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Mechanistic Insights into Honeybee Propolis as a Natural Modulator of Inflammation and Oxidative Stress: A Narrative Review

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ABSTRACT

Honeybee propolis has been used as a natural remedy for centuries to treat various diseases. This review examines the mechanistic basis of propolis's anti-inflammatory and antioxidant properties, as well as its therapeutic applications. A narrative methodology was utilized, incorporating a comprehensive literature search to identify relevant, high-quality evidence from major biomedical databases. The evidence suggests that propolis exhibits significant anti-inflammatory and antioxidant effects, primarily attributed to its diverse phytochemical composition, including caffeic acid phenethyl ester and flavonoids. These compounds regulate inflammatory signaling pathways, particularly the nuclear factor κB pathway. Furthermore, the bioactive constituents exhibit strong free radical-scavenging activity, supporting the restoration of normal cellular metabolism. Although propolis exhibits significant anti-inflammatory and antioxidant properties, most supporting evidence is derived from in vitro and preclinical studies. The limited availability of clinical data necessitates cautious interpretation of these results. Large-scale clinical trials and standardized formulations are required to establish robust evidence of its efficacy.

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ABSTRAK

Propolis lebah madu telah lama digunakan sebagai bahan alami dalam pengobatan tradisional dan kini semakin banyak diteliti karena potensinya sebagai agen antiinflamasi dan antioksidan. Tinjauan naratif ini bertujuan untuk mengkaji dasar mekanistik aktivitas antiinflamasi dan antioksidan propolis serta potensi aplikasinya dalam bidang kesehatan. Literatur yang relevan dikumpulkan dari berbagai basis data biomedis dengan menekankan bukti eksperimental, praklinis, dan klinis yang membahas komposisi bioaktif, jalur molekuler, serta efek farmakologis propolis. Bukti yang tersedia menunjukkan bahwa efek biologis propolis terutama berkaitan dengan kandungan fitokimia yang beragam, seperti flavonoid, senyawa fenolik, caffeic acid phenethyl ester (CAPE), dan artepillin C. Senyawa-senyawa tersebut berperan dalam modulasi jalur inflamasi, terutama melalui penghambatan aktivasi nuclear factor kappa B (NF-κB), penurunan mediator proinflamasi, serta pengaturan respons imun. Selain itu, propolis menunjukkan aktivitas antioksidan melalui kemampuan menangkap radikal bebas, mengurangi peroksidasi lipid, dan mendukung peningkatan sistem antioksidan endogen. Walaupun propolis memiliki potensi terapeutik yang menjanjikan, sebagian besar bukti masih berasal dari studi in vitro dan praklinis, sedangkan data klinis masih terbatas dan bervariasi. Oleh karena itu, diperlukan uji klinis berskala besar, formulasi yang terstandar, serta evaluasi keamanan dan efektivitas yang lebih kuat sebelum propolis dapat direkomendasikan secara luas sebagai terapi tambahan berbasis bahan alam.

Kata Kunci: Propolis lebah madu; Antiinflamasi; Antioksidan; Flavonoid; Caffeic acid phenethyl ester; Potensi terapeutik

1. Introduction

The Honeybee propolis (HBP) has been utilized as a complementary medicine for the treatment of various diseases for centuries. Recent advancements in the pharmaceutical industry have prompted extensive research into its pharmacological potential. Studies indicate that HBP possesses a broad spectrum of therapeutic properties, including anti-inflammatory, antioxidant, and anticancer effects [1].

Morphologically, honeybee propolis consists of granules of varying sizes and colors, including yellow, red, and dark brown, depending on its botanical source. Its aroma is strongly aromatic [2]. The chemical composition of propolis is influenced by geographical location, botanical origin, and bee species [3]. Propolis is composed of approximately 50% resin, 30% wax, 5% pollen, 10% aromatic oils, and 5% other organic residues [4]. By 2000, over 300 chemical constituents, including flavonoids, terpenes, and phenolics, had been identified in propolis. In tropical regions, particularly in Brazilian green propolis, prenylated phenylpropanoids such as artepillin C and diterpenes are predominant. Propolis from the Pacific region is characterized by geranyl flavanones, which are also present in African propolis [5]. Trace elements (Ca, K, Mg, Na, Al, B, Ba, Cr, Fe, Mn, Ni, Sr, and Zn) and toxic elements (As, Cd, Hg, and Pb) have been detected by atomic emission or absorption spectrometry in propolis samples from various Croatian regions [6]. Additionally, Br, Co, Cr, Fe, Rb, Sb, Sm, and Zn have been identified in Argentinean propolis using neutron activation analysis. These findings suggest that trace element profiles may serve as useful markers for identifying the geographic origin of propolis [7].

The use of bees and their products dates back to approximately 13,000 BC, when the ancient Egyptians depicted propolis-producing bees on vases and ornaments and used propolis to treat various diseases [8]. Propolis was also recognized in the Arab

world; Avicenna described two types of wax, with black wax likely referring to propolis. Persian manuscripts reference propolis as a remedy for eczema, myalgia, and rheumatism. During the Middle Ages, propolis fell out of favor in mainstream medicine. Its use reemerged in Europe during the Renaissance, when interest in ancient medical practices was revived. In the early nineteenth century, Nicolas Louis Vauquelin, a French pharmacist and chemist, conducted studies on propolis [9].

Despite extensive research documenting propolis's biological activities, significant knowledge gaps remain. The mechanistic pathways underlying its anti-inflammatory and antioxidant effects are not fully elucidated, as many studies provide only descriptive data [10]. Additionally, the chemical composition of propolis varies widely across botanical sources and geographic origins, complicating cross-study comparisons. The lack of standardized extracts and dosing protocols further impedes the ability to draw consistent conclusions regarding efficacy and safety [11]. Although preclinical evidence is abundant, clinical trials are both limited in number and highly heterogeneous, leading to uncertainty about propolis's therapeutic relevance in human populations. Inconsistencies in study designs, formulations, and dosages also contribute to variable findings [12]. Addressing these limitations is essential to advancing the translational potential of propolis and guiding future research toward standardized, clinically meaningful outcomes. This narrative review critically evaluates the pharmacological potential of honeybee propolis and synthesizes current evidence on its anti-inflammatory and antioxidant activities.

2. Methods

Review Design

A narrative synthesis was employed to examine the pharmacological effects of honeybee propolis, with particular emphasis on its anti-inflammatory and antioxidant properties. The narrative format provides flexibility, enabling the inclusion of diverse evidence types, such as laboratory experiments, animal studies, clinical trials, and mechanistic reports. This approach facilitates contextual interpretation of findings, highlighting both established effects and emerging therapeutic possibilities. By situating anti-inflammatory and antioxidant effects within the broader pharmacological profile of propolis, the review seeks to offer a comprehensive understanding to inform clinical practice and future research.

In contrast to systematic reviews, the narrative approach is less rigid and emphasizes thematic exploration and critical evaluation of the evidence. This method enables the identification of connections among various study types and integrates mechanistic insights with practical outcomes. Emphasizing anti-inflammatory and antioxidant effects underscores the growing importance of novel agents in addressing global infection control challenges.

Literature Search

A comprehensive literature search was conducted to identify relevant, high-quality evidence. The search extended through September 2025 and utilized combinations of keywords and Boolean operators, such as “propolis” AND (“antioxidant” OR “oxidative stress” OR “anti-inflammatory” OR “inflammation” OR “therapeutic applications”). Major biomedical databases, including PubMed, Scopus, Web of Science, and Embase, were systematically searched using both controlled vocabulary (for example, MeSH terms) and free-text keywords related to honeybee propolis, its pharmacological activity, and its anti-inflammatory and antioxidant properties. Boolean operators were used to refine the search strategy, and filters were

applied to restrict results to peer-reviewed publications. Additionally, reference lists of key articles were reviewed to identify studies not indexed in the primary databases.

The search strategy was designed to maximize comprehensiveness and minimize the risk of omitting significant evidence. No restrictions were placed on publication date, although recent studies were prioritized to capture the latest findings. Grey literature, including conference proceedings and dissertations, was included only if it met rigorous methodological standards. Search terms were refined and additional synonyms incorporated as necessary to ensure the final selection of studies encompassed all available knowledge regarding this molecule.

Inclusion and Exclusion Criteria

Studies reporting experimental, preclinical, or clinical data on the pharmacological effects of honeybee propolis, with particular emphasis on anti-inflammatory and antioxidant activity, were included. Eligible studies comprised randomized controlled trials, observational studies, laboratory experiments, and mechanistic investigations. Articles were required to provide sufficient methodological detail to permit assessment of validity and reproducibility. Only English-language publications were considered to ensure consistency in interpretation and synthesis.

Studies lacking clear methodologies, based on unreliable reports, or not focused on pharmacological outcomes were excluded. Conference abstracts without full texts, editorials, and opinion pieces were also omitted to maintain scientific rigor. Studies addressing only non-pharmacological uses of honeybee propolis, such as industrial applications, were not included. This rigorous selection process ensured that the evidence synthesized was both relevant and reliable for pharmacological analysis.

Data Extraction and Evidence Synthesis

Key details were systematically extracted from each study, including design, population or experimental model, outcomes measured, and reported pharmacological activity. Data were organized into structured tables to facilitate comparison across studies. Particular attention was given to methodological quality, reproducibility, and relevance to clinical or translational contexts. Any reporting discrepancies were documented and, when possible, clarified by consulting supplementary materials or related publications.

The evidence was synthesized narratively, integrating findings from diverse study types to identify consistent trends, mechanistic insights, and discrepancies. The synthesis emphasized themes such as variations in pharmacological potential and possible synergistic effects with other agents. Where appropriate, outcomes were compared between experimental and clinical settings. This approach facilitated the identification of knowledge gaps and the establishment of research priorities for the future.

3. Results and Discussion

Although numerous studies have investigated the biological activity of propolis, the evidence presented in this review is primarily derived from in vitro and preclinical studies. This limitation arises from the absence of clinical study results on propolis identified during the literature search

Anti-inflammatory Properties of Propolis

A Propolis is a rich source of anti-inflammatory molecules due to its complex phytochemical diversity. Brazil, for example, has at least 13 distinct types of propolis, each containing various bioactive compounds such as apigenin, artepillin C, vestitol, and

neovestitol. Pharmacological studies have demonstrated that propolis exerts potent anti-inflammatory effects [13].

While the precise anti-inflammatory mechanisms of propolis are not fully understood, its ability to downregulate proinflammatory cytokine production is well documented. Propolis has been shown to reduce IL-1β and TNF-α production in human peripheral blood mononuclear cells stimulated with lipopolysaccharide, a component of Gram-negative bacteria [14]. Red propolis significantly inhibited neutrophil migration, likely due to reduced CXCL1/KC and CXCL2/MIP-2 release, which results in decreased neutrophil chemotaxis [15]. Direct inhibition of calcium influx in neutrophils has also been identified as a mechanism that decreases neutrophil chemotaxis [16]. In patients with type 2 diabetes mellitus, propolis administration resulted in a significant decrease in serum hs-CRP and TNF-α levels, with no change in serum IL-1β and IL-6 levels [17]. In ulcer regions, propolis treatment decreased TNF-α levels and increased IL-10 levels, further supporting its anti-inflammatory potential [18].

Caffeic acid phenethyl ester (CAPE), a major constituent of propolis from honeybee hives, demonstrates significant anti-inflammatory effects. CAPE serves as a potent modulator of arachidonic acid (AA), preventing its release from the cell membrane and inhibiting the gene expression of lipoxygenases (LOX) and cyclooxygenases (COX), which are involved in AA metabolism [19]. CAPE specifically targets NF-κB signaling, modulates ERK MAPK signaling in T cells and mast cells, and regulates the PI3K/Akt pathway in various human cell lines. These mechanisms may lead to the downregulation of key inflammatory enzymes, including xanthine oxidase, cyclooxygenase, matrix metalloproteinases, and inducible nitric oxide synthase [20-23].

Flavonoids isolated from Nepalese propolis ethanol extract (PEE), including 3′,4′-dihydroxy-4-methoxydalbergione, 4-methoxydalbergion, cearoin, and chrysin, inhibited the expression of inflammatory genes such as IL-6, TNF-α, and IL-13 in bone marrow-derived mast cells (BMMC). These compounds also inhibited IKK activation, thereby preventing the degradation of IκBα and the subsequent activation of nuclear factor κB (NF-κB) [24]. Brown propolis demonstrated anti-inflammatory activity through an epigenetic mechanism, increasing the expression of miR-19a-3p and miR-203a-3p, and downregulating TNF-α mRNA and protein levels [25].

Numerous in vitro studies have provided mechanistic insights into the anti-inflammatory effects of honeybee propolis (HBP). Brazilian green propolis has been reported to inhibit inflammatory angiogenesis in murine models, markedly reducing NAG activity, a marker of activated macrophages and monocytes, at day 14 post-treatment [26]. OP6 (organic propolis) demonstrated anti-inflammatory activity by decreasing NF-κB activation and TNF-α release in macrophages, as well as by expressing a stable NF-κB-luciferase reporter gene [27]. Artepillin C, a low-molecular-weight single-ring phenol with two prenyl groups (3,5-diprenyl-4-hydroxycinnamic acid), is a major bioactive ingredient unique to Brazilian green propolis (BGP). It inhibits prostaglandin E2 and nitric oxide production by modulating key inflammatory signaling pathways such as nuclear factor kappa B [28]. In an in vivo model of chronic inflammation, green propolis extract suppressed cell migration without affecting collagen deposition. The anti-inflammatory effects included a reduction in the total number of inflammatory cells, including macrophages and neutrophils [29]. Multiple propolis extracts demonstrated significant anti-inflammatory effects in experimental models, such as thoracic capillary vessel leakage in mice, carrageenan-induced oedema, carrageenan-induced pleurisy, and acute lung injury in rats [30].

The assessment of antibacterial activity in propolis extracts typically relies on the determination of total phenolic content (TP) and flavonoid content (FP). However, TP and FP measurements do not consistently correlate with in vitro antimicrobial activity. While TP results in samples with the highest and lowest content were directly proportional to flavonoid content and antioxidant properties, these measures did not provide definitive information regarding antibacterial activity. Therefore, additional assays, such as Oxygen Radical Absorbance Capacity (ORAC) and antimicrobial tests, should be considered when establishing international quality standards for propolis [31-32].

Antioxidant Capacity of Propolis

To provide a clearer overview of the mechanistic evidence discussed in the previous sections, the major bioactive compounds, signaling pathways, and proposed anti-inflammatory and antioxidant mechanisms of honeybee propolis are summarized in **Table 1**.

Table 1. Anti-inflammatory and Antioxidant Potentials of Propolis

Effects	Active Compounds	Signaling Pathways	Mechanisms
Anti-inflammatory [13-32]	CAPE, flavonoids	NF-κB signaling	Suppresses transcription of pro inflammatory cytokines (IL-6, TNF-α, and IL-13) and neutrophil chemotaxis
	Artepillin C, flavonoids	ERK and MAPK	
	CAPE	PI3K/Akt pathway	Modulates cell survival and inflammatory signaling
	CAPE, flavonoids	Gene expression of LOX and COX	Inhibition of prostaglandin and leukotriene synthesis
	Flavonoids	Expression of IL-10	Enhances anti-inflammatory cytokine response
Antioxidant [33-48]	N. A	Free radical scavenging	Direct scavenging
		Lipid peroxidation	Inhibition of synthesis
		Endogenous antioxidant release	Stimulation of production
		Superoxide dismutase	Upregulation
		Mitochondrial stress	Mitigation

Phytochemical studies indicate that plants containing polyphenols with antioxidant properties are promising candidates for controlling and preventing various diseases [33]. In addition to polyphenols, propolis contains a diverse array of antioxidant compounds that neutralize free radicals in the body. The chemical composition of propolis varies considerably depending on climate and geographic location [34]. Administration of propolis has been shown to enhance antioxidant capacity by increasing antioxidant enzyme levels [35]. Previous studies have demonstrated that propolis can prevent oxidative stress-induced tissue damage by reducing the overproduction of malondialdehyde (MDA) and superoxide anion, as well as by

restoring the respiratory control ratio in mitochondrial tissue [36]. Consequently, propolis may improve glucose metabolism by mitigating mitochondrial oxidative stress [37]. Supplementation with Chinese propolis has been reported to inhibit tissue damage in patients with type 2 diabetes mellitus (T2DM) by increasing circulating botanical antioxidants, such as serum polyphenols and flavonoids, which were elevated following treatment [38]. Propolis has also been shown to alleviate oxidative stress in wound tissues. These protective effects underscore the potential of propolis as a wound-healing agent [39].

A limited number of in vivo studies have examined the effects of propolis on antioxidant status. In one study involving 47 healthy adults, daily intake of a powdered propolis extract for 30 days reduced free-radical-induced lipid peroxidation and increased superoxide dismutase activity. Specifically, there was a 23.2% decrease in malonaldehyde concentration, a degradation product of polyunsaturated fatty acid peroxidation, and a 20.9% increase in superoxide dismutase activity [40].

Multiple in vitro studies have evaluated the antioxidant capacity of propolis extracts. The biochemical composition and bioavailability of these extracts are significantly influenced by the choice of extraction solvent. Solvents with high ethanol concentrations yield extracts with higher antioxidant content. Polar solvents generally demonstrate greater antioxidant activity than nonpolar agents, although the specific type of propolis sample also plays a role [41]. One study found that tinctures and microcapsules containing red propolis extract exhibited antioxidant activity ranging from 77.12% to 98.06% at 50 µg/mL. This effect may be attributed to higher flavonoid levels, particularly in spray-dried microcapsules. Both tinctures and spray-dried microcapsules demonstrated similar antioxidant activity and outperformed freeze-dried microcapsules [42].

One study examined the protective effects of propolis against renal damage in diabetic rats. Diabetic rats exhibited increased renal malondialdehyde (MDA) content and decreased activities of glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT) compared to controls. Treatment with propolis significantly improved these parameters, with CAT activity restored at all tested doses, SOD at 200 and 300 mg/kg, and GSH at 300 mg/kg [43]. Propolis has also been shown to reduce oxidative damage induced by cerebral ischemia. In this context, mice treated with propolis extracts at 100 and 200 mg/kg intraperitoneally at four time points showed significant restoration of antioxidant enzyme activity, as well as decreased lipid peroxidation (LPO) and infarct volume compared to controls. Sensory-motor impairment and neurological deficits were also significantly ameliorated [44]. The free radical scavenging activity of propolis was further demonstrated in the 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical system, where the ethanolic extract of propolis (EEP) exhibited 70.96% scavenging activity at a concentration of 100 mcg [45].

The antioxidant activity of propolis is likely attributable to its high concentration of flavonoids and phenolic compounds, which are recognized as potent antioxidants [46]. These compounds have been demonstrated to scavenge free radicals that disrupt normal cellular metabolism. As a result, they protect lipids and other molecules, including vitamin C, from oxidative damage [47]. Active free radicals, along with additional factors, are implicated in cellular aging and the progression of conditions such as cardiovascular diseases, arthritis, cancer, diabetes, and neurodegenerative disorders, including Alzheimer's disease [48].

Therapeutic Applications

The therapeutic properties of propolis, attributed to its potent anti-inflammatory and antioxidant effects, have been extensively evaluated in both in vitro and preclinical studies. These effects are primarily attributed to flavonoids and natural phenols, which are considered low-toxicity, low-risk compounds with minimal side effects (**Figure 1**).

Figure 1. The therapeutic potentials of propolis. Propolis demonstrates significant therapeutic potential, exhibiting antibacterial, antiviral, cardioprotective, and anticancer properties.

Wound Healing Properties

Propolis enhances wound healing by reducing bacterial load and accelerating MMP-9-mediated inflammation [49]. It also reduces reactive oxygen species (ROS) activity in the wound bed, thereby facilitating tissue repair. Furthermore, propolis significantly influences collagen metabolism by increasing the levels of type I and type III collagens in tissues [50]. The combined reduction of ROS and increased collagen accumulation contribute to extracellular matrix balance and granulation tissue formation. Propolis also alters fibronectin metabolism by promoting the formation of a fibrous extracellular matrix and inhibiting its degradation [51]. One study evaluated biocellulose membranes containing propolis for wound treatment, concluding that the BC/propolis composite adsorbed propolis both on the surface and within its interstices, as demonstrated by SEM, X-ray diffraction, FT-IR spectroscopy, and thermogravimetric analyses. The presence of caffeic acid derivatives and flavonoids, along with notable antibacterial activity in the BC/propolis, was found to be dose-dependent [52]. Beyond wound healing, propolis has demonstrated in vitro antifungal activity against a broad spectrum of Candida albicans, C. glabrata, Trichosporon spp., and Rhodotorula spp., with all extracts inhibiting mycotic growth at various concentrations [53].

Antiviral Effects

Several studies have examined the clinical application of propolis in the treatment of viral infections. In the context of SARS-CoV-2, propolis-derived compounds

have been shown to downregulate TMPRSS2 and the anchoring protein ACE2, thereby limiting viral entry. Additionally, these compounds promote NF-κB and monocyte/macrophage immunomodulation, reduce pro-inflammatory cytokine overproduction, and decrease PAK1 activation, thereby collectively enhancing antibody production against SARS-CoV-2 [54]. Molecular docking studies indicate that flavonoid components of Egyptian propolis exhibit higher binding affinity for the COVID-3-CL protease and the spike protein than Avigan, hydroxychloroquine (HQ), and Remdesivir. Optimized liposomal formulations may further improve the delivery and cellular uptake of encapsulated propolis [55]. The antiviral activity of kaempferol (KF) and p-coumaric acid (p-CA) extracted from Brazilian propolis was evaluated against human rhinovirus (HRV)-2, HRV-3, and HRV-4 in HeLa cells using sulforhodamine B assay and real-time reverse transcription polymerase chain reaction. Results demonstrated that KF and p-CA inhibited HRV-3 infection when administered during the early post-inoculation period (0–4 h) and significantly reduced HRV-3 RNA replication. These findings suggest that KF and p-CA may impede viral entry and replication, potentially by modulating the expression of intercellular adhesion molecule-1 and interleukin-6 [56]. Another study assessed Hatay propolis as a treatment for Herpes Simplex Virus infections and concluded that both acyclovir and propolis inhibited HSV-1 replication after 24 hours of incubation. The synergistic effects of propolis with acyclovir were more pronounced against HSV-1 than HSV-2 [57].

Antibacterial Effects

Kelleher et al. reported that caffeic acid phenethyl ester (CAPE), a principal active component of propolis, exhibits anti-inflammatory effects in H. pylori-infected gastric epithelial cells. The inhibitory effect of CAPE against HpPDF may partially explain the observed inhibition of H. pylori by propolis [58]. Propolis extracts have been shown to synergistically enhance the efficacy of antibiotics, particularly those targeting cell wall synthesis, such as vancomycin and oxacillin. Propolis exerts multiple antibacterial mechanisms, including inhibition of cell division, disruption of microbial cytoplasmic membranes and cell walls, inhibition of bacterial motility, enzyme inactivation, bacteriolysis, and inhibition of protein synthesis [59]. Regarding parasitic infections, propolis inhibits the growth and adherence of Giardia duodenalis trophozoites and promotes their detachment. Clinical studies have demonstrated that propolis achieves cure rates of 52% to 60% in children and adults with giardiasis, compared to a 40% cure rate with conventional drugs [60]. Brazilian green propolis has been shown to improve immune function in aged mice, primarily through phenolic compounds such as artepillin-C. CAPE also demonstrates immunomodulatory activity by inhibiting cytokine production and T-cell proliferation, supporting the potential use of propolis in the treatment of allergic disorders, including asthma. Additionally, CAPE is implicated in the anti-gingivitis and skin-protective activities of propolis [61].

Cardioprotective Effects

Clinical observations indicate that daily administration of 226.8 mg of propolis for eight weeks may prevent deterioration of renal glomerular filtration function and elevated blood uric acid in diabetes [62]. The cardioprotective effects of propolis have also been investigated. In rat models, ISO treatment resulted in a significant decrease in antioxidant enzyme levels compared to controls. Pretreatment with propolis significantly increased the levels of SOD, GRx, GPx, and GST enzymes relative to ISO-only treated rats. Propolis pretreatment significantly reduced circulating levels of total cholesterol (TC), triglycerides (TGs), and very low-density lipoprotein cholesterol

(VLDL-C) while increasing high-density lipoprotein cholesterol (HDL-C) compared to the ISO-challenged group. Rats receiving propolis alone displayed normal cardiac muscle bundles without infarction or tissue damage, whereas ISO-treated rats showed myocardial structural changes, including coagulative necrosis, separation of cardiac muscle fibers, and infiltration of inflammatory cells [63]. In atherosclerotic lesions, propolis polyphenol extracts improved lipid profiles, decreased lesion area, and reduced TC, low-density lipoprotein cholesterol (LDL-C), triglycerides, and thiobarbituric acid-reactive substances [64]. The propolis component chrysin has been shown to inhibit plasma plasminogen activator inhibitor 1 (PAI-1) production, suggesting potential use in the treatment or prevention of thrombotic disorders [65].

Anticancer Potential

Multiple in vivo studies have demonstrated that certain propolis flavonoids inhibit the development of various cancers, including lung, oral, skin, esophageal, stomach, colorectal, prostate, and breast cancers [66]. Bioactive compounds such as genistein, quercetin, kaempferol, luteolin, chrysin, and apigenin inhibit cyclin activity, leading to cell cycle arrest. Galangin, genistein, and resveratrol exhibit antiproliferative activity against estrogen receptor-positive breast cancer cells [67]. CAPE and artepillin C possess antitumor properties through mechanisms such as suppression of cancer cell proliferation via anti-inflammatory effects, reduction of cancer stem cell populations, inhibition of specific oncogene signaling pathways, antiangiogenic activity, and modulation of the tumor microenvironment [68]. Ethanol extract of Chinese propolis (EECP) has been shown to inhibit cell proliferation, induce apoptosis, inhibit cell migration, regulate ANXA7 and p53 levels, downregulate NF-κB p65, inhibit its nuclear translocation, increase intracellular ROS, and decrease mitochondrial membrane potential [69]. Ethanol extract of propolis (EEP) restricts glioblastoma cell (C6 cell line) proliferation in vitro as effectively as temozolomide, while higher concentrations are required for cervical cancer cell lines (SiHa and CaSki) compared to cisplatin [70]. EEP also demonstrates selective toxicity against A549 cells relative to normal fibroblasts, induces G1-phase cell cycle arrest, endoplasmic reticulum stress, caspase activity, and apoptosis, and reduces mitochondrial membrane potential [71]. CA and, more notably, CAPE induce apoptosis and growth inhibition in a time- and dose-dependent manner in the breast cancer MDA-MB-231 cell line, with CAPE causing S phase cell cycle arrest [72]. CAPE has also been reported to protect neuronal cells against cisplatin-induced neurotoxicity, counteract oxidative stress, and decrease neuronal apoptosis and neuroinflammation [73]. Propolis treatment significantly increases BDNF expression in SH-SY5Y cells in a dose- and time-dependent manner, an effect abolished by PI3K inhibitor preincubation, indicating mediation via the PI3K signaling pathway [74]. Propolis inhibits cancer cell growth by inducing apoptosis in human melanoma cells or through reactive oxygen species production [75].

Discussion

This narrative review synthesizes evidence from database searches to demonstrate the in vitro anti-inflammatory and antioxidant properties of honeybee propolis, irrespective of type, origin, or geographical location. Mechanistic insights and therapeutic applications across various diseases are also discussed. Propolis types are classified according to geographical production areas, botanical sources, and chemical composition [76]. Temperate-zone propolis, commonly known as poplar propolis, is primarily derived from exudates of Populus tree buds. Birch propolis, unique to Russia,

differs from poplar propolis. Pacific propolis is found in Taiwan, Japan, and the Solomon Islands. Brazilian propolis includes green propolis from Baccharis dracunculifornia, brown propolis from Copaifera species, and red propolis from Dalbergia ecastophyllum [77]. The global chemical composition of propolis is determined by geoclimatic conditions and the botanical source of the substrate used by bees (exudates or pollen), resulting in distinct types and chemical characteristics. The concentrations of flavonoids, phenolic compounds, aromatics, and unidentified compounds contribute to the unique profiles of different propolis samples [78]. Propolis has been utilized in ointments and creams for wound healing, as well as in the treatment of burns, skin disorders, and ulcers. Additionally, various preparations have been applied to laryngological conditions, gynecological diseases, asthma, and diabetes [79].

Biological Activity of Propolis

Anti-inflammatory effects represent a primary pharmacological action of honeybee propolis. Evidence indicates that these effects are largely attributable to flavonoids and phenolic acids, which modulate inflammatory pathways such as NF-κB and COX-2. These compounds have been shown to reduce pro-inflammatory cytokines in both in vitro and in vivo models. The consistency of these findings suggests that propolis may serve as a natural anti-inflammatory agent [80]. However, variability in extraction methods and chemical composition remains a challenge, underscoring the need for standardized preparations to achieve consistent and clinically relevant outcomes.

The antioxidant capacity of propolis is a significant aspect of its pharmacological profile. It demonstrates robust antioxidant effects by scavenging free radicals and enhancing endogenous antioxidant defenses, including superoxide dismutase and glutathione peroxidase [81]. The antioxidant potential varies according to botanical and geographic origin, complicating direct comparisons across studies [82]. Given that oxidative stress is a common factor in chronic diseases, the antioxidant properties of propolis may have broad therapeutic implications. Prioritizing comparative analyses of different propolis types is essential to identify those with the most potent antioxidant profiles.

Therapeutic applications of propolis have demonstrated potential benefits across a range of conditions, including cardiovascular disease, diabetes, neurological disorders, and certain cancers [83]. These effects are primarily attributed to its anti-inflammatory, antioxidant, antimicrobial, and immune-modulating properties. However, most evidence is derived from preclinical studies [84]. Large-scale, rigorous clinical trials are necessary to establish the efficacy, safety, and optimal dosing of propolis in human populations.

Safety and Standardization

The safety profile of propolis has been widely investigated. In vitro assays show that propolis has no cytotoxic effects on immune cells in concentrations up to 100 μg mL−1 [85], suggesting it is well tolerated and safe [86]. Previous animal studies have established 2050 mg kg−1 as the LD50 of propolis in mice. The presence of flavonoids, major components of propolis, implies a low toxicity profile; for example, pinocembrin is not toxic at 1000 mg kg−1 in mice [87]. However, concerns exist about quercetin, which, at 100 mg kg−1, affects mitochondrial biogenesis in mice [88]. In humans, adverse effects generally emerge only at doses above 15 g day−1 [89]. Propolis should not be used in its crude form, as it may contain harmful contaminants. Therefore, solvents such

as ethanol, glycerol, chloroform, ether, acetone, or water must be used to remove hazardous substances and boost the yield of bioactive compounds. Propolis water extracts have 10 times lower phenolic content than ethanol extracts and retain propolis's strong flavor and aroma. Additionally, it contains allergenic components—including caffeic acid derivatives (e.g., 3-methyl-2-butenyl caffeate and phenylethyl caffeate), benzyl salicylate, and benzyl cinnamate. Therefore, for safety, propolis should be used only in processed, contaminant-free forms, and it is contraindicated in individuals with known allergies [90].

A major challenge in propolis research is the considerable variability in its composition, which is influenced by factors such as geographic origin, botanical source, season of collection, and extraction method. This heterogeneity undermines the reproducibility of research findings because different samples may contain distinct proportions of bioactive compounds, including CAPE, artepillin C, and flavonoids [91]. Consequently, the reported biological effects vary widely across studies, which complicates the establishment of consistent dosing guidelines. The lack of standardized extracts also raises significant concerns about safety and quality control, as impurities or fluctuating concentrations can affect both efficacy and the risk of adverse effects [92]. In clinical contexts, this variability limits the generalizability of study outcomes and hinders the development of propolis as a reliable therapeutic agent. Overcoming these challenges requires implementing standardized extraction protocols, comprehensive chemical profiling, and rigorous quality assurance measures to improve reproducibility and support the safe clinical application of propolis [93].

Limitations of the Review

The pharmacological potential of honeybee propolis is supported by its broad-spectrum activity and natural origin, which corresponds with the growing interest in complementary and integrative medicine. However, several methodological limitations warrant consideration. The narrative review approach, rather than a systematic framework, may lead to incomplete study selection and the omission of relevant publications, even when utilizing databases such as PubMed and Google Scholar. This methodology also introduces subjectivity in the interpretation and synthesis of evidence. Comparisons across studies are further complicated by variations in study design, participant populations, and biomarker assessments. Moreover, variability in propolis composition, absence of standardized dosing, and limited clinical evidence restrict the ability to draw definitive conclusions regarding its therapeutic applications. This review also lacks a formal quality assessment of the included studies and does not incorporate a quantitative meta-analysis to aggregate findings. Therefore, the synthesis should be regarded as a qualitative overview rather than a conclusive measure of effect size or clinical efficacy. Collaborative efforts are necessary to enhance quality control, conduct randomized controlled trials, and investigate potential synergy with conventional therapies. Addressing these gaps may support propolis's transition from a traditional remedy to a scientifically validated adjunct in contemporary pharmacotherapy. These limitations highlight the need for comprehensive systematic reviews, meta-analyses, and rigorously designed human studies to substantiate and extend current knowledge.

4. Conclusion

Honeybee propolis demonstrates notable anti-inflammatory and antioxidant properties, indicating potential biological activity. However, the majority of current evidence is derived from experimental and animal models, and robust clinical trials are

limited. Consequently, conclusions regarding its efficacy in human diseases remain preliminary, necessitating additional well-designed clinical investigations before definitive recommendations can be established. Clinical translation is impeded by methodological inconsistencies, the lack of standardized formulations, and the scarcity of large-scale clinical trials. Future research should prioritize rigorous study design, standardization of extraction and characterization protocols, and comprehensive evaluation of interactions with existing pharmacotherapies. Addressing these challenges will facilitate establishing propolis as a scientifically validated adjunct in integrative disease management

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Conflict of Interest:

The authors declare no conflict of interest.

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