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Review article

Propolis: An update on its chemical diversity, botanical origin and biological activities

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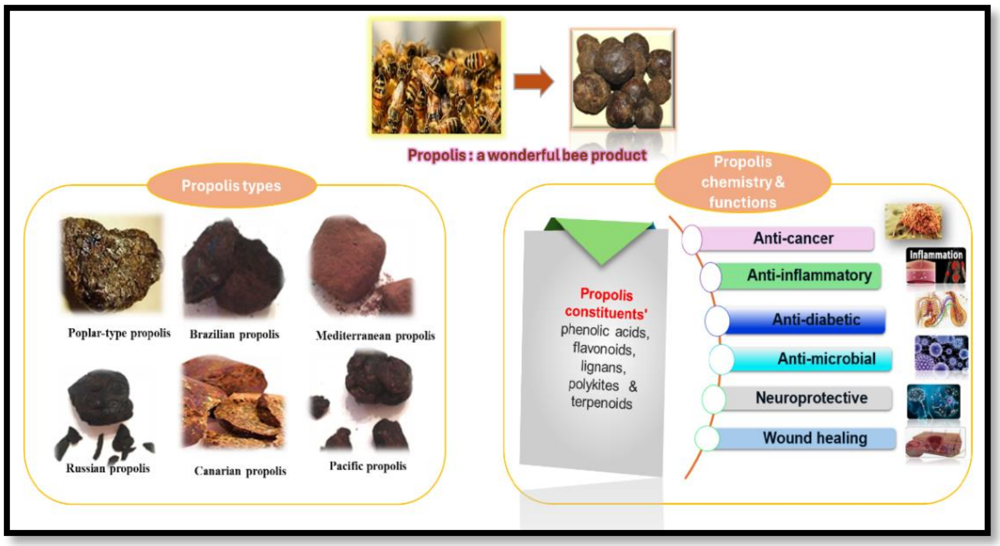

Abstract:
Propolis is a complex resinous substance meticulously harvested by honeybees from diverse botanical sources, and has garnered increasing interest due to its remarkable chemical heterogeneity and extensive range of biological activities. This review provides an exhaustive update about propolis, with an emphasis on its intricate chemical diversity, botanical provenance, and multifaceted pharmacological properties. The chemical constitution of propolis is notably variable, inflected by factors such as geographic location, plant species, and environmental conditions, resulting in a plethora of bioactive compounds, including polyphenolic constituents, flavonoids, phenolic acids, and terpenoids. The botanical origin is pivotal in shaping the phytochemical profile of propolis, with distinct types being classified based on the predominant plant resins, such as poplar, coniferous, and tropical varieties. This botanical diversity inherently modulates the spectrum of bioactivities exhibited by propolis, which encompass a broad assortment of pharmacological effects, embracing antimicrobial, anti-inflammatory, antioxidant and antitumor actions. These properties collectively position propolis as a promising candidate for therapeutic interventions in areas such as wound healing, oral health, and adjunctive cancer therapies.

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Recent investigations have underscored the synergistic potential of propolis with other phytochemicals, suggesting its capacity to enhance the efficacy of combined therapeutic approaches. However, despite its promising bioactivity, challenges persist in elucidating precise mechanisms of action and addressing safety concerns for clinical implementation. This review integrates contemporary research to provide an ample understanding of the multifarious chemical and biological potential of propolis, offering insights into its emerging role in medicinal and industrial applications.

Keywords: Propolis (bee glue), Phytochemical profile, Propolis types, Botanical origin, Biological attributes.

1. Introduction

The history of honeybees (*Apis mellifera* L.) and their products dates back to around 13,000 BC, likely coinciding with the emergence of flowering plants [1]. Evidence of beekeeping practices, including depictions of hives, has been discovered in archaeological excavations, indicating early knowledge of the practice [1, 2]. The term "propolis" originates from Ancient Greek, where the morpheme "pro" means "in front of" or "at the entrance to," and "polis" refers to "community" or "city," thus indicating a substance used for hive defense [3, 4].

Bees collect resins and beeswax from a variety of plant parts, including flowers, leaf buds, exudates, resins, gums, and mucilage. Then, they enhance these materials with their saliva through β-glucosidase enzyme action [5]. In certain instances, bees may deliberately cut plant tissues to release resin for propolis production [6].

Many bee species, including *Apis mellifera* honeybees and stingless bees from the *Meliponini tribe* generate propolis [5, 7]. Each species' propolis is extremely varied in terms of its chemical makeup. The physiochemical content and composition of propolis are greatly influenced by the botanical plants that are found within a few kilometers of beehives [7]. Propolis is used as a sealant by bees to keep their hive safe from outside attackers, prevent cracks and gaps, stabilize moisture and temperature, and prevent the growth of bacteria and fungi [8]. Propolis has long been known for its curative and medicinal qualities in various civilizations; the ancient Greeks, Romans, and Egyptians [8, 9].

Today, bees can be found in almost every habitat across the globe, ranging from equatorial rainforests and tropical deserts to the subarctic regions of North America [1]. The remarkable evolutionary success of honeybees can be attributed to their highly advanced social structure and the diverse products they produce. These products are vital for the survival of the bee colony, providing food, construction materials, and defense mechanisms. Some, such as beeswax, venom and royal jelly, are chemically produced by the bees themselves. Others, like honey, pollen, and propolis, are collected from the environment and then modified by the bees for their own purposes [3, 6].

Honeybees rely entirely on flowering plants to meet the needs of their colony. The extensive co-evolution between bees and plants has resulted in a remarkable and mutually beneficial relationship. Bees in a colony visit various plant species, so the multicolored mixtures of pollen loads are occasionally present. By examining the pollen under a microscope it is possible to successfully identify its plant family, genus and species, this is called melissopalynology [6, 10].

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Overviewing previous reports, it is observed that propolis comprises around 500 different compounds belonging to different chemical classes, such as flavonoids, phenolic compounds, polyphenols, terpenes, terpenoids, coumarins, steroids, amino acids, and aromatic acids [8, 7] Furthermore, propolis is abundant in phytochemicals that are vital for good health such as essential oils, vitamins A, B complexes, C, and E, and minerals including calcium, salt, potassium, aluminum, copper, magnesium, iron, and zinc [11, 12].

In summary, the bee; this tiny creature is a part of a very complicated and well-organized system known as the bee colony. The bees offer a unique view into phytochemicals with enormous pharmacological benefits, many of which are still unknown. The phytochemistry of honeybees is an intriguing area of research, offering the potential to uncover new ecological mutualistic relationships between flowering plants and honeybees, discover novel biologically active metabolites, and explore new applications of the well-known bee products derived from plants.

The present review outlines the different propolis types around the globe illuminating the effects of botanical origin and geographical localities in shaping their phytochemical profiles. Also, updated extensive exploration into the areas of chemical constitution, ethnopharmacological and therapeutic potentials, and perspectives for future research of this valuable bee product which has become the subject of numerous global research areas are also discussed.

2. Physical properties of propolis

Propolis is commonly referred to as "bee glue," a resinous substance (similar to wax) collected by honeybees from a variety of plant exudates, including mucilage, gums, resins, and lattices, as well as from leaf buds of plants like palm, pine, alder, poplar, beech, conifer, and birch [1, 6]. Propolis is naturally lipophilic, forming a hard and brittle material, especially when frozen. When heated to temperatures between 25°C and 45°C, it becomes soft, sticky, pliable, and gummy, and it completely melts at temperatures between 60°C and 70°C [3, 13]. It has a distinct, pleasant aromatic scent, and its color can range from yellow-green to red to dark brown, depending on its plant source and geographic origin. [14]. Due to its complex composition, propolis cannot be used in its raw form. It is commercially extracted using various solvents, such as water, methanol, ethanol, chloroform, dichloromethane, ether, and acetone, with ethanol being the preferred solvent [13].

3. Role of propolis to the honeycombs

Honeybees use propolis not only for construction and repair of their hives by closing the cracks, sealing undesired holes and smoothing the internal surfaces of the hives but also as an antiseptic product protecting the bees' honeycomb from microbial infection [3]. Further, propolis serves as a defensive weapon against external undesired invaders like snakes, lizards, and mice, [2, 6, 15].

Propolis hinders uncontrolled airflow to the hive and consequently maintains optimum internal temperature (35°C). It is also used to embalm undesired invaders such as dead mice and snakes [3, 15].

Propolis plays a crucial role in the bees' immune system acting as a detoxifying agent enhancing therapeutic effects at the colony level against various bee microbes as well as bee longevity through antioxidant-related pathways [3, 16, 17].

Further, some plants secrete potent antimicrobial resins to protect their young leaves and injured tissues, which serve as raw materials for propolis [3]. Honeybees exploit this special antimicrobial material as colony-immune defense to combat against extensive assemblage of undesired pathogens, thus

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resin derived from such plant secretions with promising antimicrobial properties is integral to the concept of "social immunity," making it unsurprising that propolis, sourced from specialized protective plant secretions, functions as a defensive tool in the hive (3).

4. Plant sources of propolis

Identifying the primary plant sources of propolis is crucial because it is a widely used commercial bee product in the food industry, contributing to beekeepers' income. Understanding the plant sources can also help increase propolis production and improve standardization. To comprehend the factors influencing the chemical diversity of propolis, it is essential to consider its plant origins.

Identifying these plant sources is a challenging task. In 1990, Crane listed approximately 60 plant species as sources of propolis based on observations of bees collecting resinous substances from leaf buds of certain trees, though this approach was only incompletely efficacious (3, 12, 18).

Over time, chemical analyses of propolis from different regions became more detailed. By comparing the chemical profiles of both plant materials and propolis, as well as analyzing the resinous substances on bees' hind legs, researchers were able to confirm the plant sources (3). Additionally, analyzing pollen grains can help characterize the local climate and vegetation around an apiary. Pollen grains stick to the resin during collection, reflecting the surrounding flora and allowing for the identification of the geographical origin of propolis (10, 19).

Despite the chemical diversity of propolis, at least six main types have been reported based on extensive studies. The origins and chemical compositions of these main types are presented in **Table 1**, while their morphological characteristics are shown in **Fig. 1**.

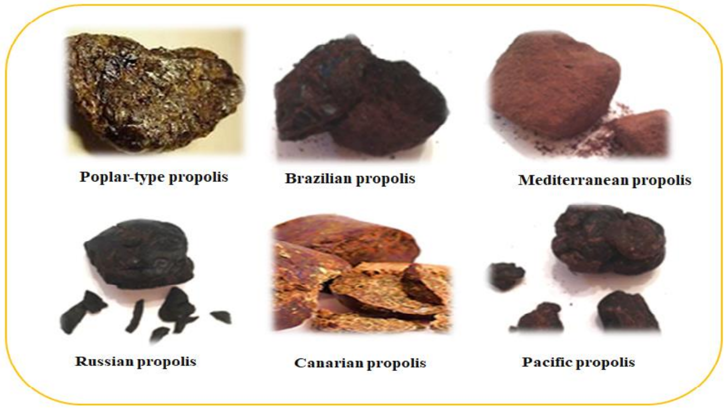

Fig. 1: The morphological features of the main types of propolis.

Table 1: Types of propolis, their origins and chemical compositions

Propolis type	Geographic origin	Plant main sources	Main chemical constituents	Reference
Poplar propolis	Europe, North America and non-tropical regions of Asia	*Populus* spp. most often *P. nigra* L.	Flavones, flavonols, flavanones, dihydroflavonols, phenolic acids and their esters	(3, 20, 21, 24, 35, 47)
Brazilian propolis	Brazil	*Baccharis* spp. predominantly *B. dracunculifolia* DC.	Prenylated *p*-coumaric acids and diterpenic acids	(20, 28, 47, 71)
Mediterranean propolis	Greece, Sicily, Cyprus and in some Croatian Adriatic islands	conifer species of *Cupressaceae* family	Diterpenes	(24, 72, 73)
Pacific propolis	Pacific regions such as Japan (Okinawa) and Taiwan	*Macaranga* spp.	C-prenylflavanones	(24, 35, 45, 74)
Canarian propolis	Canary island	Unknown	Furofuran lignans	(24, 35, 38)
Russian propolis	Russia	*Betula verrucosa* Ehrh.	phenolic glycerides flavones and flavonols	(14)

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5. Main types of propolis according to botanical sources

5.1. Poplar-type propolis

Poplar species primarily *Populus alba, P. tremula and P. nigra* have been reported as the first chemically proven "suppliers" of propolis from temperate zones and non-tropical regions of Asia [4, 20, 21]. Also, *Betula pendula, Acacia sp, Aesculus hippocastanum and Salix alba* are secondary important sources of European propolis [22]. The specificity of local flora and climatic factors in non-tropical regions determine the divergence in chemical profile of propolis from those of *Populus* species [20]. It is clear that bees select proper resin sources from different plant sources based on their availability at the particular phytogeographic zone as well as their suitability to the bees' needs [3, 23].

From a chemical and biological standpoint, poplar-type propolis is regarded as one of the most thoroughly researched types of bee glue [11, 14]. Several earlier reports reveal the distinct features of poplar propolis from chemical makeup aspect [14]. Typically, 50% resin, 30% wax, 10% essential oils, 5% pollen, and 5% of other organic substances, such as vitamins, minerals, and amino acids, make up the poplar kind (temperate) of propolis [4, 21]. Propolis of the poplar type has about 300 distinct chemical constituents. Many of these components fall into one of the following categories: (a) flavonoids, which include flavones, flavanones, flavonols, and dihydroflavonols; (b) free aromatic (phenolic) acids and their esters; (c) chalcones and dihydrochalcones; (d) terpenoid; and (f) additional substances as aldehydes, amino acids, fatty acids, sterols, and sugars [11, 14, 20].

The non-polar fractions of propolis, which are primarily composed of fatty acids, their esters, and hydrocarbons, come from beeswax, whereas the majority of polar components, such as aromatic acids, their corresponding esters, and flavonoids, come mainly from poplar exudates and bee metabolism (amino acids and glycerol phosphates) [18, 21, 24].

Firstly, characteristic flavonoids most frequently found in the poplar propolis are listed in **Tables 2 and 3.** The quantity of these flavonoids, with a broad spectrum of pharmacological activities, is considered a criterion for the quality evaluation of polar propolis [3, 4]. On the other hand, phenolic glycosides (sugar conjugates) and phenolic glycerides are seldom detected in the poplar propolis compared with their respective flavonoidal aglycones [21],

Secondly, aromatic acids typically detected in the poplar propolis can be categorized into two main classes: hydroxybenzoic acid derivatives and hydroxycinnamic acid derivatives as well as their ester derivatives [21, 24-26]. Phenolic composition of the poplar propolis type varies greatly among bees' species and significantly depends on the variability of surrounding flora in different geographical zones and the bees' inclinations toward suitable plant sources [20].

It is worth noting that the popular type of propolis encompasses diverse volatile components responsible for its distinctive aroma and one of the most essential determinants of its quality [27]. Monoterpenes such as α- and β-pinene, limonene, and eucalyptol while sesquiterpenes such as β-eudesmol, cadinol and cadinene were significantly characterized in poplar propolis essential oil [27].

5.2. Brazilian propolis

In South America, Brazil is a well-recognized tropical zone for its Brazilian propolis which is derived primarily from a native *Baccharis dracunculifolia* shrub with huge biodiversity [28]. From chemical and biological aspects, different types of Brazilian propolis including brown, green and red propolis were recently documented. It is worthy to mention

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that Brazilian propolis represents more than 10 – 15% of the worldwide production [28-30]. Green Brazilian propolis is the most well-known and thoroughly researched type of Brazilian bee glue in terms of its chemical and pharmacological characteristics, garnering significant interest from both the scientific community and the commercial sector.

The dominating chemical classes in Brazilian propolis are prenylated phenylpropanoids, diterpenes, lignans as well as flavonoids (distinct from those found in poplar propolis) [28, 29]. Besides, three new triterpenoids; melliferone and moronic acid, and anwuweizonic acid were isolated from Brazilian propolis [24] **(Table 4).**

Table 2: List of typical flavonoids found in poplar type of propolis

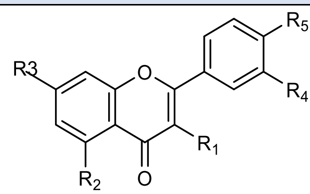
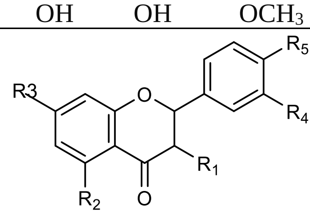
Chemical class	structure					Compound name	Ref.
Flavones & flavonols							(13, 21, 24, 26, 75)
	R1	**R2**	**R3**	**R4**	**R5**		
	H	OH	OH	H	H	Chrysin	
	H	OH	OCH_3	H	H	Tectochrysin	
	OH	OH	OH	H	H	Galangin	
	H	OH	OH	OH	OH	Luteolin	
	H	OH	OH	H	OH	Apigenin	
	OH	OH	OH	OH	OH	Quercetin	
	OH	OH	OH	H	OH	Kaempferol	
	OH	OH	OH	OCH_3	OH	Isorhamnetin	
Flavanones & flavanoles							(14, 24, 26, 49)
	R1	**R2**	**R3**	**R4**	**R5**		
	H	OH	OH	H	H	Pinocembrin	
	H	OH	OCH_3	H	H	Pinostrobin	
	OH	OH	OH	H	H	Pinobanksin	
	$OCOCH_3$	OH	OH	H	H	Pinobanksin - 3-*O*-acetate	
	$OCOC_2H_5$	OH	OH	H	H	Pinobanksin- 3-*O*-propianate	
	$OCOC_3H_7$	OH	OH	H	H	Pinobanksin-3-*O*-butyrate	
	$OCOC_4H_9$	OH	OH	H	H	Pinobanksin-3-*O*-pentanoate	
	OH	OCH_3	OH	H	H	3,7-dihydroxy-5-methoxyflavanone	
	H	OH	OH	H	OH	Naringenin	
	OH	OH	OH	OH	OH	Taxifolin	
	H	H	OH	H	OH	Liquiritigenin	

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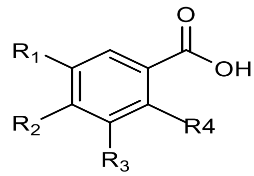
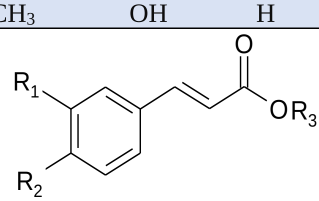
Table 3: List of phenolic acids and their esters typically found in poplar type of propolis



Class	R1	R2	R3	R4	Compound	References
Hydroxybenzoic acid derivatives	OH	OH	OH	H	Gallic acid	(14, 21, 24, 49, 76)
	OH	H	H	OH	Gentisic acid	
	OH	OH	H	H	Protocatechuic acid	
	H	H	H	OH	Salicylic acid	
	OCH_3	OH	H	H	Vanillic acid	



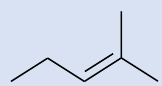
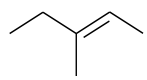
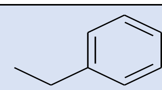
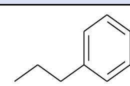
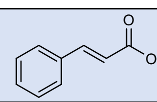
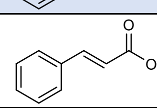
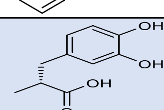
Class	R1	R2	R3	Compound	References
Hydroxycinnamic acid derivatives and their esters	H	H	H	Cinnamic acid	(14, 21, 29, 75)
	OH	OH	H	Caffeic acid	
	OH	OCH_3	H	Ferulic acid	
	H	OH	OH	*P*-coumaric acid	
	OH	OH		3-Methyl-2-butenylcaffeate	
	OH	OH		2-Methyl-2-butenylcaffeate	
	OH	OH		Benzylcaffeate	
	OH	OH		phenethylcaffeate	
	OH	OH		Cinnamylcaffeate	
	H	OCH_3		*P*-Methoxy-cinnamic acid cinnamyl ester	
	OH	OH		Rosmarinic acid	

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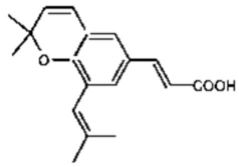
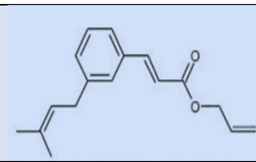
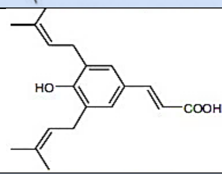
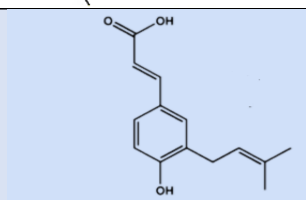
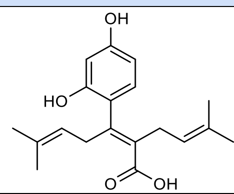
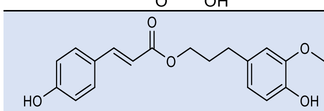
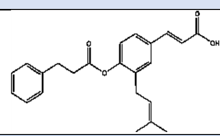
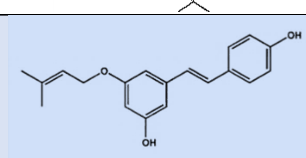
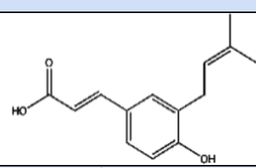
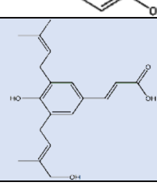
Table 4: Some compounds typically detected in Brazilian propolis

Chemical class	Structure	Compound name	Plant origin	Ref.
Prenylated phenolics		2,2-Dimethylchromene derivative	Buds of *Baccharis dracunculifolia*, family Asteraceae	(24, 29, 73, 75, 77)
		3-Prenylcinnamic acid allyl ester		
		4-Hydroxy-3,5-diprenylcinnamic acid (artepillin C)		
		3-Prenyl-4-hydroxy cinnamic acid		
		2,4-dihydroxy 2’,3’-diprenyl coumaric acid		
		Dihydroconiferyl coumarate		
		Baccharin		
		Prenylated resveratrol		
		Drupanin		
		Capillartemisin A		

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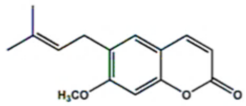
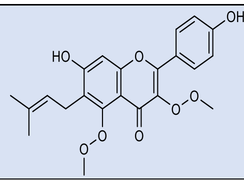
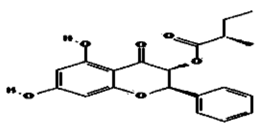
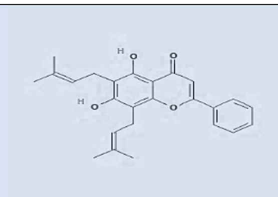
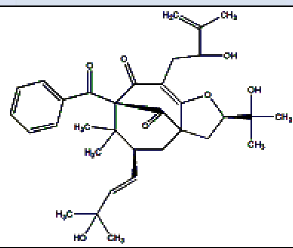
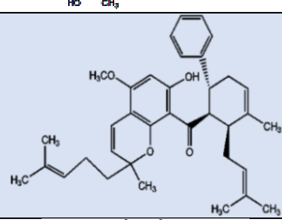
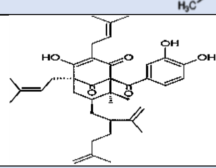
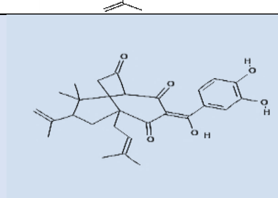
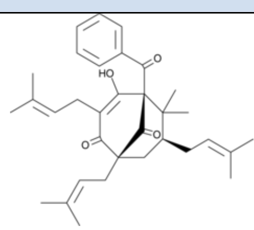
		Prenylated coumarin	
		Prenyl-dimethoxy kaempferol	
		3-O-[(S)-2-methylbutyroyl] pinobanksin	
		Diprenyl chrysin	
Polyprenylated polycyclic acylphloroglucines (PPAPs)		Hyperibone A	(24, 77, 78)
		Hyperibone B	
		garcinielliptone I	
		Gambogenone	
		Nemorosone	

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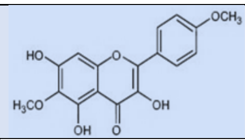
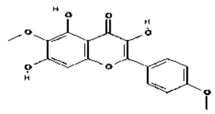
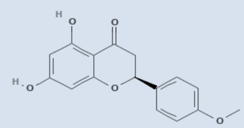
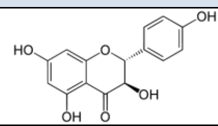
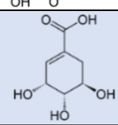
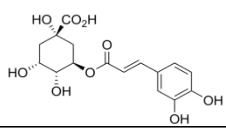
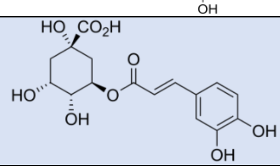
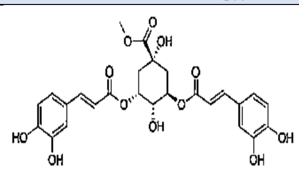
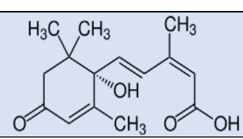
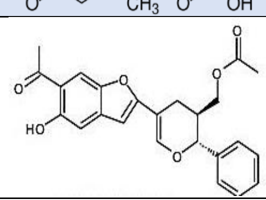
Other phenolics		6-Methoxykaempferide	
		Beturetol	
		Isosakuranetin	
		Aromadendrin	
		quinic acid	
		5-*O*-caffeoylquinic acid	(24, 77) (29)
		4-Feruoyl quinic acid	
		3 4-di-*O*-caffeoylquinic acid	
		Absisic acid	
Labdane diterpenoids		Propolis benzofuran A	(24, 28, 33, 71, 79)

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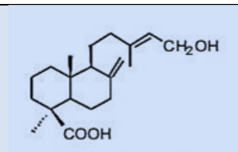
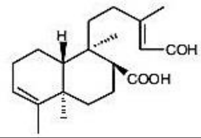
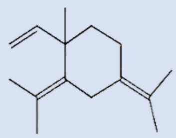
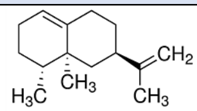
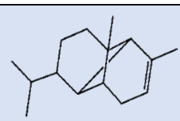
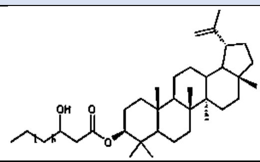
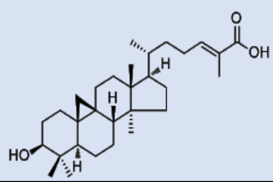
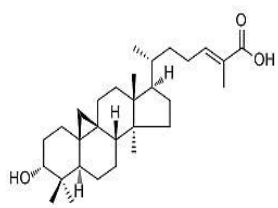
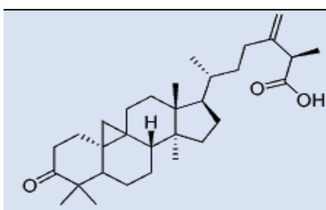
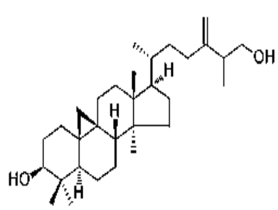
Clerodane diterpenoids		Isocupressic acid	
Sesquiterpenoids		13-Symphyoreticulic acid	
		γ-Elemene	
		Valencene	
		α-Ylangene	
Esters of long chain fatty acids and lupeol (a pentacyclic triterpene)		Procrim a (n=11)	
		Procrim b (n=13)	
Cycloartane triterpenoids		Mangiferolic acid	
		Isomangiferolic acid	
		Ambonic acid	(19, 24, 62, 75)
		24-Methylenecycloartan-3β,26-diol	

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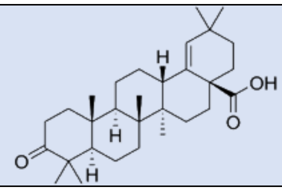
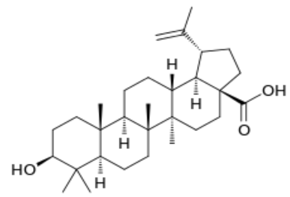
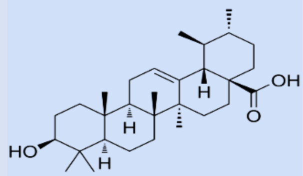
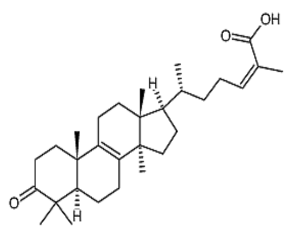
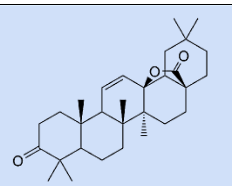
		Moronic acid	
		Betulinic acid	
Triterpenoids		Ursolic acid	
		Anwuweizonic acid	(24, 77)
		Melliferone	

5.3. Mediterranean propolis

More and more scientific contributions have unraveled a recent type of European propolis typically found in the south of Greece, Sicily and Cyprus denoted as Mediterranean propolis [31] The chief resinous sources of Mediterranean propolis turned out to be Conifer trees of *Cupressaceae* family that are widely distributed in the Mediterranean zone [3, 4, 32].

The major components of Mediterranean propolis are diterpenoids which mediate its noteworthy antibacterial activity. Such chemical profile can be found in Croatia and Malta [33], in addition to other constituents such as aliphatic hydroxy acids, aromatic and fatty acids, triterpenes along with some poplar flavonoids. However, typical poplar caffeic acid esters (pentenyl caffeate) were detected in Maltese propolis **(Table 5)** [3, 31, 34, 35].

Worth mentioning, that Greek propolis contains high levels of anthraquinones in particular emodin and chrysophanol as well as terpenes and/or flavonoids that differ from chemical profile of typical European propolis.

In Cretan propolis, diterpenes and cycloartane triterpenes were isolated and characterized. **(Table 5)** [24, 35].

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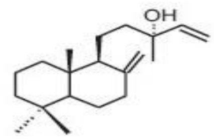
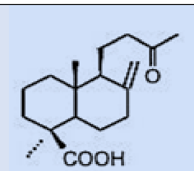
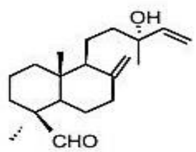
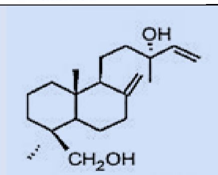
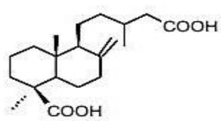
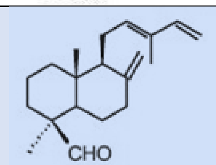
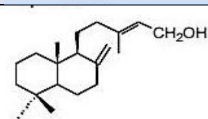
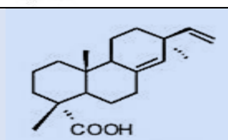
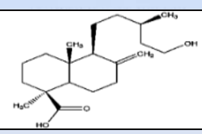
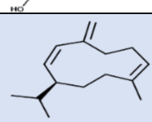
Table 5: Some compounds detected in Mediterranean propolis

Chemical class	Structure	Compound name	Plant origin	Ref.
		13-epi-Manool		
		14,15-dinor-13-oxo-8(17)-labden-19-oic acid		
		13-epi-Torulosal		
		13-epi-Torulosol		
Diterpenes		Junicedric acid	conifer species of *Cupressaceae* family	(13, 35, 68) (24, 34, 75)
		Communal		
		Copalol		
		Pimaric acid		
		Imbricatoloic acid		
		Germacrene-D		

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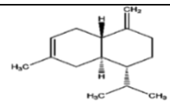
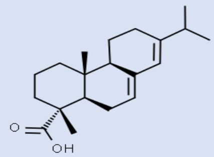
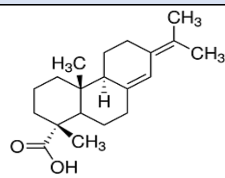
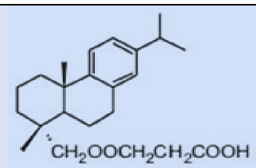
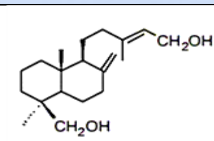
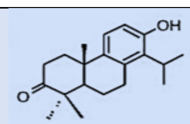
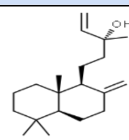
	γ-Cadinene
	Abietic acid
	Neoabietic acid
	18-Succiniloxyabieta-8,11,13-triene
	Agathadiol
	Totarolon
	Manool

5.4. Pacific propolis from Japan (Okinawa) and Taiwan:

Propolis originating from Okinawa and Taiwan with the main plant source of *Macaranga tanarius* family *Euphorbiaceae* encompasses a relatively high percentage of C-prenylflavonoids **(Table 6)** [3, 4, 13]. Pacific propolis and its C-prenylflavonoids with strong antioxidant properties exhibit noteworthy cytotoxic capabilities. [35-37].

5.5. Canarian propolis from Canary Islands:

Because of their different climatic characteristics from tropical South America and Europe, the authors that examined the samples collected from the Canary Islands found that they differ greatly from the other types examined worldwide. Investigating the chemical makeup of propolis samples from the Canary Islands is still worthwhile. The main constituents were found to be lignans, specifically the furofuran type **(Table 7)** [3, 35, 38, 39].

5.6. Russian propolis:

Phenolic glycerides are a class of compounds distinctly found in propolis samples sourced from Northern Russia [14]. These compounds along with some biologically active compounds; flavones and flavonols, apart from those reported in European propolis are attributable to the exudates of *Betula pendula* Roth *(B. verrucosa Ehr.)* [14] (**Table 8)**. Consequently, Russian propolis rapid and

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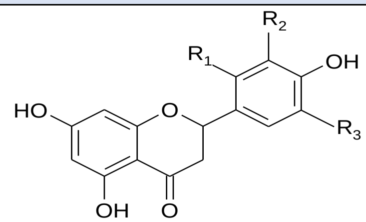
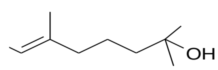
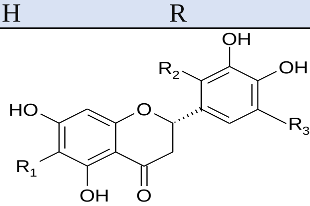
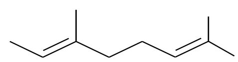
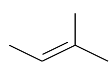
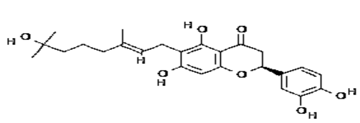
pronounced relief of the main clinical manifestations of chronic generalized periodontitis. Moreover, solution of propolis effectively reduced the aggregation function of blood plates under the conditions of experimental hemorrhagic anemia in rats [40].

Table 6: Some compounds detected in propolis from Japan (Okinawa) and Taiwan

Chemical class	Structure			Compound name	Plant origin	Ref.
C-Prenylated flavonoids	 R= 				*Macaranga tanarius* family Euphorbiaceae	(74, 80) (80) (13, 80, 81)
	R1	**R2**	**R3**			
	R	OH	H	Propolin A		
	H	OH	R	Propolin B		
	H	R	H	Propolin E		
	 R=  R'= 					
	R1	**R2**	**R3**			
	H	H	R	Isonymphaeol-B (Propolin F)		
	R	H	H	Nymphaeol-A (Propolin C)		
	H	R	H	Nymphaeol-B (Propolin D)		
	R'	R	H	Nymphaeol-C		
				Prokinawan		(24, 36)

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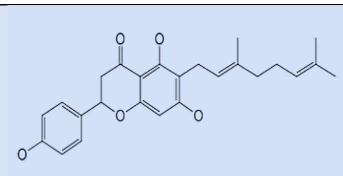
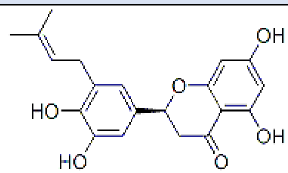
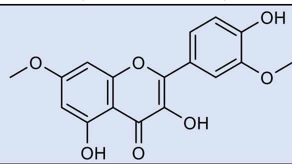
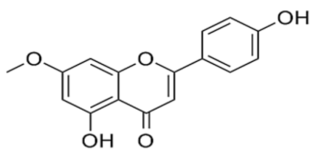
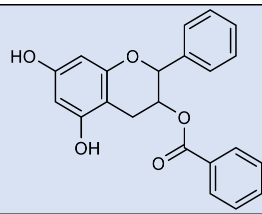
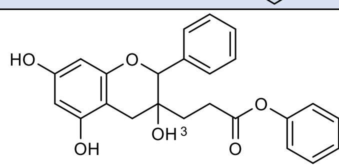
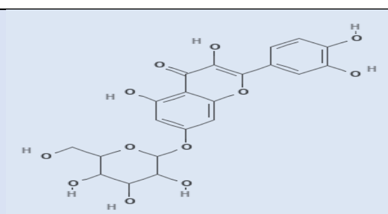
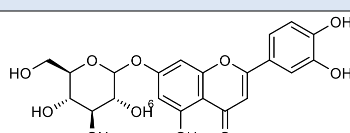
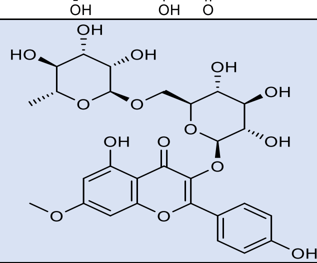
		Bonannione A	
		Sigmoidin B	
		Rhamnazin	
		Genkwanin	
Flavonoids		Pinobanksin-3-*O*-benzoate	
		Pinobanksin-3-*O*-phenylpropanoid	(14, 24, 36)
		Quercetin-7-*O*-glycoside	
Glycosides		Luteolin 7-*O*-glucoside	
		7-Methyl kaempferol-3-*O*-rutinoside	

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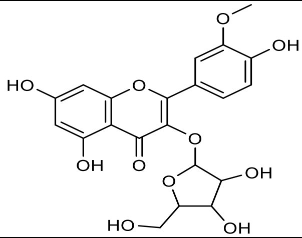
		Isorhamnetin-3-*O*-pentoside

Table 7: Some compounds detected in Canarian propolis

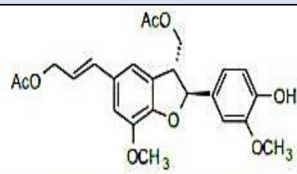
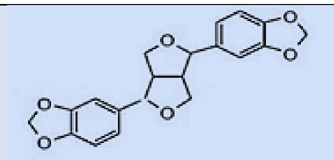
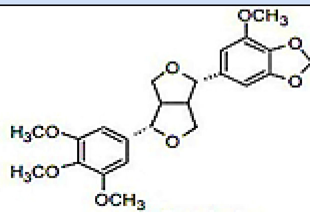
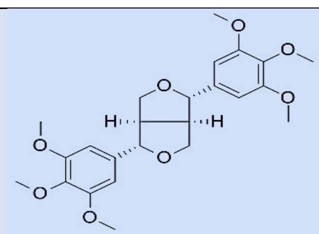
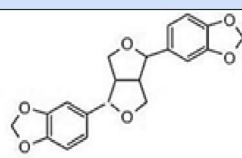
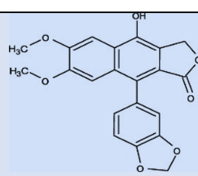
Chemical class	Structure	Compound name	Plant origin	Ref.
Lignans		3-Acetoxymethyl-5[(E)-2-formylethen-1-yl]-2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-2,3-dihydrobenzofuran	unknown	(3, 24, 38, 77)
		Sesamin		
		Seartenin		
		yangambin		
		Aschantin		
Arylnaphtalene lignans		6-Methoxy diphyllin		

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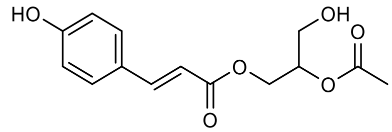
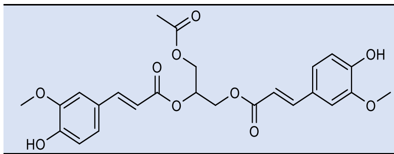
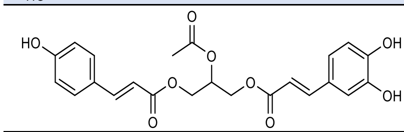
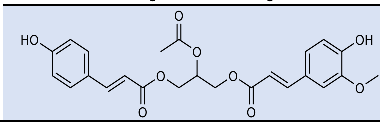
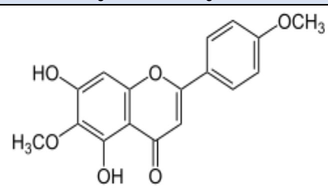
Table 8: Some compounds detected in Russian propolis

Chemical class	Structure	Compound name	Plant origin	Ref.
Phenolic glycerides		Coumaroyl acetyl glycerol	*Betula verrucosa* Ehrh.	(14)
		Diferuloyl acetyl glycerol		
		Caffeoyl coumaroyl acetyl glycerol		
		Feruloyl coumaroyl acetyl glycerol		
Flavonoids		Pectolinarigenin		(82)

6. Biological activities of propolis

Propolis is by definition a biomass that encompasses plant-derived compounds with powerful bioactivities [3]. Given this, propolis is becoming more and more popular as a natural medicine and a source of different pharmacologically active chemical entities.

In the last few decades, numerous scientific contributions concerning the diverse pharmacological activities of propolis have been documented. A schematic diagram showing various biological activities of propolis is depicted in **Fig. 2.**

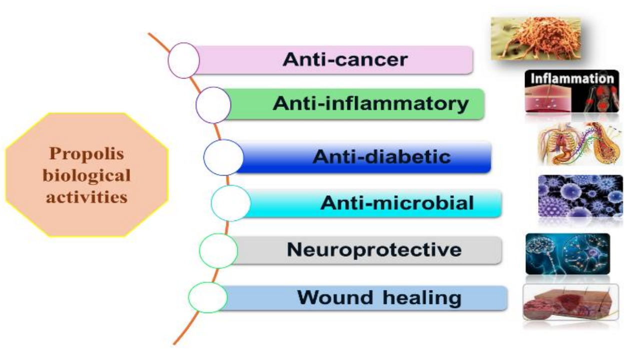


Fig. 2: A schematic diagram showing various biological activities of propolis.

6.1. Antimicrobial activity

Propolis exhibits a significant antimicrobial property against S*taphylococcus aureus, Bacillus subtilis, Candida albicans and Asparagus nigar* [25, 29, 41, 42]. Propolis serves as a bactericidal agent by shutting down bacterial cells division and proliferation, destroying bacterial cell wall and cytoplasm in addition to blocking protein synthesis [43, 44]. Data from earlier studies has demonstrated the remarkable antimicrobial potential of poplar propolis ethanolic extracts against gram-positive bacteria (*Staphylococcus aureus and Bacillus subtilis*) [41, 45, 46]. Propolis displayed a moderate zone of inhibition against *C. albicans* [13, 47]. The noteworthy antimicrobial potential of propolis was ascribable to the enrichment of bioactive compounds such as flavonoids and phenolic acids [7, 25, 39, 48].

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6.2. Antioxidant activity

Propolis is well-reputable for its pronounced antioxidant attributes. Its promising antioxidant activity, which allows it to efficiently trap reactive oxygen species (ROS) and repair the tissue damage produced by ROS, has been linked to its wide range of biological and pharmacological qualities [47, 49-51].

Due to the enrichment of phenolic components mainly flavonoids in propolis whose content ranges from 10% to 35% [36, 52], multiple pharmacological features particularly free radical scavenging activity were observed. Propolis acts as protective weapon mitigating against oxidative stress that implicates in a variety of chronic ailments such as Alzheimer's disease, rheumatoid arthritis, cancer, diabetes mellitus, and cardiovascular diseases [36, 37, 49, 52, 53].

6.3. Anti-inflammatory activity

Earlier reports pointed out that propolis possessed a distinctive anti-inflammatory capability mediated by active flavonoids and phenolic acid derivatives [54, 55]. A previous study conducted on guinea pig mast cells concluded that propolis exhibited a strong inhibitory effect against myeloperoxidase activity, NADPH-oxidase, tyrosine-protein kinase, and ornithine decarboxylase [16, 56, 57]. Further, propolis readily inhibited arachidonic acid metabolism pathway during inflammation [56, 58].

Histopathological observations displayed that caffeic acid phenethyl ester (CAPE) served as immunosuppressive agent in human T-cells and consequently suppressed inflammation effectively [59]. Moreover, CAPE has been proven to pointedly and fully shut down the activation of NF-kB triggered by a broad variety of inflammatory cytokines (IL-1, IL-6, TNF) [56].

6.4. Antitumor activity

Bee propolis is rich in phenolic acid derivatives and flavonoids with antimetastatic activity [60].

The chemo-preventive activity of propolis as well as its derived chemicals has been investigated in breast, cervical, colonic, hepatic, lung, and prostate cancer in multiple *in-vitro* and animal models however, clinical studies are lacking [35, 47, 61]. The chemo-preventive potential of propolis is possibly due to its potential to block DNA synthesis in tumor cells inducing tumor cell death and its capability to enhance macrophages which in turn regulate the functions of B, T and NK cells [13, 16, 51].

It was reported that CAPE from poplar propolis and artepillin C (3, 5-diprenyl-4-hydroxycinnamic acid) obtained from Brazilian propolis exhibited pronounced cytotoxic effect [14, 29, 62].

Also, a recent study found that techtochrysin, a principal flavonoid derived from propolis, could be exploited as an adjuvant agent for chemo-resistant colon cancer cells growth via its ability to inhibit activated NF-kappaB in animal models [61].

6.5. Cardioprotective and hepatoprotective activity

Biochemical observations supported by histopathological examination of heart sections revealed the cardioprotective impact of propolis in doxorubicin-induced myocardiopathy experimental rats [35, 47, 63].

In diabetic rats, bee propolis extracts were also found to lower blood glucose (FBG), total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDLC). This suggests that propolis may regulate blood glucose levels and blood lipid metabolism [64].

Propolis profoundly diminished the severity of hepatic necrosis induced by acetaminophen (AA, Paracetamol). Furthermore, it enhanced the hepatic enzyme activities (GST and PS) [65].

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Techtochrysin was found to enhance the level of antioxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase in hepatic tissues (66).

6.6. Wound healing activity

Propolis possesses therapeutic potential on tissues remodeling after injuries via accelerating some vital enzymatic reactions, angiogenesis and collagen fibers formation (67, 68).

Currently, a randomized controlled study has suggested that the application of propolis to post-tonsillectomy wound displayed beneficial effect on postoperative pain relieving, effective hemorrhage control, and enhancing wound healing in tonsillar fossae (69). This effect might be associated with anti-inflammatory activity of flavonoids which inhibit arachidonic acid release from cell membrane, and consequently lead to the suppression of cyclooxygenase COX-1 and COX-2 activities (69, 70).

7. Perspectives and conclusion

Propolis is a resinous honeybee product packed with plenty of biologically active metabolites exhibiting a vast array of biological attributes such as anti-inflammatory antimicrobial, antioxidant, antitumor, hepatoprotective and wound healing properties. Propolis' chemical and biological qualities have generated a lot of attention from the general public and substantial research to explore propolis-containing products in health food stores revealing its potential for the development of novel medications. Future research on propolis should take into account the flora and geographical factors of beehives, as well as the types and subspecies of bees. This will help us better understand the biology of honeybees, and the chemistry and quality of propolis with an ultimate goal to establish appropriate quantitative criteria for distinct propolis types. Furthermore, it is necessary to correlate the chemical makeup of each variety of propolis with its biological activities before incorporation in clinical investigations. Importantly, intensive well-established in vivo and clinical investigations should be conducted to provide full information regarding propolis mechanisms of action and possible interactions between propolis constituents and other medications. Undoubtedly, this information offers a new step to supplement the fundamental research with the purpose of the meaningful consequential release of numerous unprecedented nature-based scaffolds for the management of various pathological conditions and health promotion.

Credit author statement

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Mohamed M. Mohyeldin: Conceptualization, Methodology, Data curation, Writing- Original draft preparation, Supervision, Validation, Writing- Reviewing and Editing.

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Reham S. Ibrahim: Conceptualization, Methodology, Data curation, Writing- Original draft preparation, Supervision, Validation, Writing- Reviewing and Editing.

Ethics approval and consent to participate

Not applicable.

Competing interests

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.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Highlights

- Propolis is a complex resinous substance packed with a plethora of bioactive compounds including mostly polyphenolics and terpenoids.
- The botanical origin is pivotal in shaping the phytochemical profile of propolis types.
- Poplar, Brazilian and Mediterranean propolis represent the dominating types of propolis.
- Propolis exhibits multifaceted pharmacological properties primarily anti-inflammatory, anticancer, and wound healing.
- Propolis offers an ideal candidate in foodstuffs and nutraceutical applications.

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