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REVIEW ARTICLE

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Natural product biosynthesis in bacteria associated with marine organisms

Esraa Elsaeed[a], Shymaa Enany[b,c], Samar Solyman[b,d], Mohamed Shohayeb[a], and Amro Hanora[b]

[a] *Department of Microbiology and Immunology, Faculty of Pharmacy, Delta University for Science and Technology, Gamasa 11152, Egypt.*
[b] *Department of Microbiology and Immunology, Faculty of Pharmacy, Suez Canal University, Ismailia, Egypt.*
[c] *Biomedical Research Department, Armed Force College of Medicine, Cairo, Egypt.*
[d] *Department of Microbiology and Immunology, Faculty of Pharmacy, Sinai University-Elkantara branch, Egypt.*

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* Correspondence Author:

Tel: +201000323406

E-mail address:

a.hanora@pharm.suez.edu.eg

Abstract

Because antibiotics are becoming less effective and there is an increase in the number of cases of cancer, it is critical that researchers continue their search for novel natural antimicrobials and anti-cancer medicines. Screening marine organisms for the purpose of developing new medications is still in its infant stages especially from nudibranchs. Many Polyketides, non-ribosomal peptides, terpenes, and post-ribosomal peptides are synthesized by marine organisms' symbiotic bacteria. In this review, we summarized the sum of the previous works done on bacteria associated with marine organisms for identifying bioactive metabolites. We discussed whether the host is responsible for the production of these metabolites or its symbiotic bacteria. Also, factors that may affect the abundance of symbiotic bacteria and bioactive compounds such as different habitats and environmental circumstances like food and location have been shown and discussed. We also discussed why nudibranchs deserve more studies for mining secondary metabolites in their symbiotic bacteria.

Keywords: Nudibranchs; Symbiotic bacteria; Natural Product; Secondary metabolites.

1. Introduction

Several antimicrobial elements, including chlorinated acetylene, indole derivates, terpenes, glycerol derivates, macrolides, pigments, lysozymes, glycoproteins, proteins, and peptides are produced by marine bacteria (Roze et al., 2011). Bioactive chemicals from marine invertebrates have been considered as a potential medicinal source (Miller et al., 2018; Vlachou et al., 2018). Bioactive chemicals can be found in abundance in sponges, which are generally recognized as the best source. Bioactive chemicals can be also found in molluscs. There are no induced immunoglobulins in the molluscs' immune system, Reactions to microbial species are based on both cellular and humoral activities like the production of lectin, lysosomal enzymes, antimicrobial agents, etc (Roze et al., 2011).

Localization experiments undertaken by the Faulkner group (Salomon et al., 2001) demonstrated that sponge-derived natural products were localized in the microbial symbiont that probably manufactures these molecules in some circumstances. This appears to be an anomaly, as numerous examples of cellular localization studies suggested the host sponge as the biosynthetic source of these natural products (Molinski, 1993). The findings of these investigations, however, should be interpreted with caution because it is well known that microorganisms frequently and actively expel their natural products outside the cell into the surrounding medium. When a natural product is localized to a microbe, the assumption is obvious that the bacteria is the likely biosynthetic producer. When the tiny molecule is found inside a sponge cell (or another invertebrate cell), the conclusion concerning its true biosynthetic origin becomes less obvious (Moore, 1999).

Different habitats and environmental circumstances have been shown to affect the abundance of symbiotic bacteria and bioactive compounds (Zhukova, 2014). Two different studies were done in Egypt to screen for biosynthetic gene clusters (BGCs) in *C.quadricolor* symbiotic bacteria. While the first study by Elfeky et al., (2022) found BGCs in *Streptomyces sp. SCSIO 00168* and *Nocardiopsis dassonvillei RCAA4* species were abundant, the second study (Elsaeed et al., 2023) failed to detect these bacteria, the reason behind this difference may be due to different sites of samples collection.

Marine microorganisms can be stressed by surface fouling which makes it hard for the host to live, especially when they are young (Dobretsov, 2010). Higher rates of surface fouling have been linked to much higher rates of embryonic death in gastropod egg masses (Benkendorff et al., 2001). Fouling on the surface of nudibranch and polychaete egg masses can cut off oxygen to the embryos inside (Cohen and Strathmann, 1996).

Still, however, surface fouling on the egg masses of marine invertebrates could have some benefits. Pathogenic fungi can't get into crustacean eggs because there are symbiotic bacteria on the surface of the eggs (Gil-Turnes and Fenical, 1992). Fouling by microphytes, which make their food, can speed up the development of embryos in some species (Fernandes and Podolsky, 2011). In addition, Davis et al., (1989) say that a coating of fouling organisms can also be a good way to hide something or make them less tasty. Surface fouling could also protect mollusc embryos from the sun's ultraviolet rays, which damage the embryos that are sealed in a shell (Przeslawski et al., 2004).

In this review, we will discuss some natural product biosynthesis in bacteria associated with marine organisms, and the importance of these products to the host or pharmaceutical applications.

2. Non-ribosomal peptide synthetases (NRPSs)

NRPSs are an important family of enzymes which synthesize bioactive secondary metabolites. A wide range of important and diverse activities are associated with the nonribosomal peptides such as antifungals

(bacillomycin), antivirals (luzopeptin), siderophores (enterobactin), antitumors (actinomycin D), antibacterials (daptomycin), and immunosuppressants (cyclosporin) (Felnagle et al., 2008) are among the most commonly prescribed drugs.

NRPSs can synthesize over 500 distinct acyl monomer substrates (including amino acids, fatty acids, and hydroxy acids) because they can be co-synthetically or post-synthetically changed, and they can be linear or cyclic or branched in structure. There are around 1100 NRPS residues organized as modules, with each module adding a single amino acid to the peptide (Walsh, 2008).

The size of NRPSs may range from one to eighteen modules in a single protein chain. Each module has a molecular weight of more than or equal to 2 MDa. Most of the time, an elongation module is made up of the adenylation (A) domain, the peptidyl carrier protein PCP domain (also called the T domain, and the C domain. Terminal modules have Te or R domains, which release the last peptide. Some of the modules of an NRPS, like APCP (C-A-PCP)n-Te, can have more tailoring domains added (Bloudoff and Schmeing, 2017).

2.1 *Examples of NRPS from marine bacteria*

2.2.1 Endolides

Two unique N-methylated tetrapeptides, endolide A and endolide B generated by the marine-derived Stachylidium fungus isolated from the sponge Callyspongia cf. C-flamea (Almeida et al., 2016a). Endolide A showed an affinity for the vasopressin receptor, while endolide B interacted with the 5-HT2b serotonin receptor (El Maddah et al., 2016).

2.2.2 Surugamides

Cathepsin B can be inhibited by surugamide peptides, which are made by Streptomycetes found in deep-sea debris in Japan's Suruga or Sagami bays. All of them are made by the (Takada et al., 2013). NRPS biosynthetic cluster surABCD, which was first found in Streptomyces JAMM992 (Almeida et al., 2016b).

2.2.3 Marformycins

The isolate *Streptomyces drozdowiczii SCSIO 10141* from deep-sea sediments makes the natural product class marformycins (Pan et al., 1997). It was shown that inhibits *Micrococcus luteus* and two types of Propionibacterium. Genome analysis of the organism that made the protein showed that it had a large operon with 20 ORFs, including six NRPS genes (Zheng et al. 2016).

3. Polyketide Synthases (PKSs)

Bacteria, especially Actinomycetes and Cyanobacteria, make a lot of polyketides, and many of them have antibiotic properties for example the three well-known antimicrobials, Tetracycline, Erythromycin, and amphotericin (Partida-Martinez and Hertweck, 2005). The bryostatins are a group of polyketides found in aquatic bryozoans. They are thought to be made by bacteria that live with the bryozoans (Sudek et al., 2007). These chemicals keep fish from eating the bryozoans, and it is thought that they protect the young bryozoans that are still swimming until they settle down and build defences (Lopanik et al., 2006).

For modular PKSs, there are examples of up to five different protein subunits that may make up the whole synthase. These subunits may dock together to make the multifunctional enzyme. Most likely, this docking has to happen in a very specific way to work as a whole "assembly line," and the models of modular PKS structures allow for this head-to-tail docking. The modular polyketide would be made on an assembly line made up of a loading module at the beginning, then the right number of chain-extending modules in the right order, each with the right number of reductive sites, and then a thioesterase at the end (Hopwood, 1997). Just like in a vertebrate fatty acid (FASs), the thioesterase would hydrolyze the bond between the finished polyketide and the 4′-phosphopantetheine prosthetic group on the ACP domain of the last

chain-extending module. It's not clear why a modular synthase should have a specific number of subunits. For example, erythromycin and rapamycin PKSs have three and spiramycin PKS has five while seven monofunctional proteins can associate successfully in E. coli FAS.

The non-modular PKSs, on the other hand, have a very different programming mechanism. There is only one catalytic site of each type, and this site has to act over and over again to build and change the polyketide chain (Hopwood, 1997).

When iterative synthases are compared to modular synthases, iterative synthases use only malonyl CoA extender units and modular PKSs use at least some more complicated chain extenders. Iterative synthases, such as type I and type II FASs and type I and type II synthases for the aromatic class of PKSs, use malonyl CoA for every round of chain extension (Hopwood, 1997). Modular PKSs, on the other hand, use all methylmalonyl extenders.

3.1 *Examples of PKSs from marine bacteria*

3.1.1 Nocapyrones

Actinomycetes of the genus Nocardiopsis called Nocapyrones have been linked to marine invertebrates like sponges and molluscs many times. As an example, *N. alba* CR167 was taken from the cone snail *Conus rolani*, whose shell and venom protect it, and was found to make nocapyrone (Lin et al., 2013). Bioinformatic and chemical evidence could link the production of these heterocyclic natural products of the γ-pyrone class to bacteria. This is different from many previous studies, which isolated these metabolites from marine invertebrates without finding out how they were made. The putative type I PKS BGC ncp was found by sequencing and analysing the *N. alba CR167* genome and comparing it to other pyrone biosynthetic genes. It is made up of four genes: oxidoreductase (ncpA), methyltransferase (ncpB), the iterative PKS domain (ncpC), putative single acyltransferase (ncpD) (Lin et al., 2013).

The drugs Anthracimycin and chlorotonil A: Anthracimycin is a unique macrolide antibiotic. It is a 14-membered macrocyclic lactone ring with a decalin structure at its centre. Anthracimycin was first found in a marine actinobacterium called Streptomyces sp. T676 in 1995. It was recently found in another marine actinobacterium called Streptomyces sp. Anthracimycin is a great inhibitor of Gram-positive pathogens like Bacillus anthracis and Staphylococcus aureus that is resistant to methicillin and vancomycin (MRSA and VRSA) (Alt and Wilkinson, 2015). A myxobacterial strain called *Sorangium cellulosum sp. So ce1525* also gave up chlorotonil A, which has a similar structure. Like anthracimycin, chlorotonil A has strong activity against Plasmodium falciparum, the pathogen that causes malaria. It also has strong activity against bacteria and moderate activity against fungi (Jungmann et al., 2015).

3.1.2 Misakinolides

They are natural products that come from the same bacteria as nocapyrones. They were found in the marine sponge *Theonella swinhoei WA* on the Japanese island of Hachijo-Jima (Müller et al., 2017). Using bioinformatics to look at a library of DNA clones from a sponge, they found a trans-AT PKS BGC, called mis, that is about 90 kb long and has the PKS genes misC-F as well as the AT misG. Based on the phylogeny of the ketosynthase domains and the BGC architecture, it was clear that the product would be similar to misakinolide (Ueoka et al., 2015).

3.2 *Examples of PKS–NRPS hybrids from marine bacteria*

3.2.1 Haliamide

Haliangium ochraceum SMP-2 (DSM 14365T) was the first marine myxobacterium to be found in a sample of seaweed (in Miura, Japan). It made a new hybrid PKS–NRPS compound called haliamide. Haliamide has cytotoxicity prosperities against HeLa-S3 cells (Sun et al., 2016).

3.2.2 Thiolactomycin and thiotetromycins

Thiolactomycin A (20a) is a natural product made from thiotetronic acid. It was found in 1982 in Nocardia sp. no. 2-200. This class of compounds has a unique thiolactone moiety, has a wide range of antibacterial activity, and is known to act as FASII inhibitors (Oishi et al., 1982).

3.2.3 Thiomarinol

Members of the genus Pseudoalteromonas have been shown to make thiomarinol, which is a mixture of marinolic acid and dithiopyrrolone (Shiozawa et al., 1993). The hybrid molecule has antimicrobial activity against both Gram-positive and Gram-negative bacteria. It has gotten a lot of attention because of how well it works against Staphylococcus aureus which is resistant to methicillin. Thiomarinol and its derivatives are made by Pseudoalteromonas sp. SANK73390 through a pathway that combines PKS, NRPS, and FASs (Murphy et al., 2013).

3.2.4 Alterochromides

Marine species of the genus Pseudoalteromonas are a very promising source of natural products, and their genomes were found to code for many different classes of BGCs. Alterochromides belong to lipopeptides that were found to be made by multiple species of Pseudoalteromonas strains. Alterochromides have strong cytotoxic activities and antibacterial activities (Amiri Moghaddam et al., 2021).

3.2.5 Marinobactins

Some types of marine bacteria, like Marinobacter, make siderophores called amphiphilic marinobactins, which have a headgroup of six amino acids and a fatty acid tail of different lengths. Two NRPS genes, ENO16762 and ENO16763, are thought to be in charge of making marinobactins in *Marinobacter nanhaiticus D15-8W* (Kem et al., 2015).

4. Terpenes

Terpenoids are the largest and most diverse group of natural products. Terpenoids have been described and grouped into more than 400 structural families. The great majority of these have been isolated from plants and fungi (Yamada et al., 2015a). From cholesterol to vitamins A and D to carotenoids and steroids, their functional roles range greatly. Their structural varieties reflect the breadth of their functional activities. Their molecules can be either linear or polycyclic, and their sizes range from hemiterpenes with five carbons to natural rubber with thousands of isoprene units. All terpenoids are made by combining isoprene units (C5), and they are grouped by how many five-carbon units are their core structure (Mahmoud and Croteau, 2002).

Three factors contribute to the low number of known bacterial terpenes (Helfrich et al., 2019): first, an early belief that bacteria couldn't synthesize complex terpenoids led to a lack of genome mining platform bioinformatic tools for terpene BGCs and a failure to anticipate logical structure from genome sequence information. Second, Terpenes lack UV-absorbing functional groups, their weak ionisation capacities, and the presence of odiferous terpenes obscures distinctive terpene signals (branching methyl groups) in NMR investigations, making targeted extraction so difficult. As a result of those reasons, most research may prefer heterologous expression in modified host species.

Compared to PKSs and NRPSs, the sequence similarities among bacterial terpene cyclase (TCs) are not very high (Yamada et al., 2015b). antiSMASH (Blin et al., 2019) is one of the few open-source programs that can mark up bacterial terpene BGCs. There aren't as many terpene BGCs as there are in other BGC classes that antiSMASH detects because of the low conserved sequence similarity between TCs. Hence, we had to put off making efficient genome mining platforms so terpene cyclization couldn’t be studied (Hertweck, 2009).

Natural product core structures can be predicted with reasonable accuracy using the well-known biosynthetic rules of the template biosynthetic pathways, such as the colinearity rule (Hertweck, 2009). However, no equivalent rules exist for TCs (Yamada et al., 2015b). Biosynthetic machines are likely to be the cause of this discrepancy. TCs act as chaperones for oligoprenyl pyrophosphate precursors by guiding them through the cyclization process in modular assembly lines (Driller et al., 2018).

4.1 Examples of Marine Terpenes

4.1.1 The Domoic acid

When toxic algal blooms occur, Pseudonitzschia diatoms produce the toxin domoic acid (DA, 8), which poses a major risk to marine and human life. Via transcriptomic research, a conserved gene cluster (dabA-dabD) that codes for a terpene cyclase, a dioxygenase, a hypothetical protein, and a CYP450 was found (Chen and Baran, 2009).

4.1.2 Penochalasin K

It is a true indole that was found by Zhu et al. (2017) in the fungus *Penicillium chrysogenum*, which grows near mangroves. It turned out to be a fungicide that worked well against *C. gloeosporioides* and *Rhizoctonia solani*, killing them ten and two times better than the positive control, carbendazim *Penicillium italicum* and *Colletotrichum musae* were only partly stopped from growing.

4.1.3 6-hydroxylpaspalinine

Hu et al. (2017) identified 6-hydroxylpaspalinine within the fungus Penicillium sp. AS-79 which is a sea anemone that lives along the Qingdao shoreline in China. It only has mild antimicrobial activities against the Gram-negative bacterium *V. parahemolyticus*, which lives in water. There was no evidence of Gram-positive or fungicidal action.

5. Alkaloids

All living organisms produce alkaloids, which are described as basic chemicals that include one or more heterocyclic nitrogen atoms, and that are formed from amino acids most of the time. For this reason, alkaloids are referred to be basic (alkaline) substances. Alkaloids include more than 12,000 distinct compounds. This group is characterized by a wide range of structural formulas derived from various biosynthetic pathways and exhibiting a wide range of pharmacological actions (Brielmann et al., 2006).

Alkaloids can be produced from plants, fungi and marine organisms. Alkaloids-producing fungi known as ergots (family Hypocreaceae) are among the best-known and most-maligned fungi. Ergotism, caused by tainted rye, has taken the lives of tens of thousands of people worldwide (Wink, 1998). Alkaloid-producing mushrooms, on the other hand, come in a wide variety of structural and biological variations.

5.1 Examples of Alkaloids from Marine bacteria

New compounds with medical applications are being discovered in the aquatic environment. More than 15,000 chemicals, including terpenoids, alkaloids, steroids,
and nucleosides, have been identified and described from sponges alone (Agostini-Costa et al., 2017).

New Alkaloids were discovered in marine fungi. For example, ten antimicrobial pyrrolidines were discovered by marine fungus from throughout the world. The fungus *Penicillium sp. CPCC 400,817*, which grows near mangroves in Hainan, China, contains GKK1032C, according to Qi et al., (2019). Like the positive control medication vancomycin, it was effective against both methicillin-resistant and methicillin-susceptible *S. aureus*. Gram-positive bacteria were not inhibited in any way.

Meng et al. (2017) discovered brocapyrrozin A and B in the fungus *P. brocae MA-231*. This fungus was discovered in China. It is an

endophytic fungus that dwells inside the A. marina maritime mangrove plant.

5.1.1 Aminophenyl Pyrrole-derived alkaloids

APPAs are very important chemicals like the fungicide pyrrolnitrin, which is made by many proteobacterial strains such as *Pseudomonas pyrrocinia* (Linares-Otoya et al., 2019). APP was said to be a common candidate for an APPA precursor and a dead-end product in the process of making pyrrolnitrin from tryptophan, which is done by a PrnB-like enzyme.

Many Bioinformatics and phylogenetic analyses of *Rapidithrix thailandica* were used to find the biosynthetic gene cluster of APPAs, which was then confirmed in E. coli. The indolamine 2,3-dioxygenase enzyme MarC (which is similar to PrnB) oxidises tryptophan in a step that makes APP. Next, a Pictet–Spengler-like coupling reaction that doesn't need enzymes makes a library of tricyclic alkaloid marinoquinolines.

6. Why do we need to mine bacteria associated with nudibranchs

Nudibranchs are slow-moving creatures that typically defend themselves with poisonous or deterrent chemicals in ecosystems with severe competition and feeding pressure, such as coral reefs (Rogers and Paul; Zan et al. 2019). Nudibranches are one among the many marine animals that feed on sponges, which are rich in bioactive substances. Food and symbiotic bacteria have a significant impact on the bioactive chemicals present in nudibranchs (Gosliner et al., 2008). Nudibranches are one among the many marine animals that feed on sponges, which are rich in bioactive substances. Food and symbiotic bacteria have a significant impact on the bioactive chemicals present in nudibranchs (Gosliner et al., 2008).

6.1 Some natural Product Biosynthesis of Nudibranchs' bacteria

6.1.1 Antibacterial chemicals

Previous studies have discovered that symbiotic bacteria are capable of creating anti-MRSA chemicals (Kristiana et al., 2020). Pseudoalteromonas phenolic anti-MRSA substance was found in marine Sea water (Isnansetyo and Kamei, 2003). Anti-MRSA has also been studied in bacterial symbionts of some marine creatures like Tunicata, Porifera, and marine algae (Isnansetyo and Kamei, 2003). Microorganisms from nudibranchs' skin and internal organs (viscera) were found to have anti-MRSA properties (Kristiana et al., 2020b). An investigation carried out by Riyanti et al., (2009) found that they were successful in isolating 27 closely related bacteria from the bacterial symbionts of Jorunna and Chromodoris. Kristiana et al., (2019b) investigated a crude extract of nudibranch bacterial isolates. The active isolates were cultivated to produce the extract, which was tested against different pathogens. Six isolates produced extracts that were active against one pathogen, while two isolates yielded extracts that were effective against two pathogens. Riyanti et al., (2009) reported that *Streptomycetes spp.* from Panjang island, Jepara, had antibacterial activity against numerous (multidrug resistance) MDR microorganisms. In that study, only seven bacterial crude extracts had antibacterial properties. This was lower than (Böhringer et al., 2017). While Riyanti et al., (2009) focused on MDR bacteria, Böhringer et al., (2017) focused on non-MDR bacteria.

6.1.2 Fatty acids

The fatty acid composition of nudibranchs is influenced by their food source, biosynthetic processes, and the presence of symbiotic microbes within their cells. An examination of eight types of Nudibranch species found that they were all deficient in monoalkyldiacetic glycerols (MADGs) (Zhukova, 2014). Demospongic acids, non-interrupted fatty acids, odd and branched fatty acids were found in abundance in the

nudibranchs' fatty acid compositions, which differed substantially from the compositions of other marine trematodes. The odd-chain and branched fatty acids that are unique to bacteria and commonly referred to as 'bacterial fatty acids' are another unique property of the nudibranchs. The nudibranchs have an unusually high concentration of bacterial acids, which are ordinarily minor metabolites in most animals (Zhukova, 2014). In the nudibranchs, a high concentration of bacterial fatty acids could mean that the symbiotic bacteria are providing the host with nutrition. transmission electron microscopy confirmed the existence of these bacteria in epithelial cells and the glycocalyx layer obscuring the epithelium of both the notum and mantle of D. nigra (Zhukova and Eliseikina, 2012).

Inside the glycocalyx, it was discovered that the bacteria sometimes go through destructive lysis, with their components being used by the epithelial cells. Mollusc tissues are likely to use the degraded bacteria, as evidenced by large concentrations of typical fatty acids found in the tissues of *D. nigra* (nudibranch) lipids (Zhukova and Eliseikina, 2012)

7. Conclusion

Marine organisms are a rich source of bioactive chemicals produced as secondary metabolites. Researchers disagree on whether the Nudibranchs or their symbiotic bacteria are responsible for the production of these chemicals. Some experiments recognized the bacterial origin, while others recognized the host origin to be their source. The latter viewpoint, in our opinion, outweighs the former because microorganisms frequently actively expel their natural products outside the cell into the surrounding medium. Symbiotic bacteria associated with marine organisms can be influenced by a variety of factors such as food, location, and surface fouling. These factors may affect the types of secondary metabolites produced by the symbiotic bacteria.

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