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Research Article

Marine-Derived Metabolites as Antimalarial Candidates Targeting Various Life Stages

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ABSTRACT

Malaria is still a major public health issue in several areas around the world. Due to *Plasmodium falciparum*'s extensive resistance to practically all frontline treatments, massive attempts to combat malaria have been significantly hampered. The search for novel molecules in the sea organisms could lead to new therapies, including malaria. They are desperately needed to address the rise in resistance. Secondary metabolites produced by marine-derived species are structurally new and biologically potent, and they have become intriguing and valuable resources for drug discovery. Among more than 30,000 marine-derived compounds, numerous metabolites belonging to various chemical classes have shown potential efficacy against malaria. They include alkaloids, polyketides, steroids, terpenoids, peptides, and others. The current article presents concise and updated advances highlighting the potential candidates, particularly those isolated from marine sponges and cyanobacteria targeting the different stages of the malarial life cycle for disease management. Hence, this research can open novel resources of bioactive compounds for novel candidates for malaria management and other vector-borne diseases and exploring the oceans and seas treasures, where one-half of the global biodiversity exists.

Keywords: Cyanobacteria ; Malaria ; Marine products ; *Plasmodium falciparum* ; Sponge.

1. Introduction

Malaria is a potentially life-threatening parasitic disease caused by an infectious female Anopheles mosquito-borne *Plasmodium* protozoa. There has been a lot of success in combating malaria than in the past decades. Malaria nevertheless accounts for approximately 229 million cases and 409,000 fatalities in 2019. [1] Antimalarial drug resistance, which hinders malaria control, is a major public health concern. Over the past couple of decades, the rapid spread of resistance to these drugs has intensified the monitoring of their effectiveness, ensured proper control of clinical cases, and early identified evolving resistance trends to revise national policies for the treatment of malaria. Consequently, new antimalarial compounds, preferably those with a special or different structure or mode of action, are often urgently required to delay the emergence of drug resistance.

In contrast to terrestrial plants, marine organisms do not have a remarkable history of use in traditional medicine. However, recent advances in marine biology and engineering have helped in the investigation and scientific exploration of the marine environment to identify and isolate novel

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compounds. More than 30,000 compounds have been identified from about 240,000 known species of marine organisms. [2] Potential bioactivities, including anti-tumor, anti-coagulant, and antiviral effects, were among various investigated health-promoting benefits. [3,4] Particularly, many bioactive products have been developed from marine origins in recent years, representing alternative safe and effective resources for new drugs used to combat the life-threatening multi-drug resistant malaria. [5] Herein, some of the most promising antimalarials were highlighted, showing highly potent half-maximal inhibitory concentration (IC_{50}), primarily sponges- and cyanobacteria-derived, including alkaloid, sterols, peptide, and other miscellaneous derivatives.

2. Sponge-derived compounds

The oceans are the world's largest undiscovered biodiversity resource for identifying novel natural compounds with medicinal promise.[6] There are 240,000 documented macroscopic plant and animal species in the ocean, with a far more significant number of microbiological species. According to the Pharmaceutical Drugs, Global Industry Opportunities and Strategies 2021 report, the pharmaceutical drug market will increase at a compound annual growth rate of 5.78 percent from 2017 to 2021, reaching $1170.4 billion by 2021. [7] The most significant source of novel marine natural products has been marine invertebrates, which account for nearly 60% of all marine creatures. [8] Marine sponges (phylum Porifera) are one of the most important sources of bioactive molecules among marine invertebrates, accounting for over half of all novel marine natural products. [6] There are approximately 11,000 known sponge species and almost twice that number of undiscovered species. [9] To date, marine sponges have been the richest source of marine natural products reported, and sponge-derived natural products have inspired the development of several medications currently in clinical use. Marine sponges contain a vast number of bioactive secondary metabolites. Recently marine-derived compounds include alkaloids, steroids, and other compounds. Some of these organisms are demonstrated in **Figure 1,** and the identified compounds are discussed in the following sub-sections.

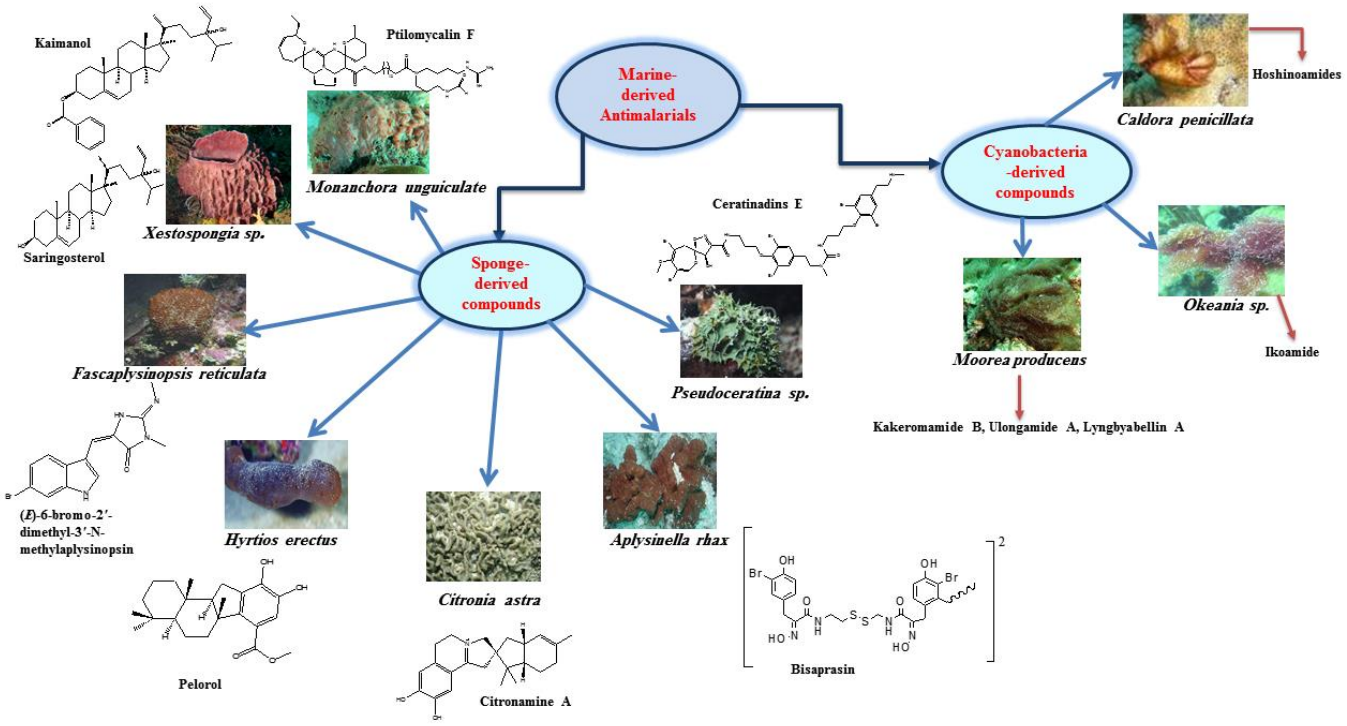

Figure 1. An overview of the most promising antimalarials derived from marine sponges and cyanobacteria.

2.1. Aplysinella rhax

A diverse range of bromotyrosine compounds, including psammaplins A, B-D, O, P, brominated hydroxybenzoic acid, and bisaprasin, were extracted from *Aplysinella rhax* sponge. Among these compounds, bisaprasin displayed the highest antimalarial activity followed by psammaplins A, P, O (IC_{50}=0.29, 0.6, 0.64, and 0.66 µM, respectively) against *P. falciparum* 3D7 colonies. [10] Bromotyrosine alkaloids were isolated from such marine sponges reported to have potential antimalarial action. [11] These compounds represent a novel discovery that expands the chemical space of this intriguing class of bioactive chemicals. After all, bromotyrosine compounds have also been recognized as possible molecular candidates for novel antiparasitic drugs.

2.2. Citronia astra

Citronia astra (family Dysideidae), an Australian marine sponge, is a source of bioactive secondary metabolites. Previous chemical studies on *C. astra* revealed the isolation of new peptides as dysinosin A, citronamides A and B, which have different structures and biological activity.[12,13] Isoquinoline alkaloid citronamine A, along with tetrapeptides citronamides A, B, dysinosin A, (6Z)-dendrolasin-5-acetate, (−)-herbadysidolide, and (−)-furodysininlactone were obtained from *C. astra*. Upon *in vitro* antimalarial investigations against 3D7 drug-sensitive and Dd2 drug-resistant colonies of *P. falciparum*, Citronamine A showed good activity against both (IC_{50}=4.3 and 5.8 µM, respectively). Citronamine A showed weak inhibition (66% at 40 µM) in the proliferation of HEK 293 cells, indicating a strong selectivity index that can convert into compounds with safer stronger anti-plasmodial activity.[14] So, citronamine A is a promising scaffold for the construction of antimalarial libraries, because of its antimalarial action and unique structure.

2.3. Fascaplysinopsis reticulata

Several bioactive tryptophan alkaloids were isolated from the sponge genus Fascaplysinopsis. Tryptophan alkaloids have been shown to have antibacterial, antiviral, and antimalarial properties, as well as cytotoxic action against numerous cancer cell lines.[15-17] A variety of tryptophan-derived alkaloids were obtained from this sponge. Among them, (*E*)-6-bromo-2′-dimethyl-3′-N-methylaplysinopsin and (*Z*)-6-bromo-2′-dimethyl-3′-*N*-methylaplysinopsin exhibited reasonable activity against *P. falciparum* (IC_{50}=8.8 and 8.0 µg/mL), respectively. [18] Tryptophan alkaloids presented a promising antimalarial action and may be a good participant in antimalarial drug discovery.

2.4. Hyrtios erectus

Hyrtios is a genus of sponges that can be found in tropical and subtropical environments, where they are mainly found as major forms of life on coral reefs. The presence of structurally diverse classes of natural products such as scalarane sesterterpenoids, acyclic triterpenoids, indole alkaloids, macrolides, sesquiterpenoids, and steroids has been reported in previous chemical studies on different Hyrtios species. [19] These chemical classes have been linked to a variety of biological activities such as anti-platelet-aggregation, antibacterial, anti-cancer, ichthyotoxic, and anti-inflammatory effects. [20-24] Smenotronic acid, ilimaquinone, and pelorol were identified from *H. erectus.* Pelorol displayed remarkable activity followed by smenotronic acid and ilimaquinone against *P. falciparum* (IC_{50}=0.8, 3.51, and 2.11 µM, respectively). [25]

2.5. Monanchora unguiculata

Guanidine alkaloid was isolated from the different active fractions of *Monanchora unguiculata*. [26] These compounds have a guanidine-containing pentacyclic ring system making unique structural types. [27] Many of these compounds were listed as having biologically important properties, such as antibacterial, cytotoxicity, antimalarial, antifungal, and antiprotozoal potential.[28-31] Guanidine alkaloids include ptilomycalins, unguiculin, crambescidins, crambescidic acid, and fromiamycalin. Ptilomycalin F and fromiamycalin demonstrated potent activity against *P. falciparum* (IC_{50}=0.23 and 0.24 µM, respectively).[32] Given the recent advances in guanidine-containing compounds and the growing interest in guanidine-containing compounds as biologically important moieties in drug design over the last decade,[33] it appears clear that these moieties hold significant promise for progressing antimalarial and antimicrobial drug discovery and development.

2.6. Pseudoceratina species

Several brominated tyrosine-derived alkaloids were obtained from the sponge *Pseudoceratina* sp. [34] From a Pseudoceratina sp. marine sponge collected in the South China Sea, fifteen new bromotyrosine-derived compounds were identified. [35] Psammaplysin F, ceratinadins E, and F were extracted from the Okinawan *Pseudoceratina* sponge. Psammaplysin F and ceratinadin E exhibited *in vitro* significant activity against *P. falciparum* K1 drug-resistant (IC_{50}= 3.77, 1.03 µg/mL) and FCR3 (IC_{50}=2.45, 0.77 µg/mL) drug-sensitive colonies, respectively with cytotoxicity less than chloroquine and artemisinin which makes them safe antimalarial candidates. [36]

2.7. Xestospongia species

Marine sponges (*Xestopongia* sp.) have been explored intensely in recent decades for their potential antiplasmodial and antibacterial capabilities, with a dozen patents already acquired from these unique organisms. [37,38] Xestoquinone-containing marine sponges of the genus *Xestospongia* are one of the world's promising antimalarial drugs.[39,40] Kaimanol and saringosterol were extracted from

the *Xestospongi*a sponge. Both sterol compounds showed promising antimalarial activity (IC_{50}=359 and 0.25 nM) against *P. falciparum* 3D7 strains. [41]

2.8. Tedaniophorbas ceratosis

Chemical diversity has indeed been linked to biological activity, and natural product structural diversity resembles that of pharmaceuticals more than synthetic library. [42] It has been widely documented that the marine environment provides unique structural motifs or scaffolds that are not found in terrestrial species or synthetic libraries. [43,44] One of These novel scaffolds is pteridine alkaloid from *Tedaniophorbas ceratosis*. [45] Tedaniophorbasins A and B, new pteridine alkaloids were extracted from this sponge. Despite displaying no inhibition against 3D7 chloroquine-sensitive and Dd2 chloroquine-resistant *P. falciparum* at a relatively high concentration (40 µM), as a novel structure, it could inspire scientists to synthesis effective derivatives. [45]

3. Cyanobacteria-derived compounds

Cyanobacteria, also described as blue-green algae, are a type of oxygenic photosynthetic prokaryote that may be found all over the world. Cyanobacteria from various habitats, particularly marine environments, have been used as a source of surprisingly diverse and biologically active compounds with antiviral, enzyme inhibition, antibacterial, immunostimulant, cytotoxic, antifungal, antitrypanosomal, anti-plasmodial, antileishmanial, and insecticidal properties for the past 50 years.[46-48] A vast array of bioactive compounds is produced by marine cyanobacteria, including peptides, polyketides, alkaloids, and other compounds. They are summarized in **Figure 1** and discussed in the following subsections. Additionally, the targets of derived peptides on the different sites of the malaria life cycle are summarized in **Figure 2**.

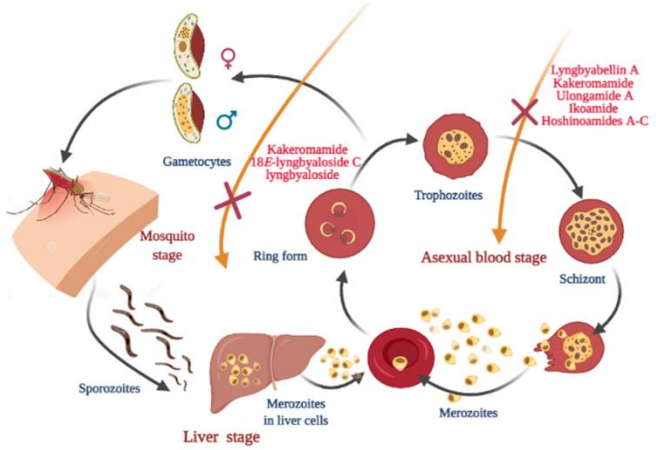

Figure 2. Malaria life cycle showing the sites of inhibitory action of different cyanobacteria-derived peptides

3.1. Moorea producens

Secondary metabolites produced by marine cyanobacteria include peptides, polyketides, alkaloids, lipids, glycosidic macrolides, and terpenes, which have different properties.[49] kakeromamide B, ulongamide A, lyngbyabellin A, 18*E*-lyngbyaloside C, and lyngbyaloside were isolated from this cyanobacterium. Lyngbyabellin A displayed potent activity against *P. falciparum* blood stages (EC_{50}= 0.15 nM), whereas kakeromamide B and ulongamide A displayed moderate activity (EC_{50}= 0.89 and 0.99 µM, respectively). Kakeromamide B, 18*E*-lyngbyaloside C, and lyngbyaloside presented moderate antimalarial activity against *P. berghei* schizonts in the liver stage (EC_{50}= 1.1, 0.71, and 0.45 µM, respectively). All compounds displayed no cytotoxicity against HepG2 human cell lines. The lack of cytotoxicity and inhibition of both the blood and liver life stages of *Plasmodium* make Kakeromamide B a promising safe lead for antimalarial drug discovery. [50] Also, the promising *Plasmodium* selectivity of lyngbyabellin, the availability of a complete synthesis method, and a large number of known lyngbyabellins all suggest further investigation as a potential malaria treatment alternative.

3.2. *Okeania* species

A new lipopeptide was identified from *Okeania* cyanobacterium. Strong antiplasmodial activity with (IC_{50}=0.14 µM) was demonstrated by ikoamide. Despite its strong antimalarial activity at 10 µM, it did not demonstrate growth-inhibitory activity against HeLa cell lines. So, the potent and selective antimalarial activity against the asexual blood stage of the *P. falciparum* 3D7 was presented by ikoamide without cytotoxicity qualifying it to become a promising safe drug against malaria. [51]

3.3. *Caldora penicillata*

Other lipopeptides hoshinoamides A, B and C extracted from *C. penicillata* cyanobacteria. [52,53] Further research into *C. penicillata* led to the identification of another hoshinoamide analogue and its chemical synthesis. All hoshinoamides did not exhibit cytotoxicity against HeLa cell lines at 10 µM. Hoshinoamides A, B, and C demonstrate the potent and selective antimalarial activity against the blood *Plasmodium* stage (IC_{50}=0.52, 1.00, and 0.96 µM, respectively).

4. Concluding remarks

Marine organisms are promising and non-traditional sources of bioactive compounds. The recent technological

advances have led to isolating and identifying thousands of marine-derived compounds belonging to various chemical classes. Many compounds with interesting antimalarial properties have been reported, which offer several possible lead compounds to develop new antimalarial drugs. Mainly, lyngbyabellin A, kaimanol, and saringosterol had a nanomolar antimalarial activity, or kakeromamide, ikoamide, hoshinoamides displayed no cytotoxicity on the tested cells. The molecules reviewed in this article revealed both the benefits and challenges of using natural marine-derived compounds to treat malaria. Nature has continued to drive drug development in this field, with natural products accounting for 9 of the 15 parasite-fighting medicines found in the last few decades. [54]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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