Mini Review
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Expanding the amplitude of propolis uses

Abstract

Propolis is an apiculture product containing beeswax, bee saliva and resins that bees collect from selected plants. Among the various uses of propolis by the hive, protection against natural enemies, chiefly of microbial origin, stands out, contributing to enhance the hive immunity and resistance against infection. Most known types of propolis have phenolic substances as main resin constituents. Several phenolic compounds from propolis including flavonoids, are active against bacteria. Experiments and clinical practice have shown that propolis is helpful in several areas, the antibacterial activity of propolis constituents being the driving force of the performance. Propolis extracts have been used as preservative of several kind of animal and plant derived foods, food packages, as well as in veterinary, dentistry and therapies for human care against infectious diseases. Propolis extracts have been used experimentally as adjuvant in antibiotic therapy against infectious diseases, with positive results regarding reduction of effective doses of the antibiotic, and is expected as well to reduce the risk of development of bacteria resistance against antibiotics. Hospital therapies have benefited of the association of propolis extract as adjuvant with drugs used in the treatment of COVID-19. Fostering the uses of propolis in therapies require the development of active fractions of propolis, containing a limited number of constituents and exact qualitative and quantitative constitution.

Keywords: phenolic substances, flavonoids, antibacterial, food preservation, standardized extracts, infectious diseases

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Introduction

Apiculture embraces several economically important products, such as honey, royal jelly, beeswax, beebread and propolis. The latter acquired high economic importance in the last three or four decades, following scientific works that revealed in propolis substances with considerable functional and biological properties.[1] Regarding the biological importance of propolis to the hive, one of them is the enhancement of social immunity in the hive, which contributes toward the defense of the colony against natural enemies.[2] Honey bees produce propolis by mixing resins they collect from several plant sources with their saliva and beeswax.[3,4] Biological properties of propolis components correspond mostly to substances derived from plant resins. Most types of propolis contain phenolic substances as major components, although terpenoids may be relevant propolis components, also derived from plant resins.[5] Types of propolis are recognized by their composition (characterized chiefly by phenolic compounds) and the plant species providing resin for the propolis production.[6] Some types of propolis are characterized by a particular component or a group of components, which is(are) ubiquitous in samples of that propolis type, and thus recognized as chemical marker(s).[6] In continuation, some examples of propolis types, plant resin source and marker compounds are presented: I) Brazilian green – resin source: *Baccharis dracunculifolia*; chemical markers: prenylated phenylpropanoids, such as artepillin C (Figure 1A); II) Brazilian red – resin source: *Dalbergia ecastaphyllum*; chemical markers: isoflavonoids, such as formononetin and vestitol (Figure 1B & 1C, respectively); III) Venezuelan and Cuban propolis – resin source: *Clusia* spp.; chemical markers: polyisoprenylated benzophenones, such as nemorosone (Figure 1D); IV) poplar propolis (temperate propolis) – resin source: *Populus* spp.; chemical markers: flavonoids with no oxygenation on the B ring, such as chrysin and pinobanksin (Figure 1E & 1F, respectively); V) Okinawan and Taiwanese propolis – resin source: *Macaranga tanarius*; chemical markers: *C*-geranyl-flavanones, such as nymphaeol A (Figure 1G).

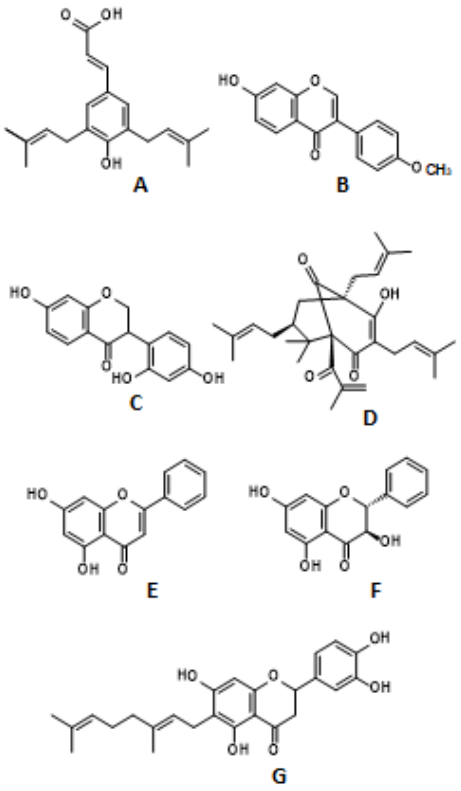

Figure 1 Structures of chemical markers of propolis types: A, Artepiliin C; B, Formononetin; C, Vestitol; D, Nemorosone; E, Chrisyn; F, Pinobanksin; G, Nymphaeol A.

Until a few decades ago, propolis was seen in apiculture as an undesirable hindrance for the production of honey, generally the most important product in most apiaries. Starting in the beginning

of the 70's, growing scientific evidence about biological activity and possible beneficial health derived from the use of propolis has led to a steady growth of interest for propolis by people in several parts of the world. Presently, propolis represents the main product of interest for apiaries in Brazil and other countries. It is consumed popularly as a complementary and alternative food and medicine. It is used also as raw material for industrial production of hygiene products, such as soaps and toothpastes, as well as cosmetics, such as creams and skin moistures.

Widening the niche of propolis uses

Alternatives for specific uses of propolis in distinct areas of food technology and health care have been proposed or tested experimentally or clinically. It is aimed in this paper to make brief comments about uses of propolis in the following areas: a) food preservation; b) veterinary; c) dentistry; d) adjuvant of antibiotics and other drugs used in human treatments. In all cases to be dealt with, the uses of propolis is due to properties of propolis that have been solidly established: antibacterial and antioxidant properties, which are exerted chiefly by its phenolic components.[7]

Food preservation

Because crude propolis contain wax and may have several unwanted constituents (including asphalt), it is essential that adequate extracts must be prepared to use the product in food protection. Alcohol is an ideal solvent for attainment of extracts with the highest content of phenolic substances. However, alcohol may be intolerable for some consumers. Water is preferable in these cases, although it has the disadvantage of extracting active propolis constituents in considerably lower proportions. Alternate solvents have been proposed, including polyethylene glycol.[8] A review by Pobiega et al.[9] reveals that propolis extract may be mixed with food and thus confer antimicrobial and antioxidant protection for meat, fish, honey, fruit juice, beer and milk. The extracts may be used to soak or wash fruits, fish and vegetables, with which the intensity of mold and bacterial intensity is reduced, and benefits may be brought to fruits by delaying their ripeness, reduce water loss and prolong the fruit firmness. Propolis extract may be applied to film packaging of fruits, vegetables and meat.

It has been shown that this measure reduces the growth of molds and yeasts, the mesophilic and psychrotrophic counts and the growth of *Enterobacteriaceae*, *Listeria* and *Staphylococcus*. Propolis was experimentally used as one among other substances aiming the preservation of pork patties during the chilled storage. It was concluded that propolis high phenolic content and antioxidant activity were determinants for reduced lipid and protein oxidation during chilled storage.[10] Propolis extracts are useful also as an alternative to sorbate for preservation of non-carbonated beverages, such as orange juice.[11] Propolis extract preserves the original quality of fruit juices due to the inhibition of bacterial growth promoted by its phenolic compounds, including flavonoids. Propolis emulsion devoid of alcohol was effective at maintaining original characteristics of fresh orange juice.[12] The antioxidant activity of these propolis constituents contribute also to preserve the natural antioxidant quality of the fruit juices.[13]

Veterinary

Regarding uses in health treatment of humans and domestic animals, propolis has a considerable advantage over conventional medicines. Most drugs widely used in therapy possess adverse side effects. Ergotamine, used to treat migraine headaches, may cause cardiac failure.[22] Propolis, on the other hand, is virtually devoid of toxic effects in animals. Results obtained with mice have established as 2050 mg kg^{-1} the LD_{50} of propolis. Flavonoids, which often are major chemical constituents of propolis (Figure 1), are known to exert low toxicity in animals. Pinocembrin, for example, is not toxic to mice, even at doses of 1000 mg kg^{-1}. The frequent use of propolis in veterinary may be indirectly evaluated by the number of patents for propolis-based products for use in treatment of animal health problems.[14] Until 2019, China had released the highest number of patents (198), followed by USA (101), and European Patent Organization (46). Several formulations have been proposed to treat distinct health problems of domestic animals, chiefly dogs and bovines. Given the current trend of increment of the population of dogs in urban areas all over the world, a parallel increase is expected regarding the use of propolis in the treatment of dog health problems. A high variety of clinical practices dealing with diseases of dogs was the object of a review.[15] A 70% hydroalcoholic extract of propolis from south Brazil was used to evaluate the physical characteristics of three formulations from the National Formulary of the Brazilian Pharmacopoeia,[16] namely cold cream, vaseline ointment, and creamy gel. The latter showed the best characteristics of stability and spreadability through 90 days of observation. It is proposed that such formulation may be useful for treatment of several animal diseases caused by bacteria and fungi, including dermal problems and otitis.[17] Positive results have been obtained combining propolis extracts with conventional antitumor drugs for treatment of osteosarcoma (spOS-2) and mesenchymal stem cells. While propolis alone had no effect, positive results could be obtained by the conjunct effect of propolis and the lowest concentration of carboplatin.[18] Milk quality and production is affected considerably if cows develop mastitis, an inflammation of the mammary glands, sometimes involving infection. Mastitis is an important cause of economic losses. Extensive use of antibiotics for control of bovine mastitis have increased concerns about the emergence of antibiotic-resistant pathogens.

Alternative therapies have been proposed, based on products from plants, recognized as possessing antibacterial activity.[19] Studies about activity *in vitro* and *in vivo* against bacteria commonly found in mastitis have been published, including environmental mastitis (*Escherichia coli*, *Enterobacter aerogenes*, *Streptococus uberis*, *S. bovis*) and contagious mastitis (*Staphylococcus aures*, *Streptococcus dysgalactiae*). A review about treatment of mastitis using propolis extracts mentions several attempts of mastitis treatments using propolis extracts alone or a combination of propolis extracts and commercial antibiotics has allowed reduction of clinical doses of antibiotics and side effects, as well as improvements in the mastitis treatment.[20] Diseases affecting goats and sheep have also been object of attempts to use propolis for their treatment. An example is caseous lymphadenitis, a chronic infectious disease, causing economic losses due to devaluation of skins and carcasses. Alcoholic extracts of Brazilian green propolis was effective at inhibiting the growth of *Corinebacterium pseudotuberculosis*. Treatment of the surgical wound with propolis extract led to complete healing one week before the treatment with iodine (conventional treatment).[21]

Dentistry

The area of human health that has most often exploited propolis extracts in therapies is dentistry. In addition to antibacterial activity, propolis has other properties useful in the treatment of teeth cavities and oral diseases, such as anti-inflammatory and regenerative.[23,24] Propolis extracts have been used for the treatment of caries, gingivitis, periodontitis and other problems treated in dentistry. Among many other beneficial results derived from uses of propolis in dentistry, it is worth mentioning improvements obtained in periodontal status and

glycemic control in patients with type 2 diabetes mellitus and chronic periodontitis.[25,26]

Treatment of infectious diseases using propolis as adjuvant of antibiotics

Several health authorities have recommended much care regarding prescriptions of antibiotics. Many unwanted, adverse side effects, have been detected regarding many currently used antibiotics.[27] Health personnel working in clinics and hospitals have been advised to treat patients with the lowest effective doses and for the shortest term possible. A phrase that has become mandatory lately in antibiotics therapy is "less is more". It has been shown that, in average, each additional day of antibiotic use is associated with a 7% increased risk of developing an antibiotic-related adverse drug event.[28] In addition to risks of adverse side effects that antibiotic-based therapies have been causing is the development of antibiotic resistant strains of pathogenic bacteria. In fact, this represents one of the most serious health problems faced presently by humanity. Factors aggravating the problem include inappropriate therapy practices, such as prescription of antibiotics to treat viral diseases, the rapid spread of antibiotic resistant strains (due to globalization), as well as the antimicrobial use to treat domestic animals.[29] Recent estimates of lives lost to the escalating problem of bacteria antibiotic-resistance are astounding: a 2019 estimate revealed 4.95 million deaths associated with the problem.[30]

The adjuvant use of propolis extracts with antibiotics in therapy against infectious diseases opens, at the same time, the opportunity to reduce the doses of antibiotics, as well as reduce the risk of development of antibiotic resistance by the bacteria. The activity of propolis acting as adjuvant of antibiotics in treatments against diseases caused by bacteria has been tested. A synergistic effect was noted, with the possibility of reduction of antibiotic doses, without loss of efficacy regarding the inhibition of the growth of *Staphyloccus aureus*. Propolis extracts acted synergistically with streptomycin and cloxacillin, and exerted moderate effect on penicillin G, doxycycline, chloramphenicol, cefradine and polymyxin B.[31] In addition, it has been shown that propolis modulates antimicrobial resistance of multidrug resistant bacteria. Adjuvant therapy combining propolis and antibiotic reduces the possibility of development of antibiotic resistance by bacteria, due the presence of several antibacterial-active phenolic substances, each with a distinct mode of action.[32] The combination of antibiotics and propolis phenolic substances represent a multitarget army, regarding the sites of action in the bacterial cell. This reduces substantially the possibility of development of antimicrobial resistance by infectious agents.

Clinical trials – COVID-19

Clinical treatments of humans using propolis have not been as frequent as in dentistry. The recent COVID-19 pandemic encouraged people to explore the potential of propolis in treatments of a disease combining actions of virus and bacteria, against which propolis has shown activity. A review commented the possibilities of propolis for the treatment of COVID-19, based on *in vitro*, *in vivo*, *in silico*, and clinical trials.[33] An effective clinical trial was conducted with 124 hospitalized COVID-19 patients, using a standardized Brazilian green propolis extract (EPP-AF) as an adjuvant therapy.[34] Patients were randomly divided in three groups, depending on doses of the extract: 400 mg day^{-1} (group 1), 800 mg day^{-1} (group 2), and no administered extract (control group). Patients of the group 1 experienced a time of recovery of 7 days, comparing with 7 days of group 2 and 12 days of the control group. In addition, patients of groups 1 and 2 had lower rate of kidney injury caused by COVID-19, comparing with the control group. The authors admit that the known anti-inflammatory and immunomodulatory effects of propolis may account for the improvements of the kidney and lung conditions of the patients treated with the propolis extract.

Production of standardized propolis extracts

Products derived from propolis are long expected to be used frequently not only in dentistry and veterinary, but also in food technology and clinical medicine.[35] A may constraint to be overcome in this regard is the high variability of propolis composition, even comparing samples from the same country and produced with the same plant species acting as resin source.[36] Current medicines typically have a precise composition of ingredients. Propolis extracts, on the contrary, are complex mixtures of components, many of them unknown even after analysis by modern powerful chromatographic techniques. Nonetheless, standardized propolis extracts have been produced: EPP-AF and PE-8, both based on Brazilian green propolis; GH-2002, from Czech propolis; Propoelix and M.E.D both from poplar propolis; s-HEP, from Eurasian propolis.[37] All proposed extracts have at least the merit of freed the product of the undesired pollen and beeswax, components that not only are innocuous biologically, but also bring problems to be incorporated in most vehicles used in medicine production. The composition of the extracts, however, still have complex composition, containing probably over a hundred components. One way of obtaining a product derived from propolis with characteristics similar to modern medicines is the fractionation of propolis extracts. Possibly a single extract may provide several highly antibacterial fractions. The aim is to obtain one or several highly active mixtures of components, comprising small number of compounds, with precise composition.[37]

Conclusion

Propolis will remain a complementary and alternative food and medicine. However, its potential in food industry and health sciences is high enough to allow perspectives of widening its use in modern areas of activity, either in food industry or health sciences. While such spread of uses has been gradually taking place in some areas such as dentistry and veterinary (although still in slowly motion), in clinical medicine it will hardly be admitted in wide fashion, although science and methodology be applied aiming the production of products with chemical characteristics similar to modern medicines.

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Conflicts of interest

The author declares that there are no any conflicts of interest.

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