

BEE PROPOLIS-A NOVEL PERSPECTIVE

Vani Mamillapalli^{1*}, Vamsi Meghana Tiyyagura¹, Mounika Katamneni¹ and Padma Latha Khantamneni²¹Department of Pharmacognosy and Phyto Chemistry, Vijaya Institute of Pharmaceutical Sciences for Women, Enikepadu, Vijayawada, Pin: 521108, Krishna District, Andhra Pradesh, India.²Department of Pharmacology, Vijaya Institute of Pharmaceutical Sciences for Women, Enikepadu, Vijayawada, Pin: 521108, Krishna District, Andhra Pradesh, India.***Corresponding Author: Vani Mamillapalli**

Department of Pharmacognosy and Phyto Chemistry, Vijaya Institute of Pharmaceutical Sciences for Women, Enikepadu, Vijayawada, Pin: 521108, Krishna District, Andhra Pradesh, India.

Article Received on 24/09/2018

Article Revised on 14/10/2018

Article Accepted on 05/11/2018

ABSTRACT

Honey bees produce a natural resinous mixture called bee propolis. Nowadays, propolis gained increasing importance as a therapeutic agent in allopathic medicines, homeopathic products and also in cosmetics in various dosage forms. The chemical composition of propolis varies according to the flora it was collected by bees. Propolis is commonly used by folk people for its healing, soothing, antiseptic and restorative capabilities in problematic skin. Bee propolis has also been studied for various biological activities such as antibacterial, antifungal, anti-hyperglycemic *etc.* This review discusses about physical and chemical properties, composition, biological activities, formulations, precautions of using bee propolis. The wide spectrum of therapeutic effects make propolis a future potential candidate in several clinical scenarios.

KEYWORDS: Propolis, Biological Activities, Composition.**INTRODUCTION**

Propolis, also called 'Bee glue', is resinous material collected by *Apis mellifera* from various tree buds which they then use to coat hive parts and to seal cracks and crevices in the hive.^[1] It is a multifunctional material used by bees in the construction and maintenance of their hives. The word "propolis" is derived from the Greek pro (for "in front of" or "at the entrance to") and polis ("community" or "city") and means a substance in defense of the hive. Propolis, or bee glue, is a brownish resinous material collected by worker bees from the leaf buds of numerous tree species like birch, poplar, pine, alder, willow, palm, *Baccharis dracunculifolia*, and *Dalbergia ecastaphyllum*.^[2]

Propolis has been used as a folk medicine since 300 BC.^[3] Recently, numerous biological properties of propolis have been reported including cytotoxic, antiherpes, free radical scavenging, antimicrobial, and anti-HIV activities.^[4] Because of the wide range of biological activities, propolis has recently been extensively used in food and beverages to improve health and prevent diseases.^[5] In order to manufacture propolis, bees may also use material actively secreted by plants or exuded from wounds in plants.^[6]

Propolis has been used by man since early times for various purposes as an antiseptic, antioxidant, anti-inflammatory, and an adhesive and to seal cracks; to protect wooden and other surfaces. Unlike many 'natural'

remedies, it possesses antibiotic, antifungal, antiviral and antitumour properties. It exhibits allergic reactions, and is relatively non-toxic.

The bees use propolis to repair combs, to strengthen the thin borders of the comb, and to make the entrance of the hive weather tight or easier to defend (Fig.1). Propolis is also used as an "embalming" substance to cover the carcass of a hive invader which the bees have killed but cannot transport out of the hive.^[7] The phytoconstituents composition in the bee propolis varies and depends upon the flora in the location. More than 500 compounds have been isolated and identified in bee propolis.^[8] Uses of products containing propolis have resulted in extensive dermal contact and it is now increasingly being used a dietary supplement.

**Fig. 1: Bee Propolis.**

BEE PROPOLIS CHARACTERISTICS

General Characteristics

Propolis is lipophilic in nature, hard, brittle, soft, pliable, gummy, and very sticky when heated. It possesses a characteristic, pleasant aromatic smell and varies in color from yellow green to red and to dark brown depending on its source and age. Depending on the origin of the resins, it also ranges from yellow to dark brown. But even transparent propolis has been reported.^[9]

Chemical Composition

Propolis is the third most important component of bee products. It is composed mainly of resin (50%), wax (30%), essential oils (10%), pollen (5%), and other organic compounds (5%).^[10] Phenolic compounds, esters, flavonoids, terpenes, beta-steroids, aromatic aldehydes, and alcohols are the important organic compounds present in propolis. Twelve different flavonoids, namely, pinocembrin, acacetin, chrysin, rutin, luteolin, kaempferol, apigenin, myricetin, catechin, naringenin, galangin, and quercetin, two phenolic acids, caffeic acid, cinnamic acid and one stilbene derivative called resveratrol have been detected in propolis extracts by capillary zone electrophoresis.^[11] Propolis also contains important vitamins, such as vitamins B₁, B₂, B₆, C, and E and useful minerals such as magnesium (Mg), calcium (Ca), potassium (K), sodium (Na), copper (Cu), zinc (Zn), manganese (Mn), and iron (Fe). A few enzymes, such as succinic dehydrogenase, glucose-6-phosphatase, adenosine triphosphatase, and acid phosphatase, are also present in propolis.^[12]

Chemical structures

Kaempferol, quercetin, galangin, chrysin, pinocembrine, p-coumaric acid, 3, 5 diprenyl-p-coumaric, saccharin are some of the chemical structures flavonoids and phenolic.

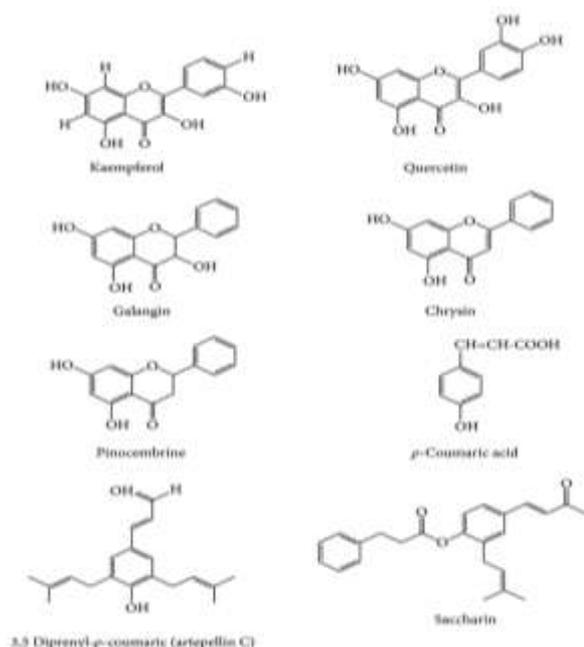


Fig. 2: Some typical flavonoids and phenolic present in bee propolis.

Melting Point: Propolis mp 25°C - 45°C, in frozen condition it becomes hard and brittle. It will become brittle at higher temperatures. Above 45°C, it will become increasingly sticky and gummy. Propolis is in liquid state at 60°C to 70°C, but the mp may vary according to sample up to 100°C.

Solubility of Propolis: Propolis is made of variable chemical constituents. Therefore, it cannot be used directly. Propolis is extracted commercially with suitable solvents such as common solvents water, methanol, ethanol, chloroform, dichloromethane, ether, and acetone. The most Many of the bactericidal components are soluble in water or alcohol.^[13] India, being a vast country, has a number of varieties of propolis differing in chemical compositions and medicinal values which are mentioned in table 1 but unfortunately it is still to be explored.

Table. 1: Solvents used for the extraction of several of propolis with different chemical composition.

Solvents	Bee propolis phytochemicals
Water	Anthocyanins, starches, tannins, saponins, terpenoids, polypeptides, lectins
Methanol	Anthocyanins, terpenoids, saponins, tannins, xanthoxylene, totarol, quassinoids, lactones, flavones, phenones, polyphenols, polypeptides, lectins
Ethanol	Tannins, Polyphenol, polyacetylene, terpenoids, sterols, and alkaloids
Chloroform	Terpenoids, flavonoids
Dichloromethane	Terpenoids, tannins, polyphenols, polyacetylenes, sterols, and alkaloids
Ether	Alkaloids, terpenoids, coumarins, and fatty acids
Acetone	Flavonols

Role of Bee Propolis in Bee Hive

Bees use bee propolis for the following uses

- Reinforce the structural stability and provide thermal insulation to the hive.
- Reduce vibration.
- Make the hive more defensible by narrowing the existing entrance (in wild colonies) to a single "choke point".
- Make the hive more defensible by sealing holes: a hive will have a propolis cache (as much as 1 pound) for emergency patch jobs.
- Prevent diseases and parasites from entering the hive, and to inhibit fungal and bacterial growth.
- Mitigate putrefaction within the hive.

Bees usually carry waste out of and away from the hive. However, if a small lizard or mouse, for example, finds its way into the hive and dies there, bees may be unable to carry it out through the hive entrance. In that case, they would attempt instead to seal the carcass in

propolis, essentially mummifying it and making it odorless and harmless.^[14]

Biological Activities of Bee Propolis

Antioxidant Activity: Indian bee propolis contains chemical constituent spinocembrin and galangin. The aqueous extract of propolis (AEP) showed higher activity compared to the ethanolic extract of propolis (EEP) which may be due to high polyphenolic content. It can be used in prevention of various free radical related diseases. Galangin also showed comparable activity with that of AEP and EEP and highest activity than pinocembrin.^[15]

The free radical scavenging effect of propolis as well as of vitamin C was studied using 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical system. The free radical scavenging activity of EEP was comparable to standard as ascorbic acid.^[13]

Antibacterial Activity

The antimicrobial property of propolis was studied by agar diffusion method against *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Candida albicans*, and *Asparagus nigar*. Ethanolic extracts of sample (Conc. 200 mg/ml) showed high antibacterial activity than methanolic extracts against gram-positive, *Bacillus subtilis*, but least activity against gram-negative bacteria, *P. aeruginosa* and *E. coli*. The yeast *C. albicans* showed the moderate zone of inhibition whereas *A. Niger* did not show any activity.^[13]

Antifungal Activity

Propolis was studied for antifungal activity in various fruit juices. It inhibited the spoilage of fruit juices due to the presence of flavonoids.^[16] Propolis, the bee duct was found to show highest antifungal activity with 40 yeast strains of *C. albicans*, *C. glabrata*, *C. krusei*, and *Trichosporon spp.*^[17] Propolis inhibited the growth of *Trichosporon spp.* (MIC 0.1–0.4 µg/ml), and *Rhodotorula spp.* (MIC <0.01 µg/ml). The most sensitive strain was found to be *Rhodotorula spp.* The most resistant strain was *C. Albicans*. Indian propolis was also found to be more effective anticaries agent against *Streptococcus mutans*.^[18]

Vaginal Use

To formulate the propolis microparticles (PMs) from Brazilian propolis and to check activity of the propolis extract (PE) against clinical yeast *C. albicans* and 31 non-*C. albicans* (*C. glabrata*, *C. tropicalis*, *C. guilliermondii*, and *C. parapsilosis*) isolates of importance in the vulvovaginal candidiasis (VVC). Moreover, the main antifungal drugs used in the treatment of VVC were also tested. *C. albicans* isolates showed resistance or dose-dependent susceptibility for the azolic drugs and amphotericin B. Non-*C. albicans* isolates showed more resistance and dose-dependent susceptibility for the azolic drugs than *C. albicans*.^[19]

Antiprotozoan activity

Antiprotozoal activity is evaluated by an *in vitro* growth inhibitory effect on a culture of parasites after incubation in the presence of different concentrations of propolis. The effect of European propolis on protozoa reported by several publications that cause diseases in humans and animals such as trichomoniasis, toxoplasmosis, giardiasis, Chagas disease, leishmaniasis, and malaria. Indeed, Antiprotozoan activity has also been reported on *Giardia lamblia*, *Trichomonas vaginalis*, *Toxoplasma gondii*, *Leishmania donovani*, and *Trypanosoma macruzi*.^[20]

Anti tumoral Activity

The chemopreventive activity of propolis in animal models and cell cultures was studied. It inhibits DNA synthesis in tumour cells, induces apoptosis of tumour cells, and activates macrophages to produce factors capable of regulating the function of B, T and NK cells, respectively. Moreover, flavonoids from propolis play a protective role against the toxicity of the chemotherapeutic agents or radiation in mice.^[21]

Anti-Inflammatory Activity

Inflammation is the complex response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, irritants, and free radicals. Anti-inflammatory activity involves the primary effect of the host defense system. Propolis has inhibitory effects on myeloperoxidase activity, NADPH-oxidase ornithine decarboxylase, tyrosine-protein-kinase, and hyaluronidase from guinea pig mast cells. Bee propolis exhibits anti-inflammatory activity because of the presence of active flavonoids and cinnamic acid derivatives such as acacetin, quercetin, and naringenin, caffeic acid phenyl ester (CAPE) and caffeic acid (CA).^[22] Dietary propolis suppresses the lipoxygenase pathway of arachidonic acid metabolism during inflammation *in vivo*. CAPE was a more potent modulator of arachidonic acid metabolism than caffeic acid, quercetin, and naringenin.^[23]

4.6 Hepatoprotective Activity

Protective potential of propolis was evaluated against mercury-induced oxidative stress and antioxidant enzymatic alteration in mice liver. Exposure to mercuric chloride (HgCl₂; 5 mg/kg; *i.p.*) induced oxidative stress by increasing lipid peroxidation and oxidized glutathione level along with concomitant decrease in glutathione and various antioxidant enzymes. Mercury intoxication deviated the activity of liver marker enzyme in serum. Conjoint treatment of propolis (200 mg/kg; *p.o.*) inhibited lipid peroxidation and oxidized glutathione level whereas increased glutathione level.^[24]

4.7 Immunomodulatory Action

The immunomodulatory action of a water-soluble derivative (WSD) of natural propolis was investigated. The oral and parenteral administration of the WSD enhanced the survival rate and the mean survival time in experimental bacterial (*Klebsiella pneumoniae*, *Staphylococcus aureus*) and fungal (*Candida albicans*)

infections in mice. An increased resistance was observed also in *Klebsiella pneumoniae* infection induced after cyclophosphamide treatment.^[25]

Formulations Used in Propolis Extract

Ethyl cellulose micro particles containing propolis ethanolic extract (PE) were prepared by the emulsification and solvent evaporation method. Three ratios of ethyl cellulose to PE dry residue value (DR) were tested (1:0.25, 1:4, and 1:10). Moreover, polysorbate 80 was used as emulsifier in the external phase (1.0 or 1.5% w/w).



Fig. 3. Marketed tablets and drops formulations.

Regular particle morphology without amorphous and/or sticking characteristics was achieved only when ethyl cellulose:DR ratio (1:0.25) and 1.0% polysorbate 80 were used. Micro particles had a mean diameter of 85.83 μm . These ethylcellulose microparticles containing propolis would be useful for developing propolis aqueous dosage forms without the strong and unpleasant taste, aromatic odour, and high ethanol concentration of PE.^[26] It is available in the form of solid and liquid dosage forms (Fig. 3).

Therapeutic Applications of Propolis

- **Canker sores:** Propolis relieves canker sores on oral administration daily for 6-13 months.
- **Cold sores:** Applying 3% propolis ointment five times daily helps improve healing time and reduce pain from cold sores.
- **Genital herpes:** Applying 3% propolis ointment four times daily for 10 days improves healing of lesions in people with genital herpes faster and more completely when compared to 5% acyclovir ointment.
- **A type of intestinal infection called giardiasis:** That taking a 30% propolis extract for 5 days can cure giardiasis in more people than the drug tinidazole.
- **Minor burns:** Early research shows that applying propolis to the skin every 3 days might help treat minor burns and prevent infections.
- **Mouth surgery:** Early research shows that using a propolis mouth rinse five times daily for 1 week might improve healing and reduce pain and swelling after mouth surgery.

- **Thrush (Oropharyngeal candidiasis):** Early research suggests that using Brazilian green propolis extract four times daily for 7 days can prevent oral thrush in people with dentures.
- **Upper respiratory tract infections:** There is some early evidence that propolis might help prevent or reduce the duration of common colds and other upper respiratory tract infections.
- **Vaginal swelling (Vaginitis):** Early research suggests that applying a 5% propolis solution vaginally for 7 days can reduce symptoms and improve quality of life in people with vaginal swelling.
- **Warts:** Early research shows that taking propolis by mouth daily for up to 3 months cures warts in some people with plane and common warts. However, propolis does not seem to treat plantar warts.^[27]
- Improving immune response.
- Nose and throat cancer
- Stomach and intestinal disorder
- Tuberculosis
- Ulcers

Special Precautions & Warnings

Propolis is safe by oral administration or external application. Lozenges prepared by using propolis can produce irritation and mouth ulcers.

- **Pregnancy and breast-feeding:** Avoid use.
- **Asthma:** Avoid using propolis in asthma.
- **Allergies:** It should not be used in persons who are allergic to bee by-products such as honey, conifers, poplars, peru balsam, and salicylates.
- **Bleeding conditions:** It increases the risk of bleeding in people with bleeding disorders. Therefore it should be avoided before 2 weeks before surgery.^[28]

CONCLUSION

Propolis has been used extensively now a days for its variable chemical components, strong pharmacological properties and low toxicity than synthetic medicines. The wide spectrum of therapeutic effects make propolis a potential therapeutic candidate in several clinical scenarios. Clinical studies are in progress to verify the effects of propolis in the prevention and treatment of diseases.

ACKNOWLEDGEMENT

Authors are thankful to Vijaya Institute of Pharmaceutical Sciences for Women, Enikepadu, Vijayawada for encouragement and support.

REFERENCES

1. Greenaway W, Scaysbrook T, and Whately F R. The composition and plant origin of propolis: a report of work Oxford. *Bee World*, 1990; 71(3): 107-118.
2. Park Y K, Paredes-Guzman J F, Aguiar C L, Alencar S M, and Fujiwara F Y. Chemical constituents in *Baccharis dracunculifolia* as the main botanical origin of Southeastern Brazilian propolis. *J Agric Food Chem*, 2004; 52(5): 1100-1103.

3. Ghisalberti E L. Propolis: a review. *Bee World*, 1979; 60(2): 59-84.
4. Matsuno T, Matsumoto Y, Saito M, and Morikawa J. Isolation and characterization of cytotoxic diterpenoid isomers from propolis. *Z Naturforsch C*, 1997; 52(9-10): 702-704.
5. Burdock G A. Review of the biological properties and toxicity of bee propolis (propolis). *Food Chem Toxicol*, 1998; 36(4): 347-363.
6. Castaldo S and Capasso F. Propolis, an old remedy used in modern medicine. *Fitoterapia*, 2002; 73(1): S1-S6.
7. Crane E. The past and present importance of bee products to man," in *Bee Products—Properties, Applications, and Apitherapy*, A. Mizrahi and Y. Lensky, Eds., pp. 1–13, Plenum Press, New York, NY, USA, 1997.
8. Makashvili ZA. From the history of Propolis. In: Remarkable hive product: Propolis. Scientific data and suggestions concerning its composition, properties and possible use in therapeutics. APIMONDIA standing commission on Bee keeping technology and equipment, Bucharest, 1978.
9. Hausen BM, Wollenweber E, Senff H, Post B. Propolis allergy. (II). the sensitizing properties of 1, 1-dimethylallyl caffeic acid ester. *Contact Dermatitis*, 1987; 17(3): 171–177.
10. Gómez-Caravaca AM, Gómez-Romero M, Arráez-Román D, Segura-Carretero A, Fernández-Gutiérrez A. Advances in the analysis of products derived from bees. *J Pharm Biomed Anal*, 2006; 41(4): 1220-34.
11. Volpi N. Separation of flavonoids and phenolic acids from propolis by Electrophoresis., *Fitoterapia*, 2004; 25(12): 1872-8.
12. Khalil ML. Biological activity of bee propolis in health and disease. *Asian Pac J Cancer Prev*, 2006; 7(1): 22-31.
13. Kumar N, Ahmad MKK, Dang R, Husain A. Antioxidant and antimicrobial activity of propolis from Tamil Nadu zone. *J. Med. Plants Res.*, 2008; 2(12): 361–364.
14. Simone-Finstrom, Michael Spivak, Marla. Propolis and bee health: The natural history and significance of resin use by honey bees. *Apidologie*, 2010; 41(3): 295–311.
15. Laskar RA, Sk I, Roy N, Begum NA. Antioxidant activity of Indian propolis and its chemical constituents. *Food Chem*, 2010; 122(1): 233-237.
16. Farnesi AP, Aquino-Ferreira R, De Jong D, Bastos JK, Soares AEE. Effects of stingless bee and honey bee propolis on four species of bacteria. *Genet Mol Res.*, 2009; 8(2): 635–640.
17. Koç AN, Silici S, Kasap F, Hörmet-Öz HT, Mavus-Buldu H, Ercal BD. Antifungal activity of the honeybee products against *Candida* spp. and *Trichosporon* spp. *J. Med. Plants Res.*, 2011; 14(1-2): 128–134.
18. Selvan A, Singh R, Prabhu D. Research article: anti-bacteria activity of bee propolis against clinical strains of *Streptococcus* mutants and synergism with chlorhexidine. *Int J Pharm Sci Res.*, 2011; 2: 85-90.
19. Dota KFD, Consolaro MEL, Svidzinski TIE, Bruschi ML. Antifungal activity of brazilian propolis microparticles against yeasts isolated from vulvo vaginal candidiasis. *Evid Based Complement Alternat Med.*, 2011.
20. De Castro SL, Salomão K, De Souza EM, Henriques-Pons A, Barbosa HS. Brazilian green propolis: effects in vitro and in vivo on *Trypanosomacruzi*. *Evid Based Complement Alternat Med.*, 2011; 185918: 1-11.
21. Oolic N. A review of propolis antitumour action in vivo and in vitro. *Java Authentication and Authorization Service*, 2010; 2:1–20.
22. Almeida ECD, Menezes H. Anti-inflammatory activity of propolis extracts: A review. *J. Venom. Anim. Toxins*, 2002; 8: 191-212.
23. Du Toit K, Buthelezi S, Bodenstern J. Anti-inflammatory and antibacterial profiles of selected compounds found in South African Propolis. *S Afr J Sci.*, 2009; 105 (11-12): 470-472.
24. Zhao J-Q, Wen Y-F, Bhadauria M, et al. Protective effects of propolis on inorganic mercury induced oxidative stress in mice. *Indian J Exp Biol.*, 2009; 47(4): 264-269.
25. Dimov V, Ivanovska N, Popov S, Bankova V. Immunomodulatory action of propolis: IV. Prophylactic activity against Gram-negative infections and adjuvant effect of the water-soluble derivative. *Vaccine*, 1992; 10(12): 817-823.
26. Avanço GB, Braschi ML. Preparation and characterization of ethylcellulose microparticles containing propolis. *J Br Astron Assoc*, 2008; 29(2): 129-134.
27. A Al Shafer, J Wallace, S Agarwal, W Bretz, and D Baugh. Effect of propolis on human fibroblasts from the pulp and periodontal ligament. *J Endod*, 2004; 30(5): 359-361.
28. L Benguedouar, M Lahouel, S Gangloff, et al. Algerian ethanolic extract of propolis and galangin decreased melanoma tumour progression in C57BL6 mice. *Annales de Dermatologieet de Vénérologie. France; Elsevier*, 2015; S294.