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New developments in propolis chemical diversity studies (since 2000)

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Abstract

New information published since the year 2000 about propolis chemical constituents is reviewed. The available information on the biological action of new found components is presented. The plant sources of bee glue are noted, taking into consideration data based on reliable chemical evidence. Perspectives of propolis chemical research are discussed.

Introduction

Honey bees have been in existence for over 125 mill. years, probably for as long as flowering plants. Their evolutionary success has allowed them to

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become a perennial species that can exploit virtually all habitats in the world. This success in the animal kingdom is due largely to the chemistry and the application of the bee products. One of these remarkable products is propolis (bee glue). Honey bees use it not only as a building and gluing material in their nests, but also as chemical defense against infections.

Bees collect propolis from plants. For "manufacturing" of propolis they use materials produced by a variety of botanical processes, in different parts of plants. These are substances actively secreted by plants as well as substances exuded from wounds in plants: lipophilic materials on leaves and leaf buds, gums, resins, lattices, etc. [1]. It has been proven that bees apply the plant material as propolis in the hive without changing it chemically [2].

As bee glue is a plant derived product, its chemical composition depends on the specificity of the local flora at the site of collection and thus on the geographic and climatic characteristics of this location. For this reason, propolis chemical composition varies significantly in different regions. This chemical diversity of propolis is merely a reflection of the biodiversity of the ecosystems inhabited by bees.

Till now, several hundreds low molecular natural compounds have been identified in propolis from different locations [3], but the amount of publications reporting new natural compounds isolated from propolis is not diminishing. Since 2000, when the last review on propolis chemistry was published, over one hundred new propolis constituents were reported. The present review is intended to systematize and generalize the latest developments in propolis chemistry and to represent the view on the chemical diversity of propolis in the first decade of the 21st Century.

What is new in propolis chemistry?

As already mentioned, the chemical composition of propolis depends on its geographic origin and plant sources. The chemical composition, on the other hand, gives the opportunity to find out the source plant in any specific location. For this reason, the suggested source plants are represented in Table 1, along with the new propolis constituents.

New compounds in propolis from the temperate zone

In the temperate zone, incl. Europe, North America [4, 5], the non-tropical regions of Asia [6, 7], South America and even in New Zealand bud exudates of indigenous or introduced poplar species (mainly *Populus nigra*) are the main source of propolis. Samples originating from these regions are characterized by similar chemical composition, the main constituents being phenolics: flavonoid aglycones, aromatic acids and their esters [8]. This propolis type, also called “poplar type propolis”, is the most profoundly studied

Table 1. New components identified in propolis (Novel natural compounds are marked with *).

No	Compound	Geographic origin	Plant source (hypothetic)	References
	Flavonoids, isoflavonoids, neoflavonoids and related compounds			
1	7-Prenylstrobopinin*	Greece	-	[9]
2	7-Prenylpinocembrin	Greece	-	[9]
8	3-O-[(S)-2-methylbutyroylpinobanksin*	China	*Populus* spp.	[10]
9	6-cynnamylchrisin*	China	*Populus* spp.	[10]
11	1-methoxybavachromanol*	Jeju Island, Korea	-	[12]
12	Laserpitin	Jeju Island, Korea	-	[12]
13	Isolaserpitin	Jeju Island, Korea	-	[12]
14	2',3'-Dihydroxy-4,4'-dimethoxychalcone*	El Sallvador	-	[13]
15	2',3'4-Trihydroxy-4'-methoxychalcone*	El Sallvador	-	[13]
16	Propolin A*	Taiwan	-	[14, 15]
17	Propolin B*	Taiwan	-	[14, 15]
18	Propolin E*	Taiwan	-	[15]
19	Isonymphaeol B*	Taiwan, Okinawa	-	[15, 16]
20	Nymphaeol A	Taiwan, Okinawa	-	[15, 16]
21	Nymphaeol B	Taiwan, Okinawa	-	[15, 16]
22	Formononetin	Cuba	-	[17]
23	Biochanin A	Cuba	Leguninosae sp.	[17]
24	*(3S)*-Vestitol	Cuba	Leguninosae sp	[17]
25	*(3S)*-7-O-Methylvestitol (isosativan)	Cuba, Brazil	Leguninosae sp	[17, 18]
26	*(3S)*-7,4'-dihydroxy-2'-methoxyisoflavan	Cuba	Leguninosae sp	[17]
27	*(6aS, 11aS)*-Medicarpin	Cuba, Nepal	Leguninosae sp	[17, 19]
28	*(6aS, 11aS)*-Homopterocarpin	Cuba	Leguninosae sp	[17]
29	*(6aR, 11aR)*-Vesticarpin	Cuba, Nepal	Leguninosae sp	[17, 19]
30	*(6aR, 11aR)*-3,8-Dihydroxy-9-methoxypterocarpan	Cuba	Leguninosae sp	[17]
31	(*6aR, 11aR)*-3-Hydroxy-8,9-dimethoxypterocarpan	Cuba	Leguninosae sp	[17]
32	*(6aR, 11aR)*-3,4-Dihydroxy-9-methoxypterocarpan	Cuba	Leguninosae sp	[17]

Table 1. Continued

33	*(2'R,6S)*-4-Hydroxy-3-methoxy-6-(1-phenyl-2-propenyl)-cyclohexan-1-one*	Nepal	*Dalbergia* spp.	[19]
34	*(2'S,6S)*-4-Hydroxy-3-methoxy-6-(1-phenyl-2-propenyl)-cyclohexan-1-one*	Nepal	*Dalbergia* spp.	[19]
35	*(6R)*-4-Hydroxy-3-methoxy-6-(1-phenyl-2-propenyl)-cyclohexan-1-on*	Nepal	*Dalbergia* spp.	[19]
36	4-Hydroxy-2-methoxy-6-(1-phenyl-2-propenyl)-cyclohexan-1-one*	Nepal	*Dalbergia* spp.	[19]
37	2-Methoxy-5[*(1R)*-phenyl-2-propenyl]-1,4-cyclohexanediol*	Nepal	*Dalbergia* spp.	[19, 20]
38	*(4R,6S)*-4-Hydroxy-6-(1-phenyl-2-propenyl)-2-cyclohexen-1-one*	Nepal	*Dalbergia* spp.	[19]
39	*(4R,6R)*-4-Hydroxy-6-(1-phenyl-2-propenyl)-2-cyclohexen-1-one*	Nepal	*Dalbergia* spp.	[19]
40	4-Hydroxy-3-methoxy-6-(1-phenyl-2-propenyl)-2-cyclohexen-1-one*	Nepal	*Dalbergia* spp.	[19, 20]
41	1,2-Dihydroxy-4-(1-phenyl-2-propenyl)-benzene*	Nepal	*Dalbergia* spp.	[19]
42	1,2-Dihydroxy-3-(1-phenyl-2-propenyl)-benzene*	Nepal	*Dalbergia* spp.	[19]
43	3-Methoxy-4-hydroxy-4-(1-phenyl-2-propenyl)-2-cyclohexen-1-one*	Nepal	*Dalbergia* spp.	[19]
44	*(S)*-4-methoxydalbergione	Nepal	*Dalbergia* spp.	[19]
45	9-Hydroxy-6,7-dimethoxydalbergiquinol	Nepal	*Dalbergia* spp.	[19]
46	Obtusaquinol	Nepal	*Dalbergia* spp.	[19]
47	4-Hydroxymedicarpin	Nepal	*Dalbergia* spp.	[19]
48	3,6,7-trihydroxyflavanone*	Nepal	*Dalbergia* spp.	[20]
49	3',4',7-Trihydroxy-5'-methoxyisoflavon*	Nepal	*Dalbergia* spp.	[20]
50	3',6,7- Trihydroxy-4'-methoxyisoflavon*	Nepal	*Dalbergia* spp.	[20]
51	3',7-Dihydroxy-4',6-dimethoxyisoflavon*	Nepal	*Dalbergia* spp.	[20]
52	3,6-Dihydroxy-5-methoxyflavan*	Nepal	*Dalbergia* spp.	[20]
53	Plathymenin	Nepal	*Dalbergia* spp.	[20]
54	7-Methoxyflavanone	Nepal	*Dalbergia* spp.	[20]
55	7-Hydroxyflavanone	Nepal	*Dalbergia* spp.	[20]
56	*(S)*-4-methoxydalbergiquinol	Nepal	*Dalbergia* spp.	[20]
57	*(S)*-3'-Hydroxy-4-methoxydalbergione	Nepal	*Dalbergia* spp.	[21]
58	*(S)*-3'4'-Dihydroxy-4-methoxydalbergione	Nepal	*Dalbergia* spp.	[21]

Table 1. Continued

59	*(2R)*-3',4',6-trihydroxy-7-methoxyflavanone	Nepal	*Dalbergia* spp.	[21]
	Prenylated p-coumaric acids			
60	3-Prenylcinnamic acid allyl ester*	Brazil	*Baccharis dracunculifolia*	[22]
61	3,4,-Dihydroxy-5-pernylcinnamic acid*	Brazil	-	[23]
62	3(3-Hydroxy-3-methylbutyl)-5-prenyl-4-hydroxycinnamic acid*	Brazil	*Baccharis dracunculifolia*	[24]
	Polyisoprenylated benzophenones			
63	Nemorosone	Cuba	*Clusia rosea*	[25]
64	Xanthochymol	Cuba, Brazil	*Clusia rosea*	[25, 18]
65	Gutifferone E	Cuba, Brazil	*Clusia rosea*	[25, 18]
66	Propolon A*	Cuba	*Clusia* spp.	[26]
67	Propolon B*	Cuba	*Clusia* spp.	[26]
68	Propolon C*	Cuba	*Clusia* spp.	[26]
69	Propolon D*	Cuba	*Clusia* spp.	[26]
70	Garcinielliptone	Cuba	*Clusia* spp.	[26]
71	Hyperibone B	Cuba	*Clusia* spp.	[26]
72	Scrobiculatone A	Venezuela	*Clusia scrobiculata*	[27]
73	Scrobiculatone B	Venezuela	*Clusia scrobiculata*	[27]
74	18-Ethyloxy-17-hydroxy-17,18-dihydroscrobiculatone A*	Venezuela	*Clusia scrobiculata*	[27]
75	18-Ethyloxy-17hydroxy-17,18-dihydroscrobiculatone B*	Venezuela	*Clusia scrobiculata*	[27]
	Benzofuran derivatives and other aromatic compounds			
76	Propois-benzofuran A*	Brazil	-	[28]
77	Propois-benzofuran B*	Brazil	-	[28]
78	3,4-(Methylenedioxy)acetophenone	Chile	-	[29]
79	Prenyletin	Chile	-	[30]
80	*(trans)*-3,5-dihydroxy-1,7-diarylhept-1-ene	Chile	-	[30]
81	2,3-Epoxy-2-(3-methyl-2-butenyl)-1,4-naphtalenedione*	Brazil	-	[18]
82	2,2-Dimethyl-8-prenyl-6-vinylchronmene*	Brazil	-	[31]
83	2,6-Diprenyl-4-vinylphenol*	Brazil	-	[31]
	Diterpenes			

Table 1. Continued

3	Copalol	Greece	-	[9]
4	13-*epi*-Torulosal	Greece	-	[9]
5	isoagatholal	Greece	-	[9]
6	13-*epi*-Torulosol	Greece	-	[9]
7	agathodiol	Greece	-	[9]
10	labd-8(17),13E-diene-15-ol*	Sicily, Italy	-	[11]
84	*ent*-8(17)-Labden-15-O-α-L-rhamnopyranoside	El Salvador	-	[32]
85	*ent*-8(17)-Labden-15-O-(3'-O-acetyl)-α-L-rhamnopyranoside*	El Salvador	-	[32]
	Triterpenes			
86	Bauer-7-en-3β-yl acetate	Brazil	-	[33]
87	Isomangiferolic acid	Brazil	*Mangifera indica*	[34]
88	Mangiferolic acid	Brazil	*Mangifera indica*	[34]
89	Mangiferonic acid	Brazil	*Mangifera indica*	[34]
90	24-Methylene-cycloartan-3β,26-diol	Brazil	*Mangifera indica*	[34]
91	Ambolic acids	Brazil	*Mangifera indica*	[34]
92	Ambonic acid	Brazil	*Mangifera indica*	[34]
93	Procrim A [lupeol 3-(*3'R*-hydroxy)-hexadecanoate]*	Brazil	*Baccharis dracunculifolia*	[35]
94	Procrim B [lupeol 3-(*3'R*-hydroxy)-octadecanoate]*	Brazil	*Baccharis dracunculifolia*	[35]
95	20(29)-lupen-3-one	Brazil	-	[18]
96	Moronic acid	Brazil	*Myrceugenia euosma*	[36]
97	Melliferone (3-oxoolean-11-en-13β,28-olide)*	Brazil	*Myrceugenia euosma*	[36]
98	Anwuweizonic acid	Brazil	*Myrceugenia euosma*	[36]
99	Betulonic acid	Brazil	*Myrceugenia euosma*	[36]
	Compounds identifed by GC-MS			
	Dihydro chalcones			
100	2',6'-Dihydroxy-4,4'-dimethoxydihydrochalcone	Canadian	*Populus trichocarpa*	[37]
101	2',6',4'-Trihydroxy-4-methoxydihydrochalcone	Canadian	*Populus trichocarpa*	[37]

Table 1. Continued

102	4,2',6'-Trihydroxy-4'-methoxydihydrochalcone	Canadian	*Populus trichocarpa*	[37]
	Phenylpropanoids			
103	*trans*-Anethol	Brazilian	-	[18]
104	Methyl eugenol	Brazilian	-	[18]
105	*trans*-Methyl isoeugenol	Brazilian	-	[18]
106	Elemicin	Brazilian	-	[18]
107	*trans*-Isoelemicin	Brazilian	-	[18]
	Sesquiterpenes			
108	α-Amorphene	Brazilian	*Baccharis* spp.	[38]
109	Ledene	Brazilian	*Baccharis* spp.	[38]
110	Dehydrocostus lactone	Brazilian	*Baccharis* spp.	[38]
	Triterpenes			
111	D:C-friedoolean-3-one	Brazilian	*Baccharis* spp.	[38]
112	D:C-friedoolean-7-en-3β-yl acetate	Brazilian	*Baccharis* spp.	[38]
113	3-Oxoolean-18-ene (germanicone)	Brazilian	*Baccharis* spp.	[38]
114	3-Oxours-18-ene	Brazilian	*Baccharis* spp.	[38]
115	β-Fernenone	Brazilian	*Baccharis* spp.	[38]
	Other compounds			
116	γ-Palmitolactone	Brazilian	*Baccharis* spp.	[38]
117	2H-pyran-2-one-tetrahydro-6-tridecyl	Brazilian	*Baccharis* spp.	[38]
118	2H-pyran-2-one-tetrahydro-6-pentadecyl	Brazilian	*Baccharis* spp.	[38]
119	2-*t*-Butylnaphto-[2,3-b]-furan-4,9-dione	Brazilian	*Baccharis* spp.	[38]
120	1-Benzylidene-2,2,3,3-tetramethylcyclopropane	Brazilian	*Baccharis* spp.	[38]
121	Methylbutane-chromane-6-propenoic acid methyl ester	Brazilian	*Baccharis* spp.	[38]
122	3-Nonadecylphenol	Brazilian	*Baccharis* spp.	[38]
123	3-Heptadecylphenol	Brazilian	*Baccharis* spp.	[38]

one, both from chemical and pharmacological point of view. Nevertheless, the studies of propolis from temperate locations that have not been explored earlier in this respect lead to the discovery of new propolis constituents. Hereunder bold figures refer to the new propolis constituents.

In a propolis sample from Greece, along with poplar bud constituents, a new prenylated flavonoid was isolated, 7-prenylstrobopinin **1**, together with six known compounds that have never been reported as constituents of propolis: 7-prenylpinocembrin **2** and six diterpene alcohols **6** – **7** [9]. Chinese propolis, in which the major components were the typical "poplar phenolics", was also the source of two new natural products: the flavonoids 3-O-[(S)-2-methylbutyroylpinobanksin **8** and 6-cynnamylchrisin **9** [10]. In propolis from the island of Sicily, several diterpenic acids has been found together with a new diterpenic alcohol, labd-8(17),13E-diene-15-ol **10** [11]. It is interesting to note that in the last five years, diterpenes have been isolated from European propolis for the first time [9, 11].

New compounds in tropical and subtropical propolis

In the last decade propolis from tropical and subtropical regions of South America and Asia has become the subject of increasing interest. This has led to the identification of many new compounds in propolis, some of them possessing remarkable biological activity.

Flavonoids and related compounds

Investigations on tropical and subtropical bee glue revealed that in many cases flavonoids and related compounds are important components of these samples. It is interesting to note that in the last 7 years, not only flavones, flavonols, and chalcones but also a number of isoflavonoid and neoflavonoid constituents have been found in bee glue.

From samples from Jeju Island, Korea, a new chalcone was isolated, 1-methoxybavachromanol **11**, together with the known coumarine derivatives **12** and **13** [12]. Two further new chalcones were found in bee glue from El Salvador [13], **14** and **15** (See Table 1). In samples originating from Pacific Islands, Okinawa and Taiwan, two research groups have found six prenylated flavanones (**16** – **21**). Four of them were novel compounds: propolins A **16**, B **17** and E **18** and isonymphaeol B **19** but all were isolated for the first tome from propolis [14 – 16].

Isoflavonoids have been isolated from Cuban red propolis: two isoflavones (**22** and **23**), three isoflavanes (**24** – **26**) and six pterocarpanes (**27** – **32**) [17]. Two of these compounds, isosativan **25** and medicarpin **27**, have been found also in Brazilian red propolis [18].

Very recently, Nepalese propolis has been identified as a source of numerous potent biologically active substances: flavonoids, isoflavonoids, and, for the first time in propolis, open-chain neoflavonoids and related compounds. Some of them were new natural compounds and most of them new for propolis

(**33 - 59**) [19 – 21]. These relatively rare secondary metabolites have been suggested to come from the Indian rosewood *Dalbergia sisoo*.

Prenylated *p*-coumaric acid derivatives

Prenylated *p*-coumaric acids are typical for the Brazilian green propolis, also called Alecrim propolis. Recently, three new representatives of this compound class have been found in Brazilian samples: 3-prenylcinnamic acid allyl ester **60** [22], 3,4,-dihydroxy-5-pernylcinnamic acid **61** [23] and 3(3-hydroxy-3-methylbutyl)-5-prenyl-4-hydroxycinnamic acid **62** [24].

Prenylatyed benzophenone derivatives

Compounds of this type have been discovered as constituents of South American propolis in the first years of the 21st century. They are typical secondary metabolites of the plants of the family *Clusiaceae*. Prernylated benzophenoes were isolated from Cuban (nemorosone **63**, xanthochymol **64** and gutifferone E **65** [25]; propolones A – D **66 - 69**, garcinielliptone **70** and hyperibone B **71** [26], Venezuelan (scrobiculatones A and B and their derivatives **72** – **75,** [27], and red Brazilian red propolis (**64** and **65**, [18]).

Benzofuran derivatives and other aromatic compounds

Two new cytotoxic benzofuran derivatives, propolis-benzofurans A and B (**76** and **77**), were isolated from Brazilian propolis [28]. Their plant source remains unknown. In bee glue from Chilean matorral, the group of Timmernamm found 3,4-(methylenedioxy)acetophenone **78**, the coumarine prenyletin **79**, and a diarylheptane as new propolis constituents **80** [29, 30]. From red Brazilian propolis, Trusheva et al. [18] isolated a prenylated naphoquinone epoxide **81**. Prenylated vinylphenol derivatives **82** and **83** have been isolated from essential oils of Brazilian propolis [31].

DI- and triterpenes

Only two diterpenes have beed added to the list of tropical propolis constituents in the period in question but they are of interest because they are representing the first glycosides found in propolis: two labdane ramnosides (**84** and **85**), found in a sample from El Salvador [32].

Most new additions are triterpenoids. Triterpenes with friedoursan **86**, [33] and cycloratne skeletone (**87** – **92**) [34] have been isolated from different samples of Brazilian propolis. Other samples of Brazilian origin were found to contain two novel long-chain alkanoic acid esters of lupeol, procrims A **93** and B **94** [35]. The triterpenic ketone lupenone **95** was found in Brazilian red propolis [18]. Of special interest are the triterpenic acid derivatives moronic

acid **96** and related compounds (**97** – **99**) with anti-HIV activity, isolated from propolis samples from Southern Brazil [36].

Compounds identifed by gc-ms

All the above-mentioned nearly 100 new propolis constituents have been isolated and identified by means of spectral methods (NMR, IR, UV, NS). In this section, the information concerning new propolis constituents identified only by GC-MS is collected. Christov et al. [37] identified (by GC-MS of silylated total extracts) in samples from subarctic Canadian provinces the usual "poplar phenolics" together with five dihydrochalcones, three of them new for propolis: 2'6'-dihydroxy-4,4'-dimethoxydihydrochalcone **100**, 2'4'6'-trihydroxy-4-methoxy-dihydrochalcone **101** and 2',6',4- trihydroxy-4'-methoxy-dihydrochalcone **102**. Another group of compounds have been identified in unpolar propolis fractions, obtained by column or thin-layer chromatography. It is interesting to note the presence of several simple phenylpropanoids (**103** – **107**) in red Brazilian propolis [18]. In an unusual sample of Brazilian propolis from the region of Sorocaba (Sao Paulio State), a number of sesqui- (**108** – **110**) and triterpenoids (**111** – **115**) and some other compounds (**116** -**123**) were identified [38].

Biological activity of new propolis constituents

It is important to note that most of the latest investigations on new propolis constituents are connected to their biological activity. This is a fruitful trend that could give important hints about the possibilities for standardization. This information is summarized in Table. 2. In Figure 1, chemical structures of selected new propolis constituents possessing valuable biological activities are shown.

Antibacterial and cytotoxic activity was found for a significant number of the new propolis constituents. Significan increase is noticed in numbers of compounds with detected antioxidant, most often antiradical activity (See Table 2). Of special interest is the anti-HIV activity of moronic acid derivatives and other triterpenoids found in Brazilian propolis [36]. The ability of neoflavonoids from Nepalese propolis to inhibit nitric oxide production makes them potential leads in finding anti-inflammatory molecules [19].

Table 2. Biological activity of new propolis constituents.

Type of activity	**Compound**	**References**
Antibacterial	**1, 2, 10**, **14**, **15**, **72**, **73**, **84**, **85**	[9, 11, 13, 32]
Cytotoxic	**16 - 18**, **20**, **21**, **63**,**76**, **77**	[14, 15, 25, 28]
Antiradical	**16**,**17**, **19 - 21, 61**, **63**,	[14, 16, 23, 25]
Ani-HIV	**96**	[36]
Nitric oxide production inhibition	**33** – **36**, **38**, **39**, **41 - 47**	[19]

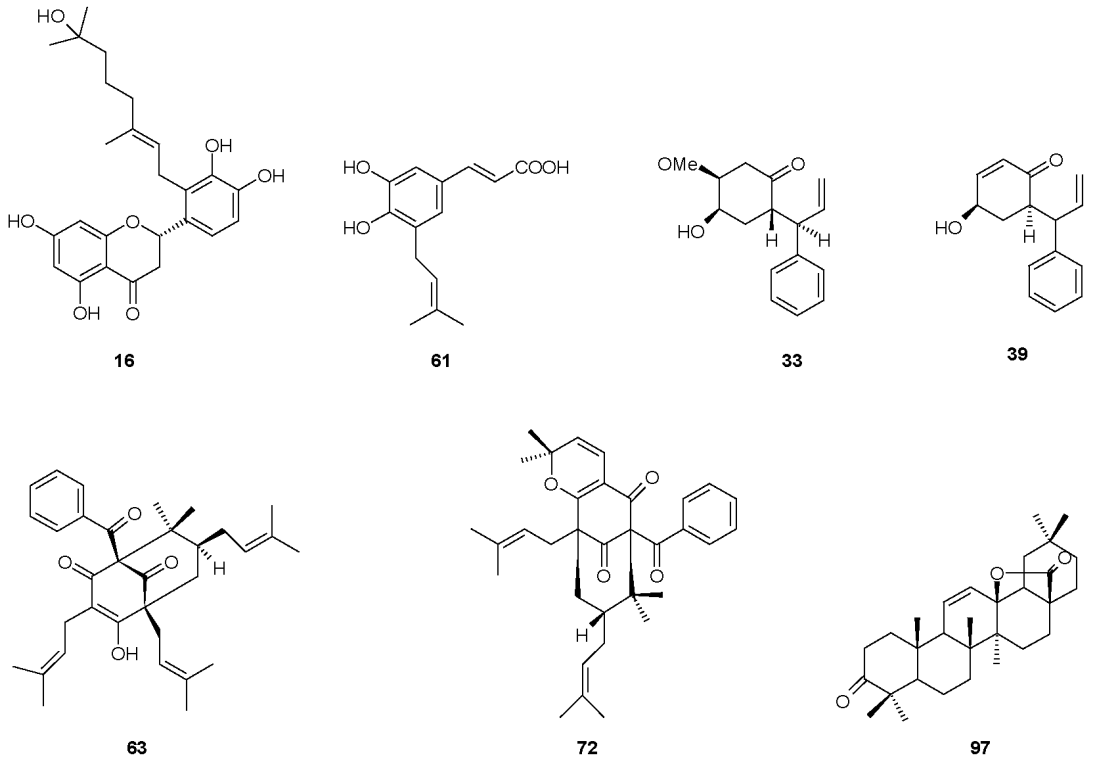


Figure 1. Chemical structures of selected new propolis constituents possessing valuable biological activities.

Concluding remarks

This survey of recent literature confirms that propolis is a natural prodct with a great potential for use in preventive medicine and in therapy. A quick glance at the wide diversity of new propolis constituents revealed in the last 7 years foretells much further research work and a distant horizon for the completion of the evaluation of the full potentiality of propolis chemistry and pharmacology. Propolis research has resulted, and, hopefully, will result in the discovery of many valuable plant substances that otherwise would hardly be found [39]. Out of 123 compounds new for propolis, found in the period 2000 – 2007, 46 or 37% are novel natural compounds. Without any doubt, bee glue remains a challenging subject for chemical and pharmacological studies in the near future.

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