https://dx.doi.org/10.21577/0103-5053.20230012

J. Braz. Chem. Soc., Vol. 34, No. 4, 485-501, 2023

Review

Marine Natural Products in the Battle against Dengue, Zika, and Chikungunya Arboviruses

Thayssa S. F. Fagundes,[a] Thatyana R. A. Vasconcelos,[a] Fernando M. dos Santos Junior,[a] Bia F. Rajsfus,[b,c] Diego Allonso,[c] José C. J. M. D. S. Menezes,[d,e] Alessandra L. Valverde[*,a] *and Vinicius R. Campos*[*,a]

[a]*Departamento de Química Orgânica, Instituto de Química, Universidade Federal Fluminense, 24020-141 Niterói-RJ, Brazil*

[b]*Instituto de Biofísica Carlos Chagas Filho, Universidade Federal do Rio de Janeiro, 21941-170 Rio de Janeiro-RJ, Brazil*

[c]*Departamento de Biotecnologia Farmacêutica, Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, 21941-170 Rio de Janeiro-RJ, Brazil*

[d]*Faculty of Pharmaceutical Sciences, Nagasaki International University, 2825-7 Huis Ten Bosch, 859-3298 Sasebo, Nagasaki, Japan*

[e]*Research & Development, Esteem Industries Pvt. Ltd. (III), 403-529 Bicholim, Goa, India*

Arthropod-borne viruses (arboviruses) are a severe public health problem worldwide, consisting of a significant part of all the emerging infectious diseases. It is estimated that arboviruses infect hundreds of millions of people globally each year, resulting in several thousand deaths. Despite their clear health threat, there are no prophylactic or pharmacological therapies available for most of them. Control of arbovirus infections is beyond pharmacological options; handling the larvae of mosquitos is an important and successful strategy, although currently available insecticides and larvicides are already associated with resistance. Therefore, searching for new strategies to prevent arbovirus infection is urgent and necessary. Marine organisms are an excellent source for structurally novel compounds due to their unique secondary metabolism, with outstanding antiviral and larvicidal activities. In the present review, we explored the ability of various marine natural products (MNPs) such as indole derivatives, diketopiperazines, scequinadoline A, cyclohexadepsipeptides, and others, to act as both antiviral and larvicidal, in an attempt to highlight their structure activity potential against the most relevant arboviruses affecting the human health.

Keywords: Dengue, Zika, Chikungunya, arbovirus, *Aedes aegypti*, marine natural products

1. Introduction

Arthropod-borne viruses (arboviruses) can be defined as viruses that depend on an intermediate invertebrate host (also known as a vector), generally, mosquitoes, flies, or ticks, which later will infect a vertebrate (avian or mammals) and complete their transmission cycle. The majority of arboviruses circulate in nature in a sylvatic enzootic cycle in which the vertebrate hosts are usually primates, rodents, or birds.[1] However, the fast-paced environmental changes, due to globalization, unplanned urbanization in either underdeveloped or in developed countries, and their poor sanitary conditions have enabled the propagation of the vector and adaptation to new territories and urban zones as well as to a new vertebrate host. Consequently, recurrent outbreaks of medium and large impact in which humans are the main host have become a reality, characterizing, the urban cycle.[2]

Arboviruses can be classified according to their main clinical outcome into three types, hemorrhagic, encephalitic, or arthritogenic. In general, each of their infections results in a myriad of symptoms, varying from asymptomatic to mild and moderate cases that can evolve into chronic, severe, and/or potentially fatal manifestations. Prognostic factors are still under discussion,[3,4] but it is known that the virus

*e-mail: alessandravalverde@id.uff.br; viniciuscampos@id.uff.br
Editor handled this article: Paulo Cezar Vieira

strain and its genotype, as well as the host's immunological and serological background significantly contribute to the severity. Clinical management of arbovirus infections relies mainly on pain relief, generally by administration of analgesics and/or anti-inflammatory drugs.[5-10] Currently, it is estimated that more than 3.9 billion people distributed in more than 129 countries are susceptible to one or more arbovirus infections, which results in more than 100 million symptomatic infections and 40,000 deaths each year worldwide.[7,10-14] Therefore, it is undeniable that arbovirus infections have a social and economic impact and represent a serious public health concern. The absence of an effective vaccine or specific antiviral drug makes the pursuit of new therapeutic and prophylactic strategies imperative. Although several potential drug candidates were already described in the literature, just a few have entered clinical trials,[15] highlighting the necessity for continuous investments in promising compounds with anti-arbovirus activity.

Up to date, more than 450 species of arboviruses have already been described, which are grouped into three distinct families (*Flaviviridae*, *Togaviridae*, and *Bunyaviridae*) and 5 genera (*Flavivirus*, *Alphavirus*, *Orthobunyavirus*, *Phlebovirus*, and *Nairovirus*).[1] Flavivirus, which include Dengue virus (DENV), yellow fever virus (YFV), Zika virus (ZIKV), Japanese encephalitis virus (JEV) and others, and alphaviruses, which have Chikungunya virus (CHIKV), Mayaro virus (MAYV) and Sindbis virus (SINDV) among its members, are the most relevant genera of arboviruses that infect humans. These are endemic in at least half of the world's territory and are responsible for frequent outbreaks with high morbidity and mortality rates. Despite that, only two vaccines, one against DENV and the other for JEV, have already been approved for human immunization, although their use is limited to a small subset of the at-risk population.[16-18] Among flaviviruses, DENV is by far the most relevant to human health. It is estimated that 390 million people are infected annually by one of the four DENV serotypes. Although most cases are asymptomatic, symptomatic manifestation occurs in more than 96 million people, in which self-limited high fever, headache, retro-orbital pain, muscle and joint pain, and cutaneous rash are the most reported symptoms.[5,19] It is expected that 10 to 15% of symptomatic dengue patients evolve to severe dengue, which is characterized by moderate to severe vascular leakage, bleeding and organ impairment, resulting in dozens of thousands of deaths each year.[20] Furthermore, ZIKV is also considered an important public health problem due to its potential to cause encephalopathies. It was originally discovered in 1947 in the Zika forest in Uganda, Africa, and circulated in the African and Southeast Asian territories until 2007. Later it reached Micronesia and rapidly propagated to the Pacific islands.[21-24] This virus emerged in the Americas in 2015 and led to relevant outbreaks of Zika fever (ZIKF) in Brazil and 33 other countries in the following two years.[13,25,26] It was postulated that at least one hundred million people have already been infected by ZIKV, which shares clinical symptoms with DENV and CHIKV.[11] Adult patients usually exhibited a sudden onset of high fever, myalgia and arthralgia, conjunctivitis, and rash. A minor percentage of infected patients develop Guillain-Barre syndrome (GBS), which is an autoimmune disease associated with peripheral nerve inflammation that leads to muscle weakness and paralysis.[9] ZIKV infection is potentially dangerous in pregnant women because of its ability to cross the placenta and infect the fetus, which might culminate in abnormal cerebral development, microcephaly, and fetal demise.[8,13] Among the alphaviruses, CHIKV is the biggest threat to health authorities. Although less life-threatening than the abovementioned viruses, 90% of infected people are symptomatic, severe and disabling arthralgia is the most relevant symptom. Approximately 40% of CHIKV patients evolve into chronic infections that can last several years, exhibiting an impactful social and economic burden.[10] Recent surveillance reports[27] have alerted to an increased mortality case due to CHIKV infection, making the effort to find a therapeutic strategy to control it more pressing. Either DENV, ZIKV, and CHIKV are transmitted by mosquitoes from *Aedes* genera, mainly *Aedes aegypti* and *Aedes albopictus*. These mosquitoes are very domesticated and endemic in all tropical and temperate zones. Management of arbovirus infections goes beyond the development of antivirals and vaccines. Vector control is the most used and interesting approach nowadays. Several strategies are currently ongoing to impair the transmission of arboviruses, either by using insecticides/larvicides or by the release of mosquitoes containing the endosymbiotic bacterium *Wolbachia pipientis* into nature.[28-30] Despite being promising, these approaches are limited either by the development of resistance to available insecticides/larvicides or by virus evolution to escape from antiviral activity exerted by *Wolbachia*.[31,32] Therefore, searching for new compounds with insecticides/larvicidal activity is extremely important in the fight against these viruses. Novel scaffolds based on natural products with antimicrobial potential can provide new drugs.[33,34]

Marine microorganisms, algae, corals, and even mangrove plants live in demanding environmental conditions that favor the production of secondary metabolites. These compounds are closely related to ecological functions, acting as chemical mediators in the interactions between

the organism and the biotic or abiotic environment.[35] Thus, marine organisms are an excellent source of structurally new compounds that may present diverse bioactivities and biotechnological applications.[36] There are two classic drugs, which were inspired by nucleosides isolated from the marine sponge *Tectitethya crypta* and marked the beginning of the use of this class of drugs for the treatment of tumors and viral diseases.[35] In addition, biological vector control is an ecological and sustainable method since it is associated with a slow rate of insect resistance development.[37] Because of this, more and more researchers are in search of bioactive marine compounds. In a recent review, Carroll *et al*.[38] reported a total of 1490 new compounds of marine origin described in 440 papers, only in 2019. However, it is believed that there is still much to be explored in terms of aquatic biodiversity.

Although the initial studies[39] have focused on compounds of sessile invertebrates, lately, marine microorganisms are valuable due to the demand for a more sustainable marine biotechnology. These organisms produce a plethora of secondary metabolites with less rigorous ethical and environmental requirements for research and development.[40] Despite this, macroorganisms have not ceased to be a source for research into new natural metabolites.[36]

Antiviral and insecticidal/larvicidal potential are among the various biological activities investigated and pointed out as promising in marine metabolites and their derivatives.[41-45] In this scenario, the knowledge of marine natural products (MNP) with the potential to combat Dengue, Zika, and Chikungunya viruses and their vectors would certainly help to leverage promising candidates for advanced stages of development of these biomaterials.

Due to the importance of new drugs to combat arboviruses, as well as our interest in marine natural products,[46-51] we summarized the most relevant scientific and technical literature on MNP with antiviral and larvicidal activity against Dengue, Zika and Chikungunya and their main vector *Aedes aegypti*.

2. Research Methodology

This review selected literature data described until August 2021. Extensive research was developed in SciFinder® and Web of Science™ databases using different combinations of the following keywords: "marine", "algae", "mangrove", "dengue", "zika", "chikungunya", "*Aedes aegypti*" and "activity".

The records were exported to the EndNote X4 program and duplicates have been removed. The screening was carried out, to exclude review articles, conference papers, book chapters, and only abstracts. After, the papers were manually grouped according to the type of marine organisms involved: microorganisms, algae, mangrove plants, and miscellaneous.

A careful investigation into the content of the papers was carried out. The inclusion criteria comprised studies that reported activity of extracts, fractions, or substances isolated from marine organisms with activity against Dengue, Zika, and Chikungunya viruses, or larvicidal/insecticide activity against *Aedes aegypti*. Articles outside these approaches were excluded for irrelevance. In the end, a total of 75 articles were selected: microorganisms (25), seaweeds (20), mangrove plants (17), and miscellaneous (13). However, in this review, we have described results for isolated substances, extracts with major metabolites identification, and nano encapsulated extracts. We also highlight the structure activity relationship in cases where it was clearly studied. Activity results for other extracts will be presented in the Supplementary Information section to assist future research in this area.

3. Marine Microorganisms

Marine microorganisms, including bacteria and fungi, are of considerable importance as rich sources of novel secondary metabolites that could be used as lead compounds for new larvicidal and/or antiviral agents.[52-54] According to Carroll *et al*.,[55] a transformation in MNPs research occurred in 2018 with a very significant increase in the number of new compounds reported from microorganisms. Comparing 2015 with 2018, there was an increase in the isolation of new MNPs from marine bacteria, fungi, and cyanobacteria by 22, 85, and 61%, respectively. In 2021 the same authors published a review[38] covering MNPs isolated in 2019 and the study of marine fungi metabolites from microorganisms is still increasing, unabated. In 2019, fungal MNPs represented almost half (47%) of the total new MNPs reported.

Some of these marine species live in high-pressure, high-salt, and low-temperature environments, which provide the opportunity for them to produce unique active substances that differ from the terrestrial ones.[56] Fungi are already used widely in agricultural fields as control agents against plant pathogens.[57] Thus, they are more likely to be perceived as a source of environment-friendly compounds. Although studies with microorganisms continue to increase, the evaluation of these metabolites in the antiviral and larvicidal activity against arboviruses is still scarce. Tables 1 and 2 show the results of the larvicidal and antiviral activities of substances isolated from these microorganisms.

Table 1. Larvicidal activity of marine microorganisms against *Aedes aegypti* mosquito

Species	Organism	Extract	Larvicidal activity	Major compounds	Reference
Bacillus licheniformis	bacteria	EtOH	LC_{50} = 79.28 μg mL^{-1}[a]	polysaccharides	58
Penicillium brefeldianum	fungi	EtOAc	LC_{50} = 452.00 μg mL^{-1} LC_{50} = 337.00 μg mL^{-1}	paspaline (**1**) fumitremorgin A (**2**)	59
Mix of *Trichoderma harzianum* and *Penicillium breviflora*	fungi	EtOAc	LC_{50} = 163.16 μg mL^{-1} LC_{50} = 243.55 μg mL^{-1}	agathic acid (**3**) nafuredin A (**4**)	60

[a]Crude extract activity. EtOH: ethanol; EtOAc: ethyl acetate; LC_{50}: 50% lethal concentration.

Table 2. Antiviral activity of marine microorganisms against Chikungunya (CHIKV), Zika (ZIKV), and Dengue virus (DENV, DENV-2)

Species	Organism	Extract	Antiviral activity		Major compounds	Reference
			Virus type	Potency		
Enterobacter agglomerans	bacteria	AMS	DENV-2	CC_{50} = 260.37 μg mL^{-1}	proteins	61
		pepsin-rich extract	DENV	CC_{50} = 129.00 μg mL^{-1}	proteins	62
Trichodesmium erythraeum	cyanobacteria	MeOH/CHL (1:2, v/v)	CHIKV	EC_{50} = 1.30 μM[a]	debromoaplysiatoxin	63
			CHIKV	EC_{50} = 2.70 μM[a]	3-methoxydebromoaplysiatoxin	
Streptomyces gougerotii and *Microbulbifer variabilis*	bacteria	EtOAc	DENV-2	EC_{50} = 12.30 μM[a]	cyclo-(4-*trans*-hydroxy-L-proline-L-leucine) (**5**)	64
			DENV-2	EC_{50} = 11.2 μM	cyclo-(4-*trans*-hydroxy-L-proline-L-phenylalanine) (**6**)	
Dichotomomyces cejpii	fungus	EtOAc	DENV-2	50.00 μM 50% of inhibition	scequinadoline A (**7**)	65
Fusarium sp.	fungus from sea star *Acanthaster planci*	EtOAc	ZIKV	EC_{50} = 7.50 μM[a]	fusaindoterpenes B (**8**)	66
			ZIKV	EC_{50} = 4.20 μM[a]	JBIR-03 (**9**)	
			ZIKV	EC_{50} = 5.00 μM[a]	1,2-bis(1*H*-indol-3-yl)ethane-1,2-dione (**10**)	
Beauveria felina	fungus from sponge *Xestospongia testudinaria*	EtOAc	ZIKV	inhibited 100% at 10.00 μM	roseotoxin B (**11**), roseotoxin (**12**), [3-me-Pro]destruxin E chlorohydrin (**13**), destruxin A (**14**), destruxin F (**15**), destruxin Ch1 (**16**), and destruxin Br1 (**17**)	67
Stachybotrys chartarum	fungus from sponge *Niphates* sp.	EtOAc	ZIKV	inhibited 100% at 5.00 μM	meroterpenoid alkaloid (**18**)	68

[a]Isolated compound activity. AMS: ammonium sulfate; CC_{50}: 50% cytotoxic concentration; MeOH: methanol; CHL: chloroform; EC_{50}: 50% effective concentration; EtOAc: ethyl acetate.

In 2018, Abinaya *et al.*[58] conducted a study of the larvicidal activity of exopolysaccharide from probiotic *Bacillus licheniformis* on *A. aegypti*. *B. licheniformis* exopolysaccharide (Bl-EPS) was extracted using ethanol (EtOH) precipitation and was evaluated in different concentrations (30.00, 60.00, 90.00, 120.00, and 150.00 μg mL^{-1}). The authors reported that mortality was 94.6% against *A. aegypti* larvae when Bl-EPS was tested at 150.00 μg mL^{-1}. The larvicidal concentration 50% (LC_{50}) value for Bl-EPS against *A. aegypti* was 79.28 μg mL^{-1}.

Seven compounds were isolated from the marine fungus *Penicillium brefeldianum* ABC190807 from mangrove sediments.[59] Both the crude extract in ethyl acetate (EtOAc) and two isolated substances showed activity against the third instar larvae of *A. aegypti*. At 250.00 μg mL^{-1}, compounds **1** and **2** exhibited lethal activity against the larvae (Figure 1).

Dong *et al.*[60] patented the method for preparing secondary metabolites of marine fungi by fermenting a mixture of *Trichoderma harzianum* and *Penicillium brefeldianum*. After concentration, the crude extract was fractionated on a silica gel column, which provided six compounds. After evaluating the activity of the compounds agathic acid (**3**) and nafuredin A (**4**) against the third instar larvae of *A. aegypti*, it was possible to observe a clear dose-response relationship after 72 h with a good correlation. Compounds **3** and **4** (Figure 2) showed LC_{50} values of 163.16 and 243.55 μg mL^{-1}, respectively.

Symbiont bacteria of algae are bioactive metabolite sources. Based on this knowledge, Ahmad *et al.*[61] observed

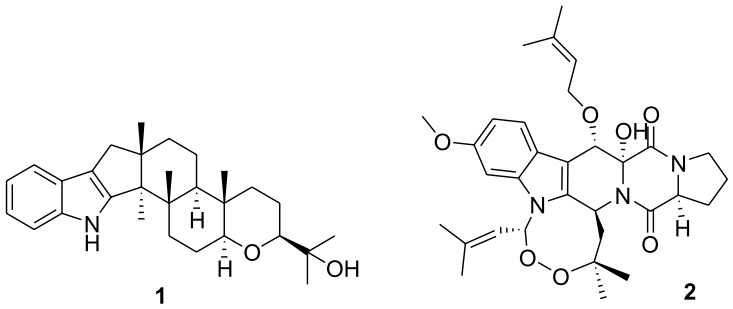


Figure 1. Structures of paspaline (**1**) and fumitremorgin A (**2**) isolated from *P. brefeldianum*.

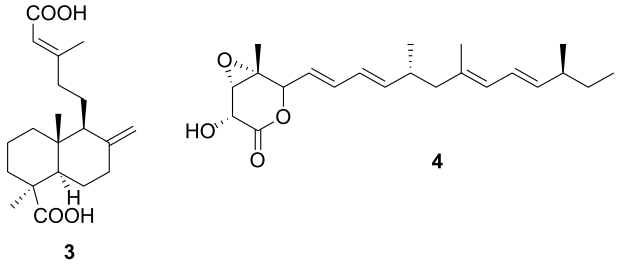


Figure 2. Structures of agatic acid (**3**) and nafuredin (**4**) isolated from *T. harzianum* and *P. brefeldianum*.

in 2019 the antiviral potential against the Dengue virus of a protein fraction isolated from *Enterobacter agglomerans* as the symbiont of brown algae *Sargassum binderi*. Antiviral activity toward DENV serotype 2 (DENV-2) in the Vero cells model indicated an inhibition percentage and CC_{50} (50% cytotoxic concentration) value of 70% and 260.37 μg mL^{-1}, respectively. The authors recommended that future studies be performed with hydrolyzed fractions to explore other potential peptide compounds with antiviral activity against DENV.

Tropical filamentous marine cyanobacteria have presented as a valuable source of novel bioactive natural products and based on this trend, Gupta *et al.*[63] reported five aplysiatoxin-related compounds from the marine cyanobacterium *Trichodesmium erythraeum*. The authors have assessed the antiviral activities of these five marine toxins using Chikungunya virus (CHIKV)-infected cells in both pre- and post-treatment studies. In pre-treatment studies, BHK21 (baby hamster kidney) cells were treated with the compounds before being infected with CHIKV. The effects of the marine-derived compounds on CHIKV replication within infected cells were assessed in post-treatment studies. Post-treatment experiments using the debrominated analogs, namely debromoaplysiatoxin and 3-methoxydebromoaplysiatoxin, displayed dose-dependent inhibition of CHIKV when tested at concentrations of 0.10 μM. Furthermore, debromoaplysiatoxin displayed the most potent antiviral activity with an EC_{50} (50% effective concentration) value of 1.30 μM and a selectivity index ($SI = CC_{50}/EC_{50}$) of 10.9.

To investigate the inhibitory effects of the EtOAc extracts of *Streptomyces gougerotii* and *Microbulbifer variabilis* on DENV-2 replication, DENV-2-infected Huh-7 cells were treated with different isolated compounds (namely two γ-butyrolactones and four diketopiperazines) at various concentrations for 3 days. Diketopiperazines cyclo-(4-*trans*-hydroxy-L-proline-L-leucine (**5**) and cyclo-(4-*trans*-hydroxy-L-proline-L-phenylalanine) (**6**) (Figure 3) exhibited a significant reduction of DENV-2 replication in these cells, exhibiting an EC_{50} of 12.30 and 11.20 μM, respectively.[64]

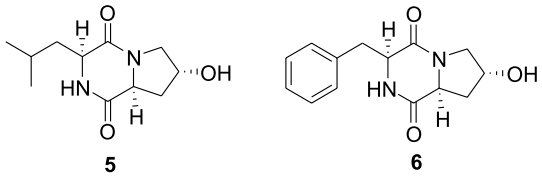


Figure 3. Structures of the diketopiperazines **5** and **6** isolated from *M. variabilis.*

The fungal strain *Dichotomomyces cejpii* F31-1, isolated from the soft coral *Lobophytum crassum*, was investigated.[65] Culture of this organism generates more than thirty metabolites, which were isolated before assessment of their inhibitory activity against DENV-2. After bioactivity-guided fractionation, the fumiquinazoline scequinadoline A (**7**, Figure 4) was isolated and exhibited significant inhibitory activity against dengue virus serotype 2 production by standard plaque assay.

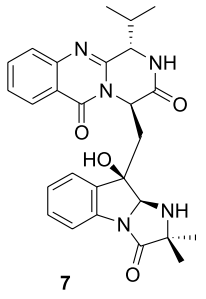


Figure 4. Structure of scequinadoline A (**7**) isolated from *D. cejpii*.

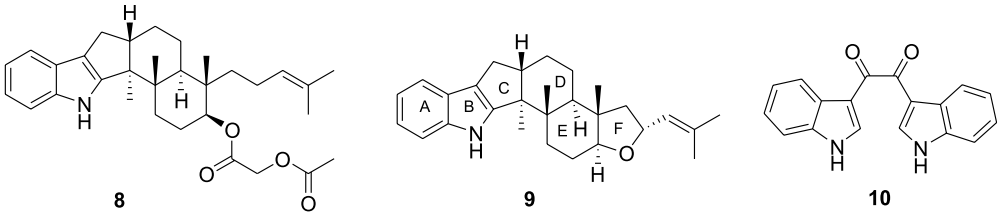


Figure 5. Structures of compounds **8**, **9**, and **10** isolated from *Fusarium* sp.

In their work, Guo *et al.*[66] studied the marine fungus *Fusarium* sp. L1 cultivated in the presence of L-tryptophan, from which were isolated 23 indole alkaloids, including six new compounds and 17 known compounds. The antiviral activity against the ZIKV of all compounds was evaluated by plaque assay on A549 cell cultures. Nine substances showed an EC_{50} ranging from 5.00-50.00 μM, where compounds **8**, **9**, and **10** (Figure 5) displayed the best results with EC_{50} values of 7.5, 4.2, and 5.0 μM, respectively. A preliminary study of the structure-activity relationship showed that the F-ring of indole diterpenes is important for antiviral activity against ZIKV. The presence of a furan moiety (F ring) increases the activity as in compound **9** (EC_{50} = 4.20 μM). Furthermore, the presence of diketones in the bisindole system **10** substantially increased activity.

Yuan *et al.*[67] established a Zika-infected cell line model for screening anti-ZIKV compounds from crude extracts. Recently, they studied the crude extract of sponge-associated fungus *Beauveria felina* SX-6-22 and thirty destruxin cyclohexadepsipeptides (DTXs) were discovered.[67] The target for therapy against Zika virus in this bioassay was the inhibition of RNA (ribonucleic acid) replication and expression of the NS5 protein (non-structural protein 5), the most conserved in the virus and essential for its replication. The authors tested the inhibition of the compounds toward total replication of RNA and NS5 production levels in ZIKV (MR766) virus-infected A549 cells. The virus replication was determined by qRT-PCR (quantitative reverse transcription-polymerase chain reaction) 24 h after infection using ivermectin as a positive control and DMSO (dimethyl sulfoxide) as a negative control. The qRT-PCR results showed that seven compounds (**11**-**17**, Figure 6) at 10.00 μM significantly inhibited ZIKV total RNA replication. In addition, western blotting analysis of NS5 in lysed A549 cells after infection for 24 h, showed that these antiviral compounds also effectively inhibited NS5 protein production. Among the DTXs analyzed, those bearing a halogen (Br or Cl) substitution or those containing an α-hidroxyisocaproic acid (α-HIC) or a 2-hydroxy-4-pentenoic acid moiety showed to be more potent than those containing hydroxy or carboxylic groups on the α-HIC moieties.

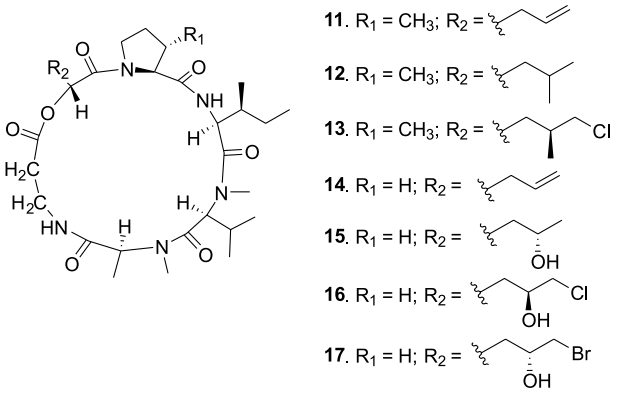


Figure 6. Structures of cyclohexadepsipeptides (**11**-**17**) isolated from *B. felina*.

In their invention, Lin *et al.*[68] disclosed the isolation of a terpene alkaloid and its antiviral properties against ZIKV. The alkaloid meroterpeoid (**18**, Figure 7) was obtained from the EtOAc extract of the fermentation broth of the marine fungus *Stachybotrys chartarum*. *In vitro* experiments showed that the meroterpenoid alkaloid could significantly inhibit ZIKV at a concentration of 5.00 μM.

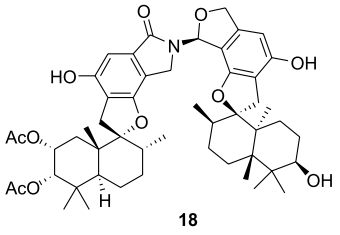


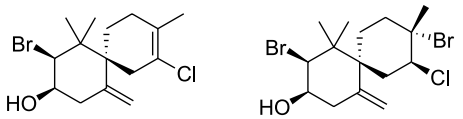
Figure 7. Structure of the meroterpenoid alkaloid (**18**) isolated from *S. chartarum*.

4. Seaweeds

Several studies in the literature have demonstrated the potential of seaweeds against numerous viruses, presenting promising CHIKV, ZIKV, and DENV antiviral activity, amongst others. Likewise, these seaweeds also exhibited potent larvicidal activity, especially against *Aedes* spp. mosquitoes.

Salvador-Neto *et al.*[69] described the potential larvicidal activity of extracts derived from the red alga *Laurencia dendroidea* J. Agardh. Their initial results demonstrated that crude extracts, at a concentration of

5.00 ppm, caused pronounced mortality of the second instar of *A. aegypti* larvae. According to the authors, two isolated molecules were responsible for the observed larvicidal activity, the halogenated sesquiterpenes (–)-elatol (**19**) and (+)-obtusol (**20**) (Figure 8). (+)-Obtusol (**20**) presented higher toxic activity than (–)-elatol (**19**), with an LC_{50} value of 3.50 ppm while (–)-elatol yielded an LC_{50} value of 10.70 ppm. Histological analysis of the larvae exposed to (+)-obtusol (**20**) revealed damage to the intestinal epithelium.

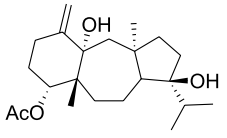


19 **20**

Figure 8. Structures of the halogenate sesquiterpenes (–)-elatol (**19**) and (+)-obtusol (**20**) isolated from the red alga *L. dendroidea*.

Different studies evaluating the crude seaweed extracts presenting larvicidal activity are described in the Supplementary Information section.

Table 3 displays studies evaluating seaweed extracts presenting antiviral activity against CHIKV, ZIKV, and DENV. A recent paper was published[72] evaluating the antiviral potential of the marine brown seaweed *Canistrocarpus cervicornis*. The work aimed to test the antiviral activity against ZIKV and CHIKV virus of the isolated diterpene dolastane (**21**, Figure 9) and its crude seaweed extract. The authors demonstrated that both products (dolastane and crude extract) yielded an interesting bioactivity profile, exhibiting a potent antiviral activity with EC_{50} 2.15 μg mL^{-1} for the crude seaweed extract and 0.75 μM for the dolastane (**21**), against ZIKV replication. Likewise, both products were also able to inhibit CHIKV replication with an EC_{50} of 2.45 μg mL^{-1} for the crude seaweed extract and 1.28 μM for the dolastane (**21**). In addition, the authors also tested the combination of different drugs as a strategy to increase the desired biological activity considerably with a decreased toxicity. The combination of *C. cervicornis* extract and the isolated dolastane with ribavirin was evaluated. It is important to highlight that the concentration of dolastane (**21**) and crude extract used in this combination with ribavirin was lower than the one evaluated individually. This lower concentration, if used individually, would not be able to expressively replicate ZIKV or CHIKV. The results obtained demonstrated that this combination determined a strong synergism in both inhibitions of ZIKV and CHIKV, reaching over 90% inhibition of replication when combined, suggesting that the combined use can be an important treatment strategy, bringing lower risk to people's health.



21

Figure 9. Structure of dolastane (**21**) diterpene isolated from the marine brown seaweed *C. cervicornis*.

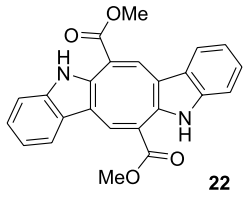
Esteves *et al.*[71] evaluated the antiviral potential of the marine green alga *Caulerpa racemosa*. Their work aimed to evaluate the antiviral activity against CHIKV of the isolated alkaloid, called caulerpin (**22**, Figure 10), to reduce the morbidity and mortality of CHIKV infection, thus contributing to a decrease in the number of infected individuals and possible consecutive outbreaks. In the

Table 3. Antiviral activity of seaweed extracts against Chikungunya (CHIKV), Zika (ZIKV), and Dengue virus (DENV-2)

Species	Organism	Extract / fraction	Antiviral activity		Major compounds	Reference
			Virus type	Potency		
Laurencia dendroidea	seaweeds	HEX	CHIK	EC_{50} = 7.78 μg mL^{-1}	elatol	70
Osmundaria obtusiloba	seaweeds	EtOH	CHIK	EC_{50} = 1.25 μg mL^{-1}	bromo-phenols	70
Ulva fasciata	seaweeds	EtOH	CHIK	EC_{50} = 18.90 μg mL^{-1}	palmitic acid and other fatty acids	70
Kappaphycus alvarezii	seaweeds	EtOH	CHIK	EC_{50} = 3.25 μg mL^{-1}	sterols	70
Caulerpa racemosa	seaweeds	ACE	CHIK	EC_{50} = 4.20 μg mL^{-1}	caulerpin	70
		ACE	CHIK	EC_{50} = 0.80 μM[a]	caulerpin (**22**)	71
Canistrocarpus cervicornis	brown seaweeds	DCM	ZIKV	EC_{50} = 0.75 μM[a]	dolastane (**21**)	72
			CHIK	EC_{50} = 1.28 μM[a]	dolastane (**21**)	
Cladosiphon okamuranus	brown seaweed	–	DENV-2	10.00 μg mL^{-1} of fucoidan reduced the infectivity by 20% compared with that in untreated cells	fucoidan (**23**) and its derivatives	73
Dictyota menstrualis	brown seaweed	DCM	ZIKV	EC_{50} = 2.80 μg mL^{-1}	diterpenes	74

[a]Isolated compound activity. HEX: hexane; EC_{50}: 50% effective concentration; EtOH: ethanol; ACE: acetone; DCM: dichloromethane.

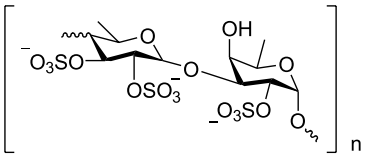
evaluation of the antiviral activity of caulerpin (**22**), the authors tested different concentrations of the isolated compound. The obtained percent inhibition results showed a 99% inhibition at concentrations of 20.00, 10.00, and 5.00 μM. A concentration of 2.50 μM showed 92% inhibition, 1.25 μM showed 75% inhibition, and 0.65 μM showed 47% inhibition, featuring an EC_{50} of 0.80 μg mL^{-1}. Therefore, the results obtained suggest that caulerpin (**22**) could be potentially studied for use in the prevention and treatment of CHIKV infections.



22

Figure 10. Structure of caulerpin alkaloid (**22**) isolated from the marine green alga *C. racemosa*.

The interesting antiviral activity against the Dengue virus using the polysaccharide fucoidan (**23**, Figure 11), isolated from the brown seaweed *Cladosiphon okamuranus* was evaluated.[73] Fucoidan (**23**) is a sulfated polysaccharide that is comprised of carbohydrate units containing glucuronic acid and sulfated fucose residues. The authors reported that fucoidan (**23**) significantly inhibited DENV-2 infection in BHK-21 cells in a dose-dependent manner. Treatment of the virus with 10.00 μg mL^{-1} fucoidan (**23**) reduced the infectivity by 20% compared with untreated cells. The inhibitory activity of fucoidan is equivalent to that of heparin, a known competitive inhibitor. The authors also tested three types of fucoidan derivatives for effects on DENV-2-infected BHK-21 cells. The results obtained showed that desulfation from fucoidan (**23**) yielded a marked suppression of the inhibitory activity. In addition, carboxy-reduction knocked out the effect of fucoidan against DENV-2 infection. These findings strongly suggest that the glucuronic acid residue as well as sulfated fucose are accounting for the inhibition of DENV-2 infection, being essential for the inhibitory activity of fucoidan (**23**).



23

Figure 11. Structure of the sulfated polysaccharide fucoidan (**23**) isolated from the brown seaweed *C. okamuranus*.

5. Mangroves

Mangrove plants were also investigated for larvicidal activity against *A. aegypti*. Extracts from different parts of the plants were prepared with different solvents and showed activity against mosquito larvae. Some samples were further characterized using gas chromatography-mass spectrometry (GC-MS) analysis and phytochemical constituent analysis (Table 4).

The first report describing the activity of three species of mangrove plants against *A. aegypti* larvae was presented by Mohammed and Chadee.[75] The aqueous extract of *Rhizophora mangle* (Rhizophoraceae) revealed an LC_{50} value of 67.6%, however, a terrestrial plant also evaluated by the authors showed better larvicidal activity. Years later, the stimulating effect on the hatching of *A. aegypti* eggs was reported[76] from aqueous extract of *R. mangle* (750.00 μg mL^{-1}). In addition, a synthetic tannic acid (500.00 μg mL^{-1}), whose chemical class is abundant in *R. mangle*, presented embryotoxic and embryostatic effects on eggs and larvae.[76]

Ali *et al.*[77] screened the larvicidal activity of EtOH extracts of other species of the Rhizophoraceae family: *Rhizophora apiculata*, *Rhizophora mucronata*, *Ceriops decandra*, and *Bruguiera cylindrica*. All species exhibited larvicidal activity (see Supplementary Information section) and the stilt root crude extract of *R. mucronata* showed the best activity (LC_{50} value of 0.028 μg mL^{-1}). EtOH and acetone (ACE) fractions of *R. mucronata* extracts also showed larvicidal activity against *A. aegypti*, and a GC-MS analysis allowed the identification of the major compounds in the fractions

Table 4. Larvicidal activity of mangrove plant extracts against *Aedes aegypti* mosquito

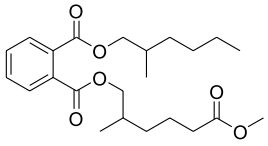
Species	Plant part	Extract	Larvicidal activity	Major compounds	Reference
Rhizophora mangle	leaf	water	LC_{50} = 67.6%	tannins	75,76
Rhizophora mucronata	stilt root	EtOH	LC_{50} = 0.028 μg mL^{-1}	acetone fraction: 2-hydroxy-1-ethyl acetate, mono (2-ethylhexyl) ester, hexanedioic acid ethanolic fraction: benzene dicarboxylic acid, phthalic acid, butanoic acid, hexadecanoic acid	77
Avicennia marina	leaf	ACE	LC_{50} = 164.00 μg mL^{-1}	eicosanoic acid; *cis*-9-hexadecenal; 1-hexyl-oleic acid; di-*N*-decylsulfone; 2-nitrocyclohexane	78

LC_{50}: 50% lethal concentration; EtOH: ethanol; ACE: acetone.

(Table 4). In addition, the authors evaluated the *in vitro* repellent activity of EtOH and ACE fractions of *R. mucronata* against *A. aegypti*, which revealed percentages of protection between 88.6 and 100% with more than 8 h of protection at a concentration of 4 mg cm^{-2}.

The Acanthaceae family also have representatives with known larvicidal activity, especially the members of the *Avicennia marina* species.[75,78,79] A research evaluated the extracts from *A. marina* leaves produced in different solvents and the results revealed that the highest larval mortality was found for the ACE extract (LC_{50} value of 0.16 mg mL^{-1}).[78] ACE extract was characterized by GC-MS analysis providing five compounds: 1-hexyl-2-nitrocyclohexane, eicosanoic acid, *cis*-9-hexadecenal, oleic acid, and di-*N*-decylsulfone. *A. marina*, as well as other species of mangrove plants, also showed potential as repellent against *A. aegypti* with a protection percentage above 80%.[80]

Studies exploring antiviral potential against DENV, ZIKV, and CHIKV of mangrove plant species are scarce. Antiviral activity against DENV was described from a phthalic acid ester (2"-(methoxycarbonyl)-5"-methylpentyl 2'-methylhexyl phthalate, **24**, Figure 12) isolated from a MeOH extract of aerial parts of the species *Acrostichum aureum* (Pteridaceae).[81] The compound exhibited an EC_{50} value of 113.50 µM against DENV-2 and also showed activity against CHIKV reducing the virus titre by 73% at a concentration of 500 µM.



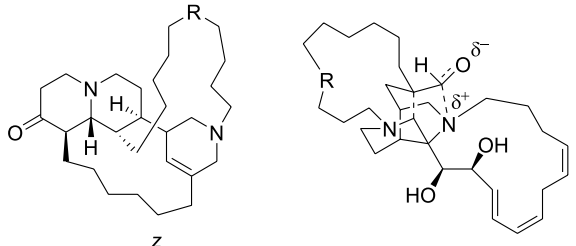
24

Figure 12. Structure of a phthalic acid ester (**24**) isolated from the mangrove plant *A. aureum*.

6. Miscellaneous

Besides bacteria, fungi, seaweeds, and mangrove plants, other marine organisms, such as a sponge, crinoid, annelid, coral, anemone, ascidian, zoanthid, fish, crab, and lily species are reported to possess interesting and diverse biological properties, including antiviral and larvicidal activity. Table 5 summarizes the information about some isolated compounds as well as extracts from such marine organisms with activity against *A. aegypti* larvae.

Some biological properties, including larvicidal on *A. aegypti*, were investigated for saraines 1-3 (**25**-**27**) and saraines A-C (**28**-**30**) (Figure 13), which are abundant polycyclic alkaloids in the sponge *Reniera sarai*.[82] These saraines were obtained from the ACE extract of the sponge collected in the Naples Gulf. The larvicidal activity against the *A. aegypti* was determined on third-age larvae and results have shown that saraines 1-3 were more active than saraines A-C; saraine 3 (**27**) was the most active, with a 46% of larval mortality at 0.20 ppm.



25. R = -CH=CH- (Z)

26. R = $-CH_2-$

27. R = CH_2-CH=CH- (Z)

28. R = $-CH_2-$

29. R = -CH=CH- (Z)

30. R = -CH=CH-CH_2- (Z)

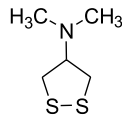
Figure 13. Structures of saraines (**25**-**30**) isolated from the sponge *R. sarai*.

Larvicidal, ovicidal and insecticidal activities against three mosquitoes species, including *A. aegypti*, were reported for nereistoxin[80] (**31**, Figure 14), a natural neurotoxin, isolated from the marine annelid *Lumbriconereis heteropoda*.[86] Samples of *L. heteropoda* were collected from the Pichavaram, Vellar, and Gulf of Mannar, India. The LC_{50} value for larvicidal activity against *A. aegypti* was 0.535 ppm after 24 h treatment (Table 5). For ovicidal activity, **31** exerted 100% mortality (zero hatchability) at 1.00 ppm, and the insecticidal LD_{50} (50% lethal dose) of 0.028 ppm after 24 h for *A. aegypti*. The authors pointed out the promising potential of nereistoxin (**31**) to be used in egg, larval, and adult mosquito control.

Table 5. Larvicidal activity of miscellaneous marine organisms isolated compounds against *Aedes aegypti* mosquito

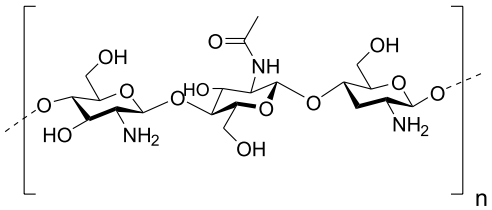
Species	Organism	Extract	Larvicidal activity	Major compounds	Reference
Reniera sarai	sponge	ACE	46% mortality (0.20 ppm)[a]	saraine 3 (**27**)	82
Lumbriconereis heteropoda	annelid	[b]	LC_{50} = 0.53 ppm[a]	nereistoxin (**31**)	83
Sardinella longiceps	fish	acetic acid and pepsin	60% mortality (1.00 µL mL^{-1})[a]	collagen	84
Ranina ranina	crab	–	LC_{50} = 4942.48 ppm[a]	chitosan (**32**)	85

[a]Isolated compound activity; [b]described by Hirayama *et al.*[86] ACE: acetone; LC_{50}: 50% lethal concentration.



31

Figure 14. Structure of nereistoxin (**31**) isolated from the annelid *L. heteropoda*.



32

Figure 15. Structure of chitosan (**32**) isolated from *R. ranina* crab shells.

Muthumari *et al*.[84] have described the larvicidal activity of collagen, a peptide extracted in two different methods: acid (acetic acid) and enzymatic (pepsin) technique from *Sardinella longiceps* fish scales against *A. aegypti*. A 60% of larval mortality was observed using pepsin solubilized collagens (PSC) at a concentration of 1.00 μL mL^{-1}. Apart from the importance of collagen for human health, this work demonstrated its potential application as a biomedical agent in controlling dengue fever.

Larvicidal property against *A. aegypti* was studied for chitosan (**32**, Figure 15), a natural deacetylated derivative of chitin, extracted from *Ranina ranina* crab shells, collected as throwaways from different sea food restaurants in Zamboanga, Philippines.[85] The acidified chitosan was tested against third instar *A. aegypti* larvae, and the results revealed a dose-dependent larvicidal activity of chitosan against *A. aegypti*. The LC_{50} of acidified chitosan was estimated at 4942.49 ppm, and at this concentration, the compound caused a disruptive mechanism in the insect's metabolism. Authors highlighted the use of waste materials as larvicides, being an environmentally safe and inexpensive alternative.

Table 6 shows the antiviral potential of some isolated compounds from different marine species against DENV and CHIKV.

Laille *et al*.[87] investigated *in vitro* antiviral activity of seven metabolites isolated from marine invertebrates from New Caledonia on DENV replication. Metabolites like callipeltin A, crambescidin, ptilomycalin A, celeromycalin, gymnochrome B, gymnochrome D and isogymnochrome D were isolated.[88,93-95] Among these compounds, only gymnochromes, isolated from the living fossil crinoid *Gymnocrinus richeri*,[88] exhibited a considerable inhibitory effect on DENV replication, especially gymnochrome D (**33**) and isogymnochrome D (**34**) (Figure 16), with a foci-reducing effect at doses lower than 1.00 μg mL^{-1} (< 0.89 nM).

Promising activity against the CHIKV infection was reported for crude extracts from coral *Sinularia kavarattiensis* collected from the Indian Ocean.[89] Moreover, they also performed a bioassay-guided chemical fractionation of *S. kavarattiensis* that resulted in the isolation of six known norcembranoids and one new compound, named kavaranolide. The strongest inhibitory effects were observed for the norcembranoids, 5-*epi*-sinuleptolide (**35**) and sinuleptolide (**36**) (Figure 17) that inhibited the CHIKV replication by more than 60% compared to the vehicle control at a concentration of 100.00 μM. It is noteworthy that the CHIKV-inhibiting potential of isolated compounds was lower than that of the crude extracts and the enriched fractions of *S. kavarattiensis*, which may indicate a synergetic activity of the compounds present in the extracts and fractions. The authors have also pointed out that the α-β-unsaturated-γ-butyrolactone moiety in both structures seems to affect biological activity, suggesting the involvement of an electrophilic conjugated function in

Table 6. Antiviral activity of some isolated compounds from miscellaneous marine organisms

Species	Organism	Extract	Antiviral activity			Reference
			Virus type	Potency	Major compounds	
Gymnocrinus richeri	crinoid	MeOH	DENV	EC_{50} < 1.00 μg mL^{-1} (< 0.89 nM)	gymnochrome D (**33**), isogymnochrome D (**34**)	87,88
Sinularia kavarattiensis	coral	MeOH	CHIKV	> 60% inhibition (100.00 μg mL^{-1})	5-*epi*-sinuleptolide (**35**), sinuleptolide (**36**)	89
Palythoa mutuki	zoanthid	EtOH	DENV	EC_{50} = 4.50 μg mL^{-1}	peridinin (**37**)	90
Eunicea laciniata *Eunicea asperula*	coral	DCM	CHIKV	EC_{50} = 1.2 μM	(1*R*,7*R*,8*R*,11*S*)-7,8-epoxy-13-ketodolabella-3,12(18)-diene (**38**)[a]	91
Zoanthus spp.	anemone	EtOH	DENV	EC_{50} = 19.61 μM	zoanthone A (**40**)	92
				EC_{50} = 10.05 μM	ajugasterone C (**41**)	

[a]Isolated from the two species. MeOH: methanol; EC_{50}: 50% effective concentration; EtOH: ethanol; DCM: dichloromethane.

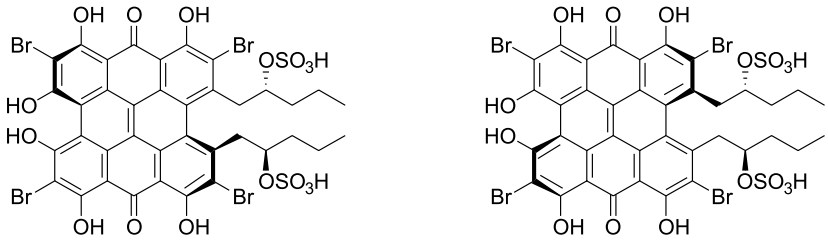


Figure 16. Structures of gymnochrome D (**33**) and isogymnochrome D (**34**) isolated from *G. richeri*.

35 and **36**, which could act as a Michael acceptor toward reactive lysine or cysteine residues in the biological targets.

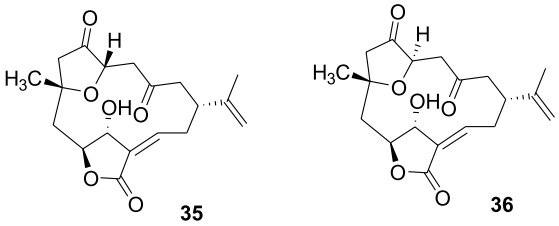


Figure 17. Structures of norcembranoids, 5-*epi*-sinuleptolide (**35**), and sinuleptolide (**36**) were isolated from *S. kavarattiensis*.

Based on the strong antiviral activity against the DENV virus of the EtOH extract of zoanthid *Palythoa mutuki*, Lee *et al*.[90] decided to isolate and investigate the antiviral activity against DENV of animal materials of *P. mutuki*. The materials were collected on the northeast coast of Taiwan and from the EtOH extract one new ecdysteroid; palythone A and eight known compounds, 20-hydroxyecdysone 2-acetate, 3-deoxy-20-hydroxyecdysone, 24-*epi*-makisterone A, 20-hydroxyecdysone 3-acetate, 2-deoxyecdysterone, 20-hydroxyecdysone, α-ecdysone, and peridinin were isolated. Peridinin (**37**, Figure 18), a common secondary metabolite in marine invertebrates and dinoflagellates, exhibited the most potent antiviral activity, with an EC_{50} of 4.50 ± 0.46 μg mL^{-1} against DENV-2, superior to that of the positive control, 2'CMC (2'-C-methylcytidine).

Antiviral activities were reported[91] for five natural and 21 semisynthetic derivatives dolabellane diterpenes against ZIKV and CHIKV viruses. Dolabellatrienone and (1*R*,7*R*,8*R*,11*S*)-7,8-epoxy-13-keto-dolabella-3,12(18)-diene isolated from the DCM extract of soft corals *Eunicea laciniata* and *Eunicea asperula*, collected in Santa Marta, Colombian Caribbean Sea, were used as starting material for the synthesis of 21 dolabellane and dolastane diterpenes. Compound (1*R*,7*R*,8*R*,11*S*)-7,8-epoxy-13-keto-dolabella-3,12(18)-diene (**38**) showed a significant activity against CHIKV with an EC_{50} value of 1.2 ± 0.1 μM, while its semisynthetic derivative, (1*R*,3*Z*,7*R*,8*R*,11*S*)-7,8-epoxy-13-ketodolabell-3-en-16-al (**39**) (Figure 19) exhibited an EC_{50} = 0.92 ± 0.08 μM against ZIKV.

Cheng *et al*.[92] described the *in vitro* antiviral activity of 14 ecdysones isolated from the EtOH extract of anemone *Zoanthus* spp. collected in Taiwan against DENV-2. The newly isolated compound zoanthone A (**40**) exhibited potent antiviral activity (EC_{50} = 19.61 ± 2.46 μM) with a selectivity index (CC_{50}/EC_{50}) value of 36.7, and the ajugasterone C (**41**), an EC_{50} of 10.05 ± 2.37 μM (Figure 20). In addition, the most active compound **41** was also tested for its EC_{50} value against DENV-1 (15.70 ± 2.36 μM), DENV-3

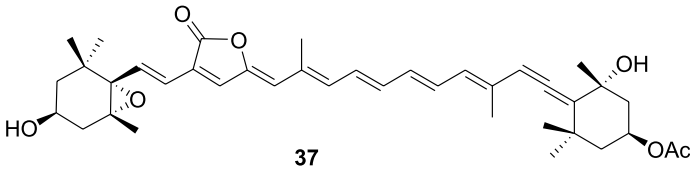


Figure 18. Structure of peridinin (**37**) isolated from *P. mutuki*.

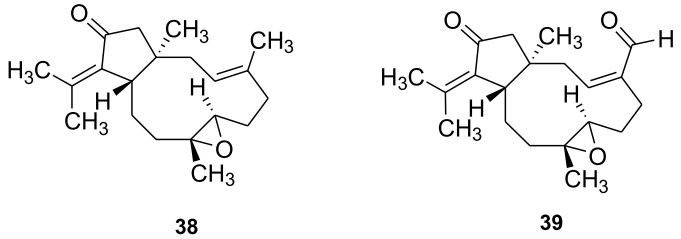


Figure 19. Structures of (1*R*,7*R*,8*R*,11*S*)-7,8-epoxy-13-keto-dolabella-3,12(18)-diene (**38**) and its semisynthetic derivative, (1*R*,3*Z*,7*R*,8*R*,11*S*)-7,8-epoxy-13-ketodolabell-3-en-16-al (**39**).

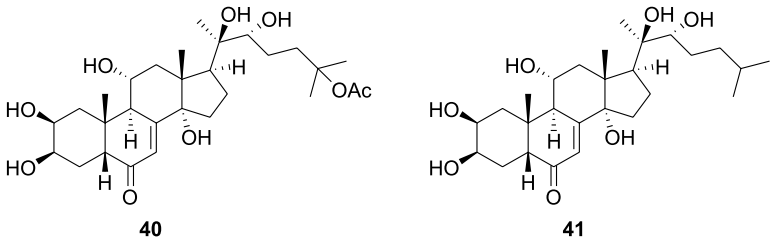


Figure 20. Structures of ecdysones zoanthone A (**40**) and ajugasterone C (**41**) isolated from *Zoanthus* spp.

(9.48 ± 0.24 μM), and DENV-4 (12.15 ± 1.22 μM), and the results demonstrated the combined activity of **41** for all Dengue virus serotypes.

7. Nano Encapsulated Extracts from Marine Organisms

Nanoencapsulation of natural extracts has proved to be a valuable green technology strategy for reducing the use of chemical pesticides. The use of nanoparticles (NPs) synthesized with extracts from marine organisms, mainly seaweeds and mangrove plants, has been presented as an eco-friendly approach to controlling DENV vector *A. aegypti* larvae.[96,97] In the literature, biosynthesized silver nanoparticles (Ag NPs) and zinc oxide nanoparticles (ZnO NPs) are often characterized by UV-visible spectroscopy, X-ray diffraction, and Fourier transform infrared spectroscopy. The larvicidal activity reported for NPs synthesized from extracts from different marine organisms is presented in Table 7.

Silver nanoparticles (Ag NPs) synthesized from aqueous extracts of mangrove plant leaves *Acanthus ilicifolius* and *Rhizophora mucronata* exhibited potent activity against *A. aegypti* larvae with LC_{50} values of 0.53[98] and 0.58 μg mL^{-1},[99] respectively. Some authors[97,100-102] also reported that the larvicidal activity of the nano-encapsulated mangrove extracts was higher than the activity of the crude extracts. The species *Sonneratia alba* (Lythraceae), for example, exhibited an LC_{50} value of 192.03 ppm for the crude extract, while the NPs synthesized with the extract revealed an LC_{50} value of 3.15 ppm.[101]

Sabatini and Devi[103] accomplished the green synthesis of Ag NPs from the brown seaweed *Steochospermum marginatum*, in which samples indicated the presence of several bioactive compounds with medicinal value. The authors tested its application for antimicrobial, anti-diabetic, ovicidal, larvicidal, and cytotoxic activity. The extract of both the biosynthesized nanoparticles and the aqueous extracts were found to be effective in killing the mosquito eggs and the larvae in a maximum mortality rate (85 and 88% of mortality of mosquito larvae for Ag NPs and aqueous extracts, respectively), however, the cytotoxicity testing of the silver nanoparticles obtained from the brown seaweed extract showed 84% less cytotoxic than the crude extract.

Recently Balaraman *et al.*[104] discussed the development of an innovative eco-friendly process to generate safer and more stable Ag NPs with a high purity using the *Sargassum myriocystum* aqueous extract. The Ag NPs were

Table 7. Larvicidal activity of nano encapsulated extracts from marine organisms against *A. aegypti*

Species	Organism	Extract	Nanoparticle	Larvicidal activity	Reference
Lumnitzera racemosa	mangrove plant (flower buds)	water	ZnO NP	LC_{50} = 24.74 μg mL^{-1}	96
Heritiera fomes	mangrove plant (leaves)	water	Ag NP	LC_{50} = 8.39 ppm	97
Acanthus ilicifolius	mangrove plant (leaves)	water	Ag NP	LC_{50} = 0.53 μg mL^{-1}	98
Rhizophora mucronata	mangrove plant (leaves)	water	Ag NP	LC_{50} = 0.58 μg mL^{-1}	99
Suaeda maritima	mangrove plant (leaves)	EtOH	Ag NP	LC_{50} = 8.66 ppm	100
Sonneratia alba	mangrove plant (leaves)	water	Ag NP	LC_{50} = 3.14 ppm	101
Bruguiera cylindrica	mangrove plant (leaves)	water	Ag NP	LC_{50} = 8.93 ppm	102
Steochospermum marginatumis	brown seaweed	water	Ag NP	85% of mortality	103
Sargassum myriocystum	brown seaweed	water	Ag NP	LC_{50} = 6.90 μg mL^{-1}	104
Stichodactyla haddoni	anemone	secreted mucus (adhesive protein)	ZnO NP	LC_{50} = 31.49 μg mL^{-1}	105
Avicennia marina	mangrove plant (leaves)	water	Ag NP	LC_{50} = 4.37 μg mL^{-1}	106
Sargassum muticum	brown seaweed	water	Ag NP	LC_{50} = 35.90 μg mL^{-1}	107
Sargassum wightii	seaweed	water	ZnO NP	LC_{50} = 49.22 μg mL^{-1}	108
Centroceras clavulatum	seaweed	water	Ag NP	LC_{50} = 21.46 ppm	109

ZnO NP: zinc oxide nanoparticle; LC_{50}: 50% lethal concentration; Ag NP: silver nanoparticle; EtOH: ethanol.

tested for antibacterial activity against clinical pathogens and larvicidal activity against the mosquito *A. aegypti*. The results obtained indicate a higher mortality percentage for Ag NPs when compared to the *S. myriocystum* seaweed extracts, yielding an LC_{50} = 6.90 and LC_{90}: 90% lethal concentration = 19.08 μg mL^{-1} for the Ag NPs, compared to the LC_{50} = 11.81 and LC_{90} = 29.78 μg mL^{-1} for the extracts of *S. myriocystum*. In addition, the results indicated that the mortality level was higher when the Ag NPs concentrations were increased. Therefore, there was a dose-dependent response of Ag NPs against *A. aegypti* larvae.

The biosynthesis of ZnO NPs was reported using adhesive protein from the sea anemone *Stichodactyla haddoni* (*Sh*Ap), collected from the coastal area in the Ramanathapuram district, India, with potential biomedical applications.[105] *Sh*Ap-ZnO NPs exhibited significant larvicidal activity against the third instar larvae of *A. aegypti*, with an LC_{50} of 31.49 μg mL^{-1}. Also, *Sh*Ap and zinc acetate were evaluated and showed LC_{50} 41.88 and 149.29 μg mL^{-1}, respectively.

NPs synthesized from mangrove extracts have also been evaluated for their activities against DENV-2. Murugan *et al.*[102] showed that 30.00 μg mL^{-1} of Ag NP synthesized with extract of the species *Bruguiera cylindrica* (Rhizophoraceae) significantly inhibited the production of DENV envelope (E) protein in Vero cells and downregulated the expression of the DENV E gene. The same research group also evaluated the antiviral activity of Ag NPs synthesized with extract of *Sonneratia alba* (Lythraceae) and only 15.00 μg mL^{-1} of Ag NP was required to strongly inhibit the DENV-2 virus with low toxicity to Vero cells.[101]

8. Conclusions

This review has gathered relevant data from a variety of works described in the literature to search for marine metabolites with potential activity in the fight against Dengue, Zika, and Chikungunya arboviruses. Assays against *Aedes aegypti* larvae were performed on extracts and substances isolated from species of different groups of marine organisms, showing good results. Mangrove plant extracts have been extensively evaluated for the same purpose; however, more comprehensive studies are needed to assess the activity of isolated substances. Another approach well presented and with excellent results was the use of extracts from marine organisms in the synthesis of nanoparticles with larvicidal activity. Substances from marine organisms with activity against DENV, ZIKV, and CHIKV viruses were also found mainly in samples of microorganisms and algae. The reported works found the active potential of substances of marine origin against larvae and viruses, are encouraging with respect to their structure activity relationship. Since there are no vaccines or specific treatments for these viruses, MNPs may become interesting candidates for drugs in the future. Furthermore, the gigantic marine biodiversity suggests that there is still much to explore in aquatic ecosystems, and that, in our view, will lead to attractive drug alternatives to help combat arboviruses.

Supplementary Information

Supplementary information is available free of charge at http://jbcs.sbq.org.br as a PDF file.

Acknowledgments

FAPERJ (APQ1 E26/010.002205/2016, E26/010.001574/2019 and E26/210.249/2021 and JCNE E-26/201.295/2022), CNPq, Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brazil (CAPES, Financial Code 001) and UFF for financial support and research fellowships.

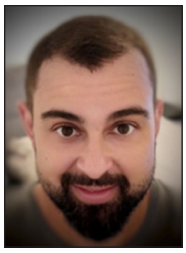
Author Contributions

Alessandra L. Valverde and Vinicius R. Campos were responsible for the conceptualization; Thayssa S. F. Fagundes, Thatyana R. A. Vasconcelos, Fernando M. dos Santos Junior, Bia F. Rajsfus, Diego Allonso, Alessandra L. Valverde, and Vinicius R. Campos for the writing - original draft preparation and review; Thayssa S. F. Fagundes and José C. J. M. D. S. Menezes for the editing. All authors have read and agreed to the published version of the manuscript.

Thayssa Fagundes *graduated in Chemistry (2014) from the Fluminense Federal University (UFF), Brazil, where she also earned her MSc (2017) and PhD (2021) degrees in Chemistry. For 10 years, she was a member of the Natural Products Laboratory (LAPROMAR) at UFF, where she currently works as a collaborating researcher. She has experience in the Chemistry of Natural Products and her research interests include metabolomic fingerprinting, isolation and structural determination of bioactive marine natural products, and also chemistry education research.*

Thatyana Rocha Alves Vasconcelos *graduated in Industrial Pharmacy (1999) and PhD degrees in Organic Chemistry (2004) from Fluminense Federal University, Brazil. She worked as a Research Specialist at the Institute of Technology in Pharmaceuticals at Oswaldo*

Cruz Foundation, Brazil (2004-2006). Since 2006, she is a Professor in the Department of Organic Chemistry at Fluminense Federal University. She has experience in Organic Synthesis, working in the design, synthesis, and spectroscopic characterization of heterocycles with potential biological activity, including anticancer, antimicrobial, and antiviral, and is also a collaborator in projects in the Chemistry of Natural Products, which involve the isolation and structural elucidation of bioactive natural products.



***Fernando Martins** obtained his PhD (2016) from Natural Products Research Institute at the Federal University of Rio de Janeiro, Brazil, under the supervision of Prof Mauro Amorim. He worked as a visiting scholar at Vanderbilt University (2015) in Prof Prasad Polavarapu's group. Following post-doctoral work (2017) at São Carlos Federal University, Brazil, under the supervision of Profs Quezia Cass and João M. Batista Jr., in 2018 he joined the Institute of Chemistry at Fluminense Federal University, Brazil, where he currently is an adjunct Professor. Fernando's research specializes in structure elucidation of natural products utilizing computational spectroscopy, mainly NMR and electronic and vibrational circular dichroism.*

***Bia Francis Rajsfus** graduated in biomedical science (2020) from the Brazilian Institute of Medicine and Rehabilitation (IBMR). Since 2019, she is a member of the Biotechnology and Structural Bioengineering Laboratory (LABGENEST), located at the Federal University of Rio de Janeiro (UFRJ), where she gained experience in Virology, Molecular Biotechnology, and Biochemistry. In 2021, she initiated her master's degree in Biological Science at the Biophysical Institute Carlos Chagas Filho (IBCCF), in UFRJ.*

***Diego Allonso** graduated in Biomedical Sciences from the Federal University of Rio de Janeiro (UFRJ), Brazil, where he also earned his MSc and PhD degrees in Biological Sciences. He is an Assistant Professor of Pharmaceutical Biotechnology at the Faculty of Pharmacy of UFRJ since 2018 and has experience in Virology, Molecular Biotechnology, and Biochemistry. His research interests include screening synthetic and natural antiviral compounds against arboviruses and the identification of novel pharmacological targets to be used in the development of antiviral compounds.*

***José Menezes** completed his PhD on the synthesis of natural products and their derivatives in 2009 from Goa University, India. Later he joined as a post-doc at the University of Aveiro, Portugal (2010-2013) for the synthesis and application of natural and synthetic porphyrins in photodynamic therapy (PDT) of cancers. José performed screening of natural compounds for modulating effects on host restriction factors like BST-2 and MARCH-8 for antiviral therapy as a Tokyo Biochemical Research Foundation post-doctoral fellow at Nagasaki International University, Japan (2016-2018). Currently, he is working at Esteem Industries (R & D center for surfactants and chemicals) in Goa as a team senior manager since 2018.*

***Alessandra Leda Valverde** is an Associate Professor in the Institute of Chemistry at Fluminense Federal University, Brazil. She received a BSc in Industrial Chemistry (1993) and MSc in Organic Chemistry (1996) from Fluminense Federal University, Brazil. Her PhD (1999) degrees in Science at Rio de Janeiro Federal University. Over the years, she also worked as a P&D Researcher at FIOCRUZ (1999-2004) and as a postdoc at the Department of Chemistry at São Carlos Federal University in 2017. She supervises postdoctoral, doctoral, master's, and undergraduate students. Her research interests involve isolation and stereostructural determination of bioactive natural products.*

***Vinicius Rangel Campos** graduated in Chemistry at the Fluminense Federal University (UFF) and earned his MSc and PhD degrees in Chemistry in 2011 and 2015, respectively, also at UFF. Since 2016, he is an Adjunct Professor at the Department of Organic Chemistry at UFF. He currently coordinates the Heterocycle Synthesis Laboratory (LASINTHET) and some of his research experiences and skills are design, synthesis, and spectroscopic characterization of nitrogen heterocycles with potential biological and technological applications (antiviral, anticancer, antibacterial, anti-corrosion and anti-fouling).*

References

1. Agarwal, A.; Parida, M.; Dash, P. K.; *Rev. Med. Virol.* **2017**, *27*, e1941. [Crossref]
2. Weaver, S. C.; *Trends Microbiol.* **2013**, *21*, 360. [Crossref]
3. Allonso, D.; Vazquez, S.; Guzman, M. G.; Mohana-Borges, R.; *Am. J. Trop. Med. Hyg.* **2013**, *88*, 506. [Crossref]
4. Rocha, D. C. P.; Souza, T. M. A.; Nunes, P. C. G.; Mohana-Borges, R.; Paes, M. V.; Guimarães, G. M. C.; Arcila, J. C. S.; Paiva, I. A.; de Azeredo, E. L.; Damasco, P. V.; de Souza, L. J.; dos Santos, F. B.; Allonso, D.; *J. Clin. Virol.* **2022**, *146*, 105054. [Crossref]
5. Halstead, S. B.; *Lancet* **2007**, *370*, 1644. [Crossref]
6. Halstead, S. B.; Dans, L. F.; *Lancet Child. Adolesc. Health* **2019**, *3*, 734. [Crossref]
7. Girard, M.; Nelson, C. B.; Picot, V.; Gubler, D. J.; *Vaccine* **2020**, *38*, 3989. [Crossref]
8. Masmejan, S.; Musso, D.; Vouga, M.; Pomar, L.; Dashraath, P.; Stojanov, M.; Panchaud, A.; Baud, D.; *Pathogens* **2020**, *9*, 898. [Crossref]
9. González-Salazar, C.; Tartaglia, J.; Dourado, M.; Franca Jr., M.; *J. Clin. Neurophysiol.* **2022**, *39*, 253. [Crossref]
10. Constant, L. E. C.; Rajsfus, B. F.; Carneiro, P. H.; Sisnande, T.; Mohana-Borges, R.; Allonso, D.; *Front. Microbiol.* **2021**, *12*, 744164. [Crossref]
11. Puntasecca, C. J.; King, C. H.; LaBeaud, A. D.; *PLoS Negl. Trop. Dis.* **2021**, *15*, e0009055. [Crossref]
12. World Health Organization, https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue, accessed in December 2022.
13. Ferraris, P.; Yssel, H.; Missé, D.; *Microbes Infect.* **2019**, *21*, 353. [Crossref]
14. Carvalho, V. L.; Long, M. T.; *Vaccines (Basel)* **2021**, *9*, 263. [Crossref]
15. U.S. National Library of Medicine Clinical Trials.gov, https://clinicaltrials.gov/ct2/home, accessed in December 2022.
16. Hegde, N.; Gore, M.; *Hum. Vaccines Immunother.* **2017**, *13*, 1320. [Crossref]
17. Martinez, D. R.; Metz, S. W.; Baric, R. S.; *Cell Host Microbe* **2021**, *29*, 13. [Crossref]
18. Nivarthi, U.; Swanstrom, J.; Delacruz, M.; Patel, B.; Durbin, A.; Whitehead, S.; Kirkpatrick, B.; Pierce, K.; Diehl, S.; Katzelnick, L.; Baric, R.; Silva, A.; *Nature Commun.* **2021**, *12*, 1102. [Crossref]
19. Bhatt, S.; Gething, P. W.; Brady, O. J.; Messina, J. P.; Farlow, A. W.; Moyes, C. L.; Drake, J. M.; Brownstein, J. S.; Hoen, A. G.; Sankoh, O.; Myers, M. F.; George, D. B.; Jaenisch, T.; Wint, G. R. W.; Simmons, C. P.; Scott, T. W.; Farrar, J. J.; Hay, S. I.; *Nature* **2013**, *496*, 504. [Crossref]
20. Rosenberger, K.; Alexander, N.; Martinez, E.; Lum, L.; Dempfle, C.-E.; Junghanss, T.; Wills, B.; Jaenisch, T.; *PLoS Negl. Trop. Dis.* **2020**, *14*, e0008076. [Crossref]
21. Dick, G. W. A.; Kitchen, S. F.; Haddow, A. J.; *Trans. R. Soc. Trop. Med. Hyg.* **1952**, *46*, 509. [Crossref]
22. Duffy, M.; Chen, T.-H.; Hancock, W.; Powers, A.; Kool, J.; Lanciotti, R.; Pretrick, M.; Marfel, M.; Holzbauer, S.; Dubray, C.; Guillaumot, L.; Griggs, A.; Bel, M.; Lambert, A.; Laven, J.; Kosoy, O.; Panella, A.; Biggerstaff, B.; Fischer, M.; Hayes, E.; *N. Engl. J. Med.* **2009**, *360*, 2536. [Crossref]
23. Cao-Lormeau, V.-M.; Roche, C.; Teissier, A.; Robin, E.; Berry, A.-L.; Mallet, H.-P.; Sall, A. A.; Musso, D.; *Emerg. Infect. Dis.* **2014**, *20*, 1085. [Crossref]
24. Dupont-Rouzeyrol, M.; O'Connor, O.; Calvez, E.; Daurès, M.; John, M.; Grangeon, J.-P.; Gourinat, A.-C.; *Emerg. Infect. Dis.* **2015**, *21*, 381. [Crossref]
25. Musso, D.; *Emerg. Infect. Dis.* **2015**, *21*, 1887. [Crossref]
26. Campos, G. S.; Bandeira, A. C.; Sardi, S. I.; *Emerg. Infect. Dis.* **2015**, *21*, 1885. [Crossref]
27. Sourisseau, M.; Schilte, C.; Casartelli, N.; Trouillet, C.; Guivel-Benhassine, F.; Rudnicka, D.; Sol-Foulon, N.; Le Roux, K.; Prevost, M.-C.; Fsihi, H.; Frenkiel, M.-P.; Blanchet, F.; Afonso, P. V.; Ceccaldi, P.-E.; Ozden, S.; Gessain, A.; Schuffenecker, I.; Verhasselt, B.; Zamborlini, A.; Saïb, A.; Rey, F. A.; Arenzana-Seisdedos, F.; Desprès, P.; Michault, A.; Albert, M. L.; Schwartz, O.; *PLoS Pathog.* **2007**, *3*, e89. [Crossref]
28. Baseggio, A.; *Parassitologia* **2008**, 99. [Crossref]
29. Ross, P. A.; *Acta Trop.* **2021**, *222*, 106045. [Crossref]
30. Caragata, E. P.; Dutra, H. L. C.; Sucupira, P. H. F.; Ferreira, A. G. A.; Moreira, L. A.; *Trends Parasitol.* **2021**, *37*, 1050. [Crossref]
31. Namias, A.; Jobe, N. B.; Paaijmans, K. P.; Huijben, S.; *eLife* **2021**, *10*, e65655. [Crossref]
32. Edenborough, K. M.; Flores, H. A.; Simmons, C. P.; Fraser, J. E.; Pierson, T. C.; *J. Virol.* **2021**, *95*, e02203-20. [Crossref]
33. Santana, A. C.; Silva Filho, R. C.; Menezes, J. C. J. M. D. S.; Allonso, D.; Campos, V. R.; *Life* **2021**, *11*, 16. [Crossref]
34. Menezes, J. C. J. M. D. S.; Campos, V. R.; *Sci. Total Environ.* **2021**, *769*, 145168. [Crossref]
35. Soares, A. R. In *Ecologia Marinha*, vol. 2; Interciência: Rio de Janeiro, 2020, p. 108.
36. Rotter, A.; Barbier, M.; Bertoni, F.; Bones, A. M.; Cancela, M. L.; Carlsson, J.; Carvalho, M. F.; Cegłowska, M.; Chirivella-Martorell, J.; Dalay, M. C.; Cueto, M.; Dailianis, T.; Deniz, I.; Díaz-Marrero, A. R.; Drakulovic, D.; Dubnika, A.; Edwards, C.; Einarsson, H.; Erdoğan, A.; Eroldoğan, O. T.; Ezra, D.; Fazi, S.; FitzGerald, R. J.; Gargan, L. M.; Gaudêncio, S. P.; Udovič, M. G.; DeNardis, N. I.; Jónsdóttir, R.; Kataržytė, M.; Klun, K.; Kotta, J.; Ktari, L.; Ljubešić, Z.; Bilela, L. L.; Mandalakis, M.; Massa-Gallucci, A.; Matijošytė, I.; Mazur-Marzec, H.; Mehiri, M.; Nielsen, S. L.; Novoveská, L.; Overlingė, D.; Perale, G.; Ramasamy, P.; Rebours, C.; Reinsch, T.; Reyes, F.; Rinkevich, B.; Robbens, J.; Röttinger, E.; Rudovica, V.; Sabotič, J.; Safarik, I.; Talve, S.; Tasdemir, D.; Schneider, X. T.; Thomas, O. P.;

Toruńska-Sitarz, A.; Varese, G. C.; Vasquez, M. I.; *Front. Mar. Sci.* **2021**, *8*, 629629. [Crossref]

37. Fukruksa, C.; Yimthin, T.; Suwannaroj, M.; Muangpat, P.; Tandhavanant, S.; Thanwisai, A.; Vitta, A.; *Parasit. Vectors* **2017**, *10*, 440. [Crossref]
38. Carroll, A. R.; Copp, B. R.; Davis, R. A.; Keyzers, R. A.; Prinsep, M. R.; *Nat. Prod. Rep.* **2021**, *38*, 362. [Crossref]
39. de la Calle, F.; *Microb. Biotechnol.* **2017**, *10*, 1293. [Crossref]
40. Carroll, A. R.; Copp, B. R.; Davis, R. A.; Keyzers, R. A.; Prinsep, M. R.; *Nat. Prod. Rep.* **2019**, *36*, 122. [Crossref]
41. Song, C.; Yang, J.; Zhang, M.; Ding, G.; Jia, C.; Qin, J.; Guo, L.; *Chem. Biodiversity* **2021**, *18*, e2001020. [Crossref]
42. Yi, M.; Lin, S.; Zhang, B.; Jin, H.; Ding, L.; *Eur. J. Med. Chem.* **2020**, *207*, 112790. [Crossref]
43. Martinez, M. J. A.; Del Olmo, L. M. B.; Benito, P. B.; *Stud. Nat. Prod. Chem.* **2008**, *35*, 101. [Crossref]
44. Gogineni, V.; Schinazi, R. F.; Hamann, M. T.; *Chem. Rev.* **2015**, *115*, 9655. [Crossref]
45. Yasuhara-Bell, J.; Lu, Y.; *Antiviral Res.* **2010**, *86*, 231. [Crossref]
46. Fernandes, C. M.; Fagundes, T. S. F.; dos Santos, N. E.; Rocha, T. S. M.; Garrett, R.; Borges, R. M.; Muricy, G.; Valverde, A. L.; Ponzio, E. A.; *Electrochim. Acta* **2019**, *312*, 137. [Crossref]
47. Silva, S. M. P.; Fagundes, T. S. F.; Chagas, H. A.; Sant'anna, R. C. S.; Aguiar-Alves, F.; Pereira, R. F. A.; Soares, A. R.; Muricy, G. R. S.; Valverde, A. L.; *Braz. J. Dev.* **2020**, *6*, 41540. [Crossref]
48. Fernandes, C. M.; Fagundes, T. S. F.; Junior, N. E. S.; Amaral, B. S.; Cass, Q. B.; Valverde, A. L.; Silva, J. C. M.; Alves, O. C.; Ponzio, E. A.; *Anal. Bioanal. Electrochem.* **2020**, *12*, 437.
49. Fagundes, T. S. F.; da Silva, L. R. G.; Brito, M. F.; Schmitz, L. S. S.; Rigato, D. B.; Jimenez, P. C.; Soares, A. R.; Costa-Lotufo, L. V.; Muricy, G.; Vasconcelos, T. R. A.; Cass, Q. B.; Valverde, A. L.; *Anal. Bioanal. Chem.* **2021**, *413*, 4301. [Crossref]
50. Fagundes, T. S. F.; Macedo, A. L.; Rigato, D. B.; Amaral, B. S.; Jimenez, P. C.; Costa-Lotufo, L. V.; Pereira, R. F. A.; Alves, F. A.; Soares, A. R.; Vasconcelos, T. R. A.; Cass, Q. B.; Valverde, A. L.; *An. Acad. Bras. Cienc.* **2021**, *93*, e20200686. [Crossref]
51. Batista, A. N. L.; dos Santos Jr., F. M.; Valverde, A. L.; Batista Jr., J. M.; *Org. Biomol. Chem.* **2019**, *17*, 9772. [Crossref]
52. Milugo, T. K.; Tchouassi, D. P.; Kavishe, R. A.; Dinglasan, R. R.; Torto, B.; *Front. Trop. Dis.* **2021**, *2*, 718804. [Crossref]
53. Liu, X.; Xu, F.; Shao, C.; She, Z.; Lin, Y.; Chan, W. L. In *Studies in Natural Products Chemistry*, vol. 35; Atta-ur-Rahman, F. R. S., ed.; Elsevier Science: The Netherlands, 2008, p. 197.
54. Debbab, A.; Aly, A. H.; Lin, W. H.; Proksch, P.; *Microb. Biotechnol.* **2010**, *3*, 544. [Crossref]
55. Carroll, A. R.; Copp, B. R.; Davis, R. A.; Keyzers, R. A.; Prinsep, M. R.; *Nat. Prod. Rep.* **2020**, *37*, 175. [Crossref]
56. Zheng, T.; Hong, H.; Wang, F.; Maskaoui, K.; Su, J. Q.; Tian, Y.; *Mar. Pollut. Bull.* **2002**, *45*, 168. [Crossref]
57. Thambugala, K. M.; Daranagama, D. A.; Phillips, A. J. L.; Kannangara, S. D.; Promputtha, I.; *Front. Cell. Infect. Microbiol.* **2020**, *10*, 604923. [Crossref]
58. Abinaya, M.; Vaseeharan, B.; Divya, M.; Vijayakumar, S.; Govindarajan, M.; Alharbi, N. S.; Khaled, J. M.; Al-Anbr, M. N.; Benelli, G.; *Environ. Sci. Pollut. Res. Int.* **2018**, *25*, 18604. [Crossref]
59. Hou, Z.-M.; Yu, S.-Q.; Tao, M.; Xia, C.-B.; Xia, Y.-L.; Wu, X.-F.; Dong, C.-Z.; *J. Chem.* **2021**, *2021*, 6640552. [Crossref]
60. Dong, C.; Hou, Z.; Tao, M.; Xia, Y.; Wu, X.; Cao, Y.; *CN pat. CN112795617A*, **2021**.
61. Ahmad, A.; Wah, I.; Massi, M. N.; Arfah, R.; Karim, H.; *J. Phys.: Conf. Ser.* **2019**, *1341*, 032012. [Crossref]
62. Ahmad, A.; Asmi, N.; Karim, H.; Massi, M. N.; Wahid, I.; Sugrani, A.; *J. Appl. Pharm. Sci.* **2021**, *11*, 39. [Crossref]
63. Gupta, D. K.; Kaur, P.; Leong, S. T.; Tan, L. T.; Prinsep, M. R.; Chu, J. J. H.; *Mar. Drugs* **2014**, *12*, 115. [Crossref]
64. Lin, C.-K.; Wang, Y.-T.; Hung, E.-M.; Yang, Y.-L.; Lee, J.-C.; Sheu, J.-h.; Liaw, C.-C.; *Planta Med.* **2017**, *83*, 158. [Crossref]
65. Wu, D.-L.; Li, H.-J.; Smith, D. R.; Jaratsittisin, J.; Xia-Ke-Er, X.-F.-K.-T.; Ma, W.-Z.; Guo, Y.-W.; Dong, J.; Shen, J.; Yang, D.-P.; Lan, W.-J.; *Mar. Drugs* **2018**, *16*, 229. [Crossref]
66. Guo, Y.-W.; Liu, X.-J.; Yuan, J.; Li, H.-J.; Mahmud, T.; Hong, M.-J.; Yu, J.-C.; Lan, W.-J.; *J. Nat. Prod.* **2020**, *83*, 3372. [Crossref]
67. Yuan, B.; Wu, Z.; Ji, W.; Liu, D.; Guo, X.; Yang, D.; Fan, A.; Jia, H.; Ma, M.; Lin, W.; *J. Biol. Chem.* **2021**, *297*, 100822. [Crossref]
68. Lin, W.; Liu, D.; Li, Y.; *CN pat. CN111440200A*, **2020**.
69. Salvador-Neto, O.; Gomes, S. A.; Soares, A. R.; Machado, F. L. S.; Samuels, R. I.; da Fonseca, R. N.; Souza-Menezes, J.; Moraes, J. L. C.; Campos, E.; Mury, F. B.; Silva, J. R.; *Mar. Drugs* **2016**, *14*, 20. [Crossref]
70. Cirne-Santos, C. C.; Barros, C. S.; Nogueira, C. C. R.; Azevedo, R. C.; Yamamoto, K. A.; Meira, G. L. S.; de Vasconcelos, Z. F. M.; Ratcliffe, N. A.; Teixeira, V. L.; Schmidt-Chanasit, J.; Ferreira, D. F.; Paixao, I. C. N. P.; *Front. Microbiol.* **2019**, *10*, 2426. [Crossref]
71. Esteves, P. O.; de Oliveira, M. C.; Barros, C. S.; Cirne-Santos, C. C.; Laneuvlille, V. T.; Paixao, I. C. P.; *Nat. Prod. Commun.* **2019**, *14*, 10. [Crossref]
72. Cirne-Santos, C. C.; Barros, C. S.; de Oliveira, M. C.; Rabelo, V. W.-H.; Azevedo, R. C.; Teixeira, V. L.; Ferreira, D. F.; Paixao, I. C. N. P.; *Sci. Rep.* **2020**, *10*, 8263. [Crossref]
73. Hidari, K. I. P. J.; Takahashi, N.; Arihara, M.; Nagaoka, M.; Morita, K.; Suzuki, T.; *Biochem. Biophys. Res. Commun.* **2008**, *376*, 91. [Crossref]
74. Cirne-Santos, C. C.; Barros, C. D.; Gomes, M. W. L.; Gomes, R.; Cavalcanti, D. N.; Obando, J. M. C.; Ramos, C. J. B.; Villaca, R. C.; Teixeira, V. L.; Paixao, I.; *Nat. Prod. Commun.* **2019**, *14*. [Crossref]
75. Mohammed, A.; Chadee, D. D.; *J. Am. Mosq. Control Assoc.* **2007**, *23*, 172. [Crossref]
76. Neto, A. A. R.; Gomes Jr., P. P.; Silva, M. C.; Lima, C. S. A.; Yara, R.; Guimaraes, E. B.; De Santana, E. S.; Da Silva, L. A.; De Lira, E. J. R. V.; Vieira, J. R. C.; *An. Acad. Bras. Cienc.* **2018**, *90*, 2141. [Crossref]

77. Ali, M. S.; Beula, J. M.; Anuradha, V.; Yogananth, N.; Ravikumar, S.; *J. Vector Borne Dis.* **2014**, *51*, 106.
78. Karthi, S.; Vinothkumar, M.; Karthic, U.; Manigandan, V.; Saravanan, R.; Vasantha-Srinivasan, P.; Kamaraj, C.; Shivakumar, M. S.; De Mandal, S.; Velusamy, A.; Krutmuang, P.; Senthil-Nathan, S.; *Environ. Sci. Pollut. Res.* **2020**, *27*, 15174. [Crossref]
79. Ali, M. S.; Ravikumar, S.; Beula, J. M.; *Asian Pac. J. Trop. Dis.* **2012**, *2*, 401. [Crossref]
80. Muhaimin; Yusnaidar; Syahri, W.; Latief, M.; Utami, A.; Bemis, R.; Amanda, H.; Heriyanti; Chaerunisaa, A. Y.; *J. Pharm. Sci. Res.* **2018**, *10*, 2228.
81. Uddin, S. J.; Bettadapura, J.; Guillon, P.; Grice I, D.; Mahalingam, S.; Tiralongo, E.; *J. Antivirals Antiretrovirals* **2013**, *5*, 139. [Crossref]
82. Caprioli, V.; Cimino, G.; De, G. A.; Madaio, A.; Scognamiglio, G.; Trivellone, E.; *Comp. Biochem. Physiol. B* **1992**, *103*, 293. [Crossref]
83. Samidurai, K.; Saravanakumar, A.; *Parasitol. Res.* **2011**, *109*, 1107. [Crossref]
84. Muthumari, K.; Anand, M.; Maruthupandy, M.; *Protein J.* **2016**, *35*, 391. [Crossref]
85. Perez, R. M.; Endaya, R. J. T.; Mohammad, F. S.; Sepe, M. C.; *Asian J. Biol. Life Sci.* **2020**, *9*, 145. [Crossref]
86. Hirayama, H.; Matsue, Y.; Komati, Y.; *J. Suizos Jpn* **1960**, *8*, 95.
87. Laille, M.; Gerald, F.; Debitus, C.; *Cell. Mol. Life Sci.* **1998**, *54*, 167. [Crossref]
88. Riccardis, F. D.; Iorizzi, M.; Minale, L.; Riccio, R.; Forges, B. R.; Debitus, C.; *J. Org. Chem.* **1991**, *56*, 6781.
89. Lillsunde, K.-E.; Festa, C.; Adel, H.; De Marino, S.; Lombardi, V.; Tilvi, S.; Nawrot, D. A.; Zampella, A.; D'Souza, L.; D'Auria, M. V.; Tammela, P.; *Mar. Drugs* **2014**, *12*, 4045. [Crossref]
90. Lee, J.-C.; Chang, F.-R.; Chen, S.-R.; Hu, H.-C.; Cheng, Y.-B.; Wu, Y.-H.; Wu, Y.-C.; Backlund, A.; *Mar. Drugs* **2016**, *14*, 151. [Crossref]
91. Garcia, F. A.; Cirne-Santos, C.; Barros, C. S.; Pinto, A. M.; Nunez, M. L. S.; Teixeira, V. L.; Resende, J. A. L. C.; Ramos, F. A.; Paixao, I. C. N. P.; Castellanos, L.; *J. Nat. Prod.* **2021**, *84*, 1373. [Crossref]
92. Cheng, Y. B.; Lee, J. C.; Lo, I. W.; Chen, S. R.; Hu, H. C.; Wu, Y. H.; Wu, Y. C.; Chang, F. R.; *Bioorg. Med. Chem. Lett.* **2016**, *26*, 2344. [Crossref]
93. Zampella, A.; D'Auria, M. V.; Paloma, L. G.; Casapullo, A.; Minale, L.; Debitus, C.; Henin, Y.; *J. Am. Chem. Soc.* **1996**, *118*, 6202. [Crossref]
94. Palagiano, E.; De Marino, S.; Minale, L.; Riccio, R.; Zollo, F.; Iorizzi, M.; Carré, J. B.; Debitus, C.; Lucarain, L.; Provost, J.; *Tetrahedron* **1995**, *51*, 3675. [Crossref]
95. Jares-Erijman, E. A.; Sakai, R.; Rinehart, K. L.; *J. Org. Chem.* **1991**, *56*, 5712. [Crossref]
96. Dhavan, P. P.; Jadhav, B. L.; *SN Appl. Sci.* **2020**, *2*, 843. [Crossref]
97. Alshehri, M. A.; Aziz, A. T.; Trivedi, S.; Alanazi, N. A.; Panneerselvam, C.; Baeshen, R.; Alatawi, A.; *J. Cluster Sci.* **2020**, *31*, 177. [Crossref]
98. Ali, M. S.; Anuradha, V.; Yogananth, N.; Rajathilagam, R.; Chanthuru, A.; Marzook, M. S.; *Int. J. Nano Dimens.* **2015**, *6*, 197.
99. Gnanadesigan, M.; Anand, M.; Ravikumar, S.; Maruthupandy, M.; Vijayakumar, V.; Selvam, S.; Dhineshkumar, M.; Kumaraguru, A. K.; *Asian Pac. J. Trop. Med.* **2011**, *4*, 799. [Crossref]
100. Suresh, U.; Murugan, K.; Panneerselvam, C.; Rajaganesh, R.; Roni, M.; Aziz, A. T.; Al-Aoh, H. A. N.; Trivedi, S.; Rehman, H.; Kumar, S.; Higuchi, A.; Canale, A.; Benelli, G.; *Physiol. Mol. Plant Pathol.* **2018**, *101*, 225. [Crossref]
101. Murugan, K.; Dinesh, D.; Paulpandi, M.; Subramaniam, J.; Rakesh, R.; Amuthavalli, P.; Panneerselvam, C.; Suresh, U.; Vadivalagan, C.; Alsalhi, M. S.; Devanesan, S.; Wei, H.; Higuchi, A.; Nicoletti, M.; Canale, A.; Benelli, G.; *J. Cluster Sci.* **2017**, *28*, 437. [Crossref]
102. Murugan, K.; Dinesh, D.; Paulpandi, M.; Subramaniam, J.; Madhiyazhagan, P.; Suresh, U.; Kumar, P. M.; Mohan, J.; Rajaganesh, R.; Althbyani, A. D. M.; Wang, L.; Wei, H.; Kalimuthu, K.; Parajulee, M. N.; Mehlhorn, H.; Benelli, G.; *Parasitol. Res.* **2015**, *114*, 4349. [Crossref]
103. Sabatini, P.; Devi, C. A.; *Int. J. Pharm. Sci. Res.* **2018**, *9*, 1555. [Crossref]
104. Balaraman, P.; Balasubramanian, B.; Kaliannan, D.; Durai, M.; Kamyab, H.; Park, S.; Chelliapan, S.; Lee, C. T.; Maluventhen, V.; Maruthupandian, A.; *Waste Biomass Valorization* **2020**, *11*, 5255. [Crossref]
105. Abinaya, M.; Rekha, R.; Sivakumar, S.; Govindarajan, M.; Alharbi, N. S.; Kadaikunnan, S.; Khaled, J. M.; Alobaidi, A. S.; Al-Anbr, M. N.; Vaseeharan, B.; *J. Cluster Sci.* **2019**, *30*, 1393. [Crossref]
106. Balakrishnan, S.; Srinivasan, M.; Mohanraj, J.; *J. Parasit. Dis.* **2014**, *40*, 991. [Crossref]
107. Trivedi, S.; Alshehri, M. A.; Aziz, A. T.; Panneerselvam, C.; Al-Aoh, H. A.; Maggi, F.; Sut, S.; Dall'Acqua, S.; *S. Afr. J. Bot.* **2021**, *139*, 432. [Crossref]
108. Ishwarya, R.; Subbaiah, S.; Vaseeharan, B.; Nazar, A. K.; Govindarajan, M.; Alharbi, N. S.; Kadaikunnan, S.; Khaled, J. M.; Al-Anbr, M. N.; *J. Photochem. Photobiol. B* **2018**, *183*, 318. [Crossref]
109. Murugan, K.; Aruna, P.; Panneerselvam, C.; Madhiyazhagan, P.; Paulpandi, M.; Subramaniam, J.; Rajaganesh, R.; Wei, H.; Alsalhi, M. S.; Devanesan, S.; Nicoletti, M.; Syuhe, B.; Canale, A.; Benelli, G.; *Parasitol. Res.* **2015**, *115*, 651. [Crossref]

Submitted: July 26, 2022
Published online: January 20, 2023