Chemico-Biological Interactions 365 (2022) 110072

Contents lists available at ScienceDirect

Chemico-Biological Interactions

journal homepage: www.elsevier.com/locate/chembioint

Review Article

Therapeutic potential of marine macrolides: An overview from 1990 to 2022

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ARTICLE INFO

Keywords:
Macrolides
Therapeutic drug targets
Structure activity relationships
Marine pharmacology

ABSTRACT

The sea is a vast ecosystem that has remained primarily unexploited and untapped, resulting in numerous organisms. Consequently, marine organisms have piqued the interest of scientists as an abundant source of natural resources with unique structural features and fascinating biological activities. Marine macrolide is a top-class natural product with a heavily oxygenated polyene backbone containing macrocyclic lactone. In the last few decades, significant efforts have been made to isolate and characterize macrolides' chemical and biological properties. Numerous macrolides are extracted from different marine organisms such as marine microorganisms, sponges, zooplankton, molluscs, cnidarians, red algae, tunicates, and bryozoans. Notably, the prominent macrolide sources are fungi, dinoflagellates, and sponges. Marine macrolides have several bioactive characteristics such as antimicrobial (antibacterial, antifungal, antimalarial, antiviral), anti-inflammatory, antidiabetic, cytotoxic, and neuroprotective activities. In brief, marine organisms are plentiful in naturally occurring macrolides, which can become the source of efficient and effective therapeutics for many diseases. This current review summarizes these exciting and promising novel marine macrolides in biological activities and possible therapeutic applications.

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https://doi.org/10.1016/j.cbi.2022.110072
Received 26 April 2022; Received in revised form 22 July 2022; Accepted 23 July 2022
Available online 8 August 2022

1. Introduction

Marine life is diverse and abundant in species. Natural products from the marine world have been a significant source of new chemical entities in the quest for potent inhibitors of multiple molecular targets [1,2]. Marine life possesses a range of bioactive compounds of great promise as functional foods and pharmaceuticals. Plenty of bioactive compounds derived from marine sources, such as chitosan, chitin, polyunsaturated fatty acids, vitamins, carotenoids, minerals, bioactive peptides, etc., offer potential health benefits. They are also prominent in conferring anti-carcinogenic and anti-inflammatory activities along with the reduction of cardiovascular disorders. A considerable amount of marine macrolides is currently used in medicine, mainly in response to bacterial and fungal infections [3,4]. According to Burja et al., the marine environment contains over 13,000 different substances [5]. Sponge [6] and cyanobacteria [7] are two vital marine organisms, including bioactive substances, primarily macrolides. Swian et al. discovered only 121 antimicrobial substances in cyanobacteria, including alkaloids, pigments, phenols, aromatic compounds, fatty acids, peptides, macrolides, porphinoids, terpenoids, and polyketides [8,9]. In contrast, Liu et al. demonstrated 118 marine macrolides, most of which had cytotoxic activity [10] (see Tables 1–7, Figs. 1–5), (See Figs. 6–9).

Macrolides are made up of 14-membered lactones (erythromycin and clarithromycin), 15-membered lactones (azithromycin), or 16-membered lactones (josamycin and tylosin) to which amino and/or neutral sugars are connected through glycosidic linkages [11]. For example, Clarithromycin, a novel 14-membered macrolide antibiotic, has been researched to determine its physicochemical qualities and acidic solution stability in comparison to erythromycin (EM). Clarithromycin (CMC) solubility in distilled water was lower than that of EM and declined with increasing temperature. CAM and EM solubility in phosphate buffer solution at 37 °C declined with increasing pH and remained constant above pH 9. The dissociation constants of CAM and EM were found using pH-solubility profiles to be 8.76 and 8.36, respectively. The partition coefficient of CAM was greater than that of EM and increased as pH rose. The degradation of CAM and EM in the acidic solution followed pseudo-first order kinetics [12]. Macrolides are among the most commonly administered broad-spectrum antibiotics, especially for respiratory infections. These medicines, particularly azithromycin, are now known to have time-dependent immunomodulatory effects that contribute to their therapeutic efficacy in both infectious and chronic inflammatory disorders. However, its growing chronic usage in airway inflammation and, more recently, azithromycin in COVID-19 has resulted in a surge in bacterial resistance. The loss of epithelial barrier protection against pathogens and pollutants is another critical element of chronic airway inflammation, such as chronic obstructive pulmonary disease and other inflammatory illnesses [13]. These immunomodulatory actions appear to be polymodal, however evidence shows that many of these effects are caused by suppression of ERK1/2 phosphorylation and nuclear factor kappa B (NF-kB) activation. Macrolides accumulate within cells, indicating that they may interact with receptors or transporters involved in cell cycle and immune control [14].

Macrolides are the compounds of the polyketides group. In medication, only a handful of these drugs are currently used in human. The most common antibacterial macrolides are azithromycin, erythromycin, clarithromycin, josamycin, roxithromycin, and spiramycin [15]. Moreover, telithromycin is the most significant among ketolides due to its equivalent or superior efficacy [15]. Additionally, Nystatin, Amphotericin B, Natamycin are the most frequently used antifungal polyene macrolides [16]. Generally, macrolides of antibacterial classes are potentially active against *Streptococcus* sp., *Staphylococcus* sp., *Haemophilus influenzae*, *Bordetella pertussis*, *Neisseria meningitis*, and *Neisseria gonorrhea*.

Additionally, they are also prescribed to treat diseases triggered by intracellular pathogens, including *Chlamydia* and *Mycoplasma* sp [17]. Antibacterial macrolides have a bacteriostatic impact. They attach reversibly to the 23S ribosomal RNA of large ribosomal subunit (the 50s) of the bacteria, preventing RNA-dependent protein synthesis [18]. Macrolides contain antifungal activity attach to ergosterol, monovalent ion such as Na+, K+, H+, and Cl-leakage, causing pore creation and fungal cell death [19]. Antibiotic resistance among bacteria has recently become such a severe problem. Microorganisms resistant to antimicrobials are estimated to cause 700,000 deaths worldwide each year [16]. Both human and animal infections are being highly resistant to antibiotics [20]. It is hoped that new drugs will be discovered to combat multidrug-resistant strains. Marine macrolides may be the source of these drugs.

Natural phytochemicals originating from marine species frequently have distinct chemical structures and significant biological activity. However, in the case of commercial macrolides, most of them are becoming resistant to antibiotics on a daily basis [21]. As a consequence, a new natural chemical from the sea may be able to assist in overcoming this predicament. In the last decades, a novel class of sea-derived bioactive compounds characterized by macrolides has attracted interest due to its possible anti-inflammatory, antimicrobial and

Table 1
List of some representative marine macrolides.

Macrolides	Source	Country	Ref.
Curvularin	*Curvularia* sp., *Eupenicillium* sp.	China	[28, 29]
(S)-dehydrocurvularin	*Curvularia* sp.	China	[29]
Modiolide A	*Paraphaeosphaeria* sp., *Curvularia* sp.	Japan	[30, 31]
Modiolide B	*Paraphaeosphaeria* sp.	Japan	[30]
Phomolide A and B	*Phomopsis* sp.	–	[32]
Xestodecalactone A-C	*Penicillium* cf. *montanense*	Indonesia	[33]
Amphidinins C–F	*Amphidinium* sp.	Japan	[34]
Dendrodolides A, C and M	*Cladosporium* sp.	China	[35]
Lasiodiplodin	Fungus No. ZZF36	China	[36]
Sporiolides A and B	*Cladosporium* sp.	Japan	[37]
Lobophorin A, B, E, F, H, and I	bacteria actinomycetes, *Streptomyces* sp.	China	[38, 39]
Zearalanone	*Penicillium* sp., *Fusarium* sp.	Japan	[40]
Bromophycolides J-Q	*Callophycus serratus*	Fiji	[41]
Butremycin	*Micromonospora* sp.	Ghana	[42]
Chalcomycin A and B	*Streptomyces* sp. B7064	Hawaii	[43]
Neurymenolides A and B	*Neurymenia fraxinifolia*	Fiji	[44]
Borrelidin	actinomycetes *Nocardiopsis* sp	Korea	[45]
Borrelidins C and D	actinomycetes *Nocardiopsis* sp	Korea	[45]
Leucascandrolide A	*Leucascandra caveolata*	New Caledonia	[46]
13-Deoxytedanolide	*Mycale adhaerens*	Japan	[47]
15G256ι	*Hypoxylon oceanicum*	China	[48]
Misakinolide A	*Theonella* sp.	Japan	[49]
Kabiramide C	*Pachastrissa nux*	Japan	[50]
Scytophycins A–E	*Scytonema pseudohofmanni*	Hawaii	[7]
Gageomacrolactins	*Bacillus subtilis*	Korea	[51]
Halichondramide	*Halichondria* sp.	Kwajalein Island	[16]
Macrolactins A, G, H, I, J, L, and M	*Schizymenia dubyi*	Japan	[52]
Macrolactins A, B, F, and W	*Bacillus subtilis*	Korea	[51]
Macrolactin W	*Bacillus* sp.	South Korea	[53]
Neomaclafungin A	*Actinoalloteichus* sp.	Japan	[54]
Phorboxazoles A and B	*Phorbas* sp.	India	[55]
Reedsmycins A-E	*Streptomyces* sp., *S. youssoufiensis*	–	[56, 57]
Marinisporolides A and B	*Marinispora* strain CNQ-140	USA	[58]
Azalomycin F	*Streptomyces* sp.	China	[59]
Bahamaolides A and B	*Streptomyces* sp.	Bahamas	[60]
PM100117 and PM100118	*Streptomyces caniferus*	–	[61]
Amantelides A and B	Oscillatoriales	Tumon Bay, Guam	[62]
Spongistatins	*Spirastrella spinispirulifera*	Southeast Africa	[63]

Table 2
Evidence of Antibacterial potentials of marine macrolides.

Marine Source	Name of the macrolide	Concentration/Effect	Testing Model	Reference
Symbiotic Dinoflagellate *Amphidinium Sp.*	Amphidinolide Q	MIC value of 16–32 μg/mL	*S. aureus, B. subtilis, Escherichia coli*	[34]
Marine-derived actinomycete	Anthracimycin	MIC value of 0.031 μg/mL	*Bacillus anthracis* (strain UM23C1–1)	[82]
Actinomycete strain identified as *Micromonospora Sp.*	Arisostatins A and B	IC_{50} value of 7 μg/mL	Antibiotic activity against gram-positive bacteria	[83]
Fijian red alga *Callophycus serratus*	Bromophycolides A	MIC value of 5.9 μM MIC value of 5.9 μM	Against Methicillin-Resistant *Staphylococcusa aureus* (MRSA) Vancomycin-Resistant *Enterococcus faecium* (VRE)	[84]
	Bromophycolides B	MIC value of 5.9 μM MIC value of 3.0 μM	Against Methicillin-Resistant *Staphylococcus aureus* (MRSA) Vancomycin-Resistant *Enterococcus faecium* (VRE)	
	Bromophycolides P	MIC value of 1.4 μM MIC value of 13 μM	Against Methicillin-Resistant *Staphylococcus aureus* (MRSA) Vancomycin-Resistant *Enterococcus faecium* (VRE)	[41]
	Bromophycolides Q	MIC value of 1.8 μM MIC value of 5.8 μM	Against Methicillin-Resistant *Staphylococcus aureus* (MRSA) Vancomycin-Resistant *Enterococcus faecium* (VRE)	
Red Sea Sponge *Callyspongia siphonella*	5-Bromo Trisindoline	MIC value of 8 μg/mL MIC value of 16 μg/mL	*Staphylococcus Aureus* *Bacillus subtilis*	[85]
	6-Bromo Trisindoline	MIC value of 4 μg/mL MIC value of 4 μg/mL	*Staphylococcus aureus* *Bacillus subtilis*	
***Micromonospora* Sp. K310**	Butremycin	MIC value of 50 μg/mL	Against *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922	[42]
Marine Strain *Streptomyces* Sp. B7064	Chalcomycin A	MIC value of 0.39 μg/mL	Against Bacteria *Staphylococcus aureus* and *Bacillus subtilis*	[81]
	Chalcomycin B	MIC value of 6.25 μg/mL		
Marine-derived actinomycete *Streptomyces* sp. 7–145	11',12'-Dehydroelaiophylin	MIC value of 1–4 μg/mL	MRSA, vancomycin-resistant *Enterococci* pathogens	[86]
Cladosporium Fungi	Dendrodolides (A, C And M)	MIC values ranging from 3.13 to 25 μM	Against *Bacillus cereus, Tetragenococcus halophilus, Staphylococcus epidermidis, Staphylococcus aureus, Escherichia coli, Pseudomonas putida, Nocardia brasiliensis, Vibrio parahaemolyticus*	[78]
Marine-Derived *Streptomyces* Sp. HK-2006–1	Dihydrochalcomycin	MIC value of 4–32 μg/mL	Against *Staphylococcus aureus*	[81]
Bacillus subtilis	Gageomacrolactins	MIC value of 0.02–0.05 μM	*Staphylococcus aureus, Bacillus subtilis, B. cereus, Escherichia coli, Salmonella typhi, Pseudomonas aeruginosa*	[51]
Marine endophytic fungus No. ZZF36	Lasiodiplodins	MIC value of 6.25 g/mL	Against *Staphylococcus aureus*	
Marine Actinomycete Strain #CNB-837	Lobophorins A, B, E Lobophorins F and I	MIC value of 2–8 μg/mL MIC value of 6.25–50 μg/mL	Against *Bacillus thuringensis* SCSIO BT01 Against *Bacillus subtilis* CMCC63501.	[39]
	Lobophorins B and H	MIC value of 1.57–3.13 μg/mL		
	Lobophorin F	MIC value of 8 μg/mL	Against *Staphylococcus aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212	[38]
Genus Marinispora	Marinomycins A–D	MIC value of 0.1–0.6 μM	Against Methicillin-Resistant *Staphylococcus aureus* (MRSA) and Vancomycin-Resistant *Enterococcus faecium*	[87]
***Streptomyces koyangensis* SCSIO 5802**	Dimeric Neoabyssomicin F And G	MIC value of 16 μg/mL	Against Methicillin-Resistant *Staphylococcus aureus*	[88]
Red Alga *Neurymenia fraxinifolia*	Neurymenolide A	IC_{50} value of 2.1 μM IC_{50} value of 4.5 μM	Methicillin-Resistant *Staphylococcus aureus* Vancomycin-Resistant *Enterococcus faecium*	[44]
Phomopsis Sp. Hzla01–1	Phomolide A	MIC value of 5–10 mg/mL	Against Bacteria *Escherichia coli* CMCC44103	[32]
	Phomolide B	MIC value of 5–10 mg/mL		[77]
***Cladosporium* Sp.**	Sporiolide A	MIC value of 16.7 μg/mL	Against *Micrococcus luteus*	[37]
	Sporiolide B	MIC value of 16.7 μg/mL		
Endophytic fungus *Cladosporium oxysporum* HDN13–314	Thiocladospolides F–J	MIC value of 4 μg/mL	*Edwardsiella tarda*	[89]

immunomodulatory activity. A significant number of diverse macrolides with vital biological activities are generated by marine entities and their symbiotics. Sponges are the prevailing sources of these secondary metabolites; however, microalgae, flagellates, macroalgae, and tunicates have been investigated, and fascinating structures have been found. Aplysiatoxins (ATXs) are a kind of dermatotoxin that has anti-proliferative, tumor-promoting, proinflammatory, and antiviral properties [22]. Aplysiatoxin and debromoaplysiatoxin were initially obtained from the sea hare Stylocheilus longicauda, however further research demonstrated that these compounds are metabolized by cyanobacteria. ATXs have so far only been isolated from marine cyanobacteria *Stylocheilus longicauda* [23]. Based on its structural features, the early isolated ATXs were classified into three groups: aplysiatoxins with a 6/12/6 tricyclic ring system with a macrolactone ring, oscillatoxins with a hexane-tetrahydried. The basic structural skeleton of ATXs (tricyclic ring systems) varies widely, although their aromatic ring-containing side chains frequently remain unaltered. Our group recently isolated two novel ATXs with uncommon carbon skeletons: neo-debromoaplysiatoxin A with a 6/10/6 fused-ring system, which we classified as an aplysiatoxin, and neo-debromoaplysiatoxin B with a 6/6/6 fused ring system, which we classified as an oscillatoxin. Aside from the structural uniqueness, these compounds have good bioactivity, exhibiting significant blocking effect against the potassium channel Kv1.5 [22]. The aplysiatoxins are the first marine macrolides isolated from the sea hare *Stylocheilus longicauda* and exhibited antifungal, immunomodulation, and antiviral properties. Above 200 marine

Table 3
Evidence of antifungal potentials of marine macrolides.

Marine Source	Name of the macrolide	Concentration/Effect	Testing Model	References
Symbiotic *Dinoflagellate amphidinium* Sp.	Amphidinolide Q	MIC value of 16–32 μg/mL	*Candida albicans*	[34]
Streptomyces hygroscopicus	Astolides A And B	MIC value of 4, 8 μg/mL	*C. albicans, A. niger* 219, *C. tropicales*	[94]
Fijian red alga *Callophycus serratus*	Bromophycolides A Bromophycolides B	MIC value of 6.7 μM MIC value of 27.7 μM	*Candida Albicans*	[84]
***Curvularia* Sp., Strain M12**	Curvularin	Higher Concentrations IC_{50} value of 50–100 μg/mL	Motility Impairing Activity Against *Phytophthora capsici* Zoospores	[28]
Bacillus subtilis	Gageomacrolactins	MIC value of 0.04–0.3 μM	*Aspergillus niger, Botrytis cinerea, Colletotrichum acutatum, Candida albicans, Rhizoctonia solani*	[51]
Sponge *Halichondria* Sp.	Halichondramide	MIC value of 12.5 pg/mL MIC value of 0.2 pg/mL	*Trichophyton mentagrophytes* Against *Candida albicans*	[16]
Theonella swinhoei	Hurghadolide A	MIC value of 31.3 μg/mL	Against *Candida albicans*	[95]
Marine *Fusarium* Sp. O5ABR26	8′-Hydroxyzearalenone	MIC value of 200 μg/mL	Against Fungus *Pyricularia oryzae*	[16]
***Janthinobacterium* Spp. ZZ145 And ZZ148**	Janthinopolyenemycins A And B	MIC value of 15.6 μg/mL MBC value of 31.25 μg/mL	*Candida Albicans*	[96]
Marine *Bacillus subtilis*	Macrolactins A, B, F, And W	MIC value of 0.04–0.3 μM	*Aspergillus niger, Botrytis cinerea, Colletotrichum acutatum, Candida albicans, Rhizoctonia solani*	[51]
Sponge *Theonella* Sp.	Misakinolide A	MIC value of 5 μg/mL	Activity against *Candida albicans*	[97]
Sponge *Chondrosia corticata*	Neohalichondramide, (19Z)-Halichondramide	12.5 mm at 25 μg/disk	*Candida Albicans*	[92]
Lithistid Sponge of the Family Neopeltidae	Neopeltolide	MIC value of 0.62 μg/mL	*Candida Albicans*	[98]
New Zealand Marine Sponge *Mycale* Sp.	Pateamine	MIC value of 1 μg/mL MIC value of 20 ng/mL MIC value of 0.4 μg/mL	*Candida albicans* *Trichophyton mentagrophytes* *Cladosporium resinae*	[99]
***Phomopsis* Sp. Hzla01–1**	Phomolide A	MIC values of 5–10 mg/mL	Fungi *Candida albicans* AS2.538 and *Saccharomyces cerevisiae* ATCC9763	[32]
	Phomolide B	MIC values of 5–10 mg/mL	Fungi *Candida albicans* AS2.538 And *Saccharomyces cerevisiae* ATCC9763	[77]
***Cladosporium* Sp.,**	Sporiolide A	MIC value of 8.4–16.7 μg/mL	Activity against *Aspergillus niger, Candida albicans, Cryptococcus neoformans, Neurospora crassa*	[37]
***Penicillium* Cf. Montanense**	Xestodecalactone B	MIC value of 20 mM and higher	Against the Yeast *Candida albicans*	[33]
Marine *Fusarium* Sp. O5ABR26	Zearalenone	MIC value of 6.25 μg/mL	Against Fungus *Pyricularia oryzae*	[16]

Table 4
Evidence of Antiviral potentials of marine macrolides.

Marine Source	Name of the macrolide	Concentration/Effect	Testing Model	Reference
***Ascomycetous* strain 222**	Balticolid	IC50 value of 0.45 μM	Inhibition of mammalian Herpes Simplex Viruses (Types I And II)	[100]
The fijian red alga *Callophycus serratus*	Bromophycolides A	IC_{50} value of 9.1,9.8 μg/mL	HIV strains 96USHIPS7 and UG/92/029 inhibition	[84]
Hamigera tarangaensis	Hamigeran B	Concentration of 132 μg per disk	Herpes and Polio	[104]
Gram-Positive Marine Bacterium	Macrolactin A	IC_{50} value of 5.0 and 8.3 μg/mL	Inhibition of mammalian Herpes Simplex Viruses (Types I And II) and protected T-Lymphoblast cells against Human HIV Viral Replication	[105]

Table 5
Evidence of Anti-Malarial potentials of marine macrolides.

Marine Source	Name of the macrolide	Concentration/Effect	Testing Model	Reference
Mangrove fungus, *Aigialus parvus* BCC 5311	Aigialomycin D	IC_{50} value of 6.6 μg/mL	*In vitro* antimalarial activity	[111]
Cyanobacterium *Okeania Hirsuta*	Acetonide A	IC_{50} value of 20 ± 3 μg/mL	Chloroquine-sensitive *Plasmodium falciparum* strain	[109]
	Acetonide B	IC_{50} value of 2.3 ± 0.2 μg/mL	HB3	
	Acetonide C	IC_{50} value of 9.7 ± 1.7 μg/mL		
	Bastimolide A	IC_{50} value of 80 nM	*Plasmodium falciparum* TM90-C2A	[108]
		IC_{50} value of 90 nM	*Plasmodium falciparum* TM90-C2B	
		IC_{50} value of 140 nM	*Plasmodium falciparum* W2	
		IC_{50} value of 270 nM	*Plasmodium falciparum* TM91-C235	
		IC_{50} value of 2.6 ± 0.2 μg/mL	Chloroquine-sensitive *Plasmodium falciparum* strain	[109]
	Bastimolide B	IC_{50} value of 5.7 ± 0.7 μg/mL	HB3	
The fijian red alga *Callophycus serratus*	Bromophycolides R–U	IC_{50} value of 0.9–8.4 μM	Against *Plasmodium Falciparum*	[106]
Sorangium cellulosum	Chlorotonil A	IC_{50} value of 4–32 nM	*Plasmodium falciparum*	[107]
Mangrove fungus, *Aigialus parvus* BCC 5311	Hypothemycin	IC_{50} value of 2.2 μg/mL	*In vitro* antimalarial activity	[111]
Thai sponge *Pachastrissa nux*	Kabiramide G	IC_{50} value of 0.7 μg/mL	Against *Plasmodium falciparum* K1	
Sponge *Pachastrissa nux*	Kabiramide L	IC_{50} value of 2.6 μM	Against *Plasmodium falciparum* K1	[50]
Lyngbya majuscula	Malyngolide	IC50 value of 19 μM	*Plasmodium falciparum*	[112]
Marine cyanobacterium	Palstimolide A	IC_{50} value of 172.5 nM	*Plasmodium falciparum* Dd2	[110]

Table 6
Evidence of Anti-inflammation and anticancer potentials of marine macrolides.

Therapeutic Effect	Marine Source	Name of the macrolide	Concentration/Effect	Testing Model	Reference
Anti-inflammatory	Sediment bacterium of the genus *Nocardiopsis*	Fijiolides A	IC_{50} value of 0.57 μM	Reducing TNF-α-inducing NFκB activation	[175]
	Marine sponge *Halichondria okadai*	Halichlorine	IC_{50} value of 7 μg/mL	Inhibition to VCAM-1	[176]
Anti-cancer	Okinawan Marine Sponge *Hyrtios altum*	Altohyrtins B–C	IC_{50} value of 0.02 ng/mL	Against KB Cell	[177]
			IC_{50} value of 0.3 ng/mL	Potent cytotoxic activity against L1210 murine leukemia cells	
	Spongia Sp	Altohyrtina	IC_{50} 3 X 10 $^{-11}$ g/mL	Potent cytotoxic activity against L1210 murine leukemia cells	[102]
			IC_{50} 1 X 10 $^{-11}$ g/mL	Human Epidermoid Carcinoma KB Cells	
	Marine dinoflagellates of the genus amphidinium	Amphidinolides A	IC_{50} value of 0.05 ng/mL	Cytotoxic activities against Murine Leukemia L1210 Cells In Vitro	[178]
	Dinoflagellate amphidinium Sp.	Amphidinolides B6	IC_{50} value of 0.6 μg/mL	Against DG-75 Cells	[179]
		Amphidinolides B7	IC_{50} value of μg/mL	Against DG-75 Cells	
		Amphidinolide C2	IC_{50} value of μg/mL	Potent Cytotoxic Activity Against L1210 Murine Leukemia Cells	[180]
			IC_{50} value of 3 μg/mL	Human Epidermoid Carcinoma KB Cells	
		Amphidinolide G	IC_{50} value of 0.0054 μg/mL	Potent cytotoxic activity against L1210 murine leukemia cells	[181]
			IC_{50} value of 0.00048 μg/mL	Human Epidermoid Carcinoma KB Cells	
		Amphidinolide H	IC_{50} value of 0.0059 μg/mL	Potent cytotoxic activity against L1210 murine leukemia cells	[181]
			IC_{50} value of 0.00052 μg/mL	Human Epidermoid Carcinoma KB Cells	
		Amphidinolides O	IC_{50} value of 1.7 μg/mL	Potent cytotoxic activity against L1210 murine leukemia cells	[182]
			IC_{50} value of 1.6 μg/mL	KB Cells	
		Amphidinolides P	IC_{50} value of 3.6 μg/mL	Potent cytotoxic activity against L1210 murine leukemia cells	[182]
			IC_{50} value of 5.8 μg/mL	KB Cells	
		Amphidinolide Q	IC_{50} value of 6.4 μg/mL	Potent cytotoxic activity against L1210 murine leukemia cells	[183]
		Amphidinolides R	IC_{50} value of 1.4 μg/mL	Potent cytotoxic activity against L1210 murine leukemia cells	[184]
			IC_{50} value of 4.0 μg/mL	Human Epidermoid Carcinoma KB Cells	
		Amphidinolides S	IC_{50} value of 0.67 μg/mL	Potent Cytotoxic Activity Against L1210 Murine Leukemia Cells	[184]
			IC_{50} value of 6.5 μg/mL	Against KB Cells	
		Amphidinolide X	IC_{50} value of 0.6 μg/mL	Potent Cytotoxic Activity Against L1210 Murine Leukemia Cells	[185]
	Japanese Sea Hare *Aplysia Kurodia*	Aplyronine A	IC_{50} value of 0.039 ng/mL	*In Vitro* Cytotoxicity Against Hela-S3 Cells	[140]
			T/C value of 545% at a dose of 0.08 mg/kg	*In Vivo* against P388 Murine Leukemia cells	
			T/C value of 556% at 0.04 mg/kg	*In Vivo* against Lewis Lung Carcinoma cells	
			T/C value of 398% at 0.04 mg/kg	*In Vivo* against Ehrlich Carcinoma cells	
			T/C value of 255% at 0.08 mg/kg	*In Vivo* against Colon 26 Carcinoma cells	
			T/C value of 201% at 0.04 mg/kg	*In Vivo* against B16 Melanoma cells	
	Aplysia kurodai	Aplyronines D–H	IC_{50} value of 0.075, 0.18, 0.19, 0.12, 9.8 nM	*In Vitro* Cytotoxicity Against Hela-S3 Cells	[186]
	Red Alga *Acanthophora Spicifera*,	Apralactone A	IC_{50} Value 1.25 μM	Human Tumor Cell Lines	[147]
	Sponge Dysidea Sp.	Arenolide	IC_{50} value of 21 mM	HCT-116 Human Colon Tumor Cell Lines	[187]
			IC_{50} value of 9.8 mM	Against A2780 Cells	
	Marine actinomycete *Salinispora arenicola*	Arenicolide A	IC_{50} value of 30 μg/mL	Human Epidermoid Carcinoma KB Cells	[188]
	Actinomycete Strain Identified as Micromonospora Sp	Arisostatins A And B	IC_{50} value of 0.4 μg/mL	Cytotoxicity Against the Human Myeloid Leukemia U937 Cell Line	[83]
	Streptomyces hygroscopicus	Astolides A And B	IC_{50} value of 1.2–1.4 μM	K-562, Pgp-Positive MDR Subline K-562/4	[94]
	Dolabella auricularia	Aurisides A	IC_{50} value of 0.17 μg/mL	*In Vitro* Cytotoxicity Against Hela-S3 Cells	[26]
		Aurisides B	IC_{50} value of 1.2 μg/mL		
	Ascidian didemnidae Sp.	Biselides A	IC_{50} value of 3.53 μM	Against NCI–H460	[189]
			IC_{50} value of 3.72 μM	Against MDA-MB-231 Cells	
		Biselides C	IC_{50} value of 18.0 μM	Against NCI–H460	
			IC_{50} value of 25.5 μM	Against MDA-MB-231 Cells	
	Marine Cyanobacterium Lyngbya Sp.	Biselyngbyolide A	IC_{50} value of 0.22 μM	*In Vitro* Cytotoxicity Against Hela-S3 Cells	[190]
			IC_{50} value of 0.027 μM	Against HL60 Cells	
		Biselyngbyolide B	IC_{50} value of 3.5, 0.82 μM	In Vitro Cytotoxicity Against Hela-S3 Cells, HL60 Cells	[191]
			IC_{50} value of 7.5 μg/mL	Human Epidermoid Carcinoma KB Cells	
	Lyngbya Sp.	Biselyngbyaside	IC_{50} value of 0.1 μg/mL	In Vitro Cytotoxicity Against Hela-S3 Cells	[192]
	Red Alga *Callophycus serratus*	Bromophycolide A	IC_{50} value of 6.7 μM	Against A2780 Cells	[84]
		Bromophycolide H	IC_{50} value of 3.88 μM	In Vitro Cytotoxicity Against DU4475 Breast Tumor Cells	[193]
		Bromophycolides J–Q	IC_{50} value of 2.1–7.2 μM	Against BT-549, DU4475, MDA-MD-468 Et Al	[41]

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Table 6 (*continued*)

Therapeutic Effect	Marine Source	Name of the macrolide	Concentration/Effect	Testing Model	Reference
		Bromophycolide K	IC_{50} value of 1.5 μM	In Vitro Cytotoxicity Against DU4475 Breast Tumor Cells	[41]
	Bugula nertina	Bryostatin 10	ED_{50} value of 0.33 μg/ml	*In Vivo* against P388 Murine Leukemia cells	[194]
	Marine Mollusk *Styloheilus longicauda*	Bryostatins 16	ED_{50} value of 0.0093 μg/mL	*In Vivo* against P388 Murine Leukemia cells	[195]
		Bryostatins 17	ED_{50} value of 0.019 μg/mL		
		Bryostatins 18	ED_{50} value of 0.033 μg/mL	*In Vivo* against P388 Murine Leukemia cells	
		Callipeltoside B	IC_{50} value of 15.1 μg/mL	Against NSCLC-N6 Cells	[103]
		Callipeltoside C	IC_{50} value of 30.0 μg/mL		[103]
	Sponge *Callyspongia* Sp.	Callyspongiolide	IC_{50} value of 70 nM	Against Jurkat J16 T	[196]
			IC_{50} value of 60 nM	Against Ramos B Lymphocytes	
	Dinoflagellate, *Amphidinium* Sp.	Caribenolide I	IC_{50} value of 1.6 nM	HCT-116 Human Colon Tumor Cell Lines	[197]
			IC_{50} value of 1.6 nM	HCT-116 Human Colon Tumor Cell Lines	
			IC_{50} value of 0.03 mg/kg	*In Vivo* against P388 Murine Leukemia cells	
	Sponge Dactylospongia Sp.	Dactylolide	IC_{50} value of 3.2 μg/mL	Against L1210, SK-OV-3 Cells	[198]
	Marine-Derived Fungus *Myrothecium roridum*	12,13-Deoxyroridin E	IC_{50} value of 25 μg/mL	Against HL-60, L1210 Cells	[199]
			IC_{50} value of 15 μg/mL		
	Lipophilic Extract Of The Sponge *Mycale adhaerens*	13-Deoxytedanolide	IC_{50} value of 0.094 ng/mL	In Vitro Cytotoxicity Against P388 Murine Leukemia Cells	[47]
			T/C value of 189% at a dose of 0.125 mg/kg	Decreases the growth rate of P388 tumors implanted in mice	
	Okinawan Marine Sponge *Hyrtios altum*	5-Desacetylaltohytrin A	IC_{50} value of 0.03 ng/mL	Against KB Cell	[177]
			IC_{50} value of 2.3 ng/mL	Potent cytotoxic activity against L1210 murine leukemia cells	
	Dolabella auricularia	Dolabelide A	IC_{50} value of 6.3 μg/mL	In Vitro Cytotoxicity Against Hela-S3 Cells	[200]
		Dolabelide B	IC_{50} value of 1.3 μg/mL		
		Dolabelides C	IC_{50} value of 1.9 μg/mL	In Vitro Cytotoxicity Against Hela-S3 Cells	[201]
		Dolabelides D	IC_{50} value of 1.5 μg/mL		
	D. auricularia	Dolastatin 19	Growth Inhibition (GI_{50}) values of 0.72 μg/mL	Against Breast MCF-7 Cell Lines	[26]
			Growth Inhibition (GI_{50}) values of 0.76 μg/mL	Against Colon KM20L2 Cell Lines	
	Papua New Guinea Marine Sponge *Cinachyrella Enigmatica*	Enigmazole A	IC_{50} value of 0.37 μg/mL	Against IC-2 Cells	[202]
	Streptomyces Species Separated from A Marine Fish	Halichoblelide B	ED_{50} value of 0.63 μM	*In Vivo* against P388 Murine Leukemia cells	[203]
	Halichondria okadai	Halichondrin B	IC_{50} value of 0.3 nM	Against L1210 Murine Leukemia Cells *In Vitro*, And Also Displayed Potent *In Vivo* Activity Against	[204]
	Hamigera tarangaensis	Hamigeran B	IC_{50} value of 8 μM.	*In Vivo* against P388 Murine Leukemia cells	[104]
	Sponge *Mycale magellanica*	30-Hydroxymycalolide A	IC_{50} value of 0.019 μg/mL	Potent cytotoxic activity against L1210 murine leukemia cells	[205]
		32-Hydroxymycalolide A	IC_{50} value of 0.013 μg/mL		
		38-Hydroxymycalolide B	IC_{50} value of 0.015 μg/mL		
	The Red Sea Sponge *Theonella Swinhoei*.	Hurghadolide A	IC_{50} value of 365 nM	HCT-116 Human Colon Tumor Cell Lines	[95]
	Marine Tunicate Eudistoma Cf. Rigida.	Iejimalides C	IC_{50} value of 4.7 μg/mL	Human Epidermoid Carcinoma KB Cells	[206]
			IC_{50} value of 0.2 μg/mL	Potent Cytotoxic Activity Against L1210 Murine Leukemia Cells Cells	
		Iejimalides D	IC_{50} value of 10 μg/mL	Human Epidermoid Carcinoma KB Cells	[206]
			IC_{50} value of 0.58 μg/mL	Potent Cytotoxic Activity Against L1210 Murine Leukemia Cells	
	Dinoflagellate *Amphidinium* Species	Iriomoteolide-2a	IC_{50} value of 0.006 μg/mL	Against DG-75 Cells	[207]
		Iriomoteolide-3a	IC_{50} value of 0.08 μg/mL	Against DG-75, Cells	[208]
		Iriomoteolide 4a	IC_{50} value of 0.8 μg/mL	Against DG-75 Cells	[209]
		Iriomoteolide 5a	IC_{50} value of 1.0 μg/mL	Against DG-75 Cells	[209]
		Iriomoteolide 9a	IC_{50} value of 15 μM	In Vitro Cytotoxicity Against Hela-S3 Cells	[210]
		Iriomoteolide-10a	IC_{50} value of 1.5 μM	In Vitro Cytotoxicity Against Hela-S3 Cells	[211]
			IC_{50} value of 1.2 μM	Against DG-75	
			IC_{50} value of 3.3 μM	Against MH134 Cells	
		Iriomoteolide 11a	IC_{50} value of 2 μM	HCT-116 Human Colon Tumor Cell Lines	[210]
		Iriomoteolide-12a	IC_{50} value of 50 μM	Against DG-75 Cells	[211]

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Table 6 (*continued*)

Therapeutic Effect	Marine Source	Name of the macrolide	Concentration/Effect	Testing Model	Reference
	Isolated from a sponge *Halichondria* Sp.	Kabiramide C	IC_{50} value of 0.01–0.03 μg/mL	Potent Cytotoxic Activity Against L1210 Murine Leukemia Cells	[212]
	Lyngbya Sp.	Koshikalide	IC_{50} value of 42 μg/mL	*In Vitro* Cytotoxicity Against Hela-S3 Cells	[213]
	Caribbean Marine Sponge *Forcepia* Sp.	Lasonolide A	IC_{50} value of 40 ng/mL	Against The A-549 Human Lung Carcinoma	[214]
			IC_{50} value of 2 ng/mL	P388 Murine Leukemia Cell Lines	
	Sponge Forcepia Sp.	Lasonolides C–E	IC_{50} value of 0.13, 4.5, 0.31 μM	Against A-549 Cells	[215]
			IC_{50} value of 0.38. 4.89, 0.57, 15.6 μM	Against PANE-1 Cells	
	Sponge *Fasciospongia rimosa*	Latrunculin S	IC_{50} value of 0.5–1.2 μg/mL	Against P388, A549, HT29, MEL28 Cells	[216]
		Laulimalide	IC_{50} value of 15 nM	Against KB Cell Line	[1].
			IC_{50} value of 6–7 nM	Against MDA-MB-435 Cell Line	
	Marine Sponge *Leiodermatium*	Leiodolides A And B	IC_{50} value of 1.4, 3.8 μg/mL	HCT-116 Human Colon Tumor Cell Lines	[217]
	L. bouillonii	Lyngbouilloside	IC_{50} value of 17 μM	Target Neuroblastoma Cells	[218]
	Lyngbya Sp.	Lyngbyabellin C	IC_{50} values of 2.1 μg/mL	Human Epidermoid Carcinoma KB Cells	[219]
			IC_{50} values of 5.3 μg/mL	Against Lovo Cells	
	Gram-Positive Marine Bacterium	Macrolactin A	IC_{50} value of 3.5 μg/mL	B 16-F10 Murine Melanoma Cancer Cells In In Vitro Assays	[102]
	Periconia Sp	Macrosphelide M	IC_{50} value of 33.2 μM	Against HL-60 Cell	[220]
	Okinawan Sponge *T. swinhoei*	Misakinolide A	IC_{50} value of 0.035 μg/mL	Potent Cytotoxic Activity Against L1210 Murine Leukemia Cells	[221]
			IC_{50} value of 0.01 μg/mL	In Vivo against P388 Murine Leukemia cells	
			IC_{50} value of 0.0005–0.005 μg/mL	Against Human Tumor Cells (HCT-8, A-549, And MDA-MB-231).	
	Genus *Marinispora*	Marinomycins A–D	LC_{50} values of 0.005–50 μM	Inhibited the growth of most of the 60 cell lines used in NCI's assays	[188]
	Spongge polyfibrospongia Sp	Miyakolide	IC_{50} values of 17.5 μg/mL	In Vivo against P388 Murine Leukemia cells	[222]
	Fungus *Paramyrothecium roridum*	Myrothecines H	IC_{50} value of 8 μM	Against Hepg-2 Cells	[223]
		Myrothecines I	IC_{50} value of 0.4 μM		
		Neolaulimalide	IC_{50} value of 50 nM	In Vivo against P388 Murine Leukemia cells	[1].
			IC_{50} value of 10 nM	Against A-549 Cell Line	
			IC_{50} value of 25 nM	Against HT-29 Cell Line	
			IC_{50} value of 25 nM	Against MEL-28 Cell Line	
	Lithistid sponge of the Family Neopeltidae	Neopeltolide	IC_{50} value of 1.2 μg/mL	Against A-549 Cell Lines	[98]
			IC_{50} value of 5.1 μg/mL	Against NCI-ADR-RES Cell Lines	
			IC_{50} value of 0.56 μg/mL	In Vivo against P388 Murine Leukemia cells	
		Neurymenolide A	IC50 value of 3.9 mM	In Vitro Cytotoxicity Against DU4475 Breast Tumor Cells	[44]
	Marine-Derived Actinomycete of The Genus Streptomyces	Octalactins A	IC_{50} value of 0.0072 μg/mL	B16–F10 Murine Melanoma Cell Lines	[102]
			IC_{50} value of 0.5 μg/mL	HCT-116 Human Colon Tumor Cell Lines	
	Antarctic Tunicate *Synoicum adareanum*	Palmerolide A	LC_{50} value of 18 μM	Against HCC-2998	[224]
			LC_{50} value of 6.5 μM	Against RXF 393	
	New Zealand Marine Sponge *Mycale* Sp.	Pateamine	IC_{50} value of 0.15 ng/mL	In Vivo against P388 Murine Leukemia cells	[99]
	Indian Ocean Sponge *Phorbas* Sp.	Phorboxazoles A And B	Growth Inhibition (GI50) values of 1.6 nM	Inhibited the growth of most of the 60 cell lines used in NCI's assays	[55,165]
			IC_{50} values of 0.25 nM	Solid tumor cells such as colon HCT 116	
	Sponge *Phorbas* Sp.	Phorbaside C	IC_{50} value of 2 μM	HCT-116 Human Colon Tumor Cell Lines	[225]
	Marine Sponge *Poecillastra* Sp.	Poecillastrins E	IC_{50} value of 6.7 ng/mL	Against 3Y1 Cells	[226]
		Poecillastrins F	IC_{50} value of 1.2 ng/mL		
		Poecillastrins G	IC_{50} value of 5.0 ng/mL		
	A Benthic Dinoflagellate, *Prorocentrum lima*	Prorocentrolide	IC_{50} value of 20 μg/mL	Cytotoxicity against L1210 Cells	[102]
	Sponge *Haliclona* Sp.	Salicylihalamides A	Growth Inhibition (GI_{50}) value of 7 ± 2 nM	Inhibited the growth of most of the 60 cell lines used in NCI's assays	[227]
		Salicylihalamides B	Growth Inhibition (GI_{50}) value of 60 ± 25 nM		
	Unidentified Nudibranch of Hawaiian Waters	Sphinxolide	IC_{50} value of 35 pg/mL	Against KB Cell Line	[228]
	Spongia Sp.	Spongidepsin	IC_{50} value of 0.56 μg/mL	Against J774.A1 Cells	[229]
			IC_{50} value of 0.66 μg/mL	Against HEK-392 Cells	
			IC_{50} value of 0.42 μg/mL	Against WEHI-164 Cells	
		Spongiastatin 1	Growth Inhibition (GI_{50}) values of 2.5–3.5 × 10^{-11} M	Against HL-60, NCI-116, DMS 114 cells	[230]

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Table 6 (*continued*)

Therapeutic Effect	Marine Source	Name of the macrolide	Concentration/Effect	Testing Model	Reference
		Spongistatin 1	Growth Inhibition (GI_{50}) values of 0.02–0.4 nM	Effective against solid tumour cell lines derived from patients with melanoma, lung cancer, colon cancer and brain tumors	[157]
			IC_{50} values of 0.02 nM	Potent cytotoxic activity against L1210 murine leukemia cells	[158]
			Growth Inhibition (GI_{50}) values of 0.03 nM	Retaining its potency against a subset of highly chemoresistant tumors types	[157]
			Growth Inhibition (GI_{50}) values of 2.5–3.5 X 10^{-11}M	*In Vivo* against P388 Murine Leukemia cells	[102]
	Caledonian Sponge *Neosiphonia superstes*	Superstolide A	IC_{50} value of 0.04 μg/mL	Cytotoxic Against NSCLC-N6-L16 (Human Bronchopulmonary Non-Small-Cell Lung Carcinoma) Cells	[231]
			IC_{50} value of 0.02 μg/mL	Murine Leukemia Cells Expressing Resistance Toward Doxorubicine P388	
	Marine Sponge *Neosiphonia Superstes*	Superstolide B	IC_{50} value of 0.005 μg/mL	Human Epidermoid Carcinoma KB Cells	[216]
			IC_{50} value of 0.003 μg/mL	*In Vivo* against P388 Murine Leukemia cells	
			IC_{50} value of 0.039 μg/mL	Against NSCLC-N6-L16 Cells	
	Okinawan Sponge *T. swinhoei*	Swinholide A	IC_{50} value of 0.03 μg/mL	Potent Cytotoxic Activity Against L1210 Murine Leukemia Cells	[221]
	The Red Sea Sponge *Theonella swinhoei*	Swinholides A	IC_{50} values of 0.041 μg/mL	Human Epidermoid Carcinoma KB Cells	[232]
		Swinholides B	IC50 value of 0.052 μg/mL		
		Swinholides C	IC_{50} value of 1.1 μg/mL		
		Swinholides I	IC_{50} value of 5.6 nM	HCT-116 Human Colon Tumor Cell Lines	[95]
	Marine Sponge	Tausalarin C	IC_{50} value of 1 μg/mL	Against K562 Cells	[233]
	Marine Sponge *Ircinia* Sp.	Tedanolide C	IC_{50} value of 0.057 μg/mL	HCT-116 Human Colon Tumor Cell Lines	[234]
	Okinawan Marine Sponge *Theonella* Sp.	Theonezolide A	IC_{50} value of 0.75 μg/mL	Cytotoxicity Against Murine Lymphoma L1210	[235]
			IC_{50} value of 0.75 μg/mL	Human Epidermoid Carcinoma KB Cells	
	Marine Sponges *Cacospongia Mycofijiensis* and *Fasciospongia Rimasa*	Zampanolide	IC_{50} value of 0.29–0.46 mM	Antiproliferative efficacy both against Docetaxel-resistant and Docetaxel-sensitive prostate cancer cell lines	[149]

macrolides have been established to emphasize active biological properties, including cytotoxicity, immunomodulation, anticancer, antifungal, and antiviral activity [24,25]. Marine macrolides demonstrate counter-proliferative cytotoxic action with different molecular targets and may be a suitable choice against drug-resistant tumor cells [1]. The literature on the biological activities of marine macrolides was investigated and analyzed in this review, which included a wide variety of bioactive properties such as antimicrobial (antibacterial, antifungal, antimalarial, antiviral), anti-inflammatory, antidiabetic, cytotoxic, and neuroprotective activities.

2. Occurrence of marine macrolides

Nature has been considered a critical reservoir of molecular diversity for a long time, and natural products are essential for discovering and developing efficient medicinal products. Specifically, a great source of bioactive compounds has demonstrated the marine environment; many modern chemotypes are not identified by terrestrial sources [26]. In the last few years, a significant number of new macrolides have been discovered from marine organisms. Many macrolides are extracted from different marine organisms such as marine microorganisms, sponges, zooplankton, mollusks, cnidarians, red algae, tunicates, and bryozoans. Remarkably, the primary macrolide sources are fungi, dinoflagellates, and sponges [27]. Most marine macrolides are biologically fascinating, and some play a crucial role as potential drug molecules or tools to support basic biological science.

3. Therapeutic potential

3.1. Marine macrolides as antimicrobial agents

Antimicrobial resistance is now a great concern to human health: both the invention of novel antimicrobials and combination treatment seek to tackle this growing resistance [64,65]. The actinomycetes have 46 prototype molecules and 17 structural variants, all of which have lactone and guanidyl side chains [66,67]. According to structure-activity analysis, the lactone ring and the terminal guanidine group of these bioactive are essential for antimicrobial action. The development of guanidyl side-chain lipoteichoic acid-targeting *Staphylococcus aureus* shows in particular that these compounds have considerable potential to evolve into anti-inflammatory and antibacterial drugs. Guanidine-containing macrolides in polyhydroxyl macrolides have shown broad-spectrum antifungal and antibacterial activity and can significantly impede the development of fungi, yeast and gram-positive bacteria [59,68,69]. The analysis of the antimicrobial mechanism showed that the primary site of action for these compounds is the cell membrane against fungi and bacteria. They can modify the permeability of the plasma membrane, causing cellular materials to escape out [64,70].

3.1.1. Antibacterial activity

Macrolides are bacteriostatic antibiotics that work by binding to the 50S ribosomal subunit to suppress protein synthesis. The extensive use of macrolides has been linked to increasing macrolide resistance in *S. pneumoniae,* and the use of macrolides to treat pneumococcal infections has been linked to clinical failures [71]. Macrolide resistance in *S. pneumoniae* is caused by ribosomal dimethylation by an enzyme encoded by erm(B), efflux by a two-component efflux pump encoded by mef (E)/mel(msr(D)), and, less typically, alterations in the macrolide ribosomal target site. A diverse set of genetic elements has evolved that promote macrolide resistance in *S. pneumoniae*, such as erm(B) on Tn917 and the mef (E)/mel operon on the 5.4- or 5.5-kb Mega element. Lasiodiplodins, resorcinolic macrolides, derived from the marine endophytic fungus No. ZZF36 was identified in the Zhanjiang Sea's brown alga *Sargassum* sp. [72]. They revealed promising inhibitory potential against *Staphylococcus aureus* (MIC 6.25 μg/mL), as well as less potent

Table 7
Evidence of Antimitotic, Antidiabetic, Anti-inflammatory potentials of marine macrolides.

Therapeutic Effect	Marine Source	Name of the macrolide	Concentration/Effect	Testing Model	Reference
Antidiabetic	*Mycosphaerella* Sp. SYSU-DZG0 I	Asperchalasine A	IC_{50} value of 15.7 mM	Inhibitory Activity Against α-Glucosidase	[240]
		Asperchalasine I	IC_{50} value of 17.1 mM		
	Aspergillus Sp. ZJ-68	Asperpanoid A	IC_{50} value of 12.4 mM		[239]
	Aspergillus versicolor SYSU-SKS025	7-Deoxy-7,14-Didehydrosydonol	IC_{50} value of 7.5 mM		[257]
	Mycosphaerella Sp. SYSU-DZG0 I	Epicoccolide B	IC_{50} value of 26.7 mM		[240]
	Sponge *Penares* Sp.	Penarolide sulfates A1	IC50 value of 1.2 μg/mL		[246]
		Penarolide sulfates A2	IC50 value of 1.5 μg/mL		
	Enteromorpha prolifera	Wailupemycins H And I (6 S, 15 R)	Ki/IC_{50} value of 16.8/19.7 mM		[236]
Antimitotic	Marine sponge *Spirastrella coccinea*	Spirastrellolide A	IC_{50} value of 100 ng/mL	Accelerating the entry of cells into mitosis	[258]
	Marine sponge *Axinella carteri*	Halistatin 1, 2	undetermined	Inhibition of tubulin polymerization	[259]
Neuroprotective activity	*Brownbryozoa* (Bugulaneritina)	Bryostatin	single-dose (25 μg/m^2) randomized double-blind Phase IIa clinical trial	Potent modulation of protein kinase C; induction of synaptogenesis and amelioration of deficits in rats and mice models of neurodegenerative diseases	[260]
	Marine-derived actinomycete *Streptomyces caniferus*	Caniferolide A		reduced neuroinflammatory markers in BV2 microglial cells activated with lipopolysaccharide (LPS)	[248]
	Soft coral (*Sinularia flexibilis*)	11-Dehydrosinulariolide		In vitro: anti-apoptotic and anti-inflammatory activity onSH-SY5Y cells treated with 6-OHDA	[253]
				In vivo: amelioration of PD symptoms in rat and zebra fish models	[261]
	Oscillatoria sp.	Palmyrolide A	IC_{50} value of 5.2 μM	Inhibited sodium influx in mouse neuroblastoma cells	[254]
			IC_{50} value of 3.7 μM	Spontaneous Ca^{2+} oscillations in primary cultures of murine cerebrocortical neurons	
	Marine mangrove fungus *Xylaria* sp	Xyloketal B	IC_{50} value of 100 μM	Inhibited ischemia-induced PC12 cell injury	[256]

inhibitory activity against *Salmonella enteritidis*, *Bacillus subtilis*, and *Candida albicans* [16]. However, 5-hydroxy-de-O-methyllasiodiplodin was only found to be potential at 100 μg/mL against *S. aureus* [73]. Contrary, Sporiolides A and B derived from the fungus Cladosporium sp. have been reported to offer significant protective action against *Micrococcus luteus* (MIC 16.7 μg/mL) [74]. Additionally, sporiolide A exerted antifungal activity against *Cryptococcus neoformans, Aspergillus niger, Neurospora crassa,* and *Candida albicans* with MICs ranging from 8.4 to 16.7 μg/mL [37].

Dunaliella salina (DS) exhibited promising antimicrobial activities at MIC of 40 mg/mL against gram-negative bacterium and fungi, and MIC for *Thalassiosira species* was 40 mg/mL against fungi and *Staphylococcus aureus*. Both sample extracts were also shown to be responsive to *Escherichia coli*. Two microalgae, namely *Chaetoceros gracilis* and *Isochvysis galbana* (IG), have shown substantial antihelmintic potential against *Pheretima posthuma* ($P < 0.01$) [75]. The actinomycetes *Streptomyces* sp. M491 contains macrolide antibiotics, chalcomycin and certain terpenes. Sporiolides, 12-membered lactones, are derived from the fungus *Cladosporium* sp. on the marine brown alga, *Actinotrichia fragilis* found at Okinawa Island and demonstrated antimicrobial activity. Particularly, sporiolides A and B were shown to be potent toward *Micrococcus luteus* [16].

Moreover, 11-hydroxycurvularin isomers from *Pseudonocardia* sp. HS7 contained in the *Holothuria moebii* sea cucumber demonstrated potential action against *E. coli* [76]. Phomolide A and B,10-membered 9-propyl-substituted macrolides, were obtained from the marine fungi *Phomopsis* sp. hzla01-1. They conferred protective action against *E. coli* CMCC44103 with MIC values 5–10 mg/mL [32,77]. Marine-based *Cladosporium* fungi produce Dendrodolides A, C, L, M, and Cladospolide B, which are 12-membered macrolides. *Cladosporium* sp. has been developed from Anthogorgiaochracea, a gorgonian found in the South China Sea. Another three dendrodolides, namely Dendrodolide A, C and M, exhibited potential antibacterial properties (MICs 3.13–25 μM) compared to *Bacillus cereus, Vibrio parahaemolyticus*, *Staphylococcus epidermidis, E. coli, Tetragenococcus halophilus, Staphylococcus aureus, Nocardia brasiliensis,* and *Pseudomonas putida* [78].

Lobophorins A and B were extracted from a marine Actinomycete identified on *Lobophora variegata*, the Caribbean brown alga. On the other hand, Lobophorins E, F, H, and I, were extracted from *Streptomyces* sp. discovered in South China Sea sediment [38]. Lobophorins A, B, E, and F showed antibacterial activities against *Bacillus thuringiensis* with MIC values ranging from 2 to 8 μg/mL. Lobophorin F displayed potential activity against *Enterococcus faecalis* and *Staphylococcus aureus* (MIC 8 μg/mL) [38]. Furthermore, lobophorins B and H demonstrated good inhibitory activity against *Bacillus subtilis* with MIC values ranging from 1.57 to 3.13 μg/mL. In the case of Lobophorins F and H, notable antimicrobial activity was observed against *Staphylococcus aureus* at 6.25–50 μg/mL MIC values [39]. Borrelidins and bromophycolides are two macrolides of interest. Borrelidins, extracted from the Korea Sea actinomycete *Nocardiopsis* sp., prevented *Enterococcus faecalis*, *Klebsiella pneumoniae*, *E. faecium*, and *Salmonella enterica* MICs ranging from 0.51 to 65 μM [16]. Bromophycolides P and Q derived from the red alga *Callophycus serratus* available in Fiji coasts exerted antibacterial effect in contrast to vancomycin-resistant *Enterococcus faecium* and methicillin-resistant *Staphylococcus aureus* (MRSA) [41]. Curvulides are bioactive compounds derived from the marine fungus *Curvularia* sp. of the red alga *Acanthophora spicifera* and can be found mainly in Fingers Reef and Guam [28]. Curvularin and (S)-dehydrocurvularin inhibited *Bacillus subtilis* growth with MICs of 1500 and above 3000 μg/mL, respectively, while *Staphylococcus aureus* had additionally been inhibited by αβ-dehydrocurvularin with MIC of 375 μg/mL [29].

Callophycus serratus is a red alga found in Yanuca, Fiji; the extract contains bromophycolides J-Q, 15 and 16-membered macrolides. From those macrolides, Bromophycolides P and Q displayed antibacterial activity against vancomycin-resistant *Enterococcus faecium* ($IC_{50} = 13$ and 5.8 μM, respectively) and methicillin-resistant *Staphylococcus aureus* ($IC_{50} = 1.4$ and 1.8 μM, respectively) [41]. However, another macrolide Butremycin showed weak activity with a MIC of 50 μg/mL against *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, and some methicillin-resistant *Staphylococcus aureus* (MRSA) strains with

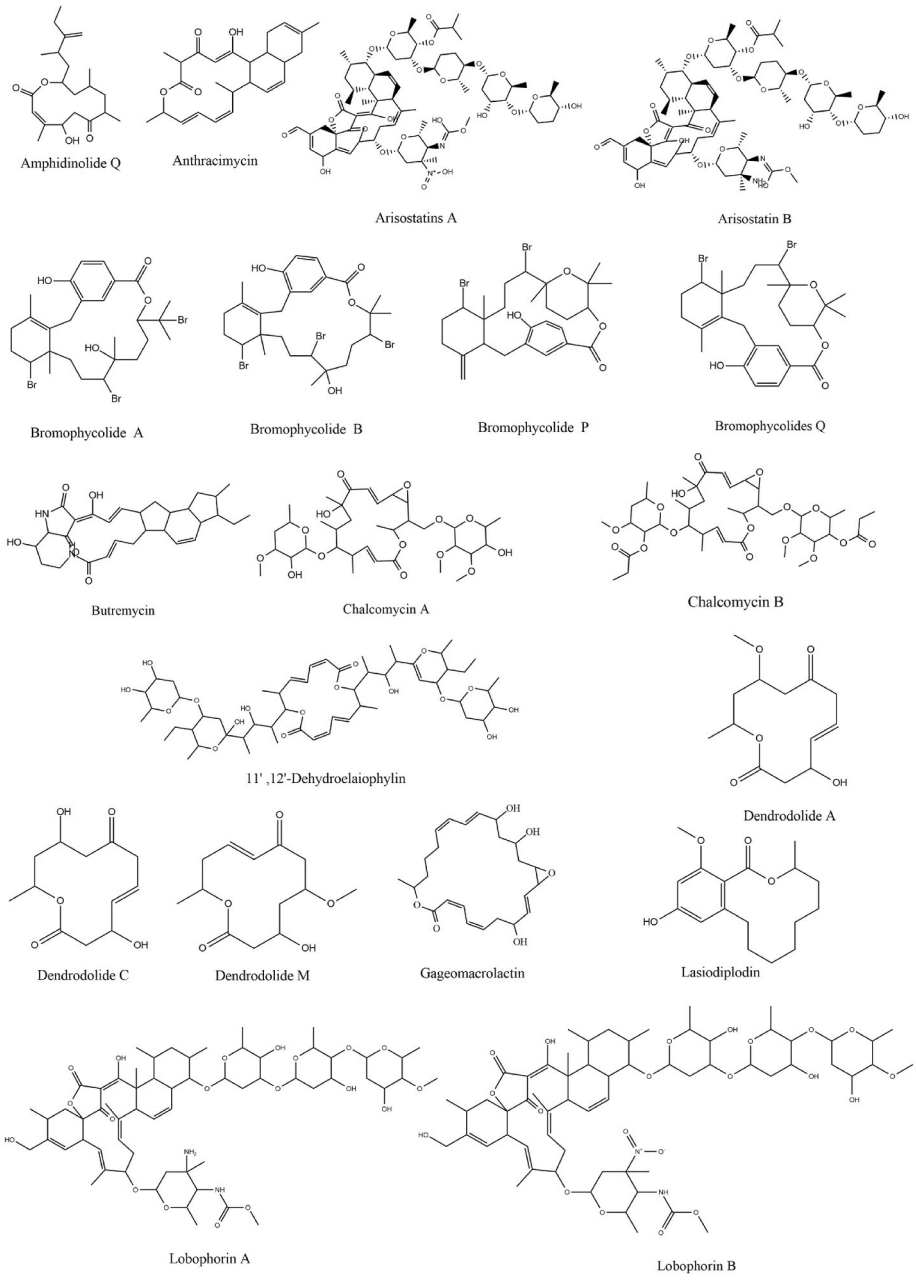

Fig. 1A. Chemical Structure of marine macrolides contains antibacterial properties.

MIC value greater than 50 μg/mL. They are extracted from *Micromonospora* sp. K310 is found in Ghana [41]. Moreover, *Bacillus subtilis* produced 24-membered three macrolactin derivatives named gageomacrolactins from marine sediment found in Gageocho, Republic of Korea. With MICs ranging from 0.02 to 0.05 μM, gageomacrolactins showed good activity against certain bacteria, namely, *Bacillus subtilis, Salmonella typhi, Staphylococcus aureus, Escherichia coli, Bacillus cereus,* and *Pseudomonas aeruginosa* [51]. Other Macrolactins A, B, D, O, S, T, and U were extracted from the *Bacillus marinus* bacterium, located on the Chinese Sea coastline. Macrolactins B with a MIC of 4.5–20.1 μg/mL and D with MIC greater than 100 μg/mL have been shown to have inhibitory action against the bacteria *Staphylococcus aureus* also against the fungi *Alternaria solani* and *Pyricularia oryzae* [79,80]. Macrolactins A, G-M were effective against *Bacillus subtilis* with MIC of 30–60 ppm and *Staphylococcus aureus* with MIC of 5–10 ppm. From those compounds, macrolactins F and K has little activity against the bacteria mentioned above with MIC value of 80 and greater than 100 respectively [52]. Macrolactin N, isolated from *Bacillus subtilis* AT29 in East China Sea sediment, demonstrated antimicrobial behaviour with a MIC of 100 μg/mL towards *E. coli* and *S. aureus* [16].

Many β-resorcylic macrolides, such as zearalenone, 5′-hydroxyzearalenol, 5′-hydroxyzearalenone, 7′-dehydrozearalenone, 8′-hydroxyzearalenone, β-zearalenol, and relgro, are present in the marine fungus *Fusarium* sp. PSU-ES73 was extracted from the seagrass *Thalassia hemprichii* obtained along the Western Pacific and Indin Oceans coasts. Only the macrolide zearalenone had weak action against *Staphylococcus aureus* ATCC25923 and methicillin-resistant *Staphylococcus aureus* SK1 (MIC of 400 μM) and *Cryptococcus neoformans* ATCC90113 (MIC of 50.26 μM). The remaining compounds were inactive [16].

Streptomyces sp. B7064, a marine strain isolated from mangrove sand near Pohoiki, Hawaii in the Pacific Ocean, yielded chalcomycin A and chalcomycin B. Both compounds had outstanding antibacterial activity against bacteria *Bacillus subtilis* and *Staphylococcus aureus* with MIC value of 6.25 μg/mL and 0.39 μg/mL respectively, but insufficient

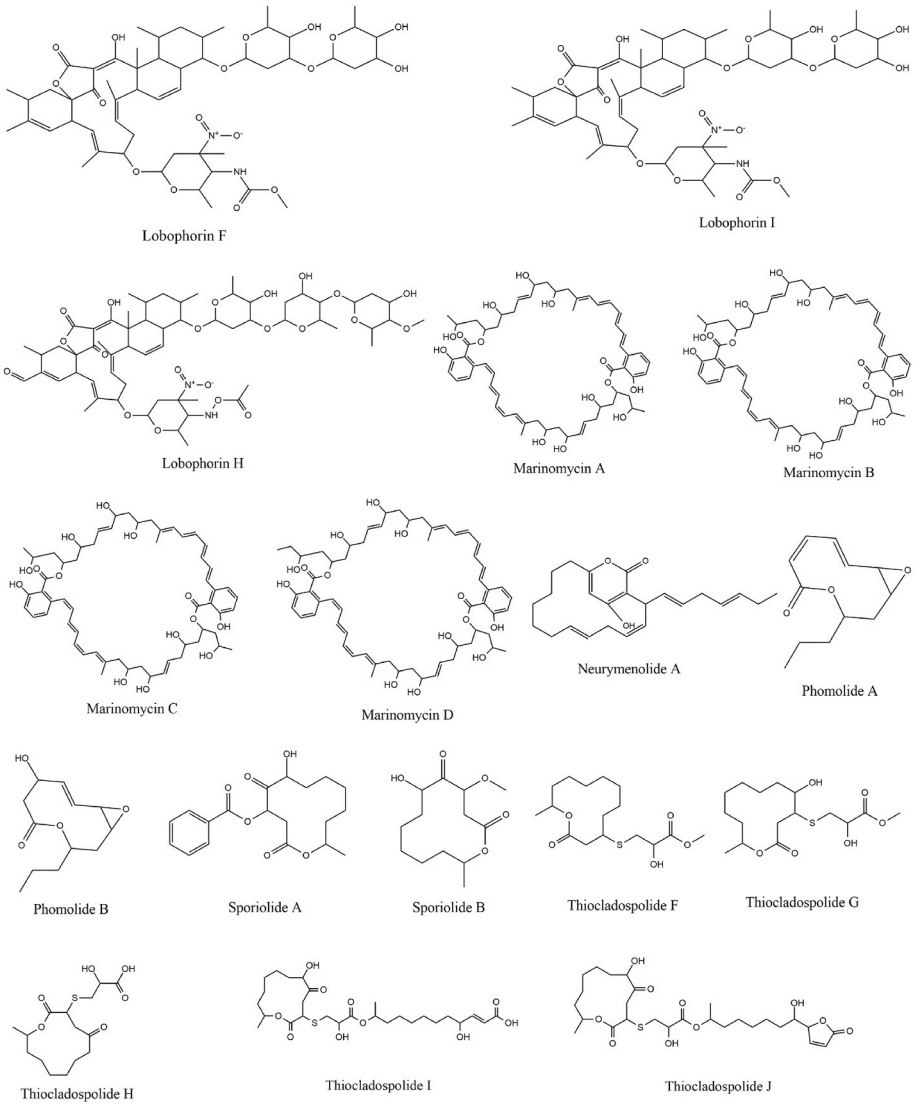

Fig. 1B. Chemical Structure of marine macrolides contains antibacterial properties.

antibacterial activity against *Escherichia coli*, with MICs greater than 50 μg/mL [43]. Another *Streptomyces* sp. HK-2006-1 was used to extract chalcomycin, chalcomycin E, and dihydrochalcomycin. Dihydrochalcomycin and chalcomycin, both with MICs of 4–32 g/mL, showed activity against *Staphylococcus aureus* [81]. Another type of macrolides with two α-pyrone rings, neurymenolides A and B, were extracted from *Neurymenia fraxinifolia* found in Taveuni, Fiji. Neurymenolide A had an IC_{50} of 2.1 μM MRSA and an IC_{50} of 4.5 μM against VREF [16].

3.1.2. Antifungal activity

Curvulides are bioactive compounds derived from the marine fungus *Curvularia* sp. of the red alga *Acanthophora spicifera* and can be found mainly in Fingers Reef and Guam [28]. Xie et al. demonstrated the anti-fungal activity Curvularin and αβ-dehydrocurvularin against *Saccharomyces cerevisiae* and *Sclerotinia sclerotiorum* with MIC of 375–750 μg/mL and above 3000 μg/mL, respectively. Curvularin and (S)-dehydrocurvularin are also effective against the fungus-like *Phytophthora capsici* and cytotoxic human tumor cell lines. At higher concentrations, curvulides showed zoospore motility impairment activity with an IC_{50} value ranging from 50 to 100 μg/mL [28]. Another macrolide, Xestodecalactones A–C, were isolated from a *Penicillium* cf. *montanense* extracted from the sponge *Xestospongia exigua* found in the Indonesian Bali Sea. Xestodecalactone B was demonstrated to be antifungal against *Candida albicans* at 20 μM and higher concentrations [33].

The *Fusarium* sp. O5ABR26 extracted from a marine sponge found in Japan's Miura Peninsula yielded several β-resorcylic macrolides. With a MIC value of 6.25 μg/mL, zearalenone was found to have the highest inhibitory action against the fungus *Pyricularia oryzae*. Simultaneously, with a MIC value of 200 μg/mL, 8′-hydroxyzearalenone was not more active against fungus [16]. Another class of 10-membered macrolides, Phomolide A and B, which are two 9-propyl-substituted, were obtained from fungi *Phomopsis* sp. hzla01-1. Both compounds conferred protective action against *Saccharomyces cerevisiae* ATCC9763 and *Candida albicans* AS2.538 (MIC 5–10 μg/mL) [32,77].

Numerous polyhydroxyl macrolides that contain guanidine exert both antibacterial and antifungal action via different mechanisms. For instance, the cell surface of Azalomycin F is mainly targeted: it decides the cellular material leakage in *Candida albicans*. It strongly inhibits amino acid absorption into the cell protein, phosphate into the nucleic acid, and the oxidative deamination of amino acid metabolism. Likewise, the plasma membrane is disrupted by niphimycin due to the interaction of this compound with phospholipids, including phosphatidylcholine and inducing ROS generations: This synergism between ROS production and plasma membrane disruption was the cause of antifungal potential towards *Saccharomyces cerevisiae* [90]. For example,

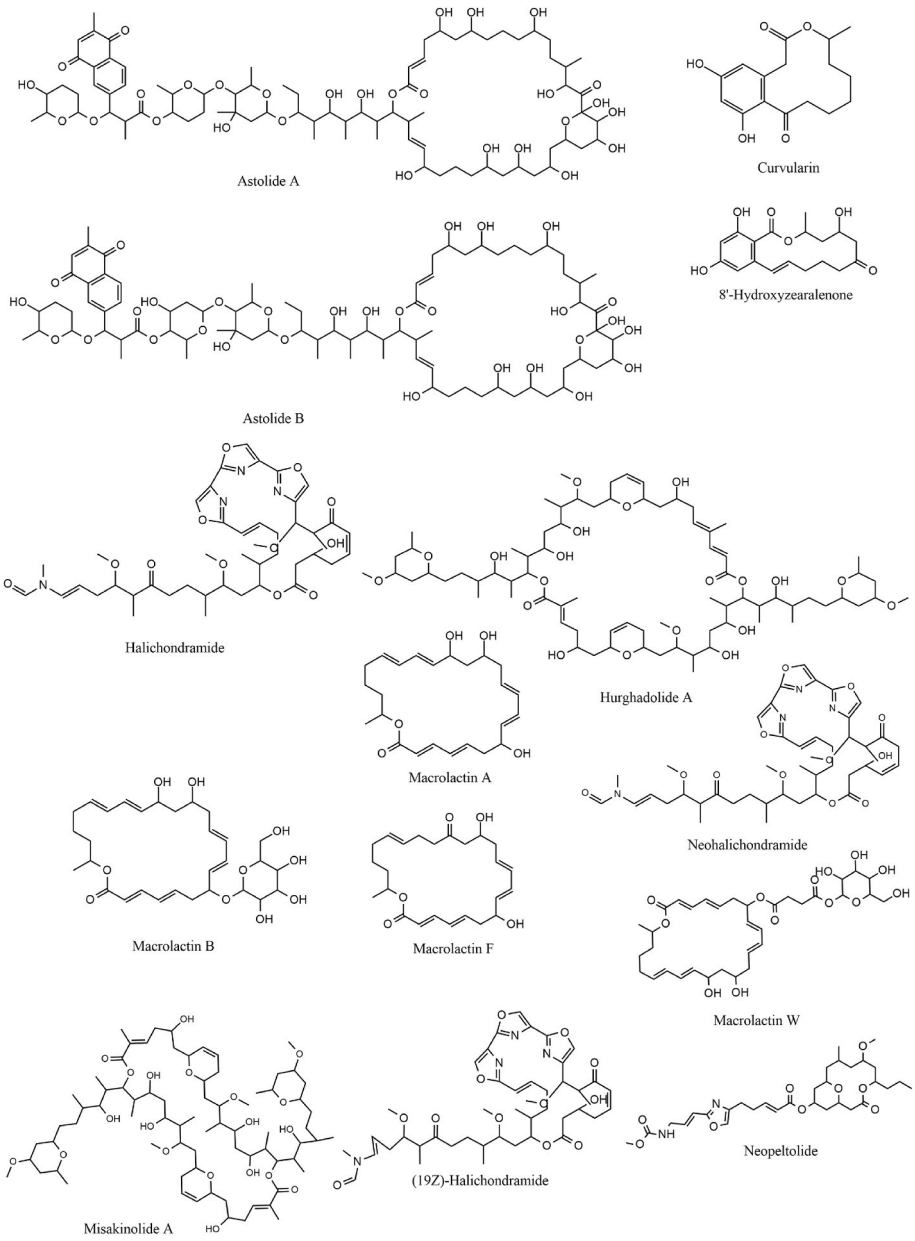

Fig. 2. Chemical Structure of marine macrolides contains antifungal properties.

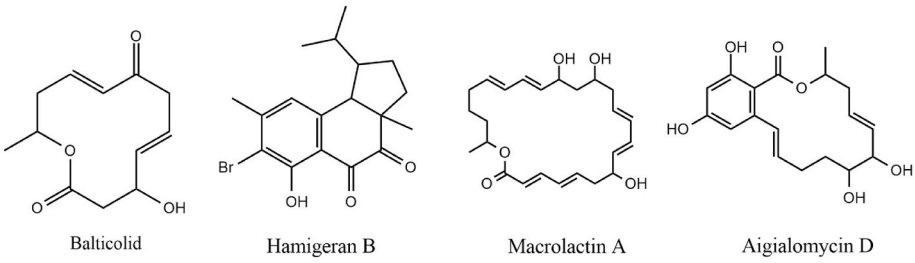

Fig. 3. Chemical Structure of marine macrolides contains antiviral properties.

amphidinolides were separated from the symbiotic dinoflagellate *Amphidinium* sp. of the 2012-7-4A strain from the marine flatworm *Amphiscolops* sp. found in Japan. Amphidinolide Q and four analogs, amphidinins C–F, were potentially active against *Trichophyton mentagrophytes* with 16–32 μg/mL of MICs. With MICs varying from 16 to 32 g/mL, amphidinolide Q was found to be selective against *Candida albicans,* and *Staphylococcus aureus* [33,34,80]

Macrolides may alter the permeability of microbes' cell membranes, leading cellular compounds to spill out. However, since fungi and bacteria have different cell envelope materials, they have different mechanisms against fungi and bacteria. For instance, 13-Deoxytedanolide, extracted from sponge *Mycale adhaerens* found in Japan, attaches firmly

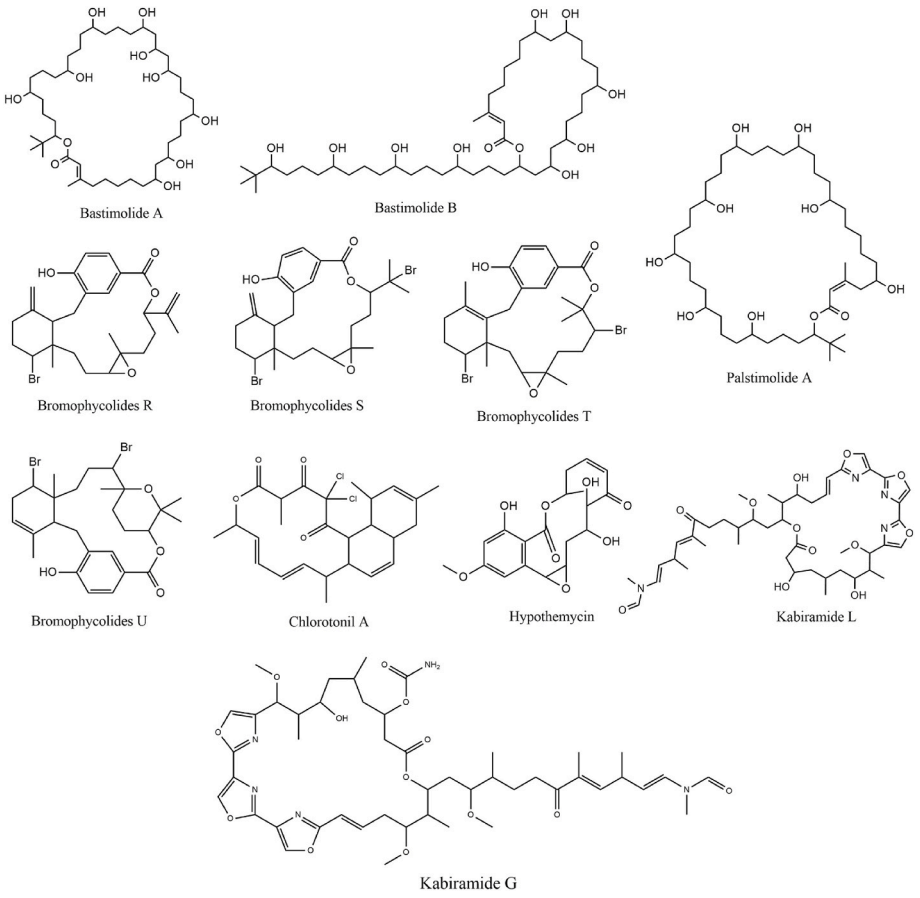

Fig. 4. Chemical Structure of marine macrolides contains antiviral properties.

to large ribosomal subunit, inhibiting *Saccharomyces cerevisiae* fungus polypeptide elongation [91].

Sakai et al. demonstrated that Misakinolide A is a macrolide with 20 members, but it also exists as a dimer with 40 members. *Theonella* sp., a sponge collected in Maeda-misaki, Okinawa, Japan, yielded misakinolide A. This compound exhibited antifungal action against *Candida albicans* (MIC 5 μg/mL) [16]. Sporiolides A and B are two other macrolides discovered in the exact location on Okinawa Island, Japan. Cladosporium sp. extract was isolated from *Actinotrichia fragilis*, a marine brown alga. With 16.7 μg/mL MICs, both sporiolides were effective against *Micrococcus luteus* [74]. Furthermore, sporiolide A was shown to have antifungal efficacy against *Candida albicans*, *Neurospora crassa, Cryptococcus neoformans*, and *Aspergillus niger*, with MICs ranging from 8.4 to 16.7 μg/mL [37].

Halichondramide is a 25-membered antibiotic that contains oxazoles. It was extracted from the Kwajalein Island's marine sponge *Halichondria* sp. which displayed antifungal action against *Candida albicans* and *Trichophyton mentagrophytes* with 0.2 pg/mL and 12.5 pg/mL MICs, respectively. Bacteria were not inhibited by halichondramide [92]. Additionally, Gageomacrolactins and macrolactins A, B, F, and W, which were extracted from marine *Bacillus subtilis* found from the Republic of Korea, prevent the development of *Colletotrichum acutatum, Rhizoctonia solani, Candida albicans, Botrytis cinerea,* and *Aspergillus niger* with MIC ranging from 0.04 to 0.3 μM [51]. Other macrolides showing significant antifungal activity were kabiramides, derived from the unidentified egg masses of the Japanese Ryukyus Islands. Particularly, kabiramide C was shown to have antifungal efficacy against *Penicillium citrium, Trichophyton interdigitale,* and *Aspergillus niger*. In addition, the anti-parasite behavior of kabiramides B, D, G, J, and K obtained from the *Pachastrissa nux* sponge contained in the Gulf of Thailand was demonstrated against *Plasmodium falciparum* K1 [93].

3.1.3. Antiviral activity

Balticolid is a 12-membered antiviral macrolide that is the by-products of naphthalenone from fungal strain 222 under the Ascomycota, collected from the reifswalder Bodden coast at Baltic Sea in Germany. The non-cytotoxic levels for the compound were evaluated on in vitro replication of both viruses to assess balticolid's antiviral effect against influenza A and HSV-I. Balticolid's HSV-I effect with IC_{50} of 0.45 μM was strongly inhibitory. On the other hand, there was no discernible antiviral activity against influenza A virus replication in vitro [100, 101]. Another antiviral macrolide Bromophycolides A and B, showed moderate antibacterial activity, antifungal activity. Bromophycolides A had strong antiviral efficacy against two strains of HIV with 9.1 and 9.8 μM IC_{50} values [84].

Macrolactins, such as macrolactin A, were extracted from a taxonomically undefinable gram-positive bacterium found in sediment at 980 m depth in the North Pacific. With 5.0 and 8.3 μg/mL IC_{50} values, macrolactin A is an effective inhibitor of mammalian Herpes simplex type I and II virus. The National Cancer Institute has looked into the possibility of utilizing macrolactin A to regulate HIV replication in human T-lymphoblast cells. The most effective protection was antiviral effects with a concentration of 10 pg/mL [102]. In the course of searching for new antiviral compounds from marine sponges, Zampella and colleagues looked at extracts from the lithistid sponge *Callipelta* sp., which showed significant *anti*-HIV efficacy in samples. They extracted the main cytotoxic constituents, callipeltins A-C, from the dichloromethane-methanol extract and given them a peptidal form. In vitro, HIV-infected cells were found to be protected by callipeltin A [103].

3.1.4. Anti-malarial activity

Lane et al. identified new diterpene–benzoate macrolides from

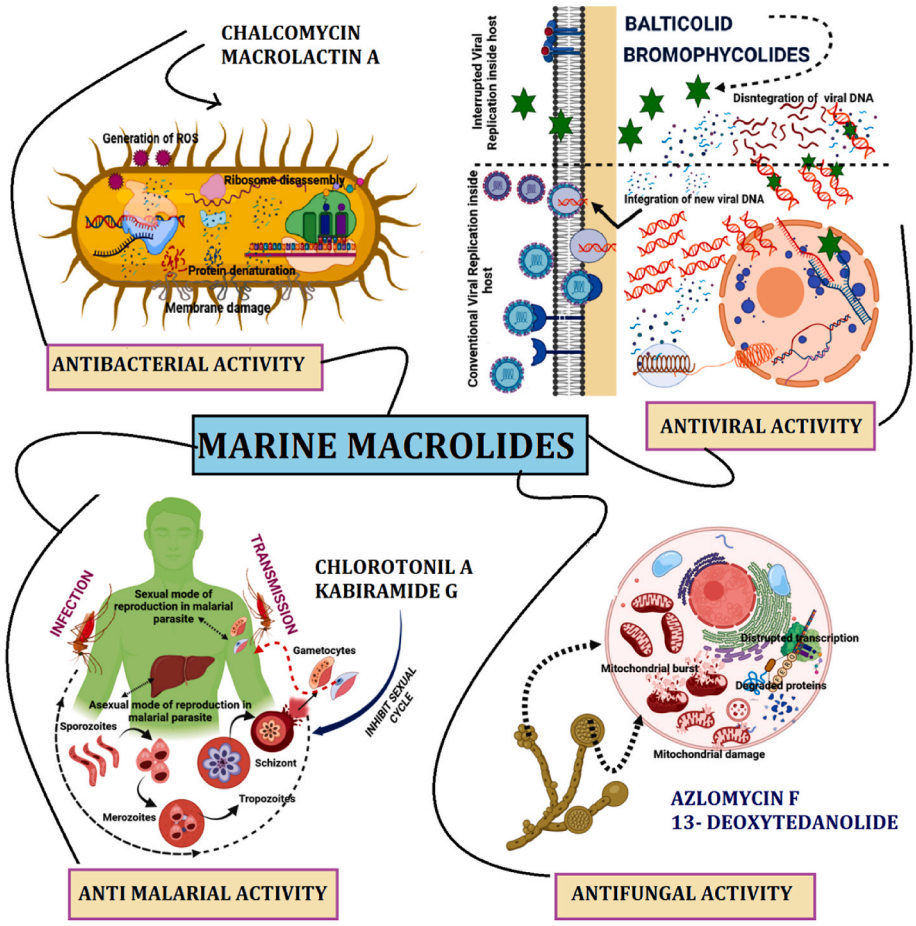

Fig. 5. Antimicrobial (antibacterial, antifungal, antiviral, antimalarial) activities of some prominent marine macrolides.

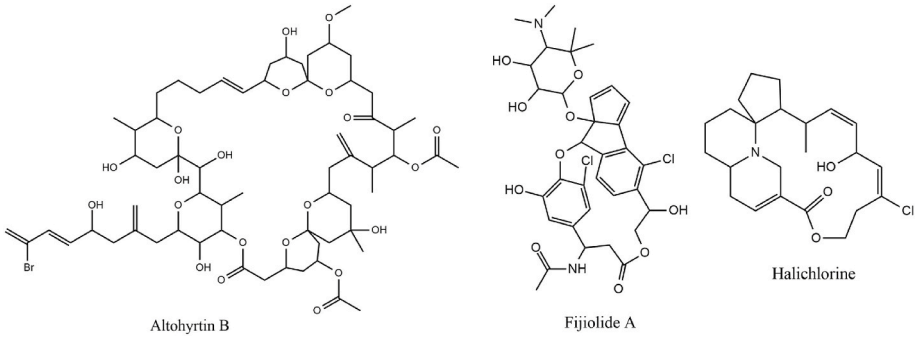

Fig. 6. Chemical Structure of marine macrolides contains anti-inflammatory properties.

Callophycus serratus, bromophycolides J, M, N, O, P, and Q, which showed active antimalarial activity against *P. falciparum* with 0.5–2.9 μM IC_{50} values [41]. Moreover, Lin et al. have extracted other bromophycolides R, S, and U from the same alga with potent activity against *P. falciparum* (IC_{50} 0.9–2.1 μM) [106]. Another 14-membered modern resorcylic macrolides, Aigialomycins A-E, were extracted from the fungus *Aigialus parvus* BCC5311, along with a recognized hypothemycin. In vitro antimalarial activity was found in hypothemycin and aigialomycin, with IC_{50} values of 2.2 and 6.6 μg/mL, respectively [107].

Similarly, another polyhydroxy 40-membered macrolide bastimolide A isolated from *Okeania hirsute,* which is a tropical marine cyanobacterium, displayed effective antimalarial activity against four resistant strains including TM91-C235, TM90-C2A, W2, and TM90-C2B of *Plasmodium falciparum* with IC_{50} values of 270, 80, 140, and 90 nM, respectively [108]. Bastimolide A is a potential antimalarial lead molecule with reasonable specificity and antimalarial activity against parasites resistant to other drugs. Further research has resulted in developing a new analog, bastimolide B, a polyhydroxy macrolide with 24-members. The position of double bond and functionalities of 1,3-diol and 1,3,5-triol in anti-malarial behavior with chloroquine-sensitive *Plasmodium falciparum* HB3 was indicated in a preliminary report of the structure-activity relationship [109]. Likewise, Malyngolide dimer, a macrolide isolated from the Panamanian marine cyanobacterium *Lyngbya majuscule*, was discovered to have mild antimalarial action against chloroquine-resistant Plasmodium falciparum (W2) (IC_{50} 19 μM) [108].

Myxobacteria belong to the phylum Proteobacteria and are soil-dwelling gram-negative bacteria. They are an abundant source of clinically valuable chemicals, like epothilones for cancer treatment and

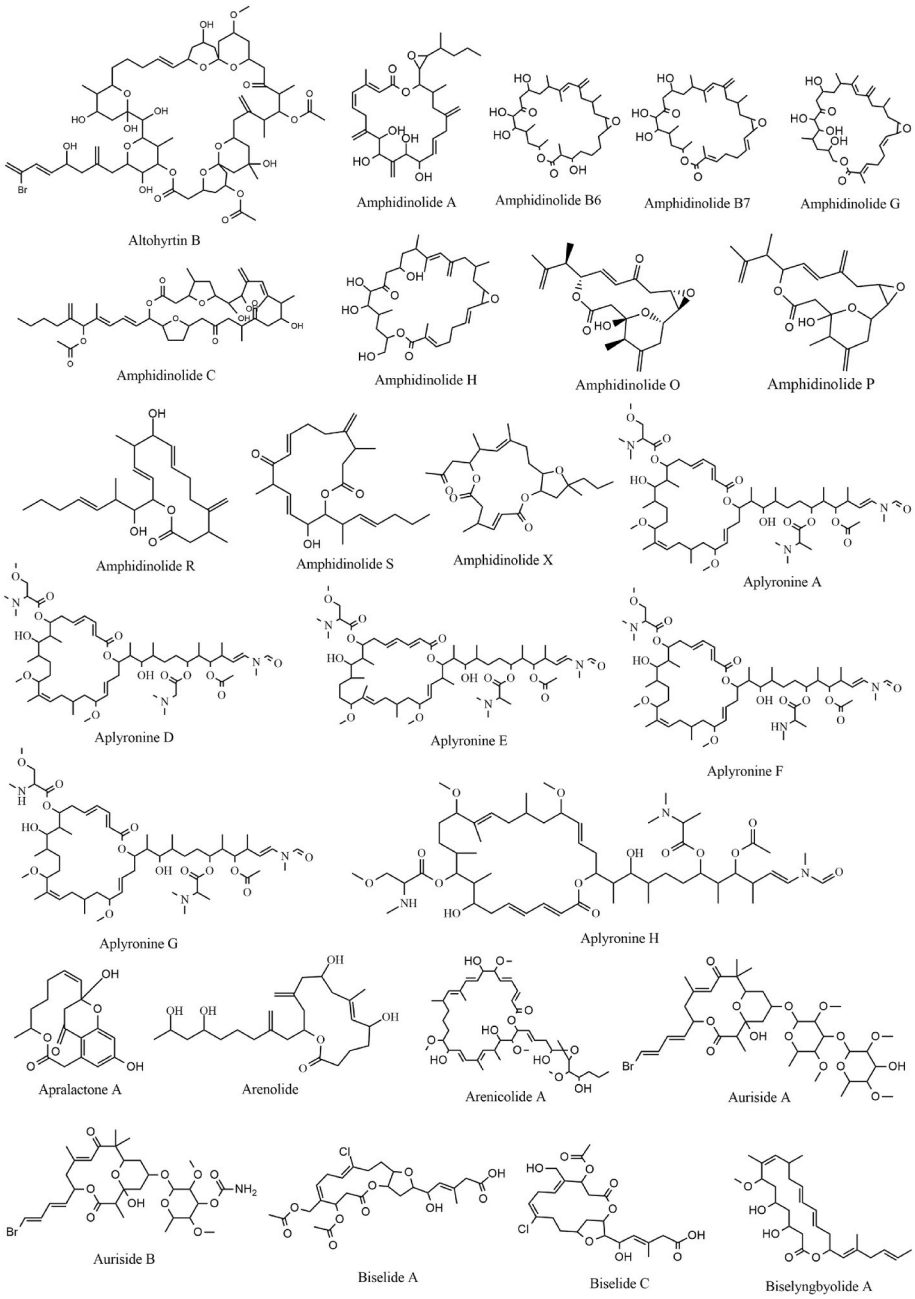

Fig. 7A. Chemical Structure of marine macrolides contains anticancer properties.

modern antibiotics. Chlorotonil A was a potential agent with IC_{50} ranging from 4 to 32 nM against laboratory strains of *Plasmodium falciparum* and Gabonese clinical isolates. Chlorotonil A is an antimalarial that works against all stages of intraerythrocytic parasite growth, including gametocytes with stage IV to V, and ring-stage parasites, and it only takes a few minutes to work [107].

The Thai sponge *Pachastrissa nux* recently yielded a sequence of trisoxazole macrolides known as kabiramide G. The sponge was obtained from different sites in the Gulf of Thailand, and the extracts of this were confirmed to have active antimalarial activity (IC_{50} of 0.7 μg/mL) against *Plasmodium falciparum* K1. Additional trisoxazole macrolides, including kabiramides J and K, were extracted following further research, and the antimalarial and cytotoxic activities of these isolated compounds were also reported [93].

Marine cyanobacteria, also known as blue-green algae, have been found to have a massive capacity for producing structurally complex natural products with a variety of biological activities, namely antiviral, antiparasitic, cytotoxic, antifungal, and antibacterial properties. A tropical cyanobacterium found at Palmyra Atoll developed palstimolide A, a 40-membered macrolactone ring containing complex polyhydroxy macrolide. With an IC_{50} of 223 nM, Palstimolide A was found to have potent antimalarial activity and intriguing anti-leishmanial activity (IC_{50} 4.67 μM). Palstimolide A also showed high antimalarial action against *Plasmodium falciparum* Dd2 blood-stage with an IC_{50} value of 172.5 nM and low toxicity (IC_{50} 5 μM) to liver HepG2 cells [101,110].

3.2. Anti-inflammatory effects

Marine macrolides have powerful antioxidant and anti-inflammatory properties, and they provide health advantages, particularly to individuals who engage in physical exercise, notably athletes [113]. ROS promotes protein, lipid, and DNA oxidation. As oxidative stress inhibits

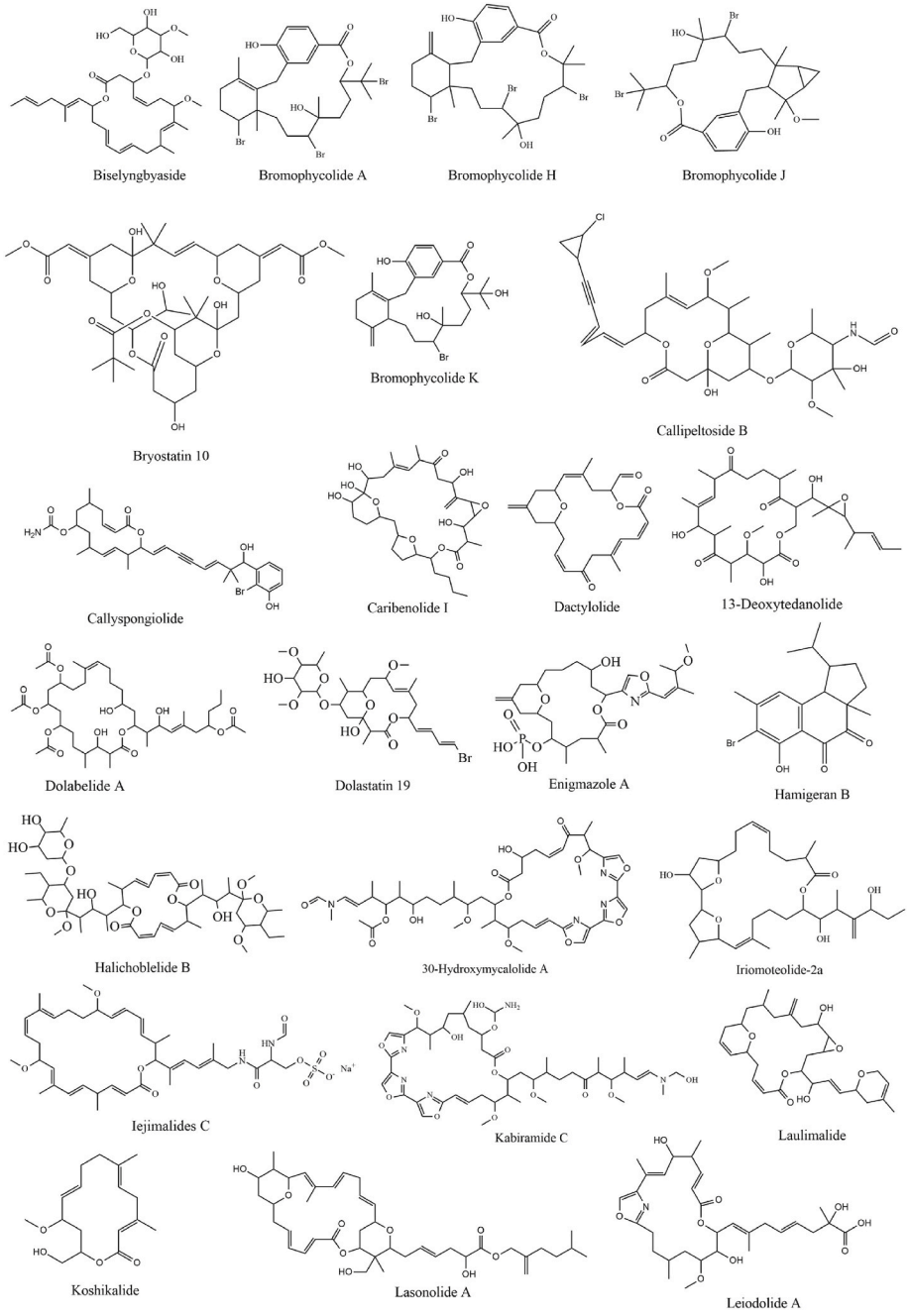

Fig. 7B. Chemical Structure of marine macrolides contains anticancer properties.

signaling pathways and degrades neural activities, external damage occurs. Inflammation and oxidative stress (OS) are inextricably linked: when leukocytes and macrophages are activated, ROS is generated, defining OS [114]. A high amount of ROS, which includes nitric oxide, hydrogen peroxide, superoxide anion, hydroxyl radical, plasma malondialdehyde, and lipid peroxide degradation products, may have a negative impact on fitness oxidative damage, impacting both tiredness and senescence [115–118]. Clinical and experimental evidence suggests that macrolides can affect inflammatory responses, potentially aiding in the treatment of infectious illnesses while also opening up new avenues for the treatment of other inflammatory ailments. Significant data, mostly from in vitro research, shows that leukocytes and neutrophils in particular are key targets for macrolide modulatory effects on host defensive responses [119,120]. This is why the 14-membered macrolide erythromycin is used to treat diffuse panbronchiolitis [119]. Macrolides also influence a number of other inflammatory mediators and processes, implying that the therapeutic indications for these medications may be greatly expanded in the future.

Physiological experiments in murine inflammatory modeling have shown that lobophorins A and B showed better antibacterial activity along with anti-inflammatory and anticancer effects than indomethacin. These compounds selectively inhibit 5-lipoxygenase, which in certain sports can help counter exercise-related inflammation due to chronic microtrauma and physical discomfort. For example, there is temporary and reversible oxidation of muscle proteins in endurance events as the temperature increases in the contracting muscles: the stress reaction is regulated by redox signaling in the absence of mechanical muscle injury. However, in some exercises, the stress response is triggered by mechanical disruption to protein structure, exacerbated a few days later by secondary damage linked to inflammatory processes. Furthermore,

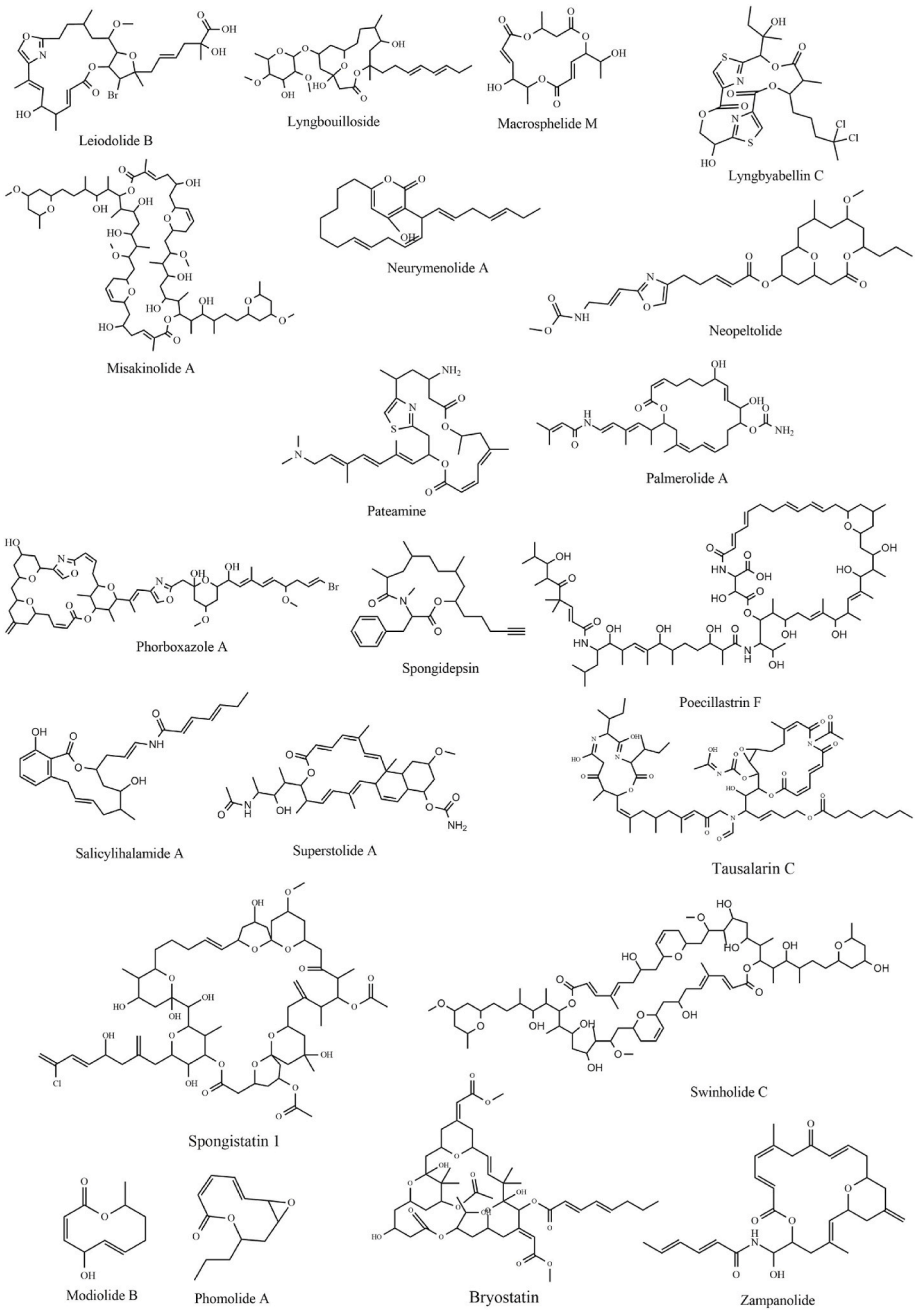

Fig. 7C. Chemical Structure of marine macrolides contains anticancer properties.

training increases the basic heat shock protein level, depending on the individual's initial workout status and a prolonged and repeated dose of practice [121].

The 14 and 16-membered homologues impaired iNOS promoter activity marginally more than curvularin itself when the anti-inflammatory effects of the synthesized compounds were tested in assays utilizing cells stably transfected with a human iNOS promoter-luciferase reporter gene construct [122]. In anti-inflammatory assays utilizing cells transfected with iNOS promoter- and GAS-dependent promoter-reporter gene constructs, neither of these ring variants achieve the inhibitory effects of (S)-curvularin itself. 4-chloro- and 5, 7-di-O-acetylcurvularin, on the other hand, was stated to be four-to fivefold more active than (S)-curvularin and less cytotoxic than the parent compound. They may be helpful to lead compounds in the quest for nonsteroidal anti-inflammatory drugs [122].

According to some recent studies [62,123], a few of the macrolide polyketides derived from the edible marine brown algae *Ecklonia cava* substantially inhibited not only the production of prostaglandin, pro-inflammatory cytokines (interleukin-6), etc. but also the expression of the gene, via ROS accumulation and the downregulation of NF-κB signaling pathway. Regulating NF-πB expression and, therefore, NF-kB-dependent genes (like inducible NO Synthase) will significantly boost cell status. Taking into consideration that certain anti-inflammatory medications, including corticosteroids, prevented NF-kB activation, both inhibition of NF-πB and increased NO development is proposed as anti-inflammatory strategies in inflammatory disorders. Since NF-πB is considered a transcription factor controlling inflammatory response genes, its inhibition could demonstrate the anti-inflammatory ability of these marine compounds [62,123].

In LPS-stimulated RAW264.7 macrophages, the anti-inflammatory properties of these metabolites were tested in vitro. Further investigation of the signaling mechanisms involved in these results revealed that

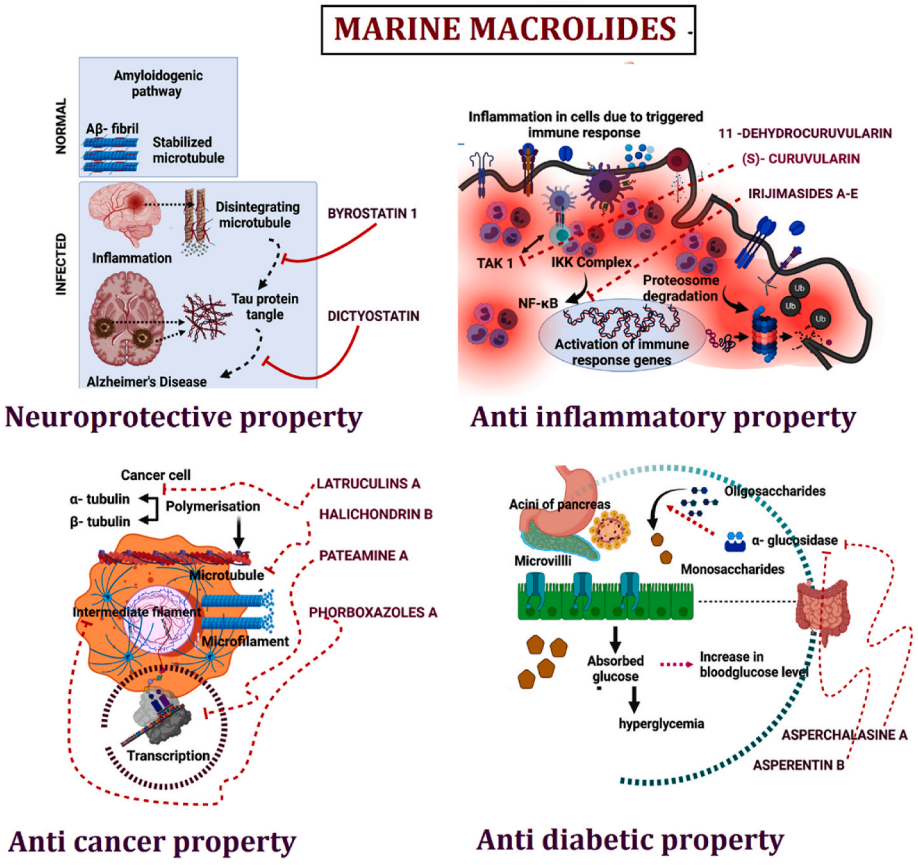

Fig. 8. Neuroprotective, anti-inflammatory, anticancer, antidiabetic activities of some important marine macrolides.

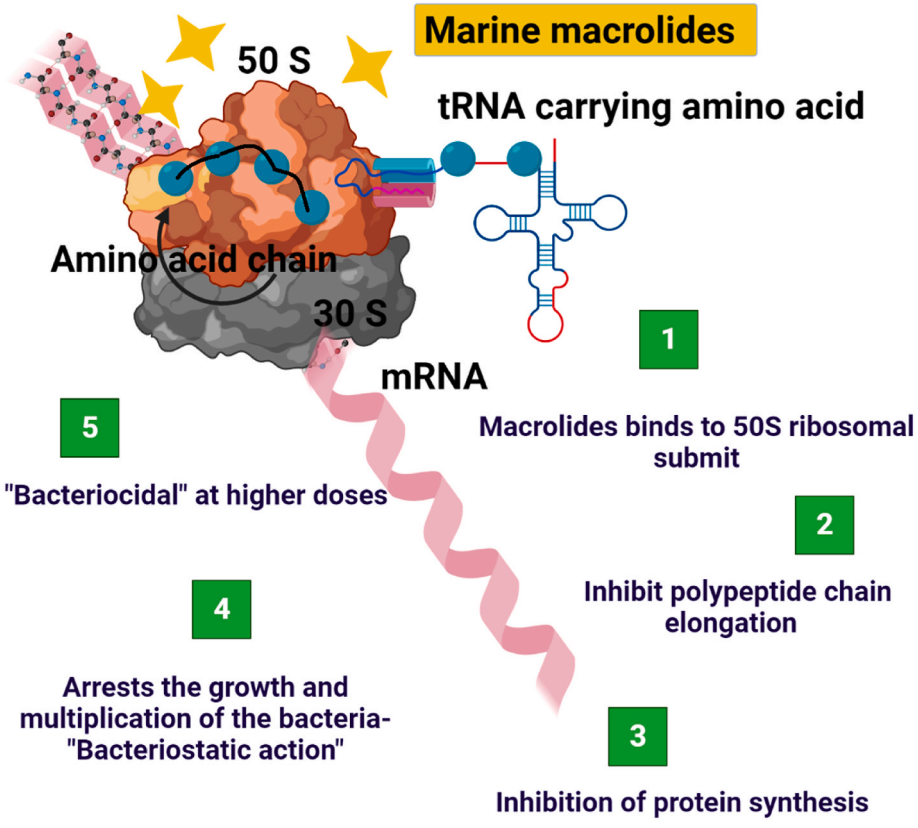

Fig. 9. Mode of action and Mechanism of resistance of macrolide.

the most active molecule, (10E, 15S)-10,11-dehydrocurvularin, decreased the production of iNOS and COX-2 in RAW264.7 macrophages induced by LPS. Additionally, it has been shown that another derivative of curvularin suppressed the upregulation of pro-inflammatory mediators and cytokines through inhibition of NF-κB, but not by pathways of mitogen-activated protein kinase (MAPK). Based on similarities in the differing magnitude of anti-inflammatory effects of these structurally associated metabolites, a major deterioration in their anti-inflammatory behavior was indicated when the 12-membered lactone ring was opened in the metabolites of the form of curvularin and blocked phenol function [124].

Additionally, a group of new 14-membered macrolides, irijimasides A-E, has recently been identified from a marine Cyanobacterium. Tartrate-resistant acid phosphatase plays a crucial role in the resorption of bone, expression in osteoclasts controlled by the NF-kappa B receptor activator (RANKL), a strong osteoclastic differentiation activator. These five macrolides inhibited RANKL-mediated TRAP behavior in RAW264 macrophage cells in the mouse, suggesting that these compounds can prevent osteoclast formation [125], positively impacting the status of bone balance.

Further study is required to characterize the stress reaction to physical activity triggered by exercise. In this regard, non-pharmacological therapies could provide macrolides with an anti-inflammatory activity; potential inhibitions of pro-inflammatory pathways assist in reducing oxidative stress disorders, maintaining muscle and bone integrity during aging [101,126,127].

3.3. Anti-cancer activities

Cancer is a group of disorders that include aberrant signaling pathways, notably those related to cell proliferation, metastasis, angiogenesis, and apoptotic mechanism illusion [128,129]. Recently, clinical treatment prospects have been harmed by fast developing medication resistance and poor efficacy. At the moment, new sorts of small anti-tumor chemicals are also necessary. As a result, the sea might provide a massive untapped pool of bioactive chemicals and molecules originating from both plants and marine species, which could be used as a useful aid or safer alternative to certain present manufactured medications due to their vital biological capabilities [130].

3.3.1. Actin targeting macrolides

In eukaryotic cells, the most prevalent intracellular protein is actin. Actin filaments are produced by assembling globular actin monomer subunits in a head-to-tail orientation to create a right-handed double-stranded helix. The actin cytoskeleton is required for many pathogenic cellular processes, including cell adhesion, angiogenesis, intracellular transport, metastasis, and cytokinesis. As a result, the actin cytoskeleton is a primary target in developing anticancer drugs [27].

Latrunculins A and B were the first identified actin-binding marine macrolides [27]. Latrunculins, derived from the *Latrunculia magnifica* sponge of the Red Sea, disrupts cellular development by actin polymerization and microfilament organization, which assess anti-proliferative consequences [121]. At submicromolar concentrations, they were shown to induce significant changes in various cytoskeletal proteins, as well as morphological changes in NI1-115 neuroblastoma and 3T3 mouse fibroblast cells [131]. Dolastatin-19 recently extracted from *Dolabella auricularia* from the Gulf of California, showed anti-proliferative action against colon and breast cancer cells [26]. Scytophycins, derived from the green and blue algae *Scytonema pseudohofmanni*, and sphinxolides from the marine sponges *Neosiphonia superstes* were also found actin-binding natural bioactive with their antiproliferation activity against human cancer cell lines [26]. In human health and drug research, the development of novel protein-protein interactions by known bioactive compounds has become a primary interest. There are currently more studies in the mechanism of action and the production of new complex actin-targeting natural products [101].

The trisoxazole-containing macrolides are among the most well-studied potent inhibitors of the actin filament network [132]. More than thirty membered macrocyclic lactones carrying a peculiar trisoxazole moiety make up this marine macrolide group. Ulapualides and Kabiramides, extracted from *Hexabranchus sanguineus*, are two of this class of compounds [133,134]. Other macrolides were found from the stony coral *Tubastrea faulkneri* and the Japanese sponge *Mycale* sp., halishigamides, and halichondramides obtained from sponges *Halichondria* genus [135], and jaspisamides purified from the Okinawan sponge Jaspis sp [136]. Mycalolide B was the first trisoxazole-containing macrolide discovered to be involved in natural actin filament dynamics and control, including actin-activated myosin Mg2+-ATPase activity suppression [137]. Later research revealed that this compound has a 1:1 molecular ratio with G-actin, hindering its polymerization. In addition, competitive binding experiments revealed that kabiramide C attaches to the same position on G-actin as gelsolin domain 1, implying that these small molecules could be used to replicate an entire group of actin-binding proteins [138]. Another potent actin-binding macrolactone is the sponge *Theonella swinhoei* isolated Swinholide A, a 22-membered macrolide with potent antifungal and cytotoxic activity [139]. Aplyronines were first extracted from the *Aplysia kurodia*, a Japanese sea hare. Aplyronine A, the main ingredient, showed high in vitro cytotoxicity (IC50 0.039 ng/mL) against HeLa–S3 cells [140].

Bryostatin 1, a cyclic macrolide derived from the *Bugula neritina* in Bryozoa, is reminiscent of cyclical, ionophore antibiotics. It is also well-recognized as a potential anticancer agent along with the modulator of protein kinase C [141,142]. It causes tumor death at the cellular level by transporting chelated cations such as Ca^{2+}, K^{+}, or Na^{+} through the cell membrane. Preliminary reports showed that bryostatin one chelated Ag^{+} indicated administering the intracellular and extracellular gradient of ion to Swiss 3T3 quiet cells. Bryostatins have a considerable ability to suppress the promotion of PKC tumors and may be used as antitumor drugs [143].

3.3.2. Microtubule targeting macrolides

Microtubules are polymers made up of the α- and β-tubulin subunits, critical elements of the mitotic spindle. Tubulin subunit assembly and disassembly to shape microtubules are also dynamically balanced methods. As a result, small molecules that disrupt this balance will stop mitosis and cause cell death. Because of the effectiveness of paclitaxel in cancer therapy, tubulin subunits have been a popular focus in medicinal chemistry science. However, discovering new tubulin-binding agents is critical not just for better comprehension of small-molecule interactions with tubulin but also for overcoming clinical multidrug resistance [144].

Zampanolide, a marine macrolide with 20-members, was derived from the sponges *Fasciospongia rimasa* and *Cacospongia mycofijiensis* and shown to be a promising lead compound for anticancer [145]. The cytotoxicity of drug-responsive and multidrug-resistant cancer cell lines showed impacts on the assembly of tubulins and the development of the microtubule package. Zampanolide had a high anti-tumor effect that was much higher than paclitaxel [146]. Plenty of investigations showed its nanomolar cytotoxicity towards OVCAR [147], HL-60, A2780 [148], and SKM-1 cell lines, with low nanomolar cytotoxicity against multi-resistant cancer cells over stretcher of the pump of P-gp multidrug tolerance [147]. The covalent attachment of medicinal products to their target effectively blocks P-capacity gp's to pump the drugs out of the cell. This approach has been successful in preclinical settings to prevent P-gp mediated drug resistance. Zampanolide can treat MRC since it attaches covalently to tubulin. The structure of zampanolide may be improved if its chemically unstable side chain is stabilized, hence the imitation of zampanolide with a stable side-chain using straight synthetic methods [149]. Zampanolide-52 was established as the candidate with optimum anti-proliferative efficacy against docetaxel-resistant and docetaxel-sensitive prostate cancer cell lines with 0.29–0.46 μM IC_{50} values [149]. These results make zampanolide quite appealing for large-scale synthetic preparation for therapeutic applications (with the

potential for oral administration), in addition to currently existing anticancer medications [150].

Many other marine macrolides were extracted from algae, sponges, and other marine invertebrates and be formed by their related microbiota. In 2010, eribulin mesylate, the analog of the marine polyether macrolide halichondrin B, was approved to treat metastatic breast cancer [151]. Halichondrin B was first extracted from *Halichondria okadai*, a Japanese naval sponge, in 1986 [152], which was later found in samples of the other poriferan organisms of the genera Phakellia, Axinella, and Lissodendoryx. Still, adequate sample quantities remained challenging to secure, impeding its clinical development [153]. The culmination of the halichondrin B synthesis in 1992 [154] along the linear sequence of 47 steps established the intermediate C1–C38 as the principal fragment showing cytotoxic behavior. Therefore, a potent and more straightforward analog of halichondrin B was obtained to preserve the correct macrolactone and omit the side chain (Halichondrin B analog E7389). Instead of the removal of half of the initial molecule, a primary amine was added.

Eribulin mesylate (Eribulin), an analogue of halichondrin B, was an active microtubule inhibitor. It connects the positive ends of each protofilament to a strong affinity, preventing microtubules from growing and resulting in G2/M phase arrest and apoptosis. The mitotic blockade caused by Eribulin is irreversible [155]. Therefore, the mechanism is different from other anti-tubulin agents because it does not influence the reducing step that induces disassembly, for example, vinca alkaloids or rising phases such as taxans. Another contact with the target may be due to such a mechanism of operation. In a strong affinity binding site, Eribulin attaches microtubules differently than other antitubulins. In comparison to vinca alkaloids or microtubular inner lumens, like taxans attached to both α- and β-subunits, eribulin binds to a site with a single intermediate interface or β-tubulin sub-unit [156]. Eribulin is a mechanistically specific inhibitor of microtubule dynamics regardless of these distinctions in site and mode of action; thus, it is being investigated widely to care for patients with taxane-resistant cancers and other solid tumors.

Spongipyrans are among the most potent cytostatic agents ever studied in the NCI's panel of 60 human carcinoma cell lines. The most powerful member, spongistatin 1 with a GI_{50} value varying from 0.02 to 0.4 nM, was particularly effective against solid tumor cell lines derived from patients with lung cancer, melanoma, brain tumors, and colon cancer. Still, it retains its potency against a subset of highly chemoresistant tumor types with a GI_{50} of 0.03 nM [157]. Spongistatin 1 was also found to have potent cytotoxic activity against L1210 murine leukemia cells with an IC_{50} value of 0.02 nM [158]. Spongistatin 1 was later discovered to inhibit glutamate-induced polymerization of distilled tubulin at low micromolar concentrations [157].

Further studies revealed that Spongipyrans, including halichondrins, are the non-competitive blockers of vinca alkaloids and dolastatin 10. Dictyostatin is a 22-membered macrolide with several discodermolide-like structural properties. It was first discovered from sponge Spongia sp. in the Maldiv and then in the deep-water sponge Corallistidae sp. in Jamaica [159,160]. This compound has efficient cytotoxic activity against many cancers cell lines with a Taxol-like mode of action, including those with multidrug resistance phenotypes, at low nanomolar concentrations. At concentrations as low as 10 nM, dictyostatin prevents human lung adenocarcinoma cells from entering the cell cycle G2/M step. In vitro, it also causes fast polymerization of distilled bovine brain tubulin [160–162]. As mentioned above, Discodermolide, a polyketide, is currently undergoing clinical trials. In addition to the action under review, paclitaxel-resistant human tumor cells with β-tubulin mutations were inhibited by this compound [161].

Laulimalide and isolaulimalide are cytotoxic macrolides with a 20-membered composition and two dihydropyran rings. Isolaulimalide is a rearrangement of laulimalide made through the acid-catalyzed attack of the hydroxyl group side chain on the *trans*-substituted epoxide moiety. They were first discovered in the sponge *Cacospongia mycofijiensis* from Vanuatu [161]. Laulimalide has active antiproliferative efficacy against multiple human carcinoma cell lines, with IC_{50} values in the low nanomolar scale, while isolaulimalide has IC_{50} values in the micromolar range. Furthermore, laulimalide has the capacity to induce tubulin polymerization in a similar way to paclitaxel [163]. Another substance Peloruside A, a macrolide derived from the Mycale hentscheli marine sponge, attaches to a non-taxoid tubulin binding position. In a human breast adenocarcinoma cell line (MCF7) that was stably expressing GFP—tubulin, Peloruside A at nanomolar levels was known to be able to disrupt the growth rate and change the length of microtubules in a concentration-dependent manner [164].

Yamada and coworkers first identified the aurisides in 1996, which are glycosylated macrolides with 14-members isolated from *Dolabella auricularia*, from the aplysiidae family of marine opisthobranchs. The cytotoxic activity of both aurisides A and B were identified against HeLa S3 cell lines, with IC50 values of 0.17 and 1.2 g/mL, respectively [26]. On the other hand, Neurymenolide A is a kind of neurymenolide. In vitro cytotoxicity was also found with an IC_{50} of 3.9 μM against DU4475 breast tumor cells, and mild to poor behavior against 11 other tumor cell lines with IC_{50} values varying from 5.4 to 28 μM [44].

3.3.3. Intermediate filament targeting macrolides

Intermediate filaments are abundant in a cell's cytoskeleton. Two stranded α-helical coiled coils of globular domains at the ends shape these filaments produced by coordinated head-to-tail and side-by-side associations with pairs of intermediate filament proteins lamins, desmin, vimentin, and keratins. Intermediate filaments run across the cytoplasm, supplying mechanical protection for the nuclear membrane and aiding cell differentiation, cell-matrix adhesion, and cell-cell adhesion. The morphology of invading cancer cells is affected by agents that interfere with this systemic structure, increasing the possibility of cell rupture. As a result, intermediate filaments have emerged as a possible target for small molecule modulation [27].

Phorboxazoles A and B are macrolides with two 26-members found from sponge Phorbas sp. extract collected from the Indian Ocean [55]. They have strong cytostatic activity. Both compounds demonstrated specificity against colon HCT 116 with an IC_{50} of 0.25 nM and suppressed the development of several of the 60 cell lines at low nanomolar concentrations used in NCI's assays with a GI_{50} of 1.6 nM [55,165]. At nanomolar concentrations, phorboxazoles caused cell cycle arrest in HeLa cells and a drastic restructuring of intermediate filaments, resulting in a massive aggregate neighboring to the nucleus. The interaction of human cytokeratins with the cyclin-dependent kinase 4 (cdk4), a crucial part of cell cycle progression the G1/S step and an established anticancer drug target, was discovered in the cytosolic partitions of HeLa cells [166]. Another macrolide extracted from the sea Negombata magnifica, a sponge from the Red Sea, was used to separate latrunculins A and B. These chemicals are linked to the disruption of cell microfilament organization [167] and have the potency to inhibit the migration activity against murine brain-metastatic melanoma B16B15b cells and highly metastatic human prostate cancer PC-3M-CT + cells [131,168].

3.3.4. Ribosome targeting macrolides

Protein synthesis happens in biological systems on the ribosome, a complex macromolecular structure that interprets genetic information from mRNA into amino acid sequence to make hundreds of proteins in each cell. In the eukaryotic protein biosynthesis process, the connection of chemicals with proteins or ribosomal subunits engaged in various phases of the dynamic translation mechanism are both potential targets for cancer treatment. Despite the fact that various structurally complicated natural compounds have been reported to hinder protein synthesis, only a small number of marine macrolides may be labeled ribosomal function inhibitors [27]. Ketolides are the most often used class of antimicrobials generated from the 14-membered ring macrolide erythromycin A. The keto group, which substitutes the L-cladinose moiety at position 3 of the macrolactone ring, is the major structural trait that

distinguishes ketolides from erythromycin [169]. The keto group improves the medicines' acid stability and allows them to attach to their ribosomal target without developing MLSB resistance in inducible strains. Other ketolides, such as ABT 773 and telithromycin (HMR 3647), have a carbamate at the C11/C12 position of the macrolactone ring [170]. The carbamate in telithromycin, the first ketolide licensed for clinical usage, is connected to an alkyl-aryl extension, which accounts for the compound's higher potency when compared to macrolides [169].

Pateamine A, an immunosuppressive agent, has been derived from various Mycale sponge organisms [99]. Later it was identified that pateamine A is a potent inhibitor of cap-dependent translation origination that attaches to eukaryotic initiation factor 4A (eIF4A), disrupting protein-protein interactions and improving the functions of its ATP-stimulated RNA binding and RNA-dependent ATPase [171]. According to additional studies, Pateamine A is a chemical stimulator of dimerization that induces an association between eIF4A and RNA and prevents eIF4A from participating in the ribosome-recruitment process of translation initiation [172]. Pateamine A's specific attachment to eIF4A shows the feasibility of using small molecules to attack highly conserved enzymes. Pateamine A has recently been identified as a promising lead compound for the production of anticancer agents, as well as an important biochemical and pharmacological tool for studying the molecular function of eukaryotic translation initiation [173].

Another marine macrolide known to impede protein synthesis of eukaryotic cells directly is 13-deoxytedanolide. This macrolide, which was initially extracted from the sponge Mycale adhaerens, has a strong cytotoxic activities against P388 murine leukemia cells in vitro with an IC_{50} of 0.094 ng/mL and inhibits the development of P388 tumors implanted in mice with a T/C value of 189% at a dose of 0.125 mg/kg [47]. Further research found that 13-deoxytedanolide attaches tightly to large ribosomal subunit (60S), inhibiting in vitro elongation of polypeptide in *Saccharomyces cerevisiae* [174].

3.4. Antidiabetic activity

Diabetes mellitus is a progressive condition of hyperglycemia along with clinical manifestations owing to the ineffectiveness of insulin that regulates blood glucose levels [236,237]. So, one strategy to avoiding DM is to delay glucose absorption by inhibiting α-glucosidase. Therefore, it is justified to investigate such inhibitory action in marine species since these inhibitors will regulate postprandial hyperglycemia in people with diabetes [238].

A study conducted by Chen, Z. et al. [236] demonstrated that Wailupemycins H and I, isolated from Streptomyces sp. culture, possess anti-diabetic potential. OUCMDZ-3434 is correlated with the Enteromorpha prolifera, marine algae. There are two new α-glucosidase inhibitors with 16.8/19.7 and 6.0/8.3 μM Ki/IC_{50} levels. Contrariwise, another promising antidiabetic compound, Asperpanoid A, was extracted from mangrove endophytic fungus Aspergillus sp.ZJ-68 culture [239]. Other molecules, such as Asperchalasine A, Epicoccolide B, and Asperchalasine I, were extracted from *Mycosphaerella* sp. SYSU-DZG01, a mangrove fungus, showed strong α-glucosidase inhibitory activity (IC_{50} 15.7, 26.7, and 17.1 μM). The outcomes concluded that asperchalasine I can be a promising candidate for the inhibition of α-glucosidase [240].

Another study carried out by Heo, S.J et al. [241] expanded the pharmacology of diphlorethohydroxycarmalol (DPHC), extracted from brown algae *Ishige okamurae*. They showed that DPHC effectively inhibited both α-amylase and α-glucosidase enzymes (IC_{50} = 0.53 and 0.16 nM) to reduce postprandial hyperglycemia in diabetic mice. These promising outcomes suggest that DPHC could be used as a diabetes nutraceutical or functional food. Li and his colleagues assessed the recognized *Sesquiterpene dysidine* from the marine sponge *Dysidea villosa* which inhibited human protein phosphatase 1B (IC_{50} = 6.70 μM), a well-characterized medication target for type 2 diabetes and obesity control [242].

Xu et al. observed that a novel bromophenol bis (2,3-dibromo-4,5-dihydroxybenzyl) ether (BDDE) derived from the red alga *Odonthalia corymbifera* and *Enteromorpha prolifera* which reduced protein tyrosine phosphatase 1B expression, triggered insulin repair pathway, in vitro glucose uptake, and decreased the blood glucose significantly in mice, thus indicating BDDE as a promising treatment option against type-2 DM [243]. Kim and his colleagues extracted the *Mycosphaerella* polyphenol dieckol from the marine brown algae *Ecklonia cava*, which reduced 3.3 times more blood glucose levels at 90 min in the alloxan-induced hyperglycemic zebrafish model compared to the control group [244]. Asperentin B, a new polyketide extracted from a deep (2769 m) Mediterranean Sea sediment-derived *Aspergillus sydowii*, hindered protein tyrosine phosphatase 1B, a key target to treat of type 2 diabetes [245]. Other macrolides, Penarolide sulfates A1 and A2 extracted from a sponge Penares sp., exhibited inhibitory activity against α-glucosidase (IC_{50} 1.2 and 1.5 μg/mL). However, they demonstrated little or no inhibitory activity against α-galactosidase [246].

3.5. Neuroprotective activity

Some marine macrolides have been shown to have neuroprotective properties [247–250]. *Bugula neritina* produces Bryostatin 1, a macrolide lactone. It's a protein kinase C active modulator that's currently being evaluated in phase II clinical studies for Alzheimer's disease [249]. The medication has shown to be beneficial in addressing both the symptoms and the causes of Alzheimer's disease in preclinical studies. Despite the fact that bryostatin was originally designed as an anti-cancer medicine, it has recently been proven to be beneficial in delaying the progression of Alzheimer's disease [247]. Several pre-clinical studies found that the chemical reduced harmful amyloid-band deposits or amyloid plaques, repaired damaged synapses, and protected against memory loss in Alzheimer's disease patients [251]. On the other hand, Gracilin A, bryostatin 1, and leucettamine B were identified as MDKIs despite the fact that none of the specified MDKIs appeared in our search results. None of these marine chemicals will cross the BBB, according to their best models, which have GBC-based probability estimates of less than 0.01 [23]. Similarly, dictyostatin resulted in the same effect, which was seen in a PS19 tau Tg mouse model. Dictyostatin, a macrolide originating from marine sponges, was first isolated from the Maldives' Spongia sp. It was clearly observed the improved number of microtubules in dictyostatin-treated PS19 mouse models following the reduction of the levels of axonal dystrophy. When opposed to vehicle-treated PS19 mouse models, *Bugula neritina* also reduced tau pathology and had a trend for an increased hippocampal neurons' survival rate. The promising findings obtained on the brain impact in dictyostatin-treated aged PS19 mouse models reaffirmed the notion that microtubule-stabilizing molecules may be useful in treating Alzheimer's disease [252].

Caniferolide A is a macrolide obtained from *Streptomyces caniferus*, a marine-derived actinomycete tested for its potential for alleviating Alzheimer's disease symptoms. The compound inhibited the nucleus translocation of NFκB-p65 and stimulated the Nrf2 pathway and neuroinflammatory markers reduction in lipopolysaccharide-activated BV2 microglial cells. It also prevents the pro-inflammatory cytokines (IL-1β, TNF-α, IL-6), reactive oxygen species (ROS), and nitric oxide production, and hinders the activities of JNK, iNOS, and p38. Furthermore, the compound inhibited BACE1 behavior and reduced Aβ-activation in microglia by significantly lowering ROS levels. In SH-SY5Y tau441 cells, the phosphorylated condition of tau protein was investigated [248]. In a review, Feng et al. discovered that the marine-derived molecule 11-dehydrosinulariolide (11-de) protects cells from 6-hydroxydopamine (6-OHDA)-mediated harm by upregulating the Akt/PI3K pathway. The therapeutic activity of 11-de was investigated using SH-SY5Y, zebrafish, and rats in that research. The findings exposed the process by which 11-de works: it enhances mitochondrial DJ-1 expression, stimulates the downstream of p-CREB, Nrf2/HO-1, and Akt/PI3K pathways. They also

demonstrated that 11-de could restore the 6-OHDA-induced down-regulation of overall swimming time in a zebrafish model of Parkinson's disease [253].

Palmyrolide A is a recent neuroprotective macrolide discovered in a marine cyanobacterial assemblage from Palmyra Atoll that includes Leptolyngbya cf. and Oscillatoria spp. It has an unusual N-methyl enamide and an interesting *t*-butyl branch, the latter of which prevents hydrolysis of the neighboring lactone ester bond. Pereira et al. found that the compound blocked sodium influx in mouse neuroblastoma cells (IC_{50} of 5.2 μM) and spontaneous Ca2+ oscillations (IC_{50} of 3.7 μM) in primary cultures of murine cerebrocortical neurons without causing cytotoxicity, which makes the compound a fascinating candidate for more pharmacological investigation [254,255]. In another study, Zhao et al. found that the reported xyloketal B compound, extracted from the fungus Xylaria sp., blocked ischemia-stimulated PC12 cellular damage with an IC_{50} value of 100 μM via a neuroprotective free radical scavenging mechanism, decrease the potential of the mitochondrial membrane, and superoxide production, implying that further research is required for successful stroke therapy [256].

4. Mode of action and mechanism of resistance

4.1. Mechanism of action

Macrolides are one of the most clinically significant antibiotic groups most often used. Their range of activity consists mainly of staphylococci, streptococci, and bacilli under the gram-positive bacteria and against intracellular bacteria and gram-negative cocci, such as *Rickettsia* and *Chlamydia*. However, gram-negative bacilli are mostly resistant, with some significant exceptions, such as *Chlamydia*, *Legionella*, *Helicobacter* and *Campylobacter, Bordetella pertussis* [262]. Chemically, Macrolides are a 14-, 15-, or 16-membered lactone ring containing sugar moieties and other substitutions attached to the lactone ring's various atoms [263]. Using a mixture of biochemical and genetic approaches, the precise location of the macrolide binding site was first determined on the large ribosomal subunit [264]. However, the specific molecular interactions between the different macrolide groups and the ribosome have only recently begun to appear with the publication of many crystallographic structures of bacterial large ribosomal subunits and their antibiotic complexes. Later, the X-ray structures corroborate previous biochemical findings that RNA is the key element of the macrolide binding site. The macrolide molecule interacts with various nucleotide residues in 23S rRNA's domain V. The exact mechanism by which macrolides suppress protein synthesis depends on the drug molecule's chemical structure. This has an impact on both its ribosomal interaction and the mode of inhibition. Thus, macrolides have been implicated in four distinct mechanisms of protein synthesis inhibition: 1) Inhibition of peptide chain's development during early stages of translation 2) Facilitation of the dissociation of peptidyl tRNA from the ribosome 3) Inhibition of the forming of peptide bonds and 4) Interference with the assembly of the 50S subunit. All of these pathways are related to the ribosome's macrolide binding region of *Rickettsia* and *Chlamydia* [265].

4.2. Mechanism of resistance

A typical process by which bacteria develop resistance to antimicrobial agents is a decrease in the antibiotic's affinity for *Chlamydia*, *Legionella*, *Helicobacter* and *Campylobacter* target. This impact can happen as a result of the drug's enzymatic detoxification or target alteration. Another option is that the molecules had less access to the destination as a result of active efflux or reduced absorption. So, there are three ways by which bacteria resist macrolides; (1) by methylation or mutation of the antibiotic's target site, which prevents the antibiotic from binding to its ribosomal target, (2) by antibiotic efflux, and (3) by drug inactivation. The three pathways have a disparate effect on pathogenic microorganisms in terms of prevalence and therapeutic consequences. When the ribosomal target is modified, broad-spectrum tolerance to macrolides is conferred, while efflux and inactivation impact just a subset of these molecules [65,262].

4.3. Macrolide resistance due to the target site modification

Protein L4 mutations impair macrolide binding explicitly or allosterically, causing resistance by blocking macrolide binding to the ribosome [266]. Moreover, drug affinity is not greatly affected by mutations in L22 ribosomal protein, although it seems to function indirectly. Since these mutants have a larger tunnel gap, the nascent peptide can slip through the macrolide molecule bound in the tunnel and displace the compound. Mutations of ribosomal protein genes are a major source of macrolide resistance, and a single mutation is enough to render cells vulnerable to a macrolide [265].

In bacteria, Erm proteins dimethylate is the only adenine in emerging 23S rRNA under the large ribosomal subunit (50S). The A2058 residue is located in a conserved region of domain V of 23S ribosomal RNA, necessary for macrolide binding [267].

In the A2058 region, demethylation of a single 23S rRNA nucleotide with Erm-type methyltransferases is the most often found macrolide binding site modifications method. A2058 dimethylation found inside the macrolide binding site significantly reduces drug affinity due to steric obstructions, making bacteria vulnerable to large macrolide antibiotic concentrations [268,269]. As a result of methylation, the attachment of macrolides to their targets is hampered. Cross-resistance to this type of medication is due to the overlapping binding sites of macrolides in 23S rRNA. Since A2058 is found inside the large ribosomal subunit and seems to be inaccessible to Erm methyltransferase, the entirely assembled ribosome is not a substrate for erm methylation [270]. Since methylation of A2058 can occur mostly during ribosome assembly, the erm enzyme has minimal time to methylate its rRNA target. So, Erm methylases are used in multiple macrolide-targeting microorganisms, including spirochetes, anaerobes, and gram-positive bacteria. So far, about 40 erm genes have been discovered. Self-transferable plasmids and transposons primarily carry these determinants in pathogenic bacteria [267].

4.4. Antibiotic efflux

In gram-negative bacteria, chromosome-encoded pumps add to the innate susceptibility of hydrophobic substances like macrolides. Two families of pumps are the ATP-binding-cassette transporter superfamily members and the main facilitator superfamily members, are involved in the acquisition of macrolide tolerance through active efflux in gram-positive bacteria [18]. The only efflux proteins gaining developed macrolide resistance in Staphylococcus organisms are plasmid-borne emsr(A) genes encoded ABC transporters. The msr(A) resistance construct was first discovered in Staphylococcus epidermidis, but it has since been discovered in several staphylococcal species like *S. aureus*. ABC transporters require ATP to act and are normally formed by a channel on the membrane's cytosolic surface that consists of two membrane-spanning and ATP-binding domains. An ABC transporter-like protein with two ATP-binding domains is generated by the msr(A) gene. The efflux process is usually multi-component, involving chromosomal genes and msr(A) to construct a fully functioning efflux pump that recognizes macrolides as well as streptogramins type B [267].

5. Conclusions

The marine habitats that have various living organisms and materials are the most prevalent in the world. Marine habitat species create a range of unusual biomolecules since the underwater ecosystem needs molecules comprising complex and effective biological compounds. Many aquatic species are abundant in natural macrolides, which will potentially be used for microbial diseases, inflammation, and cancer in

the near future. Marine macrolides are especially promising natural medicines, likely accessible to pathogens immune to presently recognized drugs. Drug resistance today poses a significant challenge to public health: developing new successful bioactive agents from natural resources is a critical pathway between diverse methods to eliminate and combat resistance. These bioactive marine compounds may be produced by chemical synthesis or recombinant DNA technology in greater amounts. Availability in large quantities will provide for more investigations in both preclinical and clinical studies. Due to its secure and prosperous drug delivery mechanism, the increasing advancement of nanotechnology will provide solutions for the efficient use of certain sea-derived compounds as pharmaceuticals with potential therapeutic potential. Further new compounds anticipate exploration in the light of the plethora of aquatic animals and in the near future medicines of marine nature that may be effective for treating various human diseases.

There have been significant advances in finding new drug leads from marine macrolides, but many works are still required in order to proceed upon therapeutic applications. Specifically, the availability dilemma greatly impedes research into a better comprehension of macrolide action mechanisms and hampers more visibility into the real therapeutic promise of these intriguing marine natural products. A response to the supply shortage of marine natural products will also be a great blessing to this research sector. Recently, multi-gram complete synthesis and biotechnological research also enhanced the fundamental function of marine macrolides. Further, in developing new lead compounds with action, the potential for synthetic intermediates and engineered synthetic analogs seems more optimistic than the production of the parent compounds. Organic synthesis, together with biochemical studies, has contributed to a full understanding of molecular marine macrolide biosynthesis, such as heterologous expression of biosynthesis in an acceptable host, which is supposed to offer exciting prospects for marine macrolide study.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgements

Funding for open access charge: Universidade de Vigo/CISUG.

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