions have been maintained and passed from parents to children in isolated communities without access to allopathic medicines (1). The proven efficacy of these plants eventually travelled beyond those communities and aroused the interest of physicians and researchers, and some were eventually used in the conventional treatment of some diseases (5). The success of this

approach was discussed at the 8th National Health Conference in 1986, which included in its final report the introduction of alternative health care practices in the public health services of the Unified Health System (Sistema Único de Saúde - SUS) in Brazil, allowing patients to choose their preferred therapy (6).

Natural, herbal, or organotherapeutic products can be as efficient as those synthesised in the laboratory, with the advantage of having lower costs and therefore being more accessible to the general population and public health services (4). However, being natural does not mean that they are without risk. Studies have shown that both medicinal plants and the drugs derived from them can have deleterious effects on health that can be exacerbated when used in combination with other drugs (4,7).

Among the natural products with therapeutic indication, propolis stands out for its numerous pharmaceutical properties. It is a resinous substance produced from plant buds by honeybees of the *Apis mellifera* species, and it works as a natural barrier to protect the hive from intruders (8). Its composition varies according to its botanical and geographical origins (9), but it generally includes waxes, balsams, vitamins, minerals, essential oils, and resin and is rich in flavonoids (10). It is classified as an organotherapeutic medicine because its complex chemical composition includes body fluids from the bees that produce it (11,12). The most commonly known pharmacologically active chemical components of propolis are flavonoids, isoflavonoids, and phenolic, caffeic and aromatic acids (13); these compounds are responsible for its antimicrobial, anti-inflammatory, antioxidant, antiviral, antifungal and anticancer activities, among others (12,14-16).

Because of its numerous positive properties, propolis has been used worldwide since ancient times (13,17) and has been widely studied by researchers of all nationalities who are trying to better understand it, discover novel properties and develop revolutionary drugs to treat diseases more

effectively and safely (18).

All drugs, whether they are natural or synthetic, may produce adverse reactions. This fact, combined with recent changes in the traditional relationships between the state and conventional medicine in public health, emphasises the need for more information on natural products and their toxic effects, especially on a substance as versatile and widely disseminated as propolis (4). This literature review was compiled by analysing the full texts of relevant articles to provide an overview of the toxic effects and allergic reactions caused by propolis.

Natural medicine

The use of natural products is expanding worldwide, including in Brazil, where sales amount to approximately 160 million dollars per year. Thus, it is a promising market, and these products are being considered for both the development of new drugs and the treatment of complex diseases, such as cancer (19,21). However, despite estimate 80% of the world population uses the healing power of plants to treat diseases, only few of the world's flora has its medicinal properties studied (22).

Although plants and their derivatives have been used for centuries, their use is empirical and, in most cases, based on anecdotal reports of successful experiences that are passed from one person to another. However, the tradition and efficacy of these products are not sufficient to validate them as effective and safe drugs (23).

The WHO defines an adverse drug reaction (ADR) as "any harmful or undesirable and unintentional effect that occurs in response to drugs at doses normally used in man for prophylaxis, diagnosis, disease treatment or for modification of physiological functions" (24). Similar to allopathic medicines, natural medicines can also have adverse effects on health. Some are immediately connected with their ingestion, and others can occur in the long term, including carcinogenic, nephrotoxic and hepatotoxic effects (23). Knowledge of a drug's safety is essential because any chemical substance is capable

of exerting a toxic effect when it comes into contact with a biological system. What determines this toxicity is the amount and concentration of the drug, the susceptibility of the organism, the route of exposure, and the exposure time (25).

Propolis, like any natural product, is not an exception to this rule. It may trigger ADRs, such as toxic and allergic reactions, which can cause discomfort, pain and even death. This may be exacerbated by the complexity of the chemical composition of propolis and the patient's self-medication habits, which become more important when multiple medications are used simultaneously (23).

Propolis toxicity

In addition to its reported chemical complexity, propolis is a product with numerous components that act alone or synergistically. Moreover, its composition can vary according to the flora and climate of the region of the hive that produces it, which makes this product difficult to standardise. However, the different chemistries of propolis originating from locations all over the world do not mean that it has widely varying properties. In general, all varieties of propolis have antimicrobial, anti-inflammatory, antioxidant and cytotoxic activities, and the bees use it for the same purpose: to protect their hives (17). Table 1 shows some kinds of propolis produced worldwide.

A substance is considered toxic when it exerts harmful effects on a living organism (26). Some components of propolis are identified as potentially toxic, such as benzyl benzoate, which can stimulate the central nervous system and cause dizziness and convulsions (27); benzoic acid, which reacts with vitamin C to form benzene, a carcinogen that can induce DNA breakdown and chromosomal damage (28); and phenol, that can injure the heart, kidneys, liver and lungs following long-term exposure at high concentrations (17,29). These toxic substances are metabolised in the liver and acute or chronic exposure to this may adversely affect the regulation of carbohydrate, protein, lipid metabolism, substance

degradation, and hormone secretion (30-32). Though, there are few identified toxic substances in propolis but insignificant number of studies has reported the low toxicity of propolis regardless of its collection time and location (33-37).

Previous studies have demonstrated the safe use of ethanol-extracted Brazilian propolis from Minas Gerais State (38,39). These studies were conducted on *Wistar* rats and *Rana catesbeiana*. Propolis ethanolic extract did not alter haematological and biochemical blood analyses, and there were no cellular changes, lesions, haemorrhages, or cell infiltrate on tissues from the stomach, oesophagus, lung, spleen, and heart (38). Epithelial cells from the kidneys, liver, and intestine did not show significant changes, and the intestinal epithelium thickness was not significantly altered (39).

Another study was conducted to test the toxicology and clinical safety of herbal medicines. Healthy human volunteers received oral administrations of 15 mL of a combination of plants, honey, and propolis for 21 consecutive days. Electrocardiographic and laboratory tests were performed before, during, and after the treatment. Results showed no signs of toxicity in the organs and systems evaluated, confirming the safety of these herbal formulations (40). Similarly, mice were treated with different concentrations of aqueous and ethanolic extract of propolis for up to 150 days and there was no adverse alteration in the seric levels of cholesterol, HDL-cholesterol, total lipids, triglycerides and specific activity of aminotransferases (AST) and lactate dehydrogenase (LDH) observed (41). Additionally, oral administration of brown Brazilian propolis extract at a concentration of up to 400mg/kg produced no toxic effects on the function of the autonomic central nervous system and motor activity of mice (42).

The toxic effect of propolis was also evaluated on mice by topical application of propolis gel in their oral cavity for 4 consecutive days and found this gel nontoxic (37). Similar result was observed by Wu et al. (43) when they evaluated the combination of chromium (III) malate complex and propolis in

diabetic rats. In addition to not causing acute toxicity in the oral cavity, the combination acted as a nutritional supplement with the ability to control blood glucose and protect against hepatic injury.

The efficacy and tolerability of a lip balm containing 0.1%, 0.5%, or 1.0% propolis concentrations were tested in herpes labialis lesions. All concentrations were effective in treating the disease, but the balm caused local irritation in some patients at 1.0% concentration, that increased healing time of the lesions. The 0.5% concentration was better tolerated by the lip epithelium and did not cause local adverse reactions (44), suggesting that the toxicity reaction is concentration dependent.

Apitherapy practice (the use of honey, propolis, royal jelly, and bee venom) in the treatment and prevention of diseases among German beekeepers was the subject of a qualitative study conducted by Hellner et al. (45) Beekeepers reported frequent use of propolis to treat colds, wounds, burns, sore throat, and gum disease, and as a general prophylactic, all without adverse experiences.

Growing interest in propolis' therapeutic properties has led to an increase in the number of studies on its application to all health areas, especially medicine and dentistry. Many studies reported positive results from propolis use in several dental fields, confirming some of its properties, such as improved surgical wound repair, biocompatibility with dental pulp, and the ability to stimulate dentin repair (36).

When used for storing avulsed teeth, propolis was able to keep 75% of the periodontal ligament cells viable, compared to 25% of calcium hydroxide-treated cells.³⁶ Combinations of 10% propolis + Dulbecco's modified Eagle's medium (DMEM), 20% propolis + DMEM and DMEM alone were equally effective in maintaining the vitality of these cells for a 24-hour period, which is superior to milk storage, in which cells remained viable for a 12-hour period (46).

Biocompatibility with dental tissues is an essential property for any material that is used in restorative

dentistry (47,48). Calcium hydroxide fulfils this requirement and is applied directly over the pulp tissue as a pulp capping agent. Calcium hydroxide elicits an excellent response (49-51) and is considered the gold standard material for the direct pulp capping procedures. In several studies, propolis has shown tissue and organic compatibility with similar or even better results than those produced by calcium hydroxide with regard to biological compatibility (52-55).

Propolis was compared to two other materials routinely used as direct pulp-capping agents: mineral trioxide aggregate (MTA) (56) and calcium hydroxide (50). The researchers found that the inflammation associated with propolis use was less severe than that caused by calcium hydroxide (55), which is the alkaline material of choice in cases of exposed pulp tissue (50).

Several studies have demonstrated that propolis acts on carcinogenic cells. The Chilean resin showed the ability to scavenge free radicals and inhibit tumour cell growth in squamous cell carcinoma, colon adenocarcinoma, and prostate cancer (57); the same carcinogenic potential was detected in propolis samples from Argentina (58) and Mexico, with the latter acting against pancreatic cancer cells (59). Buffalo et al. (60) showed that Brazilian green propolis in concentrations from 50-100 µg per 100 µL was able to act against human larynx squamous cell carcinoma proliferation. Studies that achieved similar results were performed by Funari, de Oliveira Ferro and Mathor (61) using the same propolis on mouse NIH-3T3 fibroblasts. Martinez's study (62) showed that at concentrations of 0.5% and 1%, propolis solution was cytotoxic to fibroblasts from the human oral mucosa. In contrast, lower concentrations (0.001%, 0.01%, and 0.1%) were biocompatible. These results leading the authors to conclude that propolis cytotoxicity is concentration dependent (57-62).

Allergic reactions to propolis

Allergic reactions to propolis or products contain-

ing propolis from different geographical regions are widely reported in the worldwide health literature (36,63-67). The reactions include contact dermatitis, stomatitis, lip swelling, perioral eczema, and dyspnoea (68). The most common reaction is contact dermatitis, which is generally restricted to the area where the product is applied (69-73). The major allergens in propolis are caffeate esters, which are responsible for allergies to this product in Central Europe. In countries where poplar (*Populus* sp.) is not the botanical origin, 3-methyl-2-butenyl, benzyl salicylate and benzyl cinnamate are the sensitizers associated with allergy onset (74-77).

Most allergic reactions are mediated by immunoglobulin E (IgE) and involve the skin, gastrointestinal tract and respiratory system (78) (Figure 1). However, the sensitisation mechanism is quite complex, and despite being the subject of numerous studies, it is only partly elucidated (79). The allergic process usually begins when the patient is between 2 -and 3 years old when the immune system is immature and becomes more is most prevalent in the adult population (80).

Contact hypersensitivity occurs due to T cell-mediated immune response against haptens, which are small reactive molecules with molecular weights under 500 daltons. These molecules bind to peptides and tissue proteins and are then recognised by the immune system (Figure 2). Contact hypersensitivity occurs in two phases: the sensitising (afferent) phase and the elicitation (efferent) phase. The afferent phase involves all of the steps, from contact with the allergen until the development of sensitisation. It develops over time following repeated exposure to environmental agents. The efferent phase begins immediately after contact with the hapten in a previously sensitised individual (81). Recently, other types of natural killer (NK), B1 and NK T cells were found to mediate important functions during the allergic response in contact dermatitis (82).

The prevalence of systemic reactions in bee keepers is low (6.5%): just 2% experience anaphylactic reactions. However, the risk of developing such

reactions increases when an individual has an atopic disease (83). that originates from an inherited predisposition of the immune system to favour IgE-mediated hypersensitivity reactions (84).

Cases of contact dermatitis were reported in previous studies (68,85) with incidences between 3.5% and 6.0% (68,85,86). Rare severe manifestations caused by propolis ingestion reported in the literature involve generalised skin reactions, such as severe itching with multiple erythematous papules and oedema of the face, neck, arms, abdomen, and thighs (68).

In children, the incidence of patients with propolis-induced contact dermatitis may reach 5.9%, and it is significantly more frequent in males. These results led researchers to suggest the suspension of paediatric use of products containing propolis (85). Hypersensitivity to propolis is associated with some allergic predisposition (63,73,87,88) or a history of allergic reactions to bee products, stings, and pollen (36). In some cases, this sensitisation can take years to manifest (88).

In Brazil, the consumption of these products is low compared to that in some European and Asian countries, and few clinical studies have been conducted so far. This is most likely the reason why no records of allergic reactions were found in the specialised Brazilian literature.

In conclusion, and based on the data collected to date, it is not premature to consider propolis as a safe substance when properly administered. Scientific research has shown that this resin maintains its main pharmacological properties regardless of its botanical origin, despite the difficulty in standardising its formulations. It is a versatile drug that, despite having toxic components, did not induce signs of tissue or organ toxicity at the usually employed concentrations in any of the reviewed scientific papers.

Propolis is a sensitizer capable of triggering allergic reactions in heavy users and therefore should not be administered to patients with any allergic predisposition or previous history of aller-

gies. When appropriate precautions are taken, propolis is a promising substance from a pharmacological point of view. It is versatile and does not cause undesirable side effects in most people.

It is important to highlight the need to disseminate the pharmaceutical indications of natural products and their therapeutic limits and adverse reactions to both health professionals and the general population so that such products can be safely and effectively used. To this end, more clinical studies need to be developed to achieve a better understanding of propolis, including its limits and therapeutic potential.

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Conflicts of interest statement

The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

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PROPOLIS TYPE	GEOGRAPHICAL ORIGIN	BOTANICAL ORIGIN
Poplar Propolis	Europe, North America, New Zealand, and Asia (non-tropical regions)	<i>Populus nigra</i> (17)
Brazilian Green Propolis	Brazil	<i>Baccharis dracunculifolia</i> (17)
Brazilian Red Propolis	Brazil	<i>Dalbergia ecastophyllum</i> (17)
Mediterranean Propolis	Sicily, Greece, Crete, Malta	<i>Cupressaceae</i> (unknown species) (18)
Red Propolis	Cuba, Venezuela	<i>Clusia</i> spp. (17)
Pacific Propolis	Okinawa, Taiwan, Indonesia	<i>Macaranga tanarius</i> (18)
Birch Propolis	Russia	<i>Betula verrucosa</i> (18)
Canary Propolis	Canary Islands	Unknown (17)
Tunisian Propolis	Tunisia	<i>Cistus</i> spp. (8)
Australian Propolis	Australia	<i>Xanthorrhoea</i> spp. (8)
Propolis of Sonoran Desert	North America	<i>Ambrosia deltoidea</i> (8)
Paraná Propolis	Brazil	<i>Araucaria</i> spp (89)
Chilean propolis	Colliguay	<i>Escallonia pulverulenta</i> (90)
	La Vacada and Quilaco	<i>Mentha pulegium</i> (90)

Table 1: Propolis types, geographical and botanical origins.

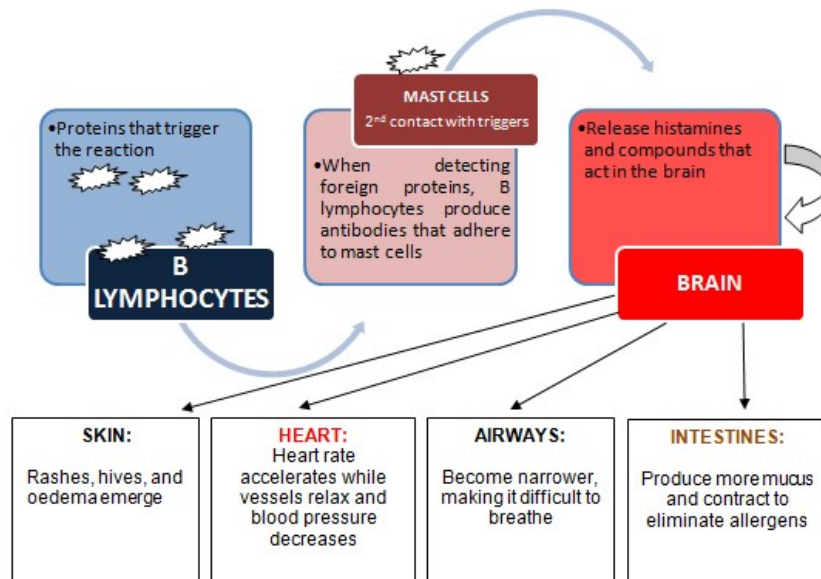


Figure 1: Defence system in action

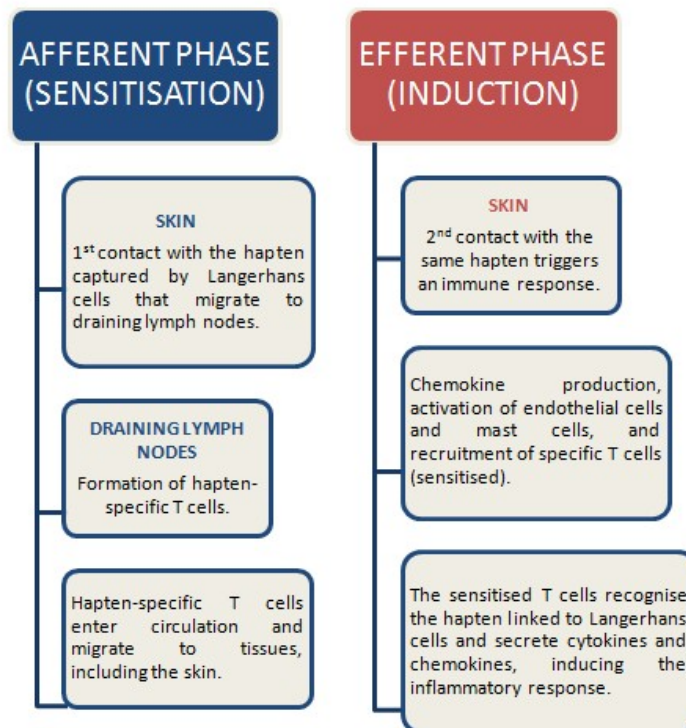


Figure 2: Pathophysiology of allergic contact dermatitis