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Propolis – therapeutic properties and application in modern medicine: A review

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Abstract
Background. Propolis (bee glue) is a natural resinous substance collected by honeybees, utilized since antiquity for its healing properties. Modern medicine increasingly employs this raw material as a complement to conventional therapies in the treatment of infections, metabolic diseases, and oral cavity disorders. **Aim**. The aim of this study is to review the current scientific literature regarding the chemical composition, pharmacological properties, and clinical applications of propolis, with particular emphasis on its antimicrobial, metabolic, and neuroprotective activities. **Material and methods**. A review of literature from 2000–2023 was conducted using PubMed, Scopus, and Google Scholar databases. In vitro, in vivo, and clinical studies regarding the biological activity of propolis were analyzed. **Results**. Propolis exhibits a broad spectrum of activity: bactericidal (including against drug-resistant strains and biofilms), antiviral (e.g., HSV, SARS-CoV-2), antifungal, and regenerative. New reports confirm its efficacy in dentistry (caries, periodontitis), glycemic control in type 2 diabetes, and its neuroprotective potential in neurodegenerative diseases. **Conclusions**. Propolis represents a promising raw material in integrative medicine. Its multidirectional action, combined with relatively low toxicity, justifies further clinical research and standardization efforts.

Key words: propolis, apitherapy, flavonoids, antibacterial activity, antioxidants.

1.Introduction
Another name for propolis is bee glue. The word "propolis" is derived from the Greek language, where pro means "before" and polis means "city" or "community". Loosely translated, it means "defense of the city" or "before the city," which perfectly reflects the protective function of this substance in the hive – it secures the bee colony against intruders, cold, and diseases [1].
The history of propolis use by humans dates back to antiquity. Egyptians used it in the process of mummification of corpses, appreciating its preservative and antiseptic properties [2]. In ancient Greece, Aristotle described in his History of Animals a substance that bees smear at the entrance to the hive, calling it "mitys". In turn, Hippocrates, the father of medicine, recommended the use of bee glue to treat skin ulcers and chronic wounds [3]. Mentions of propolis also appear in the writings of the Roman researcher Pliny the Elder, as well as in the Persian manuscripts of Avicenna, who described it as a substance that draws pus from wounds and soothes swelling. The 17th and 18th centuries in Europe brought a renaissance of interest in propolis, and during the Napoleonic Wars and World War II, it was widely used to dress soldiers' wounds in conditions where conventional medicines were unavailable [4].

It is a sticky and thick substance used by bees to line the interior of the hive, providing sealing, structural reinforcement, and defense against pathogens such as bacteria and fungi. It is produced from secretions and resins of trees and flowers, e.g., poplar, alder, ash, birch, oak, or coniferous trees with damaged bark. Depending on the type of plant from which the resin originates, propolis can take on various colors ranging from red, through greenish, to even brown. It is a substance highly sensitive to temperature fluctuations: at 15°C it is hard and brittle, at 36°C it becomes plastic, and at 70°C it liquefies. Bee glue does not dissolve in water, but it can be mixed with organic solvents, for example, alcohol. It is characterized by a distinct, balsamic odor [5].

Figure 1. Bees creating propolis to seal the hive. Artwork by: Julia Florek

2. Material and methods

This paper reviews the scientific literature concerning the biological properties and medical application of propolis. Medical databases (PubMed, Scopus, Google Scholar) were searched using the keywords: "propolis", "biological activity", "antibacterial", "dentistry", "diabetes", "neuroprotection". Original and review articles published mainly in the years 2000–2023 were included in the analysis, focusing on studies explaining the molecular mechanisms of propolis action and its clinical applications.

3. Results

3.1. Composition of propolis

The composition of propolis is variable and depends mainly on the type of plant from which the resin originates, the bee breed, the season, the location of the hive, and even the degree of environmental pollution. For example, in 2012, the stilbene 5-farnesyl-3'-hydroxyresveratrol was identified in Solomon Islands propolis, which is also present in Macaranga plants. These results suggest that Macaranga is the likely plant source of propolis from Kenya and the Solomon Islands [6]. Bee glue also undergoes modifications while being chewed by bees.

Although different honeybee species prefer different plants, the chemical profile of propolis produced by the same species is not always the same. Brazilian green and red propolis originate from Africanized A. mellifera, but this propolis is rich in prenylated phenylpropanoids and isoflavonoids, respectively. The differences result from the plants, namely B. dracunculifolia and Dalbergia ecastophyllum, which are used by bees as resin sources. Therefore, the variant chemical composition of propolis depends on the bees' preferences regarding botanical sources as well as bee species and varieties [7].

The impact of propolis collection time on its chemical composition and antibacterial activity was also investigated. Seasonal variability was observed between the concentration of vestitol, neovestitol, and isoliquiritigenin. The highest content of these components and antibacterial activity were recorded in the rainy season (period from January to May) [8]. Lignans as major chemical compounds in tropical propolis have attracted research interest worldwide. Over the last 12 years, researchers identified three lignans in Kenyan and Brazilian propolis [9].

It is estimated that up to 300 substances found in bee glue exhibit biological activity. Major components include plant resins (50-80%), waxes, polyphenols (14-16%), and pollen. Furthermore, it contains tannins, polysaccharides, essential oils, vitamins (B1, B2, B5, B6, C, D, E, provitamin A), minerals (calcium, manganese, magnesium, zinc, tin, iron, aluminum, silver, sodium, potassium, chromium, cadmium, titanium, vanadium, barium, silicon, copper), aldehydes, coumarin, sterols, fatty acids, as well as proteins, flavonoids, enzymes (α- and β-lactamase, α- and β-amylase, esterases, transhydrogenases) [10].

The great variability of the chemical composition of propolis poses the greatest challenge for modern pharmacology and Evidence-Based Medicine (EBM). Since propolis is not a single chemical compound but a complex mixture, its biological activity can vary drastically depending on the batch. To solve this problem, scientists strive to introduce strict standardization of extracts. Currently, several main chemical "types" of propolis are distinguished, which define its properties:

a. Poplar-type: Occurs in Europe, North America, and lowland regions of Asia. It is characterized by a high content of flavonoids (chrysin, galangin, pinocembrin) and caffeic acid esters (CAPE).

b. Brazilian green (Baccharis-type): Obtained from the Baccharis dracunculifolia plant. It is rich in p-coumaric acid derivatives, including artepillin C, which is responsible for its unique anticancer properties.

c. Brazilian red (Dalbergia-type): Occurs in mangrove forests, characterized by a high content of isoflavonoids (formononetin, vestitol), rarely found in other types [11].

Lack of standardization makes it difficult to compare clinical trial results and establish precise therapeutic doses, which is currently the main subject of discussion in the scientific community [12].

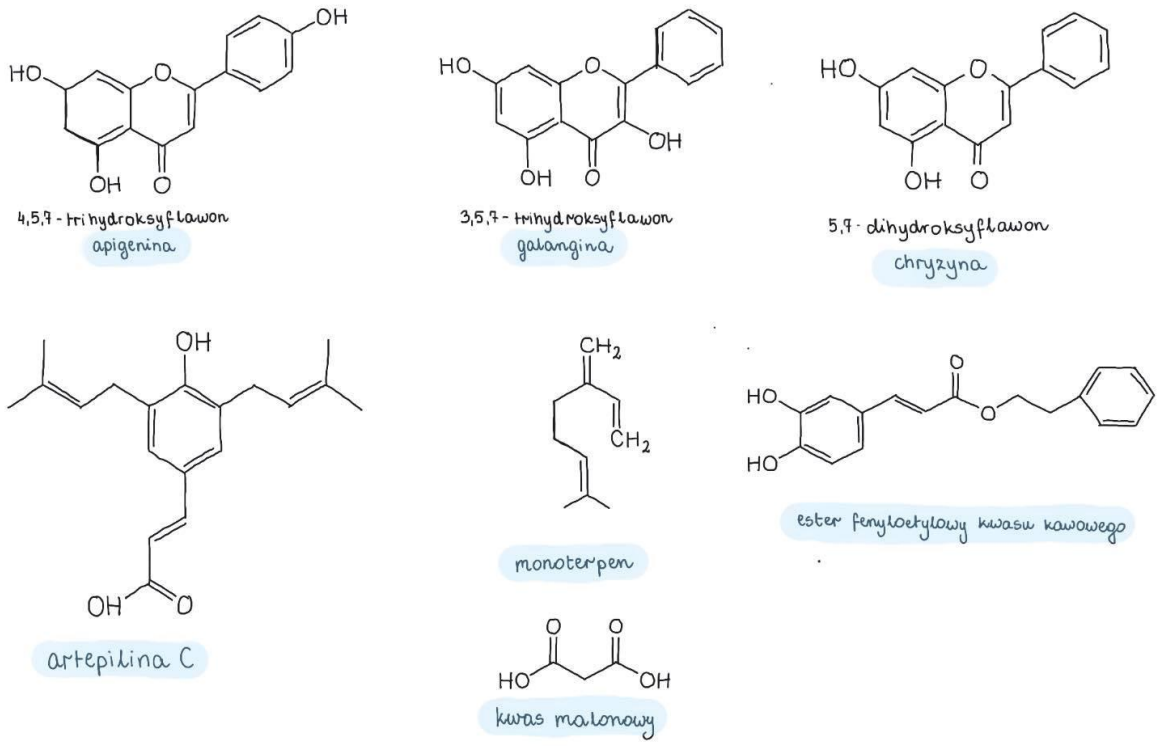

Figure 2. Key biologically active components of propolis. Artwork by: Julia Florek

3.2. Bactericidal action

Flavonoids (natural, water-soluble chemical compounds) occurring in propolis, such as apigenin, galangin, chrysin, quercetin, pinocembrin, or pinostrobin, are its main components. They function as pigments, antioxidants, and natural insecticides and fungicides, protecting against attacks from insects and fungi. Most of them are pigments accumulated in the surface layers of plant tissues, giving intense color and limiting the harmful effects of ultraviolet radiation. Flavonoids are based on the 2-phenylchroman or 3-phenylchroman (called isoflavone) skeleton, with most flavonoid types (except catechins and anthocyanidins) containing a flavone or isoflavone skeleton, with a ketone group at position 4. Flavonoids differ from each other in the number and type of substituents, with differences between compounds in individual classes usually resulting from the different structure of only one outer ring. Most flavonoids contain hydroxyl groups, one or more of which are usually linked to a sugar molecule, forming glycosides. The amount of flavonoids is used as a criterion for assessing the quality of temperate propolis [13].

Flavonoids have a broad spectrum of biological properties, such as antibacterial, antiviral, and anti-inflammatory effects [14]. In Pacific propolis, scientists identified many prenylated flavanones that showed strong antimicrobial activity because the lipophilic prenyl group can rapidly damage the cell membrane and cell wall function [15]. Propolis samples differ in flavonoid content depending on origin. In an analysis of 38 samples collected from different regions in Croatia, it was shown that the highest degree of B. subtilis growth inhibition is exhibited by samples with the highest pinocembrin content. Temperate region propolis is rich in flavonoids without a substituent in the B ring, such as chrysin, galangin, pinocembrin, pinobanksin.

An important antibacterial compound identified in green propolis is artepillin C, a 3,5-diprenyl-4-hydroxy derivative of cinnamic acid. High activity of this compound was found against B. cereus, E. aerogenes, and Arthroderma benhamiae. Studies conducted in Brazil by Veiga et al.

show a higher concentration of artepillin C in ethanolic extracts of propolis compared to hexane extracts. These extracts also showed high antibacterial activity against MRSA S. aureus [16]. In studies against the anaerobic bacterium Porphyromonas gingivalis, it was found that artepillin C has a bacteriostatic effect [17]. Artepillin C also exhibits anti-inflammatory activity with modulation of NF-kappaB and inhibition of PGE(2) and NO [18].

Brazilian red propolis is a new type of propolis that has attracted wide attention. Three dihydrochalcones 72–74, which are considered characteristic of Populus tacamahaca bud exudates, were found for the first time in Canadian samples. Some flavans 75-78 with high cytotoxic activity were also identified in Chinese and Mexican propolis [19]. Brazilian green propolis, on the other hand, is rich in phenols (phenylpropanoids) i.e., p-coumaric acid benzyl ester, pentylenyl ester, and cinnamic acid having a concurrent effect on antimicrobial activity. Ethanolic extract of propolis containing high concentrations of kaempferide, artepillin C, drupanin, and p-coumaric acid showed antioxidant and antibacterial activity against S. aureus, S. saprophyticus, Listeria monocytogenes, and E. faecalis [20].

Volatile substances constitute about 10% of propolis composition; the most important of them, exhibiting valuable biological activity (antioxidant, antimicrobial), are terpenoids. A monoterpene was identified in Brazilian propolis along with three sesquiterpenes that exhibit valuable biological activities [21]. Terpenoids are also responsible for the characteristic resinous smell and the possibility of distinguishing good quality propolis from a cheaper substitute.

The bactericidal action of propolis has been confirmed in numerous studies. Despite the diverse chemical composition depending on the aforementioned factors, all propolis types studied so far show similar antibacterial activity. To assess the sensitivity of a given bacterium to propolis, researchers often use two methods: disc diffusion and well diffusion. In the first, the size of the bacterial growth inhibition zone around a disc soaked in a specific amount of propolis is measured, and in the second method, reservoirs filled with propolis are used. According to the applicable rule, propolis extract shows a positive effect on bacteria when the zone around the disc is larger than 6 mm. Studies of Ethanolic Extract of Propolis (EEP) showed that its activity is highest against Staphylococcus aureus (Gram-positive non-spore-forming bacterium) and Bacillus cereus (Gram-positive spore-forming bacterium). MIC in their case was 0.125-0.5 mg/ml. EEP did not, however, show an effect on the growth of Gram-negative bacteria, such as E. coli and Pseudomonas aeruginosa even at a concentration higher than 1 mg/ml. The reason may be the specific structure of the outer membrane of Gram-negative bacteria and the production of hydrolytic enzymes by microorganisms, decomposing the active substances of propolis [22].

A crucial aspect of the antibacterial action of propolis is its ability to destroy bacterial biofilm. Biofilm is a complex multicellular structure in which bacteria are surrounded by an extracellular matrix produced by themselves, protecting them from antibiotics and the host's immune system. Studies have shown that ethanolic extracts of propolis (EEP) effectively inhibit biofilm formation of bacteria such as Staphylococcus aureus, Enterococcus faecalis, and Pseudomonas aeruginosa. This mechanism involves disrupting Quorum Sensing (QS) intercellular communication, which is essential for coordinating biofilm formation and virulence factor production [23]. Furthermore, propolis acts directly on the bacterial cytoplasmic membrane. Components such as galangin and pinocembrin cause a change in membrane potential, leading to increased cell membrane permeability, leakage of potassium and phosphate ions, and consequently to bacterial cell lysis [24]. Propolis also affects the inhibition of nucleic acid and bacterial protein synthesis by blocking cell division and inhibiting DNA-dependent RNA polymerase enzyme [25].

Another report of greater activity of propolis against Gram-positive bacteria than negative ones comes from the study by Torres et al., who compared two ethanolic extracts of propolis (EEP)

collected from stingless bee species, Melipona quadrifasciata and Tetragonisca angustula. The study showed greater activity of geopropolis extracts against Gram-positive bacteria (Staphylococcus aureus MSSA and MRSA, Enterococcus faecalis) than Gram-negative (Klebsiella pneumoniae, Escherichia coli). Of the two analyzed geopropolis samples, the Melipona species was more effective [26].

Raw propolis cannot be used directly in analysis or treatment. Due to the complex composition, the solvents used for its extraction have a significant impact on propolis activity. Many bactericidal substances dissolve in alcohol or alcohol and water, and some in other solvents. The antibacterial effect of propolis is directly proportional to its concentration. Devequi-Nunes et al. found approximately two times higher concentrations of phenolic compounds in ethanolic extracts of brown, green, and red propolis than in extracts obtained by supercritical extraction. Simultaneously, flavonoid levels were higher in ethanolic extracts of green and red propolis, and lower in brown propolis, compared to supercritical extraction [27]. The results of studies also depend on the bacterial strains used for them, due to different drug resistance and different virulence factors. The greatest sensitivity to the action of ethanolic propolis extract (EEP) is shown by: staphylococci, streptococci, pneumococci, tubercle bacilli, aerobic and anaerobic bacilli, corynebacteria, actinomycetes, spirochetes, viruses pathogenic to animals and humans (influenza, foot-and-mouth disease, encephalitis, herpes) and to plants.

It should be noted that the diversity of chemical composition gives propolis an additional advantage as an antibacterial agent. The combination of many active ingredients and their presence in different proportions prevents the occurrence of bacterial resistance. In a review paper by I. Przybyłek and T. M. Karpiński, 600 MIC values derived from studies on the antibacterial action of propolis were compiled. Both in the case of Gram-positive and Gram-negative bacteria, MIC values were lowest for EEP originating from Turkey and Oman. These countries are classified as Middle Eastern countries, which are famous for the fragrance trade. Local plants used for the production of fragrances are probably also a source of resin for bees producing propolis. No studies have been conducted so far on the impact of the degree of urbanization of the country on the composition and activity of propolis [28]. Additionally, it has been shown that simultaneous administration of bee glue and certain antibiotics enhances their action [29]. This is a significant fact, as it may lead to a reduction in antibiotic dosage and, consequently, minimization of their side effects.

Ethanolic extracts from four propolis samples (E1–E4) from Manaus (Brazilian Amazon) were analyzed using HPLC/DAD/ESI–MS/MS and GC/EIMS. Major components of E2 and E4 were analyzed using NMR (1H and 13C) and ESI/MS/MS. Polyprenylated benzophenones: 7-epi-nemorosone, 7-epi-clusianone (major components of E4), xanthochymol, and gambogenone (major components of E2), form a chemical profile not previously reported for Brazilian propolis. Extracts E2 and E4 were highly active against cariogenic bacteria Streptococcus mitis, Streptococcus mutans, and Streptococcus salivarius. E2 was more active than E4, likely due to the higher content of 7-epi-nemorosone, while the latter was richer in dihydroxylated compounds [30].

Since beeswax and resins are hydrophobic substances, the efficacy of lipases in reducing fatty acid levels in propolis extract was investigated. Studies conducted in Korea proved that the use of lipases helps in the extraction and isolation of active propolis compounds. This may mean that it will start to be used more widely. The participation of lysozyme TL IM increases antibacterial activity against Staphylococcus epidermidis and Propionibacterium acnes [31].

3.3. Antiviral action

Virucidal action has also been scientifically confirmed. It was found that when propolis was applied topically three times a day, it helped heal herpes faster than no treatment. Researchers discovered that propolis ointment not only reduced the amount of herpes virus present in the human body but also protected the body against the appearance of subsequent herpes outbreaks.

One of the biologically active substances of Brazilian propolis - malonic acid - showed significant anti-HIV activity (EC50 <0.1 μg/ml, TI >186) and was modified to develop stronger anti-AIDS agents [32].
Molecular simulations show that flavonoids in propolis and honey (e.g., rutin, naringin, caffeic acid phenethyl ester, luteolin, and artepillin C) can inhibit viral spike fusion in host cells, virus-host interactions that trigger a cytokine storm, and viral replication. Similar to the potent antiviral drug remdesivir, rutin, ethanolic extract of propolis (propolis liposomes) inhibited non-structural SARS-CoV-2 proteins in vitro, and these compounds together with naringin inhibited SARS-CoV-2 infection in Vero E6 cells. Propolis extracts delivered by nanocarriers show better antiviral activity against SARS-CoV-2 than ethanolic extracts. Subsequently, hospitalized COVID-19 patients receiving green Brazilian propolis or a combination of honey and Nigella sativa showed earlier viral clearance, recovery, hospital discharge, and also lower mortality than counterparts receiving standard care. Thus, the use of bee products as adjuvant treatment for COVID-19 may induce beneficial effects [33].

3.4. Application in dentistry and oral hygiene

The oral cavity is a habitat for over 700 species of bacteria, many of which are responsible for the development of caries, periodontal diseases, and halitosis. Propolis, due to its antibacterial and anti-inflammatory properties, finds wide application in modern dentistry. The key cariogenic pathogen is Streptococcus mutans, which has the ability to synthesize insoluble glucans from sucrose, enabling it to adhere to tooth enamel. Clinical and laboratory studies have confirmed that propolis extracts (especially those rich in apigenin and tt-farnesol) significantly inhibit the activity of glucosyltransferase – the enzyme responsible for this process, thereby reducing dental plaque accumulation by as much as 40-60% [34],[35].
In the case of periodontal diseases (periodontitis), propolis is effective in eliminating anaerobic bacteria Porphyromonas gingivalis and Prevotella intermedia, which are the main etiological factors of gum inflammation. Rinses containing propolis used as a supplement to standard oral hygiene lead to a significant reduction in the gingival bleeding index and reduction of periodontal pocket depth [36]. Additionally, propolis is used in the treatment of dentin hypersensitivity. This mechanism involves the obliteration (closing) of open dentinal tubules by resin components of propolis, which blocks tubular fluid flow and reduces pain sensation under thermal or chemical stimuli. Comparative studies have shown that the effectiveness of propolis in this regard is comparable to commercial preparations containing fluoride [37].

3.5. Collagen synthesis stimulating action

Propolis exhibits positive collagen metabolism in the wound during the healing process by increasing the collagen content in tissues. The study demonstrated the use of propolis as an alternative therapy for wound healing to support wound closure, especially in conditions such as diabetic foot ulcers. A clinical study conducted on patients with acne using ethanolic propolis extract showed its high efficacy in treating acne vulgaris [38].

3.6. Antioxidant action

Flavonoids also exhibit antioxidant activity due to the ability to scavenge free radicals. Thus, they delay aging processes, lower arterial blood pressure by dilating blood vessels and improving their elasticity. They also inhibit cholesterol deposition. Scientific studies show the ability to scavenge free radicals by components of bee glue. Antioxidant activity was determined based on the assessment of their antiradical activity in the DPPH test and the ability to chelate Fe2+ ions [39].

3.7. Anticancer action

Caffeic acid phenethyl ester (CAPE) contained in propolis is a natural NF-kappaB inhibitor possessing anticancer properties. Studies have demonstrated its immunostimulatory,

antiangiogenic, and cytotoxic properties against cancer cells. Many in vitro and in vivo tests confirmed the strong action of CAPE, e.g., against human colon adenocarcinoma HT-29 cells. Attention is drawn to the enhancement of the anticancer effect of drugs i.e., doxorubicin, cisplatin by CAPE, based on the reduction of cancer cell survival by up to 45 and 34% compared to drugs used alone. The main mechanism of CAPE's anticancer action is the induction of apoptosis in mutated cells [40]. There are two signaling pathways responsible for stimulating apoptosis. The first is external signaling via proteins from the TNF family, which bind to their receptors. One such molecule is the TRAIL ligand, which has five receptors, but only two of them: TRAIL-R1 and TRAIL-R2 have death domains (DD), and thanks to them, the ability to induce apoptosis. The second pathway is internal signaling, called the mitochondrial pathway, which is regulated by the balanced expression of pro- (Bax, Bid, Bak, AIF) and anti- (Bcl-2, IAPs, kinase PKB/AKT) apoptotic proteins. These proteins affect mitochondrial membrane permeability and consequently the release of cytochrome c, essential for the formation of the apoptosome - the structure initiating apoptosis. Ultimately, both pathways meet at the site of activation of specific proteases - caspases, which cause cell death via hydrolysis of key structural and functional proteins. Studies conducted in Germany showed almost complete regression of a brain tumor caused by neurofibromatosis type II in tested mice after using CAPE. It was also proven that it causes inhibition of cancer cell growth in the course of neurofibromatosis type I. In the same studies, a promising solvent capable of solubilizing caffeic acid phenethyl ester was found, which additionally acts synergistically with it [41].

Flavonoids and their derivatives, in addition to the properties described above, also exhibit cytotoxic effects on cancer-transformed cells. Studies have demonstrated this activity in vivo and in vitro against various cancer cell lines, both animal and human (human fibrosarcoma HT-1080 cells, lung adenocarcinoma A549, cervical Hela, murine colon cancer L5-26, and melanoma B16-BL6 and others). An example is the blocking of angiogenesis induced by vascular endothelial growth factor - VEGF, a mechanism often used in cancer progression. Another example is the stimulation of the expression of proteins such as: p53, p21, p27, responsible for cell cycle arrest, mainly in the G2 phase. The obtained cytotoxic activity values were in the range of IC50 = 3.4-10 μg/ml and within ED50 = 2.3-205.0 μg/ml. Multidirectional action of flavonoids on cancer cells has been demonstrated: antioxidant, antiproliferative, cell cycle blocking, angiogenesis inhibiting, apoptosis inducing, as well as inactivating carcinogens and reducing anticancer drug resistance [42]. Scientific reports from Taiwan show very strong antiproliferative and cytotoxic effects of propolins B, D, E, F against six cell lines (A2058 human melanoma line, B16F10 murine melanoma line, MCF-7 human breast cancer line, HepG2 human hepatoblastoma cell line, Hep3B human liver cancer cell line, and HT-29 human colon adenocarcinoma cell line) [43],[44],[45],[46].

Studies conducted in Italy show that propolis exhibits anticancer activity also against androgen-resistant prostate malignancies (DU145 line). These properties are the result of the cytotoxic action of propolis leading to apoptosis and necrosis [47]. Scientists from Turkey conducted in vitro studies of the effect of propolis on the MCF-7 breast cancer cell line. In immunocytochemical studies using appropriate antibodies directed against caspase 6, 8, and 9, they proved that propolis solution added in specific concentrations to cell culture stimulates the cell to apoptotic death [48]. Studies on the anticancer activity of propolis compounds belonging to groups other than those mentioned above showed the strongest cytotoxic effect of prenylated aromatic acids (artepillin C), isoflavans (mucronulatol), and prenylated benzophenones (nemorosone and plukenetione). Studies also showed a reduction in the degree of cancer metastasis to various organs under the influence of the tested substances (83.0%), as well as inhibition of cancer cells (90%) compared to control cultures [49]. Mechanisms underlying the anticancer properties of ARC (artepillin C) include induction of apoptosis, cell cycle arrest, and inhibition of p21-activated kinase 1 (PAK1), a protein characterized by many human

diseases/disorders, including COVID-19 infection [50]. When artepillin C was applied to human and murine malignant tumor cells in vitro and in vivo, it exhibited cytotoxic activity, and cancer cell growth was clearly inhibited. It was found that artepillin C causes significant damage to solid tumor and leukemic cells via MTT assay, DNA synthesis assay, and morphological observation in vitro. Following intratumoral injection of 500 micrograms of artepillin C three times a week, apoptosis, abortive mitosis, and necrosis were identified in histological observation. In addition to tumor growth inhibition, there was an increase in the CD4/CD8 T cell ratio and the total number of Th lymphocytes [51].

3.8. Antifungal action

Antifungal activity of propolis finds clinical application especially in gynecology. The main problem of today's medicine is the already mentioned growing resistance of microorganisms to chemotherapeutics. This also applies to common fungal infections. Research papers indicate that propolis has both fungicidal and fungistatic properties. Millet-Clerc and co-authors found that propolis shows significant antifungal activity against Trichophyton and Microsporum, especially in the presence of 5% propylene glycol [52]. Due to the fact that propylene glycol is completely non-toxic and constitutes a valuable base as an amphiphilic solvent for medicinal substances, preparations in which propylene glycol appears alongside propolis are often found. In turn, Fernandes Junior and colleagues analyzed the antifungal effect of ethanolic extracts of propolis against various fungal species of the genus Candida, including C. albicans, C. parapsilosis, C. tropicalis, and C. guilliermondii resistant to commonly used fluconazole and nystatin. 98% of the tested species were characterized by sensitivity to propolis at concentrations below 5% [53]. In turn, Lori noted that in in vitro studies, propolis used at concentrations of 5 or 10% prevents the growth of Trichophyton verrucosum [54].

3.9. Hepatoprotective action

Nakamura and co-authors proved that propolis allows for significant improvement in the early stages of viral hepatitis. The in vivo study was conducted on rats administered a strong hepatotoxic agent - α-naphthylisothiocyanate (ANIT) in a single dose of 75 mg/kg b.w. The first group of rats was administered ethanolic extract of Brazilian propolis at doses of 25, 50, 100 mg/kg b.w. The second group was administered vitamin E, and the third, control group, only the vehicle. In the control group, cholestasis developed and hepatocyte damage progressed, concentrations of total cholesterol, phospholipids, triglycerides, lipid peroxides, and reduced glutathione increased. In the first group receiving BEEP at a dose of 50 mg/kg b.w., no hepatocyte damage or cholestasis was observed; also, changes in concentrations of tested compounds present in serum were smaller than in the control group. Other concentrations used (25, 100 mg/kg b.w.) were not as effective. In the second group, vitamin E prevented liver cell damage, but did not inhibit cholestasis. Changes in maintaining normal levels of enzymes and metabolites present in serum were also greater than in the case of propolis use [55].

3.10. Action in metabolic diseases and diabetes

In recent years, there has been growing interest in the effect of propolis on metabolic parameters, particularly in the context of type 2 diabetes. Systematic reviews and meta-analyses of clinical trials suggest that propolis supplementation may support glycemic control. The hypoglycemic mechanism of propolis is multi-track: it involves inhibition of glucose absorption in the intestines through inhibition of α-amylase and α-glucosidase enzymes, increasing peripheral tissue sensitivity to insulin, and protecting pancreatic beta-cells against oxidative stress [56]. Studies on animal models and clinical trials involving patients with type 2 diabetes have shown that regular intake of propolis leads to a reduction in fasting glucose levels and glycated hemoglobin (HbA1c) levels, which is a key marker of long-term diabetes control [57]. Furthermore, propolis exerts a beneficial effect on the lipid profile, lowering total cholesterol, LDL fraction, and triglyceride levels, while simultaneously raising the level of "good" HDL

cholesterol. This action is attributed mainly to the presence of flavonoids, which regulate lipid metabolism through the influence on PPAR-γ nuclear receptors [58].

3.11. Neuroprotective action

Oxidative stress and chronic inflammation are key factors in the pathogenesis of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, or multiple sclerosis. Polyphenolic compounds contained in propolis, including pinocembrin, caffeic acid, and chrysin, demonstrate the ability to cross the blood-brain barrier, making them potential candidates in neuroprotection. In vivo studies have shown that propolis protects neurons against excitotoxicity induced by glutamate and against ischemic damage (e.g., after stroke). This mechanism relies on inhibiting lipid peroxidation in the brain, increasing the activity of antioxidant enzymes (SOD, catalase), and modulating signaling pathways related to neuronal apoptosis [59]. In Parkinson's disease models, it was shown that propolis extract prevents the loss of dopaminergic neurons in the substantia nigra, suggesting its potential in slowing down the progression of this disease [60].

3.12. Toxicology of propolis

Considering the fact that propolis has been used for years in folk medicine, it seems to be a safe raw material [61],[62]. However, in people with immune system hypersensitivity, propolis may trigger an allergic reaction. Particular caution should be exercised by people who have previously experienced allergies to other bee products, such as honey or bee pollen. In the case of this group of people, local application of propolis may cause: redness, swelling, and itching of the skin, while oral administration - swelling of mucous membranes, nausea, and a drop in blood pressure. Hausen and colleagues described nearly 200 cases of allergic dermatitis caused by propolis. The substance responsible for the occurrence of contact allergy incidents appears to be 1,1-dimethylallyl caffeic acid ester [63]. The second allergen is likely a flavonoid – tectochrysin. However, this compound has much weaker sensitizing properties [64].

4. Discussion

Propolis is a raw material with an extremely broad therapeutic potential, resulting from the synergistic action of hundreds of compounds contained within it. However, this same diversity poses the greatest challenge for modern pharmacology. Great variability in chemical composition depending on geographical and botanical origin complicates the standardization of preparations. For example, European (poplar) propolis differs diametrically from Brazilian (green or red) propolis, which affects differences in biological activity. Lack of standardization makes it difficult to compare clinical trial results and establish precise therapeutic doses. The toxicological aspect must also be remembered. Although propolis is a natural substance, it can induce allergic reactions, especially in individuals allergic to bee products. The main allergens are caffeic acid esters. Nevertheless, the safety profile of propolis is assessed as high compared to many synthetic drugs.

5. Conclusions

Propolis exhibits scientifically proven antibacterial, antiviral, and antifungal activity, being an effective adjunctive agent in treating infections, including those caused by drug-resistant strains. New areas of propolis application, such as dentistry, diabetology, and neurology, open perspectives for cheap and accessible adjunctive therapies in lifestyle diseases. Further research on the standardization of propolis extracts is necessary to enable their broader implementation into official medicine (EBM).

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