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REVIEW

Potential applications of marine macrolides: New drugs from the sea?

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Abstract The sea is an untapped and unexploited wide ecosystem, which results to be extremely rich in diverse species: marine organisms are a source of many substances with numerous biological activities. Important marine biologically active molecules are, among others, macrolides, which could become the source of new and effective medicaments and therapeutics, due to their potential anti-inflammatory, antimicrobial (not only antibacterial and antifungal, but also antiprotozoal and antiviral), antioxidant, immunomodulant and antitumor capacities. Aim of this review is to examine the biological activities and the potential clinical and pharmaceutical applications of these interesting and fascinating novel marine bioactive compounds.

Keywords Marine bioactives . Macrolides . Anti-inflammatory . Antimicrobial . Antitumor agents

Introduction

The marine world represents a reserve of bioactive ingredients, with a considerable potential as medicaments and functional foods. Numerous sea-derived substances, such as chitin, chitosan, polyunsaturated fatty acids (Gammone et al. 2019) carotenoids (Gammone et al. 2015; Gammone et al. 2017; D'Orazio et al. 2012), vitamins, minerals and bioactive peptides (Gammone et al. 2015; Gammone et al. 2017), can provide health benefits, such as the reduction of cardiovascular diseases, as well anti-inflammatory and anticarcinogen activities (Gammone et al. 2016). Currently, a small number of macrolides is used in medicine, mostly with antibacterial and antifungal purposes. Antibacterial macrolides (such as erythromycin, azithromycin, clarithromycin and josamycin) can act as bacteriostatics: they reversibly bind to the bacterial ribosome inhibiting RNA-dependent protein synthesis. The antifungal macrolides (such as amphotericin B and nystatin) bind to ergosterol and lead to pore formation, leakage of monovalent ions and fungal cell death (Mesa-Arango et al. 2012).

In the last decades, a new class of sea-derived bioactives, represented by marine macrolides, gained attention because of its potential anti-inflammatory, antimicrobial and immunomodulant capacity. Marine macrolides are highly oxygenated natural compounds, structurally characterized by a macrocyclic lactone. The structures of these large-ring lactones are usually very difficult to elucidate, either for the minute amounts isolated or by their intricate flexible and highly substituted skeletons. Marine organisms and their symbionts produce a large number of structurally diverse macrolides with important biological activities. The sponges represent the prevalent source of these secondary metabolites; however microalgae, macroalgae, flagellates and tunicates were also studied, thus discovering very interesting structures. The first marine macrolides were the aplysiatoxins, obtained from the sea hare *Stylocheilus longicauda*, which showed immunomodulation, antiviral and antifungal properties. At present, more than 200 marine macrolides have been discovered, paying attention to their biological active properties, such as immunomodulation, cytotoxic, anticancer, antiviral and antifungal activities. Marine macrolides exert antiproliferative cytotoxic

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activity with various molecular targets (Gammone et al. 2020; Qi et al. 2011) and they could represent a valuable option against drug-resistent tumors. Similarly, antimicrobial resistance (often related both to antibiotics' misuse and to zoonotics and even fecal bacteria present in foods), increasingly common among pathogens, is also gaining importance. The hope is to find new medicaments, able to fight against these kinds of drug-resistance. The new pharmaceutical source could be represented by marine macrolides, because of their promising potential (Napolitano et al. 2009; Qhyoshi et al. 2018; Kim et al. 2019).

Marine macrolides as antimicrobial agents

Nowadays, antimicrobial resistance is a serious threat to human health: both the development of innovative antimicrobial agents and the combination therapy are trying to fight this growing resistance (Xu et al. 2018). At present, more than 60 guanidine-containing polyhydroxyl macrolides were reported: 46 prototype compounds extracted from actinomycetes and 17 structural derivatives; all these compounds contain a lactone ring and a guanidyl side chain (Xu et al. 2017; Hong et al. 2016). Structure-activity analyses clarified that the terminal guanidine group and the lactone ring of these bioactives are pivotal for antimicrobial activities.

In particular, the discovery of guanidyl side-chain targeting to lipoteichoic acid of *Staphylococcus aureus* demonstrated that these compounds have a great potency to be developed into antibacterial and anti-inflammatory drugs. Guanidine-containing polyhydroxyl macrolides showed broad-spectrum antibacterial and antifungal activities, and they can remarkably inhibit the growth of Gram-positive bacteria, yeast, and fungi (Yuan et al. 2011; Yuan et al. 2013). The study of antimicrobial mechanisms indicated that the cell membrane was the main action site of these molecules against bacteria and fungi: they can change the plasma membrane permeability and lead to the leakage of cellular substances (Kim et al. 2013; Xu et al. 2018; Cheng et al. 2010).

Azalomycin F and its main compounds F3a, F4a, and F5a, extracted from the broth of *Streptomyces hygroscopicus azalomyceticus*, was the first guanidine-containing polyhydroxyl macrolide reported. It was recently described (Yuan et al. 2019) that azalomycin F5a can bind to the polar head of cell-membrane phospholipid and target to lipoteichoic acid against methicillin-resistant *Staphylococcus aureus*. This confirmed that cell-membrane lipids, especially 1,2-dihexadecanoyl-sn-glycero-3-phospho-1′-rac-glycerol (whose content in the cell-membrane lipids seems to increase in case of bacterial resistance to daptomycin), could be important targets of azalomycin (Xu et al. 2018; Yuan et al. 2013). Additional researches indicated the synergy of its lactone ring binding to the polar head of phospholipid and its guanidyl side-chain targeting to lipoteichoic acid, that led to the autolysis of *Staphylococcus aureus* cells (Yuan et al. 2019). The compositional analysis indicated that lysyl-phosphatidylglycerol, and cardiolipin were three major components of S. aureus cell-membrane phospholipids (Mishra et al. 2013; Short et al. 1971). Further molecular dynamics simulations displayed that azalomycin F5a had greater adhesive force to plasma membrane assembled by 1,2-dihexadecanoyl-sn-glycero-3-phospho-1′-rac-glycerol: this indicates its powerful antagonistic activity to daptomycin-resistant *Staphylococcus aureus*, with a promising potential to be developed into novel antimicrobial agents (Vickery et al. 2018; Richter et al. 2013).

Curvulides are compounds extracted from the fungus *Curvularia sp.* of the red alga *Acanthophora spicifera*, which was mostly found in Fingers Reef and Guam (Mondol et al. 2017). Curvularin and (S)-dehydrocurvularin resulted to possess anti-inflammatory activity (Ha et al. 2017) to be active against fungus-like *Phytophthora capsici* and to be cytotoxic towards human tumor cell lines (Greve et al. 2008). The two 11-hydroxycurvularin isomers isolated from the marine actinomycete *Pseudonocardia sp. HS7* found in the sea cucumber *Holothuria moebii*, displayed antibacterial activity towards Escherichia coli (Ye et al. 2016). In addition, αβ-dehydrocurvularin has anti-fungal activity against *Saccharomyces cerevisiae* with minimum inhibitory concentration (MIC) of 375–750 μg/mL and antibacterial *Staphylococcus aureus* with an MIC of 375 μg/mL. Both substances also inhibited the growth of *Bacillus subtilis* with MICs of 1500 and > 3000 μg/mL (Karpinsky 2019).

Amphidinolides were isolated from the symbiotic dinoflagellate *Amphidinium sp.* from the marine flatworm *Amphiscolops sp*. collected at Ishigaki Island, Okinawa, Japan. These compounds resulted to be active against *Trichophyton mentagrophytes* with MICs of 16–32 μg/mL. In particular, amphidinolide Q was active against *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans* with a MIC from 16 to

32 µg/mL (Kubota et al. 2014).

Lasiodiplodins are resorcinolic macrolides (Xu et al. 2014) obtained from the marine endophytic fungus No. ZZF36 found in the brown alga Sargassum sp. of Zhanjiang Sea. They exhibited a moderate inhibitory activity against *Staphylococcus aureus* with a MIC of 6.25 µg/mL, and less powerful activities against *Bacillus subtilis*, *Salmonella enteritidis* and *Candida albicans* (Karpinsky 2019). Macrolactin N, extracted from *Bacillus subtilis* AT29 in the sea sediment of East China Sea showed antibacterial activity against *Escherichia coli* and *Staphylococcus aureus*, with a MIC value of 100 µg/mL (Karpinsky 2019). Macrolactins A, B, D, O, S, T and U were isolated from the bacterium *Bacillus marinus*, found in the coastline of the Bohai Sea of China. The inhibitory activity of macrolactins B (MIC 4.5–20.1 µg/mL) and D (MIC > 100 µg/mL) was reported not only against the bacterium *Staphylococcus aureus*, but also against the fungi *Pyricularia oryzae* and *Alternaria solani* (Xue et al. 2008).

Lobophorins A and B were obtained from a marine Actinomycete found on the Caribbean brown alga *Lobophora variegata* [36]. Lobophorins E, F, H and I were isolated from *Streptomyces sp.,* found in the sediment in the South China Sea (Niu et al. 2011). Lobophorins A, B, E, and F exhibited activities against *Bacillus thuringensis* with MIC values of 2–8 µg/mL. Lobophorin F displayed antibacterial activities against *Staphylococcus aureus* and *Enterococcus faecalis* with MIC values of 8 µg/mL (Niu et al. 2011). Additionally, lobophorins B and H exhibited strong inhibitory activities (MICs of 1.57–3.13 µg/mL) against *Bacillus subtilis*. Lobophorins F and H also exerted moderate antibacterial activities against *Staphylococcus aureus* with MIC values of 6.25–50 µg/mL (Karpinsky 2019). Other interesting macrolides are represented by bromophycolides and borrelidins. Bromophycolides P and Q, which were extracted from the red alga *Callophycus serratus* found around Fiji coasts, displayed antibacterial activity against methicillin-resistant *Staphylococcus aureus* (with an IC50 of 1.4 and 1.8 µM respectively), and vancomycin-resistant *Enterococcus faecium* with an IC50 of 13 and 5.8 µM, respectively (Lane et al. 2009). Borrelidins, isolated from actinomycete Nocardiopsis sp. in Korea Sea, inhibited *Enterococcus faecalis* and *faecium*, *Klebsiella pneumoniae* and *Salmonella enterica* with MICs of 0.51–65 µM (Karpinsky 2019). Very recently, three homologous oxygenated elansolid-type of polyketide spanned macrolides (isolated from a heterotrophic marine bacterium, *Bacillus amyloliquefaciens*, found in red alga *Hypnea valentiae*), showed broad-spectrum bactericidal activity against methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus faecalis*, and drug-resistant strains of *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* with MIC ≤1.0 µg/mL (Fusetani et al. 1991).

Macrolides can change the cell membrane permeability of microbe and lead to the leakage of cellular substances, however they possess different mechanisms against bacteria and fungi as the components of their cell envelopes are different.

For example, 13-Deoxytedanolide, extracted from the sponge *Mycale adhaerens* in Japan (Kizhakkekalam et al. 2020) strongly binds to the 60S large ribosomal subunit, determining inhibition of polypeptide elongation in fungus *Saccharomyces cerevisiae*.

Sporiolides are 12-membered macrocyclic lactones (obtained from the fungus Cladosporium sp. on the marine brown alga *Actinotrichia fragilis* at Okinawa Island) which displayed both antibacterial and antifungal activity. In particular, sporiolides A and B resulted to be effective against *Micrococcus luteus* with a MIC of 16.7 µg/mL; sporiolide A also displayed antifungal activity against *Aspergillus niger*, *Candida albicans* and *Cryptococcus neoformans* with MICs of 8.4–16.7 µg/mL (Karpinsky 2019). Leucascandrolide A, which was obtained from the calcareous sponge *Leucascandra caveolata* along the east coast of New Caledonia, strongly inhibited fungi *Fusarium oxysporum*, *Helminthosporium sativum*, *Botrytis cinerea*, *Pyricularia oryzae*, and yeast *Candida albicans* (D'Ambrosio et al. 1996).

Numerous guanidine-containing polyhydroxyl macrolides can exert not only antibacterial but also antifungal activity with various mechanisms. For example, Azalomycin F primarily targets the cell surface: it determines the leakage of cellular substance from the cells of *Candida albicans*, and powerfully inhibits amino acid incorporation into cellular protein, the incorporation of phosphate into nucleic acids and oxidative deamination of amino acid metabolism (Yuan et al. 2011). Similarly, niphimycin disrupted the plasma membrane by directly interacting with phospholipids, such as phosphatidylcholine, and generating ROS residues: this synergistic combination of direct plasma membrane damage and oxidative stress was the basis of antifungal its activity against *Saccharomyces cerevisiae* (Song et al. 2019).

Other macrolides, which displayed marked antifungal activity against *Candida albicans*, were

Kabiramides, obtained from the eggmasses of an unidentified nudibranch of the japanese Ryukyus Islands. In particular, Kabiramide C resulted to be also active against *Aspergillus niger*, *Penicillium citrium* and *Trichophyton interdigitale*. Kabiramides B, D, G, J and K (extracted from the sponge *Pachastrissa nux* found in the Gulf of Thailand) demonstrated anti-parasite activity against *Plasmodium falciparum* K1 (Sirirak et al. 2011).

Similarly, bastimolide A, a polyhydroxy macrolide with a 40-membered ring from a new genus of the tropical marine cyanobacterium *Okeania hirsuta*, also showed potent antimalarial activity against four resistant strains of *Plasmodium falciparum*, with IC50 values between 80 and 270 nM. Further investigation led to the discovery of a new analogue, bastimolide B, a 24-membered polyhydroxy macrolide with a long aliphatic chain and unique terminal tert-butyl group. Bastimolide B showed strong antimalarial activity against chloroquine-sensitive *Plasmodium falciparum* strain HB3: a preliminary investigation of the structure-activity relationship revealed the importance of the double bond, as well as the 1,3-diol and 1,3,5-triol functionalities (Shao et al. 2018).

The isolation and structure determination of palstimolide A, another complex polyhydroxy macrolide (from a tropical marine cyanobacterium collected at Palmyra Atoll), was also recently reported. Palstimolide A is characterized by a 40-membered macrolactone ring, nine hydroxy group equivalents that form seven 1,5-diol and one 1,7-diol relationships around the ring, a tert-butyl moiety, and an α,β-unsaturated carbonyl moiety. Palstimolide A shows potent antimalarial activity, together with promising preliminary results as an anti-leishmanial agent. Likely, its elaborate structure provides an evolutionary advantage; however, this requires further investigation. This structural class appears to be highly attractive for drug discovery efforts because most of these metabolites show a range of biological activities, especially to intracellular parasites (Keller et al. 2020).

Additionally, antiviral activity of a new 12-membered macrolide was reported against herpes virus 1 (HSV-1): balticolid was isolated from the culture broth of fungal strain 222 belonging to the *Ascomycota*, which was collected from the coast of Baltic Sea. The structure of balticolid was determined to be (3R,11R), (4E,8E)-3-hydroxy-11-methyloxacyclododeca-4,8-diene-1,7-dione using extensive spectral data. Balticolid displayed anti-HSV-1 activity with an IC50 value of 0.45 μM (Shushni et al. 2011).

The optimum lipophilic parameters support the interesting anti-infective properties of macrolides, so that these compounds may have promising biotechnological and pharmaceutical applications against emerging multidrug-resistant pathogens.

Antitumor activities of marine macrolides

Cancer includes numerous disorders, with deregulated signaling pathways, in particular related to cell proliferation, angiogenesis, metastasis and elusion of the apoptotic mechanisms.

The increasing drug resistance and the subsequent inadequate efficacy have recently drammatically reduced the clinical therapeutical chances. For this reason, new kinds of small antitumor compounds are currently necessary. In this respect, the sea could offer a wide unexploited repository of bioactives molecules and compounds (extracted from both marine animals and plants), which can be considered an useful support or a safer alternative to common existing synthetic medicaments, thanks to their significant biological activities.

Zampanolide is a marine microtubule-stabilizing macrolide that has been shown to be a promising anticancer lead compound (Table 1). This 20-membered polyketide was extracted from the marine sponges *Fasciospongia rimasa* (in Okinawa) and *Cacospongia mycofijiensis* (along Tongan coast). It exhibited cytotoxic activity against both drug sensitive and multi-drug resistant cancer cell lines, with effects on tubulin assembly and microtubule bundle formation. Zampanolide displayed a powerful antitumor activity, even stronger than paclitaxel (Chen et al. 2014). Numerous investigations demonstrated its low-nanomolar cytotoxicity against HL-60, A2780 (Field et al. 2012), OVCAR (Ghosh et al. 2012) and SKM-1 cell lines, with low nanomolar cytotoxicity against multi-drug resistant cancer cells that overexpress the P-gp multidrug resistance pump (Ghosh et al. 2012). Covalent binding of medicaments to their target can effectively inhibit the ability of P-gp to pump the drugs out of the cell: in preclinical settings this method resulted effective in order to avoid P-gp mediated drug resistance. Since zampanolide binds covalently to tubulin, it has the potential to treat multi-drug resistant cancer. Zampanolide's structure can be improved

Table 1 The main activities and sources of marine macrolides

Macrolides	Source	Target
Aplyronine	*Aplysia kurodai*	Cervical carcinoma cell line HeLa S3, murine leukemia, Lewis lung carcinoma, colon carcinoma, melanoma
Azalomycin F	*Streptomyces sp.*	*Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli, Candida albicans*
Balticolid	*Ascomycota*	HSV-1
Bastimolide A-B	*Cyanobacterium Okeania hirsute*	*Plasmodium Falciparum*
Borrelidins	*Actinomycete Nocardiopsis*	*Salmonella enterica*
Bromophycolides	*Alga Callophycus serratus*	*Staphylococcus aureus, Enterococcus faecium*
Curvularins	*Curvularia* sp. *Eupenicillium* sp.	*Bacillus subtilis, Phytophthora capsici, Saccharomyces cerevisiae, Sclerotinia sclerotiorum*
Kabiramides	unidentified nudibranch	*Candida albicans, Aspergillus niger, Penicillium citrium, Trichophyton interdigitae*
Leucascandrolides	Sponge *Leucascandra caveolata*	*Fusarium oxysporum, Helminthosporium sativum, Phytophtora hevea, Botrytis cinerea, Pyricularia oryzae, Candida albicans*
Lobophorins	*Streptomyces* sp. Actinomycetes	*Bacillus thuringensis, Bacillus subtilis, Staphylococcus aureus, Enterococcus faecalis*
Macrolactins	*Bacillus subtilis* *Bacillus marinus*	*Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Aspergillus niger, Candida albicans, Pyricularia oryzae, Alternaria solani*
Palstimolide A	*Palmyra Atoll Cyanobacteria*	*Plasmodium falciparum*, Leishmania
Zampanolide	Sponges *Fasciospongia rimasa*	HL-60, A2780, OVCAR and SKM-1 cancer cell lines

if its chemically fragile side chain is stabilized; for this reason mimics of zampanolide with a stable side chain using straightforward synthetic methods have been created (Chen et al. 2019). More specifically, 12 novel zampanolide mimics from 51 to 62 with conjugated and planar side chains have been synthesized via a 24-step sequence for each mimic. Zampanolide-52 was identified as the candidate with optimal antiproliferative potency against both docetaxel-sensitive and docetaxel-resistant prostate cancer cell lines with IC50 values of 0.29-0.46 μM (Chen et al. 2019). These findings make zampanolide very attractive for large-scale synthetic preparation for clinical applications (with the potential for oral administration) in addition to existing anticancer drugs.

Similarly, aplyronines (extracted from *Aplysia kurodai* collected on the japanese Pacific coast), resulted to be in vitro potent antitumor substances, against the human cervical carcinoma cell line HeLa S3 (Ojika et al. 2012). Aplyronine A (Table 1) was more cytotoxic than aplyronine C with IC50 values of 0.45, 2.9 and 22 nM respectively (Kita et al. 2015). Aplyronine A showed powerful anticancer activity in mouse xenograft models, such as murine leukemia, Lewis lung carcinoma, colon carcinoma and melanoma (Suenaga et al. 2012; Futaki et al. 2019) due to its ability to interact with actin (Saito et al. 1996; Yamada et al. 2009). Actin is the most abundant protein in eukaryotic cells and is essential for the regulation of various cellular functions, such as muscle contraction, cell mobility, cell division and tumor migration. It is possible that actin-targeting agents interact with various cellular targets via unknown protein–protein interactions (Futaki et al. 2019) with a good potential in the design and development of newly classified protein–protein interaction modulators as pharmacological tools and therapeutic agents. Aplyronine A demonstrated an actin-depolymerizing effect, inhibiting the velocity and the degree of actin polymerization by forming a 1:1 complex with monomeric actin. In addition to the action of the side-chain, which binds to actin to depolymerize the filament (Saito et al. 1996), the actin-aplyronine A complex synergistically binds to tubulin at very low concentrations, inhibiting tubulin polymerization, and prevents spindle formation and mitosis in tumor cells. In additional studies, aplyronine A also led to potent caspase 3 activation in HeLa S3 cells (Yamada et al. 2009). The cytotoxicity of aplyronines D–H was also proved against HeLa S3 cells, with IC50 values from 0.075 to 9.8 nM (Ojika et al. 2012); however further investigations are required to establish a structural active relationship between the observed cytotoxicity and the binding of these aplyronines to actin/tubulin and the activation of caspase-3.

Other potential anticancer bioactives were recently evidenced (Table 1). For example, latrunculins are architecturally new compounds extracted from the Red Sea sponge *Latrunculia magnifica*, which interferes with cellular growth by disrupting actin polymerization and microfilament organization, determining antiproliferative effects (Kita et al. 2013; Kita et al. 1989); dolastatin-19, recently isolated from the sea hare *Dolabella auricularia* from the Gulf of California, whose antiproliferative activity was proved against breast and colon cancer cells (Paterson et al. 2008); scytophycins, isolated from the blue and green algae *Scytonema pseudohofmanni* (Ishibashi et al. 1986), and sphinxolides from the New Caledonian marine sponges *Neosiphonia superstes* (D'Auria et al. 1994) are also actin-binding natural bioactives: they resulted to be able to inhibit the proliferation of various human cancer cell lines (Paterson et al. 2004). The manipulation of new protein–protein interactions by natural bioactive compounds has become an important issue in the field of human health and drug discovery. Further investigations on the mechanisms of action and on the development of new diverse actin-targeting natural products are currently underway.

Marine macrolides against inflammation: Potential applications in sport

Numerous marine bioactives, such as COX inhibitors, marine steroids (D'Orazio et al. 2012), molecules interfering with factors involved in the modulation of gene expression (such as NF-κB), many antioxidant agents (Riccioni et al. 2015; Gammone et al. 2018), thermogenic substances (Gammone et al. 2015) and other natural marine compounds that could help the immune system and protect cartilage, have been recently gaining attention.

In this respect, marine macrolides displayed potential anti-inflammatory and antioxidant capacity and could provide health benefits and performance improvement, especially in those who practice physical activity (because of their increased free radicals production during exercise) and, particularly, in athletes (Gammone et al. 2014). Reacting oxygen species (ROS) enhance oxidative reactions with proteins, lipids and DNA: oxidative stress triggers signaling pathways and can impair cellular functions, determining secondary damage. There is a close relationship between oxidative stress and inflammation: in most phlogistic conditions, when macrophages and leukocytes are activated, ROS are generated, determining oxidative stress. Elevated level of ROS, such as superoxide anion, nitric oxide, hydrogen peroxide and hydroxyl radical, plasma malondialdehyde and degradation products of lipid peroxidation represent important characterizing factors of inflammatory diseases (Riccioni et al. 2018; Gammone et al. 2019; Gammone et al. 2020); their accumulation can also reduce fitness, because oxidative damage is a pivotal contributor to both fatigue and senescence (D'Orazio et al. 2012)

Physiological studies in murine inflammatory models demonstrated that lobophorins A and B, displayed not only antibacterial activity, but also anticancer and anti-inflammatory properties, even stronger than indomethacin (Kita et al. 2013). These compounds selectively inhibit 5-lipoxigenase (Jacobson et al. 1992), and this can help counter exercise-related inflammation (due to physical stress and repeated microtrauma) in numerous sports. For example, in endurance sport there is a transient and reversible oxidation of muscle proteins, while temperature augments in the contracting muscle: in absence of mechanical damage of muscle, the stress response is mediated by redox signaling. On the other hand, in some kinds of exercise, the stress response is triggered by mechanical damage to the protein structure and increased by secondary damage associated with inflammatory processes some days after the initial mechanical insult. Additionally, exercise training augments the baseline level of heat shock protein, which depends on the individual's initial training status and on a sustained and repeated dose of training (Morton et al. 2009).

Recent studies (Salvador-Reyes et al. 2015; Mayer et al. 2019) reported that some macrolide polyketides, extracted from the edible marine brown alga *Ecklonia cava*, significantly inhibited not only pro-inflammatory cytokines (especially interleukin-6) and prostaglandin E2 production, but also gene expression, by downregulating NF-κB signaling pathway and ROS accumulation. The regulation of NF-κB expression and, consequently, of NF-kB-dependent genes (such as inducible Nitric Oxide Synthase) can substantially improve cell status. Considering that many anti-inflammatory drugs, such as corticosteroids, inhibit the activation of NF-kB, both the suppression of NF-κB and the augmented NO production have been suggested as anti-inflammatory strategies in inflammatory disorders. Since NF-κB is known to be a transcription factor regulating inflammatory response gene, its inhibition could evidence the anti-inflammatory potential of these marine compounds.

In addition, irijimasides A-E, a series of new 14-membered macrolide glycosides, were recently isolated from a marine *Cyanobacterium* collected in Okinawa. Tartrate-resistant acid phosphatase (TRAP) plays an important role in bone resorption; its expression in osteoclasts is regulated by receptor activator of NF-kappaB (RANKL), a potent activator of osteoclast differentiation. All these five macrolides suppressed RANKL-induced TRAP activity in mouse RAW264 macrophage cells, indicating that these compounds can inhibit osteoclast formation (Yamano et al. 2020) and positively influence the balance of bone status.

Further research is necessary to characterize the exercise-induced stress response to physical activity. In this respect, macrolides with anti-inflammatory activity may offer a non-pharmacological intervention; the possible inhibition of pro-inflammatory pathways help fighting stress oxidative-related disorders, preserving muscle function and bone structure during aging.

Conclusions

Marine ecosystems are the most prevalent on the planet, providing a diversity of living organisms and resources. Organisms in the marine habitat produce a variety of biomolecules which are unique because the aquatic environment calls for molecules with specific and potent biological compounds. Many marine organisms are rich in natural macrolides, which could hopefully be used in the future for the treatment of microbial infections, cancer and inflammation. In particular, marine macrolides are promising natural drugs, potentially applicable against pathogens resistant to currently known medicaments.

Nowadays, drug resistance is seriously threatening human health: the discovery of new effective bioactive agents from the natural resources represents an important pathway among various strategies in order both to prevent resistance and to fight against it.

These bioactive compounds of marine origin may be obtained in larger quantities by chemical synthesis or recombinant DNA technology. Availability in large amounts would enable more extensive investigations in both preclinical and clinical trials. The increasing development of nanotechnology may provide solutions for the effective utilization of these sea-derived compounds as pharmaceuticals with a promising therapeutic potential, due to their effective and safe drug delivery system. Additional novel molecules await discovery in view of the multitude of marine organisms and hopefully, drugs of marine origin that can be useful for the treatment of numerous human diseases will be available in the foreseeable future.

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