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Therapeutic Uses, Chemical Compositions, With Special References to Oral Health Care, Market Values and Clinical Trial of Bee Propolis: An Updated Review

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Abstract

Bee propolis is a natural ingredient seen in several floras such as poplar, palm, pine, conifer secretions, gums, resins, mucilage, and leaf buds. Propolis has numerous health benefits such as enhancing immunity, lowering blood pressure, and treating allergies and skin conditions; therefore, it is widely used in the prevention and treatment of a wide range of disorders. Propolis is the subject of interest in the current study because most people emphasize natural remedies with ethnopharmacological properties. Propolis is considered a by-product of the royal jelly known as honey, which currently has no credible information relating to its standardized production method as well as its biological and pharmacological activities around the world. Propolis has been used therapeutically by humans for ages. Dental caries and oral infections are treated with propolis, due to its multifaceted chemical constituents like flavanones, pinocembrin, flavonols, galangin, caffeic acid, phenethyl ester, etc. This review article aims to explore the properties and constituents of propolis based on its potential use in general medical and oral health management.

Keywords: Propolis, Oral health, Phyto-perspective, Therapeutically, Ethnopharmacological.

Introduction

From the primeval age to till date, natural therapies had a significant role in treating different diseases worldwide both humans and animals. Herbal or natural things are an alternate source of synthetic drugs for maintaining proper health without any toxicity. It is estimated that almost 80% of people use natural remedies for their primary treatments. It is the oldest form of health care known to mankind. WHO has set precise accurate guidelines for the traditional remedies, so their popularity is increasing day by day. Most people think that "natural" medicine is superior to "unnatural" or "synthetic" drugs in terms of quality, safety, and efficacy because people believe these medicines are free of chemicals. Currently, researchers are focused on the use of a wide variety of natural products for treating a wide range of systemic diseases in pharmaceutical, bio-dental, and bio-medical applications (1). The natural product "Bee propolis" is a non-toxic, resinous, and lipophilic substance. It is generally hard but sticky, soft, and flexible when exposed to heat and breakable in cold. It has also used by humans as traditional medicine for the past 300 years. The mechanism action of propolis helps build and preserve bee hives and also has the potency to inhibit microbes and shield the honeycomb from rain. Due to its adhesive nature, it prevents foreign guests, and particles from inflowing the hive. In bee hives, propolis acts as both a nucleus and powerhouse or mitochondria of nutrients. Propolis helps to maintain homeostasis, reduce vibration, keep airflow, and prevent hives against squatter and putrefaction (2). The biochemical constituents, aroma, and color of propolis fluctuate from hive to hive, district to district, and season to season also depending on the environmental factor and type of plant pollen and species of bees. Commonly, propolis is dark brown, but it is also found in green, red, black, and white, depending upon the botanical sources. Propolis has a sweet taste but

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sometimes it can be bitter too (3). Propolis has different therapeutical activities also biocompatible with the human cell with fewer allergic reactions. Propolis is commercially available in the market in the form of lozenges, cosmetic creams, mouth rinses, and toothpaste (4). The antiseptic, astringent, antioxidant, anticancer, antimycotic, spasmolytic, anesthetic, anti-inflammatory, antifungal, antibacterial, antiulcer, and immunomodulatory activities of propolis are being investigated by scientists for their potential impact on medical research. Several investigations found that Polyphenol is found in fruits and vegetables which are the major constituents of propolis. Polyphenol has neuroprotectivity activity as it protects against neuroinflammation and oxidative stress, which are linked to both normal aging and long-term age-related disorders.

In the dentistry field, propolis is utilized as a natural remedy to treat canker sores, gum inflammation, and tooth pain (5). The report found that propolis is used in intra-canal medicine in the periodontics and endodontics fields (6). In divergence, propolis has dissimilar aromatic compounds, mainly flavonoids and phenolics have multidirectional assets. Propolis has a significant impact on preventing dental cavities in the oral cavity because it possesses bactericidal and antiadherent properties on bacteria. Moreover, propolis has several roles in the dentistry field as a cariostatic effect, improves periodontal health, anti-plaque effect if used in mouthwash, reduces dentinal hypersensitivity, endodontic disinfection, anti-inflammatory effect, cavity disinfectant, used in restorative materials respectively (7). According to a previous study, Propolis can be used as an alternative therapeutic agent with no side effects for the infectious condition of the oral cavity. The cost of Bee propolis is a little bit higher than other natural remedies. In the international market, the cost of propolis powder is up to 15000$ per kg. There is no accurate production rate of propolis available worldwide also found a lack of information based on propolis the production rate and market value in India. The global rate of propolis production is estimated to be several thousand tonnes in Japan, Korea, and Taiwan (8). The current study by various market research companies is focusing special emphasis on propolis production. In India, the collection of bee propolis is nonexistent among Indian beekeepers. It occurs due to a lack of awareness about the quality and potency of propolis with market value. Due to this, there is an urgent need for scientific research to explore the qualities of propolis. Here in this review, we discuss the ethnopharmacological properties, health benefits, efficacy, toxicity, and safety profile of propolis.

Methodology

A comprehensive and fundamental literature review was conducted in 2022 to discover the different chemical constitutions, therapeutic uses with special references to oral health care, market values, and clinical trials of bee propolis. There were several offline and online databases evaluated. The articles have been used from 2016 to 2023 year. The key data-gathering resource for this review article and research papers was published by several reputable publishers such as Springer, Taylor & Francis, Elsevier, imprints, and Hindawi. Some internet databases, such as ProQuest, EBSCO, Scopus, PubMed, NCBI, and Google Scholar, were also searched using terms related to data mining. Other sources of literature, such as conference proceedings, magazines, web pages, and book chapters, were also investigated and made available to maximize information about current bottlenecks, the quantity of research conducted, and the issue's prospective value. In this study, we examined many biological features of propolis, which will provide researchers with a thorough understanding of the current and future Biotechnology research field.

Taxonomy position and common uses

Apismelifera is commonly known as Honey bees. It belongs to the family Apidae and Genus Apis with the following taxonomic positions.

Kingdom: Animalia
Phylum: Arthropoda
Class: Insecta
Order: Hymenoptera
Family: Apidae
Genus: *Apis*

Honey bees harvest a gluey-like substance to guard their hives known as propolis. The name "Propolis" was coined by Aristotle and comes from the Greek words pro (before) and polis (city), which translate as "Before the City" or "Defender of the City," indicating that it is utilized in beehive defense, additionally it is known as bee glue (9). A thousand years ago, propolis was used

by ancient civilizations due to its medicinal value. The Greeks used propolis to cure many diseases and also used it as a regenerative substance. Propolis was utilized in wound healing by the Assyrians. The bee was precious & holy to the Egyptians, who used propolis to embalm mummies as an antibiotic, as well as an anti-putrefactive and antipyretic. Romans obey bees because, in their view, God Jupiter turned the woman Mellisa into a Bee Propolis was also used to cure skin lesions by the Romanians. It is used to cure wounds and burns, sore throats, stomach ulcers, and other ailments in the Balkan states. Propolis ethanolic extract has been used for decades as an anti-inflammatory and immunomodulatory drug. Several studies have found that Propolis has been used as a remedy for oral, throat, and dental cavities since the 12th century (10).

Zoological description

Honey

Honey is a sweet, viscous fluid made by honey bees. It is a sugar combination mostly composed of fructose (38%), glucose (32%), and a trace of maltose and sucrose, with a density of 1.38 - 1.45 kg/l at 20 °C (11). One tablespoon of honey gives around food energy of 46 kilocalories. It is used in various ways in various areas such as wound healing, cough, and topical antibiotics. In Hinduism, the local name of the honey is Madhu is one of the five life elixirs (Panchamrita). According to Vedas honey has great medicinal properties. Rosh Hashanah, the Jewish New Year, is symbolized with honey. In Hebrew Bible tradition, according to the Book of Leviticus, honey is offered to their god at the time of worship. Buddhists in Bangladesh and India celebrate Madhu Purnima which is commonly known as the Honey Full Moon Festival or Honey-offering Festival. According to the New Testament of Christianity, John the Baptist lived a long period without any health problems due to the intake of honey in their diet. In Islam, Muhammad suggested honey to use for wound healing purposes. According to the Quran, honey is a good sugar with great nutritional value (12).

Bee wax

Bee wax helps restore honey and also protects larvae and pupals in the beehive. In humans, it is used for a variety of applications such as candle making, waterproofing, soap, cosmetics, pharmaceuticals, art, shoes, furniture polish, and so on. Bee wax is used in the medical field to control bleeding during surgery from the bone surface, also used as a dental tooth filling. It uses for oil spill control, and to absorb oil or petroleum-based pollutants from water to create Petroleum Remediation Products (13).

Bee bread

Beebread is also called bee pollen. Bee workers collect pollen in their baskets from flowers and use it as a food source for the hive. Bee bread is composed of sugar, protein, minerals, vitamins, fatty acids, etc. Based on herbalists, bee pollen is used in the medical field. However, there is no evidence found that has any health benefits. The Food and Drug Administration is complete against bee pollen due to unapproved drugs such as sibutramine and phenolphthalein (14).

Bees as food

Beekeepers collect bee brood (Honeybee eggs, larvae, and pupae), which contains saturated fat, carbohydrates, protein, monounsaturated fatty acids, minerals, vitamins B, C, and D, and polyunsaturated fatty acids. Honey bee eggs, larvae, and pupae have high nutritional value and are considered a delicacy in Indonesia, Mexico, Thailand, and African countries; Chinese and Egyptians have consumed them since ancient times. Adult wild honey bees are consumed in Yunnan at special restaurants; on the other hand, it was "deep-fried with salt and pepper" and was "naturally sweet and delicious" (15).

Propolis

Bee workers collected pollen, nectar, water, and plant resin to make propolis. Propolis is sticky and above 20 °C (68 °F), but becomes hard at lower temperatures. The major function of propolis is to give structural stability, reduce water loss, increase thermal insulation, and protect from pathogens, parasites, and predators of the hives. Propolis was used in musical instruments such as violin, viola, cello, and bas. Propolis is used as a varnish ingredient by Antonio Stradivari. Propolis was used as a traditional medicine from ancient periods (Figure 1.) without any sufficient evidence to rate its effectiveness for any illnesses (16)

Figure 1(A-E): 1A: Honey bee hive-fig, 1B: Honey bees with Propolis, 1C: Honey bees collecting nectar from the flower, 1D: Propolis oil, 1E: Bee Propolis

Royal Jelly

Honey bees secrete royal jelly from the gland in the hypopharynx for larval nourishment that consists of 12.5% protein, 67% water,6% fatty acids,11% monosaccharide, 3.5% 10-hydroxy-2-decanoic acid(10-HAD) with some trace elements like pantothenic acid, (vitamin B5), antibacterial, pyridoxine (vitamin B6), vitamin C, and antibiotics. But it has some adverse effects such as allergic reactions in human-like asthma, and fatal anaphylaxis. Reported that it increases collagen production, and vasodilation, treat premenstrual or postmenopausal in human also treat Alzheimer's disease in animals. So, the European Food Safety Authority and the Food and Drug Administration of the United States couldn't even identify authentic evidence of health benefits, they prohibited the sale of royal jelly products (17).

Bee Venom

Even after separation, honey bee stings produce poison. The gland releases the pheromone that is associated with the string. The honey bee venom is called apitoxin, with major active compounds like melittin, and phospholipase A2 as active enzymes. Honey bee venom is still being studied in laboratories and medical fields for its potential activity. It is used to treat rheumatoid arthritis and immunotherapy to protect allergies from insect strings. Butfrom2018 to date there are no authorized clinical applications for bee venom and derived compounds due to its various allergic reactions (18).

Ecological condition and distribution

One integrated beekeeping development center (IBDC) has been established in each of the following states: Manipur, Himachal Pradesh, Punjab, West Bengal, Tamil Nadu, Delhi, Haryana, Bihar, Uttarakhand, Madhya Pradesh, Uttar Pradesh, Jammu & Kashmir, Tripura, Karnataka, and Andhra. This information was provided by the Ministry of Agriculture & Farmers Welfare, Government of India, on February 11, 2021, by PIB Delhi (Figure 2).

It was discovered that there is a significant correlation between rainfall and the amount of propolis produced, but no correlation between temperature and the quantity or quality of propolis. The highest yields of propolis are obtained in late autumn and the first winter. The propolis color and texture are directly dependent upon the climatic factors as, in dark, cold, or fewer humidity regions deep brown rigid propolis is found. The dark brown waxy propolis is mostly seen in high-humidity areas or during the summer seasons (19).

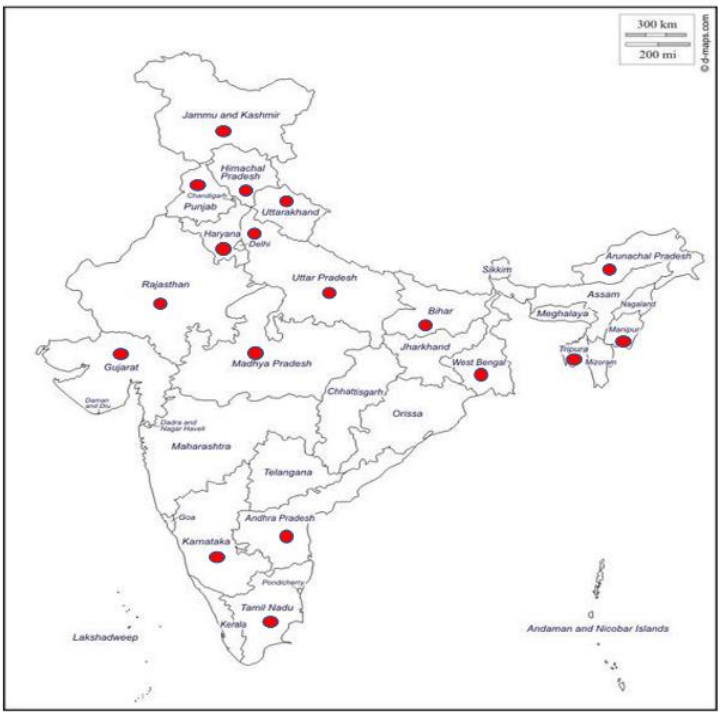

Figure 2: Apiculture development in different locations of India

Chemical composition of propolis

In a previous study, it was reported that Carboxylic acid (20.4%), alkaloids (6.4%), amino acid (2.1%), flavonoids (4.3%), steroids (11.5%), amino acid (2.1%), ketones (2.1%), terpenoids (15.0%), vitamins (2.1%), sugars (6.4%), volatile oils (2.1%), hydrocarbons (9.6%), phenols (3.2%), and other chemicals (15.0%) were found in propolis (20) as mentioned in Figure 3.

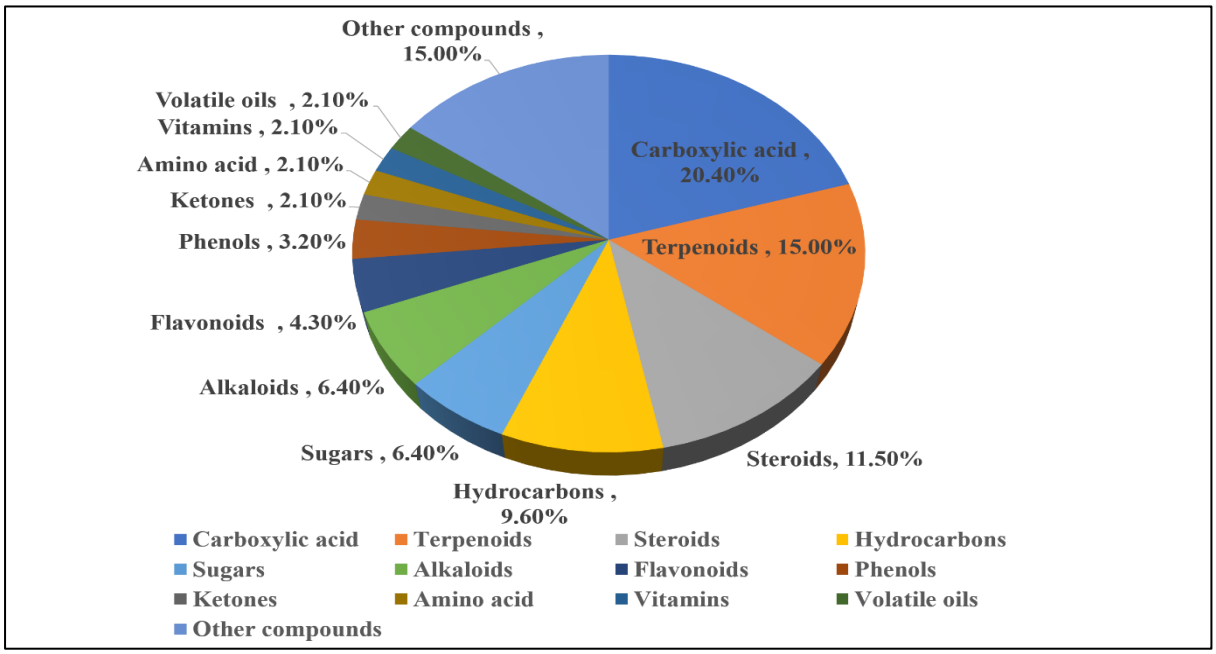

Figure 3: Phytoconstituents of bee propolis obtained by hydro-distillation

Biologically active compounds

Bioactive chemicals in bee propolis for example alkaloids, terpenes, phenylpropanoids, coumarin, stilbenes, prenylated, lignans, polyphenols, and flavonoids by-products have antioxidant properties that are beneficial to human health (21). Propolis extract contains phytoconstituents of flavonoids such as routine, acacetin, luteolin, pinocembrin, apigenin, quercetin, kaempferol, catechin, chrysin, myricetin, naringenin galangin and phenolic acids such as cinnamic, kainic acid those have antimicrobial efficacy. Flavonoids, phenols, and triterpenes are the key phytochemical compound that originates in propolis. The report found that propolis can be extracted by different solvents to determine their phytoconstituents. The water extracts of propolis (WEP) have some phytoconstituents such as saponins, starches, anthocyanins, terpenoids, quassinoids, polypeptides, tannins, and lectins; while flavones, totarol, polyphenols, lactones, xanthoxylline, phenones, anthocyanins, and polypeptides are among the phytoconstituents found in methanol extract of propolis. The ethanol extract of propolis has such phytoconstituents as tannins, polyphenols, polyacetylenes, terpenoids, sterols, and alkaloids respectively. Terpenoids and flavonoids are important constituents of the chloroform extract propolis. Dichloromethane extract of propolis has some major constituents such as terpenoids, tannins, polyphenols, polyacetylenes, flavonols, sterols, and alkaloids. In contrast, flavonoids are the major elements for acetone propolis extracts. Alkaloids, terpenoids, coumarins, and fatty acids are the primary components of ether extraction of propolis (22) (Table 1). Artepillin C (3, 5-diphenyl-p-coumaric acid) is a major constituent of Propolis phenolic compounds that shows higher antibacterial activity on *S. aureus.* An anaerobic bacterium *Porphyromonas gingivalis* was inhibited by artepillin C with membrane blebbing (23). Artepillin C also has anti-inflammatory activities that are mediated via the regulation of NF-kappa B and the inhibition of nitric oxide and prostaglandin E (2). Prenyl derivatives of propolis, such as 2-dimethyl-8-prenyl chromene, and 3-prenyl-cinnamic acid allyl ester show antibacterial activity. An ethanolic extract of propolis rich in kaempferide, Trupanion, and p-coumaric acid shows antioxidant and antibacterial action against *E. faecalis*, *Listeria monocytogenes, S. saprophyticus*, and *S. aureus* (24). Other flavonoid-derived compounds pinocembrin and apigenin of propolis show antibacterial activity in *Streptococcus mutants*. Biological investigations found Pinocembrin has antibacterial efficacy against *S. aureus, S. sobrinus, P. aeruginosa, S. mutants, L. monocytogenes, E. faecalis,* and *K. pneumonia*. Propolis is effective against Gram-negative bacteria such as *Apigenin, Salmonella enterica serotype Proteus mirabilis, Typhimurium, K. pneumonia, P. aeruginosa, and Enterobacter aerogenes*. Furthermore, Propolis derived Cinnamic acid has been proven to be effective against *Vibrio spp., Aeromonas spp., Streptococcus pyogenes, E. coli, L. monocytogenes, Mycobacterium tuberculosis, Bacillus spp., Micrococcus flavus, P. aeruginosa, Staphylococcus spp., S. enterica serotype Typhimurium* (25). Cinnamic acid inhibits bacteria by disrupting cell division, inhibiting ATPases, cell membrane, and biofilm generation, as well as possessing anti-quorum sensing activity. Other propolis constituents, for instance, quercetin, chrysin, and kaempferol have antibacterial and anti-inflammatory properties (26).

Pharmacological activities of Propolis

The resin and aromatic oils, wax (30-50%), essential oil (5-10%), and; pollen (50-70%), bioactive substances such as vitamins, minerals, phenolics, amino acids, and flavonoids are the major constitutes of propolis. Propolis shows antioxidant, antiangiogenic, and antiproliferative activity because of its phenolics and flavonoids. The anti-inflammatory study can treat Albino rats treated with formaldehyde-induced arthritis and prostaglandin E2 (PGE2)-induced paw edema. Propolis's caffeic acid phenethyl ester (CAPE), naringenin, and quercetin can suppress prostaglandin and leukotriene synthesis in zymosan-induced acute peritoibitneal inflammation both *in vivo* and *ex vivo*. In addition, propolis-derived terpenoid has potential activity in inactive inflammatory mediators such as inducible nitric oxide synthase (iNOS), interleukin (IL)-1b, and IL-10 (27). Propolis has the potency to treat the different inflammatory diseases of humans, such as diabetes, cancers, and cardiovascular disease by inhibiting the nuclear factor kappa-light-chain-enhancer (NF-kB).

Table 1: Different origin-based propolis with their phytoconstituents and biological activities

Sl. no	Methods used for Analysis	Propolis Origin	Propolis Types	Phytoconstituents	Biological Activities	References
1	GC-MS	India	Indian	9- octadecenoic acid, Decanoic acid, 9,12 hezadecanoic acid, Octadecadienoic acid,Methyl ester, 1-tetradecanol, Octadecanol, 1-dotricontanol,	Anti-inflammatory anti-microbial, anti-cancer	(28)
2	GC-MS	Greece	Mediterranean	Famotidine propionic acid(fatty acid), Limonene (Diterpenes).	Anti-microbial, anti-cancer	(28)
3	GC-MS, HPLC-DAD, LC-MS, FTMS	Brazil	Brazilian Green and red Propolis	Oleic acid, Palmitic acid, Linoleic acid, Capric acid	Antinociceptive, antihyperalgesic, antimold, local anesthesia	(29)
4	HPLC-PDA-MS	China	Poplar-type	Phenylacetic Acid(Phenolic acids), Caffeic acid	Anti-inflammatory anti-cancer	(29)
5	HPLC	Tekel	Adamawa region, Cameroon	2-Anthraquinonesulfonic acid (Anthraquinones), alpha-Hederin(Glycosides), Triterpenoid,	Antiangiogenic, antiproliferative	(29)
6	HPLC	Malaysia	T. apicalis	4-Hydroxycinnamic acid (p-coumaric), Quercetin, Hesperetin, Baicalein	Antiplatele, antithrombotic	(29)
7	GC-MS	Iranian	Popular type	Alkaloid D, 3-Bromocinnamic acid (Aromatic acid)	Anti-inflammatory anti-microbial	(29)
8	Methyl-alcohol	Europe, North America,	Poplar propolis	3-Bromocinnamic acid (Terpenes), Phenylacetic Acid (Phenolic acids)	Antibacterial, anti-inflammatoryantioxidant	(30)
9	Methanol	Russia	Birch propolis	Flavone and 3-Hydroxyflavone (flavonol)	Antibacterial, anti-inflammatoryantioxidant	(31)
10	Unknown	Cuba, Venezuela	Red (Clusia) propolis	Polyprenylated benzophenones	Anti-inflammatory anti-microbial	(32)
11	Methanol	Pacific region (Okinawa, Taiwan)	“Pacific” propolis	Naringin	Anti-inflammatory anti-microbial, wound healing	(33)
12	Unknown	Canary Islands	“Canarian” propolis	Furofuran	Antibacterial, anti-inflammatoryantioxidant.	(34)
13	Ethanol	Bulgarian	Bulgari-	5,7-Dihydroxy-6-	Anti-	(35)

			an propolis	prenylflavanone	inflammatory anti-obesity, anti-cancer.	
14	Ethanol	Solomon island	Common type	3-Iodophenol (Solophenol(A))	Anti-inflammatory anti-cancer.	(36)
15	Ethanol	Honduras	Common type	Cinnamyl cinnamate	Antiplatelet, anti-microbial, anti-cancer.	(37)
16	Ethanol	Jordanian	Jordani-an propolis	3-(4-Hydroxy-3-methoxyphenyl)propionic ac-id(Dihydroferulic acid	Anti-inflammatory anti-cancer.	(38)
17	Ethanol	Indonesia/ East Java province/ Batu City	Common type	beta-Phenethyl alcohol	Anti-cancer, anti-inflammatory	(38)
18	Ethanol	Kenyan	Kenyan propolis	Myricetin	Anti-viral, anti-allergic	(32)
19	Ethanol	Mexico/ Champoto n	Common type	3-(3,4-Dihydroxyphenyl)propionic ac-id(Dihydrocaffeic acid),3-(4-Hydroxy-3-methoxyphenyl)propionic ac-id(Dihydroferulic acid)	Antiproliferative, anti-inflamma-toryanti-viral, anti-allergic	(39)
20	Ethanol	Japan/ Okinawa	Common type	1,3-Dicaffeoylquinic acid	Anti-inflamma-toryanti-oxidant, antiproliferative	(39)
21	Ethanol	North and South Bul-garia	North and South Bulgari-an propolis	3-(3,4-Dihydroxyphenyl)propionic ac-id(Dihydrocaffeic acid) ,3-(4-Hydroxy-3-methoxyphenyl)propionic ac-id(Dihydroferulic acid) ,3',4'-Dihydroxyacetophe-none(Dihydroxyacetophenone),be ta-Phenethyl alcohol, kaempferol	Anti-carcinogenic, anti-inflammatory, anti-viral, anti-allergic	(39)
22	Ethanol	Sao Paulo state	Common type	1,3-Dicaffeoylquinic acid	Anti-oxidant, anti-cancer, antitumor	(40)
23	Ethanol	Israel	Common type	Apigenin	Anti-inflammatory, anti-viral, anti-allergic	(40)
24	Ethanol	Russia	Common type	Acacetin	Anti-inflammatory	(40)
25	Steam-distillation	Cuba	Common type	Galangin	anticancer, antibacterial, antitumor, anti-	(40)

					oxidant	
26	Hydro-distillation	Yemen	Common type	Linoleic acid	Anti-microbial	(40)
27	Hydro-distillation	Chile	Common type	Flavones (apigenin)	Anti-microbial	(40)
28	Hydro-distillation	Germany	Common type	CAPE	Anticancer	(41)
29	Ethanol	USA	Common type	Guttiferones	Anticancer	(41)
30	Ethanol	Iranian	Common type	Phenylacetic Acid(Phenolic acids), 3-Bromocinnamic acid (Terpenes)	Anti-inflammatory, antiviral, anti-oxidant, anti-cancer, anti-bacterial	(41)
31	Ethanol	Taiwan	Common type	5,7-Dihydroxy-6-prenylflavanone	Antitumor, anti-oxidant	(42)
32	Ethanol	Argentina	Common type	Kaempferol,	Antioxidant	(42)
33	Ethanol	Non-tropic regions of Asia	Common type	Quercetin	Anti-inflammatoryan-tihistamineulcer healing, capillary strengthening	(42)
34	Ethanol	Hungary	Common type	Moronic acid	Anti-HIV	(42)
35	Ethanol	New Zealand	Common type	Palmitic Acid	Hepatoprotective	(43)
36	Ethanol	Australia	Common type	Kaempferol	Anti-oxidative, anti-apoptotic	(43)

Brazilian propolis artepillin C inhibits endothelial cell proliferation *in vitro*. CAPE from propolis inhibits cancer cell metastasis in human HT1080 fibrosarcoma and CT26 colon adenocarcinoma cells via downregulating MMP. CAPE reduces NF-kB, VEGF, and MDR-1 gene expression in preclinical breast cancer models (44).

Propolis ethanolic extract exhibits antibacterial characteristics, inhibiting *Methicillin-resistant strains, Staphylococcus aureus*, and *Mycobacterium tuberculosis* H37RV strain. Pathogenic bacteria are inhibited by phenols and flavonoids by producing significant changes in the hydrophobicity of the bacterial membrane. Propolis-derived caffeic acid (and its esters), kaempferol, chrysin, galantine, and quercetin have antiviral properties against adenovirus, herpesvirus, coronavirus (particularly Sars Cov2), influenza virus, rotavirus, and HIV. *In vitro*, propolis extract liposomes are equally efficient as remdesivir in preventing Sars Cov-2 replication. Propolis aqueous extracts had greater levels of phenyl carboxylic acids and lower levels of phenolics and flavonoids than ethanolic extracts. Both extracts exhibit comparable antiviral efficacy against herpes simplex virus type 2. Kaempferol is a major constituent of propolis that works against the influenza H1N1 virus. The phenolics and flavonoids have also antiviral activity; these compounds either inhibit viral multiplication or help transport the metal ions (Zn2þ). The Zn ions have the potency to stop replication by inactive the viral enzymes (45), mentioned in the Figure 4.

Anticancer properties

Propolis has antiangiogenic and antiproliferative properties. The anti-cancer and chemo-protective effects of propolis extract were dependent on the dose. Human tongue squamous carcinoma cells are inhibited by propolis and its derivatives, such as caffeic acid, ferulic acid, chrysin, and p-

coumaric acid. In CAL27 cells, Propolis polyphenols reduce collagen synthesis, prolidase activity, and proline concentration. CAPE is a key component of propolis that possesses powerful anticancer effects. Artepillin C produced from propolis inhibits both human & mouse malignant tumor cells *in vitro* and *in vivo*. The MTT assay, DNA synthesis assay, and morphological observation *in vitro* all proved that artepillin C caused significant damage to cancer and leukemic cells (46).

Anti-bacterial activity

One of the several phenolic compounds of propolis includes (prenyl derivatives of p-coumaric acid), and artepillin C (3, 5-diphenyl-p-coumaric acid), which exhibits strong antibacterial action on MRSA *S. aureus*. The chemical constituents of propolis, i.e., 3-prenyl-cinnamic acid allyl ester and 2- dimethyl-8-prenyl chromene possess antimicrobial activity. The ethanolic extract of propolis has kaempferide, drupanin, and p-coumaric acid which showed antibacterial activity against *S. aureus, S. saprophyticus, Listeria monocytogenes*, and *E. faecalis*. Pinocembrin, galangin, pinostrobin, and apigenin are flavonoids found in propolis that exhibit antibacterial action against *Streptococcus mutants*. Furthermore, propolis-derived compounds such as ferulic acid, caffeic acids, prenylated coumaric acid, benzophenone derivatives, and diterpenic acids have been identified as antibacterial substances (47).

Antifungal activities

The ethanolic extract propolis was tested for antifungal activity against 80 *Candida species such as C. albicans>C.tropicalis>C. krusei>C. Guilliermondii* etc. The propolis extracts inhibited the growth of *Penicillium viridicatum, Candida albicans, Aspergillus ochraceus, Aspergillus flavus,* and *Penicillium notatum* at concentrations ranging from 15 to 30 mg/ml while0.25-2.0 mg/ml of propolis extract is inhibited *A. sulphureus* growth in few days (48).

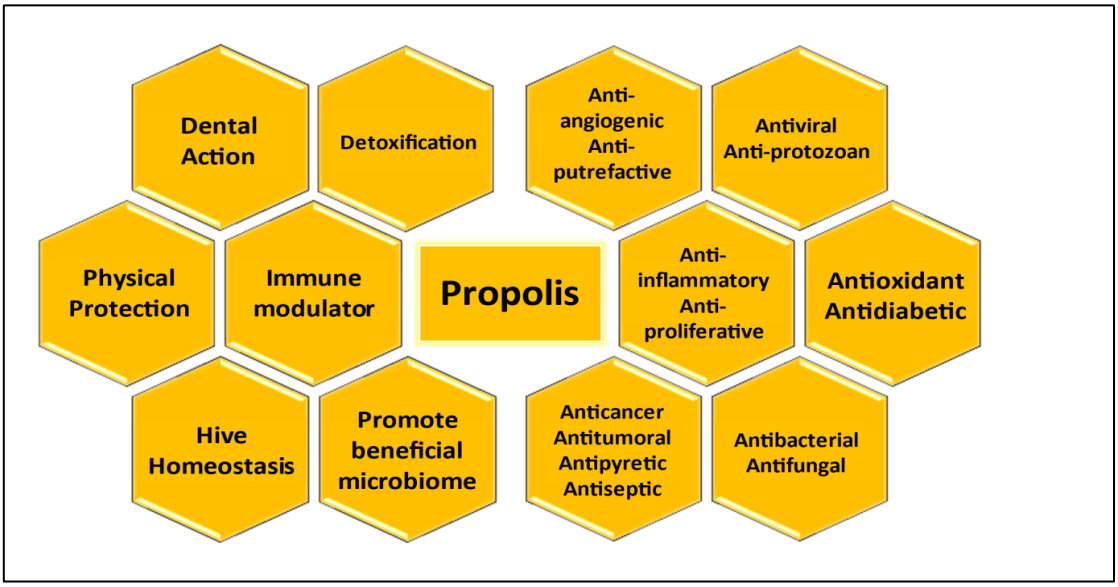

Figure 4: Biological activities of propolis

Antiviral properties:

Propolis and its derivatives, for example, 3-methyl-but-2-enyl caffeate, chrysin, galantine, quercetin, and kaempferol, have antiviral properties against HSV (Herpes simplex virus) by reducing viral DNA replication. Propolis and its phenolic components have antiherpetic effects that prevent viral penetration into cells. Propolis possesses immunomodulatory qualities that help to neutralize HSV-1 by activating Lyt-12 T cells and macrophages. It was discovered that the propolis-derived compound isopentyl ferulated significantly reduced the influenza virus A1. The aromatic compounds such as triterpenoids, moronic acid, anwuweizonic acid, also betulonic acid, were extracted from Brazilian propolis and have anti-HIV activity in H9 lymphocytes cells (49).

Anti-parasitic, anti-protozoal, and anti-helminths Activity:

The dimethyl-sulphoxide extracts of propolis (DEP) & ethanolic extracts of propolis (EEP) have the potency to inhibit *Trypanosoma cruzi* and *Trichomonas vaginalis*. Propolis and its constituents are effective against protozoan parasites that cause a variety of human diseases, such as *Trypa-*

nosoma brucei (sleeping sickness), *Trypanosoma cruzi* (Chagas disease), and *Leishmania donovani* (visceral leishmaniasis), as well as other strains of Leishmania. The *Plasmodium falciparum, Plasmodiummalariae, Plasmodium vivax*, and *Plasmodium ovale*, all of which cause malaria, are all inhibited by propolis extracts. Propolis is also effective against *Entamoeba histolytica* and *Giardia lamblia* infections, as well as multicellular organisms such as intestinal worms, including helminths like *Schistosoma spp., cestodes* like tapeworms, nematodes like roundworms, and trematodes like flukes (50).

Wound healing activity

Propolis and its chemical constituents play a vital part in wound healing and tissue regeneration. These are caused by their immunomodulatory, anti-inflammatory, and antibacterial actions. It was also found that propolis stimulates the production of collagen and its elements while reducing the number of free radicals present in inflammatory injury. It stimulates several enzymatic activities, cell metabolism, blood flow, and collagen fibers synthesis due to the presence of provitamin A, and B complex, bioflavonoids, vitamin C, arginine, and other minerals (51).

Anti-inflammatory Activity

The ethanolic extract of bee propolis can treat acute & chronic inflammation in both humans & rats. Bee Propolis derived poly-phenolic compounds have the potency to inhibit the inflammatory cytokines to treat adjuvant arthritis. Additionally, artepillin C has anti-inflammatory properties to inhibit NF-kappaB regulation, prostaglandin E (2), and nitric oxide. Caffeic acid phenethyl ester of propolis possesses anti-inflammatory activity. Quercetin, Apigenin, Caffeic acid, Acacetin, and Cinnamic acid, of propolis, have significant anti-inflammatory activity (51).

Anti-oxidant activity

Brazilian propolis is thought to have antioxidant activity due to phenolic and flavonoids. Brazilian green propolis-derived artepillin C, 3, 5, 4, and 4, 5-dicaffeoylquinic acids and 3, 4, 5-tri caffeoylquinic acid are responsible for the antioxidant activity. Although Italian and Russian propolis samples held similar polyphenolic compositions and antioxidant activity, Brazilian propolis had lower levels of polyphenols and less potent antioxidant qualities. Depending on the solvent and kind of propolis used to inhibit free radicals scavenging and inhibition of lipid peroxidation. The hexane extract of brown & green propolis and ethanol extract of brown propolis show significant antioxidant activity. The strongest antioxidant activity was discovered in dichloromethane and ethanol extracts of green propolis, as well as dichloromethane extract of brown propolis. The researchers looked into the effect of Brazilian green propolis supplementation on antioxidant capacity in type 2 diabetes mellitus (T2DM) patients (52).

Neuroprotective activity of Propolis

Due to mitochondrial damage and oxidative stress, propolis' antioxidant capabilities may protect against neurodegeneration. Brazilian green propolis decreased H2O2-induced mitochondrial-derived intracellular reactive oxygen species (ROS) and 8-oxo-2′-deoxyguanosine (DNA oxidative damage marker) intensity of immune-fluorescence signal. Propolis increases the expression of essential synaptic efficacy factors including brain-derived neurotrophic factor (BDNF) and activity-regulated cytoskeleton-associated protein (ARCAP). The results suggested that propolis protects against neuronal damage associated with Alzheimer's disease-related cognitive impairment.

Immunomodulatory Activity

In an experimental *Leishmania braziliensis* infection, the immunomodulatory effects of Brazilian propolis were investigated. In the immunomodulatory assay, macrophages were pre-treated with propolis before being infected *in vivo* with *L. braziliensis*. The TNF- and IL-12 levels were measured in supernatants from liver cells and peritoneal exudates of BALB/c mice that had been pre-treated with propolis and infected with *Leishmania promastigotes*. Macrophages incubated with propolis showed increased interiorization and parasite killing. TNF production increased in mice pre-treated with propolis, whereas IL-12 production decreased during infection. Brazilian propolis demonstrated direct parasite control as well as macrophage immunomodulation (53).

Other activities

Bee propolis has significant immunostimulant activity. As the propolis exhibits antimutagenic properties against several environmental muta-

gens such as 1-nitropyrene, 2-amino-3- methylimidazo [4, 5-f] quinoline,4-nitro-O-phenylenediamine, and benzo[a]pyrene. Propolis and its chemical constituents can treat hyperactive thyroid patients with ulcers & wounds and also, treat patients with non-specific rectal irritation. Propolis is being studied for its efficacy to cure *Helicobacter pylori* (Figure 5).

Propolis can inhibit host microorganisms by developing a physical barrier and blocking protein an enzyme that is essential for host cell invasion. Propolis suppresses replication by blocking the enzymes required for the replication of genetic material. Propolis also disrupts cellular organelles and energy-producing components to inhibit metabolism. In this regard, propolis has immunomodulatory properties. It boosts innate immunity and modifies inflammatory signalling pathways. During infection, propolis can maintain the host's intra-cellular activity (Figure 6).

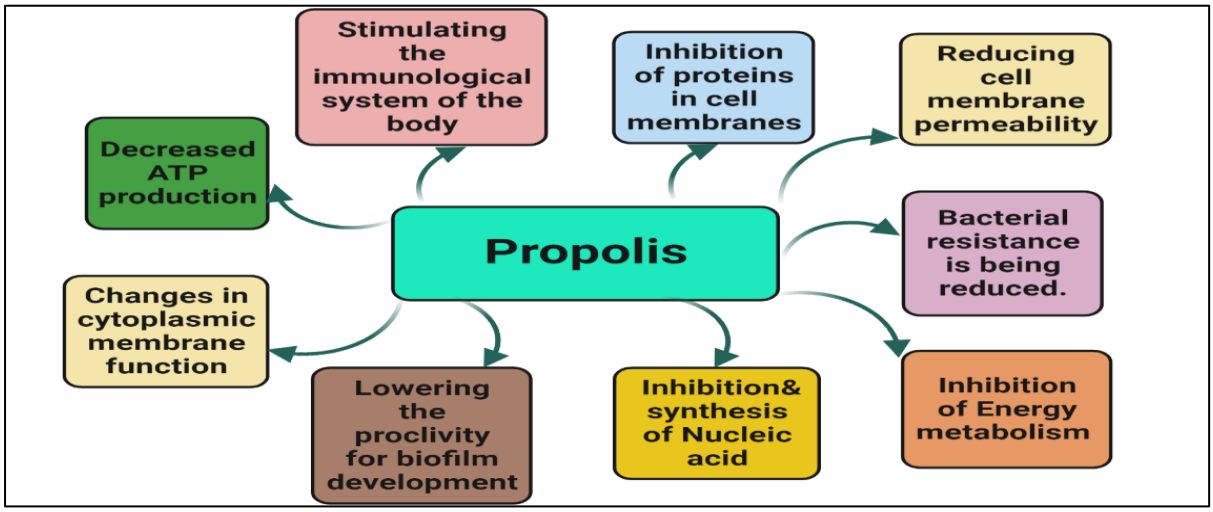

Figure 5: Propolis efficacy on the human body

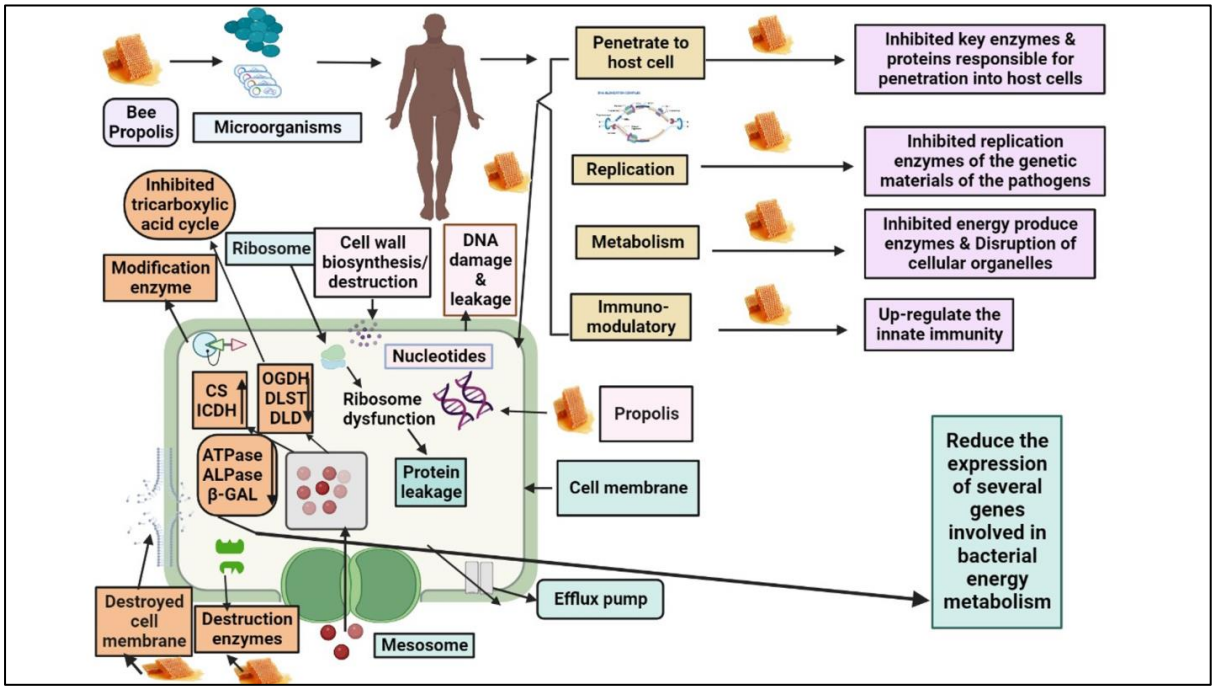

Figure 6: Immunomodulatory mechanisms of Propolis in human healthcare

Bio-efficacy of Propolis for Oral Health Care

Propolis has a wide range of potential activity in oral health care as an antioxidant, antibacterial, antiproliferative, anti-inflammatory, etc. Propolis has been treating dental caries and throat infections from the 12th century to till date. Propolis acts as an active ingredient in oral healthcare products also commercially available worldwide. Nowadays dental caries is a major burden on society and are also a common chronic disease.

The *Streptococcus mutants* and *Lactobacillus spp.* play a crucial role in caries development. Other bacteria such *asanginosus*, salivarius, *mitis,* groups of other *Actinomyces spp., Bifidobacterium spp., Propionibacterium spp., Prevotella spp., Streptococcus spp., Scardovia spp., Enterococcus faecalis, Veillonella spp.,* and *Rothiadento cariosa,* have been responsible for caries formations. The propolis can prevent the growth of *Streptococcus cricetus, Streptococcus sobrinus,* and *Streptococcus mutants*. It was also shown that propolis-enriched drinking water can reduce dental cavities by 50-60% in *S. sobrinus*-infected rats. On the other hand, Flavonoid-free propolis extracts prevented caries on both the smooth and sulcal surfaces in *S. sobrinus*-infected rats. As a result, the protective action of propolis is obtained not only from phenolics and flavonoids, but also from fatty acids including linoleic, stearic, oleic, and palmitic acids. Propolis can be used to treat dental caries periodontitis, gingivitis, and Supragingival plaque by its bactericidal effects. Propolis can treat root canals (54) by inhibiting these bacteria*; A.israelii, C. Albicans, C.perfringens, E. faecalis, F.nucleatum, P.nigrescens*,and *S. aureus*. Propolis is also used to treat dental pulp, enhance stem cell production, lower inflammatory responses also reduce the osteoclast genesis in periodontitis. Propolis exhibits antifungal properties against *Candida albicans, dermatophytes, T. tonsurans, and T. mentagrophytes*.

The extract of propolis has shown fungicidal activity against *candida* spp. such as *C. stellatoidea, C. krusei, C. parapsilosis, C. lusitaniae, C. tropicalis, C. guilliermondii, C. glabrata, C. Albicans,* and *C. Pseudotropicalis* are responsible for the oral cavity formation. Propolis-containing gel is more effective than miconazole gel for the treatment of denture sores. Propolis has antifungal properties because it inhibits the growth of fungal cell walls, hinders germ tubes, and reduces fungal colonization and biofilm development.

Oral cancer cells caused by tongue squamous carcinoma and laryngeal epidermoid carcinomaare both suppressed by propolis. One of the propolis compounds is CAPE which inhibits oral submucosa fibroblast proliferation, gingival cancer neck metastasis, and tongue squamous cell carcinoma. Proteins involved in carcinogenesis are downregulated by CAPE, leading to cell death in TW2.6 human oral cancer cells. This includes Akt, Akt1, Akt2, Akt3, phospho-Akt Ser473, phospho-Akt Thr308, glycogen synthase kinase 3 beta (GSK3b), class O forkhead box transcription factor (FOXO)1, FOXO3a, and phosphor-FOXO1 Thr24. Increased expression of tissue inhibitor of metalloproteinase-2 (TIMP-2) is one mechanism by which CAPE suppresses the proliferation and migration of SCC-9 oral cancer cells. Quercetin, another propolis flavonoid, inhibits chemically induced oral carcinogenesis in rats. Quercetin also inhibits SCC-9 oral cancer cells by decreasing the production of thymidylate synthase (TS), a critical S-phase enzyme, and SAS human oral cancer cells by increasing tumor suppressor microRNA-16 (miR-16) and decreasing homeobox A10 (HOXA10). Quercetin increases miR-22 and decreases WNT1, b-catenin, and TGFb1-induced epithelial-mesenchymal transition (EMT), to decrease oral squamous cell carcinoma cell survival and metastasis (55).

Market available products of propolis

The Propolis ethanolic extract is used in toothpaste to prevent microbial infection and cure gum irritation & inflammation. The cost of that toothpaste is Rs. 270. The propolis-based mouthwash inhibits bacterial growth in the mouth, first, dilute a tiny amount in water and rinse your mouth or gargle with this liquid before spitting it out and the price of that mouthwash is Rs. 636. The cost of propolis serum is Rs. 3500 and the cost of propolis light cream is Rs. 2431.69. The propolis hair oil is also available ataprice is Rs. 900 for 200ml. The propolis oil is best for skin concerns such as Acne-prone, aging, hyperpigmentation, post-acne mark, and inflammation, and the cost is € 24,75 for 100 ml. It is also used for healing, moisturizing, and smoothing both dry and oily skin (Figure7).

Ethno-medicinal value of propolis

Since the 16th century, bee propolis has been employed to treat joint inflammation, chronic cough, and wound healing. The biological investigations found that natural therapies such as honey, propolis, and bee wax are the best alternatives for wound healing and skin diseases. The therapeutic application of propolis is to inhibit microbes, parasites, etc and does not inhibit useful microflora. Although, propolis ethanolic extract and propolis oil are used in wound care as mouth sprays, tablets, suppositories, ointments, and others (56). The ethanolic extract of propolis can treat joint pain, toothache, and wound healing and also treat internal injuries. Raw propolis is used in mouth rinses to inhibit the growth of gingivitis and periodontitis bacteria Figure 8.

Figure 7: Some market-available products of propolis as Face cream (7A), Toothpaste (7B), Face serum (7C), Mouthwash (7D), Propolis hair oil (7E), Propolis oil (7F)

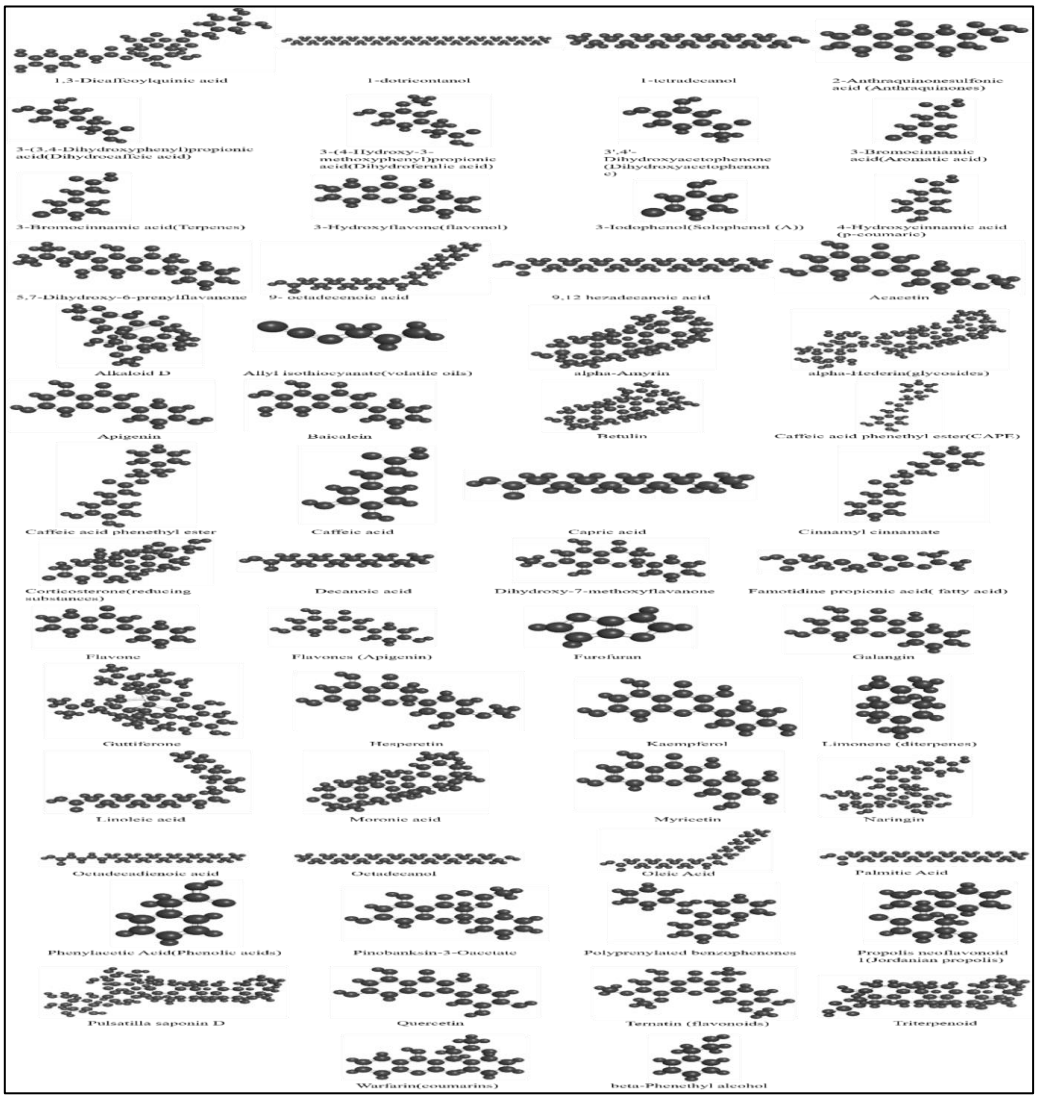

Figure 8: List of phytocompounds identified from Propolis

Clinical trial

In a 2019 clinical study, propolis was found to heal diabetic foot ulcers and reduce local inflammation by decreasing TNF-alpha and increasing IL-10. In this regard, two groups of diabetic foot ulcers (Wagner grades 1 and 2) were treated with 5% propolis ointment. The erythema and exudate in the wound milk were not affected with this therapy, however, the lesion area reduced and healed in 4 weeks with topical 5% propolis ointment. Propolis, myrrh, and bee honey (MPH) cured another diabetic foot ulcer. The patient was directed to clean the ulcer and fill it with MPH paste after debriding non-viable tissues. The ulcer healed after four weeks. Pure propolis cures oncological sores as six patients over 60 years old, both men and women, were advised to apply a thin coating of the formulation to the wound using a spatula once a day. According to the data, ulcer healing took 30 to 45 days, with an average of 39 days for the study participants (57).

In 2013, propolis was tested on venous ulcer sufferers. 28 patients (ulcer area 6.9–9.78 cm2) participated in Group 1. Propolis ointment and a short-term compression bandage helped patients. 29 patients (ulcer area 7.2–9.4 cm2) were treated by compression with an Unna's boot without propolis in Group 2. On the other hand, Group 1 healed in 6 weeks. However, Group 2 took 16 weeks to recuperate. The findings suggest that propolis ointment heals quicker than an Unna boot. One research separated 33 mercurialized patients with sacrococcygeal pilonidal disease wounds into control and placebo groups. One group received local bandages and the other 15% Anatolian propolis. The ulcers in the investigational group improved at 7 and 14 days postoperatively. As long as the lesions were not complex, propolis therapy expedited healing. Propolis helps speed wound healing in individuals with simple sacrococcygeal pilonidal cysts who prefer marsupialization because of its cheap cost, excellent patient compliance, minimal side effect profile, lack of toxicity, and great effectiveness (58).

Propolis and silver sulfadiazine were tested for treating superficial second-degree burns. Participants with bilateral burns of equal size and depth and compounded wounds were selected. The wounds were cleansed and bandaged every three days. The chemicals' antibacterial effects were similar. However, propolis reduced inflammation and promoted quicker healing than silver sulfadiazine (59).

Propolis' wound-healing capacity has been studied for a century. A 1996 Cuban research of 78 patients examined the effects of propolis (in an alcoholic vehicle) and proposal (made with propylene glycol) on mouth ulcers and surgically treated patients. A comparison of the propolis-treated groups and the control group indicated that mouth ulcers healed quicker and symptoms subsided faster. In patients with chronic ulcers of different aetiologies, propolis at concentrations from 3 to 30% increased granulation tissue, secretion odour, and pain sensitivity, demonstrating its anesthetic effect. The cultured secretions showed a reduction in bacteria, even unfavorable effects. Brazilian research in Paraná tested propolis ointment on 20 chronic ulcer patients. Vascular, diabetic, and pressure ulcers were chronic. Topical propolis treatment improved lesions' appearances, secretion, granulation tissue, discomfort, edema and local itching, and had an analgesic effect. More than 70% of ulcers healed before 13 weeks (60).

The propolis ointment is used for venous, pressure, and diabetic ulcers. Propolis ointment with a 30% concentration reduced wound healing time to 45 days, and 20% of patients achieved full wound closure. The synergistic combination of propolis' components makes its antibacterial mechanism unclear, however, certain strains are more sensitive than others. Propolis has multi-target cell action and can be effective by structurally damaging bacteria. Propolis prevents infections from invading host cells by establishing a physical barrier and blocking enzymes and proteins. Propolis disrupts cellular organelles and energy-producing components, inhibiting pathogen metabolism. Propolis increased innate immunity and altered inflammatory signalling pathways. Propolis directly suppressed iNOS catalytic activity and the lipoxygenase pathway of arachidonic acid metabolism by acting on the promoter at the NF-kB site. Propolis increased type I collagen deposition, decreased matrix metalloproteinases, proinflammatory cytokines, and eicosanoids, and improved TGF-β signal transmission. Furthermore, propolis components regulated the cellular immune response, inhibiting macrophage activation, differentiation, and leukocyte recruitment (61).

Conclusions and future scope

Propolis has a unique chemical composition and significant pharmacological effects with low toxicity, so it is widely utilized in folk medicine. Propolis is a natural remedy that has remained popular for a long time and is also mostly used in the production of drugs and foods. Phenolic acids, Flavonoids, and their esters are the pharmacologically active compounds of propolis. These chemical components inhibit bacteria, fungi, and viruses in different ways. Furthermore, propolis and its constituents have anti-inflammatory, immunomodulatory, and anticancer properties. Propolis is believed to be safer and less toxic than various synthetic drugs. Clinical studies are now being conducted to confirm propolis's effectiveness in treating and preventing diseases. Physicians should focus on the advantages of propolis as an adjuvant treatment for patients and researchers should explore novel therapeutic applications for it.

List of abbreviations

WHO - World Health Organisation; NCBI- National Centre for Biotechnology Information; 10-HAD-10-Hydroxy-2-Decanoic Acid; CAPE - Caffeic Acid Phenethyl Ester; IBDC- Integrated Beekeeping Development Centre; WEP - Water Extracts of Propolis; TIMP2- Tissue Inhibitors to Metalloproteinase2; TS - Thymidylate Synthase; EMT - Epithelial-MesenchymalTransition; PGE2 - Prostaglandin E2; iNOS - Inducible Nitric Oxide Synthase; IL - Interleukin; NF-kB - Nuclear Factor kappa-light-chain-enhancer; MMP - Matrix Metallo Proteinase expression; MDR-1 - Multi Drugs Resistance 1; HSV - Herpes Simplex Virus; DEP - Dimethyl-sulphoxide Extracts of Propolis; EEP - Ethanolic Extracts of Propolis; T2DM - Type 2 Diabetes Mellitus; ROS - Reactive Oxygen Species; BDNF - Brain-Derived Neurotrophic Factor; ARCAP - Activity-Regulated Cytoskeleton - Associated Protein; GC-MS - Gas Chromatography-Mass Spectrometry; HPLC-DAD - High-Performance Liquid Chromatography with Photodiode Array Detection; LC-MS - Liquid Chromatography / Mass Spectroscopy; FTMS - Fourier Transform Mass Spectrometry; HPLC-PDA-MS - High-Performance Liquid Chromatography with Photodiode Array Mass Spectroscopy; GSK3b - Glycogen Synthase Kinase 3 beta; FOXO - Fork-head box transcription factor.

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Authors contributions

SB and AK: conceptualized the methodology. GN: data collection, validation, and drafting of original manuscript. AK and DK: supported the scientific discussions. AS, DK, RB, and AK: supported the validation and preparation of the final manuscript. All the authors have contributed to the final revision and agreed to its publication.

Conflict of interests

All the following author(s) declare that there is no conflict of interest regarding the financial and non-financial of publication this article.

Ethics approval

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