Vol. 16(3), pp. 82-96, March, 2022
DOI: 10.5897/JMPR2021.7183
Article Number: F567C6A68840
ISSN 1996-0875

http://www.academicjournals.org/JMPR

ACADEMIC JOURNALS
Journal of Medicinal Plants Research

Full Length Research Paper

Brown macroalgae: Promising sources of bioactive products against human herpesviruses

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Received 22 September, 2021; Accepted 22 February, 2022

Marine brown macroalgae have stood out as important sources of new bioactive products, such as antimicrobial, anticoagulant, anti-inflammatory and antiviral drugs. This study aimed to review the literature on the applications of products derived from brown macroalgae as antiviral agents against human herpesviruses. To date, species of seven distinct orders of brown algae have been studied for this purpose, such as Fucales (19 species), Dictyotales (14 species), Ectocarpales (9 species), Laminariales (2 species), Scytothamnales (1 species), Sphacelariales (1 species) and Tilopteridales (1 species). The products evaluated in this review include extracts, fractions and isolated natural products, mainly terpenoids. Extracts, fractions and isolates of brown algae were evaluated against four viruses: simple herpesviruses types 1 and 2 (HSV-1 and HSV-2), human cytomegalovirus (HCMV) and Epstein–Barr Virus (VEB), also known as human herpesvirus 4 (HHV-4). This review shows products derived from brown macroalgae as potential antiherpetic agents.

Key words: Brown algae, antiviral, marine natural products.

INTRODUCTION

Infections caused by human herpesviruses are a worldwide public health problem since they are responsible for several clinical manifestations that can severely compromise the quality of life of patients and even cause death (Rechenchoski et al., 2017). Herpesviruses belong to the herpesviridae family, which has more than 80 viruses identified but only eight of them are infectious agents in humans. These eight viruses belong to different subfamilies. Herpes simplex virus 1 and 2 (HSV-1 and HSV-2) and varicella-zoster virus (VZV) belong to Alphaherpesvirinae, cytomegalovirus (CMV) and human herpesviruses 6 and 7 (HHV-6 and HHV-7) are included in Betaherpesvirinae, and Epstein-Barr virus and human herpesvirus 8(HHV-8) belongs to subfamily Gammaherpesvirinae (Frisch and Guo, 2013; McAllister and Schleiss, 2014).

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Despite the great concern with these diseases, infections by some herpesviruses such as HSV-1, HSV-2 and VZV have no cure and the treatment available is palliative. In addition, the emergence and dissemination of viral strains resistant to available antiviral drugs has been reported, which creates the need for more effective therapeutic strategies (Gilbert et al., 2002; Piret and Boivin, 2017).

Natural products play a very important role in the discovery of new drugs. It should be noted that most of the drugs approved between 1981 and 2014, especially antimicrobials, are either natural products or medications derived from or based on them (Newman and Cragg, 2016; Thomford et al., 2018). In this context, the marine environment deserves an important highlight since the oceans cover 70% of the planet's surface and present a rich biodiversity, with species of plants and invertebrates and microorganisms (Pereira and Costa-Lotufo, 2012).

Among these organisms, macroalgae are of global ecological and economic importance and can be divided according to their pigmentation into green algae (Chlorophyceae), red (Rhodophyceae) and brown algae (Phaeophyceae) (Teixeira, 2013). Due to the different environmental characteristics and stimuli of the marine environment, macroalgae are able to structurally synthesize a greater diversity of chemicals than terrestrial plants, which have attracted the attention of the pharmaceutical, cosmetic and food industries (Pimentel et al., 2018; Siahaan et al., 2018; Smit, 2004).

There have been many studies that isolate and identify new chemical substances from marine macroalgae (Carroll et al., 2019; Davis and Vasanthi, 2011). In addition to chemical studies, the biotechnological potential of algae has been widely explored, which resulted in the discovery of antibiotic, antifungal, antiparasitic, antitumor, anticoagulant, anti-inflammatory and antiviral activities in extracts, fractions and isolated primary and secondary metabolites (Cirne-Santos et al., 2018; Gutiérrez-Rodríguez et al., 2018; Pérez et al., 2016; Souza et al., 2019; Tchokouaha Yamthe et al., 2017; Torres et al., 2014).

In particular, marine brown macroalgae are important sources of antiviral products against different viruses (Ahmadi et al., 2015; Stephens et al., 2017). The present work reviews the literature on the pharmaceutical application of products obtained from brown algae as antiviral agents for the treatment of infections caused by human herpesviruses.

METHODOLOGY

To search for articles, the authors used all information available in different databases (Elsevier, Science Direct, JSTOR, Scielo, Web of Science, Medline and Scopus), which were accessed by Portal of CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior), which is a virtual library sponsored by Brazilian research agency called CAPES. The authors also included 51 reviews on natural products of marine origin from Natural Products Reports and Annual Reports on the Progress of Chemistry, Section B (Organic Chemistry), both published by the Royal Society of Chemistry between 1984 and 2016. Keywords in English included marine natural product, natural product of brown marine macroalgae, marine brown macroalgae and herpesviruses, herpesvirus and brown algae.

Currently, several brown macroalgae products have been evaluated against different human herpesviruses. A total of 47 brown algae species collected in various regions of the world were studied for this purpose (Table 1). The analysis encompasses seven orders and 13 families and evaluates different products (isolated products, fractions or extracts), which will be discussed in this review.

RESULTS AND DISCUSSION

Figure 1 presents the compounds with antiviral activity against HSV-1 isolated from brown marine algae.

The Table 2 presents the most promising candidates in the studied orders of brown macroalgae

Order Dictyotales

The order Dictyotales presents the third largest diversity among the orders of brown algae, with species distributed geographically globally, although they are mostly found in tropical and subtropical regions (Bittner et al., 2008). According to Guiry and Guiry (2020), this order encompasses 40 genera and 320 species.

To date, 14 species of this family have been explored as sources of antiviral products against human herpesviruses (Table 1). Two dolastane diterpenes (1 and 2) were isolated from dichloromethane extract and inhibited more than 90% of the replication of HSV-1 *in vitro* (Vallim et al., 2010). Subsequently, dichloromethane extract was incorporated into an ointment, with a concentration of 2% (w/w), which was able to reduce virus-induced skin lesions in BALB/c mice (de Souza Barros et al., 2017).

Most of the studied species of this family belong to the genus *Dictyota*. This can be justified by its widespread geographic distribution, such as the species *Dictyota dichotoma* already collected in countries with Greece, Hong Kong and Argentina and also by the different isolated products. Siamopoulou et al. (2004) explored the extract and isolated the prenilated guaiane diterpene, the isopachydictyolal (3), with low anti-HSV-1 activity. On the other hand, the aqueous extract showed potent activity against *in vitro* replication of HSV-1 and HSV-2 (EC50 = 24.3 and 25 µg/mL, respectively) and low cytotoxicity for Vero cells (CC50 = 925 µg/mL) (Wang et al., 2008). Twenty polysaccharides' fractions were obtained from the ethanol extract of this seaweed, presenting a high variation of antiherpetic activity. Among these, the EAR-2 fraction showed potent anti-HSV-1 activity (EC50 = 7.5 µg/mL; IS = 42 against Vero cells). Structural physical analyses indicated that the majority polysaccharide was a fucosyl-galactan (Rabanal et al., 2014). On the activity of

Table 1. Brown marine algae species and their products described with activity for human herpesviruses*.

Algae	Collection site	Extract, fractions and tested products	Antiviral activity	*References*
Dictyotales				
C. cervicornis	Búzios, RJ, Brazil	Dolastane diterpenes (**1**-**2**)	HSV-1: inhibited 90-99% of viral replication at 50 µM	*Vallim et al. (2010)*
	Angra dos Reis, RJ,Brazil	Dichloromethane extract	HSV-1: reduced virus-induced skin lesions in mice BALB/c	*de Souza Barros et al. (2017)*
Dictyopteris delicatula	Arraial do Cabo, RJ, Brazil	Dichloromethane/Methanol Extract	HSV-1: inhibited 822% of viral replication at 100 µg/mL HSV-2: inhibited 776% of viral replication at 100 µg/mL	*Soares et al. (2012)*
	Saronic Gulf, Aegean Sea, Greece	Prenylated guaine diterpene (**3**)	HSV-1: low activity against the virus until 100 µg/mL	*Siamopoulou et al. (2004)*
Dictyota dichotoma	Hong Kong, China	Aqueous extract	HSV-1: EC_{50} = 243 µg/mL HSV-2: EC_{50} = 250 µg/mL	*Wang et al. (2008)*
	Chubut Province, Argentina	Fractions with polysaccharides	HSV-1: EC_{50} = 75 – 375 µg/mL	*Rabanal et al. (2014)*
Dictyota linearis	Chios Island, Greece	Xeniane diterpenes (**7**-**10**)	HSV-1: low activity against the virus until 100 µg/mL	*Siamopoulou et al. (2004)*
Dictyota pfaffii	Atol das Rocas, RN, Brazil	Dolabellane diterpenes (**4**-**6**)	HSV-1: inhibited 81-89% of viral replication at 50 µM	*Barbosa et al. (2004)*
	Atol das Rocas, RN, Brazil	Dolabellane diterpene (**6**)	HSV-1: EC_{50} = 12 µM	*Abrantes et al. (2010)*
Dictyota menstrualis	Búzios, RJ, Brazil	Dichotomane diterpene (**11**)	HSV-1: EC_{50} = 16 µM	*Abrantes et al. (2010)*
	Arraial do Cabo, RJ, Brazil	Dichloromethane/Methanol Extract	HSV-1: inhibited 206% of viral replication at 125 µg/mL	*Soares et al. (2012)*
Dilophus fasciola	Mersa Matruh, Egypt	Sulfollilipid fraction	HSV-1: inhibited 70.12% of viral replication at 20 µg/mL	*El Baz et al. (2013)*
Lobophora variegata	Hong Kong, China	Aqueous extract	HSV-1: EC_{50} = 185 µg/mL HSV-2: EC_{50} = 90 µg/mL	*Wang et al. (2008)*
	Arraial do Cabo, RJ, Brazil	Dichloromethane/Methanol Extract	HSV-1: inhibited 92% of viral replication at 6.2 µg/mL	*Soares et al. (2012)*
Padina australis	Hong Kong, China	Aqueous extract	HSV-1: EC_{50} = 589 µg/mL HSV-2: EC_{50} = 400 µg/mL	*Wang et al. (2008)*
Padina gymnospora	Arraial do Cabo, RJ, Brazil	Dichloromethane/Methanol Extract	HSV-1: inhibited 859% of viral replication at 100 µg/mL HSV-2: inhibited 438% of viral replication at 100 µg/mL	*Soares et al. (2012)*
Padina tetrastromatica	Okha, Gujarat, India	Fractions with polysaccharides	HSV-1: EC_{50} = 074-105 µg/mL HSV-2: EC_{50} = 030-039 µg/mL	*Karmakar et al. (2010)*
Stoechospermum marginatum	Mar Arábico, Gujarat, India	Sulfated polysaccharides fractions	HSV-1: EC_{50} = 355 µg/mL HSV-2: EC_{50} = 063 µg/mL	*Adhikari et al. (2006)*

Table 1. Contd.

Stypopodium zonale	Búzios, RJ, Brazil	Meroditerpenes (**12**-**14**)	HSV-1: EC50 = 128-288 µM	*Soares et al. (2007)*
	Arraial do Cabo, RJ, Brazil	Dichloromethane/Methanol Extract	HSV-1: inhibited 968% of viral replication at 50 µg/mL HSV-2: inhibited 958% of viral replication at 50 µg/mL	*Soares et al. (2012)*
Taonia atomaria	Abuquir, Egypt	Sulfollilipid fraction	HSV-1: inhibited 5625% of viral replication at 20 µg/mL	*El Baz et al. (2013)*
Fucales				
Fucus vesiculosus	Kiel Bay, Germany	Fucoidan	HSV-1: EC_{50} = 17 µg/mL HSV-2: EC_{50} = 11 µg/mL HCMV: EC_{50} = 20 µg/mL	*Baba et al. (1988)*
Himanthalia elongata	Not mentioned	Hexanic extract Ethanolic extract Aqueous extract Fractions with polysaccharides	HSV-1: EC_{50} = 13186 µg/mL HSV-1: EC_{50} = 8324 µg/mL HSV-1: EC_{50} = 10481 µg/mL HSV-1: EC_{50} = 5907 µg/mL	*Santoyo et al. (2011)*
Cystoseira crinita	Bulgarian Black Sea Coast, Bulgaria	Aqueous extract	HSV-1: EC_{50} = 300 µg/mL	*Kamenarska et al. (2009)*
Cystoseira indica	Okha, Gujarat, India	Fractions with polysaccharides	HSV-1: EC_{50} = 28 µg/mL HSV-2: EC_{50} = 13 µg/mL	*Mandal et al. (2007)*
Cystoseira myrica	Bushehr - Persian Gulf, Iran	Filtered and autoclavated aqueous extract	HSV-1: EC_{50} = 99-125 µg/mL	*Zandi et al. (2007)*
Cystoseira usneoides	Portugal	Meroditerpenes (**15**-**18**)	HSV-1: inhibited 100% of viral replication at 10 µg	*Palma et al. (1991)*
Nizamuddinia zanardinii	Chabahr, Stanistan-Balochistan, Iran	Fractions with polysaccharides	HSV-2: EC_{50} = 0027-0607 µg/mL	*Alboofetileh et al. (2019)*
Sargassum cymosum	Cabo Frio, RJ, Brazil	Dichloromethane/Methanol Extract	HSV-1: inhibited 982% of viral replication at 50 µg/mL HSV-2: inhibited 90% of viral replication at 50 µg/mL	*Soares et al. (2012)*
Sargassum fluitans	Playa del Carmen, Quintana Roo, Mexico	Fractions with polysaccharides	HSV-1: EC_{50} = 428 µg/mL	*Bedoux et al. (2017_*
Sargassum hemiphyllum	Hong Kong, China	Aqueous extract	HSV-1: EC_{50} = 191 µg/mL HSV-2: EC_{50} = 125 µg/mL	*Wang et al. (2008)*
Sargassum horneri	Notojima, Japan	Polysaccharides	HSV-1: EC_{50} = 14 µg/mL HCMV: EC_{50} = 85 µg/mL	*Hoshino et al. (1998)*
Sargassum latifolium	Red Sea, Saudi Arabia	Sulfated polysaccharides	HSV-1: inhibited 25-41% of viral replication at 20 µg/mL	*Asker et al. (2007)*
Sargassum naozhouense	Techeng Island, Guangdong, China	Fractions with polysaccharides	HSV-1: EC_{50} = 892 µg/mL	*Peng et al. (2013)*
Sargassum patens	Hong Kong, China	Polysaccharides	HSV-1: EC_{50} = 55 µg/mL HSV-2: EC_{50} = 13 µg/mL	*Zhu et al. (2003)*

Table 1. Contd.

Sargassum polyceratium	Cabo Frio, RJ, Brazil	Dichloromethane/Methanol Extract	HSV-1: inhibited 868% of replication viral at100 µg/mL	*Soares et al. (2012)*
Sargassum thurbergii	Coastal region of South Korea	Methanolic extract	HSV-1: inhibited of viral replication at 200 µg/mL HSV-2: EC_{50} = 18-410 µg/mL	*Kim et al. (1997)* *Lee et al. (2011)*
Sargassum trichophyllum	Noto Peninsula, Japan	Polysaccharides	HSV-1: inhibited 760% of viral replication at 50 µg/mL HSV-2: inhibited 397% of viral replication at 50 µg/mL	*Soares et al. (2012)*
Sargassum vulgare	Cabo Frio, RJ, Brazil	Dichloromeyhane/Methanol Extract		
	Mangaratiba, RJ, Brazil	Sulfollilipid fractions	HSV-1: inhibited 96-999% of viral replication at 50 µg/mL HSV-2: inhibited 999% of viral replication at 50 µg/mL	*Plouguerné et al. (2013)*
Marginariella boryana	Owhiro Bay, Wellington, New Zealand	Fractions with polysaccharides	HSV-1: EC_{50} = 375 µg/mL	*Wozniak et al. (2015)*
Ectocarpales				
Adenocystis utricularis	Comodoro Rivadavia, Chubut Province, Argentina	Fractions with polysaccharides	HSV-1: EC_{50} = 028-2473 µg/mL HSV-2: EC_{50} = 052-3248 µg/mL	*Ponce et al. (2003)*
Leathesia difformis	Las Grutas, Rio Negro Province, Argentina	Fractions with polysaccharides	HSV-1: EC_{50} = 07-31 µg/mL HSV-2: EC_{50} = 05-25 µg/mL HCMV: EC_{50} = 19-75 µg/mL	*Feldman et al. (1999)*
Stilophora tenella	Bulgarian Black Sea Coast, Bulgaria	Aqueous extract Butanolic extract	HSV-1: EC_{50} = 500 µg/mL HSV-1: EC_{50} = 60 µg/mL	*Kamenarska et al. (2009)*
Papenfussiella lutea	Lower Hutt, Wellington, New Zealand	Fractions with polysaccharides	HSV-1: EC_{50} = 075 µg/mL	*Wozniak et al. (2015)*
Punctaria latifolia	Bulgarian Black Sea Coast, Bulgaria	Aqueous extract Butanolic extract Chloroformic extract	HSV-1: EC_{50} = 750 µg/mL HSV-1: EC_{50} = 70 µg/mL HSV-1: EC_{50} = 60 µg/mL	*Kamenarska et al. (2009)*
Colpomenia bullosa	South Korea	Methanolic extract	HSV-1: EC_{50} = 100 µg/mL	*Kim et al. (1997)*
Colpomenia sinuosa	Hong Kong, China	Aqueous extract	HSV-1: EC_{50} = 221 µg/mL HSV-2: EC_{50} = 125 µg/mL	*Wang et al. (2008)*
Hydroclathrus clathratus	Red Sea, El Shoaiba, Saudi Arabia	Carragenan fractions	HSV-1: EC_{50} = 1005 µg/mL	*Gomaa and Elshoubaky (2016)*
	Hong Kong, China	Aqueous extract	HSV-1: EC_{50} = 625 µg/mL HSV-2: EC_{50} < 625 µg/mL	*Wang et al. (2008)*
		Fractions with polysaccharides	HSV-1: EC_{50} = 160 µg/mL HSV-2: EC_{50} < 080 µg/mL	*Wang et al. (2010)*
		Sulphated polysaccharide	HSV-1: EC_{50} = 170 µg/mL	

Table 1. Contd.

	South Korea	Methanolic extract	HSV-1: EC_{50} = 200 µg/mL	*Kim et al. (1997)*
	Bulgarian Black Sea Coast, Bulgaria	Aqueous extract	HSV-1: EC_{50} = 400 µg/mL	*Kamenarska et al. (2009)*
Scytosiphon lomentaria				
	Comodoro Rivadavia, Chubut Province, Argentina	Fractions with polysaccharides	HSV-1: EC_{50} = 076-466 µg/mL HSV-2: EC_{50} = 122-1000 µg/mL	*Ponce et al. (2019)*
Laminariales				
	Wando, South Korea	Modified galactanas	HSV-1: EC_{50} = 242-264 µg/mL	*Kim et al. (2017)*
	Not mentioned	Sulphated fucoidan	HSV-1: EC_{50} = 140 µg/mL HSV-2: EC_{50} = 51 µg/mL HCMV: EC_{50} = 16 µg/mL	*Lee et al. (2004)*
Undaria pinnatifida				
	South Korea	Methanolic extract	HSV-1: EC_{50} = 100 µg/mL	*Kim et al. (1997)*
	Tasmania, Australia	Fractions with polysaccharides	HSV-1: EC_{50} = 10-1280 µg/mL HSV-2: EC_{50} = 0125-40 µg/mL	*Thompson and Dragar (2004)*
	Maizuru, Kyoto, Japan	Ethyl acetate fraction of methanolic extract	EBV: inhibited EBV tumor-inducing activity at 40 µg/mL	*Ohigashi et al. (1992)*
	Tasmania, Australia	Fractions with polysaccharides	HSV-1: EC_{50} = 11-46 µg/mL HSV-2: EC_{50} = 01-10 µg/mL HCMV: EC_{50} = 05-40 µg/mL	*Hemmingson et al. (2006)*
	Not mentioned	Sulfated fucoidan	HSV-1: reduced virus-induced eye lesions in BALB/c mice	*Hayashi et al. (2008)*
	Marlborough Sounds, New Zealand	Fractions with polysaccharides	HSV-1: EC_{50} = 10-71 µg/mL HSV-2: EC_{50} = 05-31 µg/mL	*Harden et al. (2009)*
Laminaria angustata	Okha, Gujarat, India	Fractions with polysaccharides	HSV-1: EC_{50} = 065 µg/mL	*Saha et al. (2012)*
Scytothamnales				
Splachnidium rugosum	Owhiro Bay, Wellington, New Zealand	Fractions with polysaccharides	HSV-1: EC_{50} = 087 µg/mL	*Wozniak et al. (2015)*
Sphacelariales				
Sphacelaria indica	Arabian Sea, Gujarat, India	Polysaccharide	HSV-1: EC_{50} = 130 µg/mL	*Bandyopadhyay et al. (2011)*
Tilopteridales				
Zanardinia prototypus	Bulgarian Black Sea Coast, Bulgaria	Chloroform extract	HSV-1: EC_{50} = 500 µg/mL	*Kamenarska et al. (2009)*

*The names of species obtained in the bibliographic references are used No taxonomic coorections and updates have been made.

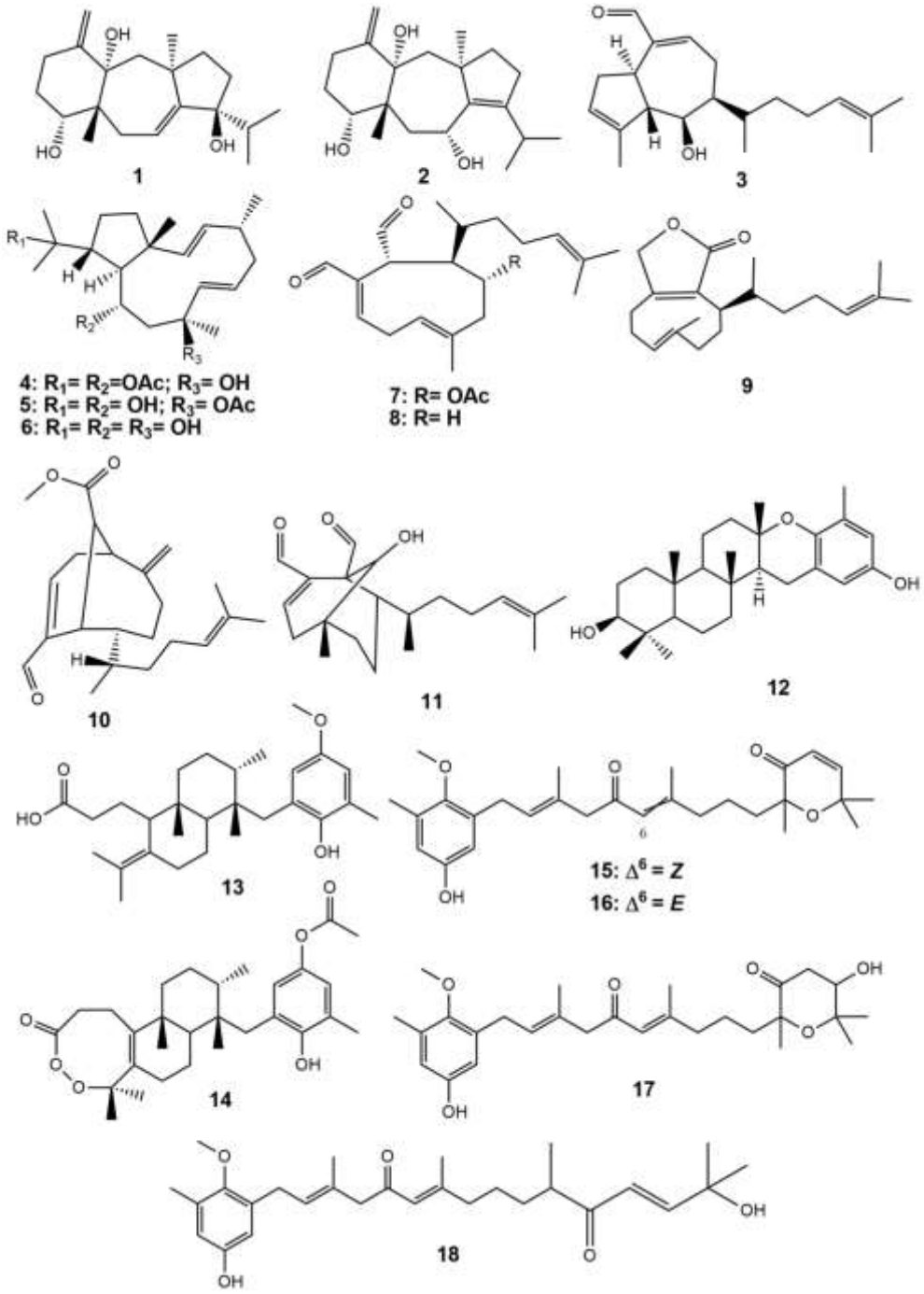

Figure 1. Compounds with antiviral activity against HSV-1 isolated from marine brown algae.

chemical components of *Dictyota pfaffii*, the studies described focused on the anti-HSV-1 activity of isolated dolabelan diterpenes (4-6), which inhibited more than 80% of virus replication *in vitro* (Barbosa et al., 2004). Complementary studies with substance 6 revealed a value of EC50 1.2 µM for trihydroled dolabellane diterpenes (Abrantes et al., 2010), which also showed low acute toxicity in BALB/c mice (Garrido et al., 2011). This evidence points to the potential of this product as an effective and safe antiviral.

Three diterpenes of the xeniane type (7-9) and one of the dichotomane type (10) were also isolated from the species *Dictyota linearis* collected in Greece, but none of them presented good anti-HSV-1 activity at the concentration of 100 µg/mL (Siamopoulou et al., 2004). Interestingly, another diterpene of the dichotomane type

(11) isolated from the *Dictyota menstrualis* from the Coast of Rio de Janeiro presented a potent anti-HSV-1 action *in vitro* (EC50 = 1.6 µM), inhibiting initial events of viral replication (Abrantes et al., 2010). However, the dichloromethane-methanol extract of this seaweed collected in a different region from Rio de Janeiro State showed low activity against this virus at 12.5 µg/mL (Soares et al., 2012).

Soares et al. (2007) also isolated three meroditerpenes (12-14) from the fractionation of dichloromethane extract from *Stypopodium zonale*, collected off the coast of the state of Rio de Janeiro, with excellent anti-HSV-1 activity (EC50 = 1.34, 1.28 and 2.38 µM, respectively) (Soares et al., 2007). Subsequently, the same group investigated the anti-HSV action of extracts obtained with dichloromethane-methanol mixture of several other brown algae collected in the same Brazilian state. Among them, the extracts of the species *Dictyopteris delicatula*, *Padina gymnospora* and *Stypopodium zonale* were able to inhibit the *in vitro* replication of both HSV-1 and HSV-2, while the extract of the species *Lobophora variegata* inhibited only the replication of HSV-1 (Soares et al., 2012). Another group also investigated the antiviral action of the aqueous extract of the last species and *Padina australis*, which presented moderate to potent activity against HSV-1 and HSV-2, indicating the presence of structurally diverse and still promising metabolites in the same species (Wang et al., 2008).

The species *Padina tetrastromatica* and *Stoechospermum marginatum* were collected in different regions of India and the antiviral potential of polysaccharides fractions were investigated. For the latter species, a fraction was obtained with sulfated polysaccharides formed mainly by fucose, but also by xylose and galactose units, similar to that reported for the studied fraction of *D. dichotoma*, which presented potent activity against HSV-1 and HSV-2 (Adhikari et al., 2006; Rabanal et al., 2014). Different fractions of sulphated polysaccharides from the seaweed *P. tetrastromatica* were evaluated and shown to be slightly more potent than the fraction of *S. marginatum*. The reason is probably related to the fact that the two species have a similar composition rich in fucose, xylose and galactose units, though *P. tetrastromatica* has a higher content of xylose and galactose (Karmakar et al., 2010).

In addition to secondary metabolites and polysaccharides, the class of sulfolilipids of this order was investigated. For example, sulfolilipid fractions of the algae *Dilophus fascíola* and *Taonia atomaria* were obtained and demonstrated the ability to inhibit *in vitro* replication of HSV-1 in 70.12 and 56.25%, respectively. Among the fractions, two major sulfollilipids were identified: sulfochinovosil-di-acylglycerol (SQDG) and sulfoquinovosil-acylglycerol (SQMG), which were previously isolated in other algae and shown to have activity against HSV-1 and HCMV (Chirasuwan et al., 2007; El Baz et al., 2013).

Order Fucales

The order Fucales presents the second largest number of species among brown algae, consisting of a total of nine families, which include 91 genera and 560 species (Guiry and Guiry, 2020). Among these, the genus *Sargassum* of the family Sargassaceae is the one with the highest number of species among the genera of brown algae and is widely distributed in tropical and subtropical regions (Mattio and Payri, 2011; Széchy and Paula, 2000).

Currently, 11 species of this genus have been described as sources of products with antiviral activity against herpesvirus (Table 1). For example, the methanolextract of *Sargassum thurbergii* inhibited the replication of HSV-1 *in vitro* to 200 µg/mL (Kim et al., 1997), while the aqueous extract of *Sargassum hemiphyllum* inhibited not only the replication of this virus, but also of HSV-2, with EC50 values of 19.1 and 12.5 µg/mL, respectively (Wang et al., 2008). In addition to these, Soares et al. (2012) also evaluated the antiviral potential of dichloromethane-methanol extracts from species collected in Cabo Frio-RJ, Brazil, against HSV-1 and HSV-2 strains resistant to acyclovir. Their analysis included, for instance, *Sargassum cymosum*, *Sargassum polyceratium* and *Sargassum vulgare*. The dichloromethane-methanol extracts were tested at different concentrations due to their different maximum non-cytotoxic concentrations and, in these conditions, all showed good activity against HSV-1 (inhibition percentage ranged from 76 to 98.2%). However, only the extracts of *S. cymosum* showed good activity against HSV-2, while the extract of *S. vulgare* showed weak antiviral activity (90 and 39.7% inhibition of viral replication), respectively (Soares et al., 2012).

In Mangaratiba-RJ, Brazil, two fractions of sulfolilipids extracted from *S. vulgare* were able to inhibit the replication of HSV-1 and HSV-2 at 50 µg/mL. The fractions contained SQDG analogues (sulfochildiacilglyceróis) with variable hydrocarbon chain sizes, indicating a promising source of new antiviral agents (Plouguerné et al., 2013).

As noted for the order Dictyotales, many groups focused their efforts on the extraction of primary metabolites such as polysaccharides and more polar fractions related from species of the genus *Sargassum*. Polysaccharide fractions of *Sargassum fluitans* and *Sargassum naozhouense* showed moderate to potent activity against HSV-1 (EC50 = 42.8 and 8.92 µg/mL, respectively). Despite this difference, both fractions consist mainly of fucanes, carrageenans or alginates (Bedoux et al., 2017; Peng et al., 2013).

Meanwhile, different polysaccharides were isolated from algae of this genus and showed antiviral activity. Among them, three sulfated polysaccharides isolated from *Sargassum latifolium* composed mainly of glucose and glycuronic acid showed anti-HSV-1 activity from weak to moderate, inhibiting viral replication from 25 to

Table 2. Most promising candidates in the studied orders of brown macroalgae.

Order	Species	Results	Products or extract fractions	Virus type
Dictyotales	*Padina tetrastromatica*	EC_{50} = 074-105 µg/mL	Polysaccharides fractions	HSV-1
		EC_{50} = 030-039 µg/mL		HSV-2
Fucales	*Fucus vesiculosus*	EC_{50} = 20 µg/mL	Fucoidan	HCMV
	Nizamuddinia zanardinii	EC_{50} = 0027-0607 µg/mL	Polysaccharides fractions	HSV-2
Ectocarpales	*Adenocystis utricularis*	EC_{50} = 028-2473 µg/mL	Polysaccharides fractions	HSV-1
		EC_{50} = 052-3248 µg/mL		HSV-2
	Leathesia difformis	EC_{50} = 07-31 µg/mL	Polysaccharides fractions	HSV-1
		EC_{50} = 05-25 µg/mL		HSV-2
		EC_{50} = 19-75 µg/mL		HCMV
	Papenfussiella lutea	EC_{50} = 075 µg/mL	Polysaccharides fractions	HSV-1
Laminariales	*Undaria pinnatifida*	EC50 = 072 µg/mL	Polysaccharides fractions	HSV-1
		EC50 = 0125-0140 µg/mL	Sulphated Galactofucan sulfatada	HSV-2
		EC50 = 01-10 µg/mL	Polysaccharides fractions	HSV-2
		EC50 = 05-40 µg/mL	Ethyl acetate fraction of methanolic extract	HCMV
		Inhibited EBV tumor-inducing activity at 40 µg/mL	-	EBV

41% at a concentration of 20 µg/mL (Asker et al., 2007). The polysaccharide isolated from *Sargassum horneri* and composed of fucoses showed potent activity against HSV-1 and HCMV (EC50 = 1.4 and 8.5 µg/mL, respectively) (Hoshino et al., 1998). A sulfated polysaccharide rich in fucose, galactose, glucose and mannose isolated from *Sargassum patens* inhibited the replication of HSV-1 and HSV-2 (EC50 = 5.5 and 1.3 µg/mL, respectively) (Zhu et al., 2003). On the other hand, a sulfated polysaccharide consisting of fucose and galactose units was able to inhibit only the replication of HSV-2, especially when the cells were treated with the substance at the time of infection (EC50 = 18 µg/mL) and not after infection (EC50 = 410 µg/mL) (Lee et al., 2011).

Still considering the family Sargassaceae, polysaccharides fractions were obtained from the species *Nizamuddinia zanardinii* and *Cystoseira indica*, which presented potent action against HSV-2, with Values of EC50 ranging from 0.027 to 1.3 µg/mL (Table 1) (Alboofetileh et al., 2019; Mandal et al., 2007). The fractions of the first species are composed of polysaccharides rich in fucose and galactose, while the fraction obtained from the second species is composed mostly of polysaccharides formed by fucose units. Despite the slightly reduced activity of this last fraction against HSV-2, it presented activity against HSV-1 (EC50 = 2.8 µg/mL) (Mandal et al., 2007). Still, it is noteworthy that it is not clear whether the fractions of *N. zanardinii* have action against HSV-1, since tests against this virus have not been reported. Despite the antiherpetic action commonly found for polysaccharide fractions, the aqueous extracts of *Cystoseira crinita* and *Cystoseira myrica* species showed a weak activity, with EC50 ranging from 99 to 300 µg/mL (Kamenarska et al., 2009; Zandi et al., 2007). This may be related to the low concentration of polysaccharides important for antiviral action in the extract. From dichloromethane-methanol

extracts of *Cystoseira usneoides*, four meroditerpenes (15-18) (Palma et al., 1991) were isolated, identified and revealed that these substances are able to completely inhibit the replication of HSV-1 *in vitro* when discs with 10 µg were used (Table 1). However, it would be useful to redo the test with standardized methods in the antiviral activity literature in order to allow for comparison with other isolated products or extracts.

Products obtained from algae from other families of this order were also investigated (Table 1). As an example, a fucoidana extracted from *Fucus vesiculosus* presented a broad antiviral spectrum against human herpesviruses, with EC50 of 1.7 µg/mL for HSV-1, 1.1 µg/mL for HSV-2, and 2.0 µg/mL for HCMV (Baba et al., 1988; Yasuhara-Bell and Lu, 2010). The polysaccharide fraction of *Marginariella boryana* was composed mainly of fucose and xylose units and inhibited the replication of HSV-1 *in vitro* with an EC50 of 3.75 µg/mL (Wozniak et al., 2015). The polysaccharide fraction of the seaweed *Himanthalia elongata* (Himanthaliaceae), rich in fucose and glucose, presented moderate antiviral activity against HSV-1 (EC50 = 59.07 µg/mL). The fact that this fraction showed a more potent activity than the other extracts tested (hexic, ethanolic and aqueous) suggests that polar substances, such as polysaccharides, may be involved in this antiviral activity (Santoyo et al., 2011).

Order Ectocarpales

The order Ectocarpales has the highest number of species among brown algae, with 770 species, 204 genera and nine families. The Chordariaceae family is the largest, containing 151 genera (Guiry and Guiry, 2020). Kim et al. (1997) conducted a screening of 89 algae of different classes, collected in British Columbia, Canada and Korea. The methanol extracts of three brown algae species had good anti-HSV1 results, one of which was *Colpomenia bullosa*. To obtain a greater amount of potent photosensitive bioactives, as observed by Hudson and Towers (1991) in terrestrial plants, a modification was introduced in the antiviral test technique. The cultivation plates were exposed to light in wavelength in the range of 320 to 600 nm. The extract from *C. bullosa* inhibited the viral replication of HSV-1 with EC50 values of 100 µg/mL (Table 1) and was not cytotoxic (Kim et al., 1997). The aqueous extract of sinuous *Colpomenia* had a higher inhibition of viral replication than the *C. bullosa* extract for HSV-1, with EC50 value of 22.1 µg/mL (Table 1). This efficiency was even higher for HSV-2 with a value of EC50 equal to 12.5 µg/mL (Table 1) (Wang et al., 2008).

Leathesia difformis collected in Las Grutas (Argentina) is a cosmopolitan brown seaweed and produces large amounts of extractable fucoidans with 80% heated ethanol. Three isolated fractions of fucoidans were found as antiviral agents against herpes simplex virus (HSV) types 1 and 2 and human cytomegalovirus (HCMV). All compounds were considered inhibitors for both HSV serotypes and HCMV, with HSV-2 being the most susceptible virus. However, one of the fractions was more active, with IC50 values in the range 0.5 to 1.9 µg/mL (Table 1) without affecting cell viability at concentrations of up to 400 µg/mL. The mode of action of this fraction was attributed to an injunction on adsorption of the virus in the host cell (Feldman et al., 1999).

Extraction of fucoidans with three different solvents, distilled water, 2% calcium chloride solution and dilute hydrochloric acid solution (pH 2) were obtained for analysis at room temperature and at 70°C. Two different types of fucoidans are present in this seaweed, the galactofucan, with the predominance of fucose and uronofucoidans which have other monosaccharides and high amounts of uronic acids. Galactofucanos have excellent inhibiting activity against herpes simplex virus 1 and 2, without cytotoxicity, while uronofucoidanas do not have antiviral activity. The room temperature extracts present considerable activity against HSV-1 and HSV-2, with EC50 values of 0.28 and 0.52 µg/mL (Table 1), respectively, and without cytotoxicity with CC50>1000 µg/mL (Ponce et al., 2003).

Brown algae were collected off the Bulgarian coast of the southern part of the Black Sea for antiviral tests against HSV-1. Three species were selected: *Stilophora tenella*, *Punctaria latifolia* and *Scytosiphon lomentaria*. Extracts with water, n-butanol and chloroform were performed, which did not obtain good inhibiting activity for HSV-1. The results of EC50 ranged from 60 µg/mL (Table 1) for the butancholic extract of *S. lomentaria* and the chloroform extract of *P. latifolia*, up to 750 µg/mL (Table 1) for the aqueous extract of *P. latifolia* (Kamenarska et al., 2009).

Wang et al. (2008) obtained aqueous extract and its sulfated polysaccharides from *Hydroclathrus clathratus* seaweed with good antiviral results against HSV-1 with EC50 values ranging from 6.25 to 1.60 µg/mL, and against HSV-2 an EC50 ranging from >6.25 to < 0.80 µg/mL (Table 1). In 2010, the same group continued studies with a purified polysaccharide called HC-b1 (sulfated polysaccharide with high molecular weight), which presented the most potent anti-HSV activity, with an EC50 of 1.70 µg/mL (Table 1). The polysaccharide showed a dose-dependent inhibition and virucidal action without toxicity and was able to protect Vero cells from HSV-1 infection when the cells were incubated with HC-b1 before exposure to the virus. HC-b1 was also shown to be a good inhibitor to the acyclovir-resistant HSV-1 strain and the clinical strain. Studies on the mechanism of antiviral action have shown that HC-b1 can inhibit the adsorption and penetration of HSV into cells (Wang et al., 2010). In another study with hot water extract of *H. clathratus*, carnagenan sulfated polysaccharides were obtained, which also presented antiviral activity with HSV-1 inhibition with an EC50 of 100.50 µg/mL (Table 1)

and low cytotoxicity.

The Herpesvirus HSV-1 induces the formation of abnormal molecules (abnormally phosphorylated beta-amyloid, AD-Like tau) characteristics of the brain with Alzheimer's disease. The *Papenfussiella lutea* extract (fucan sulfate) showed strong antiviral activity with EC50 of 0.75 µg/mL (Table 1), and prevented the accumulation of beta-amyloid and AD-Like tau induced by the HSV-1 virus.

Extracts of methanol, chloroform, n-butanol and aqueous extracts of the seaweed *S. lomentaria* obtained an unsatisfactory or non-existent inhibiting activity against the HSV-1 virus (Kim et al., 1997; Kamenarska et al., 2009). In the study with methanol extract, even with a technical modification in the antiviral test where the culture plates were exposed to light (wavelength in the range of 320-600 nm), the EC50 was 200 µg/mL (Table 1) (Kim et al., 1997). In chloroform extracts, n-butanol antiviral activity against HSV-1 was non-existent, and in the aqueous extract the activity was unsatisfactory with an EC50 of 400 µg/mL (Table 1) (Kamenarska et al., 2009). However, Ponce et al. (2019) obtained good results on antiviral activity with polysaccharides fractions of methanol extract, which inhibited HSV-1 with EC50 ranging from 0.76 to 4.66 µg/mL and HSV-2 with EC50 ranging from 1.22 to 10 µg/mL (Table 1).

Order Laminariales and order Scytothamna

Among the orders of brown macroalgae, the order Laminariales has the fourth largest number of species, having 137 species in seven families and 57 genera (Guiry and Guiry, 2020). The species with the highest number of studies on antiherpetic potential was *Undaria pinnatifida*, which belongs to the order Scytothamnales (Table 1). In 1992, the antiherpetic activity of this species was reported for the first time in the ethyl acetate fraction of the methanol extract, which significantly inhibited the tumor-inducing activity of Epstein-Barr virus (EBV) at 4 µg/mL (Table 1) (Ohigashi et al., 1992).

Subsequently, Kim et al. (1997) determined the anti-HSV-1 activity of the methanol extract of this species collected in the coastal region of South Korea, which presented an EC50 of 100 µg/mL (Table 1). Next, the same research group investigated the antiviral mechanism of action of this extract. It was observed that the methanolic extract of *U. pinnatifida* has virucide action. The antiviral activity seems to depend on photosensitizing substances given that it increased in the presence of UVA (Hudson et al., 1999). More recently, galactans isolated from *U. pinnatifida* collected in another region of South Korea were chemically modified and showed promising activity against HSV-1 (EC50 ranging from 2.42 to 2.64 µg/mL) (Kim et al., 2017).

The antiherpetic potential of *U. pinnatifida* collected in other regions of the world has also been reported (Table 1). For example, a sulfated galactofucan extract with 75% purity was obtained from this species collected in Australia, which was able to inhibit the replication of several clinical strains of HSV-1 (EC50= 1.0-128.0 µg/mL) and HSV-2 (EC50= 0.125-4.0 µg/mL) (Thompson and Dragar, 2004). A fraction of this extract was obtained in order to achieve a product of higher purity. The fraction was composed mainly of fucopiranosyl and galactopiranosyl and its activity was similar to the original extract against three human herpesviruses (HSV-1, HSV-2 and HCMV) (Hemmingson et al., 2006).

Additionally, studies with products of *U. pinnatifida* collected in the Marlborough Sounds region, New Zealand, have also been published (Table 1). Harden et al. (2009) reported the potent activity of different polysaccharide extracts against HSV-1 (EC50= 1.0-7.1 µg/mL) and HSV-2 (EC50= 0.5-3.1 µg/mL), with significant virucide activity. It was then determined that these extracts were composed mostly of fucoidans. One of them was able to significantly inhibit the formation of β-amyloid and AD-Like tau plaques induced by HSV-1 in Vero cells (Wozniak et al., 2015).

Lee et al. (2004) also reported the isolation and purification of a sulfated fucoidan from the *U. pinnatifida*, although the collection site was not specified. This product showed a powerful injunction on the *in vitro* replication of HSV-1, HSV-2 and HCMV. Furthermore, it was also observed that it reduces ocular lesions caused by HSV-1 in BALB/c mice (Table 1) (Lee et al., 2004; Hayashi et al., 2008). A fraction of xylogalactofucan polysaccharide was isolated from the Aghast Laminaria seaweed and also evaluated against the replication of HSV-1 (EC50= 0.65 µg/mL) (Saha et al., 2012).

The order Scytothamnales, which has eight species with six genera in three families (Guiry and Guiry, 2020), has only one species (*Splachnidium rugosum*) studied as antiviral potential, having a fraction of polysaccharides analyzed (Table 1). As for other species among the Phaeophyceae, a potent antiviral action of this fraction was observed against HSV-1 (EC50= 0.87 µg/mL) (Wozniak et al., 2015), which encourages the study of other species of this order as a source of new antiviral products.

Order Sphacelariales and order Tilopteridales

The order Sphacelariales comprises six families and corresponds to the fifth order with the highest number of species (total of 103) among brown algae, with six families and 24 genera (Guiry and Guiry, 2020; Silberfeld et al., 2014). From the species, *Sphacelaria indica* (Sphacelariaceae) collected in India, a polysaccharide rich in fucose, galactose and xylose was extracted and evaluated against the HSV-1 KOS strain using the RC-37 cell line (African green monkey kidney cells). This substance presented a potent antiviral activity (EC50 =

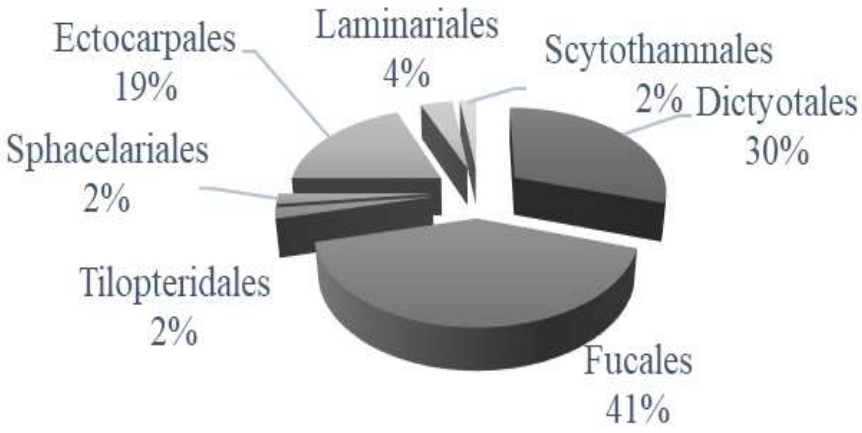

Figure 2. Distribution between orders of Phaeophyceae of extracts with antiviral activities against human herpesviruses.

1.3 µg/mL) with a selectivity index of approximately 154. Later, other experiments have shown that this polysaccharide has a virucide action, since pre-incubation with the virus results in antiviral action and treatment after infection does not inhibit the virus (Bandyopadhyay et al., 2011).

The order Tilopteridales presents a total of 21 species in four families and 21 genera (Guiry and Guiry, 2019; Silberfeld et al., 2014). Kamenarska et al. (2009) obtained the chloroform extract from *Zanardinia prototypus* (Cutleriaceae) seaweed and evaluated it against hsv-1 in mdbk cell lineage. The extract showed moderate anti-HSV-1 activity, with EC50 of 50 µg/mL and a selectivity index 14.4. These results demonstrated a good selective activity against the virus compared to the host cell according to pre-established standards (Kamenarska et al., 2009). Future studies seem interesting to investigate the natural products responsible for the observed antiviral activity. It is also important to evaluate other extracts and fractions, since this species and others of the same family and order have not yet been widely studied.

The studies presented in this review reinforce the role of brown macroalgae as important sources of new bioactive products against human herpesvirus (Figure 2). To date, the order Fucales has been the main target of these studies, with antiviral products obtained from 19 species (41% of total). Different products were explored, such as lipid extracts and terpenes isolated from *Cystoseira* species. Hydrophilic extracts and fractions and sulfated polysaccharides stand out as they presented antiviral activities against three different herpesviruses (HSV-1, HSV-2 and HCMV).

Nevertheless, further studies on the isolation and structural elucidation of bioactive metabolites were predominantly observed for the order Dictyotales, which presents the second largest number of studied species (14 species, 30% of the total). In addition to hydrophilic and lipophilic extracts and fractions, 11 diterpenes were isolated from 6 distinct species, most of them from the *Dictyota* genus. The products obtained from algae of this order were explored against two herpesviruses HSV-1 and HSV-2. The species of other orders seem to have a lower importance in the search for new antivirals; however, this may be the result of other factors, besides the absence of antiviral metabolites present in this species.

Apparently, the antiviral activity observed for lipophilic extracts (hexane and dichloromethane) is associated with the presence of metabolites of the terpene class, especially diterpenes (isolated from *Dictyota* spp.) and meroditerpenes (*S. zonale*) with a phenolic group. On the other hand, hydrophilic extracts (aqueous, ethanolic and methanolic) present sulfated polysaccharides as the main antiviral components, which may be acting directly on the viral particle or the adsorption stage.

The species with the best result for the antiviral activity against HSV-1 is *Adenocystis utricularis* of the order Ectocarpales, with EC50 of 0.28 µg/mL. The species *N. zanardinii* of the order Fucales was the most effective against HSV-2, with EC50 of 0.027 µg/mL. The species *U. pinnatifida* of the order Laminariales had the best result against HCMV, with EC50 of 0.5 µg/mL. For the Epstein-Bar virus, only one study with the species, namely *U. pinnatifida*, showed inhibition of tumor-inducing activity at 4 µg/mL.

Conclusion

Based on the work described in this review, it is clear that brown marine algae is endowed with variety structurally and chemically diverse metabolites having an great potential antiherpetic activity.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

ACKNOWLEDGEMENTS

The authors thank the support of the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) for the productivity grants (Proc 43930/2014-7- ICNP and 301964/2018-1 –VLT) and FAPERJ (Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro -Proc E-26/201442/2014 - ICNP and E-26/202794/2018 - VLT) VWR and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) for the doctoral scholarship.

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