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Propolis as a promising functional ingredient: a comprehensive review on extraction, bioactive properties, bioavailability, and industrial applications

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ABSTRACT

Propolis is a resinous complex mixture made from plant resins collected by worker bees and mixed with their own secretions. It is rich in polyphenols and flavonoids and thus has a wide range of biological activities and is considered a functional source for promoting human health. However, propolis and its bioactive compounds have poor water solubility, rapid and intense metabolism, and low oral bioavailability, which limits their wide application. In this paper, the main bioactive substances in propolis were summarized, and the biological characteristics and therapeutic potential of propolis and its bioactive substances were discussed. In addition, this paper discussed the factors affecting the bioavailability of propolis and its functional ingredients, focusing on the research progress in improving the bioavailability and bioactivity of propolis and its functional ingredients using nanoencapsulation technology. Finally, the current situation of the global propolis market and the applications of propolis products in the pharmaceutical, food, cosmetic and other industrial fields were discussed, providing useful references for promoting the development of the propolis industry.

1. Introduction

Propolis is a natural resinous complex mixture with an aromatic smell formed by mixing and processing the tree buds and resin collected by worker bees with their gland secretion[1]. The colour of propolis varies depending on its origin and age, with hues ranging from yellow to green, red, and dark brown. Propolis serves various functions in the hive, including sealing gaps and holes, regulating the temperature and humidity, protecting against invaders, and thus promoting homeostasis by inhibiting the growth of microorganisms, controlling airflow and waterproofing[2]. The chemical makeup of propolis is heavily influenced by the species, geographical region, food, and plant sources of bees. However, the overall percentage composition of most propolis remains almost unchanged, consisting mainly of resins 45%–55%, waxes 8%–35%, pollen 5%, essential oils and aromatics 5%–10%, and other organic compounds 5%[3]. Propolis has a complex chemical composition, and more than 1 000 organic compounds have been identified from propolis samples from different regions and plant sources. Among them, up to 70% of the bioactive components are mainly flavonoids, terpenes and phenols, as well as a variety of amino acids, enzymes, vitamins and various trace elements[4].

In addition, the abundant bioactive compounds found in propolis provide a diverse range of biological properties, including antioxidant, anti-diabetic, anti-fungal, anti-cancer, anti-inflammatory,

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wound healing promotion, and anti-mutagenesis effects[5]. Currently, propolis has been widely studied as an edible natural functional substance, and it has demonstrated therapeutic potential in the treatment of chronic and systemic diseases, such as diabetes, cancer, cardiovascular disease, and oral conditions[6]. Furthermore, we conducted a detailed literature survey of publications with the keywords "propolis", "functional ingredient", and "bioactivity", and using the VOS browser software (Java version 1.6.19) to construct a visual bibliometric network. The map reveals that the research hotspot in propolis-related fields in recent years were the study of flavonoids, polyphenols and antioxidant activity in propolis (Fig. 1a); the central countries engaged in propolis research were China, Brazil, Turkey, Poland, Italy, etc. (Fig. 1b); the article with the highest number of references in propolis studies was retrieved (Fig. 1c); and the primary journal source of propolis research was *Food Chemistry* (Fig. 1d), which provides a reference for further study, development, and application of propolis. In fact, the research on propolis mainly focuses on the chemical composition, while the comprehensive studies on the quality evaluation, bioavailability and application of propolis are relatively few. This paper reviews the research progress on the chemical composition and quality control of propolis, and the extraction methods, biological activity and mechanism of action, bioavailability, and the application of propolis products in different industries were discussed, which aim to provide useful references for promoting the development of the propolis industry.

2. Chemical constituents and quality control of propolis

2.1 Chemical constituents

Propolis constitutes a plentiful reservoir of naturally occurring biologically active compounds, encompassing flavonoids, terpenes, fatty acids, vitamins and minerals[1]. Flavonoids are considered the principal standard for evaluating the quality of propolis and are widely present in poplar propolis[7]. Due to the different substituents and positions, the isolated flavonoids can be classified into 11 subclasses, including flavonoids, flavonols, dihydroflavonols, isoflavones, dihydroisoflavones, chalcones, etc.[8]. At present, more than 100 flavonoids have been discovered and identified from various types of propolis, including chonosin, myricetin, quercetin, poplar, kaempferol, galangin, etc.[4]. Most terpenoids are the main volatile components present in propolis and are the main cause of the odor of

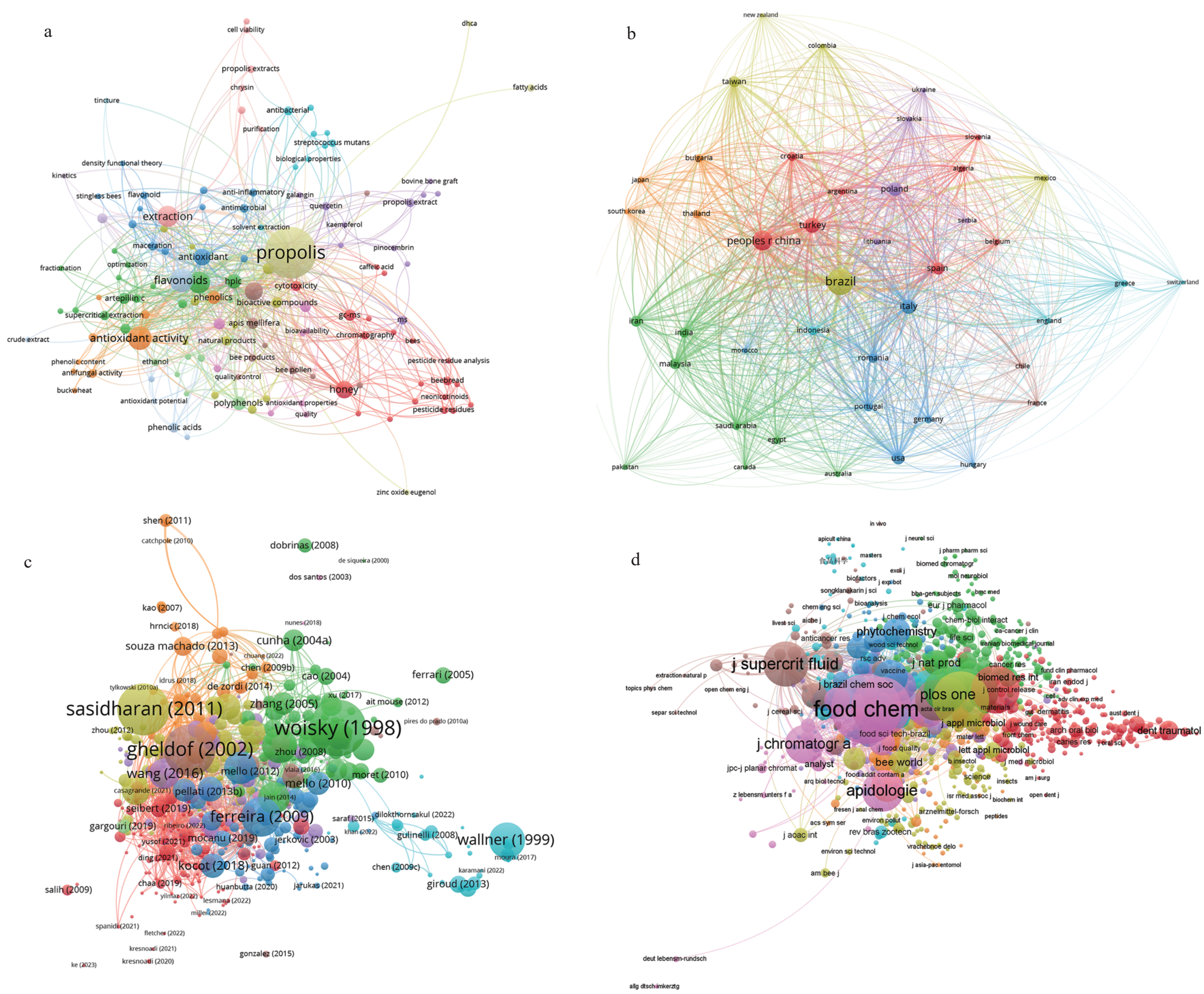

Fig. 1 Overlay visualization map of co-occurrence of keywords analysis for propolis-related (a) research fields, (b) research regions, (c) research papers, and (d) publications. Each keyword is represented by a coloured circle. The larger the circle, the greater the intensity of the search performed.

propolis. The terpenoids are represented as monoterpenes (pineol, camphor), diterpenes (junicedric acid, pimaricacid, totarolone), triterpenes (upeol, lanolin, amyone and its derivatives), and sesquiterpenes (γ-elemene, valencene, α-ylangene, α-bisabolol)[9]. Moreover, phenolic acid is another important active ingredient present in propolis. Common phenolic acids found in propolis include caffeic acid, *p*-coumaric acid, ferulic acid, gallic acid, and cinnamic acid. Additionally, propolis is rich in a diverse range of minerals, fatty acids and enzymes[10]. The primary chemical components present in propolis are listed in Table 1.

Propolis is a resinous substance with a complex and variable chemical composition that is influenced by several factors, including the sources of plants around the hive, bee species, geographic location, collection season, and light availability[11]. Based on the botanical origin and primary constituents of propolis, it can be broadly categorized into 6 types, namely poplar propolis, green (alecrim) Brazilian propolis, birch propolis, red propolis, Pacific propolis and Mediterranean propolis[9]. Poplar propolis is primarily found in temperate regions of Europe and North America, as well as non-tropical regions of Asia, China and New Zealand. Its botanical origin is derived from a species of the mountain poplar family, predominantly found in black poplar. The primary components of poplar propolis are flavonoids such as pinobanksin, apigenin, quercetin, *p*-coumaric acid, galangin, chrysin, cinnamic acid and its esters[9]. Brazilian propolis is available in various forms, including green propolis derived from *Baccharis dracunculifornia*. Chemical markers such as *p*-coumaric acid, artepillin C, and baccharin are utilized to distinguish green propolis from other propolis types. Brazilian green propolis is rich in diterpenes, lignans, valenyl phenylpropanoids, acetophenones, and flavonoids[12]. Brazilian brown propolis is obtained from the *B. dracunculifolia* leaf resin. Red propolis, derived from *Dalbergia ecastophyllum* (L.), is found in northeastern Brazil, Cuba and Mexico. Isoflavones are characteristic compounds of red propolis, which are not found in other propolis[13]. The botanical source of birch propolis collected from Russia is derived from *Betula verrucosa* and its main compounds are flavonoids and flavonols such as acacetin, apigenin, ermanin, rhamnocitrin, kaempferide, α-acetoxybetulenol[14]. *Clusia* propolis, which originates from Cuba and Venezuela, is rich in isoprene benzophenone and is derived from the secretions of the *Clusia* spp. flower[15]. Mediterranean propolis is found in Sicily, Greece, Crete, Malta, southern Italy and other regions. It is abundant in terpenoids, particularly α-pinene, which may be related to the fact that the plant sources used by bees are mainly composed of cypress and pine plants[15-16]. Greek propolis samples exhibit unique characteristics compared to typical European propolis. Specifically, they have a high content of diterpenes, but a relatively low content of phenolic esters and flavonoids[17]. Pacific propolis is produced in Indonesia, Taiwan and Okinawa, and is primarily derived from the botanical source, *Macaranga tanarius*. The characteristic compound of Pacific propolis is *C*-isopentenyl flavanone[18].

2.2 Quality control and authenticity detection of propolis

Due to the diversity of plant sources and the influence of various factors during collection and processing, the chemical composition of propolis is complex and variable, and its quality control and authenticity testing are challenging. Therefore, it is necessary to establish standardized procedures to analyze propolis products, to achieve quality and authenticity control of propolis. Firstly, the quality and authenticity of propolis are related to the raw propolis. The accidental introduction of different contaminants such as antibiotic residues, pesticides, and heavy metals during the propolis collection process can be a source of changes in the quality of the raw material. Therefore, propolis must initially undergo various purification processes to remove waxes and dirt. Secondly, the quality of propolis can be briefly evaluated by sensory analysis of colour, status, odour and taste of propolis (Table 2). In addition, the main physicochemical indicators of propolis, such as the content of propolis extract, total polyphenols and total flavonoids, are also criteria for evaluating the quality and authenticity of propolis[19].

Table 1
The main chemical components in propolis.

Compound	Specific chemical composition	Reference
Flavonoids	Tectochrysin, prokinawan, galangin, pinocembrin, chrysin, apigenin, naringenin, cearoin, pinobanksin, quercetin, kaempferide, luteolin, rutin, hispidulin, hexamethoxy flavone, macarangin, izalpinin, 7-*O*-prenylstrobopinin, medicarpin, garbanzol, alnustinol, homopterocarpin, kaempferol, 5-hydroxy-4',7-dimethoxyflavone, naringenin, sakuranetin, pinobanksin-3-acetate, isosativan, artepillin C	[8,17,152-155]
Phenolic acids and derivatives	2-Amino-3-methoxybenzoic acid, ferulic acid, *p*-coumaric acid, chlorogenic acid, gentisic acid, ellagic acid, vanilic acid, syringic acid, coumaric acid, caffeic acid phenethyl ester, pimaric acid, *p*-methoxybenzoic acid, gallic acid, cinnamic acid, protocatechuic acid, salicylic acid, caffeic acid, 3,4-dimethoxybenzoic acid, benzoic acid, benzyl salicylate, veratric acid, *p*-methoxycinnamic acid	[8,10-11,70,153, 156-157]
Terpenoids	β-Eudesmol, nerolidol, α-pinene, β-caryophyllene, α-terpineol, 1,8-cineole, β-bisabolol, terpinen-4-ol, γ-elemene, α-ylangene, linalool, α-Bisabolol, valencene, α-bisabolol, α-amyrin, cycloartenol, lupeol, squalene, α-acetoxybetulenol, kariofilen, guaiol, guaiene, β-selinene, farnesol, glutinol, linalool, β-myrcene, isocupressic acid, eucalyptol, farnesol	[12,154, 158-160]
Amino acids	Alanine, cystine, phenylalanine, isoleucine, lysine, glycine, histidine	[14,161]
Aliphatic hydrocarbons and aliphatic acids	Oleic acid, palmitoleic, palmitic acid, arachidonic, eicosenoic acid, decanoic acid, dodecanoic acid, nonanoic acid, caprylic acid, lignoceric acid, *cis*-13,16-docosadienoic acid, stearic acid, hexadecanoic acid	[17,162-163]
Sugars and sugar alcohols	*D*-Ribofuranose, talose, saccharose, galactitol, *D*-glucitol, galacturonic acid, *D*-glucose, 2-*O*-glycerylgalactose, fructose, rhamnose, β-glucosidase, *D*-fructose, sucrose	[14,161,164]
Vitamins	Vitamin B_1 (VB_1), VB_2, VB_3, VB_6, VC, VE	[14,17]
Minerals	Zn, Fe, K, Pb, Hg, Ba, Mg, Na, B, Al, Cr, Mn, Ca, Ni, Sr, As, Cd	[17,155,164]
Enzymes	Transhydrogenase, α-amylase, β-lactamase, maltase, acid phosphatase, α-lactamase, adenosine triphosphatase, β-amylase, glucose-6-phosphatase, esterase, α-lactamase	[14,155,165]
Alkaloids	Demecolcine, papaverine, thebaine, morpholine, norlobeline, pagicerine, oreophilin	[10,14,166]

Table 2
Sensory requirements of propolis.

Index	Sensory requirements
Colour	Brownish yellow, brownish red, brown, tan, taupe, turquoise, greyish black, etc.
Status	Agglomerate or slag-like, opaque, softening at temperatures above 30 °C with increasing temperature, and viscous.
Odour	Aromatic scent characteristic of propolis, a resin aroma and no odour when burned.
Taste	Slightly bitter, slightly astringent, with a slight numbness and a sense of pungency.

In addition to sensory analysis and physical and chemical index detection, the quality control of propolis, especially the search for propolis specific markers, has gradually become the focus of propolis research. It has been reported that a new rapid UHPLC-PD-MS/MS method for quantitative analysis of propolis phenolic compounds was established to control the quality of commercial propolis in Brazil[20]. Olegario et al. [21] used HS-SPME-GC-MS to determine the volatile compounds of Brazilian brown propolis to identify the region of propolis production based on the volatile profile of its geographic origin, which was used to track the origin and authenticity of the samples. It was found that the efficacy oriented fingerprint analysis of high performance thin layer chromatography (HPTLC) fingerprinting was combined with near infrared spectroscopy (NIRS) in order to achieve precise identification and high quality assessment of chemical and potency consistency of propolis samples from different geographical locations in Egypt, providing a theoretical basis for quality control of Egyptian propolis[22]. Wang et al.[23] rapidly analysed and identified 37 Chinese propolis samples by nanoelectrospray mass spectrometry combined with machine learning. By using multivariate analysis of mass spectrometry data, the differential metabolites of propolis from different climatic zones and different colours were screened to achieve high-precision differentiation and prediction between samples, which provided a reference for geographic traceability of Chinese propolis. It has been reported that 12 flavonoids and 8 phenolic acids in propolis were analysed by reversed-phase high performance liquid chromatography (rp-HPLC), using caffeic acid, ferulic acid, and *p*-coumaric acid as markers to clearly differentiate between poplar gum and propolis[24]. So far, analytical techniques such as gas chromatography (GC), HPLC, nuclear magnetic resonance spectroscopy, Fourier transform infrared spectroscopy, NIRS and different mass spectrometry techniques have been developed for the analysis of chemical components in propolis samples, providing a basis for the quality and authenticity control of propolis.

2.3 Legal regulations for propolis

The quality of propolis raw materials varies greatly due to the difference of climate, gum source plants and ecological environment in different regions of the world. Moreover, the production of propolis is difficult to meet the growing demand of propolis market, which leads to repeated counterfeiting and selling of products in the propolis market. In order to promote the internationalization and standardized development of the propolis industry, it is urgent to formulate regulations and standards on the propolis to regulate the use and quality control of propolis[19]. The European Union stipulates that propolis can be used as a food supplement, but due to the complex chemical composition of propolis, it cannot demonstrate its effect on human health conditions. Therefore, the European Food Safety Authority does not approve propolis as an essential substance on food labels[25].

For specific types of propolis, the International Honey Commission (IHC) recommends that specific criteria should be developed based on the concentration of bioactive secondary metabolites. The IHC has recommended values for the concentration of the bioactive components of the 2 most widely distributed types of propolis, European poplar-type propolis (poplar type) and Brazilian green propolis (*Baccharis* type). The International Bee Commission stipulates that the total phenolic acid, total flavone and flavonol content of poplar propolis should not be less than 21%, 4%, 4%, and the total polyphenol and total flavone content of Brazilian green propolis should not be less than 5% and 0.5%[26]. The International Standard for propolis (ISO 24381:2023), drafted by 22 countries, was officially approved by the International Organization for Standardization. This standard has made comprehensive and detailed regulations on the quality requirements, analytical methods, packaging, storage and transportation conditions of propolis. The international standard for propolis will help promote the improvement of the international trade rules framework for propolis, and have a far-reaching impact on promoting the high-quality development of the global propolis industry[27].

3. Extraction methods of bioactive components in propolis

Extraction is the first step in the process of extracting the active ingredients from crude propolis and is an important step that affects the chemical composition of propolis and thus its biological activities. Traditional extraction methods, including solvent extraction, impregnation extraction, Soxhlet extraction and hot reflux extraction, have been widely used to extract propolis flavonoids. However, these methods have disadvantages such as low extraction efficiency, poor repeatability, and environmental pollution[28]. Therefore, to overcome these shortcomings, some new extraction strategies have been developed, such as ultrasound-assisted extraction (UAE), microwave-assisted extraction (MAE), supercritical fluid extraction (SFE), etc. These unconventional technologies are designed to improve extraction efficiency and selectivity by specialized processing aids or energy inputs, which can lead to decreased consumption of organic solvents and prevent the degradation of thermally sensitive compounds. As shown in Table 3, the following part presents the latest technologies of propolis flavonoids extraction and gives the schematic diagrams of the experimental device of the unconventional extraction technologies in Fig. 2.

Table 3
Extraction methods of propolis flavonoids.

Propolis Origin	Type of extraction	Extracted compounds	Treatment conditions	Major findings	References
Extraction of propolis flavonoids with traditional organic solvents					
Romanian propolis	UAE	Polyphenolic derivatives	Ultrasonic time (10–100 min), solvent composition (water, 25% and 50% ethanol solution, *m*/*m*), liquid-solid ratio (*m*:*m* = 2:1, 4:1 and 6:1), and temperature were constant	The antibacterial and antifungal activities of all extracts were higher than those of the impregnation method, especially the 50% ethanol extract, whose antioxidant capacity was 3 times that of the impregnation extract.	[167]
Brazilian green propolis	UAE	Phenolic compounds	The concentration of ethanol is 99%, the ratio of propolis to solvent is 1:35, and the extraction time is 20 min	The extraction time was shortened obviously, and the extract had an antioxidant effect.	[168]
Chinese propolis	UAE	Volatile components	100 mL 95% ethanol, 220 W, 40 kHz, extraction time 30 min	Ultrasonic-assisted extraction could increase the yield of TFC and TPC, and the extracts had higher antioxidant and antibacterial activities.	[169]
Moroccan propolis	UAE	Polyphenols, flavonoid	Ultrasonic time 15 min, propolis/solvent ratio 30 g/mL, ethanol concentration 40%	The optimal extraction conditions for propolis resulted in a yield of 15.39%, the total phenolic content of 192 mg gallic acid equivalents (GAE)/g propolis, the total flavonoid content of 45.15 mg QE/g propolis, the DPPH-IC_{50} value of 29.8 μg/mL, and the FRAP-EC_{50} value of 128.3 μmol Fe^{2+}/g.	[170]
Brazilian green propolis	UAE	Phenolic compounds	Extraction solvent 99% ethanol, extraction time 120 min	The total phenolic content was (612.14 ± 0.84) mg GAE/g sample, and the antioxidant capacity was (534.39 ± 0.20) μmol/L ferrous sulfate/g sample (FRAP) and (72.37 ± 0.80) μmol TEAC/g DPPH.	[171]
Italian raw propolis	MAE	Polyphenols compounds	Microwave power 300 W, magnetron frequency 2 450 MHz, extraction temperature 106 °C, a solvent composition close to EtOH-H_2O 80:20 (*V*/*V*), extraction time 15 min	Shorten the extraction time and reduce the amount of solvent to improve the extraction effect. The total phenolic acid content was 5.0–120.8 mg/g, and the total flavonoid content was 2.5–168.0 mg/g.	[172]
Lithuania propolis	MAE	Hydroxycinnamic acids	Extraction time is 5 min, microwave power is 800 W (*n* = 4), and the solvents (propylene glycol solution) were 20%	The content of hydroxycinnamic acid (*p*-coumaric acid, ferulic acid and caffeic acid) in the aqueous extract of propolis was increased by microwave-assisted extraction and repeated extraction cycle.	[37]
Trigona propolis	MAE	Flavonoids, phenolic	The maximum extraction temperature was 115 °C, the sample solvent ratio was 1:5 (*m*/*V*), and the microwave power was 300 W	When the temperature was controlled below 125 °C, the extraction of propolis was completed in a shorter time (15 min) and with less solvent (the ratio of sample to solvent is 1:5 (*m*/*V*)), and the extract did not degrade.	[38]
Colombian propolis	SE, MAE, SFE	Flavonoids, polyphenols	Temperature of CO_2 was 35 °C, pressure was 200 bar	Modern MAE and SC-CO_2 extraction methods were more selective to flavonoids, the extraction rate of SC-CO_2 was higher, and the antioxidant capacity was stronger.	[173]
Red propolis	SFE	Flavonoids, phenolic	The mass ratio of CO_2/sample was 131, the co-solvent was 4% ethanol, 350 bar and 40 °C, and the CO_2 flow rate was 6 g/min	Supercritical fluid extraction (SFE) technology can obtain higher extraction rates and antioxidant compounds content.	[174]
Indonesian raw propolis	SFE	Galangin, phenethyl *p*-coumaric acid and other active compounds	50 °C, 250 bar, CO_2 flow rate 15 g/min	The yield of propolis extracted by supercritical CO_2 was 14.4% (*m*/*m*), which had good antioxidant activity, and the IC_{50} value was 24.77 μg/mL.	[175]
Italian propolis	SFE	Polyphenols	317 bar, 45 °C, test time 6.5 h	Pressure and temperature had linear or quadratic effects on flavonoids, while time had little effect. Compared with traditional ethanol extract, the extracted section has different components.	[176]
Anatolia propolis	PLE	Phenolic compounds	40 °C, 1 500 psi, ethanol:water:HCl = (70:25:5, *V*/*V*), 0.1% tert-butylhydroquinone (tBHQ) as a solvent, extracted 3 times in 15 min, cell size is 11 mL	The total content of phenolic substances in propolis samples had a parallel relationship with total phenol content and free radical scavenging performance. All propolis samples have the good anti-free radical ability, and the Trolox equivalent activity of each gram of extract was up to 500 mg.	[177]
Brazilian red propolis	PLE	Saturated and unsaturated aromatic hydrocarbons, ketones, alcohols, ethers, and terpenes	100 bar, SLR 0.04, 70 °C, 10 min per cycle	Approximately 64% of the terpenes were recovered under optimal conditions, promoting high cytotoxic activity against tested cell lines.	[178]
Extraction of propolis flavonoids with new alternative solvents					
Chinese propolis	SPE	[C12mim]Br	Ultrasonic power 300 W, ultrasonic time 20 min, pH 6.7, extractant [C12mim]Br 200 mmol/L, adsorbent MCC 5 μg/mL, oscillation time 60 s, eluent ethyl acetate	A sensitive and reliable ME-DMSPE method based on ionic liquid was established for the simultaneous extraction and preconcentration of phenolic compounds.	[179]

Table 3 (*Continued*)

Propolis Origin	Type of extraction	Extracted compounds	Treatment conditions	Major findings	References
			Extraction of propolis flavonoids with traditional organic solvents		
Brazilian red propolis	UAE	Ionic liquids, DES	Extraction time 3.3 min, power 300 W, extraction times four times	Under the optimal extraction conditions, (394.39 ± 36.30) mg RuE could be recovered, and the total antioxidant capacity was (7 595.77 ± 5.48) μmol TE/g dried biomass, which inhibited the growth of *S. aureus* and *Salmonella*.	[180]
Brazilian green propolis	Solution extraction	NADES	The extraction solvents were choline chloride:propylene glycol = 1:2 and choline chloride:lysine:water = 1:1:1, and the extraction temperature was 50 °C.	NADES, honey, and *L*-lysine aqueous solutions all show the potential to substitute ethanol or water for green propolis extraction.	[49]
Bulgaria propolis	UAE	NADES	Ultrasound for 1 h, no heating, centrifugation at 13 000 r/min for 40 min	NADES propolis extract has good antioxidant potential and can extract bioactive substances from natural sources.	[181]
Greek propolis	UAE, MAE	NADES	Choline chloride:tartaric acid = 2:1, ultrasonic power 600 W	The natural deep eutectic solvents can be used as potential solvents for extracting phenolic compounds from propolis.	[182]

Note: SC-CO_2, supercritical carbon dioxide; PLE, pressurized liquid extraction; GAE, gallic acid; QE, quercetin; DPPH, 1,1-diphenyl-2-picrylhydrazyl; IC_{50}, half maximal inhibitory concentration; FRAP, ferric ion reducing antioxidant power; EC_{50}, half-maximal effective concentration; TE, trolox equivalent; RuE, rutin equivalent; NADES, natural deep eutectic solvent; DES, deep eutectic solvent; TFC, total flavonoid content; TPC, total phenolic content.

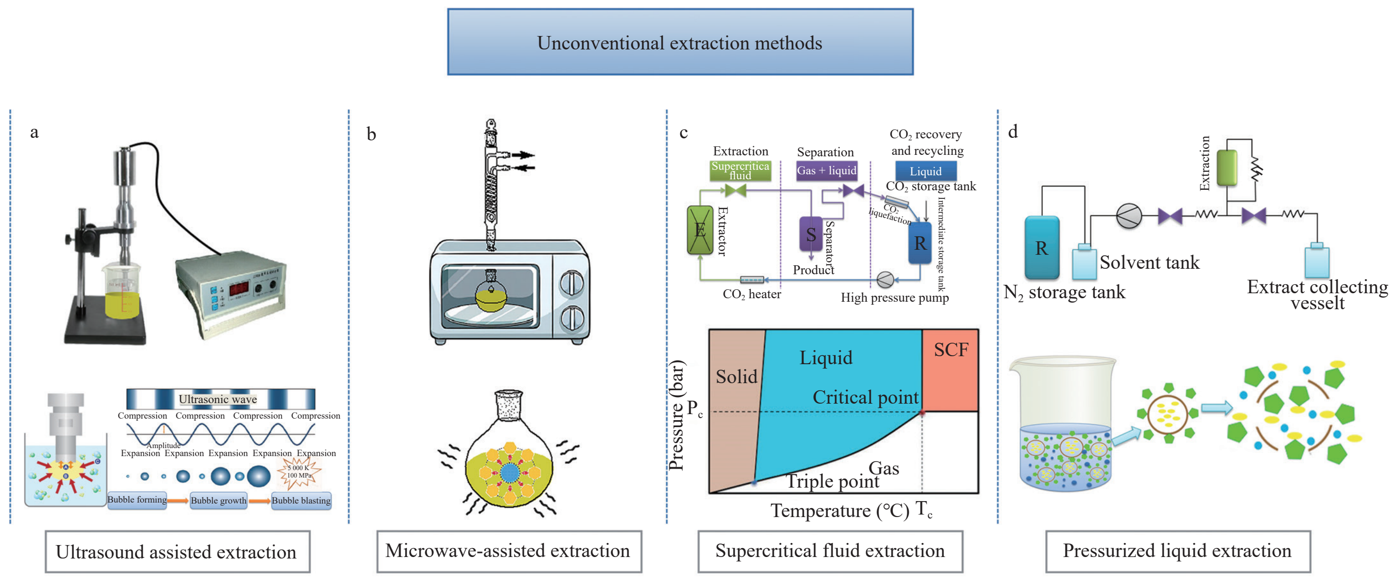

Fig. 2 Schematic diagram of experimental equipment for unconventional extraction technologies, including (a) UAE, (b) MAE, (c) SFE, (d) PLE.

3.1 UAE

UAE is a green process that utilizes sound waves ranging from 0.02 to 100.00 MHz to generate series compression and expansion to extract active compounds from complex substrates. Ultrasound induces the formation of microbubbles, which constantly expand and compress and finally break, resulting in cavitation[29]. The cavitation phenomenon leads to strong shear force, shock wave, macroscopic turbulence, and microscopic mixed and sound flow, thus improving heat and mass transfer of matrix cell wall, enhancing solvent penetration in a food matrix, accelerating diffusion, and shortening processing time while improving extraction efficiency of thermolabile compounds[30].

In recent years, UAE has been widely applied for extracting active ingredients from propolis. Maria Nichitoi et al.[31] used UAE method to extract polyphenols from Romanian propolis and compared it with previous extraction methods. The results showed that UAE could shorten the extraction time and increase the extraction efficiency, and also changed the ratio of flavonoids to polyphenolic acids. In addition, the antibacterial and antifungal activities of the ultrasonic extract with 50% ethanol were higher than those of the immersion method. Its antioxidant capacity was 3 times that of the impregnated section. Oroian et al.[32] studied the effects of ultrasonic amplitude, temperature, time, and solvent concentration on the extraction of bioactive compounds from propolis, and revealed that the optimal extraction parameters were 100% ultrasonic treatment, 70% solvent concentration, 58 °C extraction temperature, and 30 min extraction time. The extraction effect of bioactive compounds was good, with the extraction content of 459.92 mg gallic acid equivalents (GAE)/g total phenolic content (TPC) and 220.62 mg quercetin equivalents (QE)/g total flavonoid content (TFC).

3.2 MAE

MAE is a green and effective technique to extract bioactive compounds from complex matrices, utilizing high-frequency electromagnetic radiation from 0.3 to 300.0 GHz. This extraction technology is mainly through the direct interaction between electromagnetic waves and polar solvent molecules, which converts electromagnetic waves into heat energy to generate heat, which is transferred through dipole rotation and ion conduction. Heating leads to hydrogen bond breaking and ionic migration, accelerating the transfer of mass and heat, which promotes the migration of solute from inside the complex matrix to the extraction solvent medium, making it easier to extract the target compound[33]. MAE offers a faster heating rate than traditional extraction methods, thereby preventing the occurrence of a thermal gradient that may lead to the degradation of heat-sensitive bioactive compounds. In addition, MAE can also reduce extraction time, solvent, energy consumption and produce higher yields than traditional methods[34].

Oroian et al.[35] compared the extraction efficiency of phenolic compounds from propolis by double impregnation, double microwave treatment, and double UAE with 70% ethanol as extraction solvent. The UAE method exhibited a higher extraction yield and the highest content of *p*-coumaric acid among the phenolic compounds (271.65 mg/g propolis) compared to the MAE method and immersion method. Several factors affect the efficiency of MAE, including microwave power, frequency, radiation time, solvent composition and concentration, solid-liquid ratio, and extraction temperature, among others[36]. Previous studies have shown that longer irradiation times and higher radiation power lead to lower yields. In addition, higher extraction temperatures will also lead to the degradation of extracted phenolic compounds[37-38]. Therefore, optimizing the extraction time, irradiation power, and temperature within the appropriate range is crucial to improve efficiency during MAE.

3.3 SFE

SFE is a green extraction technique widely employed to recover of bioactive compounds from various materials. Supercritical fluids exhibit intermediate properties between gases and liquids, depending on the pressure, temperature and composition of the fluids. Among supercritical fluids, CO_2 is the most commonly used in extraction processes. CO_2-based SFE has the selectivity and potential for extracting heat-sensitive compounds, and compounds with low polarity and small molecules are readily soluble in supercritical carbon dioxide (SC-CO_2)[39]. However, the only disadvantage of CO_2 is that it has a low polarity, making it unsuitable for extracting polar flavonoids. Therefore, to overcome the low polarity limit of CO_2, researchers have employed chemical modifiers or co-solvents, such as methanol, water, ethanol, and acetonitrile, to increase the polarity of the supercritical fluid mixture[40].

To enhance the extraction efficiency of the target compound during supercritical extraction, various parameters, including extraction temperature, pressure, cosolvent ratio, and sample size, must be optimized. In addition, the solubility and the resistance to mass transfer of raw materials are also related to these variables[41]. Generally, the extraction efficiency of bioactive compounds can be enhanced by increasing the pressure and temperature of supercritical CO_2 to reach the optimal levels. At constant temperature, the increase in pressure leads to an increase in the density of CO_2 and its solvation ability, thus improving the diffusion and mass transfer of the target compound in the fluid[42]. Sun et al.[43] used a two-step sequential extraction process consisting of SFE and UAE to extract crude propolis, and the results showed that the yields of propolis extract, total flavonoids, and 8 characteristic flavonoids obtained by SFE were significantly higher than those obtained using supercritical CO_2 extraction. Compared with other extraction technologies, SFE has advantages such as rapid processing time, suitability for the extraction of volatile and heat-sensitive ingredients, improved productivity in terms of yield, and the use of safe solvents for environmental protection[44].

3.4 Pressurized liquid extraction (PLE)

PLE is a technique that uses a liquid solvent for extraction under high temperature and pressure, allowing the liquid solvent to extract bioactive compounds at temperatures above its atmospheric boiling point. PLE process utilizes high temperature and pressure to improve the solubility and mass transfer rate between the plant substrate and solvent, enhancing extraction efficiency[45]. The increase in temperature leads to significant changes in the physical and chemical properties of water, which breaks the interaction between matrix and analyte and leads to a higher diffusion rate of the analyte. Conversely, increasing the pressure maintains the solvent below its boiling point[39].

Contieri et al.[46] recovered flavonoids and polyphenols from Anatolian propolis by pressurized liquid extraction technology. The recoveries of polyphenols were between 97.2% and 99.7% at 40 °C, 1 500 psi, with ethanol: water: HCl (70:25:5, *V*/*V*) as the solvent for 3 extractions within 15 min. In addition, the influence of temperature on extraction efficiency also been discussed, the results showed that high temperature will lead to the degradation of polyphenols and other compounds, and reduce the extraction efficiency. In conclusion, higher temperature and pressure during the extraction process not only improves the extraction rate but also reduces the time and consumption of solvents. The extraction equipment of PLE protects oxygen and light-sensitive compounds[47]. However, the extraction of heat-sensitive compounds should be cautious because the extracted active compounds may be degraded. Therefore, PLE has been developed to be used in combination with ultrasound-assisted extraction and solid-phase extraction, which helps to increase extraction rates and improve the cost-effectiveness and sustainability of the process[48].

3.5 Alternative solvent extraction

Currently, during propolis extraction, water-ethanol solvent is the most commonly used effective solvent to extract the active ingredients of propolis. However, due to the intolerance of some people to ethanol and the insufficient use of alcohol products for those who quit drinking and children, many researchers are exploring alternative green solvents to replace traditional organic solvents[49]. In recent years, ionic liquids have attracted more and more attention because of their excellent extraction characteristics. The ionic liquid is an organic salt solution with a low melting point. More and more studies have found that ionic liquids have shortcomings such as high toxicity, complex synthesis pathway, poor stability, and biodegradation[50]. Therefore, Abbott et al.[51] proposed deep eutectic solvents (DESs) as an environmentally friendly alternative to organic solvents and ionic liquids. DESs are liquid mixtures formed by heating and stirring a hydrogen bond acceptor (HBA) and a hydrogen bond donor (HBD) in a specified proportion. Due to the charge delocalization caused by the formation of hydrogen bonds between the components of DES, its melting point is lower than that of the individual parts, so it exists in liquid form at room temperature[52]. At present, DESs are widely used for the extraction and concentration of biological organic molecules, such as flavonoids, phenols, pigments, polycyclic aromatic compounds, etc.[50]. In 2011, Choi et al. [53] proposed the concept of natural deep eutectic solvents (NADES), which are natural DESs formed by the mixture of primary metabolites of organisms (sugar, phenol, amine, organic acid, etc.) as HBA and HBD respectively. Compared with DES, NADES has the advantages of low cost, easy preparation, low toxicity, better sustainability, high biocompatibility, and solubility, and it has potential use as a green extraction medium[54].

As new green solvents, NADESs are more effective than traditional organic solvents and can improve the yield of propolis extract. Dlugosz et al.[55] described the process of obtaining antibacterial nano selenium from propolis extract and quercetin using the NADESs. The results demonstrated that the contents of flavonoids and terpenoids, and the antioxidant properties of propolis extract treated with citrate-propylene glycol-proline, were the highest. The total phenolic content of propolis extract was 30–200 mg/g propolis, and the flavonoid content was 3–70 mg QE. However, in the application of DESs as an extraction solvent, it is difficult to recover bioactive molecules. However, the above problem is avoided by using NADES to extract food or drug matrices consisting only of non-toxic food additives without the need to separate them from the extracted compounds[49]. In addition, the interference of DES and its components to the detection method generally does not exist, and it shows high compatibility in various instrument detection systems. Therefore, new combinations of DES extraction with advanced separation techniques such as HPLC, GC, and TLC are being developed[56]. The advantages and disadvantages of the different extraction techniques for propolis flavonoids are summarized in Table 4.

4. Functional properties of bioactive compounds in propolis

Propolis has a wide range of biological properties, including antioxidant, antibacterial, anti-inflammatory, antiviral, anti-inflammatory, anticancer, hypoglycemic, and neuroprotective activities. Fig. 3 shows the bioactive compounds and functional activities of propolis. These activities are discussed in the following subsections together with the mechanisms of activity involved.

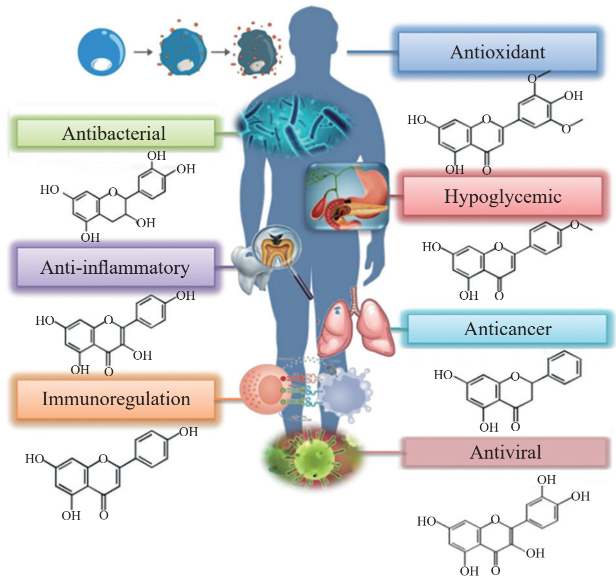

Fig. 3 Schematic diagram of bioactive compounds with different functional properties from propolis.

4.1 Antioxidant activity

Excessive free radicals in the body can lead to phospholipid oxidation of cell membranes, DNA and protein damage and tissue damage[57]. As an effective inhibitor of oxidative stress, propolis and its bioactive compounds can prevent tissue damage caused by free radicals by preventing their formation, scavenging free radicals, or promoting their degradation. They can prevent or inhibit the development of various chronic diseases, including cardiovascular disease and cancer[58-59]. In addition to inhibiting oxidation chain reaction, chelating active metal ions, and repairing the damage of biological molecules, propolis and its bioactive compounds can also prevent the formation of active substances, scavenge, neutralize, and remove active substances. Moreover, it plays an antioxidant role in the external oxidative stress model of toxic liver injury, free radical-induced damage to human erythrocyte membrane, skin damage, etc.[60-63].

In addition, propolis and its bioactive compounds promote wound healing in the skin by stimulating epithelial regeneration, regulating extracellular matrix deposition, and promoting granulation tissue formation[62]. Propolis and its bioactive compounds can also up-regulate the expression of antioxidant-related genes and protect

Table 4
Advantages and disadvantages of different extraction techniques of propolis flavonoids.

Technology	Advantages	Disadvantages	Critical parameters	References
UAE	Less solvent use, shorter extraction time and higher extraction yield	Wave attenuation occurs in high viscosity samples	Solvent type, solvent concentration, ultrasonic extraction temperature, ultrasonic time, ultrasonic power and frequency	[183]
MAE	Shorter extraction time, lower energy consumption, higher extraction yields, less solvent use and higher extraction automation	Higher cost	Microwave power, irradiation time, type of solvent, food substrate type and water content	[184]
SFE	Enhancing extraction effectiveness, decreasing the energy, solvent, and extraction time, and consumption	Complex equipment, high operating costs and high energy consumption	Temperature, pressure, the flow rate of the solvent, extraction time, and type of co-solvents	[185]
PLE	Effectively save energy and solvent, improve extraction efficiency	High energy consumption and running costs	Solvent type, pressure, extraction time	[46]
Green solvent extraction	Low cost, easy synthesis, environmentally friendly, strong solubilization ability	Higher solvent viscosity	Type of DES and moisture content	[186]

cells from tissue damage by activating specific signaling pathways, thus exerting its antioxidant activity *in vivo*. The molecular mechanism of its antioxidant action in Raw 264.7 and L929 cells was studied[62,64]. Cao et al.[62] investigated the protective effect of ethanol extract of propolis on hydrogen peroxide damaged L929 cells and its potential mechanism. The findings demonstrated that the propolis ethanol extract induced the expression of heme oxygenase-1 (*HO-1*), glutamate-cysteine ligase modified subunit (*GCLM*), and other antioxidant genes, and had the potential to alleviate oxidative stress in wound tissue.

4.2 Antibacterial activity

Current studies have shown that propolis and its bioactive compounds have inhibitory effects on bacteria, fungi, and pathogens, including *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Bacillus cereus*, and *Staphylococcus aureus*[65]. Compared with Gram-negative bacteria, most propolis showed stronger antibacterial activity against Gram-positive bacteria, especially against *S. aureus*. This difference is thought to be that the outer membrane of Gram-negative bacteria may prevent the active molecules from entering the cells and prevent the accumulation of propolis components in the cells[66]. In addition, the production of bacterial hydrolase in the outer membrane structure may damage and reduce the effectiveness of active ingredients present in propolis, making Gram-negative bacteria more resistant to propolis components[67].

Studies have shown that the ethanol extract mixture of Portuguese propolis has superior antioxidant activity and antibacterial activity compared to a single extract[68]. Propolis contains many substances, including flavonoids, phenolic acids, aldehydes, and terpenes. It can be confirmed that the antibacterial properties of propolis are attributed to the synergistic effect of various components. Among these, quercetin, as a flavonoid that exists in propolis, can bind to the subunit of DNA spinase in *Escherichia coli* to block the activity of bacteria[67]. Another study has shown that cinnamic acid inhibits the production of ATPase, cell division, and biofilm development in bacteria by causing damage to the cell membrane. This effect is associated with the disruption of critical metabolic pathways and inhibition of intracellular pH homeostasis[69]. Propolis and its bioactive compounds may also stimulate and enhance the host cell's immune system, mainly by inhibiting cell division, hindering the function of the cytoplasmic membrane, changing membrane permeability, inhibiting energy production pathway, and reducing bacterial resistance to some conventional antibiotics, etc.[67,70]. Owing to the synergistic action of its various constituents, it possesses multi-target activities in cells, making it a promising candidate for the development of novel, effective, and economic antibacterial agents with broad-spectrum biological potential[11]. The antibacterial properties of different propolis are shown in Table 5.

4.3 Antiviral activity

Currently, propolis and its bioactive compounds exhibit powerful antiviral properties against various viruses, including herpes simplex virus type 1 and type 2, influenza viruses, and human immunodeficiency virus (HIV)[71]. Caffeic acid, flavonoid, aromatic acid, and their esters in propolis can inhibit energy metabolism and synthesis of nucleic acid by destroying cell plasma membrane, thus inducing cell apoptosis or blocking cell pathways and preventing the transmission and reproduction of the virus. Due to its higher antiviral activity and low toxicity, propolis and its bioactive compounds can be used as an antiretroviral drug for HIV treatment[72].

Propolis and its bioactive compounds have demonstrated antiviral activity against the novel coronavirus SARS-CoV-2. Some studies have shown that the active substances that exist in propolis, such as artepillin C, baccharin, and quercetin, have inhibitory effects on SARS-CoV-2 in the human body[73]. The inhibitory effect of the active ingredient in propolis is mainly reflected in its impact on several important targets, such as reducing the resistance of angiotensin-converting enzyme 2, thus promoting the entry of the virus into cells. In addition, they can also regulate the immune function of macrophages, reduce and eliminate the generation of interleukin (IL)-1β and IL-6, reduce the inflammatory activity caused by COVID-19, reduce the fibrotic transcription of NF-κB and activator of transcription 3, and block the PAK1 pathway[74].

4.4 Anti-inflammatory activity

Inflammation is caused by chemical mediators released by damaged tissues and migrating cells and is an immune response of the body to pathogens and injuries. Numerous studies have shown that compounds extracted and isolated from Brazilian green, brown and red propolis have anti-inflammatory activity. It confirms that propolis and its bioactive compounds have an excellent therapeutic potential in the treatment of inflammation[75]. The main mechanisms of propolis and its bioactive compounds anti-inflammatory action include inhibition of the cyclooxygenase and prostaglandin biosynthesis, scavenging of free radicals, inhibition of the nitric oxide synthesis, reduction of inflammatory cytokines secretion, and reduction of the immunosuppressive activity[76-77]. Xu et al.[78] demonstrated that different concentrations of propolis extract and its major flavonoids had regulatory effects on reactive oxygen species (ROS) levels, antioxidant enzymes, and the expression of *HO-1* in H9c2 cells, which could activate the Nrf2 pathway and inhibit NF-κB pathway.

In addition, propolis and its bioactive compounds have been shown to promote skin healing and protection by stimulating epithelial repair, regulating extracellular matrix deposition, and promoting granulation tissue formation to accelerate skin wound healing[79]. The vanillin and phenolic acid in propolis can enter the epidermis or dermis after radiation or before the aging and maturation of dermis cells to protect them from the influence of free radicals[80]. The methanol extract of Greek propolis can significantly reduce the expression level of matrix metalloproteinase in the recombinant skin tissue model exposed to ultraviolet B (UVB) and reduce the damage of UVB to skin tissue[81]. Andritoiu et al.[82] evaluated the healing effect of propolis ointment on incision, excision, and burn wounds using rat models. The results demonstrated that propolis ointment could enhance wound healing and tissue regeneration. Furthermore, propolis has been reported to have therapeutic potential in respiratory conditions and ailments, including asthma and rhinitis. Propolis and bioactive compounds can reduce oxidative damage, reduce the expression of inflammation-related enzymes and proteins, and alleviate the symptoms of asthma in animals by up-regulating antioxidant enzymes and protein catalase, superoxide dismutase, and Nrf2 and reducing oxidation markers malondialdehyde, NO and iNOS[83].

Table 5
Antibacterial properties of different propolis flavonoids.

Geographical origin	Antibacterial component	Organism tested	MIC	References
Thailand propolis	Phenolic compounds, especially flavonoids, phenolic acids, and their esters	*Streptococcus mutans*	1.172 mg/mL	[187]
Taiwanese green propolis	Propolins C, D, F and G	*Methicillin-resistant S. aureus* (MRSA)	2 μg/mL	[188]
Egyptian propolis	Main phenolic compounds	Gram-positive bacteria (*Listeria monocytogenes*, *S. aureus*) and Gram-negative bacteria (*Salmonella enterica*, *E. coli*).	0.20 mg/mL 0.63 mg/mL 1.10 mg/mL 1.00 mg/mL	[189]
Brazilian red propolis	Crude Brazilian red propolis extract	Anaerobic endodontic pathogens	6.25–50.00 μg/mL	[190]
Brazilian red propolis	formononetin, biochanin A, and liquiritigenin	*S. aureus*, *Bacillus subtilis*, *E. coli*, *P. aeruginosa*	56.75, 28.37, 454.00, 227.00 μg/mL	[191]
Chinese propolis	Polyphenol constitutions	*Clostridium perfringens*	12.5 μg/mL 50 μg/mL 50 μg/mL 50 μg/mL	[192]
Brazilian red propolis	Luteolin and quercetin	*E. coli*, *P. aeruginosa,* bacteria *S. aureus*	128–512, 512, 64–1 024 μg/mL	[193]
Brazilian stingless propolis	Volatile geopropolis oils α-pinene	*S. aureus*, *E.coli*, *P. aeruginosa.*	103–224 μg/mL	[194]
Chinese propolis	Phenolic, flavonoid	*S. aureus*, *L. monocytogenes*, *B. subtilis*	–	[169]
Iranian propolis	Extracts of propolis	*S. aureus*, *P. aeruginosa*	0.164, 0.022, 0.082, 0.041 mg/mL	[195]
Morocco propolis	Phenolics and flavonoids	*S. aureus*, *B. subtilis*, *Bacillus cereus*, *Salmonella typhimurium*, *E. coli*, *Klebsiella pneumonia*	0.15–5.00 mg/mL	[196]
Nepalese propolis	Flavonoid aglycones and pterocarpans.	*Helicobacter pylori*, *S. aureus*, *S. aureus MRSA*, *E. coli*, *Candida kruseic*	250 μg/mL	[197]
Romanian propolis	Quercetin, polyphenols and flavonoids.	*S. aureus*, *B. cereus*	–	[198]
Brazilian green propolis	Artepillin-C, kaempferide, drupanin and *p*-coumaric acid	*S. aureus*, *L. monocytogenes*, *Enterococcus faecalis*, *S. saprophyticus*	3.1 mg/mL 3.1 mg/mL 3.1 mg/mL 6.2 mg/mL	[199]

Note: MIC, minimum inhibitory concentration.

4.5 Anticancer activity

Cancer is characterized as a malignant disease that arises from abnormal cell growth and proliferation mechanisms, which may lead to spreading and invading other tissues or organs. Many studies have shown that propolis and its bioactive compounds have good anticancer activity and have a therapeutic effect on breast cancer, liver cancer, lung cancer, and pancreatic cancer cells[84-85]. Currently, the active compounds found in propolis with anti-cancer and anti-proliferation properties include apigenin, ferulic acid, luteolin, pinocembrin, and quercetin[73]. Studies have shown that the main anti-tumor mechanisms of propolis and its compounds include inducing cell apoptosis, cell cycle arrest, immune regulation, anti-angiogenic activity, and reactive oxygen generation[86-87]. Chrysin, as an active component of propolis, can inhibit the proliferation of human tissue lymphoma cells and induce their apoptosis by inhibiting the expression of the protein complex in the cell cycle and blocking the cell cycle[88]. It is similar to the mechanism of anticancer activity of caffeic acid phenethyl ester that was reported previously[89].

Although the efficacy and safety of propolis and its bioactive compounds in preventing and treating cancer have been widely recognized, its clinical application has been hampered by its poor physical and chemical properties and limited oral bioavailability. Therefore, many studies have used propolis in nano-drug delivery systems. Al-Fakeh et al.[90] prepared palladium nanoparticles by encapsulating Saudi propolis extract with biological methods and evaluated the anticancer activity of palladium nanoparticles against breast duct cancer cells. The results showed that nanoencapsulation improved the oral delivery of propolis, improved its bioavailability, and enhanced its anti-tumor activity. Palladium nanoparticles had effective anti-tumor action against breast duct cancer, with half maximal inhibitory concentration (IC_{50}) of 104.79 μg/mL.

4.6 Hypoglycemic activity

In recent years, the prevalence of diabetes and obesity has risen rapidly, especially in developing countries such as China and India. Diabetes is a metabolic disorder characterized by hyperglycaemia and glycosuria and it was caused by either absolute or relative insulin deficiency[91]. Type 2 diabetes mellitus (T2DM), a type of diabetes mellitus, develops from dysregulation of insulin signaling and is associated with impaired regulatory and signaling mechanisms[92]. Studies have shown that propolis and its extracts show anti-diabetic activity and can be used as potentially effective drugs in treating diabetes[93].

Therefore, researchers used streptozotocin to induce rapid and irreversible necrosis of mouse beta cells to build a diabetic animal model and evaluate the therapeutic effect of propolis and its bioactive compounds on diabetic mice[94]. Propolis and its bioactive compounds can reduce blood glucose levels, reduce lipid peroxidation and eliminate free radicals caused by high blood sugar. Propolis supplementation can reduce inflammation, regulate fasting blood glucose, insulin, and glycosylated hemoglobin levels, and enhance antioxidant defense[95]. Wang et al.[96] identified 27 potential biomarkers of T2DM in fecal samples by metabonomics method. They proved that propolis ethanol extract effectively regulated the disorders of metabolic pathways of glycerophospholipids, sphingolipids, riboflavin, and sterol lipids caused by T2DM. The therapeutic potential of propolis ethanol extract in managing of T2DM has been demonstrated.

The antidiabetic effect of propolis and its bioactive compounds may be attributed to the bioactive molecules interacting with each other. Studies have demonstrated that apigenin and naringin exhibit the potential to improve glucose levels and vascular dysfunction, and they can regulate lipid metabolism and insulin resistance in rats with T2DM[97]. Chlorogenic acid promotes glucose transport through the activation of GLUT4 translocation, IRS-1, and PI3K signaling pathways. Ellagic acid exhibits potent hypoglycemic activity by inhibiting the production of IL-1 and tumor necrosis factor (TNF)-α and suppressing the pathways of AP-1 and MAPK subsequently[98]. In addition, caffeic acid phenethyl ester from propolis showed antioxidant capacity and improved insulin sensitivity, blood glucose and glycosylated hemoglobin levels, hyperlipidemia, peroxisome proliferator-activated receptor α levels, and *HO-1* expression in patients with diabetes[99]. Studies have shown that galangin and pinocembrin can increase glucose consumption and glycogen content by increasing pyruvate kinase activity, and they have a synergistic effect on improving insulin resistance[100].

5. Bioavailability and bioaccessibility of bioactive components in propolis

Despite the recognized health benefits of propolis, its poor water solubility, rapid and intense metabolism, low absorption rate, and therefore low bioavailability and bioactivity limit its clinical application. The main bioactive components in propolis are mostly flavonoids. Studies have shown that the oral bioavailability of flavonoids is generally less than 10% or even less than 5%[101]. In addition, due to the complexity of the food matrix, these flavonoids, once ingested into the body, are converted into absorbable molecular forms during digestion, which are affected by a variety of factors, leading to their release and absorption in different organs such as the mouth, stomach, small and large intestines, thus altering bioavailability[102]. The main factors contributing to the low bioavailability of propolis and its bioactive compounds, as well as strategies to improve their bioavailability, are explained below.

5.1 Factors affecting the bioavailability of propolis and its bioactive compounds

5.1.1 Chemical structure and its properties

Most of the propolis and its bioactive components are polyphenols and flavonoids, such as chrysin, pinocembrin, apigenin, ferulic acid, caffeic acid phenethyl ester, etc.[103]. Most of these compounds have the characteristics of high molecular weight, poor water solubility and low permeability. These factors have great influence on the absorption and bioavailability of bioactive compounds in propolis. High-molecular weight flavonoids are nearly impossible to absorb, which causes them to pass directly into the colon, where they are degraded by the gut flora. In addition, high molecular weight flavonoids have large steric hindrance due to their aromatic ring structure and polar groups such as hydroxyl and carboxyl groups, resulting in poor water solubility and low bioavailability[102]. Kim et al.[104] compared the oral bioavailability of apigenin-loaded W/O/W emulsions with apigenin suspensions in rats. The results showed that apigenin was rapidly metabolized after oral administration in rats, resulting in low oral bioavailability, while the oral bioavailability of apigenin-loaded emulsion was increased by about 9 times. In addition, most flavonoids exist in large-sized glycosylated forms, which have poor transmembrane transport capacity and therefore reduce metabolic and subsequent biological activity.

5.1.2 Complex gastrointestinal environment

When propolis and its bioactive substances are ingested, they are affected by multiple factors in a complex gastrointestinal environment. It mainly includes the influence of pH on bioactive substances, degradation metabolism and transformation of intestinal flora, transmembrane transport of small molecule active substances, and interaction between bioactive substances and gastrointestinal mucous[102]. Among them, the polyphenols and flavonoids in propolis will degrade, change or transform their structure under different pH conditions in the gastrointestinal environment, which significantly affects their absorption. Furthermore, the metabolites and bioavailability of flavonoids in propolis are highly influenced by the composition of the gastrointestinal microbiota. Typically, a small portion (20%) of oral polyphenols or flavonoids is absorbed in the small intestine and enters the systemic circulation, while the majority is transported to the colon. Due to the long exposure time and its resident microbiota, unabsorbed phenolics entering the colon are metabolized by the gut microbiota through deglycosylation, dehydroxylation, demethylation, and ring fission into a variety of smaller fractions that are then absorbed or excreted[105]. In addition, studies have reported the potential role of gastrointestinal mucus on the bioavailability of flavonoids. The mucous layer is selective to flavonoids, and soluble complexes such as glycosylated flavonoids and flavonoids in micelles can penetrate the mucous layer. Hydrophobic glycosides, on the other hand, cannot permeate but are pushed to the large intestine where they undergo microbial metabolism, resulting in lower bioavailability[106].

5.1.3 Interactions between propolis and its bioactive components and food substrates

Due to the complexity of the food substrate, after ingesting propolis and its bioactive components, these polyphenols or flavonoids can interact with proteins, lipids, polysaccharides and minerals in the food substrate (hydrophobic, hydrogen bond interaction, etc.) to produce stable complexes, and even irreversible covalent products[107]. It is worth noting that the reaction between the food matrix and the flavonoids has a reciprocal effect on both. On the one hand, food substrates promote the transfer of flavonoids through the gastrointestinal tract and improve their oxidative stability. On the other hand, they limit the release of flavonoids from the gastrointestinal tract, thereby reducing their absorption in the intestine and inhibiting their physiological effects[108]. Lang et al.[109] explored the effect of *α*-casein on the absorption of blueberry anthocyanins and their metabolites in rat plasma by preparing a complex of *α*-casein and blueberry anthocyanins. The results showed that *α*-casein could promote the absorption of blueberry anthocyanins and their metabolites in the bloodstream, thereby improving their bioavailability *in vivo*. Conversely, flavonoids can also alter the biological functions of certain compounds in food matrices and have different effects on their digestion and absorption. Zhang et al.[110] investigated the effects of quinoa polyphenol binding on the structure and digestive behavior of corn starch. The results showed that quinoa polyphenols form inclusion complexes with maize starch and that complexation promoted the formation and crystallization of local helical and short-range ordered structures in corn starch, leading to the resistance of starch particles to enzymatic digestion.

5.2 Strategies for bioavailability and bioactivity enhancement of bioactive compounds in propolis

Propolis and its bioactive substances have a wide range of drug therapeutic potential attributed to its biological properties such as antibacterial, anti-proliferative, anti-tumor, anti-inflammatory, and immunoregulatory. However, the application of propolis is limited due to its strong odour, unstable physical and chemical properties, insoluble in water, and low bioavailability. Therefore, in order to solve the problem of low bioavailability of propolis, many scholars have used nanoencapsulation technology to prepare drug delivery systems and encapsulate propolis and its bioactive substances in the drug delivery system. It can prevent bioactive substances in propolis from degrading metabolism in the gastrointestinal tract, improve the stability of bioactive substances in propolis to light and heat, improve their solubility and bioavailability, and achieve slow release and targeted delivery of active substances[111].

At present, studies around the world have reported that propolis extracts are encapsulated into different types of nanocarriers, such as liposomes, nanoemulsions, polymers, and metal nanoparticles. It is shown that the different delivery systems of propolis flavonoids are summarized in Table 6. These nanocarriers can enhance the bioavailability of propolis by improving its permeability, resistance to metabolic processes, and circulation time[1,111]. The nanoemulsion is a type of heterogeneous system, and it comprises oil droplets that are dispersed in water with particle sizes smaller than 300 nm. Nanoemulsion is a local drug delivery system prepared by mixing propolis with other substances in a low-energy emulsification method. This system facilitates the skin delivery of hydrophilic and lipophilic compounds. Additionally, it can be employed to enhance the local treatment of skin fungal infections and to expedite wound healing, among other applications[112-113]. In addition, the nano-lipid carrier can also be used as an ideal form of propolis encapsulation. Lipid-based drug delivery systems have been reported to prevent the degradation or hydrolysis of lipophilic drugs, enhance physical stability, hydrophilicity, and bioavailability, and facilitate the targeted and controlled release of drugs. It has been extensively employed due to its ability to overcome the challenges posed by the poor biocompatibility of microemulsion *in vivo* and the instability of liposomes[114]. In short, propolis flavonoids nanoencapsulation materials have the advantages of small volume, high solubility, and good mucosal permeability.

6. Development status of propolis and its products

6.1 The products, industry and market of propolis

With the improvement of living standards and the enhancement of health awareness of people, propolis has attracted widespread global attention due to its unique nutritional value and functional characteristics. At present, the global propolis market size has reached 675.46 million dollars and is expected to reach about 1 110.8 million dollars by 2033, with a compound annual growth rate of 5.1%. Due to the increase in genital herpes cases in the United States and the

Table 6
Forms of propolis flavonoids delivery systems.

Propolis origin	Drug delivery system	Therapeutic potential	References
Baccharis propolis	Solid lipid nanoparticles and nanostructured lipid carriers	Accelerate wound healing	[200]
Brazilian brown propolis	Nanoparticles	Anti-inflammatory, antibacterial and cytotoxic	[201]
Brazilian green propolis	Silver nanoparticles	Antifungal, antibiofilm, atoxic and nonmutagenic properties	[202]
Saudi Arabia propolis	Silver nanoparticles	Antibacterial and wound-healing activity	[203]
Brazilian red propolis	Gold nanoparticles	Antibacterial and anticancer activity	[204]
Indian propolis	Selenium nanoparticles	Antioxidant and antibacterial activities	[205]
Brazilian propolis	Nanoemulsion	Antioxidant, antibacterial and anticorrosive activities	[199]
Brazilian red propolis	Microcapsule	Stability, antioxidant activity	[206]
Dynabeille propolis	Liposome	Antioxidant, antibacterial and wound-healing activities	[207]
Egyptian propolis	Oromuco-adhesive films	Treatment of oral recurrent aphthous ulcer	[208]
Turkish propolis	Nano-vesicle	Anti-lung cancer	[209]
Indonesia	Phytosomes	Treatment of organ injured stress oxidative and skin aging	[210]
Colombian propolis	Nanostructured lipid carriers	Low cytotoxicity *in vitro*	[211]
Iran propolis	Nanostructured lipid carriers	Reduce the risk of cardiovascular diseases	[212]
Thailand propolis	Nanoparticles	Antifungal activity	[213]
Egyptian propolis	Nano-in-microparticles	Anticancer activity	[214]
Bulgaria poplar propolis	Silver nanoparticles	Antibacterial and antifungal activities	[215]
Sonoran propolis	Nanoparticles	Antiproliferative and anticancer activity	[216]

increasing demand for propolis in Canada, North America has the highest propolis market share globally at more than 36%. The abilities of propolis to enhance the immune system, promote digestive health, and reduce adult wrinkles are the major factors contributing to the second largest market share of propolis in Europe. In addition, the increase of cancer incidence rate and disposable income also promoted the expansion of the global propolis market[115].

In addition, the regulations for the use of propolis vary in different countries and regions. In countries such as the European Union, Japan and Brazil, propolis is used as a food supplement and medicinal product. However, it is worth noting that in China, propolis is only allowed to be used in medicine and health food, but not in ordinary food. The reason for this situation is that propolis is very different from ordinary food. As a health food, propolis contains certain biologically active substances with specific functional effects and specific consumption groups, whereas ordinary food does not emphasise specific functions and can be used by all people. In addition, ordinary food should pass the safety evaluation, and propolis cannot be used as ordinary food in China due to the lack of safety evaluation research data for long-term use as a food[116]. With the deepening of global basic research on propolis and the enhancement of health care awareness of people, the chemical composition and functional properties of propolis are becoming more and more clear, and the cognition of people for propolis is becoming more explicit. As a functional food ingredient, the market demand for propolis is gradually increasing, and it is widely used in food, medicine, cosmetics and other fields.

In recent years, with the increasing demand for propolis, the development of innovative propolis products has become the key for companies to occupy the market. At present, multiple companies such as Apis Flora, Herb Pharm LLC, Bee Health Ltd., Comvita Ltd., Wax Green have emerged globally to participate in the development and innovation of propolis products to meet the growing demand[117]. According to the survey, most of the propolis products on the market are in the form of capsules and tablets, and there are also a small number of products sold in the form of liquid or spray. Currently, propolis products are diversified, expanding the existing lineup by deriving new products from propolis or adding other products to meet the growing market demand. Propolis products, such as food preservatives, dietary food supplements, ointments for the treatment of skin infections, burns, and cancer, mouthwashes, toothpastes and creams with specific skin care needs, are widely used in food, medicine, health care and cosmetics[118]. Fig. 4 shows the application of propolis flavonoids in food, medicine, cosmetics and other industries.

6.2 *Applications of propolis and its products in industries*

6.2.1 *Application of functional compounds in propolis in food industry*

Propolis is widely used in the food industry due to its rich bioactive ingredients. Currently, propolis extract is mainly used for natural antioxidants and preservatives in foods. It can extend the shelf life of foods by delaying lipid oxidation, improving food stability, and

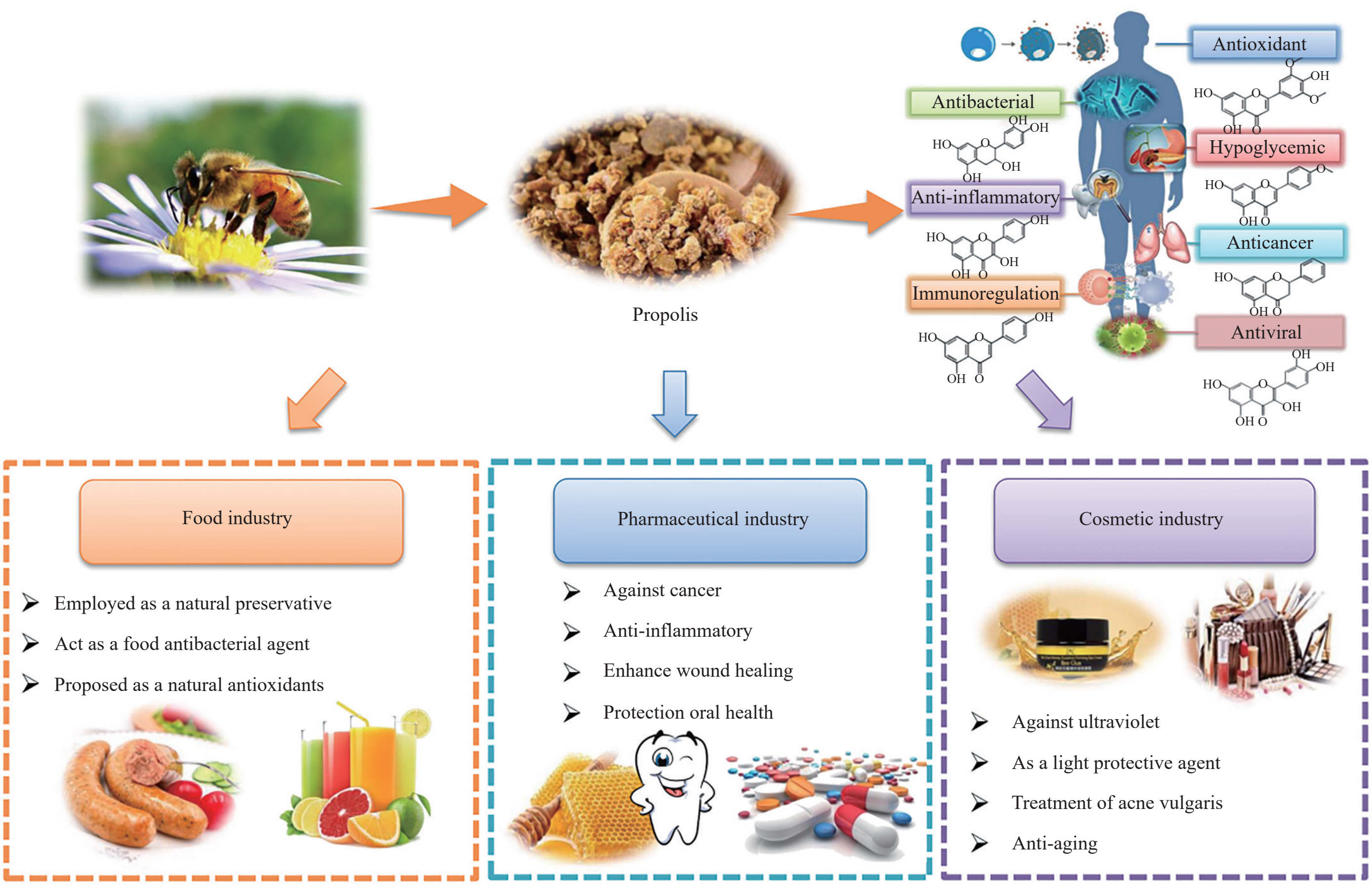

Fig. 4 Applications of propolis flavonoids in the food, medicine, and cosmetics industries.

preventing bacterial spoilage in meat, poultry, fish, dairy products, and fruit juices[119-123]. Mafra et al.[124] substituted the aqueous-alcoholic extract of red propolis for synthetic preservatives to evaluate the oxidation, microbial and sensory stability of fish sausages. The findings demonstrated that the water-alcohol extract of red propolis could delay the deterioration and lipid oxidation of Italian sausage. Santos et al.[125] used red propolis extract as a natural additive and added to yogurt to replace potassium sorbate. Studies have shown that propolis extract is rich in phenolic acids, flavonoids, and other active substances, which can be used as natural functional ingredients, and have been used as a dietary supplement in beverages to enhance human health and disease prevention[126]. The antibacterial properties of propolis are effective against a diverse spectrum of microorganisms, such as bacteria, viruses, and parasites[103]. Because of its antioxidant and antibacterial properties, the application of propolis in food has also been studied to maintain product quality. Vasilaki et al.[127] investigated the use of propolis as a potential natural antibacterial substitute for sorbate in carbonated beverages. They found that propolis helps maintain beverage quality of beverages by inhibiting the growth of fungi and reducing the degradation of ascorbic acid.

At present, propolis has been used in the formulation of film or coating, applied in the preservation of various foods, such as fruit juice, fruits, vegetables, eggs, meat, and fish[128-129]. Propolis serves as a coating that can enhance the resistance of fruit to pathogens and improve its appearance, quality, and overall shelf life by sealing the peels of the fruit epidermis, thus reducing gas exchange and water loss, and respiration[130]. In addition, propolis extract can inhibit the production of carcinogens during food processing. During meat processing, the Maillard reaction will generate carcinogens, and propolis extract can inhibit various steps of the Maillard reaction. Thus, it prevents the formation of carcinogens through the quenching and scavenging of free radicals and the trapping of α-dicarbonyl compounds[131]. For example, propolis extract was used to reduce heterocyclic aromatic amine generation in cooked beef[132].

6.2.2 Application of functional compounds in propolis in medicine industry

Propolis has many functional characteristics and biological activities, such as antioxidant, antibacterial, anti-inflammatory, anti-tumor, antiviral, analgesic, wound healing promotion, and immunomodulatory activities. It indicates that propolis has extensive pharmacological properties and a positive impact on human health[133-134]. It can be widely used in medicine as a dietary supplement to enhance health and prevent disease[135].

Currently, propolis flavonoids are widely used in cancer treatment. It has therapeutic effects on various cancers, including bladder cancer, kidney cancer, liver cancer, and skin cancer. The anti-cancer mechanism involves the regulation of various molecular targets and signaling pathways, including MAPK, NF-κB, etc.[2]. Propolis can inhibit cell proliferation, invasion, and metastasis of different cellular processes, including tumor cells, and promote cell apoptosis[136]. In addition, propolis can also effectively treat and prevent fungal infections, including candida. Its mechanism of action includes inhibition of fungal cell division, destruction of cell walls and bacterial cytoplasm, partial bacterial lysis, inhibition of protein synthesis and inhibition of the formation of water-insoluble glucan[137]. Moreover, propolis can enhance the immune system function and induce phagocytosis activity and cellular immunity, to effectively respond to various complications caused by COVID-19. It can also exert its anti-inflammatory action and modulate the immune response by downregulating the pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α and upregulating regulatory cytokine IL-10[74,138]. Propolis has also been found to have properties such as skin regeneration, wound healing and local anesthesia. It promotes wound healing through tissue remodeling, granulation tissue formation, and collagen deposition[139]. In addition, propolis has the potential to mitigate neurodegenerative damage by exerting its antioxidant properties, thereby preventing cognitive deterioration in conditions such as Alzheimer's disease and aging[140]. Propolis also manufactures oral care products such as chewing gum, toothpaste and mouthwash[141]. Propolis acts as an antibacterial agent by eliminating cariogenic bacteria, inhibiting the formation of dental plaque, and reducing the adhesion ability of bacteria by inhibiting the activity of glucosyltransferase, thus reducing the development of dental caries. Propolis has an anti-inflammatory effect on gum tissue and helps to improve gum conditions[142]. Currently, propolis can be used for various forms of local drug delivery, including gels, fibers, and powders in periodontal pockets to achieve continuous action[143].

6.2.3 Application of functional compounds in propolis in the cosmetic industry

Propolis is rich in phenols or flavonoids, which gives it anti-UV, anti-aging, sunscreen, and other properties. It has shown the potential of beauty care for the skin and has been widely used in the cosmetic industry. When human skin is excessively exposed to ultraviolet rays will cause sunburn cells, accelerate skin aging, induce inflammation, immune suppression, and even skin cancer[144]. Sunscreens are products that protect from the effects of sunlight, but they accumulate in the human body. Frequent exposure may cause adverse effects and fail to solve the biochemical mechanisms of tissue damage caused by ultraviolet rays, such as immune suppression, the release of ROS, reactive nitrogen, and degradation of extracellular matrix[145]. Therefore, the combination of active molecules with human light protection and sunscreen is selected to expand the function of sunscreen by providing additional functions. Propolis and its extracts can filter ultraviolet radiation through the absorption spectrum and minimize the penetration of radiation to the skin, thereby reducing the effects of inflammation, oxidative stress, and DNA damage[146].

At present, propolis primarily exists in cosmetics in the form of extracts. As a natural light protector, it is added to sunscreen, face cream, lotion, stick, lipstick, and other cosmetics or therapeutic products to protect skin from light aging[147]. Batista et al.[145] studied the photoprotective effects of oral or topically administered preparations containing aqueous alcohol extract of red propolis (HERP) using a mouse animal model. The findings demonstrated that HERP could effectively attenuate the inflammatory response and epithelial damage caused by UVB. Ebadi et al.[148] assessed the impact of propolis extract on the expression of *FOXO3A* and *NGF* genes in human dermal fibroblasts to investigate its anti-aging properties. The results proved that propolis extract had an excellent anti-light aging effect by increasing cell viability, decreasing β-galactosidase activity, and upregulating mRNA expression of *FOXO3A* and *NGF* genes.

In addition, propolis can smooth wrinkles and has anti-aging properties. Antioxidants such as phenolic compounds and flavonoids have played a huge role here, neutralizing the adverse effects of free radicals on the skin, fading and smoothing the skin, and reducing fatigue signs. Some studies have shown that propolis extract can be used as a dietary supplement to protect aging skeletal muscles by activating the Nrf2/HO-1 signaling pathway and reducing age-related oxidative stress[149]. Stavropoulou et al.[150] evaluated the collagenase and tyrosinase inhibitory activity of propolis extracts. The results showed that propolis is rich in antioxidants, anti-tyrosinase and anti-collagenase reagents, and has potential benefits on free radical-related degenerative diseases caused by skin aging. In addition, propolis has been added to shampoo to treat dandruff or as an antibacterial and anti-inflammatory agent to treat acne due to its antifungal and antiseborrheic properties[142,151].

7. Conclusion and future perspectives

Propolis is a resin mixture rich in polyphenols and flavonoids, which is popular in the domestic and international markets due to its various pharmacological activities. The phytochemical components and quality control methods of propolis were reviewed in this paper, which provided a reference for the authenticity identification of propolis. In addition, the biological properties and therapeutic potential of propolis and its functional components were summarized, and the factors affecting the bioavailability of propolis and its active components were discussed. Finally, the current situation of the global propolis market and the applications of propolis products in the pharmaceutical, food, cosmetic, and other industrial fields were discussed, providing useful references for promoting the development of the propolis industry.

However, it is worth noting that the chemical composition of propolis is complex and variable, leading to serious challenges in the propolis industry. Among them, the potential side effects and allergic reactions associated with the use of propolis pose a threat to the safety of consumers and limit the growth of the market. In addition, the lack of standardized quality standards or regulations between different brands and products globally has led to differences in the composition and biological properties of different propolis products, making the acceptance of propolis in human medicine still limited. These challenges require comprehensive quality control measures and standardized regulations to maintain the continued development of the propolis market. In addition, propolis and its functional components have poor water solubility, rapid and intense metabolism, and low bioavailability. In the future, more research could devote to new strategies for incorporating propolis as a functional food ingredient into the food systems. Furthermore, micellisation and activation of transporter proteins associated with the uptake of bioactives in propolis may improve the bioavailability of propolis and its bioactives, expanding the prospects for propolis applications.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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