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Insight on propolis from Mediterranean countries: chemical composition, biological activities and application fields

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Abstract

This review updates the information upon the chemical composition of propolis from all Mediterranean countries as well as their biological properties and applications. The non-volatile fraction of propolis was characterized by the presence of phenolic acids and their esters, and flavonoids. Nevertheless in some countries, diterpenes were also present: Sicily (Italy), Croatia, Malta, Creta (Greece), Turkey, Cyprus, Egypt, Lybia, Algeria and Morocco. The volatile fraction of propolis was characterized by the presence of benzoic acid and its esters, mono- and sesquiterpenes, being the oxygenated sesquiterpene β-eudesmol characteristic of poplar propolis, whereas the hydrocarbon monoterpene α-pinene has been related with the presence of conifers. Regardless the chemical composition, there are common biological properties attributed to propolis, Owing to these attributes, propolis has been target of study for applications in diverse areas, such as food, medicine and livestock.

Key-words: phenols, terpenes, coumarins, Southern European Coast, Northern African Coast, Levantine Coast

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Introduction

Propolis, from the Greek "pro" = "in front" or "in defense" and "polis" = "the city", meaning 'defense of the hive', is a strongly adhesive natural mixture manufactured by honey bees (*Apis mellifera* L.) from the buds or exudates of plants of the native vegetation near their hive. [1] Propolis is used by bees to seal holes in hives, smooth out the internal walls making the hive defensible and as a barrier against external invaders and diseases, thermal insulation, humidity and wind.[2]

Propolis has been used by mankind since the ancient times (~3000 BC), it has been extensively utilized by several civilizations as antiseptic and a raw material for numerous preparations, perfume, health foods and beverages.[3][4][5][6][7]

Generally, raw propolis is mainly composed of resin and vegetal balsam (~50%), wax (~30%), essential oils (~10%), pollen (~5%) and other substances such as debris, minerals, polysaccharides, and proteins. However, it is originated from resin material of different plant species whereby it has a chemical diversity and different raw appearance which varies considerably with the geographical origin owing to the local flora. Many studies revealed different types of propolis around the world with different chemical composition according to the plants available around the hive, the geography and climatic conditions of the harvesting site.[8]

According to the review[9], seven main types of propolis have been reported depending on their major constituents and plant origin: poplar, birch, green (alecrim) Brazilian, red, "Clusia", "Pacific" and Mediterranean. Poplar propolis (resin source is from *Populus* species) can be found in the temperate regions of Europe and North America, non-tropical regions of Asia, China and New Zealand. In this kind of propolis, flavones, flavonones, cinnamic acids and their esters are the typical components.[9][10] Birch propolis from Russia (resin source is *Betula verrucosa*) where the main compounds are flavones and flavonols different from those found in poplar type. [9][10] Green propolis from Brazil (*Baccharis* spp.) is mainly composed by prenylated phenylpropanoids, caffeoylquinic acids and diterpenes.[9][10] In red propolis found in Brazil, Cuba and Mexico arising from *Dalbergia* spp. predominates isoflavonoids, neoflavonoids, pterocarpans and lignans.[9][10][11][12][13] *Clusia* propolis originating from Cuba and Venezuela arising from flowers of *Clusia* spp. is rich in prenylated benzophenones.[9][10] Pacific propolis from Okinawa, Taiwan, Indonesia (*Macaranga tanariu*) is rich in *C*-prenyl-flavanones.[9][10] Mediterranean propolis from Sicily, Greece and Malta in which the plant

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source belongs to the Cupressaceae family[14], present the diterpenes (mainly acids of labdane type) as the major compounds.[9][15][16][17] The chemical composition of propolis from other Mediterranean countries (Algeria, Tunisia, Morocco, France, and Spain) was also previously reviewed[18]. In this review, the volatile fraction of propolis was also reported.

Even if it represents only a low percentage from the total composition, the chemical information of volatile oils in propolis, with respect to quality control and standardization purposes, can give precious information about its characterization; it may also lead to find new valuable bioactive compounds.[19]

Propolis possesses a large number of biological and pharmaceutical properties which have been scientifically demonstrated. Among those it can be highlighted the antitumoral,[20] antimicrobial,[21 – 23] antioxidative,[24][25] anti-inflammatory,[26 – 29] anti-HIV,[30] anti-neurodegenerative,[31] and antituberculosis.[32]

The increasing interest for propolis has led many worldwide researchers to study its chemical composition and biological properties, including those countries surrounded by the Mediterranean Sea. A short review was already made[18] but only focused in propolis from Algeria, Tunisia, Morocco, France, Spain and Portugal. In the present overview we are going to focus on the comparison of available data of propolis from all countries surrounded by the Mediterranean Sea (Southern Europe Coast, Levantine Coast and Northern African Coast) regarding its chemical composition of volatile and nonvolatile part, biological properties and its application in several fields. This information would be of importance for a future elaboration of new type of propolis or new propolis standard.

Chemical composition of Mediterranean propolis

Non-volatile constituents of propolis

In the last decades, propolis has become the subject of several studies carried out all over the world. However, the wide application of propolis in modern medicine has drawn growing attention to its chemical composition which is crucial for understanding its biological activities.

Many authors have shown that the observed effects could be the result of the synergistic effect of its complex constituents, itself are dependent on different parameters such the botanical origin of propolis samples.[33][34] The Mediterranean, an eco-region with a common sea that links three continents, is remarkable with the richness of its biodiversity. Twenty-two countries and territories border on the Mediterranean belonging to the Southern European,

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Levantine and Northern African Coasts; hence, the chemical compositions of propolis may vary between the different regions. As far as we found, in *Table S1*, we summarized the chemical composition of non-volatile part of Mediterranean propolis.

Southern European Coast

Hydro-alcoholic extracts of propolis from Spain were analyzed regarding their chemical composition. Kumazawa et al. [35] reported that East Andalusian ethanolic extract of propolis (EEP) was mainly composed by flavonoids (*Figure 1*) such as pinobanksin (**1**), chrysin (**2**), pinocembrin (**3**), and pinobanksin-3-acetate (**4**) and phenolic acids (*Figure 2*) such as caffeic acid (**5**), *p*-coumaric (**6**) and ferulic (**7**) acids. Caffeic acid phenethyl ester (CAPE) (**8**) was also mentioned to be present in Spanish propolis samples.[35][36][37] Volpi and Bergonzini[38] declares that propolis from Spain contain as a main bioactive compound flavonoids such as pinocembrin **3**), galangin (**9**), naringenin (**10**), acacetin (**11**) and chrysin (**2**). Also, Vivar-Quintana et al. [37] in a study in which they determined the phenolic acids present in crude propolis from Galicia and Castilla y León, Northern Spain, they found the same phenolic acids already cited by Kumazawa et al..[35] Volpi and Bergonzini[38] and Sawaya et al. [36] declares that propolis from Spain contain as main bioactive compounds flavonoids such as pinocembrin (**3**), galangin (**9**), naringenin (**10**), acacetin (**11**) and chrysin (**2**). In the other hand, in propolis samples originating from La Alcarria and Nerpio it was also reported the presence of hydrocarbons and long chain fatty acids.[39] To be concluded that whatever the geographical origin of Spanish propolis, flavonoids and phenolic acids were present in almost all tested samples.

Data regarding the chemical composition of propolis from France are scarce. Boisard et al.[40][41] declared that phenolic acids esters [benzyl caffeate (**12**) and prenyl caffeate (**13**)] and flavonoids [pinobanksin-3-acetate (**4**), pinocembrin (**3**), chrysin (**2**), galangin (**9**)] were the most abundant constituents of French propolis. Caffeic acid (**5**), *p*-coumaric acid (**6**), ferulic acid (**7**) and isoferulic acid (**14**) were also detected in those propolis samples. The study of Chasset et al.[42] was in concordance with[40][41] finding about the composition of French propolis, where they investigated propolis from different areas in France through high-performance thin-layer chromatography and mass spectrometry (HPTLC-MS). Regardless the collection area of propolis in France, phenolic acids and flavonoids predominated in the extracts. Nevertheless the individual flavonoids were not with the same abundance in all extracts and apparently without any correlation with the collection site. For example, galangin was present in both continental and mediteranean samples.[42]

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Several studies have demonstrated the existence of flavonoids as main components of Italian propolis.[15][38][43 – 48] The analysis of ethanolic extracts of propolis by several authors has showed the presence of pinocembrin (**3**), galangin (**9**), naringenin (**10**), chrysin (**2**), and apigenin (**15**) (*Figure 1*) as common flavonoids found in all analyzed samples. While Bankova et al.[15] found also in propolis samples originating from Piedmont, Emilia Romagna, and Sicily, benzyl caffeate (**12**) and phenethyl caffeate (**13**) (*Figure 2*). Nevertheless, it is noteworthy the presence of diterpenic acids (53%) in the sample from Sicily, not found in the remaining propolis samples, in contrast to the finding[46], in which diterpenes were not detected in the Italian island. Phenolic acids were also found in Italian propolis and the main present ones were *p*-coumaric acid (**6**), ferulic acid (**7**) and caffeic acid (**5**). Some phenolic acid esters, such as CAPE (**8**) were reported to be included on the chemical composition of Italian propolis (*Figure 2*).[45][47][48] From above, the authors concluded that all samples assayed from central Italy were of poplar origin. However, it is not clear that the Mediterranean propolis, characterized by the presence of diterpenes, is typical of the Mediterranean islands, since Gardini et al.[46] did not find them in Sicilyan propolis. More recently,[49] have reported the presence of new phenolic acid derivatives [boropinic acid (**16**) and 4'-geranyloxyferulic acid (**17**)] (*Figure 2*), and coumarin derivatives [umbelliferone (**18**), 7-isopentenyloxycoumarin (**19**) and auraptene (**20**)] (*Figure 3*) in Italian propolis, and[50] declared to have found two new cinnamic acids [4-(3'-hydroxymethyl-3'-methylallyloxy) cinnamic acid (**21**) and 4-(3'hydroxymethyl-3'-methylallyloxy-3-methoxycinnamic acid (**22**)] (*Figure 2*) in propolis originating from Italy.

Slovenian propolis was characterized by different phenolic acids and flavonoids as previously reported.[51] Its analysis through liquid chromatography–mass spectrometry (LC-MS) have shown the presence of various bioactive compounds namely *p*-coumaric (**6**), ferulic (**7**) and caffeic (**5**) acids, caffeic acid benzyl ester **(12)** and caffeic acid cinnamyl ester (**23**), cinnamic acid (**24**) (*Figure 2*), pinobanksin (**1**), apigenin (**15**), kaempferol (**25**), pinobanksin-3-*O*-acetate (**4**), chrysin (**2**), galangin (**9**), pinocembrin (**3**) (*Figure 1*). Therefore, the authors concluded that the phenolic profile of Slovenian propolis is comparable to that of European propolis.[51][52] More recently, a group of research has reported that propolis samples from Slovenia, Croatia and France, mainly reflected patterns characteristic of blue-type propolis rich in flavonoids and with low quantity of phenolic acids.[53]

Ethanolic extracts of propolis from several locations in Croatia, analyzed by several method such as GC-MS, two-dimensional thin-layer chromatography, HPLC-thin-layer chromatography among others, had relatively high amounts of flavonoids besides the

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presence of phenolic acids. It was found that the main flavonoids found were pinocembrin (**3**), pinobanksin (**1**), pinobanksin-3-*O*-acetate (**4**), chrysin (**2**), quercetin **(26),** kaempferol **(25)** pinocembrin-7-methyl ether **(27)** and galangin (**9**) (*Figure 1*), while benzoic (**28**), ferulic (**7**), caffeic (**5**), 3,4-dimethoxy-cinnamic (**29**), cinnamic (**21**) acids were the most abundant phenolic acids.[54 – 64] However, other authors demonstrated that Croatian propolis contain phenolic acid esters such as CAPE **(8),** benzyl caffeate **(12),** benzyl coumarate **(30)** and cinnamic acid esters.[64 – 66] On the another hand, Sobočanec et al.[67] have reported the presence of flavonoids only in propolis samples from Continental Croatia. To be noted that in propolis samples from Lokrum Island and Trogir it was reported the presence of low diterpene content.[61]

Regarding Bosnia and Herzegovina, as far as we know, only a study effectuated by Barbarić et al.[68] through HPLC, reported the presence of ferulic **(7)**, *p*-coumaric acids **(6)**, tectochrysin **(31)**, pinocembrin **(3)** and chrysin **(2)** as main common components of propolis.[68] Not so far, in Albania, Kujumgiev et al.[69] have previously reported the presence of phenolic acid ester (53%) and flavonoids (38%) in propolis samples.

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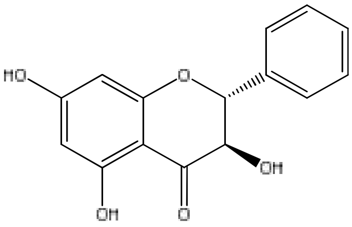
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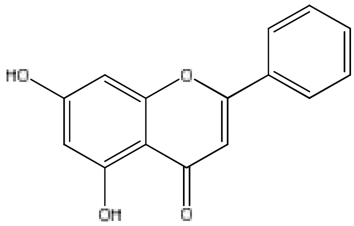
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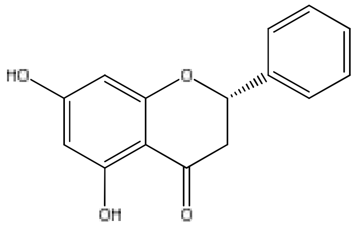
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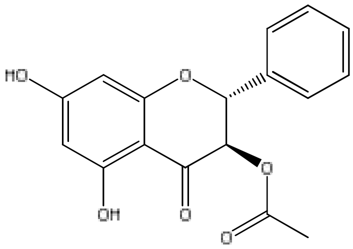
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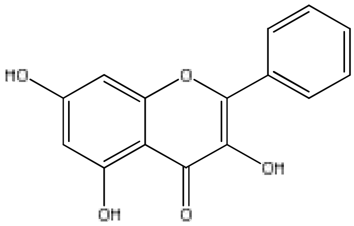
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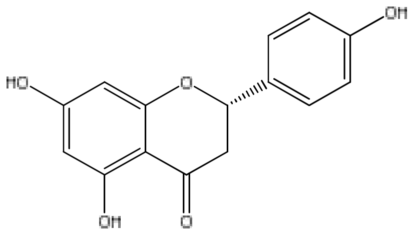
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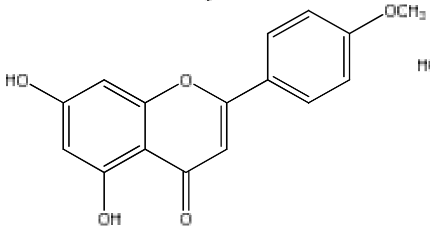
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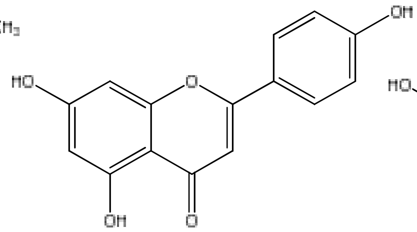
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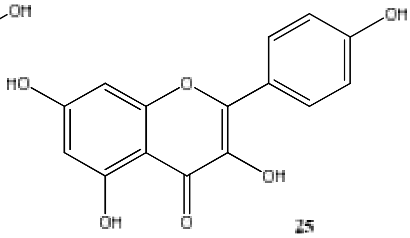
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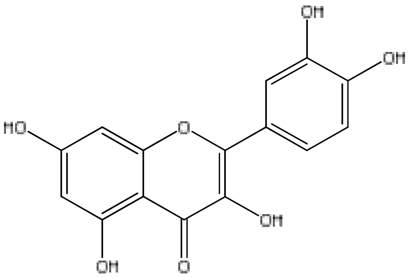
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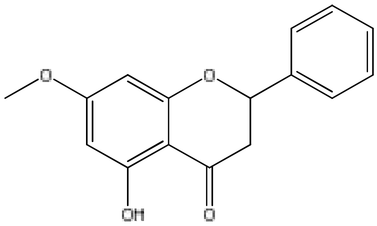
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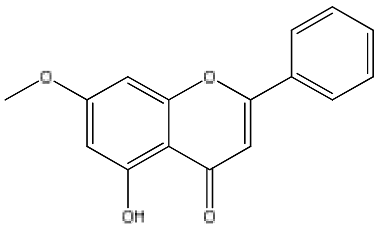
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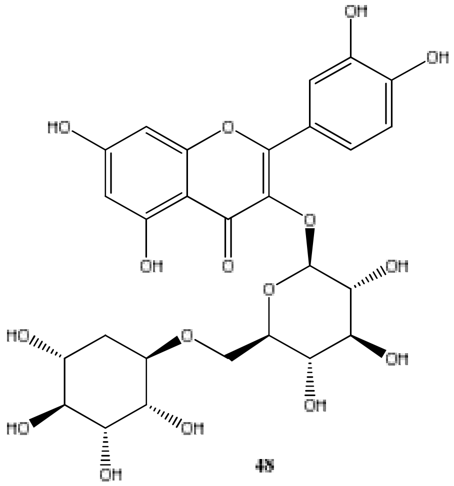
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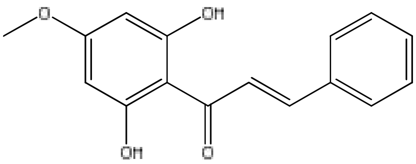
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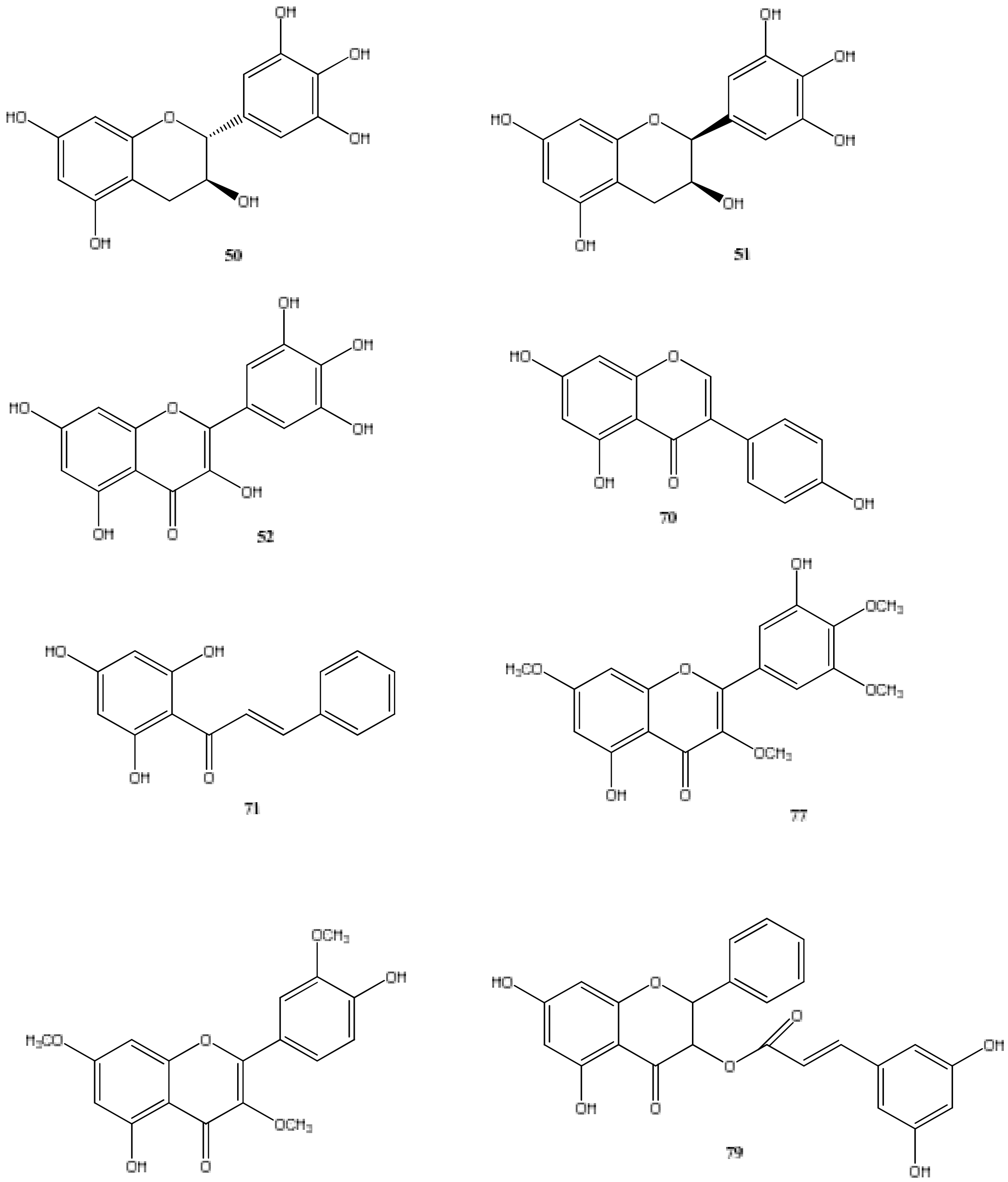

Figure 1. Examples of flavonoids and their derivatives present in Mediterranean propolis.

Investigation of the silylated ethanolic extracts of propolis from Malta analysed by GC–MS have revealed to possess the typical Mediterranean chemical profile being rich in diterpene compounds. Isocupressic (**32**), communic (**33**), pimaric (**34**) and imbricatoloic acid (**35**), together with totarol (**36**) and 13-epitorulosal (**37**) were found in all samples. Mono- and sesquiterpenyl esters of substituted benzoic acids were also detected [ferutinin (**38**), teferin (**39**), 2-acetoxy-6-*p*-methoxybenzoyl-jaeschkeanadiol (**40**) and 2-acetoxy-6-*p*-hydroxybenzoyl-jaeschkeanadiol (**41**)] *(Figure 4)*.[70] In 2012,[14] concluded that the diterpenic profile of the previous studied Maltese propolis was similar to the profile of the resin of

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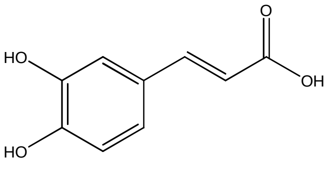
Cupressus sempervirens and consider that cypress is the principal plant source of this propolis. Later on,[71] have reported totarol (**36**) to be the most abundant diterpenoid in Maltese propolis.



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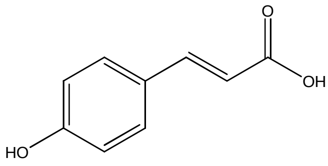

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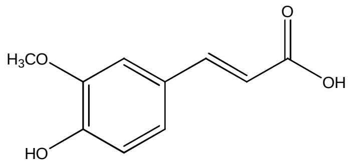

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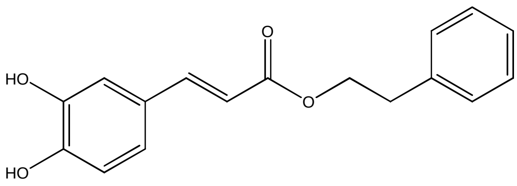

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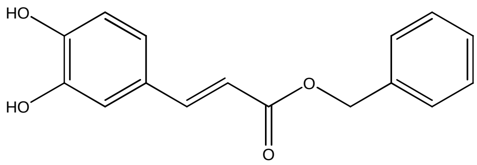

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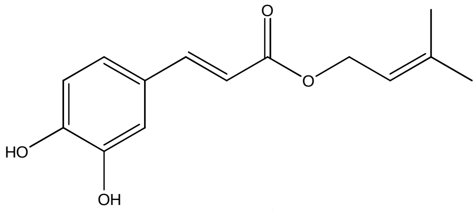

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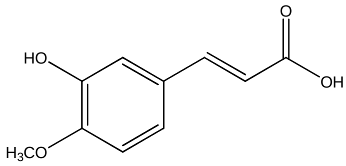

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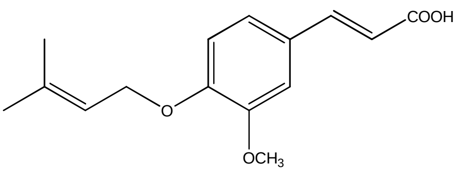

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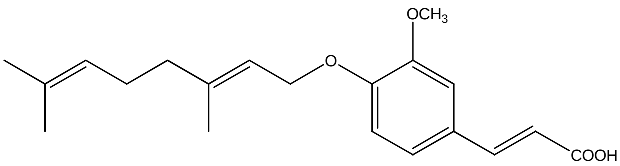

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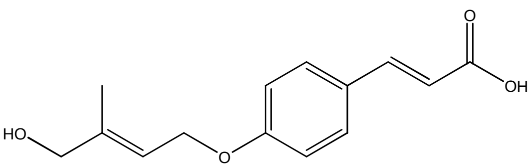

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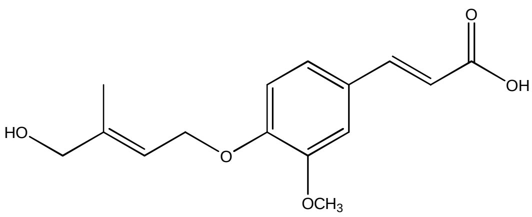

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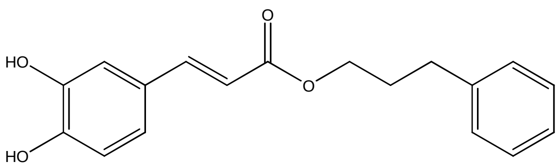

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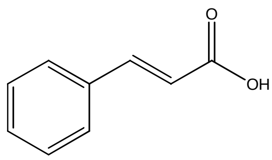

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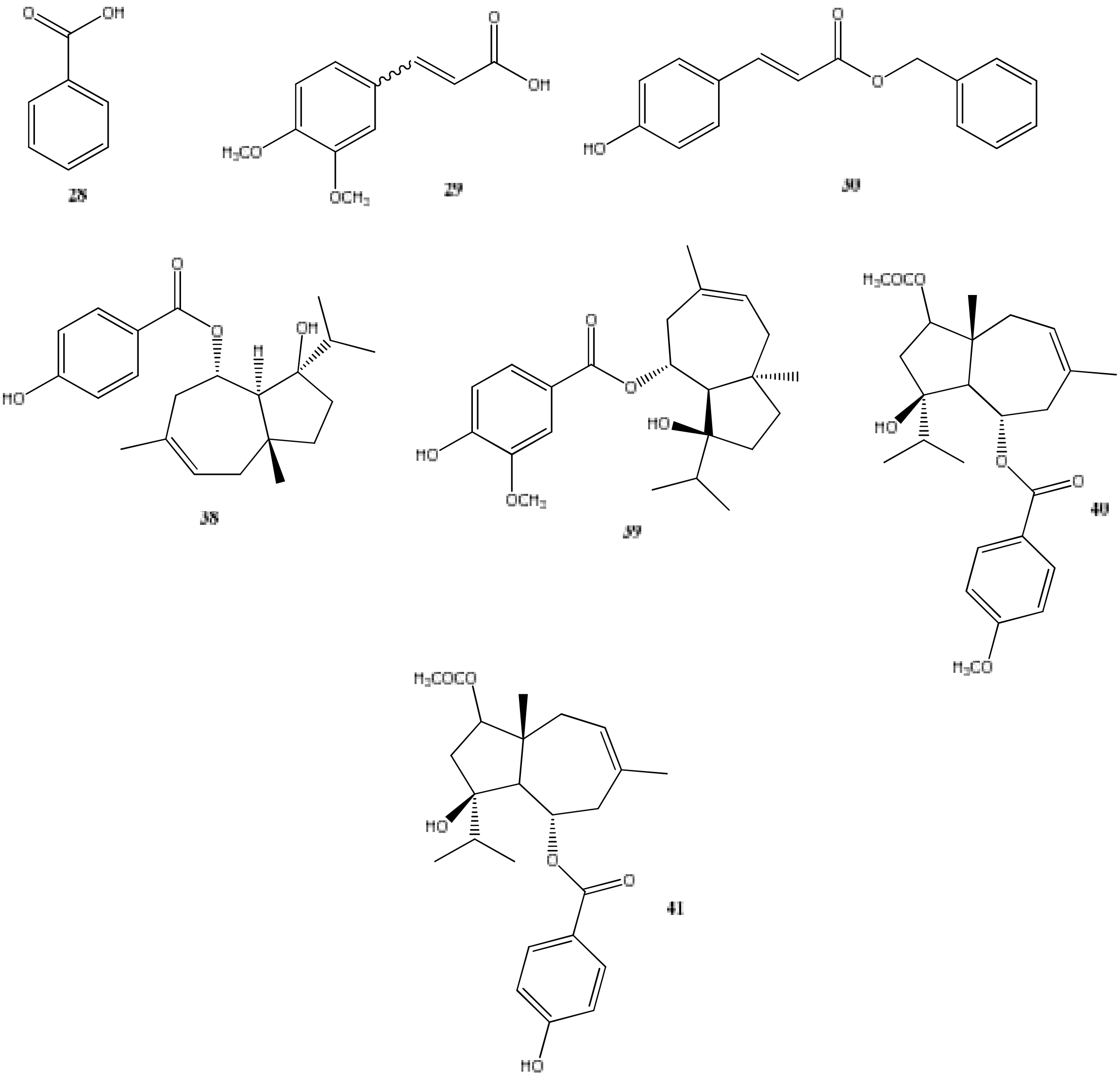

Figure 2. Examples of phenolic acids and their derivatives present in Mediterranean propolis.

In ethanolic extract of propolis from Greece, it was reported a significant amount of flavonoids [mainly chrysin (**2**), pinocembrin (**3**), pinobanksin-3-*O*-acetate (**4**), galangin (**9**), and apigenin (**15**)] (*Figure 1*), and low amounts of phenolic acids and their esters.[17][64][72 – 75]. Terpenes [mainly totarol (**36**), isopimaric acid (**42**), β-elemene (**43**), agathadiol (**44**), pimaric acid (**34**), isoagatholal (**45**) and isocupressic acid (**32**)] (*Figure 4*) were also found with the exception of propolis from Nigrita that had high amounts of flavonoids and low amounts of phenolic acids and their esters, and without diterpenic compounds.[74] In addition, in the recent study of Kasiotis et al.[76] it was not reported the presence of diterpenes in samples originating from Crete, Kos, and Amorgos (Greece), in the oposite of the finding of Popova et al.[75], where they have reported a relative high amount of this group of compounds in Crete samples. In propolis samples from Continental Greece (West North of Macedonia (Kastoria) as well as in Dodecanese islands (Rhodes), Lagouri et al.[77] did not detect diterpenes.

Kalogeropoulos et al.[17] found anthraquinones, mainly emodin (**46**) and chrysophanol (**47**) (*Figure 3*), in propolis samples from Greece.

In other countries of Southern European Coast, such as Turkey, chemical composition of propolis has widely investigated by several authors. Quercetin (**26**), rutin (**48**), chrysin (**2**), pinocembrin (**3**), pinostrobin chalcone (**49**) and pinobanksin (**1**) and its derivatives were the most repeated flavonoids found in various simples of propolis from Turkey using different method of analysis such as gas chromatography–mass spectrometry (GC/MS), high-performance liquid chromatography (HPLC) and ultrahigh-performance liquid chromatography with a linear ion trap-high resolution Orbitrap mass spectrometry system (UHPLC–LTQ/orbitrap/MS/MS),[73][78 – 95] while Erdogan et al.[96] have reported the presence of other flavonoids such as gallocatechin (**50**), epigallocatechin (**51**) and myricetin (**52**) in Anatolian propolis submitted to a pressurized liquid extraction. Other authors did not report the presence of flavonoids in Turkish propolis originating from Hatay, Ankara-Kazan and Mugla-Marmaris,[97 – 100] at the same time they declared that terpenes such as α- and β-eudesmol, isopimaric acid (**42**), dehydroabietic acid (**53**) and abietic acid (**54**) (*Figure 4*) were included in the bioactive compounds of tested propolis samples**.** Notwithstanding, the same authors reported the presence of phenolic acids and their esters, although some authors[101 – 105] described that aromatic acids and aromatic acid esters were only present with low concentration in propolis from Elazig Province. Even though, and whatever the method used to determine the chemical composition of Turkish propolis, it was reported to be rich of phenolic acids, mainly *p*-coumaric (**6**), ferulic (**7**) benzoic and caffeic (**5**) acids (*Figure 1*).[79][81 – 83][95][99][106][107] Regarding terpenes, an amount ranging between 0.15 and 27.47% was revealed in Turkish propolis.[73][79][108]. To be noted that the presence of diterpenes could not depend on the nearness to the Mediteranean Sea, because[108] described a typical poplar propolis from Izmir (Eagean Sea belonging to the Mediterranean basin) and Mediterranean type of propolis from Adana (Mediterranean Sea). Nevertheless Çelemli et al.[73] reported relatively high amounts of totarol (diterpne) in propolis from the Aegean region of Turkey.

Çetin et al.[109] in their investigations on propolis from Kayseri, they affirmed the presence of cinnamic acid **(24)** (*Figure 1*) and their esters with a high concentration. Coumarins were also reported in Turkish propolis from Hakkari, by Bayram et al.[90] in their recent study, where twenty-six coumarins were detected including angelicin (**55**), bergapten (**56**), bergaptol (**57**), columbianetin (**58**), decursin (**59**), isogeijerin (**60**), jatamansin (**61**), lomatin (**62**), methoxsalen (**63**), oroselone (**64**), osthole (**65**), oxypeucedanin (**66**), prangenin (**67**), psoralen (**68**) and seselin (**69**) (*Table S1*).

Levantine Coast

Likewise, in Greece, authors have investigated propolis from Cyprus and have signaled the presence of anthraquinones [emodin (**46**): 1.8-4.08 mg/g EEP)] and flavonoids mainly chrysin (**2**), galangin (**9**), pinocembrin (**3**); pinobanksin (**1**) and pinobanksin-3-*O*-acetate (**4**).[17][61] The presence, with high concentration, of isocupressic acid (**29**), isopimaric acid (**42**), imbricatoloic acid (**35**), agathadiol (**44**), totarol (**36**), 13-epitorulosal (**37**), abietic acid (**54**), dehydroabietic acid (**53**) (*Figure 4*) were also mentioned.[17][61]

Noureddine et al.[110] explored propolis from South of Lebanon and have concluded that bioactive compounds present in the tested extracts showed a similarity to those of southern European coast, concerning the presence of flavonoids and phenolic acids. It was reported that flavonoids were more abundant than phenolic acid including rutin (**48**), quercetin (**26**), genistein (**70**), kaempferol (**25**), chrysin (**2**), pinocembrin (**3**) and galangin (**9**).[110]

Northern African Coast

Egyptian propolis analyzed by GC-MS was a typical poplar propolis type as reported by[111] but with few differences such as the presence of di- and triterpenes but at very low concentrations. Samples from Upper and East Nile Delta in Egypt were mainly characterized by the presence aliphatic acids (lactic acid, succinic acid, stearic acid, oleic acid, palmitic acid), phenolic acids [benzoic (**28**), ferulic (**7**), caffeic (**5**), 3,4-dimethoxy-cinnamic (**29**), cinnamic (**21**) and *p*-coumaric acids (**6**)] (*Figure 2*), flavonoids [pinocembrin chalcone (**71**), pinocembrin (**3**) pinobankasin-3-acetate (**4**)] (*Figure 1*) and di- and triterpene, in lower amounts, were also detected (e.g. cycloartenol (**72**), α-amyrin (**73**), triterpenes of β-amyrin type (**74**)] (*Figure 4*).[111][112] Other authors have reported the presence of phenolic acids and di- and triterpenes in Egyptian propolis samples who also reported to find low concentration of aliphatic acids. The flavonoids found by those authors were mainly catechol, catechin and esculetin.[113]

In Libya, it was reported that propolis from different localities present the diterpenes as main bioactive compounds. Phytochemical analysis of the Libyan propolis display the presence of compounds belonged to phenolic, flavonoids, terpenoids, phytosterols and coumarines.[114][115] Siheri et al.[116] have isolated three diterpenes [13-epitorulosal (**37**), acetyl-13-epicupressic acid (**75**) and 13-*epi*cupressic acid (**76**)] (*Figure 4*) from Libyan propolis with antiprotozoal effect.

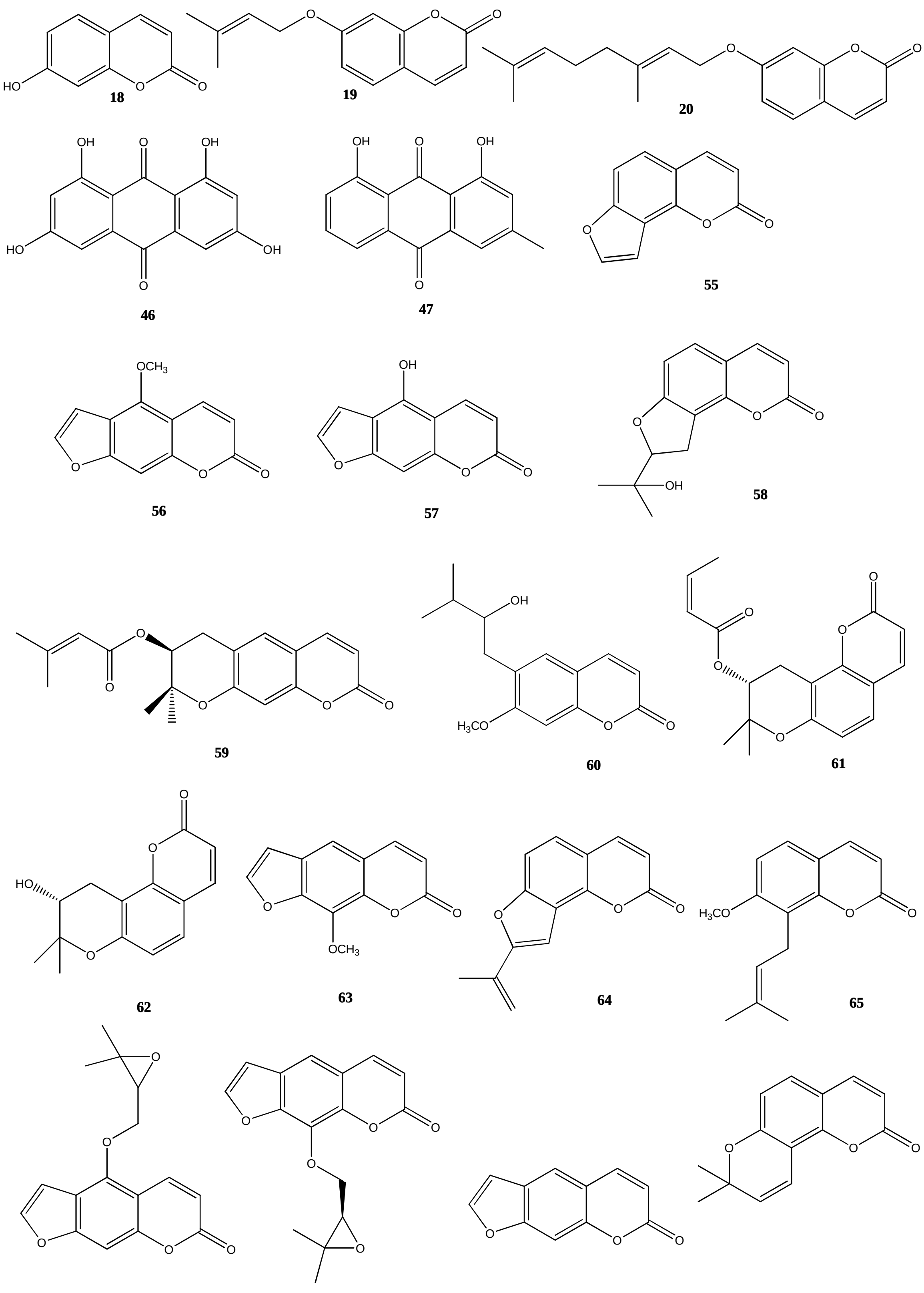

Figure 3. Examples of anthraquinones (**18-20**) and coumarins present in Mediterranean propolis.

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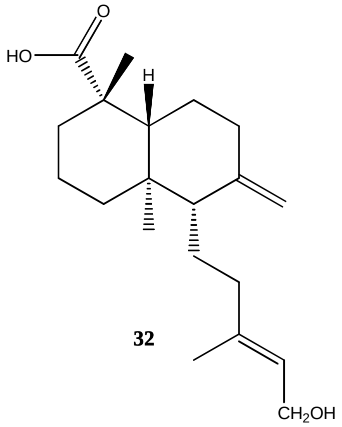

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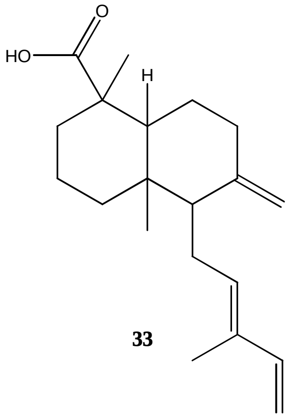

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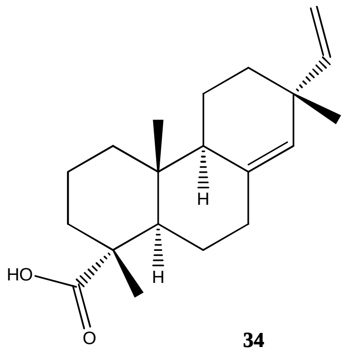

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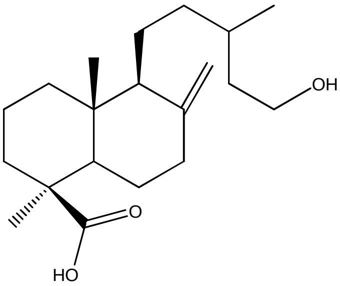

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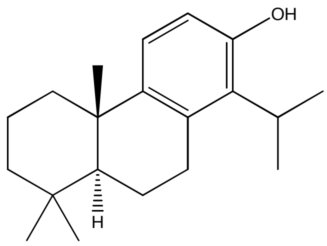

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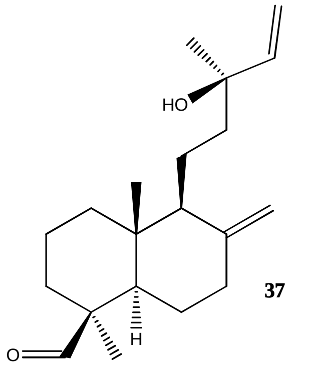

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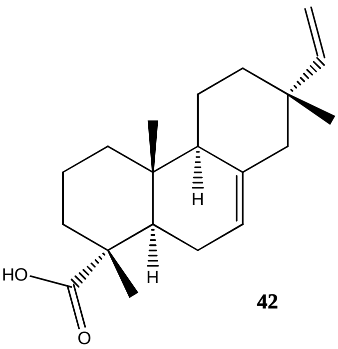

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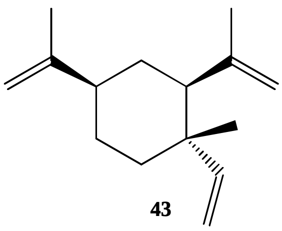

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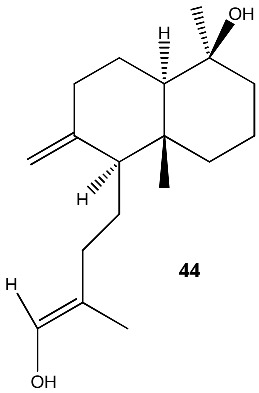

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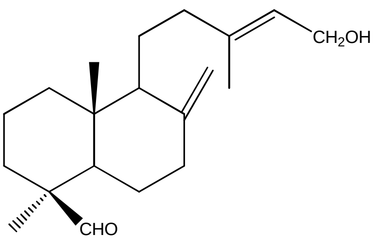

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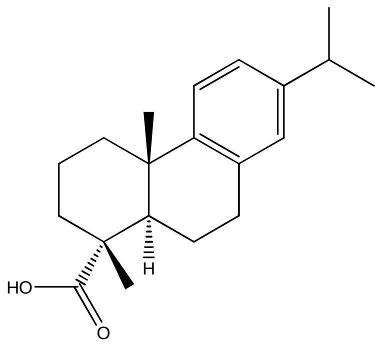

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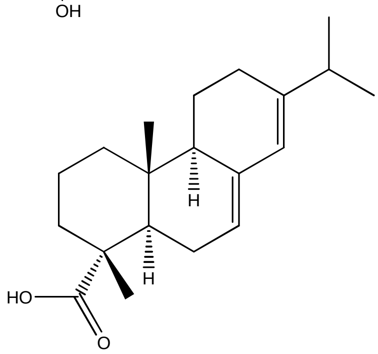

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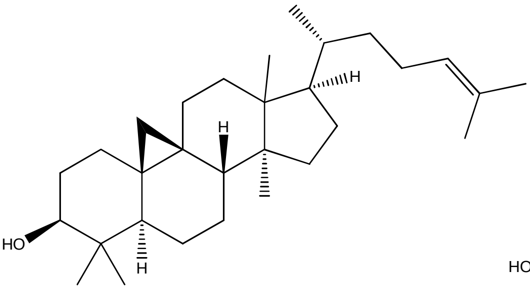
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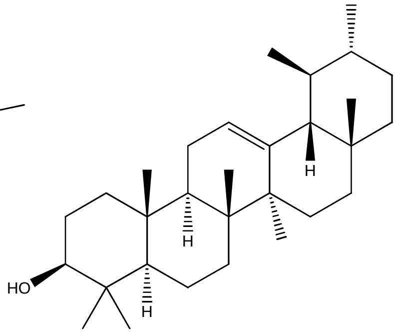
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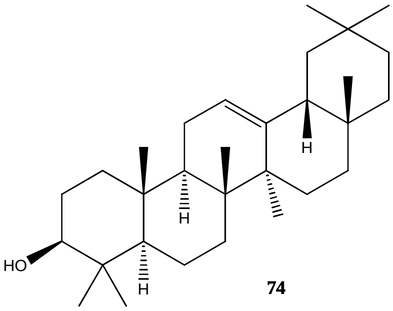
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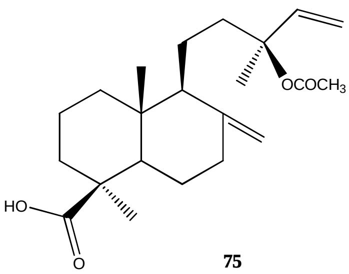
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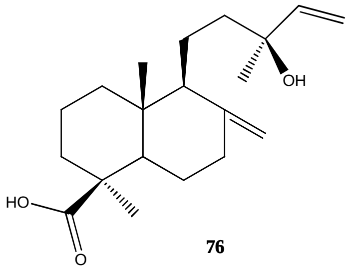
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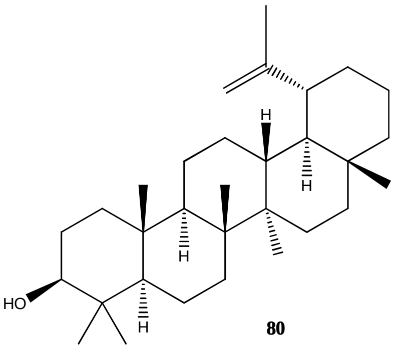
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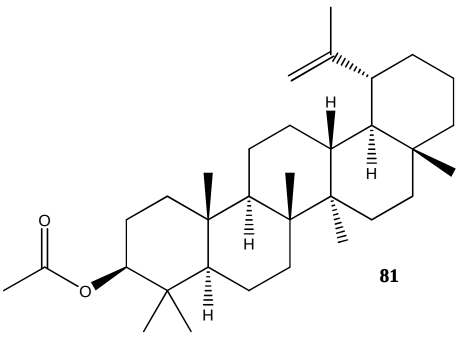
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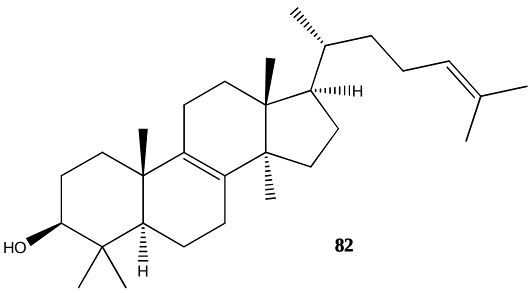
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Figure 4. Examples of terpenes and their derivatives present in Mediterranean propolis.

As far as we found, studies regarding the chemical composition of propolis from Tunisia are very scarce. HPLC analysis of Tunisian propolis collected in Menzel Mhiri showed the presence of chrysin (**2**), galangin (**9**), tectochrysin (**31**), pinocembrin (**3**), pinobanksin (**1**) and phenolic ester like dimethylallyl caffeate (**13**), phenylethyl caffeate (**8**) among others.

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Myricetin 3,7,4’,5’- tetramethyl ether (**77**) and quercetin 3,7,3’-trimethyl ether (**78**) (*Figure 1*) were also found in Tunisian propolis sample.[117]

Some authors reported that diterpenic acids and especially a compound with M=322 (hydroxyditerpenic acid), constituted the main compounds of hydro-alcoholic extracts of propolis from Algeria. Flavonoids were also detected in the same extract mainly pinobanksin (**1**) and pinobanksin 3-*O*-acetate (**4**).[74] Furthermore, flavonoids such as chrysin (**2**), apigenin (**15**), kaempferol (**25**), galangin (**9**), pinobanksin (**1**), pinobanksin-3-acetate (**4**), and pinobanksin-3-(*E*)-caffeate (**79**) among others were detected in alcoholic extracts of propolis from Algeria (*Figure 1*). Those samples were also rich on di- and triterpenic compounds.[118][119] In contrast, in Graikou et al.[61] finding, it was reported that Algerian propolis belong to a group of propolis with relatively high amounts of flavonoids and low diterpene content. In conclusion, the results obtained by diverse researcher teams reveal a co-existence of diterpenic-rich propolis and propolis rich in flavonoids.

Few investigations were done with propolis from Morocco regarding its chemical composition and it was concluded that in summary samples are characterized by high flavonoid contents.[22][120 – 123] Popova et al.[123] and El-Guendouz[22] reports the presence of di- and triterpenes in Moroccan propolis such as isocupressic acid (**32**), imbricataloic acid (**35**), communic acid (**33**), agathadiol (**44**), totarol (**36**) and 13-epicupressic acid (**76**), lupeol (**80**), α-amyrin (**73**), lupeol acetate (**81**), lanosterol (**82**), cycloartenol (**72**) (*Figure 4*), among others. Phenolic esters were also among the principal groups of bioactive compounds found in Moroccan propolis.[22][121][122]

From above, we can conclude that the reported chemical composition of propolis from different countries of Mediterranean basin is heterogenous. It is possible to find diterpenes, independent on their levels, in propolis samples from Italy (Sicily), Croatia, Malta, Greece, Turkey, Cyprus, Egypt, Lybia, Algeria and Morocco (*Table 1*). However, not all samples studied in these areas presented diterpenes. For example, there are studies showing the presence of diterpenes in propolis samples collected in the island of Crete (Greece) and other ones where this does not occur. The same is true for other Greek islands in the Aegean Sea and on the eastern coast of the country. In some propolis samples from Turkey, Italy and Lybia, they were detected coumarines, whereas in some samples from Greece and Cyprus anthraquinones were also reported. In some samples of Malta, Greece, Egypt, Algeria and Morocco, triterpenes were also detected (*Table S1*).

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327 *Table 1*. Major constituents of of the non-volatile part of propolis from different Mediterranean Sea countries

Geographical origin	Extract	Major constituents	Plant source	Bioactivity	Method	References
Six different regions of Greece	Ethanolic extracts	**Diterpenes:** 14,15-dinor-13-oxo-8(17)-labden-19-oic acid (1.5-4.9%); pimaric acid (4.3-10.8%); isoagatholal (9.2-29.1%); agathadiol (2.7-8.3%); isocupressic acid (9.2-29.1%); communic acid (1.8-6.4%); totarol (3.1-6.5%)	*Pinus* sp. and *Cupressus sempervirens*	NE	GC-MS	[75]
Southern European Coast						
Italy						
Piedmont, Emilia Romagna, and Sicily	Ethanolic extracts	**Rich on diterpenic acids (53%).**	*Pinus* sp.	NE	GC-MS	[15]
Larnaka	Ethanolic extracts	**Diterpenes:** totarol (0.32-33.74mg/g EEP), abietic acid (0.25-345.1 mg/g EEP); isopimaric acid (1.94-259.6 mg/g EEP)	Coniferae trees especially *P. nigra*	Antioxidant, antibacterial, and antifungal activities	GC–MS	[17]
Croatia						
Not reported	Ethanolic extracts	**Diterpene:** totarol (0.33-25.75%)	*Pinus* sp	NE	GC-MS	[73]
Lokrum Island and Trogir	Ethanolic extracts	**Diterpenes: (4.8-8.6%)** mainly isocupressic acid, pimaric, imbricatoloic acid, agathadiol, totarol, 13epi-torulosal, communic acid, 13-epicupressic acid, abietic acid and ferruginolon.	Cypress trees *Cupressus sempervirens*	Antibacterial and antioxidant	GC-MS	[61]
Agrinio, Arta, Preveza and Andros, Chalkidiki, …	*N*-butanol extract	Diterpenic and phenolic compounds	NI	Antimicrobial activity	GC and GC-MS	[72]
Malta						
Not reported	Ethanolic extracts	**Diterpene:** (18.7-92.5%) mainly isocupressic acid, communic acid, pimaric acid and imbricatoloic acid, totarol and 13-epitorulosal	Genus *Ferula*, *Populus* spp and *Ferula* spp.	Antibacterial *Staphylococcus aureus*	GC–MS	[70]
Turkey						
Yozgat, Izmir, Kayseri, Adana, Erzurum, Artvin	Alcohol extract	**Diterpenes (4-5%):** dihydroabietic acid, abietic acid, isopimaric acid	*Populus* spp *Populus euphratica*	Antibacterial activity	GC–MS	[79]
Not reported	NI	**Diterpenic profile**	NI	NE	GC–MS	[14]
North and Central Malta	Methanol	The diterpenoid totarol was the predominant constituent	*Pinus halepensis* Mill., *Eucalyptus gomphocephala* DC., *Cupressus sempervirens* L., *Ceratonia siliqua* L., [illegible] Miller, *Cucurbita pepo* L.	Cytotoxicity test on human cancer cell lines	GC–MS	[71]
Ankara-Kazan and Mugla-Marmaris	Ethanolic extracts	**Diterpenes**: isopimaric acid (11.17- 26.88%), dehydroabietic acid (10.61%), abietic acid (11.39%)	*Pinus brutia* L.	NE	GC–MS	[97]
Levantine Coast						
Cyprus						
Not reported	Ethanolic extracts`	**Diterpenes:** dehydroabietic acid (17.75-46.97 mg/g EEP), abietic acid (16.57-23.44 mg/g EEP), isopimaric acid (5.5-17.44 mg/g EEP)	*Pinus* sp *Prunus persica* (L.) Batsch and *Prunus armenaica* L.	Antioxidant, antibacterial, and antifungal activities	GC–MS	[17]
Greece						
South West, south and central Cyprus	Ethanolic extracts	**Diterpenes (0.7-32.6%):** mainly isocupressic acid, pimaric, imbricatoloic acid, agathadiol, totarol, 13epi-torulosal	cypress trees *Cupressus sempervirens*	Antibacterial and antioxidant effects	GC-MS	[61]
Not reported	Ethanolic extracts	**Diterpenes: (4.7-81.9%)** mainly iso- cupressic acid, pimaric, imbricatoloic acid, agathadiol, totarol, 13epi-torulosal, communic acid, 13-epi…	cypress trees *Cupressus sempervirens*	Antibacterial and antioxidant	GC-MS	[61]
Northern African Coast						
Egypt						

Not reported	Ethanolic extracts	**Di- and Triterpenes**: cycloartenol (2.05%), cycloartenol (2.12%) isomer, α-amyrin (2.53%). B-amyrin (2.44%), triterpene of α-amyrin type (2.00%-3.61%).	NI	Antioxidant and antimicrobial activities	GC/MS	[112]
Libya						
Different localities	NI	Mainly diterpenes	NI	Anti-parasitic and antimicrobial assays	LC-HRMS	[114]
North East	Ethanolic extracts	**Diterpenes:** 13-epitorulosal, acetyl-13-epi-cupressic acid and 13-epi-cupressic acid	NI	Antiprotozoal activity	HPLC–ELSD, ^{1}H and ^{13}C NMR	[116]
Algeria						
Stetif region	Ethanolic extracts	**Diterpenes:** pimaric acid (1.09%-4.69%), dehydroabietic acid (2.50 %), abietic acid (4.65%)	NI	Bactericidal and immunomodulators activities	GC/MS	[118]
Different region of Algeria	Ethanolic extracts	**Diterpenes**: cupressic acid, isocupressic acid, imbricatoloic acid, torulosal, isoagathotal ,torulosol , agathadiol , cistadiol ,18- hydroxy-*cis*-clerodan-3-ene-15-oic acid	*Populus* sp	Antioxidant activity	HPLC-DAD	[119]
M'Sila	Ethanolic extracts	**Diterpenes**: diterpenic hydroxyacid M=322 (12.4%-21.1%), pimaric acid (0.8%-1.2%)	Buds of poplars	Antimicrobial activity	GC-MS	[74]
North Algeria		**Diterpenes**: communic acid (1.7%), pimaric acid and imbricataloic acid (2.4%), dehydroabietic acid (1.8%), isocupressic acid (2.1%), junicedric acid (3.7%)	Poplar	Antioxidant and antimicrobicidal activities	GC-MS	[61]
Morocco						
Not reported	Ethanolic extracts	**Diterpenes:** isocupressic acid (3.2%-19.5%), agathadiol, (11.3%), totarol (1.5-%10.1%), 13-*epi*-cupressic acid (9.5%), communic acid (7.9%) and imbricataloic acid (2.7%-4.8%)	Poplar type *Cupressus sempervirens*	Antidiabetic and antioxidant activities	GC/MS	[121]
Region of Fez-Boulmane	Ethanolic extracts	**Diterpenes:** isocupressic acid (8.1%), imbricataloic acid (3.2%), communic acid (2.7%).	Poplar type	Atibacterial activity	GC/MS	[22]

HPLC-DAD: High-Performance Liquid Chromatography- Diode-Array Detector; GC-MS: Gas Chromatography-Mass Spectrometry; LC-HRMS: Liquid Chromatography -High Resolution Mass Spectrometry; HPLC–ELSD: Evaporative Light Scattering Detector; NMR: Nuclear Magnetic Resonance; EEP: Ethanolic Extract of Propolis; NI: Not Indicated; NE : Not Evaluated

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Volatile constituent of propolis

Identification of volatile oils in propolis can give precious information about propolis origin, although they account for only a minor portion of propolis constituents, it gives particular aromas to propolis from different origins, considered as a possible quality criterion for propolis freshness and plays an important role in propolis characterization because they are known to possess valuable biological activities, especially antibacterial, which contribute to the understanding its biological activity.[124]

Propolis volatiles have been studied by several researchers around the world, recently reviewed by[19][124]. Likewise to the non-volatile part, volatile components of propolis depend on a number of factors, such as site of collection, bee type, local flora, and also the method used for isolation and analysis. Regarding propolis volatiles from Mediterranean basin, only few studies were found and are reported in *Table S2*. The chemical pattern of the volatile part of propolis is very complex, presenting different classes of compounds (aldehydes, ketones, alcohols, esters, terpens, acids, etc.).[19]

Southern European Coast

In France there is no recent studies that targets propolis volatiles, while Clair[125] have reported the oxygen-containing sesquiterpene, in particular β-eudesmol (**83**) (*Figure 5*), was found to be the major group constituent of propolis volatile oils from France. Likewise, in Italy, researchers have found that the main bioactive compounds detected were oxygen-containing sesquiterpene such as δ-cadinene (**84**), γ–cadinene (**85**), α-muurolene (**86**), β-eudesmol (**83**), T-cadinol (**87**) and α-cadinol (**88**) (*Figure 5*). Benzoic acid (**28**) (*Figure 2*) and its esters were only found with a significant amount in Italian propolis.[126][127] It is interesting to note that, Pellati et al.[127] have concluded that volatile composition of the Italian propolis indicates a close relationship with bud exudates of *Populus* species.

The major volatile components of Croatian (Dalmatia) propolis identified included terpenes (30%), while in other region (Slavonia) benzyl alcohol (**89**), benzoic acid (**28**) and benzyl benzoate (**90**) were predominant (49%). α-Pinene (**91**), β-pinene (**92**), γ-terpinene (**93**), α-muurolene (**86**), γ-cadinene (**85**) and δ-cadinene (**84**) were also identified as components of propolis.[128] Jerković et al.[65] have also identified these volatile compounds but also α-eudesmol (**94**), β-eudesmol (**83**), γ-eudesmol (**95**), benzyl benzoate (**90**), and 4-vinyl-2-methoxyphenol (**96**) among other components, depending on the collection zone of propolis. Moreover, the procedure of extraction, simultaneous distillation extraction or headspace solid-

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phase microextraction, of propolis volatiles also influenced the amounts of the compounds, but not the qualitative profile of volatiles of Croatian propolis. In addition, the authors[65] also found a correlation between the presence of some volatiles with some phenolic compounds: eudesmol isomers and CAPE although not biosynthetically related, they are present and characteristic of black poplar propolis[19]. The presence of β-eudesmol is even the major constituent of propolis volatiles from other European countries, such as France, Hungary and Northern Italy.[19][125][127]

Steam distillation for 4 h, followed by extraction with ether/ pentane 1:1 of Albanian propolis have revealed the presence of hydrocarbons such as heptacosane, tricosane, nonacosane, heneicosane, pentacosane and hentriacontane. Cadinene (10.5%) and methoxyacetophenone (**97**) were also detected.[129]

Results of total profile of the volatile constituents of Greek propolis reveal the predominance of terpenoids against aromatic compounds where α-pinene (**91**) represented more than 45% of the total components found.[130] On another hand, in Yildirim et al. finding,[32] for Turkish propolis sample from South Eastern Anatolia (Malatya), monoterpenes, mainly α-terpinene (**98**) and α-terpineol (**99**), were the most abundant constituents. Some authors[131] explored the volatile compounds of propolis sample from Turkey by headspace-solid-phase microextraction coupled with GC/MS, and have identified oxygenated hydrocarbons, oxygenated sesquiterpenes, aromatic alcohols and esters as the main aroma-active constituent in propolis simple from North Eastern Anatolia (Turkey).

Northern African Coast

Headspace GC-MS analysis if propolis from different locations in Tunisia showed the presence of different compounds in all propolis samples. Propolis volatiles were dominated by monoterpene hydrocarbons being α-pinene (**91**) the major compound, representing more than 90% the total propolis volatiles.[132]

The volatile fraction of propolis samples collected in different locations in Algeria, analyzed through GC-MS have revealed a distinct composition dominated with 2-hexenal (**100**), myristic acid, linoleic acid, spathulenol isooctane, linoleic acid, undecane, hexadecane, *p*-cymene (**101**), palmitic acid, 4-terpineol (**102**), carvacrol (**103**), and α-cedrol (**104**) dominated.[133]

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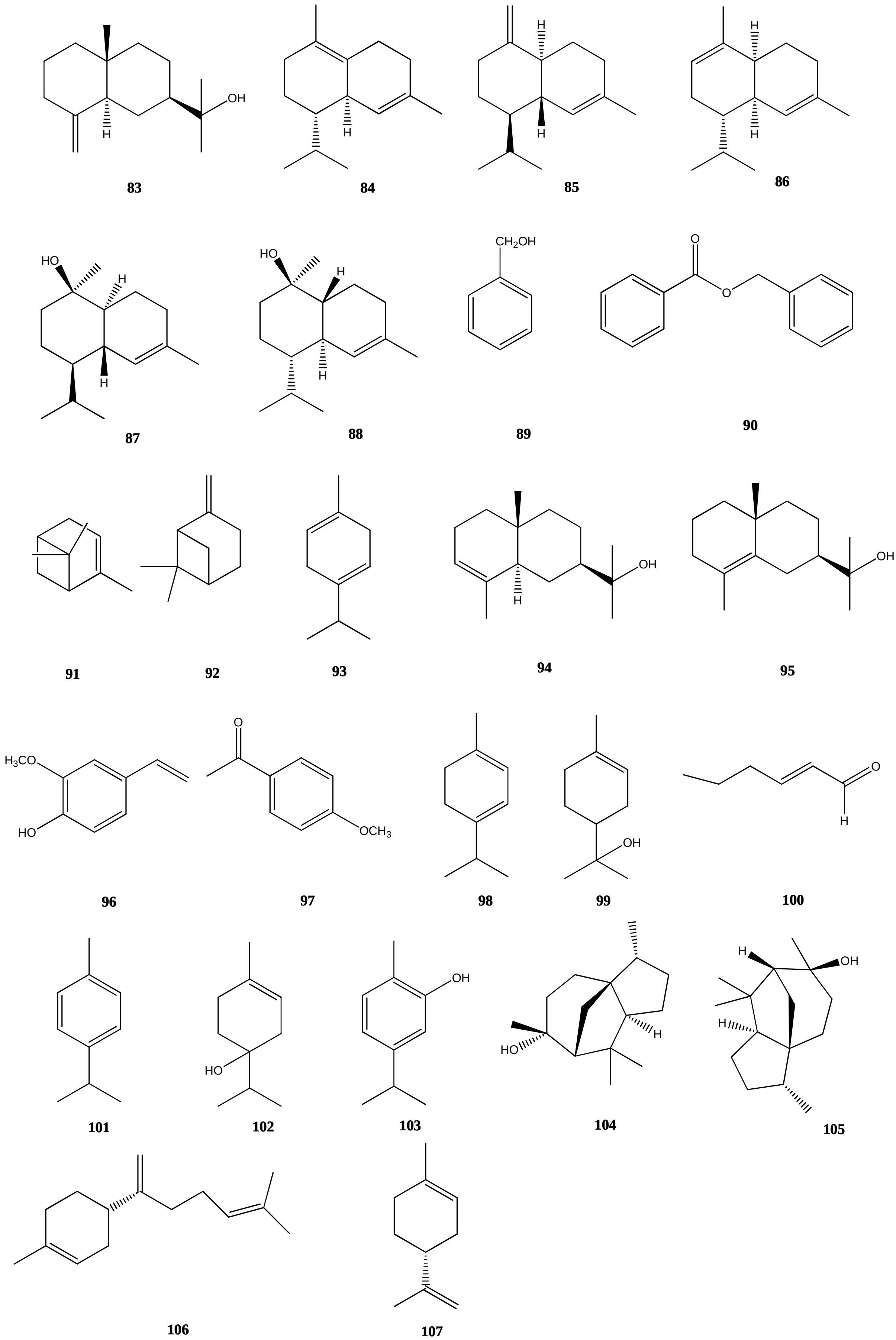

Figure 5. Examples of volatiles present in Mediterranean propolis.

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Regarding the volatile part of Moroccan propolis, it was dominated by the presence of oxygen-containing sesquiterpenes such as α-, β, and γ-eudesmol (**94**, **83**, and **95**), cedrol (**104**) and epi-cedrol (**105**). β-Bisabolene (**106**) and monoterpene hydrocarbons were the second abundant aroma-active group of components in studied propolis represented by α-pinene (**91**), α-terpinene (**98**) and limonene (**107**) among others.[134]

Information upon the volatiles'composition of propolis from the countries surrounded by the Mediterranean Sea is lower when compared to the non-volatile profile, even though it allows to observe the following trend: in propolis from poplar type, sesquiterpenes, particularly, β-eudesmol is always present in relative high amounts, whereas the monoterpenes such as α-pinene are mainly present in the Mediterranean propolis type, maybe due to the plant source used by bees which are mainly constituted by coniferous species, as for example, *Cupressus sempervirens* L..[19]

Biological activities of propolis from Mediterranean countries

Propolis, selected as a natural product, is showing a large spectrum of therapeutic properties due to its richness of different bioactive compounds.[135] Indeed, several studies have been carried out on propolis over the world in view to explore more and more its valuable biological activities. However, in this section, we reviewed those properties particularly for propolis from the Mediterranean countries that are also depicted in *Table S1* and *Table S3*. For more detailed information it is advisable to consult *Table S3*.

Antioxidant activity

The involvement of oxidative stress is believed to be responsible for the occurrence of diseases such as diabetes, cancer, inflammation, cardiovascular and many others. As well documented, antioxidants are able to prevent free radicals' generation, scavenging them and promoting their decomposition.[24] In fact, antioxidant effect of propolis has been widely studied through many assays in Mediterranean countries.

Southern European Coast

In Spain, several authors have investigated propolis from different location for its antioxidant capacities.[35][136 – 140] Those authors state the *in vitro* antioxidant capacity of Spanish propolis through several methods [2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS), 2,2-diphenyl-1-picrylhydrazyl (DPPH), Ferric Reducing Antioxidant Power (FRAP), Trolox Equivalent Antioxidant Capacity (TEAC)] and radical-scavenging effect on hydroxyl radicals antioxidant activity assay and the results revealed a significant correlation between the phenolic composition and the antioxidant activity. The activities found were dependent on the amounts of phenolic compounds, which, in turn they were dependent on the harvesting method, solvent of extraction as well as the method of extraction. The methods used were the same reported for French propolis leading to same conclusion as reported for Spanish one.[40]

Ethanolic extract of propolis samples from several region in Italy also presented an important antioxidant activity, which manifests in the preventing the lipid peroxidation, scavenging effect on superoxide anion, DPPH and inhibiting the xanthine oxidase activity.[46][141 – 144] These authors showed a potential correlation between antioxidant activity and polyphenolic content. Moreover,[144] have examined the antioxidant activity of propolis with and without CAPE and declare that propolis with CAPE was more active than propolis without CAPE, while CAPE alone was more efficient than galangin regarding its antioxidant activity, from where the similarity to the results of Spanish researchers on phenolic compounds, being the bioactive component responsible of the antioxidant activity of propolis.

Slovenian ethanolic extract of propolis was screened for its chemical and antioxidant activity and was found that antioxidant properties were related to the total phenolic contents. Propolis also found to responsible on changes in the levels of antioxidative proteins and proteins involved in ATP synthesis in *Saccharomyces cerevisiae*.[51][52][145][146]

Different propolis extracts including Croatian, Greek and Cyprus (Levantine Coast) ones were shown to possess a variable antioxidant capacity due to its richness in bioactive compounds. [17][51][62][65 – 67][77][146 – 147] Jug et al.[148] have found propolis from Dalmatia and Zagreb, Croatia, to be excellent as antioxidant agent based on the results of the antioxidant tests assayed.

Accordingly, extract of propolis, using different solvent of extraction, from different province of Turkey exhibited an effective antioxidant ability seeing different assays overall DPPH, total antioxidant activity, ferric ions (Fe^{3+}) and cupric ions (Cu^{2+}) reducing abilities, ABTS, H_2O_2 scavenging and metal chelating activities.[8][35][76][80][85][96][99][106][135][149 – 155] Furthermore this biological property of Turkish propolis was confirmed through other assay such as heat-induced oxidation of an aqueous emulsion system of β-carotene and linoleic acid assay where the total antioxidant activity increased with the increasing amount of extracts added to linoleic acid emulsion.[80] Also, a screening method for antioxidant activity used

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reversed Phase HPTLC-DPPH free radical assay.[89] In general, the antioxidant capacity of different Turkish propolis extracts was assessed to be positively correlated with their total polyphenol content. In agreement with these findings, a higher reducing power ability was observed among Algerian and Moroccan (Northern African Coast) propolis samples suggesting the most contributing role of phenolic compounds to this activity.[24][156 – 161] As noted by the reviewed articles, the authors were agreeing about crucial role of propolis as antioxidants source.

Antimicrobial activity

Southern European Coast

Antimicrobial activity is another valuable propriety of propolis. Ethanolic and propylene glycol extracts of propolis from Spain was reported to have antimicrobial activity that acts mainly on Gram-positive bacteria and yeasts, showing a positive correlation with flavonoid content and the bactericide properties.[137][140] Other authors disclosed that propolis from Roma and Apulia (Italy) and Barcelona (Spain) exhibit a fungistatic and fungicidal activity on fungi isolated from Venezuelan patients including *Candida albicans, Candida krusei, Candida guilliermondii* and *Candida tropicalis.*[140][162][163]

Benzyl caffeate, *p*-coumaric acid and pinocembrin were predominant in French propolis sample and showed a great effectiveness against tested pathogens exhibiting an important antibacterial and antifungal activities against *Staphylococcus aureus; Escherichia coli*, and *Candida albicans.*[164] More recently, Boisard et al.[41] have found the same properties of aqueous and methanolic extracts of poplar propolis, where they found a selective Gram-positive antibacterial activity, in particular against *Staphylococcus aureus* and several of its *methicillin-resistant* (MRSA) and *methicillin-susceptible* (MSSA) strains.[41] Moreover, Amoros et al.[165] have shown that 80% ethanol extract of propolis from Renne, France, possess an antiviral effect against Herpes simplex virus (HSV-1). The authors also investigate the anti-HSV-1 activity of the abundant flavonoids identified in French propolis comparing the results with those from the ethanol extract of crude propolis. The authors have found that propolis was more active than its individual compounds attributing such results to the synergic effect of propolis flavonoids.

Propolis from different place in Italy showed good antimicrobial activity against *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis, Staphylococcus aureus, Candida albicans, Streptococcus pyogenes,* Escherichia *coli, Proteus*

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mirabilis and Pseudomonas aeruginosa but not against *Enterobacteriaceae*[44][166 – 168]. Propolis from Piedmont region, where hybrids of poplar, alders, poplars, hazels and pine trees dominated, had a strong antibacterial activity against almost all strains of *Staphylococcus aureus* tested.[166] Likewise, Bisio et al.[44] investigated samples from the same region in Italy and have attributed the bacteriostatic and bactericidal properties of propolis found against *Streptococcus pyogenes* strains, to the predominance of pinocembrin and galangin in the studied samples. Later, Scazzocchio et al.[168] and Gil et al.[169] have examined the antimicrobial activity and synergistic effect with some antibiotics of ethanolic extract of propolis against bacterial clinical isolates of *Staphylococcus* spp. and *Streptococcus* spp. and demonstrated the positive action of propolis against different virulence factors of the tested strains and reports the efficiency of application of propolis along with ineffective antibacterial drugs, due to antibiotic resistance, during early stages of infection. On the other side, other authors have shown that propolis originating from Italy possess a good antibiofilm activity against *Pseudomonas aeruginosa* and could be used as adjuvant in the therapy against Pseudomonas *aeruginosa* chronic infection.

Extracts of propolis collected at Dolenjska, Slovenia, were more effective against Gram-positive bacteria than against fungi and Gram-negative bacteria tested such as *Salmonella* and *Escherichia coli*, except *Campylobacter* and declared that this different action could be associated with the total content of phenolic compounds present in the tested propolis samples which act through a synergistic manner.[51]

Croatian propolis, originating from continental and near the Mediterranean Sea, presented a robust antimicrobial capacity against *Escherichia coli*, *Staphylococcus aureus*, *Candida albicans*, *Aspergillus niger*, and *Bacillus subtilis* which correlated well with polyphenol and flavonoid content.[54][61][62] However, Mašek et al.[66] explored typical Croatian poplar type of propolis rich in aromatic acids and flavonoids with very low content of terpenes and observed a great difference in chemical composition of different extracts, but they did not find a clear correlation between chemical composition and biological activity.

Antimicrobial effect of propolis extracts from Malta was also reported. According to Popova et al.[70] all Maltese propolis samples tested were active against *Staphylococcus aureus* but only those with high concentrations of terpenyl esters showed antifungal activity against *Candida albicans*, while they were ineffective against *Escherichia coli*.

Hydroalcoholic extracts of Greek (Nigrita) and Turkish (Bursa) propolis rich in flavonoids and esters of caffeic and ferulic acids were reported to have a significant antibacterial and weak to moderate antifungal activity.[74] At the same time, one new 2,3-dihydroflavone

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derivative, 7-*O*-prenylstrobopinin, and 25 known diterpenes and phenolic compounds were identified in the *n*-butanol extract of Greek propolis from Preveza region, which showed a good antimicrobial activity against Gram (+/-) bacteria and fungi.[72] In another experiment, ethanol extracts of propolis were tested for antimicrobial activities against ten *Paenibacillus larvae* isolates, a spore forming bacteria which cause one of the most severe bacterial diseases affecting the larvae of honey bees and responsible for colony loss. The results of this study revealed a strong susceptibility of the *P. larvae* to the tested propolis.[170] Besides, it was revealed that volatiles from Greek propolis also possess antimicrobial activity against human pathogenic agents.[130]

Levantine Coast

Several authors have reported that propolis from Greece (Southern European Coast) and Cyprus to be very rich in terpene and aromatic compounds (flavonoids, phenolic acids and esters) and declared that this class of bioactive compound participate largely on the antibacterial and antifungal activities.[61] Moreover, Kalogeropoulos et al.[17] found that propolis extract from different places in Greece (Southern European Coast) and Cyprus exhibited similar antimicrobial activity, inhibiting Gram positive pathogens and fungi growth, and not affecting several lactic acid bacteria. Those propolis extracts were more efficient in large spectrum of microorganisms as compared to nisin, a food grade antibiotic.[17]

Propolis from several region of Turkey has been widely exanimated for its antibacterial and antifungal properties against different Gram$^+$ and Gram$^-$ bacteria, clinical, instant soups and foodborne isolates. *Table S1* shows the different study done on propolis from Turkey. All report of antimicrobial activity of Turkish propolis displayed a convergent. [78 – 83][91][93][95][98][105][149 – 150][170 – 191] Practically, all tested samples exhibited an antifungal and antibacterial performance. In general, antimicrobial activity varied depending on the chemical composition and origin of propolis sample, dosage of propolis, the extraction solvents and incubation period, for all test microorganisms. Withal, some authors have reported that propolis showed a good antibacterial ability against Gram positive *cocci* such as *Staphylococcus aureus, beta hem. Streptococus* and a limited activity against Gram negative bacteria such as *Escherichia coli, Pseudomonas aeruginosa*, and yeast (*Candida albicans*).[78][172][190] Other research team reported that *C. albicans* was the least sensitive microorganism toward Turkish propolis.[98] Furthermore, in Silici et al.[190] study, it was found that propolis sample gathered by *Apis mellifera caucasica* showed higher antibacterial activity than the one gathered by *Apis mellifera anatolica* and *Apis mellifera carnica*. The antibiofilm

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activity, embodied in the inhibition of biofilm formation and the reduction of established biofilm of propolis was approved also against clinical isolates.[81] Additionally, the anti-parasital effect of propolis from Kayseri, Adana, Hatay, and Bursa provinces, Turkey was screened against *Leishmania promastigote*, and it was found to be effective presenting a promising activity for drug discovery and the development of novel antileishmanial agents.[106][192][193] Also, propolis from Trabzon, Turkey, was found to possess amoebicidal, as well as cysticidal properties for *Acanthamoeba trophozoites* and cysts.[187] As well, Sahin et al.[194] affirmed that propolis showed an inhibitory potential against the zinc metalloenzyme carbonic anhydrase. Morover, Turkish propolis was able to inhibit crucial enzymes such as acetylcholinesterase, xanthine oxidase and urease.[195] According to the authors, the propolis originating from Turkey could be considered as natural product to be involved in clinical medicine and food industry.

Northern African Coast

Exploring the biological properties of Egyptian propolis from different locations, there are studies which allowed to conclude that propolis from Egypt showed a variation in the antimicrobial activity according to the propolis origin and had a concentration-dependent activity.[111][112][164][196 – 198] Besides Elbaz and Elsayad II[199] compared the antimicrobial effect of Egyptian propolis *vs* New Zealand one on *Streptococcus mutans* and *Lactobacilli* in saliva and have found that the hexane fraction of the commercial New Zealand propolis possessed the strongest antimicrobial action, while ethanolic extract was more potent on *Streptococcus mutans* than on *Lactobacilli.* In other report, propolis was checked for its synergetic effect and was characterized by a capacity of preventing the microbial growth alone and has synergistic effect when used with honey or ethanol. This activity was depending on propolis geographical origin.[200] More recently, Mokhtar et al.[201] highlighted the potential antiprotozoal activity of Egyptian propolis extract as a potent natural alternative for metronidzole in treatment of blastocystosis.

In Libya, propolis from Tukra and Al`Aquriyah, showed an important activity against *Trypanosoma brucei*, which is the aetiologic agent of sleeping sickness, and Leishmania *donovani*, which causes visceral leishmaniasis *Trypanosoma brucei*[116]. Later on, the authors[114], supported the previous finding regarding anti-parasitic activity of Libyan propolis: anti-trypanosomal, anti-leishmanial, anti-*Mycobacterium marinum*, anti-*Plasmodium falciparum* and anti-*Crithidia fasciculata*.

The anti-cariogenic and anti-biofilms activities of the ethanol extracts of propolis from Monastir, Tunisa were also reported. The tested samples were able to inhibit cancer cell proliferation, cariogenic bacteria and oral biofilms formation. The excellent activities found was attributed to specific bioactive compounds of the Tunisian propolis.[202]

Antimicrobial activity due to the presence of diterpenic compounds, was also reported in propolis samples from Algeria, particularly against bacteria.[74] It was found that propolis samples form Tiaret, Tlemcen, Sidi bel Abbes and Mascara, Algeria, were active against Gram positive bacteria (*Staphylococcus aureus*, *Bacillus subtilis* and *Bacillus cereus*), and inactive against Gram negative bacteria (*Pseudomonas aeruginosa*, *E. coli*)[203][204]. In Soltani et al.[118] study, it was demonstrated the immunomodulatory activity and the bactericidal activity of Algerian propolis against important bacterial pathogens in seabream, and was suggested that propolis could be a source of new natural biocides and/or immunomodulators in aquaculture practice. In addition, it is noteworthy that caffeic acid derivatives from propolis from Beni Belaïd area had the capacity to inhibit Stromelysin-1 enzyme enrolled in collagenolytic and elastolytic cascades, leading to cutaneous intrinsic and extrinsic aging.[205]

Finally, Moroccan propolis from different regions exhibited antibacterial activity screened through different assay including disc diffusion method, antibiofilm, anti-quorum sensing and anti-adherence assays. On the same insight of the results reported in this review, the authors related this activity to the bioactive compounds present in Moroccan propolis samples.[22][157]

From above, we can conclude that propolis from Mediterranean basin is mainly active on Gram+ bacteria and less effective regarding Gram- bacteria and yeast, as reported for other propolis with different geographical origins. Regardless the diversity of the chemical profile of propolis, generally all of them present antimicrobial activity. The role of propolis is maintaining the hive free of intruders, including microorganisms. For this reason, bees have to use the material that is available near the hives with the purpose of keeping them in healthy conditions. The plant material available for bees is different and changes according to the region but the biological properties must be effective to preserve the healthy bees.

Application fields of propolis from Mediterranean basin

As previously presented propolis from countries of the Mediterranean basin showed a great heterogeneity regarding its chemical composition and possesses a wide range of pharmacological potentials. This is attributed to the various origins of propolis, collect seasons, surrounding plants, genetic of bees, harvesting and extraction methods of propolis as already aforementioned.

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Propolis applications for various purposes such human medicine, quality of life, cosmetic, food industry and aquaculture as well as in livestock farming, with a high interest will be presented and developed in this section. In many cases, the application of propolis in the diverse fields were sustained in the fact that propolis possesses antioxidant and/or antimicrobial properties.

Several investigations have been done by researchers of the Mediterranean basin either using *in vitro* or *in vivo* assays (animal models) to find out possible applications of propolis from the Mediterranean countries in different fields. In this section, for all countries belonging to the Southern European, Levantine and Northern African Coasts, it will be reported three main fields of propolis application which are the following: medicine/pharmacy and bio-allied sciences; food industry and improvement of livestock.

The principal biological properties of propolis included anti-inflammatory, antioxidant, antimicrobial, anticancer, antidiabetic, as can be read in *Table S4* and described in this Section. Considering that the inflammation could be due to the oxidation processes; because inflammatory process induces oxidative stress and reduces cellular antioxidant capacity, leading to several diseases like diabetes, heart diseases, and even cancer, among other pathologies; the antioxidant, anti-inflammatory and antimicrobial activities of propolis are included in subsection of medicine/pharmacy and bio-allied sciences. The subsection of food industry will present all studies done with propolis from the Mediterranean countries with the purpose of preservation of food quality, although, in the third subsection (improvement of livestock) we gathered all investigation found in literature regarding growth, performance and improvement of livestock as well as some possible veterinary application.

Southern European Coast

Application in medicine, pharmacy and bio-allied science

Spanish propolis was tested for medical application by Lisbona et al.[206] who examined if the oral supplementation with propolis samples from Granada would be able to diminish oxidative aggression and free radical's generation associated to aging. In this study, the authors have found that diets supplemented with propolis in rats' models increased the glucose level, cholesterol concentrations and reduced the protein peroxidation, thus reducing the oxidative stress associated with aging. According to the authors these results could be the results of a synergic effect of different propolis components.

Recently, hydroalcoholic extract of blended propolis from France was tested in combination with cranberry regarding its capacity to reduce the mobility and biofilm formation of uropathogenic *E. coli* (UPEC) responsible of urinary tract infections.[207] In this study, it was reported that propolis potentiates strongly the effect of cranberry on UPEC, representing a promising strategy to prevent recurrent urinary tract infections. Some authors have screened the ethanol extract of propolis from west France for its photoprotective properties, and have shown that propolis exhibit an important photoprotective effect comparable to that of the positive control (homosalate). Thus, it can be used as a natural sunscreen agent.[208]

For its anticancer activity, propolis from Italy was also investigated. In a first report, Scifo et al.[209] checked the possible association of propolis and resveratrol together or with vinorelbine at low concentration in the therapy of prostate cancer, and have found that propolis provoked an apoptosis-like while resveratrol generates necrosis-like cell death for androgen-resistant prostate cancer cell line DU145. Thus, propolis and resveratrol could be used as natural therapy in low concertation with vinorelbine for cancer treatments. On the same insight, Borrelli et al.[210] have investigated the anti-carcinogenesis action of propolis extract without CAPE and CAPE alone and concluded that CAPE may be the responsible of the anticancer activity of propolis. Other authors reported a protective action of propolis in cartilage alteration resulted from joint diseases, and have shown that propolis acted by an anti-inflammatory mechanism by reducing the key molecules released during anti-inflammatory events as nitric oxide (NO) and glycosaminoglycans (GAGs).[211]

Rossi et al.[212][213] have investigated propolis and some of its components such as CAPE and galangin, regarding their anti-inflammatory activity on lungs homogenates and J774 macrophages. The COX-1 and COX-2 inhibitory activity of propolis was concentration-dependent. These authors have investigated propolis with/without CAPE and have found that propolis extract with CAPE was less potent than propolis extract deprived of CAPE, they also found that galangin had inhibitory activity on COX but lower than that of propolis or CAPE, suggesting that both CAPE and galangin participated to the anti-inflammatory activity of propolis.

Still in Italy, Rassu et al.[214] used propolis as a ‘nanocarrier’ for the formulation of solid lipid nanoparticles (SLNs) intended for topical nasal drug delivery, not only its frequent application in otolaryngology, but also for its properties in antibacterial and antiviral infections and inflammation. The *in vitro* and *ex vivo* permeation tests performed for the drug was compared with that obtained from the aqueous solution of diclofenac (anti-inflammatory drug), several formulations were done and they found that, the drug is released faster from the formulation containing 25/1 (propolis/drug, w/w) although, it more slowly crosses the lipid

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membranes of the biological membrane, slowing the absorption. Thus, the drug and flavonoids would remain in the surface of the mucosa, and deploy their therapeutic effects.

A trial to develop a new topical mucoadhesive formulation containing propolis for possible application in the stomatological field was assessed by.[215] In this study, the authors did the formulation of a mucoadhesive topical gel containing propolis, and the *in vitro* and *in vivo* tests performed showed that propolis components mainly CAPE were able to get through the *in vitro* porcine buccal mucosa, moreover, the formulated gel also presented an adequate comfort, a non-irritancy and a good acceptance by the volunteers.[215]

For the purpose of exploiting its antioxidant properties, propolis was screened by [216] for a possible use in natural sunscreens formulation for sunburn. Gregoris et al. [216] have found that propolis had a good broad spectrum UVB and UVA photoprotection, and concluded that it could be a brilliant candidate on formulation of sunscreen based natural products.

Oršolić et al.[217] (*Table S4*) have examined the effect of Croatian propolis and some of its polyphenolic derivative compounds, such as caffeic acid, and CAPE, quercetin, chrysin and naringenin on the metastatic capacity, immune reaction, apoptosis and necrosis of transplantable mammary carcinoma (MCa) of CBA mouse and it was found that propolis and its components were cytotoxic to tumor cells, they were able to induce apoptosis and necrosis, to inhibit tumor growth, to prolong survival of mice, and led to many ameliorations in several immunological parameters, such as the production of lymphocyte activating factor by peritoneal macrophages and the efficacy of those macrophages to kill tumor cell and responses of lymphocytes to mitogen.[217 – 221] The established results suggest that propolis exhibit a noteworthy antimetastatic potential and act as immunomodulatory agent. This finding presents propolis as a potential product for the control of tumor growth, referring its activity to a possible synergetic effect of its phenolic compounds. The same group of research has investigated Croatian propolis and some of its derivatives for its antitumoral capacity against the development of Ehrlich ascites tumor (EAT) alone of combined to an anticancer drug irinotecan or cisplatin. The combination of propolis with the anti-cancer drugs inhibited the growth of EAT cells and increased survival of bearing tumor animals. Moreover, propolis and its derivatives deteriorate toxic and genotoxic effects led by anticancer drugs to normal cells without influencing the irinotecan cytotoxicity in tumor cells.[221 – 224]

Further, propolis and its phenolic compounds exhibited a protector effect on experimental animals from the lethal effect of irradiation.[225 – 227] As a conclusion to those results, the authors suggested that propolis could be an adjunct to anticancer drugs to boost their antitumor activity and decrease the post chemo / radiotherapeutic deteriorated reactions as

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well as its possible use as natural therapeutic drugs to prevent or treat psoriatic complications. Furthermore, Sobočanec et al.[228] have investigated also the effect of propolis in combination with an anticancer drug (5-Fluorouracil) in mice injected with tranplantable 4T1 mammary carcinoma, and have observed, on same insight to the other investigator[229][230] that propolis boost the effect of anticancer drugs by prolonging the suppressive effect of 5FU on tumor growth, and reducing the number of metastasis and decreased dihydropyrimidine dehydrogenase (DPD) protein level.

Besides, Oršolić et al.[225][226][231], Benković et al. [227][232][233], and Lisičić et al.[234] have investigated the protective effect of Croatian propolis on psoriatic lesion regression and side effects resulted by radiation and/or chemotherapy such as cytopenias in animal models. Those authors showed that the topically application of propolis improve psoriatic-like skin lesions by suppressing functional activity of macrophages and ROS production.[231]

In addition, the possible amelioration of different damage in diabetic animals by propolis was studied by Oršolić et al.[229][230] on diabetic mice model. Treatment with propolis leads to a raise of body weight, hematological and immunological parameters of blood, 100% survival of diabetic mice, diminution of lipid peroxidation in liver, kidney and brain tissue and reduction of DNA damage in peripheral lymphocytes. Data found by Oršolić et al. [229][230] demonstrated that propolis exhibited an oxidative and anti-inflammatory potential and could be used in strategies for the prevention and treatment of diabetes mellitus.

Other researchers[235], more recently, checked different propolis samples from Croatia regarding their antiaggregatory activity on platelet aggregation, and demonstrated that propolis even in low concentrations presented an important antiaggregatory potential, suggesting that propolis supplementation may influence platelet aggregation, which can play crucial role in thrombus formation responsible of stroke or heart attacks. Moreover, Barbarić et al.[68] studied propolis samples from Bosnia and Hercegovina and Croatia regarding its cytotoxic effects on cervical tumor cell line (HeLa), and they found that it exhibited an antiproliferative and cytotoxic effect.

In Albania, Meto et al.[236] examinated the possible positive effect of propolis on the inflamed pulpal tissue after pulpotomy in piglets and have found that propolis possessed a large anti-inflammatory and regenerative effect, suggesting that it could be used clinically.

The antitumoral propriety of propolis from Greece and its isolated diterpenes was also tested on different human solid tumor cell lines, human promyelocytic leukemia cell line (ECACC) and human skin fibroblast strain AG01523c. Propolis revealed to be an important antitumor natural product due to cytostatic activity, especially that of manol which exhibited a promising profile as an antiproliferative agent.[237]

Morover, Kalogeropoulos et al.[238] elaborated a method for the encapsulation of Greek propolis extract in β -cyclodextrin (β-CD) cavity in the intention of raising the solubility of its components and use for medical application. As a result of this investigation, they found that the biodisponibility of propolis compounds was size-dependent, small molecules were more efficient in encapsulation, while their release from the β -CD was more difficult than 'bigger' molecules. The release of compounds from encapsulated propolis depends on their chemical properties and their relative abundance in the matrix.

Propolis from Turkey has been found to have a wide spectrum of biological applications. Several trials for the application of propolis as anticancer agent and related side effects using different cancer cell lines were assessed.[8][86][88][106][239 – 247]

Some authors[8][88][240][241][243 – 246] and more recently Ozdal et al.[106] have tested propolis from different locations in Turkey for their anticarcinogenic and antimitotic effect against human breast carcinoma, hepatocellular carcinoma, prostate adenocarcinoma, colon adenocarcinoma, HL-60 myeloid leukaemia, lung carcinoma and mammary adenocarcinoma cells line. Those authors concluded that the tested propolis exhibited a noteworthy capacity to inhibit the cellular growth of tumor and induced apoptosis. This high potential of propolis as anti-tumoral agents was related to its constituents especially its phenolic content. Moreover, Onbas et al.[243] have formed a microencapsulation by complex coacervation of propolis and screened its inti-inflammatory and cytotoxic potential on cancer cells, and have found that this complex has same activity as compared with propolis in free form, and suggested its possible use in the industry for the formulation of natural supplement.

On the same insight, protective effect of Turkish propolis has been widely investigated by various research groups. The experimentations done by some authors[87][104][109][151][152][246 – 254] aimed to explore the hepatoprotective, radioprotective, chemopreventive, cytoprotective, hepatoprotective as well as antigenotoxic and genotoxic potential of Turkish propolis for medical purpose. It was shown that propolis exhibited an important preventive effect enhancing the disturbance caused by different harmful agents including liver injury, DNA damage in fibroblast cells, vascular endothelial cells damage and the adverse effects on biochemical and hematological parameters. In addition, Kolankaya et al.[252] have explored the protective effect of propolis on serum lipid and liver enzymes against alcohol induced oxidative stress in male rats and have found that propolis from Bursa, Turkey, has a protective role against degenerative diseases and against alcohol-induced oxidative stress an animal model. Agca et al.[253] affirmed that Turkish propolis from Bingöl region, could be used in the prevention and treatment of neuronal impairments, including malignant tumors and neurodegenerative disorders associated with excessive astrocytic activation, as a result of the investigation done on rat brain astrocytes. Contradictory, Eraslan et al.[254] declared that the evaluation of Turkish propolis from Erzurum led to the conclusion that the tested sample was not able to completely eliminate the free radicals and the other adverse effects generated in rats treated with sodium fluoride. In the same field, Ertürküner, et al. [255] explored the effects of Turkish propolis on endotoxin-induced uveitis on male wistar albino rats and have revealed that propolis can act as anti-inflammatory agent and could be used for the treatment of ophthalmic diseases. Besides, propolis from Turkey showed immunomodulatory andtioxidant and anti-inflammatory activities in animal models[84][256 – 258] Also, it was significantly effective in healing of burned skin wounds in rat as a cream as compared to silver sulfadiazine.[259] Noteworthy that in stomatological field, propolis from Rize, Turkey, was found to have a favorable effect on the dentin bond strength of the tested self-etch adhesive to coronal denti when compared with other irrigation solutions.[260]

Application in food industry

Another area of the application of propolis is in the food industry for the prevention of foods from microbials and oxidative agents. Thus, several researches have been done. Luis-Villaroya et al.[261], in Spain, characterized a propolis-based dietary supplement (PDS) and screened its possible use as a natural additive in apple juice. The purpose of this study was to assess propolis in combination with mild heat for the inactivation of *E. coli* O157:H7 cells in apple juice, without impacting its hedonic acceptability. The results of those authors revealed that in the presence of propolis and mild heat, the heating time required for the inactivation of *E. coli* cells cycles decreased by more than 40 times. In apple juice, the thermal treatment required to achieve the goal inactivation level also decreased by, at least, 4 times. Furthermore, propolis was sensorially acceptable. Because of its favorable antioxidant and antimicrobial properties, and considering this successful study on its incorporation into apple juice, propolis can be an excellent candidate to be used for preserving different foods.[262]

Propolis could be used in alimentary industries as a natural preservative in dairy beverages according to the results of Thamnopoulos et al..[262] In this experiment, the authors added Greek propolis extract solubilized in glycerol to extended shelf-life milk, artificially contaminated with *Listeria monocytogenes*, and explored its anti-listerial effect during

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improper storage. The use of propolis with glycerol was effective reducing the growth of the pathogen in milk stored under improper refrigeration.[262]

Turkish propolis have been tested for its capacity to preserve the quality of star ruby grapefruit, sweet cherry and fresh shibuta (*Barbus grypus*) during the storage, regarding chemical, microbiological, storage life and sensory quality.[263 – 265] It was found that treatment of star ruby grapefruit and fresh shibuta with propolis before storage protected the sensory quality, fungal decay and microbiological growth, which resulted in a prolongation of the product's shelf-life.[264][265] In the opposite, Çandir et al.[263] declared that propolis adversely affected sensory quality and stem color of cherries, even if it was effective in preventing fungal decay. Furthermore, Silici et al.[191] and Koç et al.[94] examined the antifungal activity of Turkish propolis in fruit juices against mould and yeast isolated from spoiled fruit juices and affirmed that it was a good antimicrobial agent. Also, propolis appears to be useful as a natural preservative for the foods prone to microbial spoilage instead of chemical preservatives according to Sagdic et al.[266] and Silici and Karaman.[92] Torlak and Sert.[267] screened the antibacterial effectiveness of chitosan–propolis coated polypropylene films against foodborne pathogens and declared that propolis is a promising antimicrobial agent for the food packaging applications. On the other hand, the authors[100][268][269] have established also the effect of propolis on interior egg quality, weight loss, hatchability, chick performance and its antimicrobial activity on egg-shells. The eggs sprayed with propolis presented lower weight lost, a reduced bacterial activity and an improvement on interior egg quality during storage.[100][269] From those results the authors underlined the benefit of Turkish propolis on the prevention of foods during storage.

Improvement of livestock

In the fish farming field, Italian propolis was tested for its possible advantageous effect on fish eggs mortality caused by mycosis, also its effect on characteristics of fish muscle fibres was evaluated[270]. Fish fed propolis has shown a reduction of mortality of fish eggs and more rapid muscular growth, which can be of high importance to develop the field of fish farming.

Propolis application was included also in poultry farming. Seven et al.[101][271] have published research exploring the effect of propolis-supplementation (originating from Elazig and Kayseri Province, (Turkey) on basal diet of laying hens, exposed to heat stress induced oxidative damage, on several parameter including feed intake, body weight, body weight gain, feed conversion rate, nutrient digestibility, lying performance, egg production and qualities, biochemical indicators and antioxidant enzyme activities.[101][271][272] They concluded that supplementation of propolis attenuated heat stress-induced oxidative damage. In addition, it was been demonstrated that propolis could be added to laying hens diet as alternative to antibiotic for the treatment of adverse effects of heat stress.[101][102] The same experimentation was done on Japanese quail with dietary addition of propolis. Denli et al. [273] and Seven et al. [274] have shown that propolis supplementation improved feed conversion ratio, weight gain, feed efficiency, carcass weight, serum Ca level and antioxidant status. From above, propolis could be used as a natural substitute for antibiotics in poultry diets. Not only in poultry, but also in pigs and cattle farming, propolis was introduced. Yildirim et al. [32] and Çam et al. [275] explored the effect of propolis on dermatophytosis tuberculosis infection on cattle or pigs. In the dermatophytosis case, propolis effect was better than the use of Whitfield's ointment alone, because the application of propolis together with Whitfield's ointment was highly effective, while propolis showed a limited effect on the development of tuberculosis infection in pigs. On the same insight, Fuat Gulhan et al.[276] studied the influence of propolis on microbiologic, biochemical parameters, growth performance and antioxidant status in blood Rainbow trout exposed to cypermethrin 'pesticide', and it leads to a positively changes on the fillet quality and some biochemical and microbiologic functions of fishes. Also, propolis decreased the negative effects of oxidative stress induced by Long-term low flow on fish trout.[277]

Levantine Coast

Application in medicine, pharmacy and bio-allied science

Regarding the Levantine coast there is scarce investigations regarding the propolis application, which can be due to the few countries number representing this area. In Lebanon, Noureddine et al. [110] studied the anti-proliferative and proapoptotic activity of Lebanese propolis and have found similar activity to those aforementioned regarding its cytotoxicity and anti-proliferative effect.

Application in food industries field

In Cyprus some authors have tested the use of propolis from Cyprus on the post-harvest quality of pomegranate with/without modified atmosphere packaging (MAP) and have found that propolis, not only, significantly influence the maintenance of fruit, weight, juice content and visual quality and marketability, but also controlled gray mold development and slowed the occurrence of chilling injury.[278]

Northern African Coast

Application in medicine, pharmacy and bio-allied science

Propolis in Egypt was subjected to different *in vivo* investigations, such as antitumor, antibacterial and antiparasitic activities. Many authors have investigated the antitumoral capacity of Egyptian propolis against different human cancer cells. El-Khawaga, el al.[279] and Badr et al.[280] have investigated the effect of propolis from Egypt against tumor in mice induced by Ehrlich ascitis carcinoma (EAC) cell lines and have revealed that, not only, it acts as an antiproliferative and immunostimulatory agent, but also, it induces apoptosis processes. Other authors explored the possible protective effect of propolis against side effects of some anticancer drugs such as doxorubicin and cisplatin, which leads to a nephrotoxicity, reproductive toxicity, hepatotoxicity and genotoxicity.[281][282] In those authors finding, propolis defeat the toxic effect induced by doxorubicin and cisplatin including alleviating testicular functions, improving the histological manifestation of hepatic, renal and testicular disorder. Propolis protected animals from anticancer drug side effects without affecting its antitumor capacity.[281][282]

The results found by several research teams [279 – 283] supported the data cited above for other propolis originated from the countries of the Mediterranean Sea, which were characterized by their high antitumor capacity. Beyond that, Elbaz et al. [283] have constructed a new formulated propolis-loaded nano-in-microparticles (NIMs) for enhancing its anticancer property and oral delivery against human liver cancer (HepG2) and human colorectal cancer (HCT 116) cells. This research highlighted that propolis-loaded NIMs induced more cytotoxic effect on HepG2 cells than HCT-116 cells, present three-fold higher therapeutic efficiency than free propolis and leads to the apoptosis of HepG2 cells, moreover, it increases propolis solubility with a controlling release profile in different gastrointestinal tract environments. On the same insight, and more recently, Elhakim et al. [284] using a propolis sample from El Aliubiya region, constructed a sensitive electrochemical sensor containing silver nanoparticles/propolis for microRNAlet-7a detection and have been successfully tested on human serum samples, hepatocellular carcinoma patients and human liver cancer cells. This created biosensor could be used to large-scale miRNAs detection[284] which may be involved in therapeutic application.[284]

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On the other hand, propolis from Egypt, revealed a noteworthy capacity for the impairment of the anti-inflammatory score and displayed a noticeable curative effect against biological disorder appeared in mouse conalbumin-induced asthma model.[285] In addition, propolis from Egypt exhibited an antiparasitic capacity in animal model against tow human pathogenic parasite 'schistosomiasis and cryptosporidium'. Such was evidenced through the reduction of hepatic granuloma number and their lymphocytic infiltration and aggregation accompanied by restoring the synthesis of plasma proteins and alleviating the state of oxidative stress resulted from chistosomiasis infection. The same study evidenced the reduction of oocysts shedding and modulation of the leukogram, serum proteins and histopathological changes in ileum associated with *Cryptosporidium* infection.[286][287] It is noteworthy that propolis used along with Praziquantel (PZQ: drug used to treat several types of parasitic worm infections) as an adjunct, potentiate its activity in mice models.[286]

Regarding stomatological field, the use of Egyptian propolis contributed on the maintaining of the cleanliness of dental fixtures and/or treating recurrent candidiasis as a complementary and alternative treatment, especially in elders and immuno-compromised patients, it was the conclusion of Gomaa et al.[288] which investigated the possible use of propolis in the dentistry field for blocking oral *Candida* cells adhesion and, therefore, preventing their colonization.

Other use of propolis is its incorporation as 'natural product' in textile materials for the production of cotton textile with antibacterial activity for biomedical applications.[289] It was found that utilization of propolis generated a cotton textile with superior antibacterial activity, water repellent, ease of care characteristics and UV protection.

As far as we found, in Tunisia, there was only one report that states the possible application of propolis from Mahares, a south suburb of Sfax, on the nephrotoxicity damage and the change of biochemical parameter resulted from exposition to cobalt on animal model.[290] Like reported previously in this review for other propolis samples from Mediterranean countries, Tunisian propolis has the ability to control the cobalt-induced nephrotoxicity in experimental rats and their progeny. Garoui et al. [290] have related this capacity for quenching free radicals, which increased the antioxidant status and metal-chelating abilities of propolis, mainly those rich in flavones and esters compounds.

In Algeria, propolis was tested for its protective effect against peroxidative damage in heart mitochondria and oxidative stress in kidney induced by administration of doxorubicin in rats model, and revealed a high capacity to decrease peroxidative damage in the heart mitochondria, to restore the renal functions and to reduce the whole toxic effect of doxorubicin.[291][292] As a conclusion, Alyane et al.[291] and Boutabet et al.[292] declared that antioxidants from natural sources, such as propolis, may be useful in the protection of cardio/nephrotoxicity in patients who receive doxorubicin, especially during an anticancer treatment.

Other authors have found similar results as [255] for propolis from Algeria, which showed immunomodulatory and anti-inflammatory effect in animals with uveitis induced by α-tropomyosin.[293]

Mouse et al.[120] did a screening of the antitumor potential of Moroccan propolis extracts, from Beni Mellal region, in P815 tumor-bearing mice and have found that the treatment with propolis have the capacity to reduce the tumor volume as compared with the control.[120] Mountassir et al.[294] have investigated samples from the same region regarding its possible antinociceptive activity and have conclude that propolis activated both central and peripheral mechanisms to elicit the analgesic effect in tested animals.[294] Hydro-alcoholic extracts of propolis from Salé region in Morocco, have been investigated for its protective effect in proteinuria, crystaluria, nephrotoxicity and hepatotoxicity induced by ethylene glycol ingestion.[295] The authors have also evaluated the protective effect of hydro-ethanolic extract of propolis against paracetamol-induced liver and kidney damage in rats models.[296] The results of this application joined the previous results cited in this review, for the potential protective effect of propolis on hepatotoxicity and nephrotoxicity, moreover, its showed that propolis from Morocco has potential to treat and prevent urinary calculus, crystaluria and proteinuria.

El-Guendouz et al.[297] has also explored the diuretic effect of propolis on wistar rats clinically healthy and supported the results of El Menyiy et al.[295] affirming that propolis may be used in acute or chronic kidney pathological entities where oxidative process plays a major role in the pathogenesis. In addition, El-Guendouz et al.[22] has synthetized magnetite nanoparticles using propolis and exanimated its effect on inhibition of adherence of methicillin resistant strains of *S. aureus* using a catheter for medical application. This research underlined the capacity of propolis on inhibiting the adherence of *S. aureus* strains on the medical device, and it was concluded that the association of natural products with nanotechnology may constitute an alternative to combat the formation of biofilm in medical devices. Other application of Moroccan propolis was in cosmetic/pharmaceutical field. More recently, the same group of research has demonstrated that propolis can replace butylhydroxyanisole (synthetic antioxidant) on formulation of emulsion oil in water (O/W), for its high antioxidant activity.[122]

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Application in food industries

Successful experiments have been performed by[298] regarding the use of propolis originating from Cairo (Egypt) on the shelf-life and different quality criteria of fresh oriental sausage. Those authors have concluded that propolis offered a longer shelf-life, decreased the thiobarbituric acid value and total volatile base nitrogen.

Improvement of livestock and veterinary

In poultry models, propolis from Giza province (Egypt) was tested for its beneficial effects on controlling the oxidative stress induced by paraquat injection to turkey poults. Abass et al. [299] stated that propolis could improve turkey immunity and performance, particularly under inflammation and oxidative stress, since it modeled the biochemical and immunological disorders led by paraquat.

Besides, in veterinary medicine, for its antibacterial effect against *Pasteurella multocida* (*P. multocida*), causing pasteurellosis, a most important health problem in rabbit, propolis was tested. Nassar et al. [301][302] evaluated the capacity of propolis alone or along with inactivated *P. multocida* vaccine on rabbits challenged with a virulent strain of *P. multocida*. They have found that the use of propolis improved general health condition, liver and kidney functions in addition to reduction of the severity of adverse clinical signs, mortality rates, and histopathological disorder. [300][301]

In Egypt, propolis was used in other areas, such as in aquaculture for improving the growth performance and productivity of fish. In this context, on Nile tilapia fish, Abd-El-Rhman[302] evaluated the efficacity of propolis on the growth performance and the immunostimulant and resistance to *Aeromonas hydrophila*, while Kandiel et al.[303] explored the effectiveness of the supplementation of propolis in the dietary feed to crush the genotoxic and endocrine disturbing effects caused by malathion polluted water. In short, propolis acted positively on the growth, immunity and resistance of tested fish against *A. hydrophila*. Moreover, it minimized the health hazardous of malathion, such as genotoxicity and endocrine disruption, besides its high nutritional value.

Propolis allergy

The use of propolis in the Mediterranean countries has been studied for further application in food industry, medicine, cosmetics, stomatology as well as fish and poultery farming, being

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regarded as not representing side-effects, and, therefore, harmless. However, allergic reactions have been described in several case reports. In Spain, Fernández et al.[304] have reported three cases in beekeepers of occupational contact sensitization to propolis, with varied features, and considered that propolis a direct and an airborne contact allergen. Allergic contact stomatitis in two cases caused by propolis administrated for therapeutic purposes, were signaled by the same group of research Fernández et al.[305] and Cabanillas et al.[306]. Fernández et al.[305] declared that the compounds 3-methyl-2-butenyl caffeate, phenylethyl caffeate, benzyl salicylate and benzyl cinnamate found in propolis composition, are main causes of this allergy. In Italy, Pasolini et al.[307] described an allergic contact cheilitis with chronicity induced by repeated contact with propolis contained in homemade honey. Likwise Giusti et al.[308] have examinated the frequency and the features of contact sensitization to topical products containing propolis in children and have concluded that propolis showed high sensitization rate at the paediatric age. On the same insight, Hay and Greig.[09 described a case report having an acute oral mucositis with ulceration as a result of using propolis-containing lozenges. Morover, it was reported that propolis is a strong sensitizer and well known in apiarists as an occupational allergic eczematous contact dermatitis [310], also declaring that propolis is contraindicated in patients with an allergic predisposition, being a potent allergic agent. Fernández et al. [305] Menniti-Ippolito et al. [310] affirmed that the allergenic action seems to be due to caffeic acids derivates. Bellegrandi et al. [311] in a case report, reported an allergic contact dermatitis (cheilitis and stomatitis) in HIV-infected patients provoked by propolis.

Conclusion

Nowadays, there is an increased awareness on the harmful effect of synthetic products, used in different field, on human health from where the renewed interest in properties of natural products including bee products. Propolis is known as a source of natural compounds with enormous biological and pharmacological potentialities and the capacity of prevention and treatment of numerous diseases. In this report, propolis originating from countries boarding on Mediterranean Sea has been reviewed regarding the chemical composition, biological properties and different field of application.

Propolis from all countries of the Mediteranean Sea is constituted by the presence of phenolic acid and their esters and flavonoids, nevertheless in some countries the presence of diterpenes were also detected [Sicily (Italy), Croatia, Malta, Creta (Greece), Turkey, Cyprus,

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Egypt, Lybia, Algeria and Morocco], which led to the introduction of a new type of propolis (Mediterranean-type propolis). However, in some of those places, the terpenes were not detected. For example, in Crete there were found works in which diterpenes were not found in contrast to other ones in which ditepenes were present in relative high amounts. Other examples include the description of propolis from some Aegean islands or from the Eastern Coast of Greece in which diterpenes could be detected or not, depending on the research team. The very few works on propolis from some Mediterranean countries may explain the absence of the Mediterranean propolis, as happened for Spain ad France. In contrast, Turkish propolis is exhaustly studied when compared to the remaining countries bordered by the Mediterranean Sea. Despiste the volatile constituents of propolis of this region are almost unexplored, it was possible to conclude that the volatile fraction was also dependent on the plant source, for example in poplar type propolis, β-eudesmol is always present, whereas α-pinene, in considerable amounts, is mainly present in propolis collected from places where conifers predominate.

Regarding the propolis application, it is clear that it was mostly in the medicine and bio-allied sciences, through many *in vitro* assays and preclinical investigation (*in vivo*) revealing important targets and general mechanisms of action of propolis from Mediterranean countries. Unfortunately, the potential of propolis to be used in the field of the food industries, animal husbandry, cosmetic etc, was less developed.

The combined efforts done by the scientific researchers on propolis from the Mediterranean countries should be boosted in order to make better its use. Appropriate methods should be developed for the standardization of Mediterranean-propolis-type which could make challenge for a serious competition to the well-known Brazilian and Chinese ones.

As aforementioned, the investigation upon propolis, the approach of propolis typification could be according to the plant source. This report represents a strong background that can be used to explore future special propolis-Mediterranean type; nevertheless, many researches remain to be carried out by scientists for its standardization and reliability. Exploiting the available high developed methods, standardized quality controls, as well as a suitable clinical experiment is of high importance in order to ensure the quality and safety, necessary for its commercialization.

Author's Contribution Statement

S.E.G. carried out the literature review and wrote the article along with B. L. and M.G.M.

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