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The Chemical Compositions and Antimicrobial Activity of Propolis: A Review Article

Mahmood A. Al-Azzawi [1], Israa Sami Hadi[2], Israa Mamdooh Subhi [3], Ali A. Al-fahham[4]

[1] Department of Forensic Science, College of Science; Al-Karhk University of Science, Baghdad, Iraq

[2] College of Pharmacy, University of Kufa, Najaf, Iraq

[3] Department of Nursing Techniques, Institute of Medical Technology-Baghdad, Middle Technical University, Baghdad, Iraq

[4] Faculty of Nursing, University of Kufa, Iraq

ABSTRACT: The researchers have increasingly used propolis in recent alternative medicine studies, focusing on its biochemical structure, in addition to its antibacterial, antifungal, antiviral activities. The structure of biochemical components in propolis differs based on the species of the bees, country, plant source, and ecological factors. Commonly, propolis include organic compounds, pollen, essential oils, beeswax, and lipid. The organic components include aromatic acids, amino acids, steroids, coumarins, terpenoids, terpenes, polyphenols, phenolic compounds, and flavonoids. Clinical trial evidences point out that propolis and its compounds have antibacterial, antifungal, and antiviral activities. Studies have investigated the mode of action against pathogenic microbes. studies have exhibited that propolis may exert synergistic effect with antimicrobials, allowing the intake of minimal doses of antimicrobials and maximal activity against pathogenic microbes. This review highlights the chemical composition and antimicrobial activity of propolis, focusing on mode of action and clinical uses.

1. INTRODUCTION

Propolis is a bee gum: an adhesive, resinous material sourced from plant exudates— typically buds, leaves and flower— and later transformed by bee secretions and wax. Honeybees (*Apis mellifera*) produce propolis from tree sap specifically obtained from needle-leaved trees or evergreens. The final propolis product is created when bees combine the sap with their own salivary secretions and beeswax; it emerges as a dark-green substance that is used by bees to construct their hives. (Simone-Finstrom et al., 2017).

More than 500 compounds have been identified in propolis, ranging from flavonoids and phenolic compounds to terpenes, terpenoids, coumarins, and steroids. It is also a rich source of phytochemicals that include amino acids and aromatic acids along with essential oils and various vitamins (such as Zinc and iron). Propolis gathers its raw materials from different plant sources which imbues it with diverse plant pigments as well as compound varieties— based on the bee species, seasonality where it's collected, botanical origins, and geographical location details (Zullkiflee et al., 2022)

The medicinal properties of propolis are quite astounding. From being antimicrobial and cytotoxic to scavenging free radicals, propolis does it all naturally. This has led to its emerging use as a supplement in health-promoting and disease-preventive drinks— a wide scope for natural applications. For many years, propolis has been known for various reasons such as anti-septic, anti-mutagenic, anti-hepatotoxic... The list goes on including its use for cytotoxic activity against different bacteria which was further enhanced by synergism exhibited among its compounds. In vitro antibacterial activity: documented against both Gram-negative and Gram-positive bacteria with an interesting data of synergism presented between pinocembrin and galangin flavonoids— major components found in propolis (Almuhayawi, 2020).

The antibacterial effect of propolis operates at a molecular level: it triggers physicochemical transformations within the bacterial cell wall upon contact with diverse components contained in propolis, thereby increasing permeability at the cellular surface. This is achieved through a sophisticated biological process where intramolecular hydrogen bonds are formed first within the bacteria due to ingestion of propolis ethanolic extract (PEE). Antimicrobial agents then create hydrophobic interactions with either the cell wall or cytoplasmic membrane. Additionally, propolis has also demonstrated efficacy in combating bacterial biofilms (Queiroga et al., 2023).

This review highlights the chemical composition and antimicrobial activity of propolis, focusing on mode of action and clinical uses.

CHEMICAL COMPOSITION

Over 300 chemical components of propolis have been identified with the evolution of research. The most important biological active compounds are essential oils plus sugar and vitamins, steroids, coumaric acid, apigenin, amino acids, benzoic acids, naringin and gallic acid among many more such as phorbol and saponin. An interesting component worth mentioning would be caffeic acid phenethyl ester (CAPE), not forgetting caffeic acid itself or carboxylic acids (Devequi-Nunes et al., 2018).

The composition of propolis can differ greatly based on various factors such as the location of the hives, season and vegetation. This variability poses a challenge for standardization and quality control. Apart from plant resins and beeswax, propolis also includes pollen but interestingly enough, widely cited sources seem to provide this information without any experimental basis. These misleading quotations have never been traced back to any actual study that quantified, for instance, the amount of pollen present in propolis. In addition, the amount of pollen in propolis, approximately 5%, is a gross overestimation as pollen is a contaminant in propolis derived from wind-borne grains and also from the laborer bees. There is no standard composition for propolis; it differs significantly not only between types but also between regions (Salatino, 2022).

Propolis of the same kind can vary greatly in their total phenolic content. The different classes of phenolic compounds are illustrated in Figure 1. Phenolic compounds like Lignans, tannins, coumarins, benzophenones, and quinones are naturally sourced from roots, bark, leaves— even fruits and vegetables. Bankova et al. have extensively studied the relationship between chemical constituents in propolis and their plant sources; hence it is expected that different types of propolis with different chemical constituents will have varied biological active compounds as well as bioactivities and pharmaceutical activities. For instance, natural phenolic compounds play important roles for plants by protecting them from sunlight and herbivorous animals along with microbial pathogens; similarly flavonoids other than exhibiting anti-HIV activity show plasmodicidal anti-tumoral anti-inflammatory anticancer antibacterial antioxidant also acts. (Hosseinzadeh et al., 2005).

The biologically active components in plant resin are flavonoids, with properties that exhibit anti-cancer, anti-inflammatory and anti-microbial activities. The major classes of flavonoids include Chalcone, flavan-3-ol, flavanonol, flavanol, isoflavone, flavan, flavanone and flavone as depicted in figure 2. When considering antibacterial activity, it is noted that flavonoids are significant active components— chalcones demonstrate the highest antibacterial activity among the classes of flavonoids along with flavan-3-ols and flavanes; specific structural details (e.g., prenylation and hydroxylation) could contribute to enhancing their antibacterial efficiency (Bankova et al., 2000; Rubin et al., 2011).

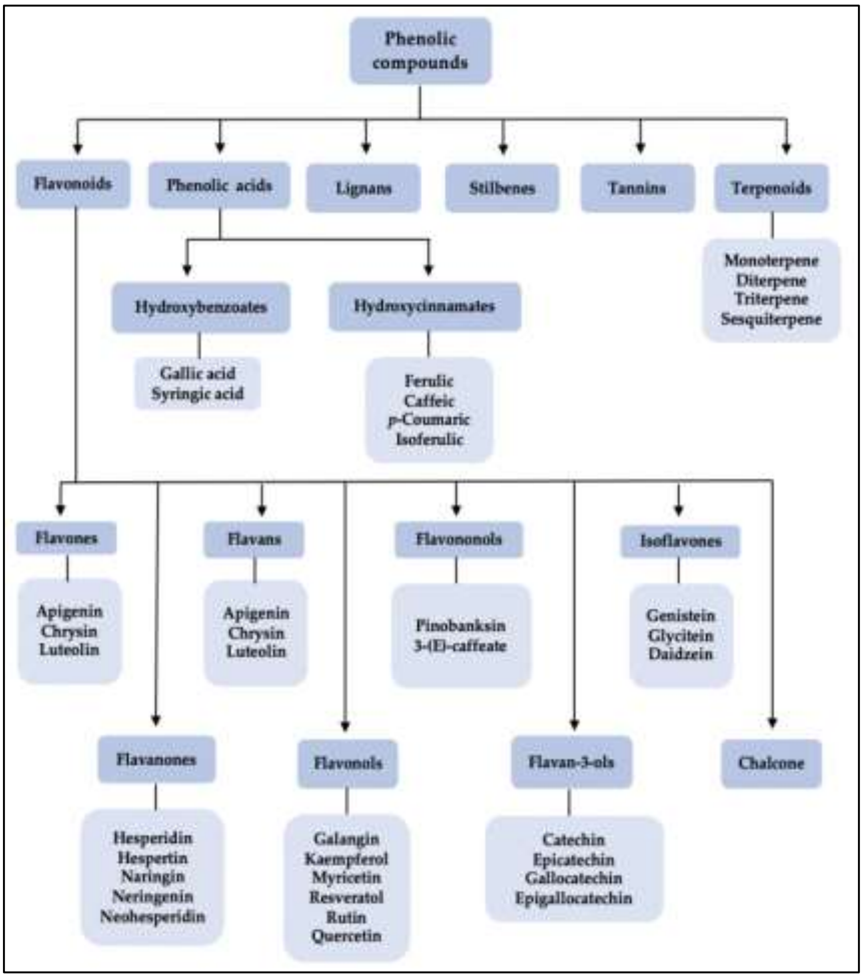

Figure 1. Classification of phenolic compounds

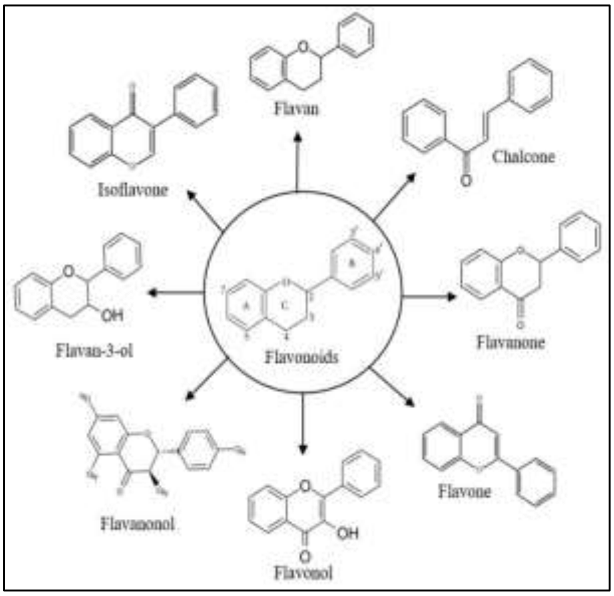

Figure 2. Classification and chemical structure of flavonoids compounds

ANTIBACTERIAL ACTIVITY

In the period leading up to 2019, reports indicated that the number of research works on antibacterial activity of propolis and its specific microorganism species had reached this number : Staphylococcus epidermidis: 16; Streptococcus mutans: 17; Klebsiella pneumoniae: 19; Proteus mirabilis: 22; Yersinia enterocolitica: 23; Enterococcus spp.: 30; Pseudomonas aeruginosa: 48; Salmonella spp.: 50; Staphylococcus aureus: 116; Escherichia coli: 120 (Przybyłek & Karpiński, 2019).

There have been about 600 species of pathogenic bacteria that are inhibited by propolis, it was found that the antibacterial potential of propolis is geographically dependent. Middle Eastern propolis was noted to be highly effective against both Gram-positive (Staphylococcus aureus) and Gram-negative (Escherichia coli) bacteria. Conversely, German, Irish and Korean propolis showed minimal activity .In contrast, the green and red types of Brazilian propolis appear to exhibit greater activity than the brown type. This particular variation is commonly sourced from the southern regions of Brazil where its production details are often vague— contributing to its uncertain composition and diverse botanical origin. (Salatino et al., 2021).

In general, propolis exhibits higher antimicrobial activity towards Gram-negative bacteria than Gram-positive ones. This is due to the unique structure of the outer membrane of Gram-negative bacteria and their ability to produce hydrolytic enzymes that can degrade the active components of propolis (Sforcin, 2016 ; Przybyłek & Karpiński, 2019).

The antibacterial effects of propolis should be viewed from dual perspectives. The first being the direct action on the microorganism itself while the second involves triggering the immune system to defend the body naturally. Among the many phenolic compounds present in propolis, Artepillin C stands out. Research conducted in Brazil by Veiga et al. revealed that ethanolic extracts of propolis have a higher concentration of artepillin C as opposed to hexane extracts, showing significant antibacterial activity on MRSA S. aureus. In another study against anaerobic bacterium Porphyromonas gingivalis, it was discovered that artepillin C exhibits bacteriostatic activity through membrane blebbin; moreover, artepillin C also demonstrates anti-inflammatory effects by modulating NF-kappaB and inhibiting nitric oxide and prostaglandin E (Paulino et al., 2008 ; Veiga et al., 2017 ; Yoshimasu et al., 2018).

The susceptibility to propolis ethanolic extract shows major differences between Staphylococcus species. Among them, S. hyicus demonstrates the highest susceptibility while S. warneri exhibits the least susceptibility. It is noteworthy that S. aureus is more susceptible than S. epidermidis. Recent research studies have pointed out the use of a flavonol component from Brazilian green propolis in treating skin infections caused by Staphylococcus aureus— this underscores the potential applications of such natural compounds in fighting bacterial infections with high efficacy levels even at low concentrations (as evidenced by luteolin's MIC value). Luteolin, which is a flavone commonly found in propolis, shows an impressive MIC value of 1.5 μg mL^{-1} against S. aureus— indicating its strong inhibitory effect on the growth of this bacterium. Another important flavonoid is quercetin: it has been widely reported as one of the most common flavonoids present both in plants and thus also frequently found among propolis compositions around different regions globally... with good reason! Quercetin demonstrates MIC values as low as 1.8 against S. aureus and even 2.5 against E.coli — suggesting its broad spectrum antibacterial activity which can target different types of bacteria effectively by interfering with various cellular processes through differential changes initiated within bacterial cells upon exposure to this specific plant-derived compound, also part of the large bioflavonoid family known for their diverse biological activities and mode of action against microorganisms that cause infections to humans and other animals (Almuhayawi, 2020).

ANTIFUNGAL ACTIVITY

An update on antifungal properties of propolis has been recently featured in a review article. Unlike antibacterial works, the research on antifungal effects has been quite sparse. The results documented so far largely revolve around Brazilian propolis— particularly the green and red variations. European propolis remains largely unexplored in this aspect; with only two primary studies done— one focused on French and the other on Portuguese propolis. There have been investigations into other types of propolis for their antifungal effects as well, such as Argentinean propolis. The studies have predominantly concentrated on various Candida species including C. tropicalis, C. parapsilosis, C. krusei, C. guilliermondii, and C. albicans; among other genera that have come under scrutiny are Trichosporon, Trichophyton, Microsporon and Aspergillus. (Zulhendri et al., 2021).

A single in vivo preclinical trial was conducted addressing effects against vulvovaginal standard and fluconazol-resistant isolates of C. albicans. The primary antifungal components in propolis have been suggested to be flavonoids, with chalcones assumed as the chief antifungal components present in extracts of Z. punctata. The antifungal action is believed to take place through apoptosis via metacaspase and Ras signaling along with suppression of expression of several fungal genes related to different aspects of pathogenesis. Pinocembrin, a major component of propolis from temperate regions, acts by reducing levels of phosphorylated adenosine nucleotides in hyphae of Penicillium italicum and damaging its cell membrane leading to ionic leakage and loss of soluble proteins (Queiroga et al., 2023).

ANTIVIRAL ACTIVITY

The potential of propolis as an antiviral agent has been demonstrated against numerous viruses. Among the early researchers in this field is Debiaggi et al. (1990) who studied flavonoids derived from propolis— quercetin, galangin, acacetin, kaempferol, and chrysin— against different strains of coronavirus, rotavirus, adenovirus and herpesvirus. Several computational as well as molecular docking studies underscore the ability of propolis along with its phenolic constituents to obstruct major proteins of SARS-CoV-2 including proteases and spike protein: hence hindering viral action (Debiaggi et al., 1990).

Another virus that propolis is efficient against is influenza. The antiviral efficacy of thirteen ethanolic extracts of Brazilian propolis against influenza virus was studied by Shimizu et al. (2008); all extracts were found to have antiviral properties with different levels of efficacy. coumaric acid, kaempferol, and apigenin — propolis-derived phenolics shown effective against Influenza by Kai et al. (2014). Additionally, Urushisaki et al. (2011) showed that water extract of propolis had antiviral activity against influenza virus: caffeoylquinic acids were the active components in this case, responsible for the antiviral properties..

The discovery of propolis within treatment regimes that not only alleviate but relieve the symptoms for COVID-19 patients has roots in clinical trials— a contribution of some of phytochemical constituents. Phenols, lipids, flavonoids, and alkaloids: these are the active elements found in propolis; tannins, saponins and polyphenols make their appearance too, each playing a significant role with the others in tow. Marcucci had indicated that antiviral actions demonstrated by caffeic acids as well as flavonoids among other components forming propolis through ingestion could impede virus transmission plus progression (Zullkiflee et al., 2022).

CONCLUSIONS

The researchers have increasingly used propolis in recent alternative medicine studies, focusing on its biochemical structure, in addition to its antibacterial, antifungal, antiviral activities. The structure of biochemical components in propolis differs based on the species of the bees, country, plant source, and ecological factors. Commonly, propolis include organic compounds, pollen, essential oils, beeswax, and lipid. The organic components include aromatic acids, amino acids, steroids, coumarins, terpenoids, terpenes, polyphenols, phenolic compounds, and flavonoids. Clinical trial evidences point out that propolis and its compounds have antibacterial, antifungal, and antiviral activities. Studies have investigated the mode of action against pathogenic microbes. studies have exhibited that propolis may exert synergistic effect with antimicrobials, allowing the intake of minimal doses of antimicrobials and maximal activity against pathogenic microbes.

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