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Indispensable Role of Indian Propolis and its Pharmacological Significance: A Review

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ABSTRACT

Honeybees naturally produced a compound called propolis gathered from diverse plant sources. Bees use propolis to build and repair their hives because of its waxy and slimy qualities, which serve as a barrier against outside intruders. It is also a well-known form of folk medicine with a diverse range of biological activities. It has also been used as a health food product in important continental nations including Asia, United States and Europe. Various databased searched in order to find published papers about propolis and its relevant properties. After a thorough evaluation, 4,140 articles were obtained, 2,472 papers in the field of pharmacology of propolis components, 834 articles on the pharmacology and medical therapeutic properties, 65 articles on the propolis component in Indian regions. Propolis is incredibly popular all over the world, but in India propolis research is not widely studied or reported. India, being a vast country, has numerous varieties of propolis differing in chemical compositions and medicinal values. This review gathers major findings on the pharmacological properties of propolis focusing on its antimicrobial, anti-tumor, ant-oxidative and anti-inflammatory properties.

Key words: Beekeeper, Honeybees, Pharmacology, Phytochemical, Propolis.

Propolis is a natural material produced by honeybees' various plant sources. Bees collect resinous exudates from various plant parts and enzymes to the propolis. The word propolis is derived from the Greek pro-, for or in defense and polis-the city, that is, defense of the hive (Ghisalberti, 1979). Due to its waxy composition and beneficial mechanical properties, bees use propolis in hive construction and maintenance to seal openings, smooth internal surfaces and protect against external intruder like Varroa mites, as well as environmental factors such as wind and water (Wagh, 2013; Vijayan *et al.,* 2023). It is also popular folk medicine having wide spectrum of biological activities (Genc *et al.,* 2020). It has also been used as a health food product in major continental like Asian, American and European countries (Fabricant and Farnsworth, 2001). Since ancient times propolis has been extensively used by man, especially in folk medicine to treat several diseases.

Historically, since ancient civilizations propolis was used for its medicinal properties. Greeks used it to treat abscesses. Assyrians put it on wounds and tumors to fight infection and to improve healing process. It's well-known fact that Egyptians used it to embalm mummies (Alvarez-Suarez *et al*., (2010); Patel, 2016; Molan, (1999); Rao *et al*., (2016); Fratellone PM *et al*., 2016; Ajibola, (2015); Coutinho, 2012). Honeybees are small to medium-sized hymenopterans insects belonging to the genus *Apis*. Two species are well known, *i.e*., *A. mellifera*, native to Europe, Asia and Africa and *A. cerana*, distributed in southern and southeastern Asia (Ruttner, 1988). Honeybees produce honey, propolis, royal jelly, pollen, beeswax and bee venom as the main products in their hives. Honey and propolis are the most widely valued honeybee products since potentially benefit to humans due to its inheritance bioactivities.

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Honeybees collect various plant exudates such as sap, resin, gums and latex. After that honeybees mixing it with saliva and wax and produce a bioactive product like propolis. (Salatino *et al.,* 2005; Marucci, 1995) Propolis is complex resinous in nature, collected and harvested by honeybees especially *Apis mellifera*. (Cornara *et al.,* 2017) Propolis reduces microbial growth on hive walls so these hives remain healthy. Moreover, propolis protects the hive against adverse environmental factors like uncontrolled airflow and extreme moisture. Propolis also provides a water-resistant lining which limits the escape of water and maintains constant humidity inside the hive. (Kuropatnicki *et al.,* 2013; Seeley and Morse, 1976; Castaldo and Capasso, 2002; Shehu *et al.,* 2016).

The chemical composition of propolis is dependent on its geographical and floral origins. Raw propolis generally reported to comprise more than about 300 constituents with diverse pharmacological activities (Huang *et al.,* 2014). The composition of propolis has been extensively studied worldwide and remarkably, most of them reported common and unique to region-specific

phytochemical compositions. Based on floral source and phytochemical profile, propolis is generally classified into Poplar (temperate), Birch, Tropical, Mediterranean and Pacific type of propolis (Salatino *et al.,* 2005).

Mostly consisting of triterpenes (50% w/w), waxes (25-30%), volatile mono- and sesquiterpenes (8-12%), giving propolis its typical resinous odor and phenolics (5-10%) (Huang *et al.,* 2014). Different phenolic acids and flavonoids documented to be present in propolis include Caffeic acid, p-Coumaric acid, Ferulic acid, Isoferulic acid, 3,4-Dimethyl-caffeic acid, Cinnamic acid, Quercetin, Quercetin methyl ethers, rutin, Pinocembrin, Pinobanksin, Pinobanksin methyl ethers, Pinobanksin ester derivatives, Apigenin, Kaempferol, Chrysin, Methoxy-chrysin, Galangin, Isorhamnetin, Luteolin-methyl-ether, Cinnamylidene acetic acid, Caffeic acid ester derivatives [*e.g.* Caffeic acid phenylethyl ester (CAPE)], p-Coumaric ester derivatives [*e.g.*: p-Coumaric prenyl ester, p-Coumaric cinnamyl ester], p-Methoxy cinnamic acid cinnamyl ester, *etc.* (Bankova *et al.* (2000); Sforcin and Bankova, 2011) Sugars and sugar alcohols: xylose, galactose, mannose, glucuronic acid, lactose, maltose, melibiose, erytritol, xylitol, inositol also has been isolated from the Bee Propolis (Bankova *et al.,* 1998).

As per Shub *et al.,* (1978), the propolis components are rich in vitamins and mineral elements. Propolis contains some minerals such as Mg, Ca, I, K, Na, Cu, Zn, Mn and Fe as well as some vitamins like B_1, B_2, B_6, C and E and a number of fatty acids. It also contains some enzymes as succinic dehydrogenase, glucose-6-phosphatase, adenosine triphosphatase and acid phosphatase.

In recent years, products derived from honeybees have become increasingly popular as health drinks and ingredients in food and beverages. These products are believed to enhance human health and may help prevent various diseases, including inflammation, heart disease, diabetes and even cancer (Samarghandian *et al.*, 2017). Worldwide, honey is the most explored apiculture product from medicinal as well as economic point of view. However, in recent researches pharmacological activity of propolis are not well documented. Thus, in this review article, we have compiled various biological properties of Indian propolis and absence of economic importance.

Keywords including propolis, pharmacology, medicine, flavonoids, phenol, honeybees, propolis, antimicrobial, antitumor, anticarcinogenic, antioxidative and chemical compounds, were search on ScienceDirect, PubMed, Google scholar, Embase and other databases in order to find published papers till Aug (2024). Then, a manual search was conducted to find more related articles.

In this study, 4140 articles were obtained, 2,472 papers in the field of pharmacology of propolis components, 834 articles on the pharmacology and medical therapeutic properties, 65 articles on the propolis component in Indian regions. Among selected reference articles, only English and full text articles were used and duplicate resources were excluded. Finally, 76 articles were included in present study.

Propolis in Indian scenario

Beekeeping is an important activity that provides economic support to rural communities by generating additional income with integrated farming system. People of India have a long connection with beekeeping and honey since ancient times. India comprises seven percent of the world's flora and has a potential to keep about 200 million bee colonies that can produce over 10 million tons of honey and other bee products (Abrol, 2023) In India beekeeping is mostly practiced as a full-time occupation along with agriculture activities. The well-known primary products of beekeeping are honey and wax, but pollen, propolis, royal jelly and bee venom are also marketable primary bee products. *A. mellifera* is more in North India because of the rich flora *viz*., Mustard, Sunflower, Eucalyptus, Safflower, *etc*. (Thomas *et al.,* 2002, Kishan *et al.,* 2017) They produce 50 to 60 kg of honey per colony per year. *A. mellifera* accounts for roughly 70-75 per cent of the honey produced in India (EAC-PM, 2019).

The Indian apiculture market reached a value of INR 20,480 million in (2021). Looking forward, the apiculture market is expected to reach INR 40,161 million by (2027), exhibiting a CAGR of 11.73% during 2022-2027. (IMARC, 2022) In this, Honey currently represents the biggest segment. However, there is no market for propolis product in India. Propolis Market is Expected to generate revenues of USD 845.5 million by (2030), with a CAGR of approximately 6.23% from (2022 to 2030) (MRF, 2022). From a single honeybee colony produced 10 to 300 gm propolis in a year still beekeepers are reluctant in collecting this product (Habip and Cengiz, 2021). Non collection of this hive product is attributed due to no market for this product in India. Only few private firms used to procure this product from beekeepers. Currently, the price of propolis worldwide varies based on its origin and quality: Chinese propolis is priced at approximately 25 to 50 euros per kilogram, while Brazilian propolis commands higher prices, ranging from 100 to 150 euros per kilogram (Bogdanov, 2016). The international market can be tapped for selling this product for better income generation. Worldwide propolis has incredible popularity, but in India the studies over propolis are not broadly studies or reported except from few regions of India. India, being a vast country, has numerous varieties of propolis differing in chemical compositions and medicinal values. Hence, Beekeeping plays avital role in rural development, by generating revenue from honey and other bee products.

Physio-chemical composition of Indian Propolis

Indian propolis is available throughout the India and its chemical composition varies because of different geographical origin. Physio-chemical composition of Indian propolis depends upon plants from which this resinous substance is collected. The chemical composition of propolis as well as its color and aroma are changed according to the geographical zones (Ghisalberti, 1979;

de Groot, 2013). Generally, propolis is yellowish brown to almost black in color and naturally available in resinous and wax form. It is a sticky and derived from honeybees used as building and insulating material to honeycombs. Its smell is pleasant due to honey, wax and vanilla but has a bitter taste. Its melting point is usually 60-700°C (Wagh, 2013, Jain *et al.,* 2015) Propolis produce a smell of aromatic resins when it burnt. It is hard and brittle when it cold but becomes soft and very sticky when warm like aromatic glue (Khalil, 2006).

Raw propolis cannot be used directly for its physio-chemical analysis due to its complex structure. Several solvents have been reported for commercial extraction which includes water, methanol, ethanol, dichloromethane, ether *etc.* These solvent systems are generally used for removal of inert compound as well as extract specific compounds. Biological activity varies depending upon extraction of solvent and method used (Wagh, 2013).

In general, Indian propolis mostly comprises the Resin (50-80%), Beeswax (8-30%), Essential oils (10-14%), Plant wax (6%), Tannin (10%), Pollen (5%) and Mechanical impurities (5%). Propolis also contains other beneficial constituents including macronutrients (calcium, manganese, zinc, tin, copper), Vitamins (pro vitamin A, Vitamin B1, B2), aromatic esters (ethyl esters of cinnamic and caffeic acid) and flavonoids (chrysin, tectochrysin) (Kumar *et al.,* (2017); Ahangari *et al.,* 2018; Park *et al.,* 2002). Kasote (2017) reported more polyphenolics compositional on HPLC analysis and confirmed the presence of other components *i.e*. gallic acid, naringin, caffeic acid, p-coumaric acid, ferulic acid, quercetin, cinnamic acid, kaempferol, chrysin, phenethyl caffeate and galanginin (Kasote, 2017; Omene *et al.,* 2013). Caffeic Acid Phenethyl Ester is considered as an active phenolic compound isolated from propolis. Several studies have shown that Caffeic Acid and its derivative compounds exhibit selective toxicity to cancer cells. (Grunberger *et al.,* 1988; Mahmoud *et al.,* 2000; Su *et al.,* 1994; Su *et al.,* (1995); Lee *et al.,* 2000; Lee *et al.,* 2005; Burke *et al.,* 1995; Chen *et al.,* 2004; Lin *et al.,* 1994).

Medical importance of Propolis

Some studies have found that Indian propolis has antioxidant, antimicrobial, anti-inflammatory and antitumor properties Aljadi *et al.* (2004), Al-Mamary *et al.* (2002), Gheldof *et al.,* (2002), Yao *et al.,* (2003), Estevinho *et al.,* 2008). Still Indian propolis is deficient in terms of complete profile for its chemical composition and therapeutic potential comparative to propolis from other parts of the world. This review gathers major findings on the pharmacological properties of propolis focusing on its antimicrobial, anti-tumor, ant- oxidative and anti-inflammatory properties.

Antibacterial properties

Propolis has been proven to have bacteriostatic activity against Streptococcus aureus, the typhoid bacillus and other microorganisms in his studies (Ghisalberti, 1979). Antimicrobial activity of propolis was also studied by Lindenfelser (1968). He examined the propolis solution in concentrations of < 10 microgram/ml demonstrated *in-vitro* activity against Bacillus larvae, the etiological agent of American foulbrood (AFB) of the honey bee, *Apis mellifera*. In pharmacological research it was found that the antibacterial activity of propolis should be considered on two levels. First, it relates to the direct action on the microorganism and the other with stimulation of the immune system resulting in activation of natural defenses of the organism (Sforcin and Bankova (2011); Takasi *et al.,* 1994). The study on the mechanisms of propolis revealed that the permeability of the cellular membrane of microorganism, disruption of membrane potential and adenosine triphosphate production as well as decreasing bacterial mobility affected by propolis. Propolis is effective against both Gram-positive and Gram-negative bacteria, including both aerobic and anaerobic types. Its antibacterial properties depend on its chemical composition (Sforcin, 2016; Przybylek and Karpinski 2019).

Antioxidant properties

Propolis, rich in flavonoids and phenolic compounds with antioxidant properties, may help protect humans from harmful oxidative processes. Ibanrikynti *et al*. (2020) analyzed anti-oxidative potential of Propolis from Meghalaya, according to their research GC-MS analysis identified twenty different groups of compounds, out of which eight compounds along with their biological activity were recorded. The main constituents of propolis from Meghalaya were N-hexadecanoic acid (34.88 %), oleic acid (26.37%), tetradecanoic acid (4.90%), 2-furancarboxaldehyde, 5- (hydroxymethyl) (3.21%) and 3,7, 11, 15-tetramethyl-2-hexadecene-1-ol (1.95%). In all of the tests, the propolis demonstrated significant antioxidant activity.

Alshehri, (2024) reported that Propolis extract shown significant protective effects on the liver and kidneys due to its antioxidant and anti-inflammatory properties. Its ability to scavenge free radicals, inhibit lipid peroxidation and boost intracellular antioxidant defenses-such as glutathione and superoxide dismutase-highlights the extensive protective mechanisms that propolis provides against oxidative stress-related damage to these organs. In the 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical system, Kumar *et al.,* (2008) compared the free radical scavenging action of propolis and vitamin C. In the concentration range of 100 mcg, the free radical scavenging activity of EEP was 70.96 percent and 72.97 per cent, respectively, after 30 minutes and 1 hour. Laskar *et al.,* (2010) reported first time the antioxidant activity of the aqueous and ethanol extracts of Indian propolis (AEP and EEP, respectively). Chemical and electrochemical assays were used to assess antioxidant activity. In all of these assays, AEP demonstrated significantly greater activity than EEP, which contradicts previous reports of propolis from other countries (Laskar *et al.,* 2010). This may be due to its

higher polyphenol content. Propolis is the bee product containing the highest amount of phenolics and thus it has been deeply studied for antioxidant and radical scavenging activities (Viuda-Martos *et al.,* 2008). As a result, Indian propolis is regarded as a rich source of natural antioxidants that can be applied to treat a variety of ailments caused by free radicals.

Anti-inflammatory properties

Inflammation is the complex biological reaction of human tissues to harmful stimuli, such as pathogens or irritants and free radicals' injuries. The anti-inflammatory activity of propolis has been reviewed by many authors. According to studies, propolis inhibits the activity of myeloperoxidase, NADPH-oxidase, ornithine decarboxylase, tyrosine kinase and hyaluronidase (Marucci, 1995; Dattatraya *et al.,* (2013); Nanaware *et al.,* (2017); Dobrowolski *et al.,* (1991); Bruno *et al.,* (2020) The anti-inflammatory activity was considered to be present due to active flavonoids and cinnamic acid derivatives. Acacetin, quercetin and naringenin are among the former, whereas caffeic acid phenyl ester (CAPE) and caffeic acid are among the later (Wagh, 2013). CAPE is considered a particularly strong anti-inflammatory constituent, able to specifically target NF-kB signaling (Armutcu *et al.,* 2015). This compound has been also found to modulate ERK MAPK signaling in T cells and mastocytes and to regulate PI3K/Akt pathway in different human cell lines (Cho *et al.,* 2014; Li *et al.,* 2017) CAPE and galangin, exhibited anti-inflammatory activity and significantly suppressed edema, pleurisy and arthritis inflammations in animal model (Borrelli *et al.,* 2002; Toit *et al.,* 2009).

An ethanol extract of propolis suppresses the production of prostaglandins and leukotrienes produced by mouse peritoneal macrophages and inhibit zymosan-induced acute peritoneal inflammation. *In-vivo*, studies show that dietary propolis significantly suppressed the lipoxygenase pathway of arachidonic acid metabolism. CAPE was also shown to be a more powerful arachidonic acid metabolic modulator than caffeic acid, quercetin, or naringenin (Mirzoeva and Calder, 1996).

Inflammation is associated with various diseases. Many studies have been found that propolis has anti-inflammatory qualities, which may be due to the presence of phenolic acids (Sadhana *et al.,* 2017). Propolis has been used in traditional medicine for a long time, however it is not a substance that can be used to treat all disorders because of their diverse pharmacological activities and chemical compositions, determining quality standards for propolis-containing products is currently a major challenge (Ramos and Miranda, 2007). One of beneficial traditional medicinal properties of propolis is an anti-inflammatory effect and propolis is commonly used for the treatment of some inflammatory diseases.

Anticancer properties

Numerous bioactive compounds reported in propolis that exhibit anticancer properties (Altabbal *et al.,* 2023). Various authors have reviewed the tumor-blocking effects of propolis extracts and their constituents, noting that polyphenols possess chemopreventive properties and that honey with higher phenolic content is more effective in inhibiting cancer cell proliferation (Jaganathan and Mandal, 2009).

As per reported evidence, the anticancer mechanisms of propolis vary widely *i.e.*, anti-angiogenesis, induction of apoptosis, cell cycle arrest and anti-proliferation action. Various mechanisms of action have been disclosed for major compound, including suppression of tyrosine kinase activity and induction of cell cycle arrest in G1 or G2/M phase. Apoptosis, cell-cycle arrest and interference with metabolic pathways have been considered as the underlying processes (Patel, 2016). It has been proven that the antioxidant capacity of Indian stingless bee propolis supports its anticancer activities (Bankova *et al.,* 2013).

Inhibitory effects of honey on various kinds of cancer have been studied both *in vitro* and in animal models, while only few clinical studies have been conducted and their results are controversial (Cornara *et al.,* 2017). Several studies have reported that natural bee products suppress tumor cell growth and induce apoptosis of carcinogenic cells, indicating the potential application of these natural compounds (or their active components) as part of an alternative medical treatment of human tumors (Tamura *et al.,* 1985; Yusuf *et al.,* 2007).

According to Xuan *et al.* (2014) propolis has the potential to cure human breast cancer due to its anticancer action through inducing apoptosis in breast cancer cells. It also exhibits low or no toxicity towards normal cells due to its selectively toxic properties against tumor cells and is believed that propolis may become a prominent agent to treat breast cancer.

Another study conducted by Benguedouar *et al.* (2015) on the effect of ethanolic extract of Algerian propolis on melanoma tumour growth discovered that galangin, a prevalent flavonoid in propolis, significantly caused apoptosis and suppressed melanoma cells *in-vitro*.Turkish propolis has also been demonstrated to have a specific cytotoxic effect on human lung cancer cells, triggering endoplasmic reticulum stress, apoptosis and caspase activity, as well as lowering mitochondrial membrane potential. This suggests that propolis has the ability to reduce cancer cell growth (Demir *et al.,* 2016).

CONCLUSION

Propolis has been known since 300 BC throughout the world for its traditional medicinal values. In this review, research data has been systematically together from various databases. According to the published literature, active research on Indian propolis started since last decade. The first research publication on Indian propolis appeared in 2004. So far, only a few bioactivities have been evaluated to Indian propolis. Various studies have found that propolis has antioxidant, antimicrobial, anti-inflammatory and antitumor properties.

Currently, there is insufficient concrete data regarding these compounds in Indian propolis, as their concentrations may be influenced by environmental conditions, geographic location and seasonal variations. The limited production of propolis in India can be primarily attributed to the insufficient scientific information and inadequate evaluation of the product. Propolis production is almost neglected practice among Indian beekeepers due to lack of awareness about its value and market potential. Hence, Beekeeping plays vital role in rural development, by generating revenue from honey and other bee products. The lack of scientific investigations and lack of awareness about the quality of indigenous propolis on Indian propolis endorses that there is urgent necessity to initiate scientific research programs to explore the potentials of original Indian Propolis.

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Conflict of interest

All authors declare that they have no conflict of interest.

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