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Review

Polyprenylated Benzophenones from Propolis: Botanical Origin, Structural Diversity, and Agrochemical Potential

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Abstract

Polyprenylated benzophenones (PPBs) are a structurally diverse class of polyphenolic compounds found in tropical propolis from South America and East Africa, produced by both *Apis mellifera* L. (Hymenoptera: Apidae) and stingless bees. Derived primarily from the floral and latex resins of the Clusiaceae family—predominantly the genus *Clusia*—these compounds have oxidized bicyclononane ring systems and are characterized using advanced HPLC (high-performance liquid chromatography), GC-MS (gas chromatography–mass spectrometry), and NMR (nuclear magnetic resonance) techniques. While extensively studied for their biomedical properties, PPBs represent an unexploited resource for sustainable agriculture. This review summarizes the botanical origin, structural diversity, and geographical distribution of propolis PPBs, highlighting their potential as "biorational" crop protection agents. Individual PPBs and PPB-rich extracts have demonstrated potent antimicrobial mechanisms via membrane disruption against some plant pathogens, insect growth-regulating effects against pests (e.g., clusianone), and phytotoxic properties (e.g., guttiferone-A). However, direct investigations into their agrochemical efficacy remain scarce; given these highly promising properties, research must be significantly intensified. This review emphasizes the need for targeted research into extraction optimization and structure–activity relationships of PPBs to develop the next generation of eco-friendly agrochemical formulations.

Keywords: bee glue; polyphenolic secondary metabolites; plant origin; agrochemical potential

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1. Introduction

Propolis (bee glue) is a resinous bee product produced by honey bees. Bees collect resinous plant exudates and mix them with beeswax to make propolis, which they use to seal holes in the hive and to cover the bodies of "intruders" killed in the hive and too big to be carried out by the bees, thus preventing putrefaction [1,2]. It constitutes an important component of the bees' social immunity, preventing the development of pathogenic microorganisms within the hive [3], and for this reason it has been used by humans as a remedy since ancient times [1]. The chemical composition of propolis is complex and highly variable, depending on its geographical and botanical origin. Phenolic compounds are among its most important constituents, although different propolis types contain distinct classes of phenolics, including flavonoid aglycones, phenolic acids and their esters, coumarins, xanthones, stilbenes, lignans, and benzophenones. In temperate

zones, propolis contains mainly flavonoid aglycones coming from the bud exudates of *Populus* trees, while in tropical regions the chemical composition of bee glue is much more diverse due to the biodiversity in the tropics: different phenolics, prenylated *p*-coumaric acids, flavonoids and benzophenones, and terpenes are present in different samples [4]. Benzophenones were first identified in propolis in 1993 by Tomas-Barberan et al. [5].

Benzophenones occurring in propolis belong predominantly to the group of polyprenylated benzophenones (PPBs). These compounds have attracted considerable attention because of their remarkable structural diversity and broad spectrum of biological activities. Numerous studies have demonstrated antifungal, antimicrobial, antiviral, anti-inflammatory, antioxidant, cytotoxic, anticancer, and anti-HIV properties of natural PPBs [6–8]. Such a diversity of biological effects suggests that these compounds may be promising not only for pharmaceutical applications but also for the development of environmentally friendly agrochemicals. In recent years, the search for bio-based crop protection agents has intensified because of the increasing demand for sustainable agricultural practices and the emergence of resistance to conventional pesticides. Natural products have historically provided important leads for agrochemical development, particularly compounds exhibiting antifungal, antibacterial, insecticidal, and phytopathogen-suppressing activities. Interestingly, several polyprenylated benzophenones isolated from species of the genera *Clusia* and *Garcinia*, some of which are identical to compounds found in propolis, have been reported to possess biological activities relevant to crop protection, e.g., insecticidal [9], phytotoxic [10], potent antibacterial and antifungal [7]. These findings provide experimental support for the hypothesis that polyprenylated benzophenones may represent a valuable source of agrochemical applications. Therefore, the present review summarizes the current knowledge on polyprenylated benzophenones occurring in propolis, including their structural diversity, geographical distribution, botanical origin, and biological activities, with particular emphasis on their prospects as lead compounds for the development of sustainable crop protection agents.

2. Polyprenylated Benzophenones Found in Propolis: Structure and Geographical Origin

Natural benzophenones display great structural diversity but share a common skeleton: phenol-carbonyl-phenol (more precisely, 2,4,6-trihydroxybenzophenone). Propolis polyprenylated benzophenones contain an oxidized bicyclononane ring system, mostly the bicyclo[3.3.1]nonane-2,4,9-trione system. The A-ring, derived from the shikimic acid pathway, is a benzene ring containing no, one, or two substituents. The B-ring is derived from the acetate–malonate pathway and frequently undergoes prenylation and cyclization/s leading to the formation of bicyclononane ring system. Polyprenylated benzophenones from propolis belong to type A and type B basic benzophenone skeletons [7] (Figure 1). Rearrangement of geranyl and phenyl groups may generate novel and unusual ring systems, resulting in additional prenyl-derived rings in some compounds [7].

Propolis, containing benzophenones, was only found in tropical regions, predominantly in South America. From Brazilian propolis of different regions, hyperibone A (**1**) has been isolated [11] (Figure 2). UPLCMSPDA (ultra-performance liquid chromatography–mass spectrometry–photodiode array detection) analysis revealed the presence of three benzophenones in Brazilian red propolis from Minas Gerais State [12]: guttiferone E (**2**), xanthochymol (**3**), and oblongifolin A (**4**). Compounds **2** and **3** were isolated, whereas guttiferones were detected by LC-MS (liquid chromatography–mass spectrometry) in Brazilian propolis samples collected in the states of Alagoas and Paraiba [13–15]. Oblongifolin B (**5**) and guttiferone E (**2**) were isolated from propolis originating from the state of Bahia [16]. In a propolis sample from the state of Amazonas, compound **3**, together

with gambogenone (**6**), 7-*epi*-nemorosone (**7**), and 7-*epi*-clusianone (**8**) were isolated. In addition, other benzophenone derivatives including methyl insigninone (**9**), aristophenone A (**10**), 18-ethyloxy-17-hydroxy-17,18-dihydroscrobiculatone B (**11**), derivatives of dimethyl weddellianone A and B, propolones, and a scrobiculatone derivative were tentatively characterized by HPLC/DAD/ESI–MS/MS (high-performance liquid chromatography–diode array detection–electrospray ionization tandem mass spectrometry) [17].

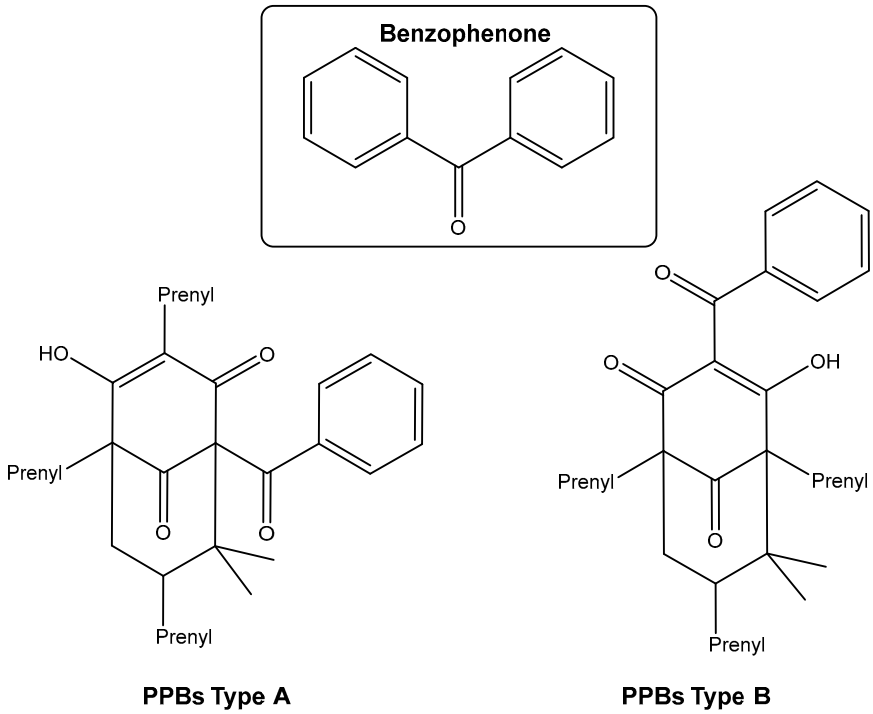
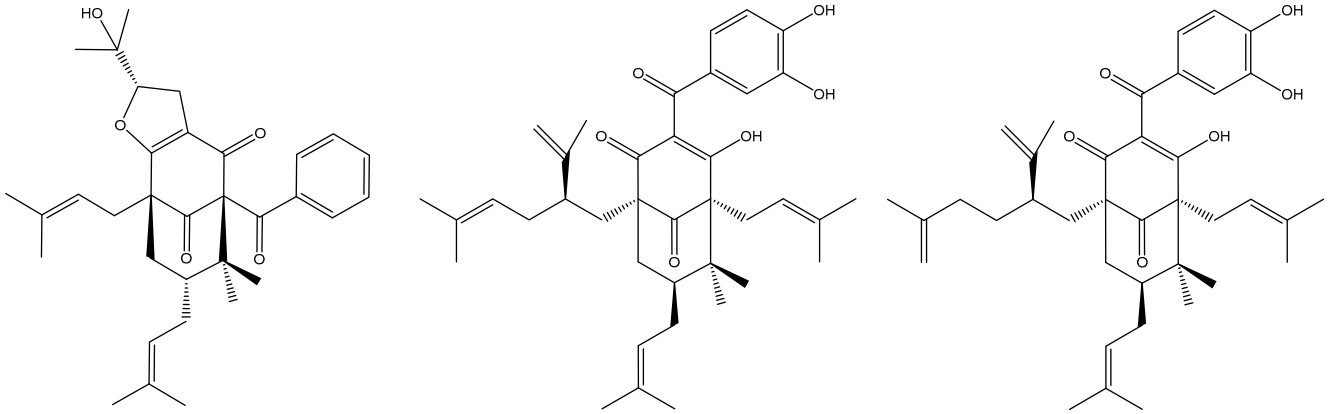
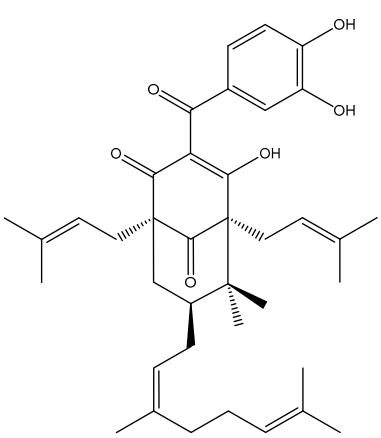


Figure 1. Basic skeletons of propolis polyprenylated benzophenones (PPBs).

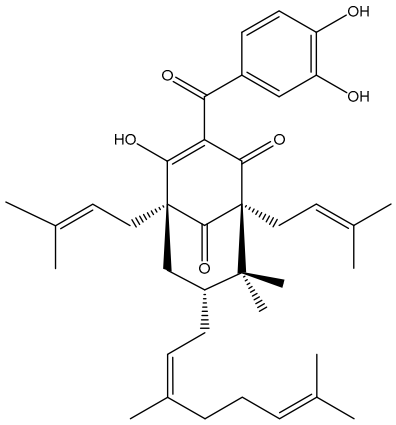


Hyperibone A (**1**) Guttiferone E (**2**) Xanthochymol (**3**)

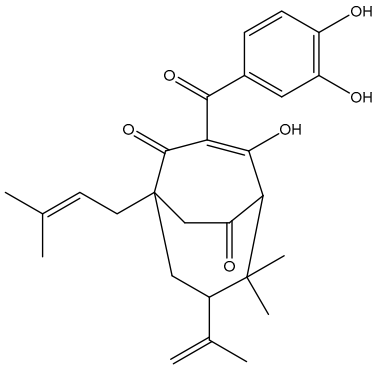
Figure 2. *Cont*.



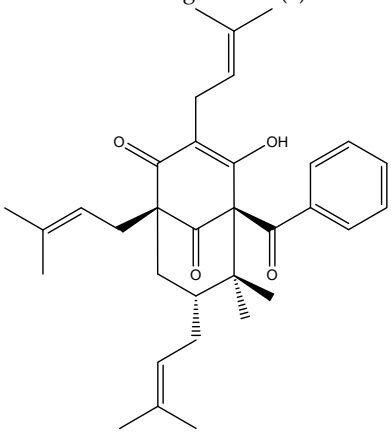
Oblongifolin A (**4**)



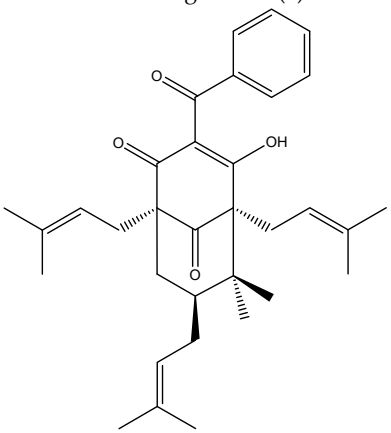
Oblongifolin B (**5**)



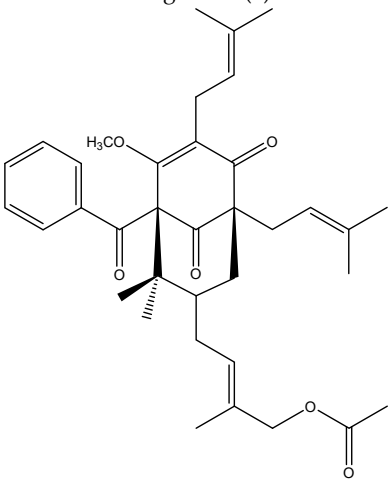
Gambogenone (**6**)



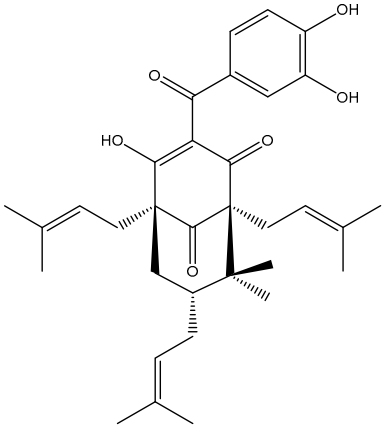
7-*epi*-Nemorosone (**7**)



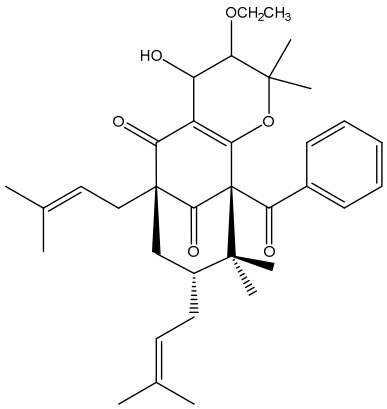
7-*epi*-Clusianone (**8**)



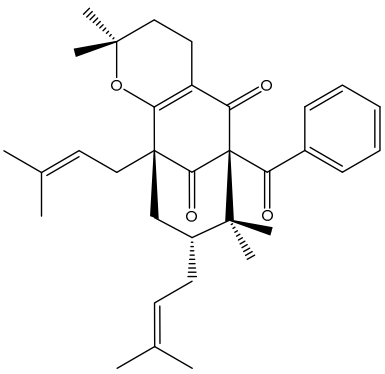
Insigninone (**9**)



Aristophenone A (**10**)

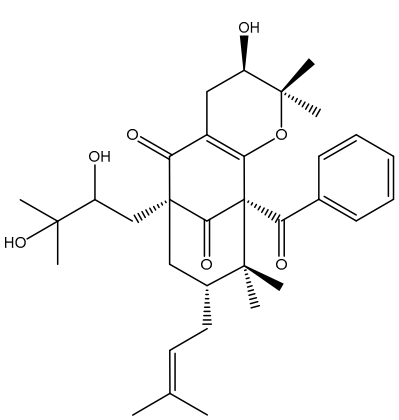


18-Ethyloxy-17-hydroxy-17,18-dihydroscrobiculatone B (**11**)

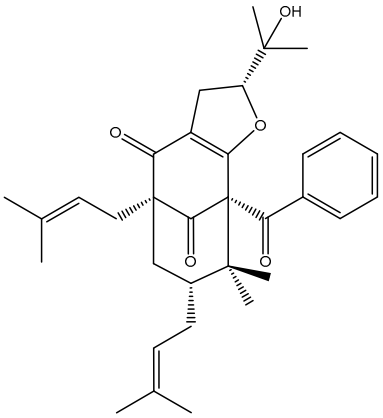


Propolone A (**12**)

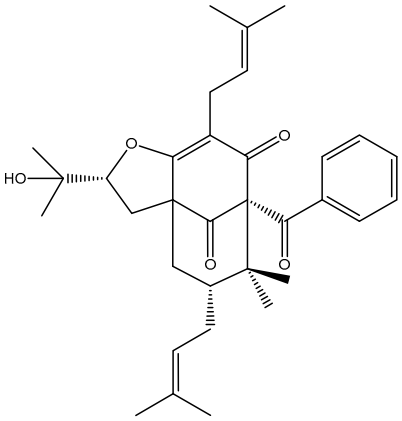
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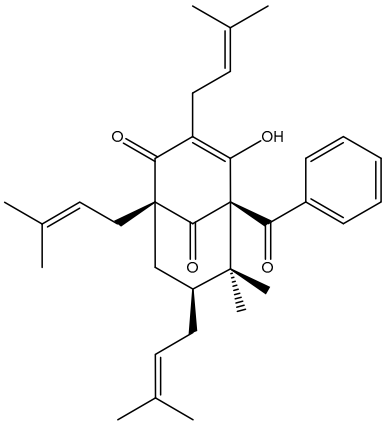
Propolone B (**13**)



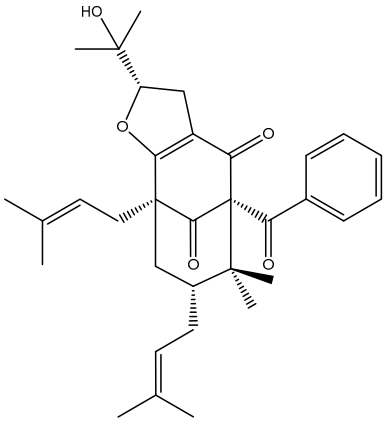
Propolone C (**14**)



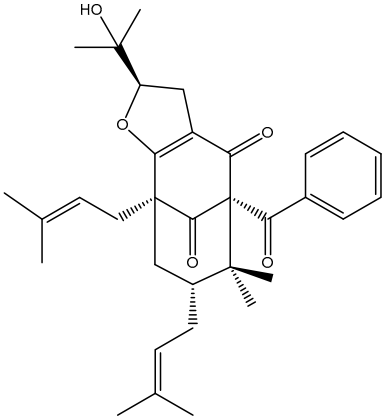
Propolone D (**15**)



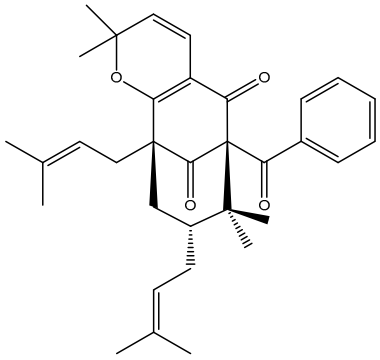
Nemorosone (**16**)



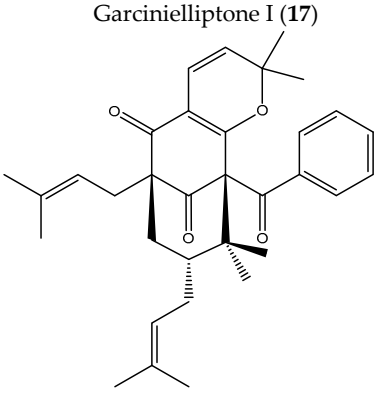
Garcinielliptone I (**17**)



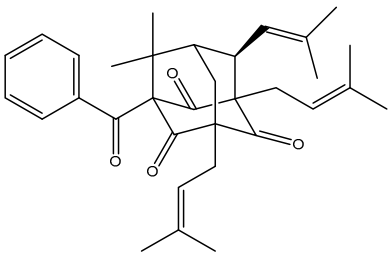
Hyperibone B (**18**)



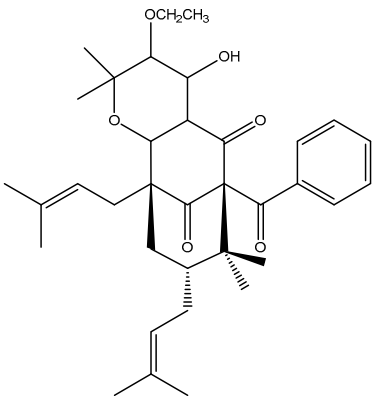
Scrobiculatones A (**19**)



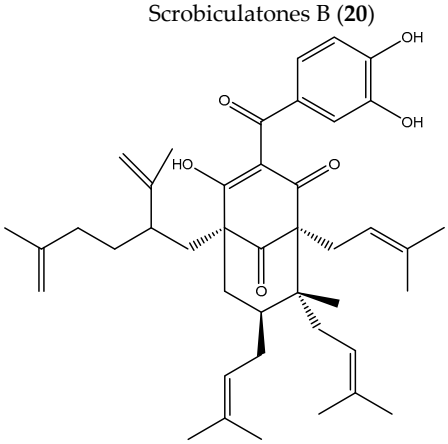
Scrobiculatones B (**20**)



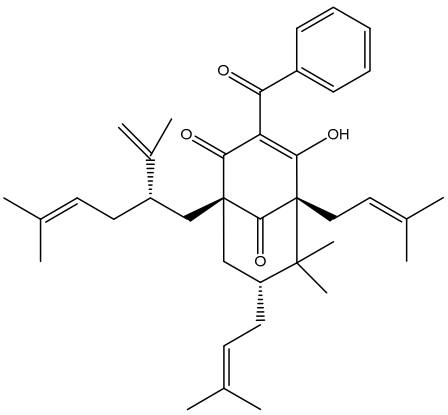
Plukenetion A (**21**)



18-Ethyloxy-17-hydroxy-17,18-dihydroscrobiculatone A (**22**)



Guttiferone C (**23**)



Garcimultiflorone K (**24**)

Figure 2. Structures of polyprenylated benzophenones found in propolis.

Cuban propolis has also been shown to contain and yield numerous prenylated benzophenones, including guttiferone E (**2**), xanthochymol (**3**), propolones A–D (**12–15**), nemorosone (**16**), garcinielliptone I (**17**) and hyperibone B (**18**) [18–20]. Scrobiculatones A and B (**19** and **20**) were detected in propolis extracts by NMR, HPLC-PDA (high-performance liquid chromatography–diode array detection) and HPLC-ESI/MS (high-performance liquid chromatography–electrospray ionization mass spectrometry), and subsequently confirmed following isolation [21]. Plukenetion A (**21**) was also detected in propolis from Cuba as well as in propolis from Florida [22].

Nemorosone (**16**) has been reported in propolis from Colombia [23], Ecuador [24] and Costa Rica [25,26].

From Venezuelan propolis, scrobiculatones A and B (**19** and **20**), isolated as an inseparable equilibrium mixture, were characterized together with 18-ethyloxy-17-hydroxy-17,18-dihydroscrobiculatone A (**22**) and 18-ethyloxy-17-hydroxy-17,18-dihydroscrobiculatone B (**11**) [27]. The latter ethyloxy derivatives may be regarded as extraction artefacts formed during ethanol extraction [27].

It is important to note that PPBs have been detected not only in *Apis mellifera* bee glue but also in stingless bee propolis and geopropolis. In the study of Venezuelan propolis, Tomas-Barberan et al. [5] found prenylated benzophenones in stingless bee propolis of *Friesomelitta varia*, *Melipona favosa*, *Melipona compressipes*, *Scaptotrigona depilis*, and *Paratrigona anduzei*. The presence of prenylated benzophenones was also reported in geopropolis of Brazilian *Melipona scutellaris* from Bahia, based on GC-MS analysis [28]. Using LC-MS/MS (liquid chromatography–tandem mass spectrometry), compounds **3**, **6**, **7**, **10** and guttiferone C (**23**) were detected in propolis of the stingless bee *Frieseomelitta longipe*, as well as in a number of geopropolis samples of *Melipona seminigra* collected from different locations in the state of Amazonas [29] and of *Melipona subnitida* from different locations in the Rio Grande do Norte [29,30]. More recently, untargeted LC-ESI-MS/MS (liquid chromatography–electrospray ionization–tandem mass spectrometry) combined with molecular networking revealed a diverse array of prenylated benzophenones in propolis from the Amazonian stingless bee *Duckeola ghilianii*. One of them, garcimultiflorone K (**24**), was isolated and its structure confirmed by NMR spectra [31].

The only report describing prenylated benzophenones in propolis outside South America concerns the tentative identification of nemorosone (**16**) and a geranyl benzophenone in propolis from Malawi, East Africa, by HPLC–DAD–HRMS^n (high-performance liquid chromatography–diode-array detection–high-resolution multi-stage mass spectrometry) [32].

3. Botanical Origin of Propolis Benzophenones

The bees collect plant resins for propolis production, so the polyprenylated benzophenones obviously are constituents of some resinous material of botanical origin.

The Clusiaceae family (formerly Guttiferae) is well known to produce various polyprenylated benzophenones. In Tropical South America, the genera *Clusia, Garcinia*, and *Symphonia*, in the Clusiaceae family, are widespread, particularly in the Amazon and Brazilian ecosystems, with *Clusia* being the most common [33]. *Clusia* species are known to produce resin: these plants have channel systems that cross plant tissues producing resinous latex [34]. In addition, many species of *Clusia* exude floral resins, serving as pollinator reward: the bees collect this material to make propolis and during this process perform pollination [35]. For this reason, *Clusia* species are the major source of polyprenylated benzophenones in propolis.

Comparison of the constituents of propolis and plant resins can indicate the plant origin of propolis. In this way, the specific plant species providing resin for a particular

propolis sample have been identified, as demonstrated in Table 1. This table includes only those compounds for which there is specific data regarding their plant origin.

Table 1. Source plants of benzophenones found in propolis [a].

Compound	Source Plant	Geographic Origin	References
Guttiferone E (**2**) [b]	*Clusia rosea*	Cuba	[19]
	Clusia spp.	Brazil (Alagoas)	[13]
	Garcinia spp.	Brazil (Amazonas)	[17]
	Symphonia globulifera	Brazil (Bahia)	[16]
Xanthochymol (**3**)	*Clusia rosea*	Cuba	[19]
	Clusia spp.	Brazil (Alagoas)	[13]
	Clusia spp.	Brazil (Amazonas)	[17]
Oblongifolin A (**4**)	Guttiferae	Brazil (Minas Gerais)	[12]
	Guttiferae	Brazil (Sergipe, Alagoas, Paraíba, Roraima)	[15]
Oblongifolin B (**5**)	Guttiferae	Brazil (Minas Gerais)	[12]
7-*epi*-Nemorosone (**7**)	*Clusia* spp.	Brazil (Amazonas)	[17]
7-*epi*-Clusianone (**8**)	*Clusia* spp.	Brazil (Amazonas)	[17]
Methyl insigninone (**9**)	*Clusia insignis*	Brazil (Amazonas)	[17]
Propolone A (**12**)	*Clusia* spp.	Cuba	[18]
Nemorosone (**16**)	*Clusia rosea*	Cuba	[19]
	Clusia rosea	Ecuador	[26]
	Clusia spp.	Costa Rica	[25]
	Clusia valerioi	Costa Rica	[25]
Scrobiculatones A and B (**19** and **20**)	*Clusia scrobiculata*	Venezuela	[27]
Plukenetione A (**21**)	*Clusia plukenetii*	Cuba and Florida	[22]
Guttiferone C (**23**)	*Vismia* spp.	Brazil (Amazonas)	[36]
Prenylated benzophenones	*Clusia rosea, Clusia minor*	Venezuela	[5]

[a] In this Table, only compounds with known botanical origin are included. [b] The numbers correspond to the numbers in Figure 2.

Obviously, the source of prenylated benzophenones in propolis are mainly *Clusia* species. *Symphonia globulifera* is also detected among the sources of these compounds in bee glue but is more seldom used by bees (Table 1), probably due to the specificity of the flora near the hives.

In the regions where they grow, Clusiaceae plants are the preferred source of resin for bees, but often the bees utilize resinous materials from several plants and benzophenones are mixed with other secondary metabolites, such as isoflavonoids in red Brazilian propolis [13], triterpenes [13,17,23], and fatty acids [37]. *Clusia* type propolis can be found in Cuba: the brown Cuban propolis [21]. It is important to note that in Brazil, the red propolis contains polyprenylated benzophenones, together with *Dalbergia* metabolites, while in Cuban red propolis, no benzophenones have been detected [38].

4. Analysis of Prenylated Benzophenones in Propolis

Polyprenylated benzophenones possess diverse and valuable biological activities and contribute significantly to the pharmacological potential of the respective propolis. For this reason, it is important to detect their presence and to perform quantification of these compounds in propolis samples.

Hyphenated chromatographic techniques are most widely used for analysis of phenolics, including polyprenylated benzophenones in bee glue.

HPLC is the most often applied method for phenolics, including polyprenylated benzophenones in propolis. The HPLC–UV/HPLC–DAD analytical method was established

and validated to quantify total benzophenones (as garcinol) at 260 nm in Brazilian red propolis [12]. Pires et al. [39] described the development and validation of an RP-HPLC-UV (reversed-phase high-performance liquid chromatography with ultraviolet detection) method to characterize benzophenone-rich red Brazilian propolis, using a mixture of guttiferone E and xanthochymol, and isolated oblongifolin B as chemical standards.

GC-MS is less common for benzophenones (due to low volatility) but can be used after derivatization (silylation) [23,28,40].

For structure elucidation of isolated polyprenylated benzophenones, mass spectrometry, and particularly MS^n, has been successfully applied [41]. NMR spectroscopy is the most powerful method for structure elucidation of natural products, and it has been successfully used for polyprenylated benzophenones as well [18,20,27].

Further development of analytical procedures, especially with respect to standardization of this propolis type, will be very useful.

5. Biological Activity of Propolis Benzophenones Relevant to Their Agrochemical Potential

Propolis of different chemical types has demonstrated multifaceted benefits for pest control, crop cultivation and overall agricultural sustainability [42]. Thus, benzophenones containing propolis are also of interest in this respect.

It is known that polyprenylated benzophenones are biosynthesized as defensive compounds in plants and thus possess a broad range of valuable bioactivities: antibacterial, antifungal, antiviral, antioxidant, antiparasitic, cytotoxic and effects on cancer cells [10].

It is not surprising that propolis in general has antimicrobial properties, taking into consideration that it is a part of bees' social immunity and a chemical weapon against pathogens. Benzophenone-containing propolis extracts have demonstrated activity against numerous bacteria and fungi, such as *Staphylococcus aureus*, *Enterococcus faecalis*, *Actinomyces naeslundii* and *Pseudomonas aeruginosa* [43]. Individual polyprenylated benzophenones, isolated from Clusiaceae plants, many of which have been found in propolis, possess potential against numerous bacteria and fungi, mostly human pathogens [6]. Among them, *Pseudomonas aeruginosa* and some fungi are of interest for agrochemical problems. It is known that *P. ageruginosa* can cause rot in various plants under some conditions [44], and fungi are among the most important plant pathogens [45]. Therefore, future studies on the potential of propolis polyprenylated benzophenones as natural phytoprotective compounds with antimicrobial properties are promising and should be performed.

The mechanism of antimicrobial action of prenylated benzophenones is based on membrane disruption. Their lipophilic prenyl side chains facilitate insertion into microbial lipid bilayers, while phenolic functionalities enable interactions with polar head groups, resulting in increased membrane permeability [46].

There are further limited but promising communications about the agrochemical potential of polyprenylated benzophenones. Recently, guttiferone A isolated from *Garcinia gardeniana* demonstrated phytotoxic activity against *Sorghum bicolor*; it was more active than glyphosate, even in lower concentrations [10]. Guttiferone A has not been found in propolis, but there are several other guttiferones in propolis, and they could be the starting point for the development of new environmentally friendly phytotoxic agrochemicals.

There is as well some evidence that polyprenylated benzophenones from *Clusia* species, found also in propolis, possess insecticidal and insect development-disrupting properties against the hemipterans. Clusianone acts as a natural insect growth regulator by interfering with molting and endocrine signaling of *Dysdercus peruvianus*, which damages cotton seeds and spoils the cotton fibers [9]. Moreover, clusianone and related compounds exhibited larvicidal potency, suggesting utility in vector control strategies [47]. However, comprehen-

sive insecticidal screening of isolated PPBs from *Clusia*/propolis remains very limited, and further studies are needed into their mechanisms of action and spectrum of activity.

As propolis benzophenones are phenolic compounds, they have pronounced antioxidant properties. Antioxidants are known to function as stress-mitigating agrochemicals [48]. Their application enhances plant tolerance to drought, salinity, ozone, heat, and heavy metals by strengthening antioxidant defenses, limiting oxidative damage, and supporting growth and yield. In certain cases, they also stimulate a plant's natural immune response by causing the production of metabolites that reduce damage and fight off infection [49–51]. Antioxidants applied topically support crops in withstanding environmental stress and regaining their potential, resulting in the maximum yield [51].

There are numerous publications confirming the antioxidant potential of PPBs from propolis and of PPB-rich propolis extracts. Nemorosone (**16**) isolated from Cuban propolis scavenged DPPH free radicals in the same order of magnitude as the reference α-tocopherol [19]. Nemorosone-containing Ecuadorian propolis demonstrated good antioxidant activity in DPPH and FRAP tests [26]. Extracts of propolis samples from Venezuela acted as effective inhibitors during triglyceride autoxidation at 100 °C; this activity might be connected to the presence of prenylated benzophenones in the samples, indicated by GC-MS [40]. Brazilian red propolis extract enriched in benzophenones has shown promising results against UV-induced skin damage [52]. Stingless bee propolis rich in benzophenones demonstrated an intracellular antioxidant effect, reducing ROS in THP-1 cells upon oxidative stress induced by H_2O_2 [31]. In addition, propolis containing polyprenylated benzophenones has demonstrated anti-inflammatory activity, performing significant reductions in the levels of pro-inflammatory cytokines [31].

However, no investigations *in planta* have been carried out to test the effect of antioxidant PPBs on mitigating stress. This gap should be filled; research is needed in this promising area.

Obviously, the structure of PPBs is important for their activity, but no structure–activity relationship research in the agrochemical field has been performed so far, and no structure–agro activity correlation of PPBs is known. The only study concerning the structure–activity relationship of benzophenones demonstrated that benzophenone derivatives with methyl, methoxy, hydroxy or halogen substituents inhibited growth and caused chlorosis in various plants, but no polyprenylated benzophenones were tested [53]. There are a few limited but promising communications about the actual agrochemical potential of polyprenylated benzophenones.

6. Conclusions

Polyprenylated benzophenones are a distinctive class of polyphenolic compounds found in certain types of propolis, particularly tropical propolis produced by bees that collect resins from plants of the genus *Clusia*.

The presence and concentration of PPBs are often used as chemical markers of specific propolis types, such as Cuban, Brazilian red or Venezuelan propolis. These compounds contribute substantially to the biological effects of propolis. They have demonstrated a wide range of activities: antimicrobial, antioxidant, anti-inflammatory, and cytotoxic (especially anticancer) effects [3–5].

Apart from this documented biomedical usefulness, polyprenylated benzophenones represent a highly valuable yet largely unexploited potential in agrochemistry. As the agricultural sector faces increasing pressure to develop sustainable and ecological agricultural practices, these naturally derived compounds offer a promising alternative. Their potent biological properties make them excellent candidates for "biorational" crop protection agents capable of targeting devastating plant pathogens with potentially fewer ecotoxicological im-

pacts than traditional synthetic preparations. It is our hope that this review will encourage researchers in the area of agrochemistry to focus on optimizing extraction, concentration and purification protocols of these propolis compounds; on their potential for crop protection; on structure–activity relationships; evaluation of phytotoxicity, selectivity, and non-target effects; assessment of degradation and environmental persistence; and possible applications for the next generation of eco-friendly, targeted pest management formulations.

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