Antiviral and antibacterial properties of phloroglucinols: a review on naturally occurring and (semi)synthetic derivatives with potential therapeutic interest.

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Abstract

Phloroglucinol and derived compounds comprise a huge class of secondary metabolites widely distributed in plants and brown algae. A vast array of biological activities including antioxidant, anti-inflammatory, antimicrobial, and anticancer have been associated to this class of compounds. In this review, the available data on the antiviral and antibacterial capacity of phloroglucinols have been analysed. Some of these compounds and derivatives show important antimicrobial properties *in vitro*. Phloroglucinols have been shown to be effective against viruses such as HIV, herpes or enterovirus, and preliminary data through docking analysis suggest that they can be effective against SARS-CoV-19. Also, some phloroglucinols derivatives have shown antibacterial effects against diverse bacteria strains including *Bacillus subtilis* and *Staphylococcus aureus*, and (semi)synthetic development of novel compounds have led to phloroglucinols with a significantly increased biological activity. However, therapeutic use of these compounds is hindered by the absence of *in vivo* studies and scarcity of information on their mechanisms of action, and hence further research efforts are required. On the basis of this consideration, our work aims to gather data regarding the efficacy of natural-occurring and synthetic phloroglucinol derivatives as antiviral and antibacterial agents against human pathogens, which have been published during the last three decades. The recollection of results reported in the current review represents a valuable source of updated information that will potentially help researchers in the development of novel antimicrobial agents.

Keywords: algae; antimicrobial; *Hypericum*; phloroglucinol; SARS-CoV-19; semisynthesis

1. Introduction

Phloroglucionols (PGs) are a family of naturally occurring phenols that have been isolated from numerous plant species. All members of this chemical class share a common core structure, i.e. the 1,3,5-trihydroxybenzene moiety [phloroglucinol (**1**), **Figure 1**], which has been isolated from natural sources, and has several different applications, ranging from medicine to cosmetics, pesticides, paints, cements and dyeing (1). Despite the wide distribution of PGs in nature, some of these compounds are particularly abundant in *Hypericum* species, of which they represent the chemotaxonomic markers (2). Examples are hypericin, pseudohypericin, japonicins A–D, and sarothralens A–D (3-5). Since ancient times, plants belonging to *Hypericum* species have represented valuable remedies included in the traditional medical culture of different Regions of the World, and still nowadays they are used as astringents, antipyretics, diuretics, antiphlogistics and analgesics in Europe, America, Africa, and Asia (6). Furthermore, *H. perforatum* L. (St. John's wort) is widely used to treat mild to moderate clinical depression (6). The medicinal properties of this plant species have been correlated to hypericin, pseudohypericin and other characteristic phloroglucinol derivatives with pleiotropic biological effects, which have been exhaustively summarized in a recent review by Bridi and Meirelles (7). Other natural sources of bioactive PGs have been described during the last decades, as a consequence of the increasing interest of the Scientific Community in exploring the potential usefulness of these compounds as therapeutic agents.

Naturally occurring PGs are known also for their antiviral and antibacterial properties. Although the antiviral properties of phloroglucinol were reported in the '50s, to the best of our knowledge, the first report of the antiviral activity of these compounds was by Chan and Shultis (8). In this study, the authors described the effects of three acyl-phloroglucinol derivatives isolated from the Australian plant *Melicope sessiliflora* C.T. White (status ambiguous according to worldflroraonline.org) on types I and II *Herpes simplex* virus. Similarly, Rios et al. (1991) (9) described for the first time the antibacterial properties of natural PGs. The authors showed the effects of italipyrone and plicatipyrone isolated from Spanish *Helichrysum stoechas* (L.) Moench against several gram-positive bacterial strains. Furthermore, the biological activity of synthetic and semi-synthetic phloroglucinol derivatives has also been reported, indicating their potential usefulness as novel therapeutic agents.

More recently, the emergence of the COVID-19 pandemic has prioritised the search for strategies to counteract the SARS-CoV-2 virus, and the need to discover and develop novel antiviral agents has become of paramount importance. This review covers advances in the field of PGs which have been reported in

the literature since the late 1980s. The molecular structures of naturally occurring and synthetic phloroglucinol derivatives are here reviewed, along with information regarding their antiviral and antibacterial properties. Finally, a perspective on their potential usefulness as future lead compounds for the development of novel antimicrobial agents is presented in the final sections of the article.

2. Chemistry of phloroglucinols

Phloroglucinol (**1**) is a benzenetriol presenting hydroxyl groups in positions 1, 3, and 5. Natural phloroglucinol derivatives vary in their structural complexity, and are classified as monomeric and polymeric. This last group comprises dimeric and trimeric derivatives and higher polymers, as well as phlorotannins. These latter are high molecular weight compounds that result from the polymerization of several phloroglucinol units, usually bonded each other by ether bonds. Naturally-occurring phloroglucinol derivatives are frequently encountered as glycosides. Monocyclic PGs include acylated, halogenated, and/or prenylated derivatives, as well as phloroglucinol-terpene adducts. Simple acyl PGs represent the largest category of natural phloroglucinols. Halogenated PGs are mostly mono-halogenated and contain chlorine and bromine atoms. Prenylated PGs include mono-, di-, poly-prenylated and/or geranylated derivatives. Phloroglucinol-terpene adducts consist in a large number of compounds diffused in several plant species: among the others, the most widely characterized are those found in *Eucalyptus* species, which are classified into two groups, namely euglobals (chroman-containing adducts) and macrocarpals (non-chroman-containing adducts) (1, 10-12). Other examples are the Diels–Alder adducts calliviminones and cleistocaltones, described respectively in *Callistemon* (13) and *Cleistocalyx* (14) species, or the more recently discovered baeckfrutones from *Baeckea frutescens* (15). Generic structures of these naturally-occurring PGs are summarized in **Figure 1.**

Phloroglucinol derivatives occurring in brown algae can be classified according to the type of linkages between phloroglucinol units and their content of hydroxyl groups. These include fucols (with aryl-aryl linkage), phlorethols (with aryl-ether linkages), fucophlorethols (with aryl-aryl and aryl-ether units), fuhalols (with aryl-ether linkages and additional hydroxyl groups in every third ring), carmalols (with a dibenzodioxin moiety and derived from phlorethols) and eckols (with at least one three-ring moiety with a dibenzodioxin element substituted by a phenoxyl group at C-4) (16).

3. Natural occurrence of phloroglucinols: plants, algae, and microorganisms

Phloroglucinol derivatives are widely present in the plant families Aspidiaceae, Cannabinaceae, Clusiaceae, Compositae, Crassulaceae, Euphorbiaceae, Fagaceae, Guttiferae, Lauraceae, Myrtaceae, as well as Rosaceae and Rutaceae, but have also been identified in marine and microbial sources (11). These include simple compounds such as phloroglucinol β-D-glucoside (phlorin) from *Cannabis sativa* L. (17) and *Citrus* fruits (18), as well as more complex structures such as the myrtucommulones, oligomeric acylphloroglucinols, and phloroglucinol-terpene adducts from the Myrtaceae (19), phloroglucinol derivatives with an *α*,*β*-unsaturated spiroketal unit with five-membered rings (helispiroketals A–H), and other derivatives from *Helichrysum* spp. (Asteraceae) (20), prenylated PGs from hops (*Humulus lupulus* L.) (21), polyprenylated acylphloroglucinols from *Garcinia* spp. (Clusiaceae) (22, 23), and dimeric and acyl-phloroglucinols from *Mallotus* spp. (Euphorbiaceae) (24-26). PGs have also been reported as the main phytoconstituents of ferns from the genus *Dryopteris* (27-29).

PGs also occur naturally in microbes and marine organisms (11). They are present mostly as monocyclic derivatives, and are particularly widespread within species of two genera of brown algae (phylum Ochrophyta), namely, *Cystophora* and *Zonaria*. Within this latter, *Zonaria spiralis* represents an exception, containing mainly dimeric structures (30). Phlorotannins are predominant in other species of brown algae including *Ecklonia, Eisenia*, and *Ishige* spp. (16). A number of halogenated phlorotannins have also been isolated from the brown alga *Carpophyllum angustifolium* (31).

Among microbes that produce PGs are bacterial species belonging to the Pseudomonadaceae family, including *Pseudomonas* spp., which biosynthesise acetyl derivatives (32).

4. Natural phloroglucinols as potential antiviral agents: targets

Many phloroglucinol derivatives have been tested for their activities against a wide range of viruses with good to excellent results. The occurrence of these compounds in Nature and their antiviral activities are described below.

4.1. Avian influenza virus

Avian influenza virus (AVI) is the etiological agent that causes avian (bird) influenza (flu). The AVI viruses are naturally occurring and are endemic in wild aquatic birds, but can also occur in domestic poultry, as well as in other bird and animal populations (33). While AVI viruses do not normally impact humans, there have been occasional outbreaks of human infections (34). There are few treatments for these infections, but recent research has shown that several naturally occurring compounds may inhibit

AVI replication. For example, a phloroglucinol derivative named dryocrassin-ABBA (**2**) (**Figure 2**) was isolated from the roots of *Dryopteris crassirhizoma* Nakai (Dryopteridaceae), a traditional Chinese herbal medicine used to treat viral infections (33). This compound was tested in mice infected with amantadine-resistant AVI (H5N1strain) at doses of 12.5, 18 and 33 mg/kg body weight. Treatment with (**2**) significantly improved survival rates, and reduced lung lesions, viral load, and inflammatory cytokine concentrations. Survival rates were 87% in mice treated with the 33 mg/kg dose and 80% in mice treated with the 18 mg/kg dose, as compared with only 53% in the control group treated with amantadine hydrochloride (positive control), and 20% in the untreated group (negative control). The lung viral loads in mice treated with 18 or 33 mg/kg doses were significantly lower as compared with the controls, but not significantly different from the amantadine treated group (33). Another study evaluated the active PGs from *D. crassirhizoma* on isolated H5N1 (35). The results showed that (**2**) exhibited the best inhibitory effects on H5N1 neuraminidase with an IC_{50} of 18.59 ± 4.53 μM.

The algae *E. cava* has been shown to be a potential source of anti-influenza compounds. The inhibitory activities of (**1**), eckol (**3**), 7-phloroeckol (**4**), phlorofucofuroeckol (**5**), and dieckol (**6**) (**Figure 2**) from *E. cava* were shown to act as neuraminidases inhibitors in H1N1, H3N2, and H9N2 strains of influenza A. Among these, (**5**) exhibited the most potent inhibitory activities toward H1N1, whereas (**6**) potently inhibited H3N2 and H9N2 (36). In a more recent work, Cho et al. reported that (**5**) from *E. cava* is the most active phlorotannin of this species against the influenza A H1N1 and H9N2 strains (EC_{50} value of 13.48 μM) (37).

4.2. Epstein-Barr virus

The Epstein-Barr virus (EBV) is a human herpes virus 4 and is spread primarily through saliva. This virus is common worldwide and is the etiological agent for infectious mononucleosis, as well as other illnesses (38). While most people who are infected with the virus will not have symptoms, some will have serious symptoms such as extreme fatigue, swollen lymph nodes and rashes that may take months to resolve. Currently, the treatment for EBV is bed rest, fluids, and supportive care to reduce symptoms, as there are few medications to treat the condition. Takasaki and Konoshima (39) identified euglobals G1 (**7**), G2 (**8**) and G3 (**9**) (**Figure 3**) in *Eucalyptus globulus* Labill. (Myrtaceae), i.e. naturally-occurring, monomeric phloroglucinol derivatives with a chromane ring. *In vitro* testing showed that these compounds inhibited EBV early antigen (EBV-EA) induction, and further showed that the acyl-phloroglucinol nucleus was essential for this activity (39). Furthermore, the antiviral activities of these compounds against EBV-EA

depended on the increased lipophilicity of the N-substituent derivatives, the most active being those containing benzyl, octyl, decyl and phenylpropyl in addition to simple esters of 3-nitrofluoroglycinecarboxylic acid (39). Later, Honda and Tokuda (40) identified a series of 3-nitrophloroglucinecarboxylic acid derivatives, namely 3-nitro-2,4,6-trihydroxythiobenzamides and 3-nitro-phloroglucinecarboxylates, with activity against EBV-EA in Raji cells. More specifically, 2,4,6-trihydroxy-3-nitro-N-nonylbenzothioamide (**10**) and O-decyl 2,4,6-trihydroxy-3-nitrobenzoate (**11**) (**Figure 3**) were the most potent inhibitors. Also, phloroglucinols from hop have been reported to inhibit the activation of EBV-EA in the same cellular model. Specifically, the activity of 5-deprenyllupulonol C (**12**), lupulone C (**13**), colupox a (**14**), and lupulone E (**15**) (**Figure 3**) was demonstrated by IC_{50} values in the range of 215–358 mol ratio/32 pmol TPA (12-O-tetradecanoylphorbol 13-acetate, activator of EBV-EA) (41).

4.3. Enterovirus (EV71)

The lesser-known *Enteroviruses* (Picornaviridae) are small, single-stranded RNA viruses belonging to the genus *Enterovirus*. Infection with the *Enterovirus* (EV71) is problematic as this causes serious neurological disorders and has been associated with high morbidity and mortality in infants and young children (42). Currently, there are no vaccines or antiviral drugs available for the clinical treatment of EV71, thus the development of natural products for this viral infection would be clinically significant.

A traditional Chinese medicine (TCM), *Garcinia oblongifolia* Champ. ex Benth (Clusiaceae) used to treat gastrointestinal disorders was tested for its effects against EV71. An acetone extract of the leaves of this plant exhibited significant anti-EV71 activities *in vitro* (42). Bioassay-guided fractionation of the extract led to the isolation and identification of twelve novel prenylated benzoylphloroglucinols, namely the oblongifolins J−U. When tested against EV71, the PGs oblongifolin J (**16**) and oblongifolin M (**17**) (**Figure 4**) were more active than the control drug ribavirin (IC_{50} = 253.1 μM). Furthermore, these compounds exhibited significant anti-EV71 activity in African green monkey kidney (Vero) cells, with respective IC_{50} values of 31.1 and 16.1 μM. In addition, the selectivity indices of these compounds were 1.5 and 2.4 in Vero cells, respectively (42).

4.5. Herpes simplex (HSV) and polio viruses

Herpes simplex virus (HSV) types I and II are the etiological agents for genital herpes, a common cause of infections worldwide, and in need of new treatment options (43). Four antiviral PGs isolated from

Kunzea species in 1992 showed good activities against *herpes simplex* type I and polio type I viruses (44). Compounds 1-(2,6-dihydroxy-4-methoxyphenyl)ethanone (**18**) and 1-(2,4-dihydroxy-6-methoxyphenyl)-2-methylpropan-1-one (**19**) (isobutyryl methoxyresorcinol derivatives, **Figure 5**) inhibited the cytotoxic effects of both viruses at a concentration of 5 µg/disk, while semimyrtucommulone (**20**) and a combination of its analogues 4-[1-(2,6-dihydroxy-3-isobutyryl-4-methoxyphenyl)-2,3-dimethylbutyl]-5-hydroxy-2,2,6,6-tetramethylcyclohex-4-ene-1,3-dione (**21**) and 4-{1-[2,6-dihydroxy-4-methoxy-3-(3-methylbutanoyl)phenyl]-3-methylbutyl}-5-hydroxy-2,2,6,6-tetramethylcyclohex-4-ene-1,3-dione (**22**) (**Figure 5**) exhibited similar activities at 40 µg/disk (44). Also, in 1992, Chiba and Takakuwa (45) reported that the polyprenylated phloroglucinols chinesin I (**23**) and II (**24**) (**Figure 5**), isolated from flowers of *Hypericum monogynum* L. (syn. *Hypericum chinense* L., Hypericaceae), inhibited the replication of HSV-I and II at 10 µg/mL.

In 2017, Okba and El Gedaily (46) reported that a phloroglucinol-rich extract obtained from the leaves of *Eucalyptus sideroxylon* Cunn. ex Woolls (Myrtaceae) had antiviral activities against HSV. In this study, the extract was tested against hepatitis A (HAV), herpes simplex type 1 (HSV-I), herpes simplex type II (HSV-II), coxsackie (CoxB4), and adenoviruses. The extract was not cytotoxic but reduced the replication of HSV-II by reducing viral replication (IC_{50} = 189.36 µg/mL, 87.65% inhibition) and attachment in Vero cells (IC_{50} = 199.34 µg/mL, 83.13% inhibition) (46). The extract was not active against the other viruses tested.

Cleistocaltone A (**25**) (**Figure 5**) is a phloroglucinol derivative isolated from the plant *Syzygium nervosum* A.Cunn. ex DC. (syn. *Cleistocalyx operculatus* (Roxb.) Merr. & L.M.Perry, Myrtaceae) (43). This compound reduced the replication of HSV-I and GFP-HSV-I (an HSV strain containing an enhanced green fluorescent protein construct), as well as showing concentration-dependent activity against RSV-1 with an IC_{50} of 7.50 µM (43). Cao and Wu (47) isolated and identified six new triketone-phloroglucinol-monoterpene derivatives (callistrilones F – K) from the leaves and twigs of the tree *Callistemon rigidus* R.Br. (Myrtaceae). Callistrilone H (**26**) and I (**27**) (**Figure 5**) showed good antiviral activity against HSV-I, having IC_{50} of 10.0 and 12.5 µM, respectively (47). The prenylated acylphloroglucinol sessiliflorene (**28**) (**Figure 5**) isolated from a hexane extract of *M. sessiliflora*, was also shown to inhibit the replication of HSV i*n vitro* (11). Finally, Chen et al. reported the anti HSV-I activity of ten enantiomeric pairs of the acylphloroglucinol meroterpenoids (±)-dryocrassoids A−J (**29-38**) and five methylene-bis-phlorobutyrophenone derivatives, namely albaspidin AA (**39**), albaspidin AB (**40**), araspindin BB (**41**), and 1-{3-[(3-acetyl-2,4,6-trihydroxyphenyl)methyl]-2,4,6-trihydroxyphenyl} butanone (**42**) (**Figure 5**),

isolated from the rhizomes of *Dryopteris crassirhizoma*. Their IC_{50} values were comprised within the range 22.51–97.89 μM (48). All the tested compounds showed also anti-RSV effect together with the dimer albaspidin AP (**43**) (**Figure 5**), with IC_{50} values ranging from 11.45 to 50.25 μM.

4.6. Kaposi's sarcoma-associated herpes virus (KSHV)

Kaposi's sarcoma-associated herpes virus (KSHV) is the virus responsible for the development of Castleman's disease, Kaposi's sarcoma and effusion lymphoma (49). Current antiviral agents are not effective against KSHV, thus new treatments for this virus are urgently needed. Four acylphloroglucinols, named the (±)-japonicols A−D (**44-47**) (**Figure 6**), were isolated from *Hypericum japonicum* Thunb. (Hypericaceae) and found to have 2-oxabicyclo[3.3.1]nonane, pyrano[3,2-b]pyran, and benzo[b]cyclopenta[e]oxepine ring systems, respectively (49). These compounds exhibited moderate activity against KSHV, with (±)-japonicol B (**45**) having the best activity with an EC_{50} of 8.75 μM and a selectivity index of 16.06 (49). Other active PGs were isolated from the same plant species, namely several acylphloroglucinol-based meroterpenoid enantiomers. Amongst all the isolated compounds, (+)-japonicols E (**48**) and H (**49**) (**Figure 6**) showed the strongest inhibitory activities towards the lytic replication of KSHV in Vero cells (IC_{50} = 8.30 and 4.90 μM, and selectivity indexes = 23.49 and 25.70, respectively) (50). Qualitative and quantitative SAR and molecular docking studies for these two derivatives indicated thymidylate synthase (kTS) and protease (kPr) as possible targets. Results allowed also to observe the molecular interaction between (+)-japonicols H and kPr: this was driven by hydrogen bonding to Arg199, Arg200, Pro217, Ser240 and Tyr282 with an additional salt bridge between 5′-OH and Arg199. Moreover, the remote vinyl group was inserted in a hydrophobic pocket formed by Phe115, Val158, Pro218 and other hydrophobic residues (50).

4.7. Human immunodeficiency virus (HIV)

Human immunodeficiency virus (HIV-1), the etiological agent of acquired immunodeficiency syndrome (AIDS), remains a global health threat, despite the development of more than thirty drugs for its treatment (2). Therefore, it is essential that new treatments continue to be developed. Of the five classes of drugs for the treatment of HIV/AIDS, most are reverse transcriptase inhibitors.

Some phloroglucinol derivatives isolated from *Hypericum scruglii* Bacch., Brullo & Salmeri (status ambiguous according to worldflroraonline.org, Hypericaceae) collected in Sardinia (Italy) showed a wide range of activities against HIV (2). This study demonstrated that 3-geranyl-1-(2'-methyl-butanoyl)-

phloroglucinol (**50**), 3-geranyl-1-(2'-methylpropanoyl) phloroglucinol (**51**), and 3-(13-hydroxygeranyl)-1-(2'-methylbutanoyl) phloroglucinol (**52**) (**Figure 7**) inhibited HIV-1 reverse transcriptase activity (IC_{50} = 4.1-25.5 µM). Another compound, 1,3,5-benzentriol 2-[(2*S*,3*R*)-3-(3,4-dihydroxyl-phenyl)-2,3-dihydroxylpropyl] (**53**) (**Figure 7**) showed weak activity (2). Since it is well known that compounds that inhibit HIV-1 RNase H activity can also impact HIV-1 integrase activity, these investigators also evaluated their effect on HIV-1 integrase activity, using raltegravir as the positive control. Three compounds, namely (**50-52**), inhibited HIV-1 integrase activities with an IC_{50} of 7.3 to 13 µM (2).

Mallotojaponin (**54**) and mallotochromene (**55**) (**Figure 7**), two PGs isolated from the pericarps of *Mallotus japonicus* (L.f.) Müll.Arg. (Euphorbiaceae), inhibited the activity of HIV-reverse transcriptase with a 70% inhibition at a concentration of 10 µg/mL (51). Furthermore, arzanol (**56**) (**Figure 7**), a prenylated heterodimeric phloroglucinyl pyrone, isolated from an acetone extract of *Helichrysum italicum* subsp. *microphyllum* (Willd.) Nyman (Asteraceae), exhibited strong activity against the nuclear factor (NF)-κB, with an IC_{50} of 5 µg/mL (52). Arzanol was also found to inhibit tumour necrosis factor (TNF) receptor-induced HIV-1 long terminal repeat transactivation in stably transfected T cells at a concentration of 5 µM (52).

Finally, also a phlorotannin derived from brown algae has shown promising anti-HIV activity *in vitro*. Specifically, 8,8'-bieckol (**57**) (**Figure 7**) produced by *Ecklonia cava* showed significant inhibitory results on HIV-1 reverse transcriptase (RT). The inhibitory activity of (**57**) against HIV-1 RT was comparable to that of nevirapine (IC_{50} = 0.51 µM and 0.28 µM, respectively), and was regulated by a competition against dUTP/dTTP (K_i = 0.78 µM) (53).

4.8. Respiratory syncytial virus

Respiratory syncytial virus (RSV) is a commonly occurring upper respiratory virus that usually causes mild, cold-like symptoms (54). However, RSV may cause serious, life-threatening upper respiratory tract infections in paediatric or geriatric patients, as well as in immune-compromised patients and patients with underlying medical conditions. Because the drugs available against RSV are scarce, finding new natural-based products is of interest. In one study, Song and Su (54) isolated and identified two compounds, named cleistocaltones A (**58**) and B (**59**) (**Figure 8**), from the plant *S. nervosum*. The *in vitro* antiviral activities of these compounds were evaluated against RSV using ribavirin as the positive control (IC_{50} = 15 µM) (54). Both compounds reduced the expression of respiratory (human) syncytial virus F proteins (RSV F proteins) with an IC_{50} of 6.75 and 2.81 µM, respectively. Other PGs isolated from *Rhodomyrtus tomentosa*

leaves, namely rhodomentosones A (**60**) and B (**61**) (**Figure 8**), have also been reported to inhibit RSV *in vitro*, with IC_{50} values of 12.50 and 15.00 µM, respectively (55). More recently, Deng et al. reported the isolation of other active PGs from the same plant species, namely (+)-rhodomyrtosone B (**62**) and (-)-rhodomyrtone (**63**) (**Figure 8**). Both the compounds were active against RSV, showing IC_{50} values of 3.00 µM and 0.39 µM, respectively (56).

In another work, Fuchimoto et al. showed that humulone (**64**) (**Figure 8**), which is the main constituent of hop (*Humulus lupulus*) bitter acids, can prevented the expression of RSV/G-protein, formation of virus filaments and release of IL-8 and chemokine RANTES in a dose-dependent manner in RSV-infected human nasal epithelial cells (57).

4.9. SARS CoV-2

SARS-CoV-2, the virus responsible for COVID-19, has one of the largest genomes of all the RNA viruses (58). The virus is composed of four primary structural proteins including: spike (S), nucleocapsid (N), membrane (M) and envelope (E), all of which are encoded in the viral genome (59). There are also numerous non-structural proteins (NSPs) that are involved in the regulation and assembly of the virus and its passage into the immune system. In a molecular docking study, an H-bond was formed between the hydroxyl group of (**1**) and Arg188 and Gln189. Also, a p-alkyl bond was formed between Met165 with the cyclohexandiol of (**1**), suggesting that this compound may be a good drug candidate for the treatment of SARS-CoV-2 virus (59). Interestingly, an *in silico* study using (**1**) found similar results as the compound bound to the main viral protease M^{pro} (60). In another study, although (**1**) did not have any significant activity against SARS-CoV $3CL^{pro}$, isolated phlorotannins competitively inhibited SARS-CoV $3CL^{pro}$ in a cell-free/based system with IC_{50} values ranging from 2.7 to 164.7 µM (61). Other phlorotannins characteristic for brown seaweed [(**5**), eckol hexaacetate (**65**), fucofuroeckol B (**66**), and bifuhalol hexaacetate (**67**) (**Figure 9**)] have been recently reported to exert antagonist effects on selected SARS-CoV targets *in silico*, namely $3CL^{pro}$, RdRp, and S^{pro}. Moreover, the same compounds were analyzed to be druggable with no major violations from all the ADMET profiling parameters (62). Compounds (**6**), (**57**), and 6,6'-bieckol (**68**) (**Figure 9**), three phlorotannins from *Ecklonia cava*, were indicated by Gentile et al. as other potential SARS-CoV M^{pro} inhibitors *in silico*, and their interactions with the protease were characterized by calculated free binding energies (ΔG_B) of −12.9 and −12.1 kcal/mol, respectively (63).

A target-based virtual screening with LC/MS identified phoroglucinol-terpenoid inhibitors of SARS-CoV-2 from *Dryopteris wallichiana* (Spreng.) Hyl. (64). In other study, the anticoronaviral activity of PGs from

297 rhizome of *D. crassirhizoma* was tested by targeting the main protease of SARS-CoV-2 (65). This study
298 concluded that compound (**2**) has a therapeutic potential against coronavirus infections. The compound
299 was effective in inhibiting the replication of the virus *in vitro* in a dose-dependent manner (IC_{50} = 46.48
300 μM), and it showed a low toxicity in mice (lethal dose >10 mg/kg) after 5-day repeated-dose treatment.
301 Finally, pharmacokinetic studies of (**2**) showed good microsomal stability, low hERG inhibition, low
302 CYP450 inhibition, long half-life (5.5–12.6 h) and high plasma exposure (AUC 19.3–65 μg·h/mL) (65).
303
304 ***4.10. Vesicular stomatitis virus***
305 Vesicular stomatitis virus (VSV, Rhabdoviridae) is a zoonotic arbovirus that consists of a single strand of
306 negative-sense RNA. The transmission of VSV occurs in animals after insect bites, and may cause severe
307 disease in cattle, horses, and swine, producing symptoms that are similar to those observed in hoof and
308 mouth disease (45). VSV infections in humans occur infrequently, and usually cause a mild flu-like illness,
309 but occasionally may cause severe disease. In one study, Chiba and Takakuwa (45) tested the effectiveness
310 of compounds (**23**) and (**24**) isolated from flowers of *H. chinense* L. and synthetic PGs against VSV, and
311 demonstrated that synthetic monoacylphloroglucinols and polyprenylated phloroglucinols inhibited the
312 viral replication at concentrations of 14-32 μg/mL. Interestingly, diacylphloroglucinols were the most
313 active and inhibited the replication of VSV at concentrations of 0.4-1.2 μg/mL (45). Among these, di-
314 isovalerylphloroglucinol (**69**) (**Figure 9**) gave the best results.
315
316 ## 5. Natural phloroglucinols as potential antibacterial agents: targets
317 Today, morbidity and mortality in the developing world related to infectious diseases accounts for about
318 50% of all deaths (66). Because of the increasing prevalence of life-threatening bacterial, fungal and viral
319 infections and the ability of these pathogens to develop resistance to current treatment strategies, there is
320 a great need for new compounds to combat them (67). According to the World Health Organization
321 (WHO), medicinal plants would be the best source to obtain a variety of drugs including antibacterial
322 agents, and hence such plants should be investigated for their activity (68).
323 Many studies have reported that phloroglucinol compounds and derivatives have antimicrobial activities
324 against diverse human pathogens. Recently, an exhaustive review article resuming literature data about
325 the antibacterial activity of PGs has been published by Khan et al. (69), hence here we summarized some
326 exemplificative results in **Table 1.** Chemical structures of PGs reported in Table 1 (**70-97**) are shown in
327 **Figure 10.**

Among the different classes of PGs, phlorotannins, and especially those isolated from algae, have been most widely explored for their antibacterial activity and several reviews on the topic have been published during the last years (70-72). Mechanisms of action on the basis of phlorotannins' antibacterial activity have been also proposed. These comprise their interaction with bacterial enzymes involved in metabolic pathways and membrane proteins, directly inhibiting oxidative phosphorylation. These interactions are enhanced by the presence of available hydroxyl groups in phlorotannins that can bind to the amide groups of bacterial proteins via hydrophobic interactions and hydrogen bonding, and usually lead to the lysis of bacterial cells (73).

6. (semi)Synthetic approaches to antiviral and antibacterial phloroglucinols

Semisynthesis is an essential tool for enhancing the biological properties of parent natural products. Semisynthesis and biological activities of semisynthetic derivatives have been extensively explored during the last decade; this has allowed the development of new promising products for therapeutic application (90). Although natural products are an important starting point for the development of drugs, they can rarely be directly employed to treat disease. Structural modifications of naturally-occurring compounds are necessary to increase their therapeutic potency or their specificity (91). Thus, increasing lipophilicity or inserting halogen atoms in natural compounds are excellent examples of chemical modifications that contribute to increased biological activity.

Research on the synthesis of PGs has focused on their reaction with other compounds to form phloroglucinol derivatives with improved biological activity. PGs can be modified by chemical reactions with acylphloroglucinols, phloroglucinol terpenes, glycoside PGs, halogen PGs, dimer and trimer PGs, phlorotannins, or cyclic polyketides (11). For example, the anticancer agent ethyl-2-(3,5-dihydroxyphenol) was synthesized by reacting phloroglucinol with ethyl 2-chloro acetate under reflux for 24 hours at a temperature of 56ºC (92).

Phloroglucinol-based derivatives representing monoacyl-, diacyl-, dimeric acyl-, alkylated monoacyl-, and the nitrogen-containing alkylated monoacylphloroglucinols have been synthesized and evaluated for their anti-inflammatory activities (93). Among experimental compounds, diacylphloroglucinol and alkylated monoacylphloroglucinol were found to be dual inhibitors of inducible nitric oxide synthetase (iNOS) and NF-κB (93). The anti-inflammatory activity of diacylphloroglucinol mediated by iNOS and NF-κB inhibition, appears to be consistent with the previously reported data for the analogue compound

(**81**) (94). This latter is a well-known bacterial secondary metabolite, which inhibits the metabolic activity of bacteria without affecting their viability (95).

During the SARS-CoV-2 pandemic, there has been significantly increased interest in improving phloroglucinol semisynthesis in order to enhance antiviral activity. An efficient and eco-friendly route for the synthesis of dimeric 2,4-diacetylphloroglucinol analogues and their potential as SARS-CoV-2 main protease antagonists was developed. Molecular docking studies to permit the rapid screening of possible therapeutic ligands showed that the derivative methylene-bis diacetylphloroglucinol (**98**) (**Figure 11**) exerted a marked binding against the crystal structure for SARS-CoV $3CL^{pro}$ (96). Diacylphloroglucinols such as compound (**81**) prepared by reacting phloroglucinol with corresponding acid in presence of BF_3 also showed anti-herpes virus activity (97).

PGs with a general formula with R1–R6 H, alkyl or acyl chains of variable length, aryl, halogen, nitro, alkylene, alkenylene, etc., are known as directly active components or can be used in combination with other antiviral compounds such as zidovudine (AZT), zalcitabine (DDC), and HIV protease inhibitors (97). For example, polyprenylated acylphloroglucinols have interesting biological activities including anticancer and antibacterial properties. The synthesis of type-B polycyclic polyprenylated acylphloroglucinol 7-*epi*-clusianone (**99**) (**Figure 11**) has been developed by establishing the *cis* relationship with the allyl group C(4) and the methyl ester C(2) at the initial stage of the synthesis (98). At the same time, the antimicrobial activities of the prenylated pyrone-phloroglucinol (**83**), isolated from the aerial parts of *Achyrocline satureioides* (Lam.) DC. (Compositae), and some of its semisynthetic derivatives against a selected panel of gram-positive and gram-negative bacteria were reported (81). The antimicrobial activity against *Staphylococcus aureus* of naturally-occurring PGs from *H. japonicum* and *Agrimonia pilosa* Ledeb. (Rosaceae) and synthetic PGs was also confirmed. The most active compounds were synthetic PGs such as compound (**98**) and n-butanoylphloroglucinol (**100**) (**Figure 11**) (99).

The plants (for example, *Arabidopsis* as a model) can be engineered to produce phloroglucinol using a bacterial gene (100). Phyto-production of phloroglucinol paves the way for further genetic manipulations to enhance the level of PGs with implications for their commercial production (100). This is another kind of semisynthesis which is important to enhance the production of phloroglucinol and its derivatives.

The first total synthesis of a monomeric phloroglucinol [(1*R**,2*S**)-2-hydroxy-2-isobutyl-4,4,6,6-tetramethyl-3,5-dioxocyclohexyl acetate] (**101**) (**Figure 11**), previously isolated from *Myrtus communis* L. (Myrtaceae), was achieved by stereo-selective reduction of a symmetrical ±-ketol as a key step (101). Previously it was observed that oligomeric acylphloroglucinols from myrtle (*M. communis*), namely

389 compound (**20**) and myrtucommulone A (**102**) (**Figure 11**), showed significant antibacterial activity
390 against multidrug-resistant (MDR) clinically relevant bacteria (102).
391
392 **7. Conclusions and future prospects**
393 Phloroglucinol and its derivatives are phenolic compounds with high structural diversity, and are widely
394 distributed in Nature, from plants to several brown algae. Previous studies have reported that PGs have
395 antimicrobial activity against varieties of microorganisms including bacteria and viruses. There is
396 abundant *in vitro* evidence in the scientific literature suggesting that PGs exert antiviral activity against a
397 wide range of viruses, including HIV, enteroviruses, and HSV; some preliminary data suggests that their
398 antiviral effects may extend to SARS-CoV-19. In addition, some of these compounds showed antibacterial
399 activity at low concentrations. The possibility to modify the chemical structures of isolated natural PGs
400 through semisynthesis represents an opportunity to increase the diversity of these compounds and develop
401 novel antiviral and antibacterial agents. *De-novo* chemical synthesis represents also a route for the
402 discovery of novel bioactive PGs. Nevertheless, this latter should be pursued by focusing on eco-
403 sustainable synthetic procedures, since traditional chemical synthesis is regarded as an environmental
404 threat due to the need of large amounts of toxic solvents and reagents. Furthermore, attention should be
405 payed also to process scalability, in order to facilitate the transfer of laboratory-scale procedures to the
406 industrial level.

407 Mechanisms of action of antimicrobial PGs are still largely unknown, hence further investigation is also
408 required in this direction. Overall, future studies *in vitro* should be addressed to explore the molecular
409 targets of these compounds in virus and bacteria, so to rationalize the design of novel efficient drugs. For
410 this aim, *in silico* molecular studies will help in the preliminary identification of druggable targets.

411 Finally, literature shows the lack of results about the activity *in vivo* of antimicrobial PGs, hence animal
412 studies and clinical trials will be required to assess the efficacy and safety of the most promising candidate
413 drugs.

414

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Table 1. Phloroglucinol derivatives tested against different pathogenic bacteria.

Phloroglucinol derivative evaluated	Source	Finding of the study	References
2-Methyl-4-[2',4',6'-trihydroxy-3'-(2-methylpropanoyl) phenyl]but-2-enyl acetate (**70**)	*Helichrysum caespititium* (DC.) Sond. ex Harv. (Asteraceae)	Antimicrobial activity against *Bacillus cereus, B. pumilus* and *Micrococcus kristinae* at 0.5 µg/mL, and *Staphylococcus aureus* at 5.0 µg/mL	(74)
Eugenial C (**71**) and eugenial D (**72**)	*Eugenia umbelliflora* O.Berg (Myrtaceae) fruits	Antibacterial activity against *Staphylococcus aureus*	(75)
Uliginosin B (**73**); japonicin A (**74**)	*Hypericum myrianthum* Cham. & Schlecht. (Hypericaceae)	Antibacterial activity against *Staphylococcus aureus*	(76)
Flavaspidic acids PB (**75**) and AB (**76**)	*Dryopteris crassirhizoma* Nakai (Dryopteridaceae)	Antimicrobial activity against *Streptococcus mutans* and *Bacillus subtilis*	(77)
Eurobusone B (**77**); eucarobustol E (**78**); macrocarpals A (**79**) and B (**80**)	*Eucalyptus robusta* (Myrtaceae) leaves	Antimicrobial activity against *Staphylococcus aureus, Pseudomonas aeruginosa* and *Bacillus subtilis*	(78)
2,4-Diacetylphloroglucinol (**81**)	Plant-colonizing *Pseudomonas* spp.	Antimicrobial activity	(79)
Aspidin BB (**82**)	*Dryopteris fragrans* (L.) Schott (Dryopteridaceae)	Antibacterial activity against *Staphylococcus aureus* by induction of peroxidation of membranes, DNA damage and protein degradation	(80)
23-Methyl-6-*O*-demethylauricepyrone (**83**); achyrofuran (**84**); 3-[{5,7-dihydroxy-2,2-dimethyl-8-(2-(*S*)-methylbutanoyl)-2H-	*Achyrocline satureioides* (Lam.) DC. (Compositae)	Antimicrobial activity against gram positive and negative bacteria	(81)

chromen-6-yl}methyl]-6-ethyl-4-hydroxy-5-methyl-2H-pyran-2-one (**85**); 3-[{4,6-dihydroxy-7-(2-(*S*)-methylbutanoyl)-2-(prop-1-en-2-yl)-2,3-dihydrobenzofuran-5-yl}methyl]-6-ethyl-4-hydroxy-5-methyl-2H-pyran-2-one (**86**); 1',1''-[6,7,9-trihydroxy-8-(2-hydroxy-3-methylbut-3-en-1-yl)-3,3-dimethyl-3H-benzofuro[2,3-f]chromene-5,10-diyl]bis(2-(*S*)-methyl-butan-1-one) (**87**)			
Humulone (**64**), lupulone (**88**); xanthohumol (**89**)	*Humulus lupulus* L.	Antibacterial properties against planktonic and biofilm-dwelling Staphylococci (*S. epidermidis* CCM 7221, *S. aureus* CCM 4223, and methicillin-resistant *S. epidermidis* 15895, *S. capitis* spp. *ureolyticus* 16300 and *S. aureus* 4591)	(82)
Compound (**89**)	*Humulus lupulus* L.	Active against *Bacteroides fragilis*, *Clostridium perfringens* and *Clostridium difficile*	(83)
Myrtucommulones D (**90**) and E (**91**)	*Myrtus communis* L.	Antibacterial activity against *Staphylococcus aureus*	(84)
Eucalrobusone F (**92**)	*Eucalyptus camaldulensis* Dehnh	Antibacterial activity against methicillin-resistant *S. aureus* (MRSA)	(85)
Watsonianone A (**93**)	*Callistemon viminalis*	Antibacterial activity against *S. aureus* and *Escherichia coli*	(86)

Isomyrtucommulone B (**94**)	*Callistemon salignus*	Antibacterial activity against *Escherichia coli*	(87)
Rhodomyrtone A (**95**)	*Rhodomyrtus tomentosa*	Effective against epidemic methicillin-resistant *Staphylococcus aureus* 16 (EMRSA-16) and *Enterococcus faecalis* ATCC 29212	(88)
Bullataketals A (**96**) and B (**97**)	*Lophomyrtus bullata*	Active against *Bacillus subtilis*	(89)