RECENT ADVANCES IN THE APPLICATION OF MARINE NATURAL PRODUCTS AS ANTIMICROBIAL AGENTS

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Frontiers in Antimicrobial Agents

(Volume 3)

Recent Advances in the Application of Marine Natural Products as Antimicrobial Agents

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FOREWORD

Frontiers in Antimicrobial Agents Vol. 3, Recent Advances in the Application of Marine Natural Products as Antimicrobial Agents, is an important book. The marine environment represents a unique resource that enfolds an enormous biological diversity ranging from viruses, single cells such as prokaryotes (bacteria and archaea), fungi and algae; to higher plants, invertebrates and higher organisms such as mammals. This enormous, largely unexplored diversity has, in recent years, been mined for its potential as a source of unique biologically active chemical diversity that can be harnessed into novel biomedical applications. These natural compounds are defined as biologically active products such as secondary metabolites, enzymes, lipids, etc. Many of these compounds are produced by the oceans' diverse microbial communities and are being exploited as important sources of bioactive and complex secondary metabolites with the potential to treat several diseases ranging from cancer to incurable antibiotic-resistant diseases. Some of these compounds can be used as antifoulants, preventing the settlement of unwanted organisms in the marine environment, and used in preventing biofilm formation in medical devices. The promise of such a wealth of novel compounds has led to a plethora of studies searching for novel compounds. Recently, novel antimicrobial agents have been isolated from bacteria or fungi found in the marine environment. Importantly, many of these compounds show clear promise in curing diseases that have, to date, been considered chronic and resistant. Indeed, recent publications have been emphasizing the role of marine microorganisms in the discovery of novel bioactive products, revealing that approximately 60% of these novel products come from marine bacteria. The new impetus for the study of these novel products has been advanced through the use of both cultures-dependent and independent methodologies, in particular on the novel and stronger molecular and analytical tools that have enabled the identification of new molecules with antimicrobial potentials. In addition, the use of new synthetic biology platforms enables researchers to mimic and develop less toxic derivatives of some of the novel materials discovered in the marine environment. These tools will greatly enlarge the repertoire of novel bioactive chemicals. This book provides an important compilation of studies revealing the potential of mining the ocean for novel bioactive compounds using the new tools available to us.

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PREFACE

The number of new antimicrobials on the market has decreased during the last two decades. On the other hand, harmful pathogenic organisms have acquired a high resistance rate, indicating that current antimicrobials are no longer effective. As a consequence, more effort must be put into discovering and commercialising novel antimicrobial agents. Despite significant advances in chemical synthesis and engineering biosynthesis of antimicrobial agents, nature remains the most versatile and the richest source for finding new antimicrobial agents.

The marine environment is a rich central hub, filled with a diverse array of animals, plants, and microorganisms. Therefore, the exploration of marine resources properly may lead to the discovery of novel bioactive compounds that could lead to breakthrough treatments for various human ailments. Several bioactive compounds from the marine environment are now in various stages of development, indicating that marine natural products may be used as a source of novel therapeutic compounds. Furthermore, a rising number of compounds derived from marine environments are undergoing clinical trials, indicating that this field's influence on the health industry is intensifying. As a result, this book aims to provide in-depth information about natural bioactive compounds that have been discovered as novel antimicrobial agents in different marine habitats. This book is a valuable instrument for both beginners and experts in the field of natural product science, marine microbiology and biotechnology.

This book is divided into seventeen chapters. The 1st chapter gives a brief overview of the significance of antimicrobial drug development. It describes various discovery platforms, ranging from target-based discovery to current innovative strategies and the difficulties associated with each platform. The 2nd chapter briefly discusses the importance of marine natural product research in discovering structurally distinct and effective antimicrobial agents. With appropriate evidence from the past, chapters 3, 4, and 5 details the possibility of employing microorganisms, bacteria, bacterial viruses, and cyanobacteria as natural antimicrobial agents from the marine environment.

Chapter 6 describes the usage of marine algae as a source of novel antimicrobials in various applications. In Chapter 7, the antimicrobial activity of mangrove extracts and their metabolites against several multidrug-resistant pathogens is extensively addressed. The patenting of natural bioactive compounds obtained from mangroves is also discussed in this chapter. Chapter 8 describes the chemistry and antimicrobial activity of bioactive compounds from several species of sponges.

Apart from marine bioactive compounds, bioactive components/substances from marine habitats, such as antimicrobial peptides, biosurfactants, and polysaccharides, have been investigated thoroughly for their various therapeutic potentials. Chapter 9 highlights the need to establish a focused development strategy to accelerate the progress of marine antimicrobial peptides and their potential use in microbial infection control. In addition, Chapter 10 discusses the inhibitory potential of antimicrobial peptides derived from diverse marine invertebrates against a wide range of pathogenic organisms. Chapters 11 and 12, respectively, discuss the extraction of biosurfactants and polysaccharides from different marine sources and the molecular mechanisms underlying their antimicrobial properties.

The rise of antimicrobial drug resistance and the difficulties associated, including its discovery, has led to the development of alternative therapeutic interventions. As a result,

several approaches have been developed. Chapters 13, 14 and 15, among the various therapies and approaches, emphasise the promise of synthetic drug discovery, combinatorial therapy, and nanomedicine to develop novel and effective antimicrobial drugs from various marine habitats, respectively.

Thousands of studies on the antimicrobial properties of marine natural products and extracts derived from marine organisms have been published. Still, there seems to be minimal information accessible on marine natural product clinical trials and patents. Therefore, chapters 16 and 17 intensely update on recent clinical trials and patents involving the various therapeutic potentials of marine natural compounds, with a special emphasis on antimicrobial properties.

We appreciate and acknowledge the technical assistance and support provided by the Bentham Books publishing team. We would like to express our gratitude to all of the authors who generously contributed to this book and everyone who helped us bring it to reality, including our family, friends, and colleagues. Finally, we would like to express our gratitude to Almighty God for providing all the inspiration, good thoughts, insights, and pathways necessary to accomplish this book project.

We welcome readers' suggestions and comments for future improvements.

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CHAPTER 1

Antimicrobial Drug Discovery Approaches, Challenges, and Development

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Abstract: The need for the identification of novel antimicrobial agents is greater than ever due to the emergence of multidrug resistance (MDR) among clinically important pathogens which pose serious threats to public health worldwide. Unfortunately, the pace of discovery and development of new antimicrobial agents to treat MDR infection has significantly slowed down. Identifying new targets and chemical classes is not easy, and reinvestigating old strategies by testing new compounds on known targets and expecting novel outcomes, seems not only a failure but a border on insanity. The development of new antimicrobial agents, chiefly those with novel mechanism(s) of action, remains essential, but this alone does not guarantee success. It is important to explore diverse information from multiple strategies, including multi-omics, bioinformatics, system biology and other non-conventional approaches. In this chapter, we give a brief background on the importance of antimicrobial drug discovery, detail several discovery platforms from target-based discovery to the current innovative strategy being evaluated, and list the challenges alongside each platform.

Keywords: Antibiotics, Antimicrobial agents, Antimicrobial resistance, Anti-virulence strategy, Bacteria, Broad-spectrum, Challenges, Comparative genomics, Computational method, Drug discovery, Essential Genes, Genomics, *In silico* approach, Multi-drug resistance, Nanotechnology, Narrow-spectrum, Natural products, Omics, Phage therapy, Photodynamic therapy, Target-based drug discovery.

INTRODUCTION

Antimicrobial drugs have modernized our ability to control infectious diseases, and their clinical availability has led to a remarkable decrease in human and

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animal morbidity and mortality. After the introduction of penicillin and the subsequent discovery of other antimicrobial drugs, antiseptics, disinfectants and vaccines, victory against infectious diseases was declared [1]. At the time when this was declared, pharmaceutical companies had the misconception that there were enough antimicrobial drugs to fight infectious diseases, and the research and development focus shifted to other clinical conditions such as cancer, diabetes, and heart disease [2]. However, the continuous usage of antimicrobial drugs, sometimes inappropriately, gradually led to the development of multi-drug resistant (MDR) and extensively drug-resistant (XDR) pathogens (also known as "superbugs"). Penicillin was first used clinically in the 1940s and saved millions of lives during World War II. By 1944, an estimated half of all clinical *Staphylococcus* isolates were becoming resistant to penicillin [3]. Since most antibiotics are the products of microorganisms, the emergence of resistance should not be a surprise. In 2019, the Centers for Disease Control and Prevention (CDC) has listed 18 antimicrobial resistance (AMR) bacterial and fungal pathogens into three categories based on the level of threat to humanity- urgent, serious, and concerning (Table **1**) [4].

Table 1. 2019 AMR threat reports by CDC [4].

Urgent Threats	• *Candida auris* • Carbapenem-resistant *Acinetobacter* • Carbapenem-resistant Enterobacterales • *Clostridioides difficile* • Drug-resistant *Neisseria gonorrhoeae*
Serious Threats	• Drug-resistant *Campylobacter* • Drug-resistant *Candida* • Drug-resistant nontyphoidal *Salmonella* • Drug-resistant *Salmonella* serotype Typhi • Drug-resistant *Shigella* • Drug-resistant *Streptococcus pneumoniae* • Drug-resistant Tuberculosis • ESBL-producing Enterobacterales • Multidrug-resistant *Pseudomonas aeruginosa* • Methicillin-resistant *Staphylococcus aureus* (MRSA) • Vancomycin-resistant Enterococci (VRE)
Concerning Threats	• Erythromycin-Resistant Group A *Streptococcus* • Clindamycin-resistant Group B *Streptococcus*

Recently, the WHO declared that AMR is one of the top ten global public threats challenging human health is alarming [5]. The rapid spread of "superbugs", including *Klebsiella pneumoniae*, *Escherichia coli*, *Neisseria gonorrhoeae,* methicillin-resistant *Staphylococcus aureus* (MRSA) and *Mycobacterium tuberculosis* (TB) is alarming [5]. Half a million new cases of rifampicin-resistant

TB were identified globally, of which the majority have MDR-TB (*i.e.*, confers resistance to the two most important anti-TB drugs, including rifampicin and isoniazid) [6]. Whilst 700,000 people die each year due to drug-resistant infections, 230,000 people die from MDR tuberculosis alone [7]. If no action is taken, MDR infections are predicted to kill 10 million people annually by 2050 [8].

To continue effective antimicrobial therapy and combat the MDR threat, we need either a continual supply of new drugs or to prolong the lifespan of existing antimicrobials [9]. The "golden age" of drug discovery (*i.e.*, the early 1940s to late 1970s) is not likely to happen without significant government funding and subsidies, due to the divestment of the pharmaceutical industry from developing new antimicrobial drugs or screening of compound libraries [10, 11]. Both economic and scientific hurdles equally contribute to this divestment stem. From an economic perspective, new antimicrobial drugs are not as profitable as drugs that are used in the treatment of chronic conditions such as asthma, cancer, diabetes, heart disease, high blood pressure and psychiatric disorders [12 - 16], chiefly because antibiotic treatments are much shorter in duration and are often successful [17]. Additionally, in an attempt to limit the acquisition of drug resistance, new antimicrobial drugs are widely held in stockpiles for cases in which no existing antibiotics are effective, further affecting profitability [17]. There are considerable scientific challenges facing the discovery of new antimicrobial drugs, exemplified by the fact that only two new antibiotic classes have been deployed to the clinic since the late 1970's. The vast majority of new antibiotics have been designed from previously approved scaffolds in which many bacteria already possess resistance mechanisms [18]. Hence, the emphasis is laid on the reinvigoration of the drug discovery approaches, but it is a well-known fact that all low-hanging fruits have been exploited already, and those new findings, even if effective, cannot fulfill the demand and will likely be a short-term solution [19].

In light of the serious MDR threat, several initiatives have aimed to develop and introduce novel antimicrobials into the clinic. In 2014, American President Obama signed an executive order entitled "Combating Antibiotic-Resistant Bacteria," which was intended to take a comprehensive approach towards preventing the emergence of AMR among pathogens and, also for developing next-generation antibiotics (https://obamawhitehouse.archives.gov/the-pres--office/2014/09/18/executive-order combating-antibiotic-resistant-bacteria). This initiative funded multiple government agencies with 1.2 billion US dollars to fight AMR infections. In addition, "The Innovative Medicines Initiative's New Drugs for Bad Bugs" was funded by European Commission, which envisioned developing and evaluating novel antimicrobials by creating Public-Private

CHAPTER 2

Marine Natural Products as Tools for Discovering New Antimicrobial Targets

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Abstract: The discovery of drugs for human ailments has been greatly attributed to nature ever since the existence of mankind. Continuous isolation of metabolites from terrestrial resources leads to a bargaining effect on the synthesis of novel compounds. Remarkably, marine biotope, one of nature's resources, accommodates approximately 75% of the global surface. To acclimatize in a marine environment characterized by unique circumstances that diverge from the individuals present in other habitation, marine organisms occasionally accumulate structurally distinctive bioactive secondary metabolites that are deficient in terrestrial organisms. Marine metabolites are currently employed as the key components in pharmacological research and drug discovery, acting as drugs and active lead molecules towards the development of novel antimicrobials. Numerous marine metabolites that are derived from macro and microorganisms have attained the level of clinical assessment. Hence, marine environments are considered tools for discovering new antimicrobial agents as they comprise a vast untapped reservoir of metabolite diversity.

Keywords: Antibiotic resistance, Marine biotope, Marine drugs, Marine metabolomics, Secondary metabolites.

INTRODUCTION

The messy use of antibiotics, which leads to multiple-drug resistance among pathogenic bacteria, induces an imperative that necessitates the development of

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new strategies to manage microbial infections. Countless marine natural products have been utilized in the strategy of drug discovery. Being an important source of drugs, marine metabolites are considered vital candidates in the discovery of novel drugs nowadays. It is because of the presence of distinctive molecules with similar structures synthesized by marine inhabitants, encompassing several halogen atoms and stereogenic centres [1]. These characteristic features have attracted the interest of researchers in the recent past. Such marine metabolites could be explored in the field of medicine to discover novel antimicrobial drugs to cure several diseases [2]. Hence, unveiling the concealed marine milieu possessing distinct macro and microorganisms is greatly anticipated to offer novel bioactive leads with unique bioactivities, which could plausibly meet the needs in the field of medicine and the environment globally. Consequently, marine products are bestowed with proficient antimicrobial activities, thus acting as an important lead environment that has become an active and fascinating field. Due to the growing evidence that several antimicrobial and anticancer drugs are isolated from marine invertebrates, algae and their associated bacteria, besides the vast biodiversity of marine microorganisms, the attention on marine environmental research has greatly amplified.

MARINE NATURAL PRODUCTS AS ANTIMICROBIAL AGENTS

The discovery of antibiotics has been widely attributed to natural products since the amazing discovery of penicillin. Considering, marine resources as a new antimicrobial tool ended in the identification of 10,000 active metabolites [3] with potential pharmacological effects, including antibacterial, antipathogenic, antiviral, antifungal, antimitotic and antiprotozoal. Currently, new targets have been included in the search for novel antimicrobials, such as the development of biofilm and subsequent biofouling by targeting cell-to-cell communication and other mechanisms of action.

MARINE MICROORGANISMS AS A SOURCE OF ANTIFOULING AGENTS

All immersed surfaces are considered to be exposed to microbial colonization by bacteria, microalgae and some invertebrates inside a multifaceted layer named biofouling [4]. The initial colonizers in this layer are bacteria, and their other mode of growth, the so-called biofilm formation, develops in different stages [5]. Such biofilms are found abundantly in nature and are formed whilst a free-floating planktonic bacteria stick onto a biotic or abiotic surface and instigate the microcolony formation, which continues living as a community sheathed in an extracellular matrix [6] to confer a high degree of resistance against antibiotics and host immune response [7]. Hence, inhibition of biofilms is anticipated to play

a critical role in the prevention of biofilm-based biofouling [8]. Several chemical biocides and organotin compounds, most notably tributyltin, were employed as potent antifouling compounds in reducing the attachment of biofouling organisms to surfaces that are submerged in marine [8, 9]. Chemical biocides and, unfortunately, treatment of tributyltin-based compounds are known to cause serious adverse effects on humans, such as liver impairment, hypoglycemia, glycosuria, and respiratory disorders [10]. Similarly, they had an adverse effect on marine organisms in the form of immunosuppression, endocrinopathic, neurotoxic, hepatotoxic, nephrotoxic, gonadotoxic, embryotoxic, fetotoxic, and developmental effects [10]. Consequently, the International Maritime Organization (IMO) banned the exploitation of organotin compounds as antifouling agents. It is noteworthy to mention that WHO has outlawed the usage of biocides based on organotin compounds from the year 1990. Similarly, the usage of antibiotics as biocides led to the emergence of resistance among bacteria present in the biofilm architecture. Despite an array of approaches implemented to deal with biofouling, it is imperative to explore novel and effective technologies to overcome the issues related to environmental toxicology and the emergence of resistance among biofilm-forming pathogens. The application of chemical defenses seems to be an important antifouling strategy as it helps to sustain the surfaces that remain free of fouling from sessile marine organisms [5]. Such antifouling compounds may perhaps be secluded from sponges, algae, bryozoans, and corals, which produce such compounds apparently to offer shelter from predators and foulers, along with diminishing competition for living space [11]. Application of such marine-derived substances is found safer than commercial toxic antifoulants and biocides due to their availability, compatibility, stability and less toxicity when exposed to diverse environmental settings [12].

More particularly, the identification of antifouling compounds isolated from marine sources is surprising [13, 14]. De Nys *et al.* (2006) [15] found the antifouling activity of brominated furanones derived from marine seaweed. Similar to this activity, meroditerpenoids secluded from the brown alga *Halidrys siliquosa* showed a pronounced inhibitory effect on the settlement of cyprids such as *Balanus amphitrite* [16]. An antifouling compound floridoside, extorted from the red alga *Grateloupia turuturu* was found to display a potent anti-barnacle activity [17]. Surprisingly, a mangrove-derived diterpene isolated from *Ceriops tagal* effectively inhibited the settlement of cyprid *B. albicostatus* without any toxic effects [18]. Particularly, promising was hydroquinone A acetate and dihydrospongin II isolated from Mediterranean sponges, which displayed good antifouling activity against barnacle larvae [19].

Besides, compounds derived from marine-associated bacteria and fungi are acknowledged as substantial sources of harmless antifoulants [13]. Most notably,

CHAPTER 3

An Overview of the Antimicrobials from Marine Bacteria

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Abstract: The marine environment comprised huge biological diversity and remained the least explored location for prospecting novel antimicrobial agents. Marine bacteria, in specific, are considered an essential source of therapeutically valuable biologically active secondary metabolites. As bacteria are ubiquitous, they evolve with a certain unique mechanism to thrive under stressful conditions like competitive habitats, much-varied temperatures, light, pH and pressure. In these harsh environments, surprisingly, bacteria in these regions produce many natural bioactive compounds with unique molecular scaffolds and structural complexity. This untapped biological resource may become a source for the cure of several crises facing the world in the 21st century, such as the emergence of multi and pan-drug-resistant bacterial and fungal pathogens and pandemic and epidemic outbreaks of viral infections. This chapter discusses the role of natural secondary metabolites from marine-derived bacteria as a tool in the fight against emerging and re-emerging infectious diseases.

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INFECTIOUS DISEASES

Infectious disease is an infection that emerges and spreads among humans at an increasing rate in terms of incidence or geographical range [1]. Every nation tirelessly works to eradicate the infectious diseases causing human pathogenic microorganisms since World War II. In addition to developing advanced military weaponry, strategies considering public health have also become a prime focus. All over the world, we are engaged meticulously in developing medical weaponry like antimicrobials and vaccines to obliterate viral, fungal and bacterial enemies. Yet, infectious diseases are rising at an unprecedented rate and have significantly shattered public health and global economics. In the current scenario, the rise of infectious diseases is of particular interest in social, economic, environmental, and ecological factors [2]. Stern evolution of variant strains warrants the burgeoning incidences of infectious disease outbreaks in developing countries. Further, there are factors like zoonotic diseases, the evolution of pathogens with pandemic potential, host susceptibility, food habits, industrial farming of livestock, the emergence of drug resistance strains in livestock, increase in human population, globalisation, human migration, and habitation to the new environment that has influence over the emergence and re-emergence of disease with pandemic potentials [3]. The ever-increasing emergence or re-emergence of infectious diseases heightens the global impact of infectious diseases in this century [3].

Researchers estimate that a new infectious disease emerges on an average scale of approximately eight months. More than 35 infectious diseases have emerged since 1980 [4]. Viruses are reckoned to be the leading etiological agent of contagious disease by having millions of mortality rates and more morbidity rates. The world has been exposed to vast incidences of viral pandemics. By claiming hordes of lives, the pandemic history was imprinted with the names of viruses, namely, HIV (Human Immunodeficiency Virus), Ebola, Zika, MERS (Middle East Respiratory Syndrome Corona Viruses), SARS, Swine flu and now with SARS-CoV-2 for their devastating effect [3, 5]. The Ebola outbreak claimed nearly 11,000 lives among the infected 28,000 people. Likewise, the incidences of SARS-CoV in 2002-2003 left 774 deaths and 8000 infected people around 35 countries, and MERS-CoV also claimed 688 human lives and infected 2500 people from 27 countries. The ongoing outbreak caused by the novel coronavirus disease-2019, COVID-19, was officially announced as a global pandemic by World Health Organization (WHO), and has spread to nearly all countries and territories

globally. The disease nearly infected 229,858,719 lives and claimed 4,713,543 deaths as of 23 September 2021 [6].

Next to viral infections, infections caused by bacteria and fungi are predominating. The discovery of the first antibiotic, penicillin, revolutionised medical history by saving millions of lives from deadly bacterial infections. The subsequent discovery of antibacterial and antifungal agents made it quite possible to control bacterial and fungal infections, respectively. However, the inappropriate and overuse of antibiotics pave the way for the emergence of antibiotic-resistant strains. According to the report of the Infectious Disease Society of America (IDSA), ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter sp.*) pathogens have a high propensity towards the development of resistant strains [7]. Hence the infections of these bacterial pathogens are considered highly dangerous in clinical settings and in people with clinical complications. Like bacterial pathogens, fungal pathogens are also potent in causing infections in neonates, elderly people or people with clinical complications. The genus of *Candida*, *Aspergillus*, and *Fusarium* are a few examples of human fungal pathogens capable of emerging as multidrug-resistant strains [8]. Estimates of the European Union and the USA on antimicrobial resistance described nearly 25000 and 23000 death rates per year, respectively [9, 10]. Further, the total economic losses include healthcare and productivity losses estimated at around €1.5 billion per annum because of antimicrobial resistance. In addition, WHO's Global Report on Surveillance report (2014) delineates the severity of antimicrobial drug resistance on a global scale [9]. Also, the report states the extent, spread, emergence and outcome of antimicrobial drug resistance.

ANTIBIOTICS AND RESISTANCE MECHANISM

With the discovery of penicillin in 1928, the golden age of antibiotics started and peaked in the mid-1950s. Arguably, the introduction of antibiotics was the greatest triumph in the medical field in the 20th century [11]. Antibiotics play a significant role in other medical treatments like open-heart surgery, organ transplants and so on, apart from treating infectious diseases [12]. Based on the structure and the affinity towards the drug targets, the antibiotics are classified as penicillins, cephalosporins, carbapenems, polymyxins, tetracyclines quinolones, macrolides, diaminopyrimidines, aminoglycosides, and sulphonamides [11]. The target-specific action of the antibiotics, like affecting the cell wall synthesis, protein synthesis, disruption of nucleic acids machinery, and targeting the metabolic pathways, and cell wall disruption, ensures the elimination of pathogens [13]. Widespread use of antibiotics imposes an intense selection pressure among pathogens to resist the antibiotics, *i.e.*, the ability to grow even in

CHAPTER 4

Marine Bacterial Viruses: The Inevitable Natural Antimicrobial Agents in the Marine Environment

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Abstract: Antimicrobial property has been the reason for investigation in several plants and microorganisms. The health issues and environmental hazards defined by the extensive use of chemical antimicrobials have become a buried fact due to the emergence of bio-based antimicrobial agents. Considering the impact of chemical antimicrobials on the environment, many natural antimicrobial agents have been formulated and recommended for application in food systems. Several food-borne outbreaks are associated with the intake of marine foods and are highly linked with harmful microbial pathogens. Marine bacterial pathogens have been extensively reported for several outbreaks in the last few decades. Vibriosis is the most devastating disease faced by marine organisms. The associated pathogens have also been channelized to humans through seafood consumption. There also exist some deadly bacterial pathogens in marine environments, which are responsible for huge economic losses in seafood processing sectors. It is high time to mitigate this bacterial jeopardy. The extended anthropogenic activity on the coastal lines has also increased the virulence of these bacterial pathogens by inducing multidrug resistance. Based on several reports in the pre and post-antibiotic era, phage therapy is revitalised to overcome the limitations encountered in antibiotic therapy. Marine bacteriophages are documented as abundantly available viruses in the marine environment. Their ubiquitous and inevitable nature can be utilized to engage them as natural antimicrobial agents from the marine environment and its allied sources. This chapter summarized the feasibility of employing bacterial viruses from the marine environment as natural antimicrobial agents with proper evidence from the past.

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INTRODUCTION

Among the known microorganisms, viruses are comparatively much smaller than other microbes. Bacteriophages or bacterial viruses are a group of viruses that survive through bacterial lysis. Bacterial viruses are obligate parasitic organisms that live by utilising the host machinery of bacterial cells. Marine ecology is treasured with many living organisms, and the abundant bacteriophages are one among them, which were discovered in 1947. About 5x 10^{12} to 1 x 10^{13} bacteriophages are found per square meter of sediments in the deep sea. This abundance assures their prominent role in biogeochemical cycles in the marine environment [1]. The enormous population of bacteriophages makes them effective antimicrobial agents that curtail burgeoning bacterial pathogens. Moreover, they are responsible for balancing bacterial populations in the oceans. *Podoviridae*, *Myoviridae* and *Siphoviridae* are the main phage groups identified and characterized from marine sources, while many other phages in the ocean are yet to be studied [2]. As the application of bacteriophages is widely studied against human, animal, plant and food bacterial pathogens, marine phages must be investigated further to precise their efficacy as effectual natural antimicrobial agents. This chapter summarizes the efficacy and possibility of utilising marine bacterial viruses as natural anti-microbial agents. The cycle of events that occurs in lysing the bacterial host is called phage therapy. This chapter will detail how phage therapy was discovered, its application, and the approaches devised to engage its application against bacterial pathogens in marine foods.

ENGAGING BACTERIOPHAGES AS NATURAL ANTIMICROBIALS

Bacteriophages were discovered prior to the introduction of antibiotics. Lack of research and proper evidence to state the advantages of phage therapy limited its application till the awareness on the demerits of antibiotic application emerged. The pioneer research on bacteriophages began in the late 19th century. During a cholera outbreak in India in 1896, a British bacteriologist proposed the presence of a biological source that mitigated the population of bacterial pathogens responsible for the cholera outbreak in the rivers- Ganga and Yamuna. A transmissible glassy transformation was observed by Fredrick Twort, a British microbiologist, while studying the growth media for the *Vaccinia* virus. In 1917, Felid d'Herelle demonstrated the presence of antibacterial agents in stools collected from patients suffering from shigellosis, and bacillary dysentery. These antibacterial agents developed a visible zone of lysis over a bacterial lawn and

named them bacteriophages. After the invention of the electronic microscope, the structure of bacteriophages, along with the description of bacterial lysis in sequential steps after phage adsorption onto the bacterial membrane, was detailed by Luria and Anderson. Moreover, in 1941, X-ray crystallography assisted in understanding the phage structure. Later, the discovery of antibiotics dominated phage application over several ambiguities [3 - 7].

Natural antimicrobials are usually extracted from plant sources, while microorganisms produce a few. The hunt for a better alternative to hazardous chemical antimicrobials never ceased, even after several investigations on various natural resources [8]. Bacteriophages are one such natural antimicrobial agents that can be produced and formulated for application. The choice of phage relies upon the type of its reproduction. Phages undergo lytic and lysogenic cycles, of which lytic phages are preferred for application as natural antimicrobials. Though lysogenic/temperate phages can shift to a lytic cycle under stress, strictly lytic/virulent phages are suitable for non-hazardous and biocompatible applications as natural antimicrobial agents [9, 10]. The sequential steps involved in lysing the bacterial host *via* the lytic cycle describe the antimicrobial metabolism of bacteriophages. This process does not require any external factor to induce the lytic mechanism. Once the bacteriophage finds a suitable receptor on the outer membrane of bacteria, the lytic cycle commences. The burst size and lysing time vary based on the type of bacteriophage that infects a bacterial host. Approximately, 50 to 300 phage progenies are released every 30 to 60 minutes of a single phage infection. Each of these phage progenies will adhere to the remaining bacterial pathogen (specific targets) and multiply, thus resulting in a large number of phage progenies while mitigating or eliminating the host population. It is inferred that strictly lytic bacteriophages are suitable for antimicrobial therapy [10 - 13]. Fig. (**1**) represents the cycle of events that occur in the life cycle of bacteriophages.

The emerging antibiotic resistance is a threat to humankind. Therefore, it is necessary to revitalise the application of bacteriophages. History reports several successful trials of phage therapy to treat bacterial diseases in humans, animals and plants. Application of bacteriophages prevailed in the treatment of pathogenic bacterial infections in humans and animals, eradication of phytopathogens in agricultural crops, water treatment to eliminate the disease-causing water-borne bacterial pathogens and to control or prevent the invasion of bacterial pathogens that cause food-borne illness and intoxication through food consumption in humans. They are used as therapeutic agents in the pharmacological application and also as biosensors [14 - 16]. The widened application results in the control of emerging antibiotic resistance among microbial pathogens. Eventually, therapeutic application in humans against multi-drug-resistant bacterial pathogens

CHAPTER 5

Marine Cyanobacteria: Sustainable Resource for Vibrant Antimicrobial Agents

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Abstract: Marine cyanobacteria are oxygenic, gram-negative nitrogen-fixing photosynthetic prokaryotes in different environments. It is a universal organism present in aquatic and terrestrial and also extensively scattered in extreme habitats such as hot springs, deserts and glacial environments. Growing concerns over disease outbreaks and other environmental concerns require alternative ways that are economically viable, sustainable, as well as feasible. Recently, cyanobacteria have achieved much consideration because of their potential relevance in various fields, including aquaculture, wastewater treatment, food, fodder, and the production of secondary metabolites, including polysaccharides, vitamins, toxins, enzymes and pharmaceuticals; they also secrete important novel bioactive antimicrobials including antibacterial, antifungal and anti-viral compounds. The emergence of antimicrobial resistance among pathogenic microbes against common antibiotics imposed the search for new antimicrobial agents from natural sources. Various features of cyanobacteria, including their ability to produce novel antimicrobials, make them suitable candidates for their exploitation as a natural source. Hence, this chapter presents an overview of marine cyanobacterial features, antimicrobials isolated from marine cyanobacteria, as well as the mode of action. Among the known cyanobacterial bioactive compounds, many are pharmacologically important and hold immense potential for drug development at the clinical level.

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INTRODUCTION

Marine cyanobacteria have the distinction of being the oldest known fossils, almost 3.5 billion years old in the record [1]. Cyanobacteria are mostly found in the aquatic environment, and named photosynthetic prokaryotes are often called "Blue-Green Algae" (BGA; *i.e.*, they exist in the water and synthesis their own food). The term was given on the origin of their photosynthetic activities before their structural relationship with bacteria [2]. According to Bergey's Manual of systemic classification, cyanobacteria are named oxygenic phototrophic bacteria and are included in volume 3 of the Manual. They are very strong to thrive in adverse conditions of the environment; and are widely distributed in hot springs, deserts, and glacial environments [3]. Cyanobacteria are the main organisms as they are exploited in different areas of biotechnology [4]. The adaptability of cyanobacteria to tough environments has improved certain mechanisms within them to produce novel secondary metabolites. Over the years, cyanobacteria have been widely screened for active metabolites with diverse pharmacological properties [5 - 8].

The characteristics that make cyanobacteria generally undesirable are the major potential for possible economic values. BGA is the source of many helpful products [9] and carries capable physiological processes, including light-dependent hydrogen development by bio-photolysis [10]. Extensive research has taken place to make use of the multiple strains of cyanobacteria and its products in the relevant fields of biotechnology. Generally, it is used as food or fodder because of its rich content of proteins, vitamins and vital pigments, essential and non-essential growth factors [11]. It also acts as a natural source for producing substances with diverse pharmaceutical interests (such as natural antibiotics) [12, 16].

GENERAL CHARACTERISTIC FEATURES OF MARINE CYANOBACTERIA

Cyanobacteria from marine origin require major vital factors and can be quickly developed using sunlight, water and obligatory elements like carbon (C), potassium (K), phosphorus (P), sulfur (S), nitrogen (N) and iron (Fe). They are ubiquitous but richly found in diverse areas like water bodies (lagoons, lakes, ponds, rivers and different stagnant water bodies) [13, 14]. Like all other prokaryotic organisms, membrane-bound nuclei, chloroplasts, mitochondria,

endoplasmic reticulum and Golgi apparatus are absent in cyanobacteria. However, cyanobacteria cells have ribosomes. It contains ribonucleic acid (RNA) and is liable for protein synthesis. Cyanobacterial ribosomes are approximately one-third smaller in size when compared to eukaryotes and perform similar functions in both cells. Certain cyanobacteria, especially planktonic forms, hold gas vesicles that help with their buoyancy. Some other strains have a sheath for attachment to other cells or form threads into colonies. Another important characteristic is the ability to exist without vitamins. But, they utilize P, Fe ammonia or nitrate and other micronutrients for growth. A filamentous cyanobacterium doesn't require sunlight and grows in the dark; it depends on sugar from glucose or sucrose as a carbon source [15, 31].

PIGMENTS AND CHROMOPHORES

Chlorophyll (Chl) is the leading light-harvesting pigment in cyanobacteria and other photoautotrophic organisms [17]. Six different types of Chl have been reported previously in cyanobacteria. They are Chls a, b, d, f and divinyl- Chls a and b. All these types naturally occur in cyanobacteria except Chl a, the most copious chlorophyll pigment in cyanobacterial species [18]. In cyanobacteria, light-harvesting complexes are self-arranged and named phycobilisomes. Besides, various types of yellow colour carotenoids, the blue pigment phycobilin, and, in some species, the red pigment phycoerythrin, also present in most of the cyanobacteria [19]. The mixture of phycobilin and Chl produces the characteristic blue-green colour from which these organisms obtain their popular name. Due to the presence of other pigments, many species are actually green, brown, yellow, black, or red. Examples of some pigments found in this group are Chl a, P-carotene, Antheraxanthin, Flavacin, Lutein, Myxoxanthophyll, Oscilloxanthin, Zeaxanthin, Allophycocyanin, Phycocyanin and Phycoerythrin [20].

APPLICATIONS OF MARINE CYANOBACTERIA

The vast knowledge of cyanobacteria helps to explore their broad applications in various fields of biotechnology. At present, cyanobacteria achieve more consideration due to their rich resource of compounds and have been thought of as one of the most gifted groups of organisms [21, 22]. These cyanobacterial metabolites exert activities including antibacterial [23], antifungal [24], antiviral [25], anticancer [26], antiplasmodial [27], algicide [28] and immunosuppressive nature [29]. Cyanobacteria have several biomedical uses in aquaculture, diet supplements, fuel, composts, stains and the production of various secondary metabolites with diverse clinical potential. They are an excellent source of vitamins, proteins and other fundamental elements for life. Quite a few of these active compounds have clinical applications and are useful for discovering more

CHAPTER 6

Reconnoitering Cell Factories of Marine Algae for Antimicrobials

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Abstract: Antimicrobial compounds are groups consistent with the microorganisms that they could potentially act against bacteria or fungi. It is expected to kill microorganisms or inhibit their growth and activity. As the case of antimicrobial resistance increases, nature has been generous in providing compounds with the potential to treat various ailments and infectious diseases. Bacteria, fungi and plants are known to own a good list of antibacterial molecules. Although research has been carried out to reveal the antimicrobial potential of natural products, the significance of vast terrestrial and marine Animalia has gained momentum. Though the naturally available antimicrobial agents obtained from plants, animals and microbial sources are considered safe in comparison with synthetic molecules, the outbreak of pathogens needs exploration over and above the reported ones. As the synthetic antimicrobials soon become immune to pathogens, it makes emphasis on antimicrobials from novel origins that have a long duration of effectiveness. The marine environment houses a wide and taxonomically diverse species of algae, mollusks, sponges, corals and tunicates. These organisms have adapted to survive the infectious environment by producing pharmacologically active compounds of phlorotannins, fatty acids, polysaccharides, peptides, and terpenes that help in battling bacterial annexation. As marine algae provide considerable opportunities in antimicrobials, the optimization in the methodologies leading to extraction and purification plays a greater role in capturing the antimicrobial activity of the bioactive molecules. Though an outsized number of potential antimicrobial compounds from marine algae have been identified and isolated, the majority of those compounds are yet to be categorized and commercialized. Recent research in algae focused on "omics" where metagenomics, metatranscriptomics and metaproteomics are done to understand better pathway leading to the synthesis of various functional molecules.

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INTRODUCTION

An antimicrobial compound efficiently kills microorganisms or inhibits their growth and activity. Antimicrobial medicines are grouped consistent with the microorganisms they could potentially act, *viz*., against bacteria (antibiotics) and fungi (antifungals). Antimicrobial use has been a common practice for a minimum of 2000 years, where ancient Egyptians, as well as Greeks, were reported to use specific molds and extracts of plants to treat many infections [1]. Medicinal herbs and both marines and terrestrial organisms, including fungi and bacteria, were some prominent sources of natural compounds reported for antimicrobial activity. The potential is huge, and there is still a diverse fauna and flora that, once systematically explored, could be an additional factory of antimicrobial leads, drugs and medicines. As of date, mainstream antimicrobials are discovered from prokaryotes; however, eukaryotic origin, mainly from fungal and plant sources, also gained attention. The lack of a potent bioactive molecule in the treatment of various emerging disorders has always compelled the exploration of novel sources.

Reports on antifungal compounds date back to the path-breaking discovery of the first beta-lactam drug antibiotic - Penicillin which targets the cell membrane of bacteria and is obtained from the fungus *Penicillium notatum*. There are various edible fungi (mushrooms) that are rich in antioxidants and antibacterial molecules studied against both Gram +ve and Gram -ve bacteria. An example includes medicinal lignicolous fungi like *Ganoderma lucidum, Ganoderma applanatum*, *Meripilus giganteus, Laetiporus sulphureus*, winter mushroom, *Coriolus versicolor*, Oyster mushroom and *Panus tigrinus* that unveiled bactericidal action, particularly against *Staphylococcus aureus,Bacillus subtilis* and *Micrococcus luteus*. Yeast and yeast-like fungi *Aureobasidium pullulans, Citeromyces matritensis, Cryptococcus laurentii, Rhodotorula glutinis* and *Sporobolomyces roseus* also showed to retain antimicrobial action against *Pseudomonas fluorescens* and *S. aureus*. Cephalosporins, a category of β-lactam antibiotic synthesized by the marine fungus *Acremonium,* are efficient against a wide number of Gram +ve and Gram – ve organisms. Fungi isolated from other marine sources, including marine sponges, sea sediments, tumbled twigs, mangroves, and sea squids belonging to the *Aspergillus, Penicillium, Cladosporium, Trichoderma,*

Pestalotiopsis, Phomopsis, Gliomastix, possess antimicrobial activities against bacterial pathogens [2].

Bacteria are known to own a good list of antibacterial molecules. The genus *Streptomyces* is documented for the assembly of a broad array of antimicrobials. *Streptomyces antibioticus* is understood to supply actinomycin, *Streptomyces lavendulae* yields streptothricin, and *Streptomyces griseus* produces streptomycin. It was improved to Gentamycin which is reserved for many serious infections. Though there are similarities between marine and terrestrial bacteria, the adaptations made by organisms during the adversities in a marine environment with regard to chemical and physical conditions have facilitated the production of many novel compounds to assist in their survival [3].

Plants are rich sources of bioactives that are known to exhibit good potential in the treatment of various diseases and infections. The commonest means of therapeutics from plants include herbs, fruits and leaves, and have been in practice for several hundreds of years. Plants like *Plucheaarguta Boiss* (Compositae) are sources of sesquiterpenes, *Perovska abrotanoides* Kerel (Labiateae) synthesize triterpene, *Guaiacum oflcinale* (Zygophyllaceae) are known for triterpenoidal saponins, and *Cocculushirsutus* (L.) Diels (Menispermaceae) reports isoquinoline alkaloids. These biologically active metabolites are antibacterial against Gram +ve bacteria *viz*. *S. aureus, Corynebacterium xerosis, S. pyogenes* and *Bacillus anthracis* and Gram –ve organisms, including *Proteus vulgaris, Shigella flexneri, Klebsiella ozaenae, Shigella boydii, P. pseudomallei, K. pneumoniae* and *E. coli*. These secondary metabolites are their potential antibacterials when used alone or as synergists or potentiators of other antibacterial agents. Secondary metabolites from plant parts, fruits, vegetables and spices have a decisive role in the treatment of several diseases. Turmeric, a common culinary product derived from the rhizome, has been in use for hundreds of years for wound healing, and inflammation, beneficial in handling microbial infections, abdominal pain, arthritis and metabolic disorders. Similarly, honey is reported in antibacterial and wound-healing properties. It showed antimicrobial action against *E. coli*, *Enterobacter aerogenes*, *S. typhimurium, S. aureus*, β-haemolytic streptococci and vancomycin-resistant Enterococci (VRE).

Research has been carried out to reveal the antimicrobial property of natural products sourced from microbes and plants. Of the ~8.0 million species of animals reported from various ecological niches, only small numbers are investigated for their antimicrobial effectiveness. Attention was gained by snakes; the venom of the common night adder, gaboon adder, puff adder, *Dendroaspis augusticeps*, eastern black mamba, forest cobra, snouted cobra and Mozambique black-necked cobra was tested and found effective against several pathogens like *S. aureus, E.*

CHAPTER 7

Antimicrobials from Mangroves

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Abstract: Mangroves are a promising source of antimicrobials owing to the bioavailability of genes, plant metabolites and biological diversity. Mangroves are known for their many biological properties, such as antibacterial, antifungal, antiviral and anti-cancer activities *etc.* Besides mangroves, the microbes associated with mangroves are called endophytes, which are proven effective antimicrobials and are also well-known for their many other pharmacological properties. Mangrove extracts coated with nanoparticles exhibit better antimicrobial activity due to their easy absorption and distribution properties. The antimicrobial activity of mangroves is due to the presence of abundant phenolic and flavonoid compounds, especially tannins, and to the antioxidant property of the bioactive substances present in the mangroves. Thus, mangroves have a great bioprospecting potential for developing the most potent antimicrobials to treat pathogenic bacteria, viruses and fungi. This chapter deals with the antibacterial, anti-viral, anti-mycotic, anti-virulence and anti-biofilm properties of mangrove extracts and mangrove endophytes against various pathogenic and multidrug-resistant microbes. In addition, patenting of natural compounds from mangroves and their endophytes, as well as metabolomics and proteomics, are also discussed in this chapter.

Keywords: Anti-biofilm, Antibiotics, Anti-fungal, Antimicrobial, Anti-mycotic, Anti-viral, Anti-virulence, Bioactive substances, Mangroves, Metabolomics, Nanoparticles, Patents.

INTRODUCTION

Mangroves are a paradise for biologically active chemicals. The mangroves are woody plants, colonizing the intertidal mudflats in tropical and sub-tropical regions of the world. They are remarkably adapted to harsh coastal conditions,

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such as seawater, periodic inundation and exposure to heavy winds, waves, floods, strong currents and anaerobic soil. There are no other groups of plants in the entire plant kingdom with such highly developed adaptations [1 - 5]. In order to adapt to the stressful environment, the mangroves produce a wide variety of natural products belonging to different chemical classes, such as alkaloids, phenols, steroids, terpenoids, flavonoids, saponins, and tannins. These phytochemicals have unique biological activities such as antifungal, antibacterial, antiviral, antifeedant, pesticidal, and molluscicidal properties [6 - 8].

Mangroves have been traditionally used for medicinal purpose [8, 9]. Local people consume *Acrostichum* leaves as vegetable, and *Sonneratia* fruits as beverage, and the local people believe they are well-protected from diseases after consuming mangrove products [10, 11]. But, these traditional uses lack sufficient scientific validation. The efforts in promoting patents will help society to generate profit-oriented employment opportunities. Among the bioactive substances, antimicrobials are of great importance in the present context of non-availability of the most potent antimicrobial drugs till-today for applications. Continued use of antibiotics is increasingly making the pathogenic microbes resistant to the antibiotics and causing chemical pollution that is hazardous to the environment. Hence, it is a matter of necessity to find out cheaper, safer and the most effective antimicrobials.

Antimicrobial is an agent that kills microorganisms or inhibits their growth. Antibacterials are antibiotics used to control bacteria, while antifungals are used against fungi. There is a need to find out more potent antibiotics that can control a wide variety of pathogenic bacteria, especially multi-drug resistant strains. Similarly, more potent antifungal drugs are required as the pathogenic fungi are efficient in enzymatically degrading the drug chemicals, thereby nullifying their antifungal effect. The present chapter deals with antibacterial, antifungal, anti-viral, anti-mycotic, anti-virulence and anti-biofilm properties of mangroves, endophytic microbes and nanoparticles synthesized by mangroves.

UNIQUENESS OF MANGROVES

Mangroves are among the most productive ecosystems on the earth, and their biomass is greater than any other aquatic ecosystems [1, 3]. The mangrove system is biologically diverse that supports a wide variety of microbes, plants and animals due to the diversified habitats of the mangrove system, such as forests, mudflats and water bodies. The mangroves are not only biologically diverse, but also chemically diverse, with different classes of primary and secondary metabolites. Among the chemicals, the mangroves are a rich source of phenol-based compounds such as tannins. The presence of tannin at the level of 2.41 to

21.42 mg/g, and the presence of gallotannins varies from 0.013 to 3.555 mg/g [12, 13]. The phenol-based compounds have strong antioxidant and antimicrobial properties.

A predominant group of polyphenols is catechin. Catechin reacts with polyphenol oxidase and promotes the synthesis of two important compounds such as theaflavins and thearubigins. The former is a flavouring chemical, and the latter is a nerve-stimulant. These two chemicals are essential ingredients of black tea. Kathiresan and his team have developed a protocol for the preparation of tea from a mangrove plant, namely *Ceriops decandra*, which is equivalent to the taste of conventional tea. The toxicity study with an *in vivo* animal model system has proven the quality of mangrove tea as a non-toxic drink. Mangrove tea has high antioxidant activity, capable of preventing oral cancer as proved in the albino rat animal model [14].

ANTIBACTERIALS FROM MANGROVES

Mangrove species have been screened for antibacterial activity against human pathogenic strains of bacteria (Table **1**). The antibacterial activity of mangroves such as*Avicennia marina, A. officinalis, A. germinans, Rhizophora mangle, Ceriops decandra*, *Sonneratia alba* and *S. caseolaris* has been tested against various bacterial pathogens. This study has found the efficient antibacterial activity of *A. germinans* against *Escherichia coli*, and that of *R. mangle* against *Staphylococcus aureus* and *Bacillus subtilis* [15]. Thus the antibacterial effect varies with mangrove species and tested pathogenic bacterial strains.

The phenolic compounds extracted from *A. marina* exhibit potent antibacterial activity [16] and polyisoprenoids show antibacterial properties against *E. coli* and *S. aureus* [17]. *A. marina* is reported to have strong antibacterial and anti-proliferative activities, which are attributed to the bioactive compounds present in the plant, and these compounds are naphthoquinone-derivatives, namely avicequinone A, stenocar- poquinone B, avicequinone C, and a mixture of avicennone D and avicenone E [18]. *A. marina* is shown to have antibiotic and anti-skin tumour activities and these activities are due to the presence of an acyclic diterpene phytol in the plant [19]. The lignin extracted from *C. decandra* is shown to have effective antibacterial action. Further, the *in vivo* experiment using a mice model system has proven the efficacy of lignin against *E. coli* infection. Lignin is well-known for its antioxidant properties [20]. In addition to antibiotic effects, mangroves like *S. caseolaris* do have significant antibacterial activity against the wood-fouling bacteria, which cause wood spoilage, a serious

CHAPTER 8

A Recent Update on Sponge Bioprospecting and its Antimicrobial Properties: Their Biological Mode of Action

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Abstract: In recent decades, both the growing global resistance to existing antibiotics and the shortage of new groups of compounds identified have become a public health concern. In order to solve it, researchers are now focusing their attention on unconventional sources, including microbes from harsh environments. In this context, the aim of this study was to determine whether marine sponges have the ability to inhibit the growth of microorganisms that are terrestrial in origin and pathogenic to humans. The majority of these chemicals have so far been found in marine invertebrates, primarily sponges. Marine sponges are a rich source of structurally specific natural substances, some exhibiting a diverse variety of biological activities. Also, excellent sponge drug candidates are often overlooked because the sponges are either rare or difficult to obtain, or both. Sponges have piqued the interest of scientists who want to learn more about the associated microbial community and the useful metabolites they produce, which can be used in pharmaceutical and biotechnological applications. The ecological importance of mutualistic relationships between marine sponges and their related microbes cannot be overstated. These bioactive compounds from microbes protect their hosts from a variety of microbial diseases. These results indicate that the antimicrobial properties of marine sponge extracts may be used as a complementary or replacement method for treating microbial infections.

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Keywords: Antibacterial, Antibiotics, Antifungal, Antimicrobial, Antiprotozoal , Antiviral, Bacteria, Bioactive compounds, Environmental, Fungus, Health concern, Marine invertebrates, Marine sponges, Metabolites, Microbes, Natural substances, Pathogenic, Porifera, Public health, Viruses .

INTRODUCTION

The maritime environment is a treasure trove of biologically and pharmaceutically active natural chemicals. Marine sponges are one of the world's oldest biological forms, dating back 630 million years. Especially compared to coral reefs, they constitute the second biggest benthic community, and the diversity of sponge species outnumbers the richness of other organisms in the community. They are sessile sea filter feeders (phylum Porifera) with effective defense systems against external invaders, including viruses, bacteria, and eukaryotic organisms [1 - 4]. Microbial symbionts, such as bacteria, fungi, viruses, and archaea, are plentiful in many sponges, accounting for up to 50% of the sponge biomass in high microbially rich sponges [5, 6]. The bioactive secondary metabolites collected from sponges are assumed to be the result of functional enzyme clusters originating from sponges and their associated microorganisms. Sponges and their associated microbes have been found to contain over 5,300 different products, with over 200 novel sponge metabolites described each year. As infectious microorganisms change and develop resistance to existing medications, the marine sponge provides novel leads against bacterial, viral, fungal, and parasitic diseases. Furthermore, a rising number of possibilities, such as lasonolides (anti-fungal activity), manzamine A (activity against malaria, tuberculosis, HIV, and others), and psammaplin A (antibacterial activity), have been identified as potential routes for future clinical testing [7, 8]. Human pathogenic bacteria's tolerance to commercial antibiotic compounds has become a major problem all over the world [9, 10].

Sponges as a source of antibiotics are hampered by the need for vast volumes of sponge biomass for the generation of bioactive compounds and the difficulty in cultivation [11]. Multiple studies have discovered a broad spectrum of antibacterial properties in sponge-associated microorganisms, indicating that these microbial populations could be a valuable source of novel antimicrobials [5].

There are more therapeutic and diagnostic tests for sponge-derived chemicals than for any other marine species. Many of the bioactive substances found in sponges are produced by microbial communities [12, 13]. The importance of these sponge-associated microbes in metabolic transportation, feeding, and defense for marine sponges has been well illustrated [14 - 17]. Marine species, notably marine

sponges, yielded more than 15,000 active chemicals. Different bioactive compounds are extracted from various marine sponges (Fig. **1**).

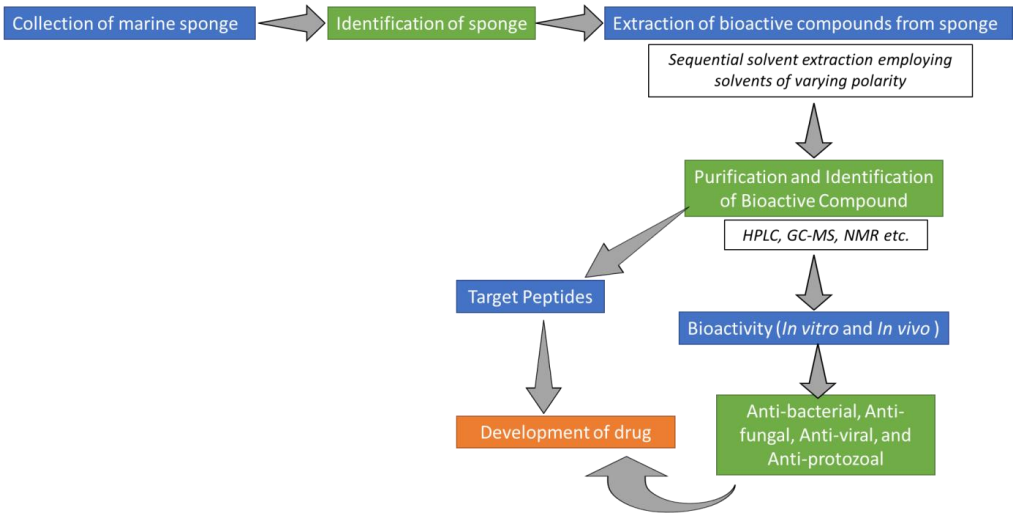

Fig. (1). Schematic representation of extracting bioactive components from marine sponges.

Novel bioactive compounds produced by sponges and sponge-associated microbes (novel terpenoids, steroids, macrolides, peptides and alkaloids) are being explored as potential sources of future medications for diseases such as antibiotic-resistant infections, malaria and cancer [18 - 20]. Many sponge species have yielded antibacterial, anti-fungal, anti-inflammatory, anti-cancer, and anti-malarial chemicals [1]. Marine sponges have traditionally been regarded as a substantial source of unique marine natural products, as well as compounds with therapeutic value. Marine sponges have produced a wide range of very potent and bioactive chemicals, resulting in innovative therapeutic leads to treating life-threatening disorders [21]. This chapter focuses on the chemistry and biological activity of bioactive compounds from several species of sea sponges.

SYSTEMATIC CLASSIFICATION OF ANTIMICROBIAL COMPOUNDS OF MARINE SPONGES

Systematic classifications of antimicrobial compounds of marine sponges are given in Fig. (**2**).

Antibacterial Activity of Marine Sponges

Despite structural differences, bioactive substances derived from marine sponges have been exposed to pathogenic human bacterial strains such as *Escherichia coli,*

CHAPTER 9

Antimicrobial Peptides: A Recent Update in the Pros, Cons, and Opportunities as Potential Antimicrobial Agents from Marine Resources

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Abstract: The emergence of multidrug-resistant (MDR) among pathogenic organism puts human and animal lives at stake. As a result of that, researchers in the scientific community tirelessly made efforts to search for novel antimicrobial agents to combat the pathogenesis of multidrug-resistant pathogens. Marine environment represents a vast diversity of lives that interact with each other and thus have to protect themselves against infectious pathogens. Hence, they present an armamentarium of diversified biomolecules with different mechanisms of action, which aids the survival of the host in the very same environment. Among the natural biomolecules, antimicrobial peptides (AMPs) gain more attention owing to their potential action as antimicrobial agents against several infectious diseases. With the emergence of MDR pathogens, AMPs are currently deemed to be the next generation of antibiotics. The quest of these AMPs was initially focused on the terrestrial environment for years. By knowing the presence of the least explored and diverse organism, the focus on the quest of AMPs is now heading toward the marine ecosystem. The current chapter focuses on the benefits, confronts and chances of using AMPs against MDR pathogens, and also emphasizes

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the need and importance of designing a focused development tactic to support the advancement and potential application of AMPs in medicine.

Keywords: Antimicrobial peptides, Antibacterial peptides, Antifungal peptides, Antimycobacterial peptides, Antiprotozoal peptides, Antiviral peptides, Marine environment, Multidrug-resistant pathogens.

ANTIMICROBIAL RESISTANCE WEAKENS TREATMENT OPTIONS

Globally, the use of antibiotics has transformed traditional medical practices. A countless lives have been saved since the discovery of antibiotics. However, the inappropriate and overuse of antibiotics in medical, agricultural and veterinary sectors with high portability of plants and movability of humans and animals have inevitably led to the ubiquitous reach of antimicrobial-resistant (AMR) organisms [1]. Considering the field of medicine amid the emergence of multi-drug resistant (MDR), extensively-drug resistant and pan-drug resistant pathogens, we are now moving towards the post-antibiotic era, where the magic bullets hold no or less efficiency [2]. In this dismal situation, a normal curable illness or a regular surgery would become life-threatening. Giving less importance to this situation or the AMR is not cautiously addressed, it would spare the life of 10 million people by the year 2050 with an economic loss of one hundred trillion US$ [1]. Underpinning the statement of the Centre for Disease Control and Prevention, it is estimated that ~2 million people get infected in response to AMR infections every year. Moreover, AMR infections nearly spared 50,000 lives per year in Europe and the US alone [3]. The present incidence of SARS-CoV-2, which caused Coronavirus disease 2019 (COVID-19), has been declared a global pandemic by WHO [4]. COVID-19 is one of the largest viral threats with huge loss of public health and socioeconomic issues around the globe that humanity witnessed in the last 10 decades in any form of microbial infections [5].

Given the rise in AMR and the challenges in conventional drug discovery and marketing, it would be wise to search for non-conventional approaches to curb the spread of AMR [6]. Among the several non-conventional approaches that have been currently investigated, such as vaccines, antibodies, bacteriophages, lysins, and probiotics, this chapter focussed on the use of antimicrobial peptides (AMPs) as a potential drug candidate to curb the infections out of AMR pathogens. AMPs are now being considered as the potential antimicrobial drug candidate of the future for their broad spectrum activity and diverse action mechanism [7]. AMPs have shown potential against bacteria, fungi, protists, parasites and viruses. Apart from its antimicrobial activity, the use of AMPs has extended in cancer studies [8, 9]. Some of these AMPs are in the clinical stages. Investigation of AMPs as antimicrobial drug candidates is a promising and emerging field, which requires a

lot of investigations in terms of searching, purification, characterization and modification of AMPs for their successful therapeutic applications [8, 10]. In the field of drug discovery, marine resources are screened a lot since it contains a diverse group of organisms adapted to different biological niches with unique response strategies. The organisms residing in different biological conditions, such as pressure (piezophile), salt (halophile) and temperature (thermophile and psychrophile), are reported to produce bioactives that tolerate these conditions [11, 12]. Due to the given fact that the compounds evolved in a manner to work under these selective conditions, the compounds identified from this ecosystem tend to differ in their structure or biochemical characteristic, which in turn used as a lead structure for the development of novel drug candidates by pharmaceutical companies [11]. With this view of light, the present work divulges the AMPs, especially from marine environments, as a potential antimicrobial drug candidates for treating infections outs of AMR pathogens.

MARINE ENVIRONMENT: A LEAST EXPLORED SOURCE FOR BIOACTIVES

The diversity present in the marine environment is very much distant from being completely explored. Most of the organisms are unique to this environment. So far, 230,000 species c.a have been classified, and nearly 2 million species remain undiscovered [13]. In the last few decades, the prime focus of the researchers from the terrestrial environment has shifted towards the marine environment by the identification of potentially bioactive compounds such as chitin, omega-3 oils, minerals (calcium), carotenoids, peptides, and so on [12]. Indeed, the marine environment is a wealthy resource hub, which is filled with a variety of plants, animals and microorganisms. The habituating environment plays a pivotal role in determining the characteristic of bioactive compounds produced by an organism. The thermostable enzyme DNA polymerase from *Thermus aquaticus* is a perfect example, which is isolated from a hot spring in Yellowstone National Park [14]. The marine environment presents with different (extremely low to extremely high) temperatures, light, pressure and salinity. Additionally, the limitations with space and nutrition create a highly competitive environment, where the residing organisms tend to develop either adaptive or antagonistic strategies [15]. In order to survive this harsh environment, the organisms present in the marine environment adapt different survival strategies, which include the production of primary and secondary metabolites with distinct and significant activities [16]. From the database of The Dictionary of Marine Natural Products, and MarinLit (http://pubs.rsc.org/marinlit), a total of 30,000 compounds have been enlisted from marine resources to date with an average yearly incorporation of nearly 1200 new compounds [17]. Yet, the quest for the identification of novel bioactive compounds is ever-increasing, and never ends because 50 to 80% of the life forms

CHAPTER 10

Antimicrobial Peptides from Marine Invertebrates

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Abstract: This chapter centers on the novel marine metabolites from marine organisms, especially peptides and other therapeutic agents. The major component of the innate immune defense system, also regarded as the first line of defense, is the antimicrobial peptide, which not only boosts resistance but also displays promising curative properties. The isolation, potential antimicrobial activity, various properties, mechanism and sources of diversified antimicrobial peptides distributed in various phyla of marine invertebrates, along with their potential role in the therapeutic arena, are explored. The most popular conotoxin peptide Zincnotide was available as a drug (Prialt®) and entered the market as a potent analgesic agent. Ethionamide (Trecator®), a nicotinamide derivative, isolated from porifera possessing antibacterial activity, is used to treat tuberculosis. Similarly, a number of peptides have been reported for exhibiting antimicrobial activities in marine organisms. Hence, the present chapter is mainly focusing on the list of marine invertebrates' antimicrobial peptides and their therapeutic applications.

Keywords: Amino acid, Anti-microbial, Arenicin, Bioactive molecule, Didemnin, Ecteinasicidin, Marine drugs, Marine invertebrates, Mytilin, Peptide, Perinerin, Plicatamide, Thionalamide, Zincnotide.

INTRODUCTION

The field of marine natural products is now becoming more sophisticated. Instead of looking for new metabolites, searches are underway for compounds that exhibit pharmacologically useful bioactive activity. Methods are now available to identify a wide range of biomarkers, such as CNS membrane-active toxins, ion channel effectors, anticancer agents, tumour promoters, anti-bacterial agents, and antiviral agents. About 16,000 marine natural products have been isolated from marine life and have been reported in about 6,800 publications in the past two decades.

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PEPTIDES

Peptides are important active substances that are present in many marine species and have been extensively studied. In most cases, the origin and role of marine active peptides are uncertain. Their potential activity is not related to their role, such as antitumor, antidiabetic, neuroprotective, and cardioprotective activities. The discovery of this bio-regulatory role will encourage the use of peptides as a potential drug for the treatment of cancer, diabetes or high blood pressure, along with a description of the mechanistic functions of marine peptides.

Bioactive peptides were first identified in marine species as neurotoxin, cardiotonic peptides, antiviral and antitumor peptides, cardiotoxin, and antimicrobial peptides. The broad bioactivity spectrum of marine peptides has high potential nutraceutical and medicinal values, which attract the attention of the pharmaceutical and nutraceutical industry, hoping that they can be used in the treatment or prevention of various diseases. Nutraceutical is a word formed by the combination of “nutrition” and “pharmaceutical”. In recent years, substantial research efforts have been dedicated to this area, and it was projected that the global nutraceutical market would reach USD 250 billion by 2018.

ANTIMICROBIAL PEPTIDES

The Antimicrobial Peptides AMPs are a class of peptides (naturally occurring short chains of amino acid monomers connected by amine bonds) that widely exist in nature, and they are a very important part of the innate immune system of different organisms. They have a wide range of inhibitory effects in averse to bacteria, fungi, parasites and viruses. AMPs are also known as host defense peptides or the first line of defense against infection in many organisms. They represent an evolutionary and protection strategy of organisms in opposition to invading pathogens, including bacteria and viruses [1, 2]. Rich sources of AMPs have been isolated from marine organisms using biochemical, *in-silico* and various genetic approaches. The marine vertebrate immunity system is characterized by somatic gene rearrangement, clonal selection and expansion and discriminative ability, including lymphocytes which impart specificity and memory. Contrary to that, marine invertebrate lacks acquired memory type immunity based on T- Lymphocyte subsets and clonally derived immune globins. Although many tissues contain these peptides, Hemlymph is the main source of AMPs in marine invertebrates.

CLASSIFICATION OF AMPS

Although all characterized AMPs have widely diverse sequences, they are tentatively classified into four distinct groups based on amino acid sequences,

secondary structures, and functional similarities [1]. The linear basic peptides forming amphipathic α-helices conformation and deprived of cysteine residues [2]; peptides containing cysteine residues with one to six intra-molecular disulphide bonds [3]; peptides with an over-representation of proline, arginine, glycine residues or tryptophan-rich peptide, such as apidaecins, drosocin, attacins and diptericins [3, 4]; and [4] the peptides produced by the hydrolysis of large inactive or proteins with little activity, such as oncorhyncin I, oncorhyncin II and oncorhyncin III from histone H1 and H6 of fish *Oncorhynchus* [5]. Some researchers have also divided AMPs according to their original host, with five different types of AMPs usually recognized: insect, mammalian, plant, microbial and amphibian [6]. Accordingly, AMPs from marine mollusks will be designated as molluscan AMPs.

MODE OF ACTION OF AMPS

Despite their variations in structure and size, AMPs are usually characterised by their cationic and hydrophobic nature, which was considered crucial for the initial interaction between the peptide and bacterial membrane [7]. According to previous research, their mode of action was similar to a pore-forming action or a deterrent effect regardless of the actual targeted action [8]. Three models have been proposed to interpret the action mechanisms; the Barrel-stave model, the Toroid al model and the Carpet-like model. The three models are all established on the presumption that AMPs could initially interact with the bacterial cytoplasm membrane by electrostatic bonding between the cationic peptide and the negatively charged components present on the outer bacterial envelope, such as phosphate groups within the Lipopolysaccharide (LPS) of gram-negative bacteria or lipoteichoic acids present on the surfaces of gram-positive bacteria.

ANTIMICROBIAL PEPTIDES IN MARINE INVERTEBRATES

Antimicrobial Peptides from Sponges

Antimicrobial peptides (MPs) play an important role in internal defence and can be considered host defence peptides. They are generally amphiphilic, have high cysteine content and are positively charged. MPs can protect hosts from infectious diseases, which makes them attractive as medical agents [9]. The maritime environment is significantly different from that of the rest of the world, which is more hostile and competitive. Marine organisms live very close to pathogens and are developed under such effective defence agents [10] under aggressive environmental pressure. Marine AMPs appear to be structurally different from their counterparts produced by the Earth's species [11]. They usually have novel and tax-specific or even species-specific compounds [12, 13]. Marine MPs are structurally diverse, exhibit a wide range of anti-infective activities, exhibit low

CHAPTER 11

Marine Biosurfactants as Potential Agents to Combat Multi-Drug Resistant Pathogens

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Abstract: Increasing threats due to microbial infections during disease outbreaks resulted in excessive usage of antibiotics. Even during viral disease outbreaks, antibacterial agents are widely prescribed to control bacterial co-infections as a precautionary measure. Moreover, inappropriate use of antibiotics steered towards the development of resistance against a diverse group of antibiotics. Dispersion of multidrug-resistant (MDR) pathogens in the environment is one of the reasons for the development of multi-drug resistance among opportunistic and commensal organisms. This poses a major risk to the healthcare sector. Excessive usage of antibiotics not only results in antibiotic resistance but also in multiple healths associated diseases in humans, such as ulcers, abdominal cramps and discomfort, and anaphylactic shock. Hence, a safe, target-oriented drug with or without minimum side effects is demanded to control multi-drug resistant (MDR) pathogens. The marine environment hosts the habituation of several plants, animals, and microorganisms. It also harbors novel, potent therapeutic agents against emerging pathogens. Recent research reports state that biosurfactants from marine bacteria, fungi, algae, animals, and plants possess targeted activity against human pathogens. These biosurfactants restrict the growth of microbial pathogens by several mechanisms. Biofilm formation is the major mechanism adopted by many MDR strains to overcome antibiotic treatment. Biosurfactants are reported to prevent even compact biofilms by preventing the adhesion of pathogenic bacteria to the host system or clinical devices. Also, they inhibit cell-to-cell signalling and down-regulate the genes coding for biofilm formation, thereby ensuring the complete removal of MDR pathogens. Novel biosurfactants from marine sources render a wide opportunity in drug selection to combat multi-drug resistant organisms.

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Keywords: Anti-adhesive, Anti-biofilm, Antibiotic treatment, Antifungal, Antimicrobials, Anti-viral, Biosurfactants, Cell membrane disruption, Drug synergism, Glycolipids, Holothuroids, Inhibition of protein synthesis, Lipopeptides, Lipoproteins, Marine biosurfactants, Micellisation, Multi-drug resistance, Saponins, Sophorolipids, Triterpenoid aglycon.

INTRODUCTION

The marine environment occupies 71% of the earth's surface, encompassing various kinds of fauna and flora. Depending on the geographical location, depth and mixing of freshwater into the marine environment influences the composition of dissolved minerals (N/P/K/Ca/Mg/S/Cl, *etc.*), salts, and organic compounds (ranges to approximately 3.5%). The presence of minerals influences the flourishing of primary producers, algae that supports the dwelling population of heterotrophic bacteria, predatory protozoans, and fauna in the marine environment. A total of around 238,414 million species are present in the ocean. Among these, 91% of the organisms are yet to be explored. The marine environment serves as a vital source to fulfill the requirement of mankind, including therapeutic drugs.

The major factor that determines the mortality rate in human beings throughout the world is determined by primary and secondary microbial infections. Different kinds of antibiotics are introduced so far to treat these infectious agents. Anyhow, microorganisms have gained resistance towards both traditional and semi-synthetic antibiotics. Antibiotics are life-savers, but their long-time application can result in side effects and contribute to the development of antibiotic resistance [1]. Especially during the COVID pandemic situation, overexploitation of antibiotics increased the prevalence of antibiotic resistance among microbial pathogens. Evidence indicates that up to 15% of severely affected COVID-19 patients developed bacterial co-infection and are in antibiotic treatment, whereas 75% of them used it inappropriately [2]. Moreover, bacterial infectious agents in the host system form a protective biofilm, which causes metabolic gradients and prevent early aggressive antibiotic prophylaxis or therapy. These biofilms are resistant to both combinations of antibiotics and semi-synthetic antibiotics in use, and therefore, an efficient agent is required to dissolve the biofilm [3]. Vancomycin, vaborbactam, and ethambutol are a few life-saving drugs and the last choice to control MDR pathogens. Eventually, antibiotics in combinations are also found ineffective to disrupt biofilms. A natural, biocompatible, potent emulsifier as well as a novel drug from the marine environment could be the right choice to treat such drug-resistant pathogens, including superbugs.

One of the major active compounds synthesized by living forms in small quantities that are active against other biological forms is biosurfactants. In general, biosurfactants are produced by the living organisms for quorum sensing or emulsification of hydrocarbons or for competitive inhibition of other predatory/ antagonistic organisms. They are chemical compounds with fatty acid side chains which are readily biodegradable and can be produced from renewable, cheaper substrates and recovered by adopting inexpensive methods [4]. The advantageous properties of biosurfactants are non-allergenic, non-toxic, biodegradable, and their implacable effectiveness at extreme temperatures (30^{o}C – 100^{o}C), pH (2 - 12), salinity (around 20%) and ease of synthesis [5]. Perhaps, the use of biosurfactants s by living forms in the marine environment could be a possible approach to combat highly variable, and drug-resistant pathogenic microorganisms.

MULTIDRUG-RESISTANT PATHOGENS

The advent of antibiotics made us mitigate the infections caused by pathogenic microorganisms. But the adaptable behavior of microorganisms to evolve themselves as drug-resistant pathogens is a major threat to the healthcare sector. Regular usage of different antibiotics against the same pathogen, with or without the physician's recommendation, aids these pathogens to evolve as multidrug-resistant (MDR) pathogens. Extensively drug resistance (XDR) refers to resistance to one or two antibiotics that belong to the same or different categories of antibiotics in use, while MDR refers to resistance to at least one antibiotic in three or more categories of antibiotics in use. Moreover, there is another resistance called Pan Drug resistance (PDR) which refers to resistance to at least one antibiotic in each category of antibiotics in use [6]. Bacteria, fungi, and viruses have acquired MDR characteristics and become difficult for any kind of antibiotic treatment. Also, unhygienic practices and sanitation conditions promote the spread of these MDR strains in both common and hospital environments. In such an environment, treating the infections becomes challenging and obviously upsurges the mortality rate of patients with primary infections, secondary infections, and comorbidities. These MDR strains acquire antimicrobial resistance (AMR) through different mechanisms and become global health threats. The World Health Organization (WHO) considers the development of resistance towards life-saving antibiotics by microbes as one of the top ten threats to global public health in society.

For common microbial infections, including urinary tract infections (UTI), sepsis, sexually transmitted diseases (STD), and some forms of diarrhea, microbial pathogens acquired PDR and indicating that pharmaceuticals are running out of effective antibiotics to control the menace [7].

CHAPTER 12

Bioactive Polysaccharides with Antimicrobial Proficiency from Marine Environment

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Abstract: Marine environment upholds vast biodiversity, which also acts as a treasurer of a huge variety of bioactive molecules. Bioactive components of marine origin range from peptides, lipids, fatty acids, proteins, minerals, phenolic compounds, vitamins, terpenoids, polyketides, polysaccharides *etc.* Marine-derived peptides have been explored to a larger extent for their biological applications. In recent years, polysaccharides, one of the essential macromolecules in all forms of living, have been gaining attention for their relevance in biological applications. Among the polysaccharides derived from various living forms, marine-derived polysaccharides are effective in terms of their biological activities owing to their structural diversity, composition, availability *etc.* Marine polysaccharides exhibit a broad spectrum of biological and pharmacological activities ranging from anti-inflammatory, antioxidant, anticancerous, antidiabetic, antioxidant, antidiabetic and immunomodulatory activities. Additionally, these bioactive polysaccharides also exert antimicrobial activities against a broad range of clinically important pathogenic organisms. Due to their excellent antimicrobial activities, marine polysaccharides, their sulfated derivatives and polysaccharide-based nanoparticles are gaining attention in biomedical applications such as wound dressing, drug delivery, tissue engineering *etc.*

Keywords: Antimicrobial, Bioactives, Biomedical application, Exopolysaccharide, Marine, Polysaccharides , Sulfated polysaccharides.

INTRODUCTION

In ancient times, natural products, their extracts and permutation have been used as the sole basis of therapy for treatments ranging from uncomplicated to lethal diseases. The revitalization of modern science introduced synthetic drug molecules with specific molecular targets. According to the theory of natural

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selection by Charles Darwin, in the last few decades, there has been increasing evidence of ineffectiveness in antimicrobial therapy against numerous human infectious pathogens owing to the upsurge in antibiotic resistance due to selection pressure [1 - 3]. Thus, in recent times, antimicrobial resistance has become an unavoidable phenomenon in the healthcare setting that requires immediate attention. Despite research on numerous biosynthesis and synthetic molecules with therapeutic efficacy, abundant natural resources remain to be either unexplored or less explored for the availability of bioactive molecules. Among the various environments, the marine ecosystem embraces the vast biodiversity with abundant novel bioactive molecules [4 - 6]. Most currently available therapeutics derived from natural sources are of terrestrial origin. Several reports have stated the superiority of marine-derived molecules over the actives from the terrestrial origin in terms of novel chemical moieties and their proficiency [7 - 9]. Thus, exploring the marine environment for novel bioactives against infectious organisms will provide a new avenue for the discovery of efficacious therapeutics. Numerous marine micro and macro organisms have been shown to produce a variety of bioactive molecules with wide spectrum therapeutic potential. Among the various bioactive components, including peptides, lipids, fatty acids, proteins, minerals, phenolic compounds, vitamins, terpenoids, polyketides *etc.*, [10] polysaccharides, have gained recent research interest owing to their chemical nature and associated biological activities [11 - 13]. This chapter outlines the bioactive polysaccharides derived from marine sources, established extraction procedures, derivatives of major polysaccharides and their application in treating infectious diseases.

MARINE POLYSACCHARIDES

Polysaccharides are biopolymers with repeating structures of carbohydrate moieties that are linked together with glycosidic bonds. Polysaccharides are found in a variety of sources, including microorganisms such as bacteria, fungi and macroorganisms involving algae, plants, seaweeds *etc*. [14]. This form of the biological organic component is hugely produced and decomposed within the marine environment. Algae and phytoplankton represent the major source of polysaccharides from oceanic [15]. Besides macroorganisms, the microbial community surviving in harsh marine environments such as extreme thermal, saline conditions, coastal thermal springs, and cold and hydrothermal vents excretes/synthesizes several metabolites so as to exist and endure the physicochemical stress. Structural diversity in the marine polysaccharides presents them as an astonishing source for the drug discovery process [16].

Polysaccharides are an integral part of certain vital biological processes, including cell-to-cell contact, facilitating adhesion, immune recognition function and other

commitment in structural integrity, cell wall synthesis, prevention of pathogen encounter *etc*. [17, 18]. These polysaccharides also perform storage (*e.g.*, glycogen, starch) and structural (*e.g.*, cellulose, chitin) functions in organisms.

Several advantages of marine polysaccharides, including their abundant availability, structural diversity, biodegradability, reasonable economy and biocompatibility, bestow them huge attention in recent research [19]. Further to their therapeutic value, polysaccharides extracted from marine algae are perceived as non-toxic and non-immunogenic, and due to these safety aspects, these polymeric substances are significantly gaining attention in various clinical applications, including drug delivery systems, tissue engineering *etc*. [20 - 22].

Among the various forms, exopolysaccharides from marine microbes have exceptional therapeutic properties [16], and their use in biomedical applications and biotechnological approaches has been initiated [23, 24].

Classification of polysaccharides is based on their repeating units of chemical structure. When similar monosaccharide moieties are repeatedly linked by glycosidic bonds, the polymer is generally known as homopolysaccharides, whereas a mixture of different monosaccharide moieties links up to form heteropolysaccharides. Based on the glycosidic bond linkage between the carbon atoms, the polysaccharides can either form linear or branched chains [25 - 27].

MARINE POLYSACCHARIDES EXTRACTION PROCEDURE/PROCESS

Marine samples can be collected, dried and grinded prior to pre-treatment procedures. During pre-treatment, the impurities such as pigments, lipids and low molecular weight compounds have to be removed using solvent mixtures at different polarities. Pigments, lipids and monosaccharides can be removed using low-polarity solvents (dichloromethane, chloroform), semipolar solvents (methanol, ethanol) and high-polar solvents (water), respectively [28, 29]. Since extraction of polysaccharides from marine sources such as seaweeds is difficult due to their firmer cell wall, pre-treatment has to be done to weaken the cell walls. Different means, such as cell lysis, can be achieved using chemical, mechanical, enzymatic, thermal, or sophisticated technology, such as ultrasound and microwave irradiation. Comparing to the conventional methods, advanced energy-based methods have shown a significant upsurge in polysaccharide yield. The general principle of extraction is that target components with bioactivity should be extracted with a minimum co-extraction of other polysaccharide constituents [30]. Following are a few of the extraction procedures demonstrated by researches for extracting polysaccharides from marine sources.

CHAPTER 13

Synthetic Derivatives from Marine Natural Products as Potential Antimicrobial Drugs

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Abstract: The marine environment havens a massive number of species that are the source of a wide range of structurally diverse bioactive secondary metabolites. The importance of marine natural products (MNPs) in drug discovery has been documented extensively with their impact on the development of existing drugs. Despite the promising activity of MNPs, most of them suffer from their complex structures, instability, and poor solubility. The synthetic derivatives of natural products cover the chemical derivatization of scaffolds isolated from marine sources and are highly applicable as chemical biosynthesis and structural modifications provide new insights into the bioactivities and the dealings against specific targets that are important for exploring the indefinite chemical space. Also, engineering of the biosynthetic pathway has shown its ability to drive analogies arising from a variety of alterations, including replacement of residues, feeding with non-natural precursors, and enzyme knockout. Such arrays of synthetic compounds execute functionally distinct biological activities against various microbial pathogens, considering MNPs valuable products in the current era of drug discovery. This chapter describes the strategies and principles for the development of synthetic drugs, as divulged by several fruitful medicines that are derived from marine origin.

Keywords: Antimicrobial peptide, Baringolin, Chloral hydrate, Chrysophaentin, Clathrodin, Drug discovery, Epinecidin, Genetic mutation, Genome mining, Holothuroidin 2, Isatin, Marine organisms, Marine natural products, Marine sponges, Oroidin, Penicimonoterpene, Structural modification, Structure-activity relationship, Synthetic antimicrobials, Turgencin.

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INTRODUCTION

Among the growing challenges to public health, infectious diseases occupy a prominent position, since they cause several disabilities that increase the global mortality rate [1]. Natural products are a pivot for the discovery of new and efficacious antimicrobial agents that are employed for infectious disease treatment [2]. Over the past several decades, more than 30,000 secondary metabolites have been identified in marine settings [3, 4].

Traditionally, the natural bioactive derivatives were identified as promising therapeutic agents through bioassay-guided research and chemical structure analysis [5]. Most of the presently known antimicrobial agents have been revealed to confer antibacterial, antifungal and antiviral activities by directly interfering with cell wall synthesis, plasma membrane integrity, nucleic acid synthesis and ribosomal function in microbial cells [6]. One of the challenges of traditional antimicrobials is that microbes have adapted and become resistant to antimicrobial drugs. This happens due to drug inactivation, target modification, and increased efflux in microbial cells [7]. When the microbial pathogens become resistant to those antimicrobials, they are denoted as “superbugs”. According to a World Health Organization report, superbugs pose too much threat to human health and kill millions of individuals every year [8]. The continuous development of antimicrobial resistance has raised demands for the discovery of novel antimicrobial derivatives.

Currently, the development of novel drugs with a precise mode of action that can efficiently afford a therapeutic activity is one of the most vital tasks for academic researchers and pharmaceutical industries. To counter this challenge, researchers have now developed synthetic drugs from natural products through chemical diversity and structural modifications, wherein the synthetic molecules are produced from the complex chemical building blocks of natural products. Pharmaceutical companies generally support drug discovery in several therapeutic areas dedicated to product development. Attention to the therapeutic target regions is made at the utmost corporate stages, commonly involving clinicians, market economists, *etc.* In this chapter, we describe some aspects and principles of the development of synthetic drugs from marine natural products (MNPs) as successful antimicrobial agents, including structural simplification, interpreting the mechanism, and optimization of stability and solubility. In recent years, some successful cases of the development of synthetic drugs by MNPs have been illustrated.

MARINE NATURAL PRODUCTS: SCAFFOLDS FOR DRUG DISCOVERY

The marine environment is a rich source of multifarious natural products with enormous biological properties. Several structurally diverse secondary metabolites have been isolated from marine sources, including porifera, mollusca, algae, weeds, seagrasses, microorganisms, *etc*. [9]. The most common groups of bioactive metabolites in MNPs are flavonols, alkaloids, fatty acids, terpenoids, lipids, phenolic compounds, polyketides and peptides [10, 11]. These metabolites are retained in various marine species in highly stressful underwater environments of atmospheric pressure, temperature, light, and nutrients [12]. Their structural diversity and diverse potential biological activities, such as anticancer, antimicrobial, anticoagulant, anti-inflammatory, *etc.*, have made MNPs a renewable source for exploring novel bioactive drugs [10, 13, 14]. Among them, marine biota is increasingly being recognized as a source of potential antimicrobial agents. Marine flora and fauna have been proven to be very productive in terms of secondary metabolites. Marine sponges are the most prosperous and earliest metazoans, belonging to the genus Porifera [15] and have the largest number of bioactive metabolites [16]. So far, the bioactive secondary metabolites from marine organisms may have potential compatibility in the pharmaceutical field to provide a stable base for the marine industry [17, 18]. Over the past few decades, preclinical pharmacology has been carried out around 260 marine compounds at various stages of clinical trials for their potential as antimicrobial agents [19].

In the successful drug development of the often complex MNPs, approaches are available to overcome the obstacles, despite the need to meet several challenges, including complex structure, poor solubility and stability. Technological advances such as chemical synthesis, structure modification, fragmentation and ring distortion strategies provide novel opportunities to develop synthetic natural products for marine species.

SYNTHETIC DRUG DISCOVERY

Natural products uncover the chances for synthetic organic biologists to develop innovative strategies [20] that are important for exploring the unknown chemical space, which is described by diversity and is obviously separated from synthetic libraries [21]. The first synthetic drug, chloral hydrate, was introduced as a sedative-hypnotic medicine; it is still occasionally prescribed in several countries. It is derived from trichloroacetaldehyde by the addition of one equivalent of water (Fig. **1**).

CHAPTER 14

Marine Metabolites: An Untapped Resource for Combinatorial Approaches against Antimicrobial Resistance

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Abstract: Antimicrobial resistance (AMR) in pathogens of clinical importance has been reported as the most commonly used antibiotics. The discovery of antimicrobial agents is in a sharp decline due to the high probability of rediscovery, high costs, and low income. Hence, the development of combinatorial antimicrobial approaches to treat AMR-related infections has gained greater attention in recent decades. Marine organisms are a rich source of structurally and chemically diversified bioactive compounds for drug discovery to address the emergence of antimicrobial resistance. Researchers have identified several bioactive metabolites from marine resources and reported on their pharmacological activities. Interestingly, marine-derived metabolites such as antimicrobial peptides, alkaloids, anthraquinones, and polysaccharides were shown to enhance the action of antibiotics by means of synergistic activity. However, numerous marine-derived compounds are yet to be evaluated for their inherent proficiency to increase the efficiency of the antibiotics and research in this regard is expected to save time, expenses and successful identification of potential compounds to treat AMR infectious diseases.

Keywords: Additive effect, Antibacterial, Antifungal, Anti-infective therapy, Antimicrobial, Antimicrobial resistance, Bioactive compounds, Biofilm formation, Combinatorial approaches, Drug candidates, ESKAPE pathogens, Fractional inhibitory concentration, Indifferent effect, Marine environment, Marine metabolites, Quorum sensing, Synergistic effect.

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INTRODUCTION

The discovery of penicillin by Sir Alexander Fleming has changed the course of medicine and facilitated clinicians to successfully deal with a number of infectious diseases [1]. Since then, numerous antibiotics have been identified to fight against infectious agents. Inappropriate and indiscriminate use of antibiotics in clinical and agricultural settings has, in turn, resulted in the emergence of antimicrobial resistance (AMR) in an alarming number of infectious agents. According to the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO), the emergence of AMR in clinically important pathogens poses a real threat to global health and the economy of developing and underdeveloped countries. Several researchers have reported that infection caused by antimicrobial-resistant bacteria is often associated with financial concerns, longer stays in hospital or intensive care units, excessive use of antibiotics and increasing morbidity and mortality [2 – 4]. The prevalence of AMR in nosocomial pathogens, particularly ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* species) limits the therapeutic choices, aggravates the severity of the existing disease, and increases mortality in patients with the weakened immune system [5].

MARINE METABOLITES

The Marine ecosystem serves as a reservoir of ~50% of our Earth's biodiversity [6]. Among marine organisms, marine microbes are considered the most trustable resource for novel bioactive compounds. As marine microbes thrive under extreme conditions and to cope-up with frequently changing physical and chemical conditions, marine bacteria and actinomycetes, microalgae and macroalgae produce structurally diverse secondary metabolites, polysaccharides, alkaloids, sterols, lactones, fatty acids, peptides, halogenated compounds and other bioactive compounds of pharmacological importance [7 – 9]. A recent study showed the good oral bioavailability of ~60% of the marine-derived compounds that are effective against multidrug-resistant (MDR) pathogens [10]. Development of high throughput next-generation technologies, bioinformatic tools, function-driven metagenomic tools and genome mining tools have increased the probability of identification of novel compounds and gene clusters from marine resources [11, 12]. Furthermore, metabolomic analysis/metabolic fingerprinting of marine samples using high-end gas-solid and gas-liquid chromatography, highly sensitive mass spectrometers and hyphenated techniques such as capillary electrophoresis-mass spectrometers (CE-MS), high-performance liquid chromatography-mass spectrometers (HPLC-MS) and high-performance liquid

chromatography-nuclear magnetic resonance spectrometers (HPLC-NMR) have research to the next level [13].

MECHANISM OF ANTIMICROBIAL RESISTANCE

Microbes acquire AMR by means of efflux pumps, by decreasing membrane permeability, degradation of antibiotics by enzymes (β-lactamases), target site alteration (mutations, methylation), horizontal gene transfer (transformation, transduction and conjugation), modification of antibiotics (acetylation, phosphorylation, adenylation), and global adaptation strategies (quorum sensing, biofilm formation) [14].

Enzymatic Degradation/Modification of Antibiotics

β -lactamase is the first identified antibiotic degrading enzyme by Abraham and Chain in 1940, and more than 2800 have been identified and described from numerous pathogens [15, 16]. β -Lactamases are classified into 4 classes such as class A, C and D (which utilise serine to hydrolyse β-lactam ring) and class B (which are metallo-β-lactamases (MBL) requires $Zn2^{+}$ for hydrolysis) [17]. Aminoglycoside-modifying enzymes (AMEs) are another group of enzymes that confer resistance to aminoglycoside antibiotics in ESKAPE pathogens. Based on the biochemical activities such as modification of hydroxyl groups, amino groups and sugar moieties of aminoglycosides, AMEs are classified into three classes, namely O-adenyltransferases (ANT), N-acetyltransferases (AAC), O-phosphotransferases (APH) [18, 19].

Target Site Modification

Target site modification mediated AMR includes three mechanisms. In brief, alteration of target enzymes, for example, penicillin-binding proteins (PBP) present on the cell wall, results in the low affinity towards β-lactam antibiotics. Methicillin resistance *S. aureus* (MRSA) [20], *E. faecalis* and *E. faecium* [14, 21] expressing chromosomal *mecA* genes encoding modified PBPs are resistant to β-lactam antibiotics. In addition, point mutations and multiple mutations in DNA gyrase and topoisomerase IV confer resistance to fluoroquinolones in clinically important gram-negative and gram-positive pathogens [14]. Substitution of threonine 83 to isoleucine, threonine 133 to methionine in gyrase A, and serine 87 to leucine in topoisomerase C resulted in a high level of resistance against quinolone and fluoroquinolone in *P. aeruginosa* [22, 23]. Modifications in the ribosome (23S rRNA and 50S rRNA) block the binding of ribosome-targeting antibiotics (for example, linezolid, chloramphenicol, clindamycin, lefamulin *etc.*) [24]. Methyltransferases such as *erm*-encoded rRNA methyltransferases and Cfr rRNA methyltransferase present in *S. aureus* and *Enterococcus* spp methylate the

CHAPTER 15

Nanomedicine from Seaweed and its Sulfated Polysaccharide Mediated Silver Nanoparticles for Microbial Disease Control

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Abstract: Worldwide, aquaculture organisms are often infected by viruses, bacteria, fungi, and parasites. These organisms are responsible for the high mortality, leading to major financial loss in this industry. Controlling microbial diseases in aquaculture is not that easy; it is much more difficult than prevention because it is a complex environment. Farmers are using different strategies to overcome this issue; however, recognizing new dietary supplements for preventing the disease is always helpful to aquaculture farmers. More recently, the bioreduction of nanoparticles using seaweed extract and its sulfated polysaccharides are fascinated because of the presence of various bioactive properties. Also, it is well-accepted that the green chemistry approach is a superior alternative to the synthesis of non-toxic nanoparticles. This chapter covers the major microbial disease in aquaculture and its management, the application of nanoparticles in aquaculture, the importance of seaweed and its sulfated polysaccharide-mediated silver nanoparticles and its role in Vibriosis and WSSV disease control in aquaculture. This chapter provides a superior understanding to the researchers for formulating novel health supplements using seaweed and its sulfated polysaccharides mediated nanoparticles to overcome bacterial and viral disease in aquaculture.

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Keywords: Seaweed, Silver nanoparticles, Sulfated Polysaccharide, Vibriosis, WSSV.

INTRODUCTION

Globally, aquaculture is one of the fastest-growing food sectors and is considered to be an imperative segment. However, due to various factors, cultured organism is often affected by diverse pathogens, which cause high mortalities and lead to massive economic losses to the industry. Moreover, it is a great challenge for aquaculturists to tackle diseases using the currently available materials. To solve this problem, farmers, technicians, and researchers are searching for new strategies and novel bioactive compounds to sustain aquaculture production. Seaweeds are commercially important renewable marine living resources and contain essential neutraceutical and pharmaceutical compounds, such as polysaccharides, proteins, polyphenols, lipids, minerals, and vitamins [1]. Among these compounds, sulfated polysaccharides (SPs) are complex polymers that have caught the attention of researchers as well as the food, biomedical, and pharmaceutical industries due to their bioactive potential [2,3]. Besides, the SPs play an important role in the aquaculture industry as substitutes for antibiotics that confer protection against pathogens [4]. Dietary supplementation with SPs in aquatic animals enhances their growth, immune response, and disease tolerance. The compounds present in seaweeds are of great value in the pharmaceutical sector due to their excellent features like convenience, functionality, ease to modify the surface to bind with drugs, the ability for drug delivery, as well as being biocompatible and eco-friendly [5]. Furthermore, the functional groups present in seaweed act as excellent reducing and stabilizing agent for the synthesis of various metallic nanoparticles (NPs) such as silver, gold, zinc, platinum, and silica. Due to their bioactive ability, biosynthesized NPs using seaweed extract and their SPs can be explored effectively to control microbial disease in aquaculture. These nanomaterials can be easily mixed with feed and used as an additive in aquaculture to manage shrimp and fish disease. This chapter provides a clear idea about the major microbial disease in aquaculture, disease management, and the therapeutic potential of seaweed-mediated silver nanoparticles (AgNPs), SPs, and SPs-mediated AgNPs.

MICROBIAL DISEASE IN AQUACULTURE

Vibriosis

The occurrence of Vibriosis in the aquaculture system was first reported in 1954 by Rucker, without any detailed discussion of the symptoms of the disease [6]. Later, severe mortality and multibillion-dollar losses in the field of aquaculture in several countries drew world-wide attention toward this disease [7]. In the past

two decades, globally, the prevalence of Vibriosis (caused by *Vibrio* spp) has increased in coastal and marine aquaculture, often associated with low survival rates in the hatchery and grow-out systems [8]. Evidence has been found that these bacteria enter into the host system through motility, using their flagellum, establish themselves *via* adhesion properties, and then multiply easily by avoiding the host defense mechanism using their virulence factors. They damage the host tissue as well as cells, finally causing mortality, and then they exit from the host and enter into a new organism [9]. Defoirdt *et al.* [7] report that the enzymes, hemolysins, and proteases secreted by *Vibrio* species are capable of damaging the host tissues and causing mortality. The chief clinical signs of Vibriosis in shrimps are reddish carapace, melanosis of the skin, tail necrosis, redness of the legs, white gut as well as white faecal matter, sluggish movement, and muscle opacity [10]. Also, it causes significant mortality in finfish cultured in the coastal environment and is commonly depicted by different names such as "red pest," salt-water furunculosis, red boil, and pike pest. The major *Vibrio* spp. associated with shrimp and finfish diseases are *V. harveyi, V. parahaemolyticus, V. alginolyticus, V. anguillarum, V. vulnificus, V. alginolyticus*, *V. fluvialis* and *V. splendidus* [11, 12]. The initial symptoms of finfish infected with Vibriosis are usually lethargy, loss of appetite, and changes in the external morphology. Later, the disease progresses to exophthalmia ("pop-eye"), skin discoloration with bloody blotches (erythema) around the fish fins and mouth (external), and the gut and rectum (internal) are filled with a bloody fluid [13]. Antibiotic and chemotherapeutic agents continue to be important disease control measures in the aquaculture industry. However, this method causes key issues like the accumulation of antibiotic residues in animal tissues, and bacterial resistance to specific drugs, which also affects the beneficial microbial population in the gastrointestinal tract of aquatic species, and, more importantly, contaminates the ecosystem [14]. Therefore, it is necessary to use antimicrobial substances to overcome these problems [15]. Currently, the available control measures do not effectively combat Vibriosis. Therefore, researchers are working toward finding a novel antimicrobial substance to overcome this disease in aquaculture.

Virus

Today, more than 20 types of viruses are responsible for causing disease in shrimps; of these, 7 viruses are currently listed by the World Organization for Animal Health (OIE), and 6 of them are White Spot Syndrome Virus (WSSV), Yellow Head Virus (YHV), Taura Syndrome Virus (TSV), Monodon Baculovirus (MBV), Hepatopancreatic parvovirus (HPV), and Infectious hypodermal and hematopoietic necrosis virus (IHHNV), reported in the Asian region. Among these, the White Spot Syndrome Virus is a major disease-causing agent in shrimp. Globally, WSSV is frequently affecting all Penaeidae shrimps [16]. This virus

CHAPTER 16

Preclinical Drug Entities in Clinical Trial Pipeline from Marine Source

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Abstract: The massive increase in the world's population has placed an undue strain on the available resources for pharmaceuticals. As a result, drug producers are constantly on the lookout for new resources that will allow them to build effective and safe pharmaceuticals to meet the growing demands of the world's population. However, three fourth of the earth's surface is covered by the marine environment, studies into the pharmacology of marine creatures have been limited, and much of what has been discovered is still undiscovered. The marine environment is a plethora and diversified source of novel medications to treat important diseases like cancer and malaria, among others. Marine natural products have distinct, previously unexplored diversifications as well as a diverse range of intriguing biological potentialities that are characterized by unique mechanisms of action. Recently discovered and preclinically researched marine bioactive antimicrobials are the focus of this chapter.

Keywords: Antibiotic-resistant bacteria, Antimicrobials, Aquaculture, Bioactive chemicals, Biological potentialities, Cancer drug, Clinical investigations, Clinical trial, Cytarabine, Cytotoxicity, Desertomycin G, Environmental conditions, Genetic engineering, Marine natural products, Marine origin, Marine sponge, Marine-derived drug, Preclinical to Drug, Preclinical, Secondary metabolites.

INTRODUCTION

Oceans encompass almost seventy percent of the surface of earth, and they provide habitat to the world's biologically diverse creatures. Many organisms and

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locations under the ocean's surface have yet to be discovered and recognized [1]. Different species have developed in response to the diverse environmental conditions found on the ocean's surfaces, each of which may have its own set of metabolic processes [2]. In the pharmaceutical business, food industry, and cosmetic sector, bioactive chemicals extracted from recognized marine species are frequently employed. Many substances derived from marine resources are now undergoing preclinical and clinical studies at various levels of development [3]. Many of the compounds do not receive final permission for public usage from the appropriate authorities for a variety of reasons [4]. These trials themselves cost a lot to investors. The challenges behind the process of converting laboratory-tested marine compounds into drugs are huge, which should be easier in the future. Advanced techniques and funding are required to harvest a huge number of potent compounds from marine resources. It was 50 years ago today when Cytarabine, the very first marine-derived drug, was introduced into medical practice [5]. In 2019, the scientific and medical communities commemorated this milestone by holding a symposium. Cytarabine (also known as Ara-C or Cytosar-U®) was initially discovered in a marine sponge and has since been shown to destroy cancer cells by interfering with DNA polymerase activity [6]. Over the course of history, plants have served as the primary source of several medicinal medicines and cosmetic goods. A large number of FDA-approved medicines were developed from diverse medicinal plant species between 1981 and 2014. Some important medicines are paclitaxel (Taxol®), docetaxel, topotecan, irinotecan, vinblastine (VBL), vincristine (VCR), vinorelbine (VRL), and etoposide [7].

Nowadays, marine bio-discovery is an attractive and productive term among researchers in the hunt for marine natural products (MNPs) that have economically considerable properties to produce and medical applications in a variety of fields such as agrochemicals, cosmetics, nutraceuticals, and pharmaceutical goods [8]. Due to their high concentrations of bioactive chemical ingredients, marine invertebrates and their symbiotically or parasitically associated microorganisms having a valuable source of novel bioactive compounds for the development of novel pharmaceutical agents with potent cancer-combating, viral-combating, and antimicrobial properties in the past few years [9]. Having a huge chemical variety of microbial natural products, the potential for structurally innovative compounds, and the vast diversity of biological functions that they possess are all well-known characteristics [10].

Based on the previously discussed relevance of compounds of marine origin, either historically or in current medicine or drug development, we sought to provide a quick review of clinically authorized and preclinical studied marine bioactive products, as well as to offer the latest outcomes in this chapter.

DRUGS IN CLINICAL TRIAL

Due to the emerging antimicrobial resistance among bacteria, it urges the whole world to find new antibiotics or other alternatives. Anti-microbial compounds from the marine environment against antibiotic-resistant bacteria are working well in preclinical trials. Till early 2020, there were nearly 11 drugs approved by FDA, EMEA and ATGA for use in the marine environment [11]. Several compounds are in the pipeline of clinical trials. Numerous compounds are in their preclinical trials [12].

In the period of 1980s and 1990s, nearly 50% of drugs approved by the FDA were of marine origin. Among them, a lot of the approved drugs are for the treatment of cancer and drug-resistant pathogens. The approved drugs are Cytarabine (Ara-C) (1969), Vidarabine (Ara-A) (1976) - discontinued in US, Ziconotide (2004), Omega-3-acid ethyl esters (2004), Nelarabine (2005), Trabectedin (2007), Fludarabine (2008), Eribulin mesylate (2010), Brentuximab vedotin (2011), Plitidepsin (2018), Polatuzumab vedotin (2019) [13 - 15]. It takes years to launch a marine-derived drug into the market for public use. Still there are a lot of natural compounds in a clinical trial. Any drug can be approved based on clinical trials, which changes the count of the compounds in the various phases of the clinical trial every year.

COMPOUNDS IN PHASE III TRIAL

The introduction of advanced chemical and physicochemical methods and techniques has also resulted in the isolation and structural elucidation of innovative modest marine secondary metabolites that were previously unnoticeable and/or difficult to isolate or discover (Table **1**). Over the past 20 years, the number of structures that have been discovered and isolated has nearly doubled. For example, according to research by John Faulkner, 869 novel structures were identified from marine organisms during the year 2000 [15], which demonstrates the importance of this field of study. According to research by John Blunt *et al.* [16], the number had increased to 1003 compounds each year by 2010, while a relatively recent publication by Anthony Carroll *et al.* documented 1490 novel molecules identified in the year 2017. Furthermore, the development of new and better organic synthesis processes made it feasible to synthesis promising active substances in sufficient quantities to be used in subsequent preclinical and clinical investigations [17].

CHAPTER 17

Recent Update on the Patents of Antimicrobial Marine Natural Products

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Abstract: Marine environment has long been shown as the source of diverse organisms and niche for numerous bioactive agents. Marine natural products are of recent interest attributing to their novelty and abundant potential in the field of medicine as well as others. In spite of this recent attention, the marine environment still exists as an under-explored and untapped resource for bioactive agents, highlighting the presence of plentiful opportunities. Bioactive molecules of marine origin have been frequently reported from the microorganisms associated with marine sediments, seawater, coral and its mucus; higher-order marine organisms, mangroves, sponges, seaweeds and sea grasses, *etc*. Last decade has shown copious publications reporting the bioactive potentials of marine natural products such as antimicrobial, antiviral, antiparasitic, anticancer, antioxidant, anti-inflammatory and anti-infective properties. Recent studies have also opened an avenue in marine natural product research where the discovered natural products are chemically modified to attain increased bioactivity. Such modified or altered marine natural products were of great demand in pharmaceutical, food, cosmetic and chemical industries, and hence protected by product and process patents. This chapter summarizes the intellectual property rights in the form of patents protecting marine natural products with antimicrobial potentials, including antibacterial, antifungal and antibiofilm activities. This chapter also highlights the patents and applications of modified or semi-synthetic agents related to marine natural sources with antimicrobial properties.

Keywords: Antibacterial, Antibiofilm, Antifungal, Antimicrobial, Anti-virulence, Bioactive agents, Coral, Mangroves, Marine microbes, Marine natural products, Sponges.

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INTRODUCTION

The marine environment is the most complex and diverse one compared to the others. It displays numerous well-differentiated habitats or niches within it, thus favouring a set of organisms unique to that niche [1]. Since the environment is complex, with several organisms coexisting in numerous niches, marine organisms produce different agents to protect them from predators as well as to define their niches [2]. Such secreted or produced biomolecules are unique and with various bioactive properties that are of interest to humans. The potentials of marine biomolecules have been explored for more than a century, yet studies on them have gained prime interest only in the past decade [3].

The marine environment harbours numerous and diverse organisms, and reports claim that most of the marine organisms, in particular the unicellular organisms, remain unexplored even today. Discovery and search of biomolecules from terrestrial regions were extensively explored due to their easiness in obtaining samples, wherein the marine environment holds a plethora of novel molecules which are untapped owing to the difficulty to access and mimic the marine niche *in vitro* [4]. Reports have claimed that there are approximately 11,000 marine natural products divulged this far in contrast to 155,000 natural products from terrestrial sources, explaining the magnitude of resources submerged under the sea (Fig. **1**) [3]. Culturing marine microorganisms remains the major hurdle even today, which disrupts their studies to reveal their true potentials. The inclusion of culture-independent method to study marine environments has given a different perspective on their bioactive potentials in addition to their microbial diversity and richness [5]. Numerous studies have attempted to tap the genomic information obtained from such culture-independent methods to synthesize the bioactive agents of interest. Growing demand for novel biomolecules led to the expansion of pharmaceutical research horizon towards marine environments, which provided fruitful novel agents with potential bioactivities such as antimicrobial, antiviral, antiparasitic, anti-inflammatory, anticancer, antibiofilm, anti-infective and antifungal activities.

MARINE BIO-PROSPECTING

Marine natural products are derived from marine sponges, tunicates, corals, ascidians, echinoderms, bryozoans, molluscs, mangroves, macro and microalgae, cyanobacteria and other marine microorganisms, including marine bacteria [3, 6 - 9]. Marine bacteria associated with marine sediments, water, mangrove rhizosphere soil, sponges, seaweeds, sea grass and coral mucus have been reported to produce numerous natural products with bioactive potentials [10 - 16] (Fig. **2**).

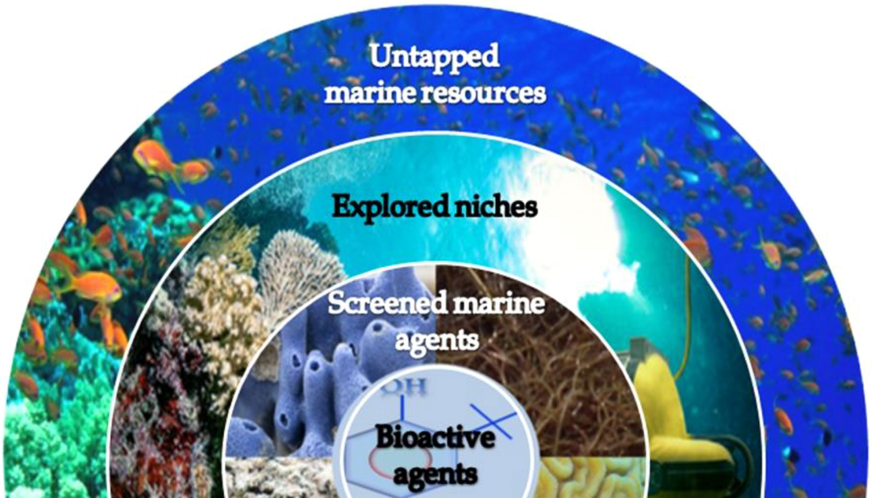

Fig. (1). Marine environment as a rich reserve for bioactive agents.

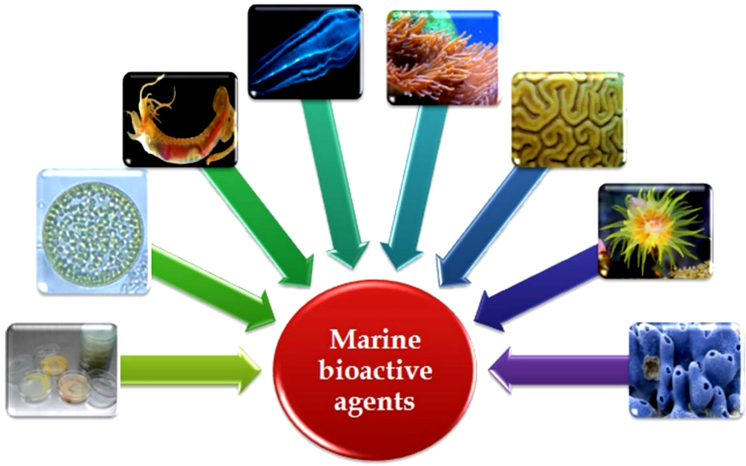

Fig. (2). Marine sources with reported antimicrobial agents.

Marine natural products are obtained after several processes starting from sample collection, identification and classification of the marine organisms, extraction of products with plausible bioactivity, purification of the potential bioactive agent, structure elucidation for the bioactive agent, determining the mechanism of its action, establishing the efficacy and safety of the identified bioactive agents in animal studies, improving the bioactivity by structure modification studies and finally *in vitro* synthesis or organic synthesis for the continuous supply [3, 17 - 20]. The marine natural products with potential activities that could be of human interest will be protected by filing patent applications claiming either the product

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