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Health from the hive: therapeutic potential of propolis–a review

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Abstract

The use of alternative medicine products has increased tremendously in recent decades. Honey bees (Apis mellifera) create propolis naturally from a variety of botanical sources. Since ancient times, propolis has been used for its antibacterial, antifungal, and anti-inflammatory properties. Due to functional benefits of propolis, many food sectors have employed it to improve the quality and wellness of products. In this review, we focus on compiling relevant information about propolis research related to the nutritional composition and the bioactive compounds in propolis along with their therapeutic importance and their effectiveness against various types of chronic medical conditions viz. diabetes, obesity, and cancer. The study could generate both new and accessible alternatives and the use of propolis for the treatment of various diseases and will help to effectively evaluate the safety of its use.

Keywords: Propolis; Good health & well-being; Bioactive compounds; COVID-19; Chronic diseases.

1. Introduction

Propolis is also known as “bee glue,” a word that refers to the resinous substance collected by bees from a variety of plants. It is a Greek phrase that means “defend” for “pro” and “city or community” for “polis,” or the beehive (Pasupuleti et al., 2017). It is (a resinous substance) produced by the bee *Apis mellifera* from plant exudates (Valenzuela-Barra et al., 2015). Tiny gaps [less than 6 millimeters (1/4 in)] are filled with propolis, whereas larger gaps are filled with beeswax. Its hue varies according to the botanical source, although dark brown is the most prevalent. It is sticky at temperatures above 20 °C (68 °F), but becomes stiff and brittle at lower temperatures. During foraging, worker bees collect pollen and nectar, as well as water and plant resin for propolis synthesis (Simone-Finstrom and Spivak, 2010). Propolis is used by bees to seal the hive and protect it from the elements like rain and cold winter winds. The chemical content and nature of propolis is influenced by environmental circumstances and harvested materials (Ferreira et al., 2017). Traditional medicine has long use of propolis, but there isn’t enough data to determine its usefulness in treating any diseases. It has anti-inflammatory, antibacterial, antifungal (Sforcin, 2016), antiseptic, antioxidant, antimycotic, antiulcer, anticancer, and immune-modulatory properties, and is useful to treat a variety of ailments (Li et al., 2015). Propolis activity is highly dependent on seasonal and geographical conditions, with Middle Eastern propolis demonstrating the strongest antibacterial potency. Propolis and its primary flavonoid constituents should not be discounted, and clinical trials should be conducted for better understanding of their potential applications in numerous sectors of medicine. Clinical trials on the antibacterial potential of biotechnological products and their usage in novel medications should be carried out. This review attempts to highlight some of the most current scientific results related to propolis and its components’ antibacterial characteristics (Almuhayawi, 2020). Propolis has been shown in several tests to have no toxicity or adverse effects in both animal models and people (Demir et al., 2016). The most common solvent for obtaining low wax propolis extracts rich in physiologically active chemicals is ethanol (Sforcin, 2016).

Table 1. Major bioactive compound found in Propolis

Propolis	Major bioactive compounds	Therapeutic properties	References
Populus spp Ferula spp.	Rutin, Apinegin, Genistein, Catechol, Catechin, Esculetin, Tectochrysin	Antioxidant, reduce the symptoms of menopause and control blood glucose	El-Guendouz et al., 2019
Poplar spp. Mediterranean cypress	Catechin, Quercetin, Rutin, Acacetin, Apigenin, Pinocembrin, Chrysin, Kaempferol	Antioxidant, support blood circulation	Chaa et al., 2019
Rosewood, Fabaceae	Quercetin, Naringenin, Isorhamnetin, Quercetin 3-Odiglucoside	Control blood sugar, kill cancer cells, prevent heart disease, anti-myocardial ischemia	Silva et al., 2019
Heterotrigona itama, Geniotrigona thoracica	Phenolics and flavonoids	Antioxidants anti-inflammation, anti-viral properties.	Ibrahim et al., 2016
Poplar type	Pinocembrin, galangin and phenolic acids.	Anti-viral, anti-tumor, anti-microbial, anti-mutagenic, antioxidant	Ristivojević et al., 2015
Mangifera type	Cardols, cardanols, anacardic acid	Antioxidant, antimutagenic and anti tumoral activity	Popova et al., 2021
Brazilian Propolis	Sesquiterpenes, benezene propanoic acids and longipinene	Anti-cancer, anti plasmodial and anti-inflammatory activities	Berretta et al., 2017
European propolis	Flavonoids, cinnamic acid	Anti oxidant and anti inflammatory properties	Alotaibi et al., 2019
Russian Propolis	Flavones and flavonols	Anti-inflammatory effects, prevent the development of cardiovascular disease, diabetes, cancer etc	Miguel and Antunes, 2011
Cuban propolis	Prenylated benzophenones, propolones A–D, clusianone, hyperibone B, garcinielliptone I, xanthochymol, and guttiferone	Anti-nociceptive, anti-inflammatory, anti-cancer properties	Pardo Andreu et al., 2015
Red propolis	Flavonoids, benzophenones, pterocarpens, triterpenes	Antifungal, antiviral, cytotoxic, anti-HIV	Rufatto et al., 2017
Mediterranean type	Totarol, terpenic acids, ferruginol	Anti-bacterial, anti-cancer, anti-microbial	Bankova et al., 2016

2. Historic usage of propolis

Propolis has its medical applications from ancient time of Greeks, Romans, Persians, and Egyptians (Rojczyk et al., 2020). Traditional medicine has employed propolis. Its use is as old as honey and has been utilized by humans for thousands of years. Egyptian people use propolis in the art of mummifying the corpses (Wali et al., 2017). The bees use propolis and wax to hide the carcass of an invader that was killed but could not be moved out of the hive. The bees prevent the spread of infection produced by the decomposing body in this way. In the 1960s propolis was responsible for the hive's lower bacterial incidence. Propolis was a key element in polyanthus, a perfume that included propolis, olibanum, styrax, and fragrant plants for Greek people (Kuropatnicki et al., 2013).

Some of the medical characteristics of propolis, as well as its usage as an antibacterial and wound healing agent were described by Aristotle, Pliny, and Galen. Propolis was mostly employed by Arabian physicians during the mediaeval period. It was employed as an antipyretic by New World civilizations such as the Incas. It has been classified as an official medication in the London pharmacopoeia since the 18th century. It has gained popularity in Europe between the 17th and 20th century as a result of its antibacterial properties. It was employed as an antibacterial and anti-inflammatory drug during World War II (Santos et al., 2020). Since 300 BC, man has been employed propolis as a traditional medicine. Its medicinal properties were known to Roman and Greek doctors, and other scientists like Dioscorides (Ferreira et al., 2017).

3. Chemical composition of propolis

The chemical makeup of propolis varies depending on a variety of environmental conditions, including climate, local vegetation, harvest season, and geographic origin (Pobiega et al., 2019a). Plant origin and chemical makeup separate the following types of propolis: Green (Alecrim) propolis, red (Clusia) propolis, Pacific propolis, and Canarian propolis. Different chemical compositions distinguish propolis varieties, which defines their biological capabilities (Pobiega et al., 2017). Algerian propolis has a lot of action against food borne pathogens such Gram-positive bacteria *Bacillus cereus* and *Staphylococcus aureus*, while Korean propolis has a lot of inhibitory effect, especially against *B. cereus* vegetative cells. Turkish propolis ethanol extract had robust antilisterial action, with slightly less potent effect against *Salmonella Enteritidis* (Pobiega et al., 2019a).

More than 300 chemical compounds have been identified in propolis such as polyphenols and terpenoids. These compounds are considered to be the most active (Table 1) (Przybyłek and Karpiński, 2019).

Aromatic acids like ferulic, cinnamic, caffeic, benzoic, salicylic and p-cumaric are also present in propolis. In propolis microelements and macro-elements (Mn, Fe, Mg, Zn, Si, Ca, K, Na, Cu and vitamins B2, B1, B6, C and E) are also found. In propolis there is number of active ingredients present which makes it bacterial resistance (Przybyłek and Karpiński, 2019). The main components in propolis consist of plant resins (50%), waxes (30%), 10% essential oils, 5% pollens and organic substances are discussed in Table 2.

Table 2. Composition of propolis

Chemical composition	Percentage	Properties	References
Plant resins	50%	Resin is a substance produced by trees that drips from their branches and trunks in the spring. The bees collect plant resins in the hive, modify them, and utilise them as a sealer, polisher, cleaner, and mummifier of dead insects in the hive.	Ahangari et al., 2018
Waxes	30%	It has anti-inflammatory and anti-oxidant activities.	Tinto et al., 2017
Organic substances	5%	n-alkanes, n-alkenes, n-alkanals, and methyl n-alkanoates were the most common chemicals found.	Alqarni et al., 2015
Pollens	5%	Pollens contain more than 96 different nutrients. Rich in amino acids, hormones, vitamins, minerals.	Ahangari et al., 2018

4. Health benefits for humans

The usage of propolis has a significant impact on human health and has a variety of purposes. In addition to cytotoxic effects, it is now employed as an antibacterial, antifungal, anti-inflammatory, antiviral, analgesic, antioxidant, antitumoural, antiprotozoal, anticancer, antihypertensive, anticarcinogenic, and anti-hepatotoxic agent (Figure 1) (Anjum et al., 2019).

HSV-1, HSV-2, Influenza virus types A and B, Parainfluenza virus, Adenovirus, Human immunodeficiency virus, infectious bursal disease virus, and avian reovirus, Newcastle virus disease, bovine rotavirus, pseudorabies virus, feline calicivirus, canine adenovirus type 2, and diarrhoea virus have all been shown to be subject to potent and broad-spectrum antiviral activity in propolis extracts from temperate climates (Scorza et al., 2020). Propolis has been used by humans in different domains since ancient times, most notably in traditional medicine, and as a result, it's known over the world in a natural way substance that improves health and prevents illnesses (Figure 2) (Zabaiou et al., 2017). The chemical makeup of propolis has pharmacological impact (Pobiega et al., 2019b). Propolis has been tested against a variety of viral disease organisms, with initial results prompting study into the most beneficial components, which might then be used to formulate more active and targeted medications. In an in-vitro model, propolis was found to have antiviral action against DNA and RNA viruses (poliovirus, herpes simplex virus, and adenovirus) (cultured cells). The propolis results at concentration 30 µg/ml observed highest against poliovirus and herpes virus with 99.9% inhibition of the later (Ripari et al., 2021).

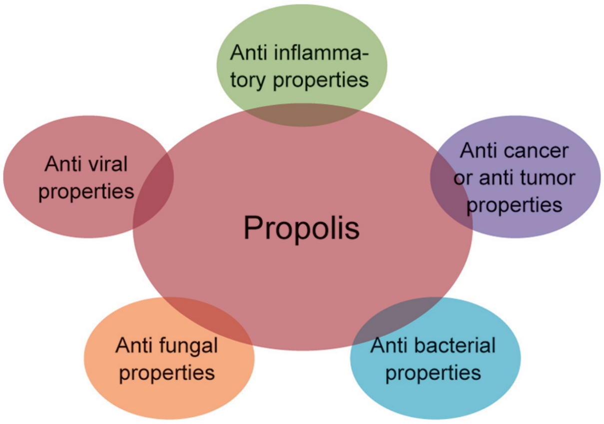

Figure 1. Medicinal properties of propolis.

Inflammation can be defined as a complex signalling pathway interaction between the immune system and injured tissues that aims to restore homeostasis. Flavonoids, phenolic acids and their esters, terpenoids, steroids, and amino acids appear to be associated to propolis anti-inflammatory activities, with CAPE being the most studied. The anti-inflammatory properties of propolis can be mediated in a variety of ways (Braakhuis et al., 2019).

Propolis has been used to treat traumatic neurological disorders such as ischemia and epilepsy. It is also used in degenerative disorders like Parkinson's disease, Alzheimer's disease, and multiple sclerosis. Although the mechanisms and causes of neurological dysfunction are uncertain, they appear to be connected to increased oxidative stress, inflammatory signalling activation, and slow immunological responses in brain tissue (Braakhuis et al., 2019). Propolis aids in mitigating both SARS-CoV-2 infection processes and COVID-19 sickness. Propolis has carefully been investigated and is now widely used as a natural treatment alternative in many countries. It is important in veterinary medicine because of its antibacterial, antifungal, antiviral, antiparasitic, hepatoprotective, and immunomodulatory characteristics. Because propolis products are not standardized and differ in their components and biological activity, their usage as a health-promoting supplement in human medicine is limited in many countries. Propolis should be regarded a resource in the fight against the COVID-19 pandemic as a nutraceutical or functional food. Propolis inhibits PAK-1, which may aid in the prevention of lung fibrosis and the restoration of a normal immune response. Propolis has been demonstrated to interact with ACE2 and TMPRSS2, which might help to prevent or reduce SARS-CoV-2 host cell invasion. Chronic inflammation, characterized by systemically high amounts of pro-inflammatory cytokines, is more frequent in the elderly, which can lead to a cytokine storm, which is a primary cause of COVID-19 death. Antioxidants included in propolis could be assisting to halt or stop the ageing process (Berretta et al., 2020). SARS researchers have been paying close attention to quercetin, a flavonol found in propolis, because it has been revealed to be an effective amino peptidase inhibitor when paired with vitamin C. In vitro, quercetin and its derivatives inhibit SARS-CoV-1 and MERS-main CoV's protease. The cellular response to unfolded proteins is also affected by quercetin (UPR). Because corona viruses can use the UPR to complete their whole replication cycle, quercetin's control of this pathway could have anti-corona virus properties (Bachevski et al., 2020).

The study of optimum gut health and gastrointestinal bacterial characterization is a topic of concern right now, with some claiming that disease states are induced by microbiota imbalances in the gut (Clemente et al., 2012). A diverse range of gut microbiota produces microbial bioactive compounds such as short chain fatty acids, which have specific health advantages. An international group has

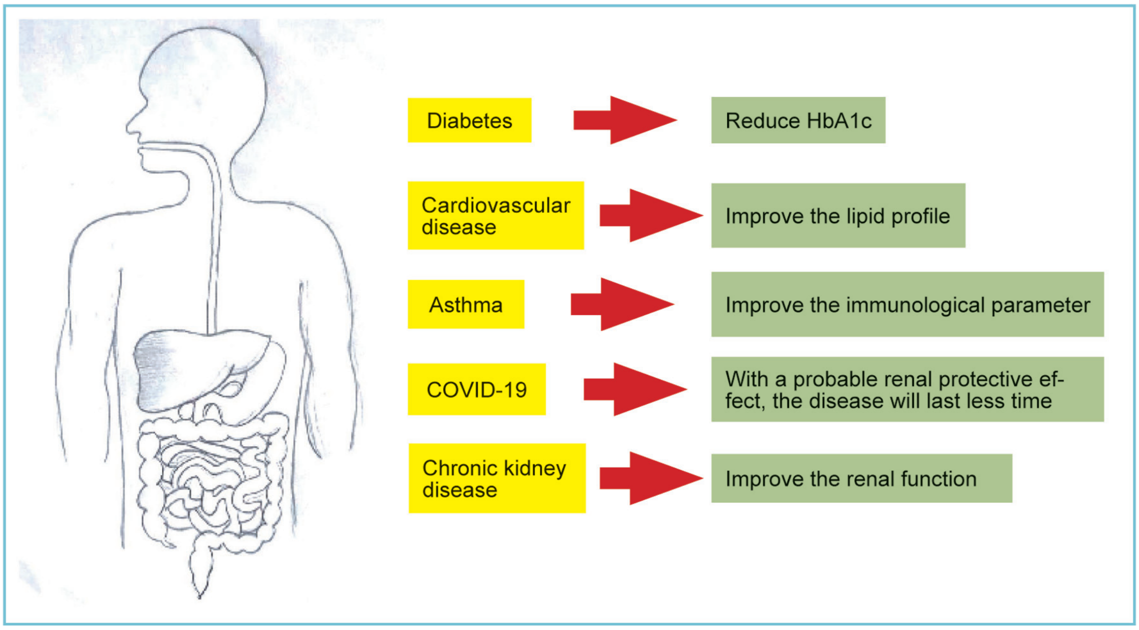

Figure 2. Therapeutic benefits of propolis for human health.

designated polyphenols, including propolis components, as prebiotics because they are selectively digested by gut microbiota (Solanki et al., 2016). Propolis polyphenols may help to maintain a healthy gut microbiota by reducing pathogenic bacteria development and prevents adhering to human gut cells (Alkhaldy et al., 2019). Antiseptic, antifungal, bacteriostatic, astringent, antioxidant, diastolic, anti-inflammatory, and aesthetic properties are all present in propolis preparations (Grecka et al., 2019). Chemotherapy is very helpful in treating all types of cancer but after the therapy cancer survivors are at high risk for number of health problems and one of the major problem is infertility. Indian propolis extracts can be helpful for the protection and rejuvination of testicular tissues from chemotherapy induced damage by reducing the DNA damage and elevating the antioxidant activity (Kumari et al., 2017). Propolis has antimicrobial properties which stimulate the immune system that activates the natural defense system of the organisms. The antimicrobial activity of propolis is higher in gram positive than in gram negative bacteria (Przybyłek and Karpiński, 2019).

5. Some in-vitro, in-vivo and human clinical trials of propolis

5.1. Anti-cancerous properties

With 14 million new cases and 8.2 million deaths from cancer in 2012, cancer is a terrible illness that affects people all over the world (Khan et al., 2021). Utilizing organic compounds like propolis can lessen the consequences of cancer. Propolis and its constituents are thought to alter cell cycle regulators such cyclin D, cyclin-dependent kinases Cdk-2/4/6, and cyclin-dependent kinase inhibitors. These inhibitors stop the progression of the cancer cell cycle (G2/M phase) at stage G0/G1 by overexpressing p21 and p27 expression (Chiu et al., 2020). Studies show that ethanol-extracted Cameroonian propolis up-regulated cell cycle proteins (CDK1, pCDK1, and related cyclins A and B) in both the cell cultures (DU145 and PC3) while down-regulating CDK2 and pCDK2 proteins solely in PC3 cells. Cameroonian propolis also enhanced the proportion of DU145 and PC3 cells in G0/G1 phase (Zingue et al., 2020; Forma and Brys 2021).

5.2. Type-2-diabetes inhibition properties

Propolis influences hypoglycemic activity, according to current studies, which may help prevent diabetes. Moreover, it modifies metabolism of blood lipid levels and resultant reduces lipid peroxidation and scavenges free radicals. In one study consumption of Iranian propolis for 90 days can improve insulin sensitivity in Type-2-diabetes mellitus (T2DM) patients and dramatically lower their serum levels of HbA1C, insulin, and 2-hpp glucose. Numerous researches reported that propolis improved insulin sensitivity in T2DM models and reduced blood glucose, insulin, and HbA1C levels (Zakerkish et al., 2019).

5.3. Anti-obesity properties

An important public health risk is obesity. Among other disorders, it is linked to an increase in the occurrence of cancer, type 2 diabetes, dyslipidemia, and cardiovascular diseases (Smith and Smith, 2016; Rivera-Yañez et al., 2020). A study conducted on certain variety of Brazilian red propolis (0–100 µg/mL) reported an increase in adiponectin mRNA in 3T3-L1 preadipocytes, which was most likely caused by PPAR- activating the adiponectin promoter. In the same study, propolis treatment for eight days restored adiponectin expression in differentiated 3T3-L1 cells that had been exposed to TNF. This finding suggests the efficacy of Brazilian red propolis as a dietary supplement for the prevention and treatment of obesity and disorders linked to it (Iio et al., 2010; Rivera-Yañez et al., 2020). Brazilian green propolis (100 µg/mL) directly increased leptin expression, according to an in vitro test utilising differentiated 3T3-L1 adipocytes (Washio et al., 2015). Although in vitro studies have contributed to a better understanding of propolis' ac-

Table 3. Propolis extracts and its current strategies for use in food technology

Current strategies	Applications	References
Mixing with food	Antimicrobial, total bacterial, *staphylococcus*, and *listeria* counts are reduced. Reduction in the number of spoiling bacteria and yeast. Example–fish, meat, milk, fruit juice.	Pobiega et al., 2019a
Soaking and washing of food	Antioxidant in fruits. Antimicrobial–reduction of yeast and molds contamination. Reduction of total bacterial count. Improve quality, delayed ripening. Reduction of water loss, maintaining firmness. Example–fruits, juices etc	Pobiega et al., 2019a
Active Packaging film	Nontoxic, bio-degradable, biopolymer based packaging. Example–beef, fruits etc	Yong and Liu, 2021

tivity against obesity, the majority only assess a chemical or molecular aspect, therefore its impact is still limited. The research did not take into account the multifaceted nature of this disease; as a result, in vivo investigations are crucial to the development of clinical trials (Jensen et al., 2021; Aravani et al., 2021).

5.4. Anti-inflammatory effects

Strong anti-inflammatory properties have been attributed to propolis. The in vitro and in vivo research have been conducted in recent years on the effects of propolis on inflammation (Ying-Hua et al., 2012; Pahlavani et al., 2020). Propolis, a product of honeybee colonies that has anti-inflammatory properties, contains caffeic acid phenethyl ester (CAPE), a significant component. A powerful Arachidonic acid (AA) modulator, CAPE limits the release of AA from the cell membrane and blocks the expression of the genes for the lipoxygenase (LOX) and cyclooxygenase (COX) enzymes, which are essential for the pathways leading to AA metabolism. The ethanol extract of propolis suppressed leukotriene and prostaglandin synthesis in both in vitro and in vivo experiments. Propolis's ability to inhibit prostaglandin endoperoxide synthase may be due to its flavonoids, which have been shown to have this effect (Mirzoeva and Calder, 1996; Pahlavani et al., 2020). Additionally, it inhibits the activation of COX-1, COX-2, and the gene that controls COX-2 production (Pahlavani et al., 2020).

5.5. Benefits of propolis in food industry

Propolis is also used in food quality. The use of propolis extracts in food industry has been briefly discussed in Table 3. It is a natural preservative that can be applied directly to meat products, but its effectiveness is dependent on concentration. The propolis ethanol extract at low concentration (0.5–1%) prevented the growth of proteolytic and lipolytic bacteria, as well as moulds and yeasts, in fresh oriental and Egyptian beef sausages (Pobiega et al., 2019b).

Propolis extracts can be eaten or administered typically to lower the count or entirely remove food borne pathogens and saprophytic bacteria in meals. Immersion of foods containing propolis extracts or use of specially manufactured extracts of propolis in coatings is a means of limiting propolis unique flavour and odour, which may have a detrimental impact on the sensory characteristics of the meal to which it is added (Pobiega et al., 2019a). Propolis is already utilized in a variety of foods as a natural preservative. One study substituted chemical preservatives with a propolis green extract in a non-carbonated orange soft drink, therefore increasing the product's bioactivity (Vasilaki et al., 2019). Propolis can be employed as a natural preservative in dairy drinks in the food industry (El-Guendouz et al., 2019). Propolis can directly be added to the meat products but its activity directly depends upon the concentration. In low concentration propolis inhibits the growth of molds and yeast. Propolis extracts can also inhibit the growth of food borne pathogens in meat (Pobiega et al., 2019b).

The different extracts of propolis and their effects on food products have been discussed in Table 4. Ethanol extract of propolis (Iranian propolis) also work against fish bacterial pathogen that increases the shelf life of the fish (Payandan et al., 2017). Propolis has been used as a natural preservative in several foods (Duman and Ozpolat, 2015). It proved efficient against oxidation and change of quality indicators when added to dairy beverages and traditional Turkish sausages, for example (Cottica et al., 2015). The number of noroviral genome decreased when propolis water extract is used in fresh juices (Liao et al., 2021). Propolis based chewing gums helps in reduction of pathogenic microbial load

Table 4. Effects of propolis on food products

Food product	Propolis	Effect of propolis	References
Non-carbonated soft drinks	Propolis green extract	Increase the bioactivity of the product.	Vasilaki et al., 2019
Dairy drinks	Propolis extract	Act as natural preservatives.	El-Guendouz et al., 2019
Meat products	Propolis extract	Inhibit the growth of food borne pathogen.	Pobiega et al., 2019b
Fresh juices	Propolis water extract	Reduce the number of noroviral genome.	Liao et al., 2021
Fish	Ethonal extract of Propolis	Increase the shelf life of the fish	Payandan et al., 2017
Chewing gum	Propolis extract	Reduce the pathogenic microbial load	Zulhendri et al., 2022
Beverages	Propolis extract	Inhibit the fungal growth and degradation of ascorbic acid	Vasilaki et al., 2019
Craft beer	Propolis extract	Increase the anti-oxidant value	Ulloa et al., 2017
Orange juice	Propolis extract	inhibit bacterial growth, degradation of L-ascorbic acid	Yang et al., 2017

and improves dentin mineralization (Zulhendri et al., 2022). Commercial milk, yogurt, and Kefir with a 0.5 percent sugar boost of propolis resulted in best organoleptic characteristics for each product (Luo et al., 2021).

6. Future prospects

Propolis has a lot of benefits, but there is still a lot to study on it in terms of humans and food. Many individuals are still unaware of the benefits of propolis. Because of its antifungal and antiviral properties it can be quite useful in the production of medications and other items during a COVID-19 period. Despite the fact that it may be highly beneficial to human health by delivering a variety of advantages, many people are ignorant of this. As per today's lifestyle human health is degrading day by day, so by knowing the benefits of propolis one can make a little change in human health. Propolis can also be very helpful in treating the respiratory problems. Few studies have investigated the effect of propolis on treating the lungs infection (Magnavacca et al., 2022). Skin healing, neurodegenerative, gut health, atherosclerosis and wound healing properties are also found in propolis (Braakhuis et al., 2019). Number of medicines can be prepared in future also that can be helpful against oral diseases, gut health, skin diseases, timorous disease, viral diseases, fungal diseases respiratory diseases etc. In food industries also propolis is very helpful as one can use it to increase the shelf life and make the product bacteria free.

7. Conclusion

This paper highlights the importance of propolis in human health and in food industries. Propolis has many properties that makes it very beneficial for human health such as antiviral, anti-microbial, anti-bacterial properties. Propolis, also called bee glue, is now in fashion to use in food industries as a natural preservative and chemical preservative. It can be helpful in removing the food borne pathogen and bacteria to make the food healthier, hence helping in maintaining good health & well-being. By dipping the food in propolis we can add a different aroma and flavour to the food. In food packaging, propolis can be useful in increasing the shelf life of the product. It can increase the bioactivity of the food products. By considering all the usefulness of the propolis in human health and in food industries more weight should be brought to the incorporation and use of it.

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Conflict of interest

The authors declare no conflict of interest.

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