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Recent exploration of bioactive pigments from marine bacteria

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ABSTRACT: Microbial pigments of marine origin are gaining increasing attention in current research due to their widely perceived applications as natural food colorants, antioxidants, antimicrobial compounds, anticancer agents, and immune stimulators. This review is a short acknowledgement of the significant progress achieved over the past five years of studies on pigments from marine bacterial isolates. Herein, we also discuss the typical challenges, as well as recent technical developments, in isolating and cultivating marine bacteria and in conducting determination of pigments as critical considerations in doing research in this field.

KEYWORDS: bioactive pigments, combinatorial approaches, culture cultivation, genome mining, marine bacteria

INTRODUCTION

Marine microorganisms, due to their rich biodiversity and genetic capacity, represent a significant source of natural product discovery [1], with success rates up to 4 times higher than other naturally derived compounds [2]. In common microbial cultures, such as marine agar, seawater-based rich media agar, and Zobell agar medium, several marine gram-positive and gram-negative bacteria appear to produce an array of pigments [3], such as carotenes (yellow to red), prodiginines (red), phenazines (yellow crystalline, deep-red solution in sulfuric acid), quinones (bright yellow), and violacein (purple). These marine bacterial pigments are being explored for their production, which is clinically and industrially important because they have demonstrated various biological activities, such as antioxidant, antimicrobial, and anticancer, as well as acting to stimulate immunity [4].

In the 1960s, research on natural marine products began to flourish [5], primarily due to advances in instrumentation for structure elucidation, particularly the mass spectrometry, and isolation techniques as well as the availability of scuba gear for the collection of marine organisms at certain depths. Highlights of achievements have been frequently reviewed and indicate the structural complexity and potent biological activities of these pigments. In the PubMed search engine, using the keyword "novel pigments; marine bacteria", the number of articles reporting on bacterial marine pigments increased from only 8 articles in 2002 to 84 articles by 2015 (Fig. 1). These articles include research on the isolation and determination of new compounds and on new bacterial species or strains, research on bioactivity assays and therapeutic studies of pigments, and review articles. The number of pub-

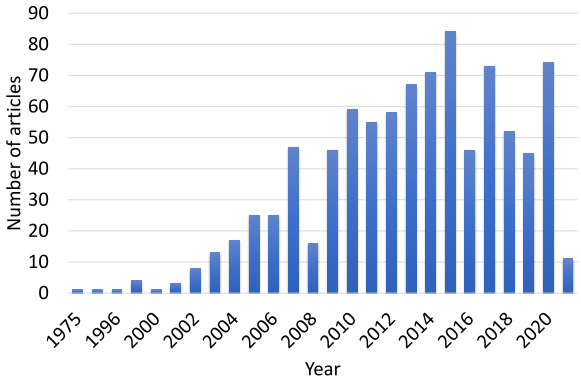

Fig. 1 Search results using the keyword "novel pigment; marine bacteria" in the search engine provided by https://pubmed.ncbi.nlm.nih.gov/ from 1975 to 2021 for journal articles.

lished articles on marine bacterial pigments has shown a rather downhill trend since 2015, despite the untapped potential of marine biodiversity.

HIGHLIGHTS DURING THE PAST FIVE YEARS

The most recent pigments that were extracted from marine bacterial isolates that have been characterized in the past five years are listed in Table 1. At least 17 species have been successfully isolated from their native habitat, including in seawater, sediments, and in association or affiliation with marine invertebrates. It has been extensively reviewed that marine sediment holds untapped potential for novel taxonomic and bioactive bacterial diversity comparable to seawater [6], in which both aerobic and anaerobic microbial ecosystems exist that persist on very low fluxes of bioavailable energy over geologic time [7]. It was reported that seawater and sediments comprise a similar number of distinct bacterial species with a mean ± standard deviation (SD) of 1378 ± 61 species for seawater and 1452 ± 74 species for sediments [6]. Living together and using invertebrates as hosts and microorganisms as symbionts is also common in marine environments [8]. Marine invertebrates, particularly sessile invertebrates, often rely upon chemical defence, and symbiosis with biochemically versatile microorganisms is an efficient strategy for survival [9]. In the absence of their microbial symbionts, most marine invertebrates cannot survive [10, 11]. Microbial symbionts have been shown to produce a variety of tailored biochemical traits due to coevolution with their specific host, making them a rich source of secondary metabolites, particularly pigments with medically and commercially attractive bioactivities [12–14].

Several new and rare compounds have been characterized over the past five years (Table 1). Carotenoids are a family of yellow to orange-red pigments, generally comprising a 40-carbon skeleton composed of 8-isoprene units. In carotenoid groups, seven rare compounds include the C_{45} and C_{50} carotenoids. By 2017, more than 250 carotenoids of marine origin had been identified [15], and the unique compositions present in marine microorganisms have promoted the use of carotenoids as a chemical signature for rapid chemotaxonomic profiling. Six new and rare carotenoids that have been reported in the past five years include 2′-isopentenyldehydrosaproxanthin (C_{45} carotenoid) from *Arthrobacter* sp. P40 [16], decaprenoxanthin and its glucosylated derivatives (C_{50} carotenoids) from *Rhodopirellula rubra* LF2^T [17], and zeaxanthin sulfate from *Erythrobacter flavus* KJ5 [18]. Newly identified marine bacteria that produce high levels of astaxanthin and its derivatives, such as 2′-hydroxyastaxanthin and 2,2′-dihydroxyastaxanthin, have also been reported [19, 20]. The unique structure of astaxanthin, which contains both a keto group and hydroxyls, plays an important role in neutralizing reactive oxygen species (ROS) [21].

Newly characterized bioactive pigments from the quinone group have also been reported, such as fridamycins H and fridamycins I from *Actinokineospora spheciospongiae* sp. nov., along with three known compounds, actinosporins C, D, and G [22]. Mersaquinone, a new tetracene derivative that exhibits antibacterial activity against methicillin-resistant *Staphylococcus aureus*, was successfully characterized and reported [23]. In addition, two new polycyclic anthraquinones, N-acetyl-N demethyl-mayamycin and Streptoanthraquinone A, were found in *Streptomyces* sp. 182SMLY, which were successfully isolated from a sample of marine sediment at a 3.6 m depth [24]. Although prodiginines were initially identified from the terrestrial bacterium *Serrantia marcescens*, these compounds were subsequently obtained from several bacteria in different marine habitats, such as *Pseudomonas rubra* strains PS1 and SB14, which were isolated from seawater [25], and *Zooshikella* sp. and *Streptomyces* sp. that were isolated from sediment [26]. Phenazine pigments, including phenazine-1-carboxylic acid and pyocyanin, were successfully characterized from *Pseudomonas aeruginosa* isolated from sediment [27, 28]. New *Pseudoalteromonas byunsanensis* strains JW1T and JW3 isolated from surface seawater were found to produce violacein [29].

MAIN CHALLENGES

The low percentage of microbes that can be readily cultured and sustainably grown under laboratory conditions is one of the primary hurdles to continued characterization of bioactive pigments. In fact, more than 99% of marine microorganisms have not been successfully cultured under laboratory conditions [30]. Approximately 107 types of bacteria were isolated from one gram of sediment, and only 5% of those microorganisms were able to be grown in the lab [31]. This phenomenon is referred to as the "great plate count anomaly" [32], a term to describe differences in the order of magnitude

Table 1 Most recent bio-pigments extracted from marine bacterial isolates have been characterized in the last five years.

Pigment	Chemical Formula	λ_{max} (nm)	Molecular ion (m/z)	Marine bacterial species	Therapeutic application	Ref.
Carotenoid group						
Decaprenoxanthin	$C_{50}H_{72}O_2$	417, 442, 471	705.6 $[M+H]^+$	*Arthrobacter* sp. P40	Antioxidant	[17]
Decaprenoxanthin monoglucoside	$C_{56}H_{82}O_7$	417, 442, 471	867.6 $[M+H]^+$	*Arthrobacter* sp. P40	Antioxidant	[17]
Decaprenoxanthin diglucoside	$C_{62}H_{92}O_{12}$	417, 442, 471	1029.6 $[M+H]^+$	*Arthrobacter* sp. P40	Antioxidant	[17]
2′-Hydroxy-astaxanthin	$C_{40}H_{52}O_5$	478	613 $[M+H]^+$	*Brevundimonas* sp. strain N-5	Antioxidant	[19]
2,2′-Dihydroxy-astaxanthin	$C_{40}H_{52}O_6$	478	629.0 $[M+H]^+$	*Brevundimonas scallop* *Brevundimonas* sp. strain N-5	Antioxidant	[19, 20]
Dehydroflexixanthin	$C_{40}H_{52}O_3$	–	581 $[M+H]^+$	*Rhodopirellula rubra* LF2^T	Antioxidant	[16]
2′-Isopentenyldehy-drosaproxanthin	$C_{45}H_{64}O_2$	470, 500	637 $[M+H]^+$	*Rhodopirellula rubra* LF2^T	Antioxidant	[16]
Saproxanthin	$C_{40}H_{56}O_2$	444, 470, 500	590 $[M+Na]^+$	*Rhodopirellula rubra* LF2^T *Rubinisphaera brasiliensis* Gr7	Antioxidant	[16]
Zeaxanthin-sulfate	$C_{40}H_{55}SO_5Na$	427, 453, 481	648.5 $[M-Na]^-$	*Erythrobacter flavus* KJ5	Antioxidant	[18, 41]
Quinone group						
Bisantraquinone 1	$C_{32}H_{25}O_9$	229, 261, 287, 361, 415	553.15 $[M+H]^+$	*Ecteinascidia turbinada*	Antibacterial Anticancer	[44]
Fridamycins H	$C_{25}H_{26}O_{11}$	231, 253, 293	503.15 $[M+H]^+$	*Actinokineospora spheciospon-giae* sp. nov.	Antitrypanosomal	[22]
Fridamycins I	$C_{32}H_{33}NO_{10}Na$	232, 253, 294	614 $[M+H]^+$	*Actinokineospora spheciospon-giae* sp. nov.	Antitrypanosomal	
N-acetyl-N demethyl-mayamycin	$C_{27}H_{25}NO_8$	328, 443	514.15 $[M+Na]^+$	*Streptomyces* sp. 182SMLY	Antibacteria	[24]
Mersaquinone	$C_{19}H_{12}O_6$	218, 277, 308, 350, 480, 515, 550	337.07 $[M+H]^+$	*Streptomyces* sp.	Antibacterial	[23]
Streptoanthra-quinone A	$C_{28}H_{22}O_8$	220, 330, 445	509.12 $[M+Na]^+$	*Streptomyces* sp. 182SMLY	Antibacterial	[24]
Prodigiosin group						
Prodigiosin	$C_{20}H_{25}N_3O$	537	324.4 $[M+H]^+$	*Pseudomonas rubra* strain PS1 and SB14 *Zooshikella* sp. *Streptomyces* sp.	Antibacterial Anticancer Anti-inflammatory	[25, 26]
Phenazine group						
Phenazine-1-carboxylic acid	$C_{13}H_8N_2O_2$	252, 365, 354	247.05 $[M+Na]^+$	*Pseudomonas aeruginosa* strain PA31x	Antibacterial Antifungal	[27]
Pyocyanin	$C_{13}H_{11}N_2O$	201, 238, 318, 710, 886	211 $[M]^+$	*Pseudomonas aeruginosa*	Antibacterial	[28, 45]
Violacein group						
Violacein	$C_{20}H_{13}N_3O_3$	585	344.12 $[M+H]^+$	*Janthinobacterium lividum* *Chromobacterium violaceum* *Pseudoalteromonas byunsanensis*	Antimicrobial Anticancer	[29, 46, 47]

between the numbers of cells from the natural environment that form colonies on agar media and the number countable by microscopic examination. Unfortunately, in marine ecosystems, only 0.01 to 0.1% of oceanic marine bacterial cells produce colonies using standard plating techniques [33]. The next challenge is achieving an adequate amount of the desired metabolites to allow identification of bacterial bioactive pigments and their bioactivity, a tedious process [34]. Another challenge in this research corresponds to genome mining. As the number of available genomes is increasing, genome mining is becoming a challenging method to identify new natural products and to validate data [35].

DEVELOPMENTS AND CONSIDERATIONS

There are a number of reasons that marine microorganisms are difficult to cultivate in the laboratory, including a lack of adequate growth conditions, low growth rates, poor development of colonies, requirement for metabolites generated by other microbes, and the presence of dormant cells [36]. Various cultivation strategies have been proposed and reviewed, such as the *in situ* cultivation technique that uses diffusion chambers, microbial traps, iChip (isolation chip), iTip (*in situ* cultivation by tip), and double encapsulation techniques [37]. Another promising new cultivation and screening strategy

with the advantages of being high throughput, microscale, single-cell resolution, and automation potential, called the microfluidic droplet-based technique, has also been introduced [38].

Inducing stress or external stimulation has been a recent research trend and strategy to increase pigment production in the biotechnological process; for example, enhanced production of pyocyanin from *Pseudomonas aeruginosa* was successful with cottonseed meal [39]. The blue, yellow, white, green, incandescent lamp, red halogen, and fluorescence lamp were used for enhancing the carotenoid content, or another example using gamma radiation for an enhanced production of prodigiosin [40].

Recently, combinatorial approaches using simultaneous bioinformatics, genetics, and analytical tools have introduced new strategies for the discovery of bioactive pigments from marine bacterial isolates. As all pigments have a genetic basis, the ability to obtain and interpret genetic information have been the first step in daily based protocol for structural elucidation, a process that is increasingly available at low cost to non-specialists. Setiyono et al [18] applied analysis of the complete genome sequence of the marine bacterium *Erythrobacter flavus* strain KJ5 [41] to reveal the possibility of a new carotenoid present, by comparing the carotenoids composition produced by *E. longus* and *E. nanhaesediminis*, members of the genus *Erythrobacter* that have close sequence similarity and were therefore assumed to have a similar carotenoid biosynthesis pathway. Identification of sulfate attachment to the zeaxanthin carotenoid was then resolved by a tandem mass spectrometry (MS/MS) detected in negative ion mode using multiple reaction monitoring (MRM). Another example showed that BLAST analysis of antimicrobial prodiginine pigments from *Pseudomonas rubra* strains PS1 and SB14 to identify highly similar sequences (megablast) resulted in identification of two primary pigments, prodigiosin and cycloprodigiosin, and their derivatives [25]. Recently, with genome mining, the process of extracting information from genome sequences to detect biosynthetic pathways of bioactive natural products and their possible functional and chemical interactions has become available [35].

In combination with liquid chromatography (LC), mass spectrometry has become the gold standard for a high-throughput qualitative and quantitative profiling of natural product compounds [42], especially pigments. Other hyphenated technique such as nuclear magnetic resonance coupled with LC (LC-NMR) is also useful analytical platforms for detection, identification, and quantification of compounds in extracts. NMR analysis is reproducible and provides detailed structural information, although it generally profiles only major constituents, in other words, it has relatively low sensitivity. Thousands of sets of MS/MS data have been recorded and continuously developed in publicly accessible databases. Open-access knowledge bases containing tandem mass spectrometry, such as the Global Natural Products Social Molecular Networking (GNPS, https://gnps.ucsd.edu/ProteoSAFe/static/gnps-splash.jsp) and the Natural Product Atlas (https://www.npatlas.org/joomla/), which provide a tool to explore the structure of microbial natural products, are available and have greatly enhanced the efficiency of the replication processes, leading to identification of new molecules [43]. Specifically, for the carotenoid group, the Carotenoid Database (http://carotenoiddb.jp/), at the time of writing, provides information on 1204 natural carotenoids in 722 source organisms, including their biosynthetic pathways, structures and similarity search, and some biological activities.

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