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Marine Bacteria Is the Cell Factory to Produce Bioactive Pigments: A Prospective Pigment Source in the Ocean

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The course of investigations of bioactive compounds like bacterial pigments from the marine environment has greatly expanded in the recent decades. Despite the huge concern in secluding and collecting marine bacteria, microbial metabolites are progressively alluring to science due to their wide ranging applications in various fields, particularly those with distinctive color pigments. This review is a short appraisal of the studies undertaken over the past 5 years on the bacterial pigments sourced from the marine environment. Herein, we have reviewed the potential of different bacterial species isolated from marine environment in diverse studies that are producing bioactive pigments that have potential commercial applications.

Keywords: production, pigments, bioactive, cell factory, bacteria, marine

INTRODUCTION

Marine environments are one of the most important eco-systems of our earth that are yet to be explored to understand their full potential. They contain immeasurable and uncountable undiscovered mysterious black boxes holding colossal information that is to be decoded scientifically and exploited for the benefit of mankind. Marine environments are home to a multitude of organisms ranging from whales that are to a height of a building to microorganisms that are nano-scale life forms. The marine microorganisms are renowned to maintain and regulate the Bio-geo chemical cycle in the ocean environment and the interactions of the microbial community in the ocean to maintain such a biogeochemical cycle extraordinarily; metabolomics studies by profiling the variety of molecules reveal that the organisms produce to interact (Sogin et al., 2019). More than 6,000 and 10,000 species of prokaryotes and protists have been described so far (Aryal et al., 2015); yet the ocean hides an even more complex diversity of microorganisms that we are yet to fathom by appropriate investigations and explorations. Currently, the marine bacteria are being explored for their production of clinically and industrially important secondary metabolites; the pigments produced by marine bacteria as a result of quorum sensing are of current interest due to their anti-microbial, anti-cancer, photoprotective, anti-parasitic, and immunosuppressive activities (Ramesh et al., 2019). The modification of current natural compounds to synthetic compounds seems to be slow compared to the exponential evolution of resistant organisms which forces our hands to look for alternatives where secondary metabolites from marine bacteria seem to be the answer (Andryukov et al., 2019). Bacterial

pigments are also used as fluorescence-based indicators for labeling antibodies, screen several reactions, and also to cure the damage caused by free radicals (DeLange and Glazer, 1989). The marine bacteria produce various pigments like carotene, melanin, phenazine, pyrrole, violacein, and quinones (**Figure 1**). This review evaluates the advancements that were made in the studies of marine bacterial pigments in the past 5 years and their prospective applications in various fields (**Table 1**).

PHENAZINE

Phenazines are redox-active, small nitrogen-containing aromatic compounds produced by a diverse range of bacterial genera, including *Streptomyces* (terrestrial), *Pseudomonas* (ubiquitous), *Actinomycetes* (terrestrial and aquatic), *Pelagibacter* (aquatic), and *Vibrio* (aquatic), under the control of quorum sensing and also a nitrogenous aromatic compounds of reverse redox potential converting molecular oxygen into toxic reactive oxygen species and are used in a broad spectrum of antibiotics, anti-viral, insecticidal agent, anti-cancerous, antiprotozoal agents (Pierson and Pierson, 2010; Soliev et al., 2011; Guttenberger et al., 2017). Phenazine also functions as a respiratory pigment which is pyocyanin (blue) and *Pseudomonas* sp., has been highly researched (**Figure 1**). The biosynthesis of phenazine is catalyzed by five enzymes PhzE, PhzD, PhzF, PhzB, PhzG where PhzE converts chorismic acid to 2-amino-2-deoxyisochorismic acid (ADIC) by diffusion of NH3 from GATase1 to active MST domain of the enzyme by ligand binding and end with Ψ face ofC2 chorismate and converted to DHHA by PhzD by acid/base catalytic system and is isomerized by PhzF by utilizing glutamate and catalyze by proton shift into AOCHC; but it is still unstable by forming aminoketone AOCHC and goes into a second condensation reaction of AOCHC into a secondary molecular structure which is accelerated by PhzB and by conjugation HHPDC is produced which is unstable and undergoes oxidative decarboxylation resulting in THPCA which is a PhzG substrate producing PCA and if PhzG binds to HHPDC oxidation takes place producing PDC the two final core phenazine compounds (Blankenfeldt and Parsons, 2014). Liang et al. (2017) isolated six phenazines from *Streptomyces* sp., 182SMLY with three new phenazine compound (-)- streptophenazines M–O and three already known phenazine 1-carbomethoxyphenazine; (-)-streptophenazines A; streptophenazines B where it was tested against the proliferation of glioma cell lines but didn't have any inhibitory effect on proliferating glioma cells and it was also screened against *E. coli* and MRSA, but only streptophenazines B was effective against MRSA compared to control norfloxacin which inhibited both *E. coli* and MRSA. Phenazine compound pyocyanin has been isolated from marine *P. aeruginosa* by Li et al. (2018), and demonstrated to be acting as an anti-chlamydial agent with a dose of IC50 (0.02 μM) inhibiting its infectivity by directly targeting Elementary body (EB) but low doses didn't seem to increase the host ROS. The IC50 dose of pyocyanin did not show any immune suppressant activity and performed equally to the IC50 dose of Tetracycline against MRSA supporting the clinical use of pyocyanin for treatment. Patil et al. (2016a,b), reported that GS-33 marine P. aeruginosa produced Phenazine-1- carboxylic acid which inhibited the charcoal root rot caused by M. phaseolina, promotes plant growth, and even conferred resistance of plants toward saline conditions by producing NH3 and solubilizing phosphate. The GS-33 isolate PCA was also reported to inhibit skin melanoma in low doses in human cell melanoma cell lines SK-MEL-2 and when combined with the commercial SPF lotions showed a synergistic increase of around 10–30% UV-B protection. Cytotoxic studies revealed that concentration up to 100 ppm PCA was safe which showed hemolysis around permissible levels. The limited commercial availability of substituted phenazines indicates that their synthesis presents a challenge for the synthetic chemist. To date, no efficient and generally applicable synthesis of substituted phenazines exists (Laursen and Nielsen, 2004).

CAROTENE

Carotene is synthesized mainly by plants followed by other microorganisms like filamentous fungi, yeast, and bacteria which have been reported to display Pro-vitamin Activity and displays strong antioxidant activity. Carotene is used as food colorants, cosmetics, and in feed industries where their color ranges from yellow to red (Da Costa Cardoso et al., 2017). Carotene is a C40 Polyunsaturated hydrocarbon compound a resultant of condensation of C20 compounds (Liang et al., 2006). The biosynthesis of carotene takes place by two core terpenoids Isopentenyl pyrophosphate and dimethylallyl pyrophosphate which is synthesized from the MEP pathway and DXP pathway where the IPP and DMAPP are condensed into GGPP and FPP and converted to phytoene by phytoene synthase and metabolized into lycopene by lycopene synthase and finally to β-carotene by Lycopene β-cyclase and further undergoes five intermediates to produce astaxanthin (Zhang et al., 2020). Afra et al. (2017) has reported the isolation of red-colored carotenoid pigment from marine *Arthrobacter* sp., G20 which displayed excellent anti-oxidant activity where its EC50 scavenging activity was equivalent to β-carotene and α-tocopherol. Mild tumor-suppressive activities were observed in esophageal cancer cells but specific anti-proliferative activities were observed in the KYSE30 cell line where the cells were found to be round a characteristic feature of apoptotic cells. But, the extracted carotene pigment didn't show any appreciable anti-microbial activity. Kallscheuer et al. (2019) reported two planctomycetes strain *R. rubra* LF2T and *R. brasiliensis* Gr7 producing three carotenoid compounds saproxanthin, flexixanthin, 2′-isopentenyldehydrosaproxanthin and established biosynthetic pathway for the production of carotenoids. Asker (2017) have testified the production of carotenoids astaxanthin, 2- hydroxyastaxanthin, and 2,2′-dihydroxyastaxanthin by *Brevundimonas* sp. strain N-5 which was isolated and characterized by high-throughput sequencing. Hegazy et al. (2020) have demonstrated that haloarchea *Natrialba* sp., displayed antiproliferative and apoptotic activity against colon, breast, liver, and cervical cancer cells by interfering and inhibiting the MMP-9pathway and displayed anti-viral activity

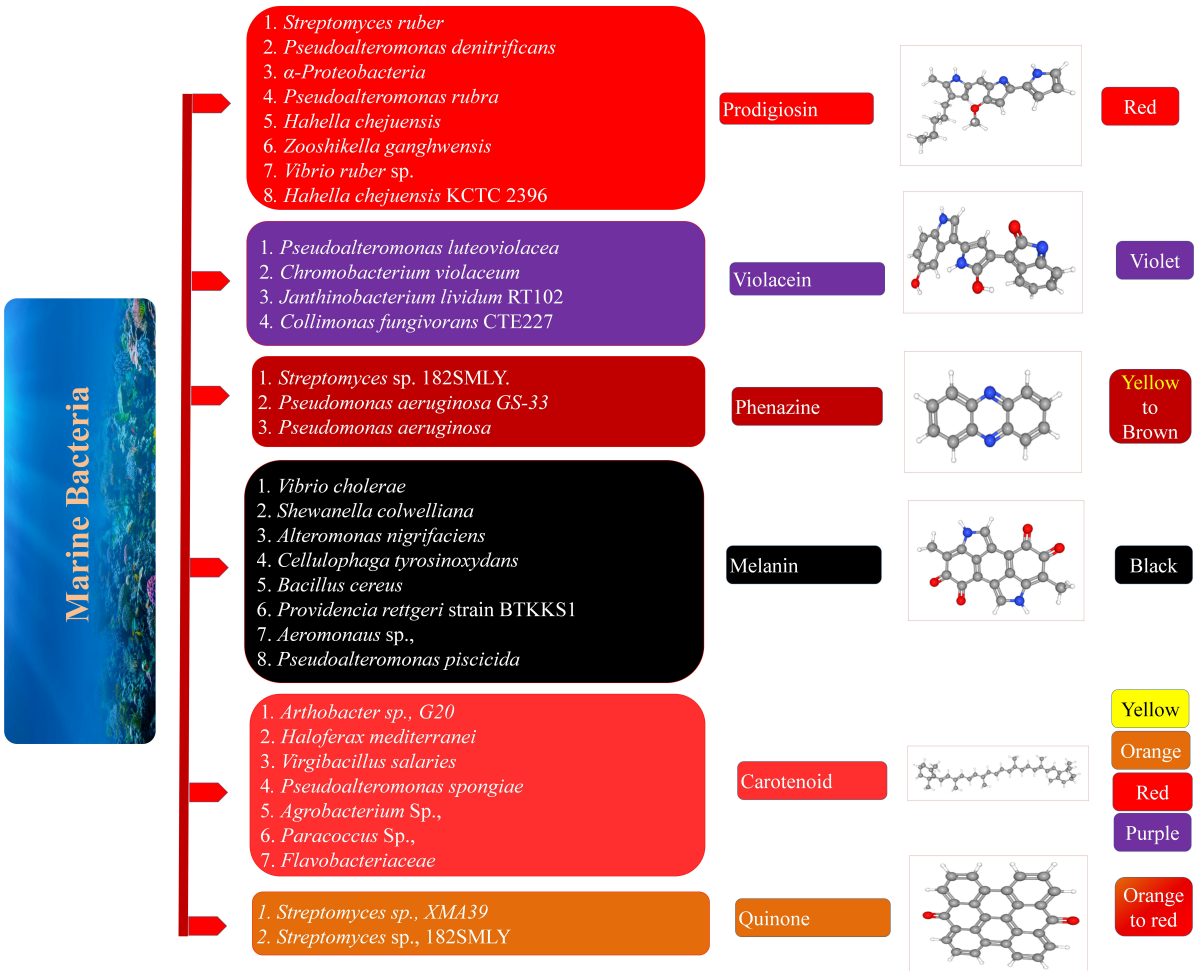

FIGURE 1 | Types of marine bacterial pigments.

by suppressing replication against HCV and HBV by inhibiting HCV NS5B polymerase and HBV-DNA dependent DNA polymerase. Earlier, synthetic β,β-carotene was produced on an industrial scale and used as a feed and food dye. Of the nearly 700 naturally occurring carotenoids, only a few are synthesized on an industrial scale. Among them are lycopene, canthaxanthin, astaxanthin, β,β-carotene, β-apo-8′-carotenal, β-apo-8′-carotene, and cytranaxanthin. Wittig reactions of Grignard compounds are used to obtain carotenoids (Alvarez et al., 2014; Bogacz-Radomska and Harasym, 2018).

MELANIN

Bacterial Melanin is a product of biosynthesis of L-tyrosine via the enzyme tyrosinase oxidizing it into L-3, 4-dihydroxyphenylalanine which is further metabolized into dopachrome and finally converted to melanin by oxidoreduction where the color usually ranges from black-brown in color (El-Naggar and El-Ewasy, 2017). Traditional melanin nanoparticle synthesis usually takes around 12 h, but Wang et al. (2020) demonstrated the production of melanin nanoparticle synthesis in bacteria within 30 min by controlling the growth of cell-free conditions by changing the salinity concentration of the medium and incubation period. This demonstrates the exciting potential of bacteria as melanin pigment factories and melanin has a broad range of usages such as anti-oxidative, anti-cancer, anti-bacterial, anti-viral properties also displaying thermal resistance, radiation damage by absorption of wide range electromagnetic spectrum, and even chemical resistance (Narsing Rao et al., 2017). Vijayan et al. (2017) isolated 156 sponge-associated bacteria out of which 14% displayed melanin production and its extraction from the sponge made the sponge colorless hinting the synergy between bacteria and the sponge for its photoprotective role and out of the 14% melanin-producing isolates 56% were observed to be *Vibrio* sp., and the remaining isolates were *Providencia* sp., *Bacillus* sp., *S. algae, S. sciuri, P. maritimus, S. roseus, G. creatinolyticus*; but the *Vibrio* sp., were selected for its high pigment production and the extracted pigment was observed for the photoprotective role from UV where highest efficiency was noted at 200 ppm displaying 65% protective effect in mouse

TABLE 1 | Microorganisms and its corresponding pigments.

Organism	Pigment	References
Shewanella algae	Melanin	Vijayan et al., 2017
Staphylococcus sciuri	Melanin	Vijayan et al., 2017
Planococcus maritimus	Melanin	Vijayan et al., 2017
Salinicoccus roseus	Melanin	Vijayan et al., 2017
Glutamicibacter Creatinolyticus	Melanin	Vijayan et al., 2017
Providencia sp.,	Melanin	Vijayan et al., 2017
Bacillus sp.,	Melanin	Vijayan et al., 2017
Pseudomonas stutzeri	Melanin	Manirethan et al., 2018, 2020
Pseudolateromonas lipolytica	Melanin	Kurian and Bhat, 2018
Chromobacterium violaceum	Violacein	Füller et al., 2016
Janithobacter lividum	Violacein	Füller et al., 2016
Psudoalteromonas amlolytica	Violacein	Wu et al., 2017
Streptomyces sp., XMA39	Quinone	Liang et al., 2016
Streptomyces sp., 182SMLY	Quinone	Jiang et al., 2018
Zooshikella sp.,	Prodigiosin	Ramesh et al., 2020
Streptomyces sp.,	Prodigiosin	Ramesh et al., 2020
Vibryoruber DSM 14379	Prodigiosin	Danevčič et al., 2016
Actinomyces sp.,	Prodigiosin	Abdelfattah et al., 2019
Hahella sp., KA22	Prodigiosin	Abdelfattah et al., 2019
GS-33 marine Pseudomonas aeruginosa	Phenazine	Patil et al., 2016a,b
pseudomonas aeruginosa	Phenazine	Li et al., 2018
streptomyces sp.,	Phenazine	Liang et al., 2017
Arthrobacter sp., G20	Carotene	Afra et al., 2017
Rhodopirellula rubra LF2T	Carotene	Kallscheuer et al., 2019
Rubinisphaera brasiliensis Gr7	Carotene	Kallscheuer et al., 2019
Natrialba sp.,	Carotene	Hegazy et al., 2020
Brevundimonas sp.,	Carotene	Asker, 2017

fibroblast L-929 cells and brine shrimp compared to the control at 30% but levels higher than 200 pmm of melanin didn't show much efficiency or any cytotoxic effects up to 500 ppm due to the transfer of extra energy to oxygen species producing Reactive oxygen species (**Figure 1**). Melanin extracted from bacteria has also been reported in heavy metal treatment, prevent fouling and formation of biofilm. Manirethan et al. (2018, 2020) used the melanin pigment extracted from gram-negative bacterium *P. stutzeri* for the absorption of heavy metals like copper, mercury, chromium, lead, and Arsenic where the absorption may be due to the presence of the COOH, NH, phenolic OH groups where maximum efficiency was absorbed in a pH ranging from mildly acidic to neutral. As a twist Melanin impregnated with copper and iron on its surface proved to be efficient in removing arsenic by chemisorption and it was also noted that melanin exhibited thermostability up to 120°C and showed peak absorption of arsenic at pH of 4–6 where XPS studies showed that arsenite before binding to Cu-, Fe-Impregnated melanin oxidized to arsenate and finally removing the Cu and Fe by Hcl treatment for the recycling of melanin and again impregnating it with fresh Cu and Fe element for absorption which showed 99% efficiency to 4 absorption and desorption cycles. *P. stutzeri* BTCZ10 strain was reported to play a photoprotective role by displaying SPF value equivalent to sunscreen showed by Kurian and Bhat (2018). Zeng et al. (2017) reported the hyperpigmentation of pyomelanin which is a complex of polyphenolic heteropolymer produced under elevated temperature by marine hmgA mutant *P. lipolytica* displaying anti-fouling activity. Kiran et al. (2017) confirmed the anti-microbial activity against *S. aureus, B. subtilis, E. coli,* and *P. aeruginosa* displayed strong anti-biofilm activity against MDSA by nano-melanin synthesized by sonication of *Pseudomonas* sp., isolated from marine sponge *T. citrine* where the efficiency of nano-melanin was observed to be higher than the traditional melanin.

PRODIGIOSIN

Prodigiosin is blood-red colored compounds that display strong anti-microbial, cytotoxic, and immune suppressive activities by a range of mechanisms like decoupling H/Cl- transporters modulating the pH of the cell and cleaves the DNA in the presence of copper (Huryn and Wipf, 2008). Prodigiosin biosynthesis undergoes a bifurcation pathway consisting of two systems a unique maltose-binding protein (MBP) and a common monolayer-protected cluster (MPC) biosynthesis. The 2-methyl-3-n-amyl-pyrrole (MAP) biosynthesis utilizes three genes pigB, pigD and pigE whereas the 4-methoxy-2,2′-bipyrrole-5-carbaldehyde (MBC) biosynthesis uses seven genes pigA, pigFpigG, pigH, pigI, pigJ, pigL, and pigM and the products MAP and MBP are condensed together to form prodigiosin (Sakai-Kawada et al., 2019). Ramesh et al. (2020) isolated 17 different strains from south Andaman which produce pigments ranging from brown, yellow, red, and orange (**Figure 1**) where strain *Zooshikella* sp S2.1 and *Streptomyces* sp., BSE6.1 producing red pigment were confirmed to be prodigiosin was selected for further application in the use as food colorants and displayed effective antibacterial activity against *S. aureus* at concentrations of 150 to 400 μg/mL. Marine *V. ruber* DSM 14379 isolated by Danevčič et al. (2016) exhibited the production of prodigiosin which showed strong bactericidal activity during the exponential phase of *B. subtilis* and bacteriostatic activity during stationary growth where it interferes with the cytoplasmic membrane and it also induces autolysin activity enhancing the killing of *B. subtilis*; however it was observed that the decrease of autolysin resulted in the abolished activity of prodigiosin. Abdelfattah et al. (2019), testified the antioxidant and anti-inflammatory activity of prodigiosin extracted from *Actinomyces* sp., isolated from sponge *S. mastoidea* against HCl/ethanol gastric lesion by over-expressing HO-1 resulting in elevated mucous production antioxidant activity, increasing HSP activity, apoptosis inhibition, and stabilizing cellular membrane thus preventing gastric injury. Prodigiosin has also been reported as an algicidal agent. Zhang et al. (2016) confirmed the algicidal activity of *P. globosa* by prodigiosin from *Hahella* sp., KA22 where prodigiosin inhibits photosynthesis by increasing ROS activity and finally necrotizes due to oxidative damage of the cells.

VIOLACEIN AND QUINONE

Violacein an indole derivative is a purple-colored pigment exhibiting anti-tumor, anti-microbial properties mainly produced by *C. violaceum* and *J. lividum* (Masuelli et al., 2016). The biosynthesis of violacein starts from the oxidation of the precursor molecule tryptophan into indole-3-pyruvic acid by the flavoenzyme VioA, where VioB couples the two IPA imine molecule forming the intermediate Imine dimer and in the presence of Violacein biosynthesis protein VioE the dimer is converted to protodeoxyviolaceinic acid where VioD hydroxylates forming proto violacein ic acid and VioC hydroxylates and undergoes oxidative decarboxylation producing violacein (Durán et al., 2007; Füller et al., 2016). Wu et al. (2017) described a novel-violacein producing organism and characterized it which was isolated from the surface of seawater of the Arabian sea and by 16S typing, the strains JW1T and JW3 were closely related to *Pseudoalteromonas* sp., and displayed independent lineage where there seem to be a display phylogenetic and chemotaxonomic differences, phenotypic properties and hence the name *P. amylolytica* was proposed. Currently, *C. violaceum* is being used as a bioassay strain for quorum sensing and quorum quenching activity for violaceum production to understand the QS or QQ activity of the desired strain (Liu et al., 2018; Balakrishnan et al., 2020; Singh et al., 2020). Quinone displays the anti-viral, anti-cancer, anti-microbial and insecticidal activities where the color ranges from yellow to red (Soliev et al., 2011). Liang et al. (2016) reports the suppression of glioma cell lines by two polycyclic quinones N-acetyl-N-demethyl rapamycin and strepto anthraquinone A at IC50 extracted from marine *Streptomyces* sp., 182SMLY which induced apoptosis in glioma cells. N-acetyl-N-demethylmayamycin was shown to be highly effective against MRSA. Quinones are also reported to display anti-fungal activities. Jiang et al. (2018) extracted medermycin-type naphthoquinones -strepoxepinmycin A to D and medermycin from *Streptomyces* sp., XMA39 where C and D showed cytotoxicity against HCT-116 and PC-3 cell lines and moderate inhibition of ROCK2 kinase was also observed. Collectively all the five compounds exhibited antagonistic activity against *E. coli, S. aureus*, and *Candida* sp. (**Figure 1**).

FUTURE PERSPECTIVE

Recently, a number of review papers have appeared in the literature, and they give an outline of all findings of the marine environment and its isolates. However, in this mini-review, we focus exclusively on the active marine bacterial pigmented compounds and its potential applications have been stated. The secondary metabolites of marine bacteria are gaining importance for its remarkable potential as anti-cancer, anti-microbial, anti-parasitic, insecticidal, anti-fowling, and anti-biofilm properties. The continuous evolution of the resistance observed in pathogenic microbiota poses a significant threat corresponding to the time taken for the discovery of new drugs. The gap of altering the present product into a synthetic drug could be bridged by utilizing the full potential of the microorganism in the marine environment as the marine organisms for its survival produces secondary metabolites for competing with organisms in the community and when extracted it is of great potential. Due to the growth of high-throughput sequencing, metagenome, and the rapidly growing field of metabolomics study enables us to cultivate bacteria that are usually viable but non-cultivable. Despite the enormous difficulty in isolating and harvesting marine bacteria, significant progress has been achieved in this field, and investigations of bioactive compounds produced by these species are rapidly increasing. It has given us the set of tools to view from a distinct perspective helping us to understand the synergy that takes place in the marine ecosystem. Microbial pigments are of great interest due to its long fetching application from industry to pharmaceutical companies. Further large-scale studies are required to understand the interaction and evolution of these microorganisms that enable them to produce these pigments. Bacteria as pigment production units are of great interest due to its rapid production (or) fermentation of pigments. From the time consuming traditional synthesis of pigments bacterial pigment production could be achieved in a matter of minutes to hours by manipulating the cell-free condition, growth, and nutrients in the growth medium. This enables us to elect marine bacteria as a superior source factory for bioactive pigment production.

AUTHOR CONTRIBUTIONS

PV and CV: conceptualization, original draft preparation, and writing. LD: writing, review, and editing. AV: review. All authors contributed to the article and approved the submitted version.

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