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Propolis in Human Health: Unraveling Chemistry, Applications, and Efficacy

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Abstract:

The paper explores the diverse aspects of propolis, a resinous substance created by bees from botanical sources, presenting a comprehensive overview of its chemistry, applications, and efficacy in human health. Propolis, colloquially known as "bee glue," serves as a versatile material in hive construction and defense against diseases and predators. Its chemical composition, influenced by geographic origins, comprises a myriad of bioactive compounds, including flavonoids, phenolic acids, terpenoids, and more. The study delves into the pharmacological activities of propolis, emphasizing its antioxidant, antimicrobial, anti-inflammatory, and anticancer properties. Propolis exhibits a direct correlation between its biological activity and the quality of its chemical constituents. The antioxidant activity, attributed to flavonoids, plays a crucial role in mitigating oxidative stress and associated chronic inflammation. Furthermore, the paper discusses the therapeutic potential of propolis in various health conditions, such as diabetes mellitus, cardiovascular diseases, asthma, COPD, and wound healing. In diabetes, propolis shows promise in reducing blood glucose levels and insulin resistance. Its cardioprotective effects are linked to antioxidant compounds, addressing oxidative stress in cardiovascular diseases. Propolis demonstrates anti-allergic and anti-inflammatory effects in respiratory conditions, providing potential relief for asthma and COPD patients. Additionally, propolis accelerates wound healing through its immunomodulatory, antimicrobial, and antioxidant properties. In conclusion, propolis emerges as a natural resource with significant potential for human health, presenting a diverse array of bioactive compounds that contribute to its therapeutic efficacy across various medical conditions. The multifaceted nature of propolis makes it a subject of growing interest for further research and exploration in the field of medicine and healthcare.

Key words: "propolis" ; "anticancer" ; "antioxidant" ; "anti-inflammatory" ; "chronic diseases"

Introduction:

The bounty of bioactive compounds within natural products has long captivated scientific interest, given the vast array of chemicals inherent in nature and their extensive medicinal and

therapeutic potential.. Stepping into this realm, propolis emerges as a compelling prospect, showcasing a plethora of advantageous effects across diverse in vivo and in vitro studies [1].

Bees diligently gather an assortment of raw materials, such as resins, beeswax, and more, from the diverse flora surrounding their hive. Infusing these with their enzymatic saliva rich in β-glucosidase, they concoct propolis—an invaluable resinous creation. Distinct bee species, from Apis mellifera honeybees to stingless bees of the Meliponini tribe, fashion varied propolis, each boasting unique chemical compositions. The lush botanical landscape within a few kilometers of the hives profoundly shapes the composition and physiochemical makeup of this propolis [2,3,4].

Termed colloquially as "bee glue," propolis emerges as a versatile substance in hive construction and maintenance. Bees ingeniously manufacture propolis by blending beeswax and saliva, utilizing it as a strategic defense mechanism for the hive [5].

The etymology of "propolis" traces back to the Greek roots "pro" and "polis," embodying the essence of being "in favor of the city [6].” Essentially, propolis, a tacky, gummy, and balsamic amalgamation harvested from botanical sources, becomes a shield wielded by bees, notably Apis mellifera L. It cloaks and fortifies the hive against diseases spawned by fungi, yeast, bacteria, and the menacing presence of predators [7]. Primarily sourced from the resin nestled in poplar, birch, and conifer buds and bark, foraging bees skillfully amass these resins, concocting a medley of resinous substances, pollen, waxes, and enzymes [8,9]. Propolis serves bees as both construction material and sealant, orchestrating homeostasis, dampening vibrations, facilitating airflow, thwarting intruders, and averting putrefaction [10]. The granules exhibit an array of sizes and hues (yellow, red, and dark brown), contingent on the botanical origin, emitting a potent aromatic fragrance [11]. Initially rigid and crumbly, propolis metamorphoses into a viscous, sticky consistency upon manipulation and gentle heating, ultimately liquefying around 70 °C [12].

Lately, there has been a growing fascination with researching propolis and its various components due to advancements and enhancements in medical technology. Propolis, aside from its healing and therapeutic qualities in addressing different persistent illnesses, has proven to be successful in managing burns and wounds, treating diabetes, addressing gynecological

issues, as well as conditions related to the skin, larynx, , and gastrointestinal diseases. Furthermore, it has shown efficacy in neurodegenerative problems, respiratory issues, cardiovascular disorders, and even in the context of COVID-19.

Physical properties and chemical composition

A widely acknowledged fact is that the pharmacological effect of a medicinal plant is evident through its chemical constituents. In varying percentages, raw propolis comprises mainly lipids (50%), waxes (30%), essential oils (10%), pollens (5%), and other organic substances (5%). Its rather complex chemical profile is attributed to this multitude of components. Many studies reported that organic substances of propolis contain, in particular: carboxylic acids (20%). sugars (6%): d-Altrose, d-glucose, maltose, d-fructose, alkaloids (6%), amino acids (2%), phenolic acids (3%), metals: aluminum, sodium, potassium, calcium, copper, magnesium, iron, zinc, silicon, tin, manganese, nickel, chrome [20, 21], flavonoids (4%): apigenin, acacetin, chrysin, galangin, genistein, hesperetin, kaempferol, kaempferide, luteolin, naringenin, pinobanksin, pinocembrin, quercetin, tetrochrysin, ketones (2%), steroids (12%), alcohols: glycerol, erythritol, α-cedrol, xylitoldihydrochalcones, aldehydes, chalcones, vitamins (2%): Vitamin A (retinol), vitamin B1 (thiamine), vitamin B2 (riboflavin), vitamin B3 (nicotinamide), vitamin B6 (pyridoxine), vitamin B9 (folic acid), vitamin C (ascorbic acid), and vitamin E (tocopherol), terpenoids (15%), aliphatic acids, aromatic esters and acids: benzoic acids, caffeic acid, cinnamic acid, coumaric acid, ferulic acid, gallic acid, caffeic acid phenethyl ester, 2-propenoic acid methyl ester, 4,3-acetyloxycaffeate, 3,4 dimethoxy-trimethylsilyl esters, 3-methoxy-4-cinnamate, carbohydrates (10%) and also beeswax [13,14,15,16,17,18,19,22,23]

Propolis, sourced from various plants and regions, exhibits a range of colors and melting points. The melting point varies between 60 °C and 70 °C, with some types reaching 100 °C. To obtain commercial extracts of propolis, ethanol is the preferred solvent, although methanol, chloroform, ether, and acetone are also utilized [24,25]

The origin's influence on propolis' chemical makeup poses a challenge in unequivocally categorizing its substances and therapeutic attributes. The distinctive qualitative-quantitative phytochemical variations tied to its geographic distribution render propolis both chemically and biologically unique. Tunisian propolis, for instance, stands out for its methoxyylated flavonoids like quercetin 3,7,3‘-trimethyl ether and myricetin 3,7,4',5' tetramethylether from Cistus spp.,

Cistaceae, leaf exudates [26]. Conversely, New Zealand propolis showcases hydroflavonoids, like pinocembrin and pinobanksin, constituting around 70% of the total flavonoids from Populus nigra L., Salicaceae, bud exudates.

Contrastingly, in Uruguayan and Chinese varieties, these hydroflavonoids are detected in less than 10%, while in Brazil, they constitute up to 50% [27, 28]. The prevalent flavonoids in Chinese and Uruguayan types are largely flavones and flavonols. Comparative analyses across propolis samples from Europe, South America, and Asia reveal distinctions. European and Chinese propolis primarily feature various flavonoids, phenolic acids, and relative esters. In contrast, Brazilian propolis is rich in terpenoids and prenylated derivatives of p-coumaric acid, like artepillin C from Baccharis dracunculifolia DC, Asteraceae, in southeastern and western-central Brazil [29, 30]. This highlights a substantial difference between propolis from tropical areas (South America) and temperate regions (Europe). The former is characterized by substances with a hydroxycinnamic acid nucleus (C6–C3 backbone), while the latter predominantly features a flavonoid (C6-C3–C6 backbone) composition.

The connection between the chemical constituents present in propolis and their botanical origins has been thoroughly chronicled by Bankova et al.. It can be predicted that propolis, comprised of diverse chemical constituents, harbors an array of biologically active compounds, bioactivities, and pharmaceutical functionalities. Notably, phenolic compounds play vital roles in safeguarding plants against sunlight, herbivorous animals, and microbial pathogens. Much like flavonoids, phenolic compounds also demonstrate various biological activities such as antioxidant, antibacterial, anticancer, anti-inflammatory, antitumor, plasmodicidal, and anti-HIV effects [31,32].

Numerous studies have illustrated the direct correlation between the biological activity and quality of propolis and its chemical constituents [33]. Hence, it comes as no surprise that, in addition to its physicochemical properties, the chemical constituents of propolis serve as a standardized parameter for assessing its quality [34]. Apigenin, chrysin, galangin, luteolin, kaempferol, pinobanksin, pinocembrin, quercetin, caffeic acid, cinnamic acid, p-coumaric acid, ferulic acid, artepillin C, CAPE, and coumarin are among the common bioactive compounds responsible for propolis' biological and pharmaceutical properties.

Limonene, α-cubebene, and β-caryophyllene exemplify some of the prevailing terpenes found in propolis, while triterpenes like lupeol and β-amyrin have also been identified [35]. These volatile biosynthetic compounds, classified as terpenes and triterpenes, are of plant origin. Propolis additionally contains other volatile compounds, including esters derived from fatty acids and organic acids. In the plant realm, these volatile compounds play a crucial role in attracting insects to facilitate the pollination process. They also hold potential applications as spices, fragrances, and flavors in industries like perfumery, cosmetics, pharmacies, and food products. The extensive spectrum of biological activities attributed to these volatile compounds includes analgesic, anticancer, anti-inflammatory, antitumor, antifungal, antimicrobial, antiviral, and antiparasitic effects [36,37].

Pharmacological activities:

Antioxidant activity

Persistent chronic inflammation, often triggered by oxidative stress, is well recognized for its capacity to activate various transcription factors, including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), activator protein 1, tumor protein, hypoxia-inducible factor 1-alpha, peroxisome proliferator-activated receptor gamma, and nuclear factor erythroid 2-related factor 2 (Nrf2) [38]. NF-κB, a complex protein, governs DNA transcription and plays a crucial role in cellular responses to stress, cytokines, free radicals, ultraviolet irradiation, oxidized low-density lipoproteins (LDL), and bacterial or viral antigens. Notably, propolis can activate the Nrf2 transcription factor, a key regulator of antioxidant proteins. The interaction of Nrf2 with the antioxidant response element initiates the transcription of several antioxidant enzymes, including heme oxygenase-1, regulatory and catalytic subunits of γ-glutamate-cysteine ligase, GPx, glutathione reductase, CAT, SOD, and glutathione-S-transferase [39]. Although the clinical implications of propolis' antioxidant activity are challenging to pinpoint, we delve into its anti-inflammatory and neuroprotective properties below, both grounded in antioxidant principles.

To mitigate tissue damage induced by oxidative stress, endogenous antioxidant systems have evolved protective mechanisms. These encompass enzymes like superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT), along with antioxidant nutrients such as ascorbic acid, glutathione, and flavonoids [40]. The well-documented antioxidant activity of propolis and its constituents has been extensively explored [41], consistently revealing a

reduction in oxidative stress markers [42]. Propolis' flavonoids emerge as potent antioxidants, adept at scavenging free radicals and safeguarding cell membranes from lipid peroxidation [43]. Thanks to the chemical structure of its polyphenols, propolis effectively eradicates free radicals [44]. Malondialdehyde concentrations, commonly used as potential biomarkers for oxidative stress and indicators of oxidative lipid damage, further substantiate these findings.

Antimicrobial activity

Antimicrobial activity has been observed in all types of propolis, regardless of their origin and the compounds they contain. This suggests that the antimicrobial effectiveness of propolis is more a result of the collective compounds rather than individual ones [42]. The compounds present in propolis seem to hinder the division of bacterial cells and induce dysfunction in the cytoplasm, thereby deactivating bacterial growth and activity. Propolis has exhibited diverse antibacterial effects against various pathogens, including Vancomycin-resistant Enterococcus faecium, Streptococcus pyogenes, Staphylococcus epidermidis, Staphylococcus aureus, P. larvae, Neisseria gonorrhoeae, Listeria monocytogene, Helicobacter pylori, Escherichia coli, Enterococcus faecalis, and Bifidobacterium infantis [5,20,45,46]. Either by directly engaging with microbial cells or by triggering the host cells' immune system, propolis exerts its effects [47]. The hypothesized mechanisms encompass enhancing cell membrane permeability, reducing bacterial mobility, inhibiting bacterial adherence and division and disrupting membrane potential. [48,49]. These biological actions are closely tied to the existence of flavonoids, phenolic acids, dihydrochalcones, chalcones, terpene esters, terpenoids, aliphatic acids and esters, metals and aromatic compounds [13]. Associated with antibacterial activity, the flavonoid components of propolis, such as galagin, pinocembrin, and pinostrobin, play a significant role. These flavonoids are known to enhance bacterial membrane permeability and impede bacterial genetic coding [5]. Additionally, they have been documented to hinder the attachment and formation of biofilms, obstruct nucleic acid synthesis, and disrupt the energy metabolism of bacteria [50]. Consequently, flavonoids prove to be effective agents against bacteria.

Like its antibacterial effects, propolis' antiviral activity is attributed to various mechanisms, with research primarily focusing on CAPE and related compounds. CAPE has been shown to suppress the in vitro replication of the hepatitis C virus [5], showcasing its dual antibacterial and antiviral effects. Furthermore, CAPE hinders the NF-kB activation process [51] and acts as

an inhibitor of HIV-1 integrase produced by retroviruses, preventing the integration of genetic material into the host's DNA cell.

Anti-inflammatory activity

Inflammation is defined as an interaction between the immune system and injured tissues designed to restore homeostasis via complex signaling pathways [52]. The anti-inflammatory activity of propolis appears related to its associated constituents: terpenoids, phenolic acids, flavonoids, and their esters, steroids and amino acids, with CAPE being the most studied compound. The main mechanisms underlying the anti-inflammatory activity of propolis include: (1) free radical scavenging; (2) the inhibition of cyclooxygenase (COX) and consequent inhibition of prostaglandin biosynthesis; (3) inhibition of nitric oxide synthesis; (4) immunosuppressive activity and (5) reduction in the concentration of inflammatory cytokines [53].

Having a significant influence on inflammation [54], propolis regulates various inflammatory mediators by either up-regulating or down-regulating them [55]. Numerous compounds with anti-inflammatory effects have been isolated from propolis [56]. Neovestitol inhibits NO production and reduced GM-CSF, IL-6, IL-4, TNF-alpha and IFN-gamma. It has also increased IL-10 production, down-regulated genes related to nitric oxide production like NF-κB, IL-1β, and TNF-α signaling pathways [57]. Caffeic acid inhibited NO production, p38 MAPK, JNK1/2 and NF-κB [58]. CAPE Decreased IL-6R, IL-6, IL-8, enhanced IL10, suppressed cytokine signaling-3 [59]. Inhibited COX-1 and COX-2 [60]. Reduced the induction of the inflammatory pathway, c-jun-N-terminal kinase, NF-κB, COX-2 expression [61]. Inhibited upregulation of TNF-α and COX-2 [62]. Quercetin, galangin, luteolin inhibited IL-1β and TNF-α. β-Amyrine acetate and lupeol acetate inhibits ROS. 2-Hydroxy-8-prenylbiochanin A inhibits NO [63]. Daidzein inhibited macrophages and neutrophils infiltration, attenuated MPO activity, inhibited TLR4,MyD88 protein and NF-κB activation [64]. Isoliquiritigenin inhibit adhesion of neutrophil, ICAM-1, VCAM1, E-selectin and TNF-α expression, translocation of the p65 subunit of NF-κB by blocking the phosphorylation and subsequent degradation of IκBα [65]. Pinocembrin modulates the production of TNF-α, IL-1β, IL-6 and IL-10 via inhibiting the phosphorylation of IκBα, ERK1/2, JNK and p38MAPK [66]. Galangin inhibit inflammatory cytokines IL-1β and IL-6, and proinflammatory genes, such as iNOS, ERK1/2, NFkB p65 activation, and neutrophil migration [67,68]. Apigenin inhibits inflammatory cytokines,

ERK1/2, NF-kB activation, and neutrophil migration [69]. Artepillin C: inhibition of TNF-α, down regulation of adiponectin, increase of PPAR-γ activity, inhibition of TNF-α-induced JNK signaling [55]. Decrease of inflammatory cells, modulation of matrix [56]. Reduction in NO synthesis [70]. Inhibition of IL-1β, IL-3, IL-4, IL-5, IL-9, IL-12 p40, IL-13, IL-17, TNF-α, G-CSF, GMCSF, MCP-1, MIP-1α, MIP-1β, RANTES, KC and NF-κB pathway [71].

Anticancer activity

Cancer, according to the World Health Organization (WHO), is a leading global cause of mortality, characterized by the abnormal growth of cells with the potential to spread and invade other parts of the body. The development of drug resistance in cancer cells can lead to reduced efficacy of certain drugs, and some cancer cells may show resistance to chemotherapy. While there is currently no cure for cancer, various treatments exist to help minimize the spread of tumors. In light of the limited effectiveness of current medications, scientific research has turned its focus to deriving potential cancer treatments from natural resources. Natural products have become increasingly popular as alternative drugs, given the wide array of natural bioactive compounds that offer beneficial effects on human health. Additionally, it has been noted that a majority of anticancer agents are sourced from natural products [72]. A number of substances have been isolated from propolis that may exhibit anticancer activity.

Hyperibone A and nemorosone show a cytotoxic effect on HeLa tumor cells [73]. Cardol increases caspase-3 and -9 activity and PARP; causes apoptosis; decreases mitochondrial membrane potential; has an antiproliferative effect; causes an G0/G1 cell cycle arrest on a SW620 human colorectal cancer cell line [74]. Liquiritigenin, formononetin, medicarpin, biochanin A, retusapurpurin increases Bax/Bcl-2 ratio levels on a carcinoma BCL-5637 [75]. Pinobanksin-3-acetate inhibits proliferation and induces apoptosis through up-regulation and down-regulation of multiple genes involved in cell apoptosis, cytokinetics, colorectal carcinogenesis and calcium signaling. Chrysin up-regulates the p21(waf1/cip1) gene expression and inhibits histone deacetylase 8 on a MDA-MB-231 breast cancer cell [76]. DMEP-A-C shows cytotoxic activity and metastatic proliferation inhibition on head and neck squamous cell carcinoma (HNSCC) cell lines. Caffeic acid phenethyl ester down-regulates mortalin and up-regulates GADD45α and p53 tumor suppressor proteins on human cancer cells, SKOV3 (ovarian carcinoma), HT1080 (fibrosarcoma), A549 (lung carcinoma), HeLa (cervical carcinoma), U2OS (osteosarcoma), MCF7 and MDA-MB-231 (breast adenocarcinoma) [77].

Artepillin C shows abrogation of mortalin-p53 complexes causing the activation of p53 on HT1080 (fibrosarcoma), A549 (lung carcinoma) and U2OS (osteosarcoma) human cell lines [78]. Flavonoids and phenolic acid activate caspases-3, -8 and -9 on the human tongue squamous cell carcinoma cell line [79]. They also inhibit proliferation of human rectal and colon cancer cells. Epigallocatechin-3-gallate shows cytotoxic effect and decrease of cell viability on BT-20, BT-549, MDA-MB-231 and MDA-MB-436 cells [80]. *p*-Coumaric acid shows cytotoxic effect and decrease of cell viability on four triple-negative breast cancer cell lines (BT-20, BT-549, MDA-MB-231, and MDA-MB-436 cells) [80]. Caffeic acid and pinocembrin have an antiproliferative effect [81]. Novel 2-phenoxychromone; 3-*O*-methylquercetin; 3,6,4′-trimethoxychrysin; 3,6-dimethoxyapigenin have an antiproliferative effect and inhibit cell growth on DLD-1 (human colon cancer), A549 (human lung cancer) cancer cell lines, MCF-7 (human breast cancer) [82]. Propolone A-B shows antiproliferative effect on ovarian cancer cell line [83]. Chrysin, pinobanksin, pinobanksin-3-*O*-propanoate, pinobanksin-3-*O*-butyrate, pinobanksin-3-*O*-pentanoate, pinobanksin-3-*O*-hexanoate have an antiproliferative activity through apoptotic induction on a B-cell lymphoma cell line [84]. Galangin causes apoptosis on human colon cancer and human triple negative breast cancer cell lines [85]. Myricetin causes inhibition of cell growth and apoptosis on human triple negative breast cancer (MDA-MB-231) cell lines [85]. Luteolin shows a cytotoxic effect and causes apoptosis on human colon cancer (HCT-116) and human triple negative breast cancer (MDA-MB-231) cell lines [85].

Propolis in the treatment of various diseases:

Diabetes Mellitus (Type 2)

Medical condition type 2 diabetes mellitus (T2DM) is characterized by an elevated level of blood sugar (glucose) caused by the body's inability to produce enough insulin. In the research of natural compounds as a means of prevention, T2DM has attracted great interest [36]. In recent studies, propolis has emerged as a potent player, exhibiting significant impacts on T2DM patients by reducing blood glucose levels, serum insulin, and glycosylated hemoglobin (HbA1c) [86,87,88]. The influential effects of propolis on glucose metabolism involve suppressing intestinal α-glucosidase activity in carbohydrate digestion and stimulating β-cells in the pancreas, leading to increased insulin secretion [36].

Zakerkish et al. highlighted that T2DM patients receiving propolis supplementation for 12 weeks experienced reduced insulin levels and insulin resistance [86]. Moreover, reports emphasize the critical role of free radicals, oxidative stress, and inflammatory cytokines in the development and complications of T2DM [88]. Propolis, with its active constituents, acts as a scavenger for free radicals, lowering blood glucose levels and modulating blood lipid metabolism [37]. The resulting oxidative stress, marked by the production of reactive oxygen species (ROS), triggers inflammation and inflammatory mediators [35].

ROS-associated T2DM induces oxidative damage to vital organs like the heart, kidneys, nerves, and eyes [35]. Subclinical inflammation, linked to insulin resistance and characteristics of metabolic syndrome and hyperglycemia, alters the absorption of intestinal carbohydrates and prompts glucose uptake by peripheral tissue due to high glucose levels [36]. Consequently, propolis exerts antihyperglycemic effects by inhibiting glucose production from dietary carbohydrates, regulating postprandial glucose levels, and improving insulin resistance [36].

Furthermore, propolis enhances the glycemic and lipid profiles of T2DM patients [87], solidifying its status as a promising agent for preventing and controlling diabetes mellitus.

Many components of propolis have a positive effect on blood glucose levels. Astrapterocarpan, medicarpin, 8-prenylnaringenin inhibit α-Amylase and α-glucosidase [89]. Propolis and bee pollen extracts cause reduction of blood glucose and insulin resistance [90]. PE (propolis extract) conjugated with chitosan polyacrylic (CS-PAA) nanoparticles suppress blood glucose levels. Tectochrysin inhibits α-Glucosidase. PE also causes: α-Glucosidase inhibition [57]; decrease of the G6Pase expression by inhibiting the autophosphorylation of GSK3α and β, which are involved in the activation of GSK3 [91]; reduce glucagon, FBG level, and improve insulin and islet of Langerhans regeneration; reduction of cholesterol and triglycerides/increase of PPARα protein level in the liver [92]; reduction of total cholesterol, LDL and triglycerides [93]; reduction of total cholesterol and triglycerides, without any effect on HDL, decrease of atherosclerotic lesion development in aortic root [94]; maltase and α -amylase inhibition [95]; reduction of plasma level of insulin and HOMA-R index of insulin resistance [96].

Cardiovascular disease

One of the leading risk factors worldwide associated with heart and blood vessels, causing heart attack, stroke, and angina, is cardiovascular disease (CVD). Typically, CVD is a result of the narrowing or blocking of blood vessels [97]. Intriguingly, positive effects of propolis on the treatment of cardiovascular diseases such as hypertension, atherosclerosis, and ischemia-reperfusion (IR) injury have been suggested. The likelihood of CVDs being impacted by risk factors such as oxidative stress and obesity is considerable, but propolis supplementation, with its bioactive components, could mitigate the risks associated with CVD [98]. The results of conducted research typically indicate that the cardio-protective effects stem from the antioxidant activity of propolis and its constituent compounds [99]. Oxidative stress is implicated in the initiation of cardiovascular disease, where low-density lipoprotein oxidation initiates atherogenesis – the developmental process of plaques on artery walls. This leads to atherosclerosis, characterized by thickening of artery walls and restriction of blood flow, culminating in cardiovascular disease [100]. Epidemiological studies have unveiled a positive correlation between a flavonoid-rich diet and increased longevity, along with a reduced incidence of cardiovascular disease.

In addition to the well-recognized antioxidant effects, polyphenols engage with the generation of nitric oxide (NO) from vascular endothelium. This not only results in vasodilation but also in the expression of genes that protect the cardiovascular system [99].

Due to its active ingredients, particularly phenolic compounds like chrysin, luteolin, pinocembrin, and quercetin, propolis boasts a range of cardioprotective properties [101]. These phenolic compounds effectively reduce the activity of cyclooxygenase, as well as the production of reactive oxygen species (ROS) and nitric oxide (NO), contributing to the antioxidant prowess of propolis [102]. It is suggested that Malaysian propolis exhibits cardioprotective activity and antioxidant properties, countering isoproterenol-induced oxidative stress through cytotoxic radical-scavenging [103] Another significant compound in propolis, CAPE, not only possesses antioxidant properties but also demonstrates protective effects against ischemia-reperfusion (IR) injury in various tissues, including the brain, colon, heart, and liver [101]. Furthermore, the flavonoids present in propolis showcase the ability to impede the progression of pathological cardiac hypertrophy and heart conditions [104].

Asthma and COPD

Research on asthma and its alternative medicinal treatments, utilizing natural resources like bee products such as propolis, has significantly increased. Asthma, a long-term inflammatory condition, leads to narrow and swollen airways in the lungs, resulting in chest tightness, wheezing, and difficulty breathing, especially upon allergen inhalation. The beneficial effects of propolis on asthmatic conditions are evident, thanks to its anti-allergic, anti-asthmatic, and anti-inflammatory properties. These effects can be attributed to the inhibitory impact on the activation of basophil and mast cells [105,106].

A chronic lung disease caused by an obstruction of airflow, resulting in breathing difficulties, wheezing, coughing, and mucus production, is Chronic Obstructive Pulmonary Disease (COPD). COPD has various causes, including genetic disorders, exposure to air pollution and dust, with smoking being the most common factor [107]. The use of natural products in COPD treatment, particularly antibiotics, has seen an increase [108].

Recent studies have highlighted the beneficial and effective properties of propolis in treating asthma, respiratory diseases, and coughs [109,110]. Propolis is rich in various effective components such as flavonoids, phenolic compounds, phenolic acids, terpenes, and terpenoids. Moreover, it boasts a broad spectrum of therapeutic properties, including anti-inflammatory, antioxidant, antimicrobial, and immunomodulatory effects [109,110,111,112,113].

Many chemicals in propolis have positive effects on asthma. Benzyl caffeate, CAPE, chrysin, galangin, geranyl caffeate, kaempferide, kaempferol, naringenin, pinocembrin, artepillin C, baccharin, 3-methyl-2-butenyl caffeate cause: exhibits anti-inflammatory and anti-allergic activities, inhibits allergen-induced inflammation, inhibits ROS production, inhibits mast cell degranulation, Blocks NF-κB expression in macrophage cell lineage [114,115,116].

Other substances can have a positive effect on COPD. CAPE, cinnamic acid, p-coumaric acid, aromadendrin, caffeic acid, N-acetylcysteine prevents acute lung inflammation, reduces pro-inflammatory cytokines, inhibits the NF-κB pathway and
reduces stomatitis, oral infections, and dental plaque [109,117,118,119].

Wound healing

Wound healing, a multi-step and intricate process, faces hurdles from various internal and environmental factors [120]. The skin, a frontline defender of the human body, is exceptionally prominent. It can undergo disturbances caused by inflammation and bacterial infections, often demanding prolonged therapy for a thorough healing [121].

Recent insights highlight propolis as a contributor to wound healing in a time-dependent fashion. The properties of propolis, including immunomodulatory [122], antimicrobial [123], antioxidant, analgesic, and anti-inflammatory [124], might actively expedite the wound healing process [125].

Recent research demonstrates the significant impact of propolis on wound healing by upregulating the healing process at the tissue level, enhancing cell influx, and collagen deposition [126]. The preventive effects of propolis, attributed to amino acids, flavonoids, phenolic acids, terpenes, and vitamins, are well-documented [127]. Propolis extract exhibits protective activity by regulating antioxidant-related genes, including heme oxygenase 1 (HO-1), GCLM, and GCLC, in wounded tissue [128].

Topical use of propolis reduces the number of mast cells, favoring wound healing [129]. Isolated bioactive constituents from propolis, such as CAPE and other active compounds, effectively decrease mast cell levels and improve surgical wounds during the acute inflammation phase [130]. The antioxidant activities of propolis are particularly noteworthy in the post-wounding oxidative stress scenario, supporting tissue repair [131,132]. The polyphenolic compounds of propolis play a protective role by reducing protein breakdown and maintaining cellular membrane integrity, decreasing peroxidation, and hemolysis [133].

Propolis extract rich in galangin has the ability to inhibit superoxide anion production and suppress oxidative stress in wound injuries [134]. Additionally, CAPE, along with other polyphenols, upregulates the expression of the aminopeptidase (AMP) gene, aiding in re-epithelializing skin cells in chronic wounds [135, 136]. This action also reduces lipid peroxidation, minimizing DNA and protein breakage [134].

Enhancing re-epithelialization, a critical phase in wound healing involving keratinocyte migration and proliferation [137], is achieved by propolis and its chemical constituents that

increase aquaporin-3 (AQP3) gene expression [125]. AQP3-facilitated water transport plays a pivotal role in cell migration and hyperproliferation, thereby accelerating the healing of cutaneous wounds and stimulating epidermal keratinocytes [125].

In conclusion, propolis from various countries regulates numerous signaling pathways, including mast cell regulation via AQP-3, VEGF, NF-kB, and caspase-1 pathways, contributing significantly to the process of wound healing.

Conclusion:

In conclusion, propolis emerges as a multifaceted natural substance with a rich chemical composition and a myriad of potential health benefits. Originating from the ingenious efforts of bees, propolis serves not only as a structural element in hive construction but also as a potent defense mechanism against various threats, including microbes and predators.

The chemical composition of propolis is intricate, encompassing a wide array of bioactive compounds such as lipids, waxes, essential oils, pollens, organic substances, carboxylic acids, sugars, alkaloids, amino acids, phenolic acids, metals, flavonoids, ketones, steroids, alcohols, vitamins, terpenoids, and more. The diversity in chemical constituents is strongly influenced by the geographical origin of propolis, leading to distinct qualitative-quantitative variations in different regional varieties.

The pharmacological activities of propolis are extensive and well-documented. Its antioxidant properties, attributed to various bioactive compounds, make it a potential candidate for mitigating oxidative stress-related conditions. Propolis exhibits notable antimicrobial effects against a spectrum of pathogens, demonstrating its potential as a natural antibiotic. The anti-inflammatory properties of propolis, mediated by compounds like CAPE, contribute to its efficacy in managing inflammatory conditions. Moreover, propolis showcases anticancer activities, inhibiting the growth of various cancer cells through multiple mechanisms.

Propolis has shown promise in addressing specific health conditions, including diabetes mellitus, cardiovascular diseases, respiratory conditions like asthma and COPD, and wound healing. In diabetes, propolis demonstrates antihyperglycemic effects by modulating glucose metabolism and reducing oxidative stress. Its cardioprotective effects, attributed to antioxidant and anti-inflammatory properties, make it a potential adjunct in cardiovascular disease management. Asthma and COPD benefit from propolis' anti-inflammatory and anti-allergic actions, alleviating symptoms associated with these respiratory conditions. Additionally,

propolis accelerates wound healing through its immunomodulatory, antimicrobial, and antioxidant properties.

The intricate interplay of propolis' chemical constituents and its diverse pharmacological activities underscores its potential as a natural therapeutic agent. However, further research is essential to unravel specific mechanisms, standardize formulations, and establish optimal dosages for various health applications. Propolis stands at the intersection of traditional knowledge and modern scientific exploration, offering a rich source for the development of novel therapeutic interventions in human health.

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