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DISCOVERY OF NOVEL ANTIBIOTICS FROM MARINE MICROORGANISMS

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Abstract
Despite making up over 70% of the planet's surface, marine-derived microbial natural products have not yet been fully utilized. The marine ecosystem is home to a wide variety of exotic microorganisms that create bioactive chemicals in order to survive in particular environmental niches. In the development of cross-relationships between bacteria and their eukaryotic hosts, chemically mediated interactions are also crucial. In these interactions, organisms that produce antimicrobials (also known as "antimicrobials") may prevent the host surface from becoming over-colonized in exchange for an environment that is rich in nutrients. A number of obstacles, including unsuitable growth conditions, time-consuming purification procedures, and ineffective de-replication, have impeded the finding and characterisation of marine microbial bioactive, as has been the case with the discovery of bioactivity generally. Improved microbial cultivation technologies, microbial (meta-)genomics, and new sensitive structural elucidation tools are progressively overcoming them. Here, we outline how future discoveries and developments of new medications derived from marine microbes will unavoidably increase as a result of these technological advancements and our growing understanding of microbial and chemical ecology.
Keywords: marine epibiotic microorganisms, bioactive, antimicrobial

1. INTRODUCTION

Over a million natural products have been isolated from a variety of living things, including plants, animals, and microorganisms, and 40–60% of these are terrestrial compounds produced from plants [1]. Many bioactive properties, including antibacterial, antifungal, antiprotozoal, antinematode, anticancer, antiviral, and anti-inflammatory properties, are present in 20–25% of the natural products. The oldest archaeological sources mention the use of plants and plant-derived products for the treatment of human illness, a practice that dates back thousands of years[6]. In contrast, it wasn't until the 20th century that researchers started looking into the possibility of using microorganisms to manufacture medicinal substances[4]. However, in this very little period, microbial origins account for around 10% of all currently recognized physiologically active natural compounds[8]. These make up the majority of antibiotics and provide strong evidence of the potential of microbes as a new source for the synthesis of chemicals with biological activity[2]. Indeed, by the 20th century, the foundation of modern medications was made up of bioactives produced from microbes. For example, 30–80% of the actinomycete and

fungal isolates screened in various investigations have been found to synthesize antimicrobials. Furthermore, computer models estimate that there are about 107 antibiotics from actinomycetes that are currently unknown[10]. The extensive recent investigations of the ocean's microbial diversity, especially that of the microorganisms connected to marine algae and invertebrates, can provide a new supply of bioactives[9]. According to certain research, "living surfaces" are one type of habitat that is abundant in bioactive epibiotic microorganisms. However, little is known about the enormous biotechnology potential of marine epibiotic microbes[11]. While isolating targeted bio-active producer microorganisms, this paper examines the suitability of probing novel sources that may be bio-actively rich and the significance of taking into account the chemical ecology of host-microorganism marine symbiosis [3]. Previously, the maritime environment was thought to be a "desert" setting with limited living forms. It is now known, meanwhile, that the oceans are home to a vast amount of live microbiota, with millions of cells per milliliter and species richness and variety expected to surpass that of most of the planet's rainforests. Finding new bioactives would be made possible by the likelihood that microbial variety would equate to metabolic diversity[12]. Many difficulties arise when using marine eukaryotes that produce bioactives for large-scale production, primarily because the eukaryotic organism is typically killed during the bioactive's extraction process and because some of these eukaryotes must be hand-harvested using SCUBA instead of being cultured in a lab[14]. The question of these species' sustainability in the natural world is also brought up. The bulk of marine microorganisms that can produce bioactive compounds, on the other hand, are easily controlled and cultivated in bioreactors, making them the most abundant renewable source of bioactive compounds[16]. With an astounding diversity of life forms usually living in close proximity to one another, the maritime environment is a highly complex system[18]. In the last ten years, the relationships between microorganisms and eukaryotes have gained substantial attention. Every marine eukaryote's surface is home to microorganisms that live connected in wildly diverse communities, frequently embedded in a matrix to form biofilms. The microbial consortia that inhabit different eukaryotes differ greatly from one another and from those that inhabit nearby waters. For instance, there was minimal to no overlap seen in the DGGE-based examination of similarity between the microbial community makeup of the coral and the nearby saltwater. Furthermore, studies have demonstrated the existence of distinct, stable communities residing on geographically separated members of the same species, demonstrating host specificity[15].

2. REVIEW OF LITERATURE

Surface-associated microorganisms are said to have more specialized and stable adaptations, tailored to the microenvironment provided by a specific host, as opposed to planktonic free-living microorganisms, which usually experience changes in environmental conditions that require rapid, short-term adaptive processes. The tight cross-relationships between microbial epibionts and their eukaryotic hosts are highlighted by the great specificity of microbial assemblages on a variety of marine eukaryotes. Indeed, it has been shown that certain epibiotic microorganisms are essential to the eukaryote's regular life and development, such as in the establishment of host morphology. Additionally, it has been shown that host-specific bacteria are important to the host because they can be vertically transmitted from the parent eukaryotic cell to its progeny [5]. Bivalves and ascidians found in sponges have been documented to exhibit this type of microbial community member inheritance. It has been hypothesized that the microbial partners create chemical microenvironments with the eukaryotic host and live there by cycling nutrients and avoiding host predation by producing bioactive molecules, even though the nature of the interaction between the microbial hosts and the microorganisms is unknown. Bacteria connected with the marine surface frequently share metabolic similarities with their hosts.

Other marine eukaryotes, on the other hand, depend relatively more on the metabolites that their microbial symbionts provide for their life. For instance, certain sea sponges can survive in low-nutrient environments because they can rely on their autotrophic cyanobacterial symbionts for over 50% of their energy needs and rely on the carbon from their photosynthetic cyanobacterial symbionts [13]. Microbes and the host may have close metabolic relationships that make it difficult to identify the partner organism that produces a particular metabolite. Consequently, it has been discovered that certain beneficial substances that were formerly attributed to eukaryotes are really generated by related bacteria. The marine ecosystem appears to be characterized by interactions between epibiotic bacteria and their hosts, whereby the microbes are believed to obtain nutrients from the eukaryote and the host benefits from the diverse array of bioactives produced by its own associated microbe. For instance, it has been shown that the gamma-proteobacterium, which produces a range of bioactive chemicals, can help protect the host from surface colonization by generating antibacterial, antilarval, and antiprotozoal substances. Similarly, a single gram-negative bacterium that produces an antifungal chemical that is highly efficient against the fungus, a worldwide pathogen of many crustaceans, covers nearly all of the surfaces of healthy lobster Homarus americanus embryos. Production of antimicrobials by epiphytic microbes might also give an advantage to producers in competition with other surface-associated microbes.

3. MATERIALS AND METHODS

There are a few key phases in the standard technique for isolating the natural products of marine epibiotic bacteria. Separating the microbe from its surroundings is the first step in its isolation. In the past, isolating microorganisms was typically done at random. With the advent of modern understanding, it is now recognized that the source of microbial samples might contribute to high bioactive discovery success rates. Therefore, as was previously mentioned, microorganisms derived from marine living surfaces can greatly increase the likelihood of obtaining bioactive producing strains because of the numerous and occasionally chemically mediated interactions between the microorganisms and their host as well as among members of the epibiotic community. Individual isolates are screened for biological activity after being cultivated in a lab on nutritional media. For example, in the case of antimicrobials, this is done by inhibiting the development of bacteria surrounding the test organism [7]. To make sure the organism isn't already being used for the activity, the phenotypic and phylogenetic characterisation of the bioactive generating microbe is carried out as the initial de-replication. This is done to maximize the likelihood of discovering a novel bioactive molecule. After the biologically active chemicals have been isolated and purified, their chemical structure is clarified. In this case, a second de-replication is possible to omit known chemicals. After new compounds are discovered, the producer organism's different growing circumstances can be evaluated to increase their output.

overall plan for finding natural chemicals with microbial origins that are biologically active, like antimicrobials. Microorganisms from the environment, such as the surfaces of marine eukaryotes, are first sampled. They are then screened for antibacterial activity and the producing organism is identified. The chemical structure of the bioactive molecule is determined and isolated. To obtain the required yields of the molecule for usage in subsequent generations of in vivo tests and product development, optimal production can be accomplished. One fundamental drawback of microbially produced bioactives, including those derived from the marine surface, is that the majority of environmental strains lack the capacity to thrive on synthetic culture media. Most (98–99%) of the bacteria are thought to be incompatible with traditional cultivation techniques. However, because a greater proportion of eukaryote-associated microbes can occasionally be cultured, sea living surfaces might prove beneficial. Increased access to the organism's physiology is one of the many benefits of being able to cultivate it in vitro. This can enable large-scale fermentation production as well as the adjustment of various growth factors to produce various products at their best. The most successful microorganism-growth techniques have been those that try to cultivate the organisms under conditions that are similar to the physical and chemical characteristics of their natural habitats. These close ties that frequently exist between microbial epibionts and marine eukaryotic cells obviously create settings that are challenging to replicate using standard laboratory techniques.

Therefore, the conditions in the microenvironment provided by its host are said to be important in developing appropriate culturing regimes for such bacteria. This has been used successfully to isolate the bacterium Oscillatoria, which is symbiotic with sponges and is cultivated in hyperosmotic media equal to the osmolarity of the sponge. It is necessary to consider and optimize the cultivation parameters, such as temperature, aeration, media pH, incubation duration, and medium composition, since these may have an impact on the production of the intended metabolite. This probably entails cultivating a producer strain in ideal circumstances for the active ingredient's synthesis. These ideal circumstances for optimum strain propagation may differ greatly from those for product creation. The generating organism is occasionally cultivated in parallel under a variety of settings, and the changes in metabolic spectra are studied. To generate the highest amount of bioactives, marine surface water-associated microbes might also need to be maintained in circumstances that mimic their native habitat. DNA sequencing information derived from environmental DNA sequencing (also known as the "metagenome") can be crucial in determining the metabolic capacities of organisms found in a given environment and, consequently, in designing specific culture conditions. The creation of that method was highlighted by the identification of this microorganism's inferred ability to fix nitrogen utilizing sequence data for an acid mine drainage biofilm community. In the last ten years, the isolation of novel bioactives through direct culturing of microbes has been replaced by genomics. It's interesting to note that the original purpose of functional metagenomics was to address the biotechnological potential of unculturable microbes. With this method, environmental DNA (also known as "environmental DNA") is inserted into a host organism, such as E. coli, and libraries are functionally screened to check for the desired activity in clones.

4. RESULT AND DISCUSSION

However, the hit rate of using metagenomic functional screening to recover bioactive generating clones is currently poor, typically around 1 in 10,000, or even lower, to as low as 1 in 730,000 tested clones, notwithstanding some success. The limited ability of host expression strains to create chemicals obtained from foreign sources is the main explanation for this low hit rate. Therefore, it is anticipated that the metagenomics functional screen

positive clone hit rate will be significantly increased through optimization of such strains. For instance, it has been demonstrated that using a range of host expression strains can help express the target metabolite. More precisely, if the producer microorganisms are known, these strains are typically selected based on potential similarities, such as the use of the same codons and the availability of specialized machinery required for the manufacture of the corresponding metabolites[17]].

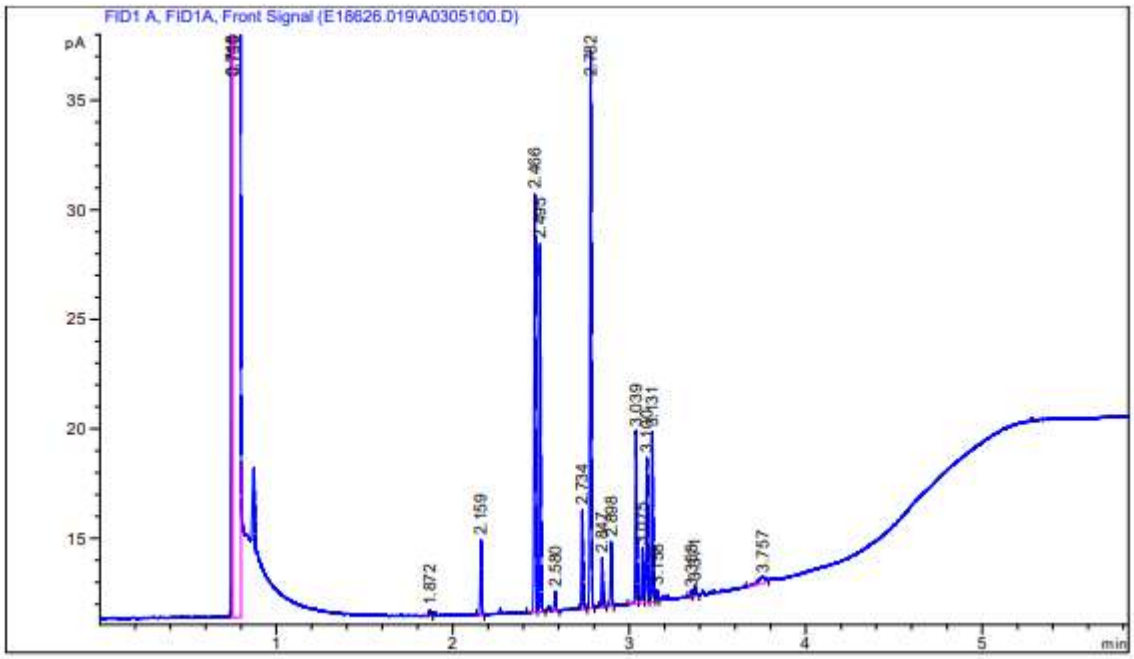
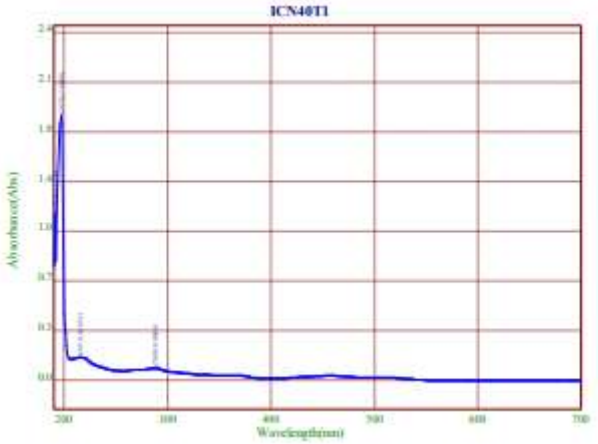
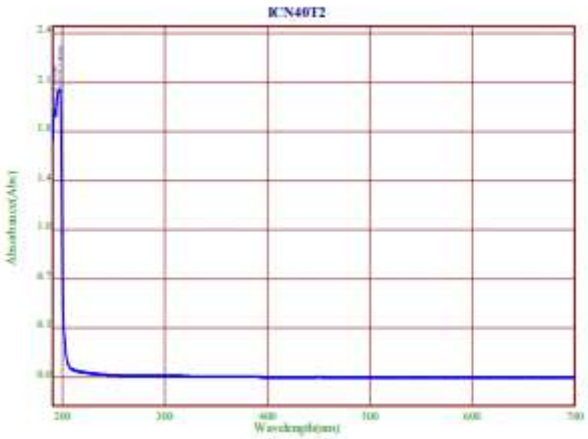


Figure 1: GC-MS chromatogram

As an alternative, genes encoding novel structures of known classes of compounds, such as polyketide synthases (PKS) and non-ribosomal peptide synthetases (NRPS), which are typically involved in the biosynthesis of bioactive secondary metabolites, may be revealed by shotgun sequencing of environmental DNA and downstream analysis. For instance, nine NRPS were discovered during a recent genome analysis of P. tunicata. Recently, two of these NRPS compounds with their anticipated bioactivity were discovered in the lab through heterologous expression, and by altering the growth conditions of the native P. tunicata strain, their existence was also verified. Furthermore, the establishment of culturing conditions that are conducive to the generation of bioactives has been emphasized due to the availability of sequence information from a wide range of microorganisms. The idea that non-bioactive producing organisms can be made to create bioactive metabolites under the right growth conditions is suggested by a number of examples of genes used in the manufacture of bioactives from these organisms. Exploring comparatively under-explored habitats also assists in the identification of novel microorganisms and chemical scaffolds, and thereby minimize existing compound re-discovery.



(a)



(b)

Figure 2: UV spectrum

Numerous unusual microorganisms, including the recently identified marine taxa, have been found to live in the oceans. Furthermore, it was discovered that some of these group members produced bioactive metabolites with novel structures; for instance, a number of compounds with cytotoxic action were successfully identified. Similarly, marine actinomycetes and cyanobacterial bacteria have recently yielded structurally novel chemicals called Marin eosins. Structure-new chemicals and other recent marine bioactive natural products fall unde. This supports the idea that the distinct physical and chemical characteristics of the marine environment can give rise to life forms that may eventually be able to manufacture metabolites using novel chemical scaffolds.

5. CONCLUSION

The discovery of previously unexplored sources, such as the marine living-surface habitat, has the potential to yield new bioactive-producing microbes that could lead to further drug development. Microorganisms are increasingly being hailed as the most appropriate renewable source of bioactives. Aside from that, a rational strategy that considers the special ecological interactions found in the marine environment, like those covered in this review, can also significantly help in optimizing the output of finding new organisms that produce bioactive substances. This could potentially avoid the constant re-discovery of known compounds and the waste of resources required for large-scale high-throughput screens. "The application of genetic engineering to redirect biosynthetic pathways to natural products in order to make new and modified structures using nature's biosynthetic machinery" is one of the alternatives for combinatorial biosynthesis. Combinatorial biosynthesis creates libraries of hybrid structures by combining genes from several biosynthetic pathways. In practice, though, this method is highly cumbersome. First of all, it is quite expensive and labor-intensive because it entails the creation of several mutant organisms. Second, it depends on the biosynthetic pathways' enzymes' low substrate specificity, which isn't always the case because most enzymes are very specific.

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